The acute effects of dopaminergic medication and deep brain stimulation of subthalamic nucleus on basic executive functions including shifting, updating and inhibition in Parkinson's disease patients

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Declaration

I, Yu-Ting Huang, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

Acknowledgment

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『光陰不會往後退，應拋開傷心憶記，願再試高飛的滋味。』
趁風再起，願逆風萬里高飛。

Abstract

The general aim of the present PhD thesis is to investigate the effects of two common treatments of Parkinson's disease (PD), dopamine medication and deep brain stimulation (DBS) of the subthalamic nucleus (STN), on executive functions (EFs) including the abilities of shifting, updating and inhibition in patients relative to age-matched healthy controls. The thesis consisted of four studies. **Study 1** examined the acute effect of dopamine medication on PD patients who had been previously diagnosed with impulsive control disorders (ICDs) using a moving dots paradigm to assess their abilities of context monitoring. **Study 2** created predictive models using behavioural data from the previous studies to build classification predictive models, to demonstrate that behavioural patterns on a moving dots task could potentially be used as a screening tool in predicting vulnerability to develop ICDs in PD patients. **Study 3 e**xamined the acute effects of STN DBS on task switching using a moving dots paradigm in PD patients. **Study 4** investigated the acute effects of STN DBS on reprogramming actions when encountering surprising events, using a probabilistic reaction time (RT) task. It was hypothesised that for both treatments, being ON states would induce impaired executive functions that lead to faster RTs and more incorrect responses in PD patients, due to the 'dopamine overdose hypothesis' and the DBS interrupting the role of the STN in inhibitory control. In summary, the acute manipulation of both treatments did not render significantly negative effects on PD patients behaviourally. However, PD patients still showed certain difference on task performance compared to age-matched healthy controls, which may shed lights on the role of basal ganglia in basic abilities of EFs. Furthermore, the behavioural patterns on tasks involving core aspects of EFs may potentially be used to predict the onset of ICDs, which provides benefits to clinical purpose.

Impact statement

Parkinson's disease (PD) is the second most common neurodegenerative movement disorder, which affects 1% of the population over the age of 60 (de Lau & Breteler, 2006). The basal ganglia dysfunction is closely related to the motor and non-motor symptoms observed in PD. Two common treatments for PD include dopamine medication and deep brain stimulation (DBS) of the subthalamic nucleus (STN). Despite effectively ameliorating motor symptoms, clinical observations have shown that PD patients may develop side effects on cognitive functions such as diminished verbal fluency, impaired executive functions and impulse control disorders (ICD) induced by the treatments. By collecting behavioural data from PD patients ON versus OFF treatments, the present PhD thesis investigated the acute effects of both treatments on behavioural tasks in PD patients. The behavioural data were further compared to age-matched healthy controls (HCs). In addition, hierarchical drift diffusion models (HDDM) were applied to the behavioural data to derive the underlying mental processes.

In general, the results showed that both treatments are robustly effective in ameliorating motor symptoms and produced no significantly negative effects on task performance and psychological measures in PD patients. Both treatments are therefore supported to be safe procedures in treating patients with PD. Theoretically speaking, the present results are in line with the hypothesis that action execution is associated with both the quality/reliability of sensory information and the inner drive to be fast and accurate, instead of simply related to speed and accuracy trade-off

modulation. In addition, the results support the roles of dopamine and the STN in motor control and inhibition through the basal ganglia pathways. Clinically speaking, the results suggest that while some evidence has shown that medical and surgical treatments can induce negative side effects on cognition for PD patients, such side effects may be small and specific to individuals. Despite receiving benefits from both treatments, PD patients still showed certain deficits when performing the tasks compared to age-matched HCs. The results thus indicate that factors other than acute influence of treatments are involved in controlling executive functions in PD patients. Effects of long term treatments, disease progress, individual difference, genetic factors, environmental as well as social factors are in need to be considered for patient-centred care. More importantly, PD patients who had been clinically diagnosed with impulse control disorders (ICD) have been shown to have different behavioural patterns on a moving dots task compared to PD patients who had never been diagnosed with ICDs. The results suggest that tasks of similar characteristics may potentially be used as a screening tool to prevent the medication-induced ICDs by identifying PD patients who may be vulnerable to developing ICDs before the medication treatment.

Taken together, the present thesis proposes a potential new screening tool for ICDs in PD patients that can have clinical benefits on preventing the negative side effects, and provides insights on the theoretical roles of dopamine and the STN in executive functions associated with the abilities of shifting, updating and inhibition.

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Chapter 1 Introduction

Chapter 2. The role of dopamine in perceptual decision-making: the acute manipulation of dopaminergic medication did not induce impulsive behaviour in Parkinson's disease patients with impulse control disorders on perceptual decision-making

Chapter 1 General introduction

Parkinson's disease (PD) is the second most common neurodegenerative movement disorder, which affects 1% of the population over the age of 60 (de Lau & Breteler, 2006). It has been established that the basal ganglia dysfunction directly connects to the movement disorder (DeLong, 1990). Currently there is no cure for the disease, however there are two common treatments that have been developed to treat PD patients: dopamine medication and deep brain stimulation (DBS) of the subthalamic nucleus (STN). Both treatments have been suggested to efficiently ameliorate motor symptoms in PD, however, the treatments have also been suggested to induce cognitive side effects such as impulsive behaviours, impaired executive functions (EFs) and impaired verbal fluency (Weintraub, David, Evans, Grant & Stacy, 2015; Gotham, Brown, & Marsden, 1988; Cools, Barker, Sahakian, & Robbins, 2001; Swainson et al, 2000; Walter & Vitek, 2004). It is hypothesised that dopamine medication inude side effects in PD patients could be the results of 'dopmaine overdose hypothesis', which suggest that while dopamine medication remedies the dopamine depleted areas in the brain it would overstimulate relatively intact brain areas thus leads to impaired cognitive functions (Cools et al., 2001, 2006), and DBS of the STN would interrupt the inhibition function of the STN, leading to impaired inhibitory control in PD patients (Frank et al., 2007; Green et al., 2013). Broadly speaking, these side effects induced by treatments in PD patients could potentially be generalised to the impairment on three basic EFs: shifting, updating and inhibition. which is also closely associated with the basal ganglia dysfunctions. In addition, behavioural tasks such as moving dots paradigm and probabilistic reaction time (RT)

task can provide links associating cognitive and motor processes that are involved in the basic EFs. Therefore, in the present thesis I attempt to investigate the acute effects of treatments of PD, namely dopamine medication and STN DBS, on basic EFs including shifting, updating and inhibition using moving dots paradigm and a probabilistic RT task.

The acute effects of treatments were assessed by comparing the behavioural data ON treatment and OFF treatment within PD patients. RTs and response accuracy of the behavioural tasks were collected as the dependent variables. Computational models such as hierarchical drift diffusion model were further applied to the behavioural data to study the underlying mental processes. Performance of PD patients OFF/ON treatments was further compared to age-matched healthy controls. The present thesis is composed of the following chapters:

Chapter 1 is the general introduction including reviews on (1) general concepts on the three basic EFs including shifting, updating and inhibition, (2) the anatomy and structure of the basal ganglia, and the circuits linking action and cognition; (3) pathology, symptoms and the treatments of PD; (4) the acute effects of the two treatments (i.e. dopamine medication and STN DBS) on cognitive functions associated with context monitoring in PD patients; (5) general aims and methodologies of the studies.

Chapter 2 introduces a behavioural study investigating the acute effect of dopamine medication on PD patients who had been previously diagnosed with ICDs, using a random moving dots paradigm. It was hypothesised that based on ‘dopamine

overdose hypothesis', when response speed was emphasised while making a response, PD patients with ICDs 'ON medication' would show faster RTs and more incorrect responses due to impaired basic EFs that leads to failed context monitoring, in contrast to when response accuracy was emphasised. Contrary to prediction, the results showed that acute manipulation of dopamine medication did not have significant negative effects on the behavioural parameters of PD patients. Moreover, the application of hierarchical drift diffusion model (HDDM) to the behavioural data showed that PD patients with ICD history did not show significant impairments on context monitoring. The results seem to suggest that PD patients with ICD history and PD patients without ICD may show difference when performing certain tasks compared to previosuu study (Huang et al., 2015), which may further indicate that the behavioural parameters of the tasks could potentially be used as an input in building predictive models, providing clinical benefits to patient-centred health care.

Following the previous results, Chapter 3 presents a study using behavioural data from the moving dots tasks as one of the input variables in training a predictive model with machine learning algorithms to classify PD patients with and without an ICD history. It was hypothesised that performance on the moving dots task could be used as a screening tool to predict potential development of ICDs. The results showed that behavioural parameters from moving dots tasks could potentially be used as a screening tool in predicting vulnerability to develop ICDs in PD patients. The results combining previous studies suggest that it is possible to use behavioural parameters to predict the onset of ICDs in PD patients, tasks associated with the abilities of shifting, updating and inhibition may be used in unmedicated PD patients, so that clinicians are

more likely to take appropriate precautionary action to prevent the onset of ICDs.

On the other hand, to explore the acute effects of STN DBS on the basic EFs in PD patients, Chapter 4 & Chapter 5 each presents a behavioural study on the subject. Chapter 4 presents a behavioural study examining the acute effect of STN DBS on how PD patients performed a block-designed moving dots task that attempted to assess the effects of STN DBS on task-switching. In addition, the mioving dots task also provide the investigation of making resposnes under speed and accuracy instructions (Speed/Accuracy trade-off) and at the same time estimating the reliability of sensory information. It was hypothesised that PD patients ON stimulation would have impaired task-swithcing abilities dues to the hypothetical effects of DBS on interrupting functions of STN on inhibitory control, resulting in faster RTs and more incorrect responses when it is required to switch between automatic and controlled behaviours. Contrary to prediction, the present study shows no negative effect on task switching behaviours induced by the acute manipulations of STN DBS on a block-designed moving dots task. However, PD patients with STN DBS ON did show deficits on task switching during the Inhibition/Switching part of the Colour Word Interference Test compared to age-matched HCs. The evidence suggests that task-switching may involve fundamentally different but related cognitive processes, which are controlled by distinct brain areas. Moreover, the above results are in line with the hypothesis that the reliability of sensory information plays an important role on modulating SAT. Furthermore, PD patients still showed subtle difference on underlying cognitive components under the effects of DBS, which supports a role of

the STN on SAT and sensory information integration. It may be due to the suboptimal design of the behavioural tasks that the effects of STN DBS on impairing inhibitory control.

To further explore the hypothesis of STN DBS impairing inhibitory control in PD patients, Chapter 5 introduces a study assessing the acute effect of STN DBS on how PD patients reprogamme their actions after encpuntering unexpected events, which is closely related to inhibition, and cognitive flexibility. It was hypothesised that when ON STN DBS, PD patients would fail to reprogram the action while environmental context changed, which leads to faster RTs and more incorrect responses during the trials that are unexpected (in the study the unexpectedness was defined as improbable trials that was based on the frequency of the sequence). The results show that all participants were able to react fast during Predictable blocks/Probable trials than Unpredictable blocks/Improbable trials. In addition, response accuracy did not differ between Predictable and Unpredictable blocks for all participants, but for HCs response accuracy was higher during Probable trials than Improbable trials, such a difference was not observed in PD patients across stimulation states.

Furthermore, PD patients exhibited robust speed and accuracy trade-offs when performing the probabilistic RT task, which may indicate that PD patients, especially PD patients OFF stimulation, were predominately aiming to act fast therefore sacrificed response accuracy. In summary, the two studies did not show an effect of DBS on inducing impairedinhibitory control in PD patients, however it did not rule out the the possibility of STN DBS to impaire motor/cognition control through

inhibiton in PD patients. Moreover, in both studies PD patients treated with STN DBS were assessed ON medication, which may be the reason why the results did not reflect the hypothetical effects of DBS on interrupting the role of STN in cognitive and motor control.

Chapter 6 summarises and discusses the findings from previous experimental chapters and provides directions for future studies investigating relevant research topics. The appendices contain the questionnaires and consent forms used in the studies, and the programming codes with additional figures for the statistical and computational models. Figure 1.1 illustrates a schematic framework of the present thesis.

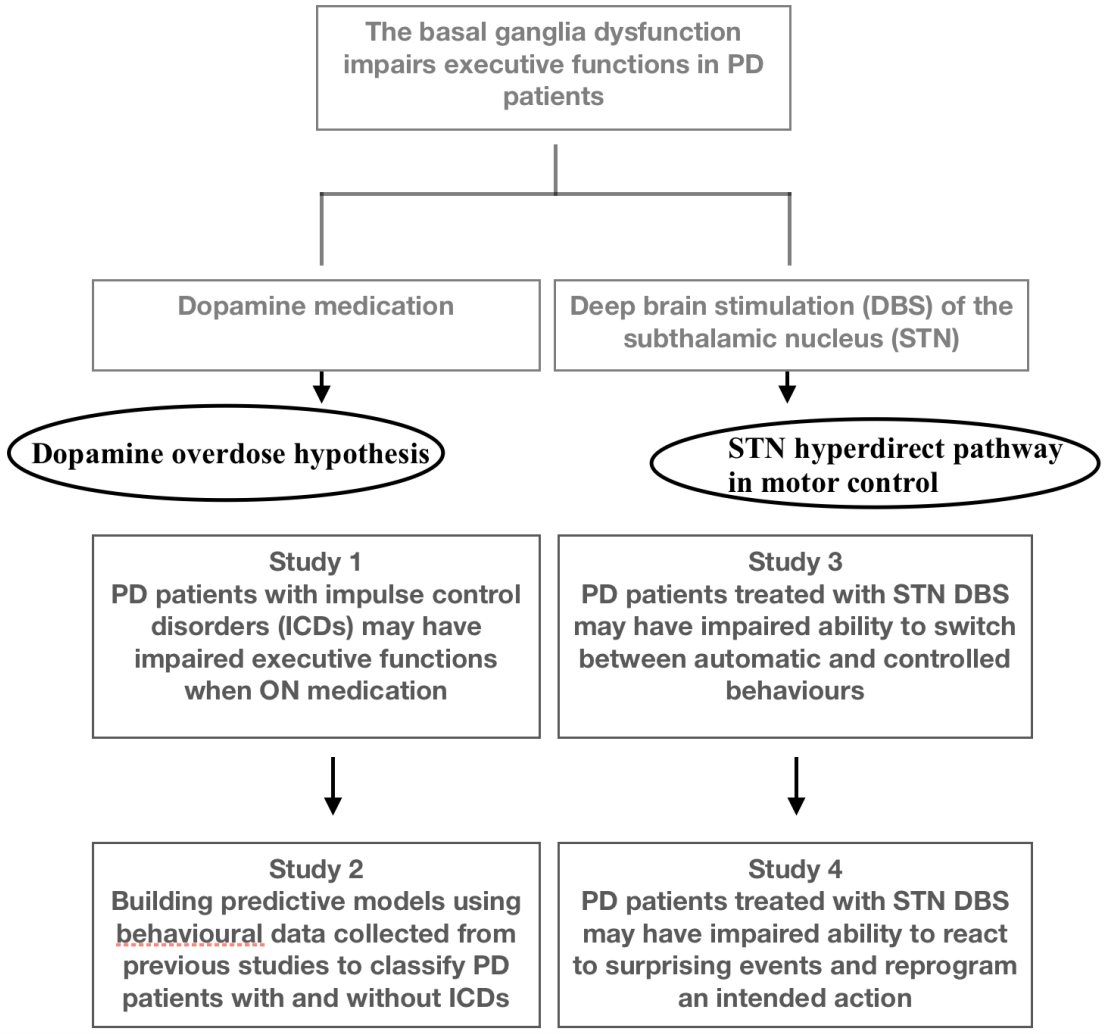

Figure 1.1 A schematic framework of the present PhD thesis. The role of dopmamine was investigated by assessing the acute effect of dopamine medication on behavioural data in PD patients based on dopamine overdose hypopthesis. The rold of the subthalamic nucleus (STN) was investigated by assessing deep brain stimulation (DBS) of STN on behavioural data in PD patients based on the role of the STN hyperdirect pathway in motor control.

1-1 Executive functions

Executive functions (EFs) is an umbrella term that refers to a family of top-down mental processes that control other brain processes (Diamond, 2013; Najdowski, Persicke, & Kung, 2014), which are skills essential for mental health, physical health, and almost every aspect of life. Table 1.1 lists the associations between EFs and the aspect of life and their references. In summary, impaired EFs may result from impaired inhibitory control, thus resulting in mental health and physical health problems (Baler & Volkow, 2006; Diamond, 2005; Lui & Tannock, 2007; Fairchild et al., 2009). In addition, 'cognitive control', which refers to the ability to coordinate lower-level sensory, memory and/or motor operations in relation with internal goals (Miller, 2000; Koechlin, Ody & Kouneiher, 2003), is sometimes interchangeable to EFs by some researchers (Aron, 2007; Miller & Cohen, 2001). Cognitive control is essential for higher cognition processes such as solving complex or novel tasks, correcting errors and overcoming habitual responses. Some studies associate cognitive control closely to the ability of task switching (Monsell. 2003; Kim, Cilles, Johnson, & Gold, 2012). In the present thesis I use the term 'executive functions' to represent the broad functions, whereas 'cognitive control' in the present thesis would be considered as a synonym to cognitive flexibility (task-switching) which would be further explored in later sections.

Aspects of life	The ways in which EFs are relevant to that aspect of life	References
Mental health	EFs are impaired in many mental disorders, including:	
	- Addictions	Baler & Volkow 2006
	- Attention deficit hyperactivity (ADHD)	Diamond 2005, Lui & Tannock 2007
	- Conduct disorder	Fairchild et al. 2009
	- Depression	Taylor-Tavares et al. 2007
	- Obsessive compulsive disorder (OCD)	Penadés et al. 2007
	- Schizophrenia	Barch 2005
Physical health	Poorer EFs are associated with obesity, overeating, substance abuse, and poor treatment adherence	Crescioni et al. 2011, Miller et al. 2011, Riggs et al. 2010
Quality of life	People with better EFs enjoy a better quality of life	Brown & Landgraf 2010, Davis et al. 2010
School readiness	EFs are more important for school readiness than are IQ or entry-level reading or math	Blair & Razza 2007, Morrison et al. 2010
School success	EFs predict both math and reading competence throughout the school years	Borella et al. 2010, Duncan et al. 2007, Gathercole et al. 2004
Job success	Poor EFs lead to poor productivity and difficulty finding and keeping a job	Bailey 2007
Marital harmony	A partner with poor EFs can be more difficult to get along with, less dependable, and/or more likely to act on impulse	Eakin et al. 2004
Public safety	Poor EFs lead to social problems (including crime, reckless behavior, violence, and emotional outbursts)	Broidy et al. 2003, Denson et al. 2011

Table 1.1 Executive functions (EFs) are important to many aspects of life. Table from Diamond (2013).

In addition to the difficulty to precisely define EFs, the study of EFs is challenging due to task-impurity (Miyake, Friedman, Emerson, Witzki, & Howerter, 2000), as any target EF must be embedded within a particular task context, the measures derived from any laboratory tasks to assess EFs would necessarily include non-EF processes (Miyake & Friedman, 2012). To ease such an issue, Miyake & Friedman (2012) have been using a 'latent-variable' approach, of which researchers select multiple exemplar tasks sharing little non-EF variance and statistically extract the common variables, resulting in 'purer' latent variable as the measures to study EFs. Moreover, the researchers have primarily focused on the study of three EFs: updating (constant monitoring and modifying working memory contents based on sampled information), shifting (switching flexibly between tasks and/or mental sets), and inhibition (deliberately suppressing intended or prepotent actions) (Miyake & Friedman, 2012).

Figure 1.2 illustrates the unity/diversity framework that reflects a shift in recent research goal to specifying the cognitive and biological underpinnings of the unity and diversity (Miyake & Friedman, 2012).

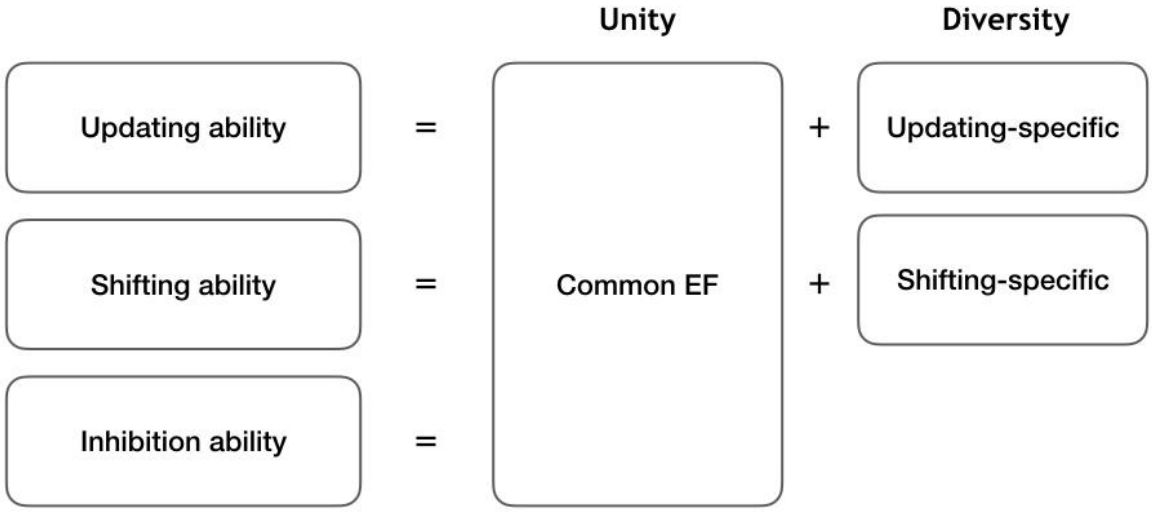

Figure 1.2 Schematic representation of the unity and diversity of three executive functions (EFs). Each EF is hypothesised to be the combination of a unity component (i.e. common EF) and a diversity component that is specific to the particular EF (e.g. updating-specific EF for updating ability). In this figure, a specific diversity component for inhibition is missing due to previous studies showing that once the unity component (i.e. common EF) is accounted for, no unique variance would be left for the inhibition ability (Friedman et al., 2008; 2011). Figure adapted from Miyake & Friedman (2012).

In association with the three EFs (i.e. updating, shifting, and inhibition) proposed by Miyakie & Friedman (2012), there is also an agreement on the existence of three core EFs: working memory, inhibition, and cognitive flexibility (Lehto, Juujarvi, Kooistra,

& Pulkkinen, 2003; Miyake et al., 2000). Figure 1.3 illustrates the basic level EFs (such as working memory, inhibitory control, and cognitive flexibility), higher level EFs (such as reasoning, problem-solving, and planning), and their associated concepts.

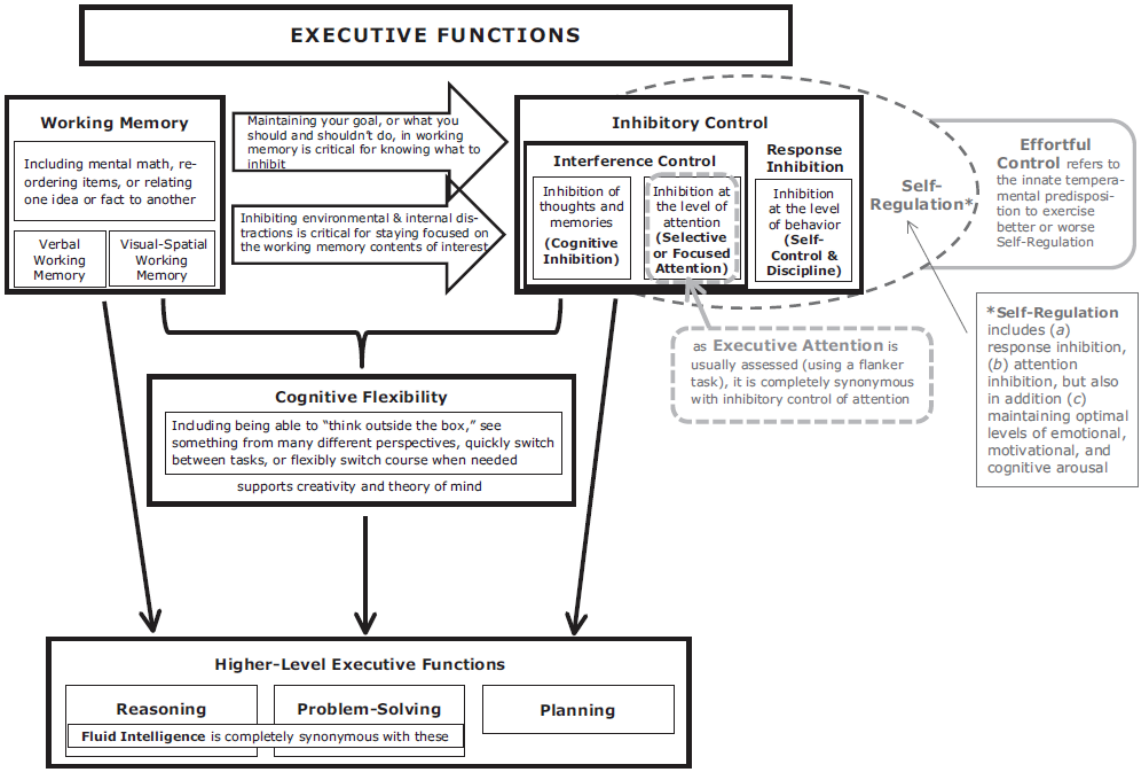

Figure 1.3 Executive functions and related terms. Figure and caption from Diamond (2013).

Working memory (WM) contains the cognitive capacity that is responsible to hold information in mind and mentally working with it (Baddeley & Hitch, 1994; Smith & Jonides, 1999). One of the most common concepts linked to executive functions is the multicomponent model of WM proposed by Baddeley & Hitch (1974), which

suggests that WM comprises a phonological loop for manipulating and storing speech-based information and a visuospatial sketchpad for visual and spatial information. In addition, WM is critical for reasoning and planning (Suß, Oberauer, Wittmann, Wilhelm, & Schulze, 2002; Owen et al., 2010), and is crucial for inhibitory control as information must be hold in mind to guide future behaviours (Diamond, 2013). Conversely, inhibitory control is crucial for WM as the mind is required to inhibit internal and external distractions to keep the goal in mind and to avoid mind-wandering (Kane et al., 2007; Mason et al., 2007; Smallwood & Schooler, 2009). In addition, inhibitory control supports WM by suppressing irrelevant information from the limited-capacity workspace (Hasher & Zacks, 1998; Zacks & Hashers, 2006). Duncan et al (2008) showed that participants with poorer EFs failed to switch rules when being instructed to, which has been associated to failure in clearing up irrelevant information from the limited-capacity WM workspace. Despite evidence showing that inhibitory control and WM are intertwined, the influence of each skill may be controlled for (Diamond, 2013). It has been suggested that WM and inhibitory control rely on the same limited-capacity system, therefore increasing demands on one would affect the performance of the other (Engle & Kane, 2004; Wais & Gazzaley, 2011). The neural basis of WM involves the activation of the prefrontal cortex in top-down modulation (D'Esposito et al., 1995; Bunge, Klingberg, Jacobsen, & Gabrieli, 2000; Zento et al., 2011). Some researchers view WM as the primary skill and that inhibitory control is the derivative (Egner & Hirsch, 2005; Hanania & Smith, 2010; Nieuwenhuis & Yeung, 2005), while another group of researchers find the two skills separable by viewing WM as the activation of goal and

inhibitory control as suppression on irrelevant tasks (Davidson, Amso, Anderson, & Diamond, 2006; Zanto, Rubens, Thangavel, & Gazzaley, 2011). It remains debatable on the exact relationships between WM and inhibitory control, however it is undeniable that the two cognitive skills are associable and that WM is an important part of EFs.

Inhibition includes self-control (behavioural inhibition) and interference control (selective attention and cognitive inhibition), which involves the ability to control one's attention, thoughts, behaviours, and/or emotions to override existing internal/external cues or goals, in order to adapt to current environment and execute more appropriate actions (Diamond, 2013). Inhibitory control of attention includes selectively choosing to pay attention or ignore (i.e. inhibit attention) specific stimuli in order to fulfil a set goal or intention (Posner & DiGirolamo, 1998; Theeuwes, 2010). Another aspect of inhibitory control is self-control or self-regulation ability, which includes (1) controlling over one's behaviour and emotions to prevent from acting impulsively, (2) having the discipline to overlook distractions and focus on completing a task despite temptation to quit and (3) delayed gratification that involves giving up a small immediate reward in exchange for a larger reward later (Diamond, 2013). Psychological measures of inhibitory control include the Stroop task (MacLeod, 1991), Simon task (Hommel, 2011), Flanker task (Eriksen & Eriksen, 1974; Mullane, Corkum, Klein, & McLaughlin, 2009), antisaccade tasks (Luna, 2009; Munoz & Everling, 2004), delay-of-gratification tasks (Kochanska, Coy, & Murray, 2001; Sethi, Mischel, Aber, Shoda, & Rodriguez, 2000), Go/NoGo tasks (Cragg &

Nation, 2008), and stop-signal tasks (Verbruggen & Logan, 2008). Note that despite the effect of Stroop task is sometimes referred to as 'Stroop inhibition', it has also been suggested that Stroop task demonstrates more of an interference effect resulting from conflict (MacLeod, Dodd, Sheard, Wilson, & Bibi, 2003). In addition, Stroop task has also been considered to be a type of cognitive flexibility task (Golden & Freshwater, 1978; Moore & Malinowski, 2009). Most of the mentioned tasks require the inhibitory control to execute an action over another, whereas the Go/NoGo tasks and stop-signal tasks require participants to inhibit an action without making another. The basal ganglia are closely associated with the underlying neural mechanisms of inhibitory control, which is one of the core hypotheses of the present thesis and would be further discussed in later sections.

Cognitive flexibility also refers to as set shifting, mental flexibility or mental set shifting, which relies on both WM and inhibition and is closely related to creativity and theory of mind (Diamond, 2013). The aspects of cognitive flexibility include: (1) the ability to change perspectives spatially and interpersonally that requires the inhibition of previous perspective and activating WM to switch to a different perspective, which is associated with 'thinking outside the box' (i.e. creativity) and 'put yourself in someone else's shoes' (i.e. theory of mind), and (2) the ability to adjust in accordance to the dynamically changing environment such as task demands, priorities, admitting being wrong and reacting to unexpected events. Cognitive flexibility has been suggested to be crucial to problem-solving abilities especially when facing novel and surprising condition, which is also closely related to

attentional processes (Canas, Quesada, Antoli, & Fajardo, 2003). With the growing interest in the beneficial effects of buddhist meditation on well-beings and emotions (Barinaga, 2003; Ekman, Davidson, Ricard, & Wallace, 2005), recent studies have also focused on how meditation and mindfulness may have on cognitive flexibility. Evidence has revealed that meditation improves mood (Davidson et al., 2003), cognitive performance (Cahn & Polich, 2006) and enhances attentional processes (Jha, Krpmpinger, & Baime, 2007; Moore & Malinowski, 2009) not only in clinical researches but in nonclinical populations as well (Eberth & Sedlmeier, 2012). Psychological measures including the Stroop Color and Word Test (Golden, 1975), Trail Making Test Part B (TMT; Reitan & Wolfson, 1993), Wisconsin Card Sorting Test (WCST; Berg, 1948), self-report measures such as the Alternate Uses Test (Wilson et al., 1975), Attributional Style Questionnaire (ASQ; Peterson et al., 1982) and Cognitive Flexibility Scale (CFS; Martin & Rubin, 1995) have been used to measure cognitive flexibility. Human studies have shown that left ventrolateral prefrontal cortex plays an important role in facilitating flexible performance (Miller & Cohen, 2001; Badre & Wagner, 2007; 2009). Furthermore, studies have shown that brain areas such as anterior cingulate cortex (ACC), and the basal ganglia are involved in conflict resolution and controlling the execution of actions (Koechlin et al., 2003; Chein & Schneider, 2005; Aron, Robbins & Poldrack, 2004; Frank, 2005; Aron & Poldrack, 2006; Aron, 2007). In later sections I would further explore the crucial involvement of the basal ganglia in cognitive flexibility especially task switching.

Taken together from the above studies, the fundamental abilities of EFs include shifting, updating and inhibition. In addition, the underlying neural mechanisms of these EFs are closely related to the functions of the basal ganglia, which is impaired due to dopamine neuron loss in patients with PD. The research interest of the present thesis therefore lies in investigating the acute effects of treatments of PD on these EFs associated in PD patients, in the following sections of Chapter 1 I explore different functions that are considered to be associated with the EFs, including (1) context monitoring, (2) controlled and automatic processing and task-switching paradigm, (3) speed and accuracy trade-offs, and their underlying neural mechanisms. In addition, the selected functions have been suggested to be impaired in PD patients by previous studies, which would also be explored in later sections.

1-1-1 Context monitoring

Through evolution the human brain has developed the abilities to adapt to the constantly changing environment by gathering and interpreting limited sensory information, compute the desired decisions directed by different goals and motivations to execute appropriate actions, which is an important skill for survival in a dynamic world. Among these vital abilities, inhibition is an exceptionally critical part to control behaviours in order to perform more context-appropriate actions (Chatham et al., 2013).

In the field of neuroscience and psychology, inhibition has many meanings and has

been studied extensively (Aron, 2007). Response inhibition, which is a particular domain of inhibition, has been widely used in experimental studies to account for the concept of inhibitory control (MacLeod, Dodd, Sheard, Wilson, & Bibi, 2003), and has been linked to the functioning of frontal cortex and basal ganglia (Wiecki & Frank, 2012). Logan & Cowen (1984) proposed a formal model stating that a control signal, including error during performance or an external indication to stop, would activate a 'stopping process' that suppresses the underlying ongoing thoughts and actions. The model introduced the stop-signal procedure to account for the act of control when actions/thoughts are no longer relevant to the current goals, however the estimate of the model cannot untangled the time spent detecting and/or interpreting the stop signals and the time for motor stopping per se to take place (Logan & Cowen, 1984). Moreover, Chatham et al (2012) proposed that in order to effectively demonstrate inhibitory control, it is important to first monitor the environmental signals to support behaviours that may be contingent on the specific context, such a concept is termed 'context monitoring'. In most laboratory studies of response inhibition, motor stopping and context monitoring are inseparable as subjects were required to cancel a prepotent or a planned response after receiving a signal indicating the subjects to stop (Chikazoe et al., 2009; Logan & Gowan, 1984; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Sharp et al., 2010; Cai & Leung, 2011; Dodds, Morein-Zamir, & Robbins, 2011; Aron, 2010). To determine whether context monitoring or motor stopping may reflect the cognitively-controlled processes required for response inhibition, Chatham et al (2012) used computational, hemodynamic, electrophysiological and pupillometric techniques to assess the

characteristics of cognitive control. The results showed that context monitoring, rather than motor stopping, requires more effortful, controlled, and prefrontal-based processes during response inhibition task. The concept of context monitoring is in a sense intermingled with information updating and the ability to adapt to the dynamically changing environment (i.e. shifting).

1-1-2 Controlled and automatic processing and task-switching paradigm

Many daily tasks are well-learned routines; however, it is important to maintain the flexibility as to adjust to the dynamically changing environment if alternative tasks need to be performed. Imaging driving or walking the same route to work every day, the constant practicing of the same task has become habitual that evokes similar actions therefore the behaviour becomes automatic. However, if the usual road to work has been closed due to constructions, the human brain needs to be able to adapt to the new situation, collect new data and re-direct the way to work in time.

Effective cognition requires an optimal balance between endogenous control (i.e. goal-directed deliberate intentions) that prevents disruption of an ongoing task, and the exogenous influences that modulate the flexibility to perform other task when appropriate, such effective cognition is referred to as task switching (Monsell, 2003). For highly practiced tasks such as daily routines, it has been proposed that the neocortex consolidates the associations between stimuli and actions, which are initially encoded in the basal ganglia (Ashby et al., 2007; Hadj-Bouziane et al., 2003). Therefore, the basal ganglia have more involvement when learning a new task and/or

during task switching compared to when performing a well-practiced task (Piton et al., 2016). The behavioural switching may occur after receiving error feedback (retroactive switching) or when the subject detects the change of context and responds to it (proactive switching) (Isoda & Hikosaka, 2010). It has been proposed that the two switching are controlled by different regions in the medial frontal cortex, anterior cingulate cortex (ACC) and the pre-supplementary motor area (pre-SMA) (Isoda & Hikosaka, 2010). While different brain regions may be separately involved in mediating retroactive and proactive switching, it has been proposed that the two type of behavioural switching are both related to motor suppression as the outcome of behavioural switching is the change of motor behaviour (Hikosada & Isoda, 2010). As previously discussed, the ACC has been proposed to modulate the conflict monitoring system that detect and integrate response conflict, and send signals to the basal ganglia to control the execution of actions (Botvinick et al., 1999). In particular, the STN receives direct projections from the pre-SMA and cingulate cortex that compose conflict monitoring systems, which allows the STN to implement cognitive control by sending NoGo signals via diffuse excitatory projections to basal ganglia output nuclei (Mink, 1996; Parent & Hazrati, 1995; Frank et al., 2007).

Theoretically, a dual processing of automatic and controlled processing cognitive may be used to explain cognitive control (Schneider & Schiffrin, 1977; Schiffrib & Schneider, 1977). Schneider & Chein (2003) have proposed a detailed computational model, which employs a large network of distributed data modules that can categorize, buffer, associate and prioritize information. Each module communicates with a central

control system, which is composed of five processors including a goal processor, an attention controller, an activity monitor, an episodic store and a gating & report relay. Furthermore, when the data modules are able to transmit the outputs without he mediation of the control system, the transition from controlled to automatic processing arises in the model. Figure 1.4 illustrates the hypothetical mapping of the five processors to brain regions, which shows that the executive Goal Processor is assumed to be located in dorsolateral prefrontal cortex (DLPFC). The Attention Controller maps to posterior parietal cortex (PPC) and the Activity Monitor to ACC. The Episodic Store maps to the medial temporal lobe (MTL), including the structures of the hippocampal complex. The Gating & Report Relay maps to the thalamus (THAL), with different thalamic nuclei connecting to alternative Control System processors, receiving report signals from the Data Matrix modules, and sending output gain signals to the modules.

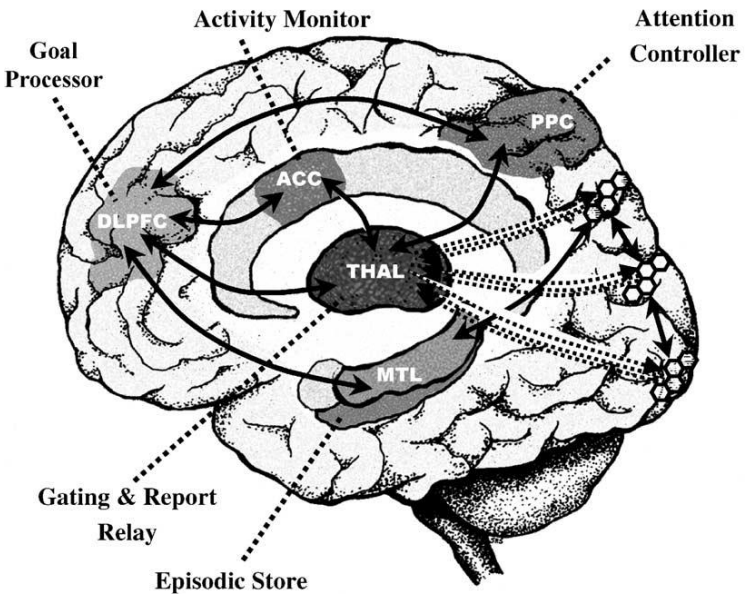

Figure 1.4 Hypothetical mapping of the five processors to brain regions. The arrows between regions illustrate known anatomical pathways. Shown on the right are

sample modules in the visual region of the Data Matrix, with report and control signals form each tier connecting to the thalamus. Figure from Schneider & Chein (2003).

Functional imaging studies have proved evidence on supporting the roles of prefrontal cortex (PFC) and ACC in modulating cognitive control (Koechlin et al., 2003; Chein & Schneider, 2005). In addition, MacDonald et al (2000) proposed that the two brain regions had dissociable roles in cognitive control: the DLPFC provides top-down control of the behaviour whereas the ACC evaluates the processes during conflicts, using event-related functional magnetic resonance imaging (fMRI) techniques. Moreover, Botvinick et al (2004) have further proposed the role of the ACC during conflict monitoring that triggers compensatory adjustments in cognitive control. As briefly mentioned in previous sections, frontal-basal ganglia circuits have been proposed to be involved in conflict resolution and controlling the execution of actions (Aron, Robbins & Poldrack, 2004; Frank, 2005; Aron & Poldrack, 2006; Aron, 2007; van den Wildenberg et al., 2006; Wylie et al., 2009), which suggests a potential role of the basal ganglia in cognitive control. Moreover, switching from automatic to controlled responses requires control monitoring and suppressing the automatic processing. Hikosaka & Isoda (2010) have proposed two modes of behavioural switching: retroactive switching and proactive switching (Figure 1.5). Suppose there exist context α and context β that are associated with procedure A and procedure B separately. The correct mapping between the context and the procedure would lead to reward. Retroactive switching refers to when context cue is absent or unknown, an

agent must learn from errors (i.e. failed to receive reward) to switch from procedure A to procedure B, whereas the proactive switching is triggered by a cue that is associated with the context change, so that the agent would switch procedures without experiencing errors. Note that Braver et al (2007) have proposed proactive control and reactive control of cognitive function, which refers to the continuing process before the onset of a crucial stimulus and the temporal process after the onset of the crucial stimulus. The proactive and reactive control of cognitive function (Braver et al., 2007) do not explain how behaviours may switch under different context, whereas the retroactive switching and proactive switching proposed by Hikosaka & Isoda (2010) specifically defined the switching process.

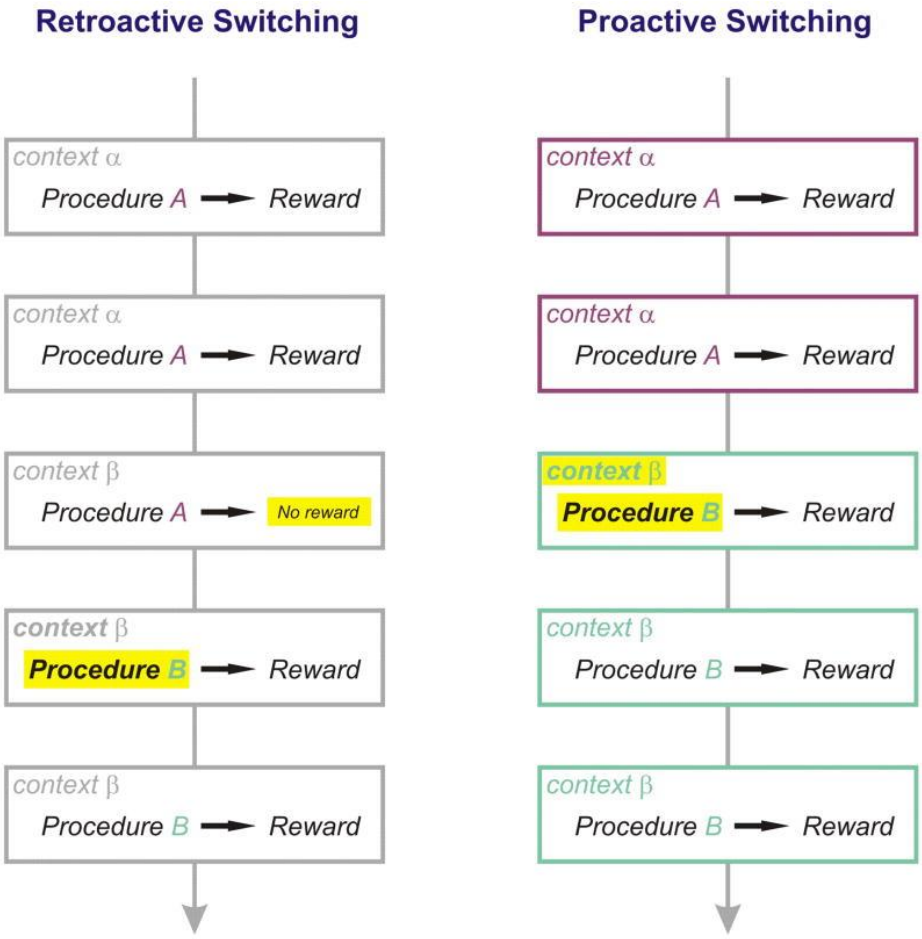

Figure 1.5 Retroactive switching (left) is triggered by a failure (decreased reward value or an error). In this case the context cue is either absent or unknown to the animal (indicated by gray rectangles). Proactive switching (right) is triggered by a cue signaling a context change so that the subject will not experience the failure. This is possible, however, only after the subject has learned the meaning of the cue (indicated by purple and green rectangles). Highlighted in yellow are triggers of behavioral switching and switched procedures. Figure from Isoda & Hikosaka (2010).

It has been proposed that the two switching are controlled by different regions in the medial frontal cortex, ACC and the pre-supplementary motor area (pre-SMA) (Isoda & Hikosaka, 2010). Retroactive switching consists of learning from negative feedbacks and implementing alternative actions therefore brain regions associated with these functions such as ACC are highly likely to be involved. In primate studies, evidence has shown that ACC neurons were activated when switching movements based on the reduced amount of reward (Shima & Tanji, 1998; Johnston et al., 2007), and that ACC neurons generated error-related potentials after making incorrect responses (Gemba et al., 1986; Wang et al., 2005; Emeric et al., 2008). Human as well as primate studies have suggested a prominent role of pre-SMA on motor suppression and conflict monitoring (Luders et al., 1995; Rushworth et al., 2002; Nachev et al., 2005, 2007; Isoda, 2005; Ullsperger & Cramon, 2001; Garavan et al., 2003). In addition, human studies such as fMRI and EEG studies have found activation of the ACC activity after error trials or error feedback, supporting the role of the ACC in retroactive switching (Garavan et al., 2003; Li et al., 2008; Menon et al., 2001;

Ullsperger et al., 2001; Modirrousta et al., 2008; Holroyd & Coles, 2002). Furthermore, it has been proposed that the retroactive switching function of the ACC may be mediated by its connection to the lateral prefrontal cortex (LPFC) or to the striatum, where the former connection is believed to be involved in the execution of procedure implementation (Pandya et al., 1981; Morecraft & Hoesen, 1993) and the later connection is associated with its role in action selection and associative learning (Haber et al., 2006; Hikosaka et al., 2000; Pasupathy & Miller, 2005).

On the other hand, the feature of proactive switching includes conflicts in information processing, which is closely related to the updating ability of basic EFs. There are four basic phenomena defined within the task-switching paradigm: switch cost (response are slower on a switch trail than on a non-switch trial), preparation effect (the average switch cost is reduced if practice is allowed prior the task), residual cost (switch cost would not completely be eliminated by preparation, instead it reaches a substantial asymptote) and mix cost (Monsell, 2003). Among these four phenomena, the occurrence of switch cost has been proposed to be due to the suppression of the old procedure and the facilitation of the new procedure (Isoada & Hikosaka, 2010). Human studies using fMRI techniques have found that the activation of the pre-SMA strongly associated with proactive switching (Tanji, 1994; Dove et al., 2000; Rushmore et al., 2002). Such an association between pre-SMA activity and proactive switching may be related to its role in motor suppression and action selection during conflict monitoring (Luders et al., 1995; Rushworth et al., 2002; Nachev et al., 2005, 2007; Isoda, 2005; Ullsperger & Cramon, 2001; Garavan et al., 2003). Figure 1.6

illustrates the neural mechanism of proactive switching in oculomotor behaviour.

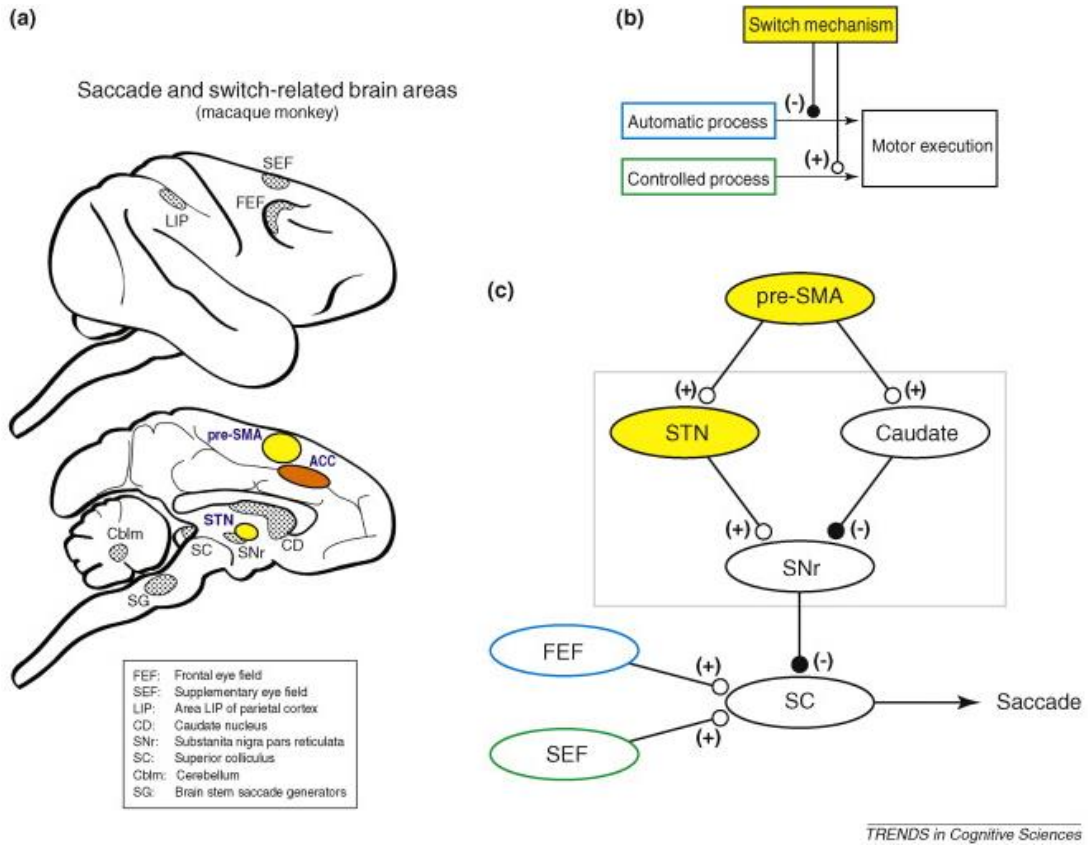

Figure 1.6 Neural mechanism of proactive switching in oculomotor behaviour. A neural mechanism of behavioral switching must be able to (1) detect a change in the context, (2) suppress the prepotent, automatic process, and (3) facilitate the alternative, controlled process (conceptual scheme). The suppression must occur quickly because the automatic process emits a motor signal quickly; the facilitation can occur thereafter because the controlled process is slow. Recent studies have suggested that the pre-SMA, together with other frontal cortical areas, acts as a switch mechanism and the basal ganglia may mediate the switch-related signal from the cortical areas. In our study using saccadic eye movement, many neurons in the pre-SMA became active selectively and proactively on switch trials (Box 2). It was also shown, using a

go-nogo task, that some pre-SMA neurons suppress the prepotent saccade, others facilitate the alternative saccade, and the rest have both functions. The suppressive pre-SMA neurons tended to be active earlier than the facilitatory pre-SMA neurons, consistent with the conceptual scheme. In the basal ganglia, the STN may serve to suppress the automatic saccade by enhancing the inhibitory output of the basal ganglia (SNr) on the SC or the thalamo-cortical network. The caudate nucleus might serve to facilitate the controlled saccade by disinhibiting the target of the basal ganglia. We speculate that the signals for the automatic and controlled saccades are carried mainly by the frontal eye field (FEF) and the supplementary eye field (SEF) respectively. In the possible neural network, excitatory and inhibitory connections are indicated by (+) and (−) respectively. Figure and caption from Isoda & Hikosaka (2010).

1-1-3 Speed/Accuracy Trade-off and moving dots paradigm

In order to make an accurate or appropriate decision/action, one has to inhibit the urge to act in order to gather more information to guide behaviour, however such an inhibition may lead to failure in making timely responses. Such a dilemma is known as speed and accuracy trade-off (SAT) (Schouten et al., 1967; Wickelgren et al., 1977; Chittka et al., 2009). In the present section I would briefly introduce SAT, moving dots paradigm, and more importantly, their relationships with executive functions and context monitoring.

Abstract mathematical models have been exclusively used to study SAT for almost

half a century (Bogacz, Wagenmakers, Forstmann, & Nieuwenhuis, 2010). Sequential sampling models attribute SAT effects to changes in the amount of evidence needed for a response, which in the model is represented by the changes in the value of the decision criteria (Ratcliff & Smith, 2004). In sequential sampling models, the gradual process of gathering sensory information in favour of one choice is defined as the drift of an abstract decision variable toward a decision threshold (Domenech & Dreher, 2010). Mathematical models can account for SAT in two ways: either by changing the baseline of the accumulator or by changing the threshold (Bogacz et al., 2010). In addition, most models assume that SAT is controlled by the distance between the initial starting point (i.e. the baseline activity) and the decision threshold. If this interval is large, decisions are accurate but slow; conversely, if the interval is small, decisions are fast but error-prone (Bogacz et al., 2010). In the sequential sampling framework, two factors would determine the performance in experimental task, firstly the quality of the information derived from processing the stimuli and secondly the quantity of information needed before a decision is made. The framework thus may account for the main relationship between accuracy and response time in two-choice decisions. Theoretically, whether to make a fast but prone to error response/decision or make an accurate but slow response/decision should be determined by (1) an internal and/or an external drive to be accurate or fast, and (2) the quality of information necessary for achieving the goals. The former may be reflected as the distance between decision threshold and the baseline in the mathematical models, whereas the latter may be represented by the rate of accumulation of information (Ratcliff & McKoon, 2008). The diffusion model

(Ratcliff, 1978) provides a framework for the study of SAT modulation based on behavioural data collected from binary decision-making tasks. The model separates the quality of evidence accumulated to reach decision threshold and other non-decision processes such as stimulus encoding and response execution (Ratcliff & McKoon, 2008). In this model, it is assumed that a decision is made through the noisy process that gathers information over time to reach decision boundaries or criteria. The decision-making process begins from the starting point, once it reaches one of the decision boundaries a decision is made and a response is initiated. Within the drift diffusion model framework, SAT leads to the decrease of the boundary separation results, which means that RTs decrease at the cost of making more errors. The rate of accumulating information is defined as the drift rate in the diffusion model, which is usually determined by the quality of the information provided by the stimuli. The top panel of Figure 1.7 illustrates the framework of the diffusion model.

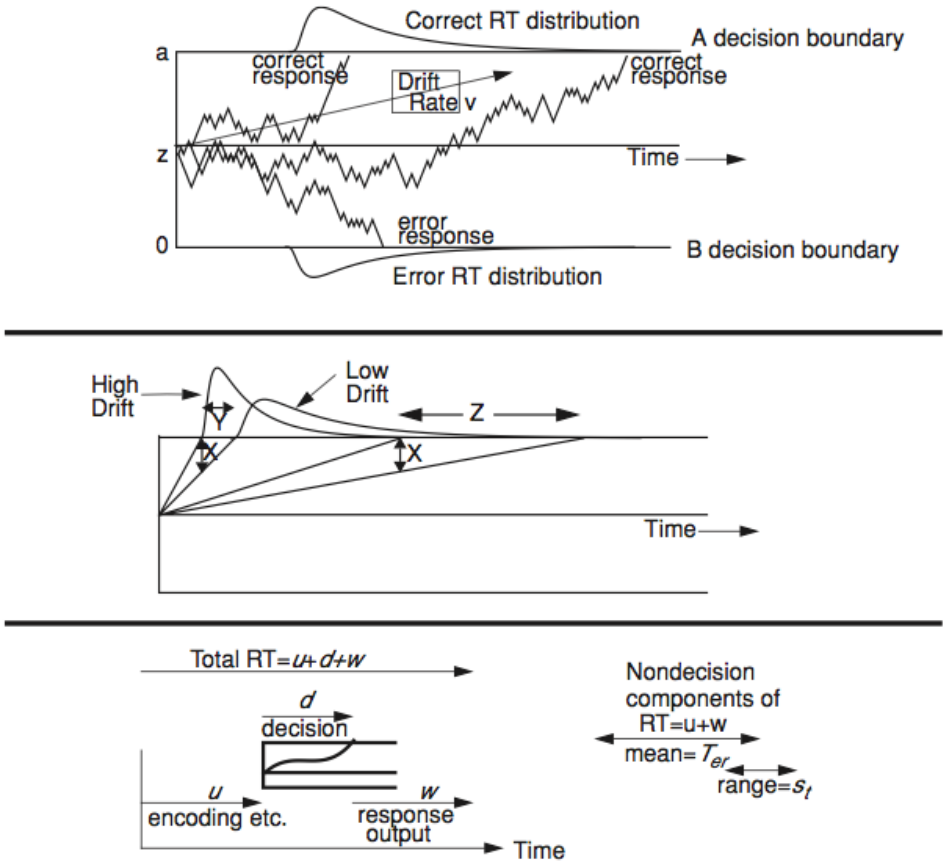

Figure 1.7 The drift diffusion model. Top Panel: Three simulated paths with drift rate (v), boundary separation (a) and starting point (z). Middle Panel: An equal size slowdown in drift rate (X) produces a small shift in the leading edge of the response time distribution (Y) and larger shift in the tail (Z) on fast and slow processes from each of two drift rates. Bottom Panel: Encoding time (u), Decision time (d) and response output time (w). The non-decision component equals the sum of (u) and (w) with mean (T_{er}) and with variability represented by a uniform distribution with range S_t. Figure and caption from Ratcliff & McKoon (2008).

With the advanced development of neural imaging techniques, the neural basis of SAT has attracted much attention in recent years. Despite different task design and analysis,

fMRI studies on SAT showed that when speed was emphasised to make responses, activity in the striatum was increased (Forstmann et al., 2008; Ivanoff et al., 2008; van Veen et al., 2008). Consistent with such results, a recent fMRI study also demonstrated that striatal activation is associated with an 'urgent signal' during perceptual decision making in human participants (van Maanen, Fontanesi, Hawkins, & Forstmann, 2016). Four theories have been proposed to account for the underlying neural mechanisms of such a trade-off: the cortical theory, the striatal theory, the STN theory and the synaptic theory, which stand for different circuits that modulate the balance between making a fast and making an accurate response (Bogacz et al., 2010). Three of the four theories (the cortical theory, the striatal theory, the synaptic theory) are based on the mechanism that the speed instructions increase the baseline of cortical integrators and cause changes in the corresponding circuits (Forstmann et al., 2008; Furman & Wang, 2008; Roxin & Ledberg, 2008; van Veen et al., 2008; Lo & Wang, 2006). Previous fMRI studies support the striatal theory and the cortical theory on suggesting that speed pressure is interpreted as an increased control signal that modulates cortical and striatal activity (Forstmann et al., 2008; Ivanoff et al., 2008; van Veen et al., 2008; Forstmann et al., 2016). In addition, the STN theory proposes that when accuracy is emphasised, frontal areas send additional; excitatory signals to the STN, leading to increased STN activity that results in slower and more accurate choices (Frank, Scheres, & Sherman, 2007; Utter & Basso, 2008). The STN theory is supported by the fMRI studies showing that when participants attempt to stop an initiated action, frontal areas that project to the STN and the STN activity would increase (Aron & Poldrack, 2006; Aron, Behrens, Smith, Frank, & Poldrack, 2007). It

can therefore be assumed that the SAT is controlled by a dual process that when speed is emphasised to make responses, frontal activation sends signals to the striatum and creates the urgent signal to promote timely action. Conversely, when accuracy is emphasised the frontal areas would send excitatory signals to the STN, increased STN activity would therefore support the inhibition of an intended action to allow more time for information accumulation. Such processes are associated with context monitoring as in the laboratory environment, whether to be fast or to be accurate is explicitly instructed by external cues, at the same time the noise of the stimuli can be manipulated.

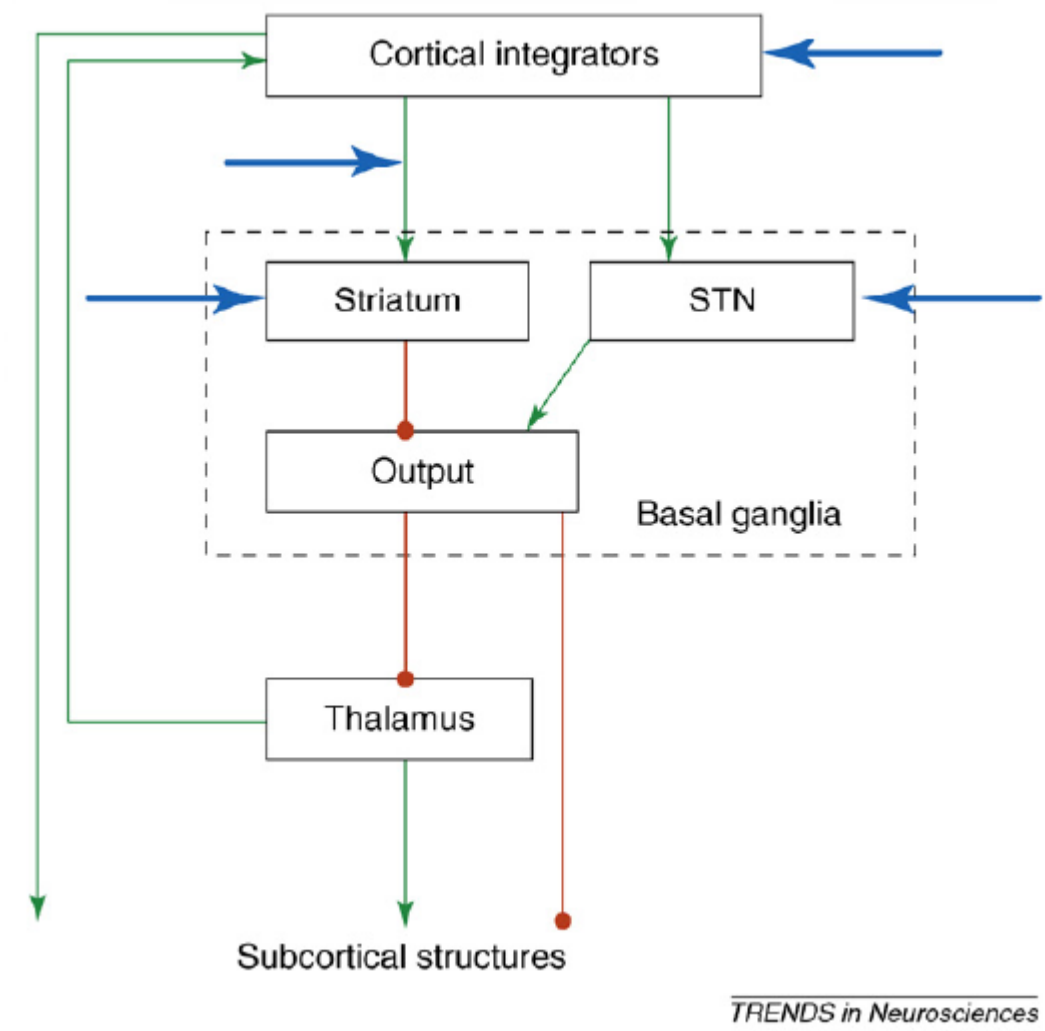

Figure 1.8 Schematic representation of the cortico–basal-ganglia–thalamic circuit. STN = subthalamic nucleus. Output = substantia nigra pars reticulata and the external segment of globus pallidus in primates. Thin arrows denote excitatory connections; lines with filled circles denote inhibitory connections. Blue arrows indicate the areas where the input controlling SAT could be provided. Figure and caption from Bogacz, Wagenmakers, Forstmann & Nieuwenhuis (2010)..

Moving dots paradigm is often used to investigate SAT both in animal and in human studies (Britten, Shadlen, Newsome, & Movshon, 1992; Gold & Shadlen, 2007). The task requires participants to decide whether a cloud of dots, which is visually

presented on a computer screen, is moving to the left or to the right. When Speed is emphasised while making a response, animals and humans may be able to act in a timely manner, but may sacrifice the accuracy of responses and vice versa. This characteristic of the moving dots paradigm permits the investigation on the cognitive flexibility to switch between acting fast and acting accurately. Moreover, the different coherence of moving dots provides a chance to manipulate different task difficulty, namely, the quality of sensory information. The paradigm therefore provides a suitable candidate to study the SAT and the underlying neural mechanism. In the present thesis, different moving dots tasks were selected to assess the abilities to (1) shift the internal drive or adapt to the external experimental instructions either to be fast or to be accurate, and (2) to sample and integrate environmental information to meet the intended goals. The former is related to the basic EF shifting whereas the latter is considered to be associated with the basic EF updating proposed by Miyake & Friedman (2012). Detail of the computerised tasks would be further introduced in Chapter 1 section 5.

1-2 The Basal Ganglia

1-2-1. Structure

Anatomically, the basal ganglia (Figure 1.9) are subcortical nuclei consisting of the striatum, the subthalamic nucleus, the substantia nigra pars compacta and pars reticulata (SNc, SNr), the globus pallidus (internal and external segments; GPi, GPe). The GPi and the SNr are the main output nuclei of the basal ganglia. The neostriatum is composed of the putamen and the caudate nucleus, with the former being the motor

part of this brain region. Figure 1.9 shows that the basal ganglia are the largest subcortical structures in the human forebrain. The basal ganglia receive inputs from the neocortex and project massively to thalamic nuclei, which in turn project to the frontal cortex.

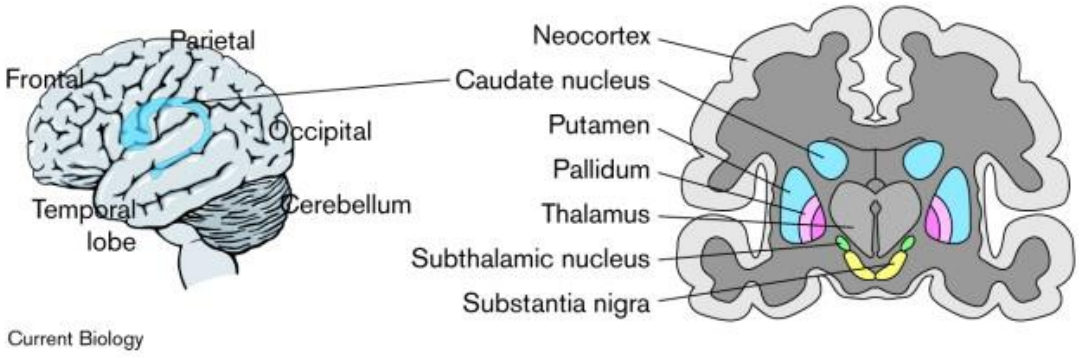

Figure 1.9 Basic anatomy of the brain that shows the major regions within the basal ganglia. The blue part indicates striatum, which is composed of putamen and caudate nucleus. The pink part represents pallidum, which made up of outer and inner segments. The green part represents the thalamus and the yellow part represents the substantia nigra. Figure and caption from Graybiel (2000).

Figure 1.10 shows the basal ganglia-thalamocortical circuits that are composed of the combination of 'open' and 'closed-loops' features. As part of the 'motor circuit' the putamen, the posterior part of the striatum, receives substantial and somatotopically organized projections from the motor and somatosensory cortices, the arcuate premotor area, and the supplementary motor area (Alexander, DeLong & Strick, 1986). The associative circuit between the dorsal caudate and the dorsolateral prefrontal cortex, the limbic circuit between the ventral striatum and the anterior cingulate cortex, the orbitofrontal circuit between the ventral striatum and the

orbitofrontal cortex and finally the oculomotor circuit between the body of the caudate and the frontal eye fields are the other four fronto-striatal circuits described by Alexander et al (1986).

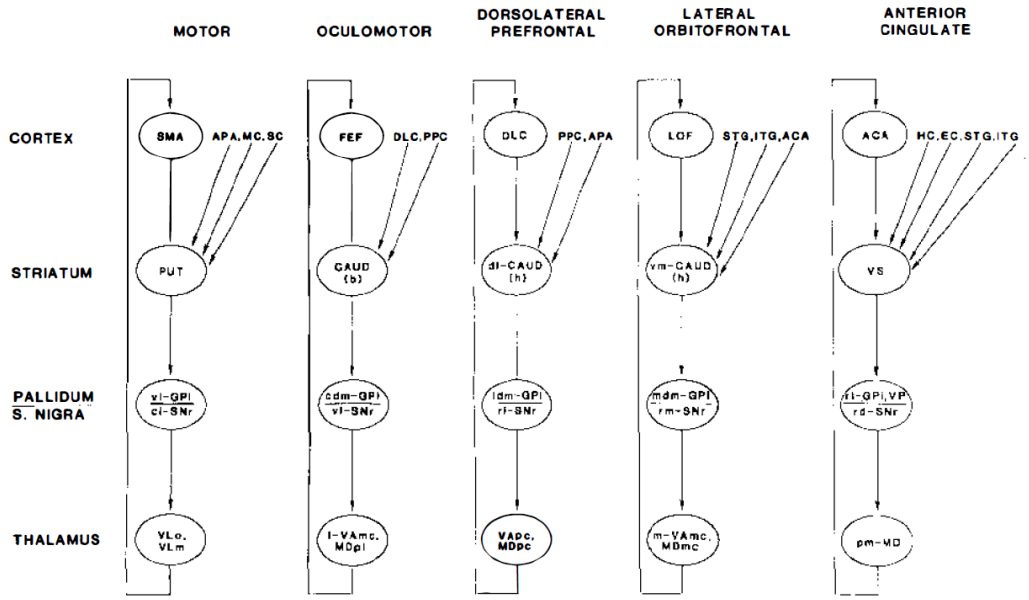

Figure 1.10 Parallel organization of the five basal ganglia-thalamocortical circuits. Each circuit engages specific regions of the cerebral cortex, striatum, pallidum, substantia nigra and thalamus. Abbreviations are as follows: ACA : anterior cingulate area; APA: arcuate premotor area; CAUD: caudate, (b) body (h) head; DLC: dorsolateral prefrontal cortex; EC: entorhinal cortex; FEF: frontal eye fields; GPi: internal segment of globus pallidus; HC: hippocampal cortex; ITG: inferior temporal gyrus; LOF: lateral orbitofrontal cortex; MC: motor cortex; MDpl : medialis dorsalis pars paralamellaris; MDmc: medialis dorsalis pars magnocell ularis ; MDpc: medialis dorsalis pars parvocellularis; PPC : posterior parietal cortex; PUT: putamen; SC : somatosensory cortex; SMA : supplementary motor area; SNr: substantia nigra pars reticulata; STG: superior temporal gyrus; V Amc: ventralis anterior pars

magnocellularis; Vapc: ventralis anterior pars parvocellularis; VLm: ventralis lateralis pars medialis; VLo: ventralis lateralis pars oralis; VP: ventral pallidum; VS : ventral striatum; c1-: caudolateral; cdm- : caudal dorsomedial; dl-: dorsolateral; 1-: lateral; Idm-: lateral dorsomedial; m-: medial; mdm-: medial dorsomedial; pm: posteromedial; rd-: rostrodorsal; r1-: rostrolateral; rm-: rostromedial; vm-: ventromedial. Figure and caption from Alexander, DeLong & Strick (1986)

1-2-2. The basal ganglia and executive functions: updating, shifting, and inhibition

The brain contains many motor pattern generators that each of them is responsible in generating a specific body movement (Kim & Hikosaka, 2015; Grillner et al., 1998). By receiving sensory inputs or internal states, these mechanisms are activated to produce corresponding actions. However, the overall behaviour can be uncontrollable if all mechanisms are triggered at the same time without management. To prevent such chaotic situation, the brain has developed a mechanism to supress all of the motor circuits. The basal ganglia have been identified to play the major role in such function. The final output neurons are all GABAergic and inhibitory in the basal ganglia, and are connected to the motor mechanisms (Takakusaki et al., 2004; Grillner et al., 2005). Dysfunction of the basal ganglia often leads to motor deficits including involuntary movement such as PD (DeLong, 1990). Extensive studies in human and in animal models (Marsden & Obeso, 1994; Aron & Poldrack, 2006; Hikosaka, 2002; Jin, Tecuapetla & Costa, 2014; Cui et al., 2013) have provided large evidence for the

involvement of the basal ganglia in action suppression and motor control.

Figure 1.11 shows the direct, indirect and hyperdirect pathways in the basal ganglia. Classical models of the basal ganglia function circuit suggest that the direct pathway serves as the 'Go' pathway as the GABAergic inhibitory connections from the striatum to the SNr/GPi that lead to a reduction of inhibition on action, whereas the SNr/GPi neurons receive indirect inputs from the striatum via the GPe and possibly the STN to inhibit motor action (indirect 'No Go' pathway) (DeLong, 1990; Albin, Young & Penney, 1989; Kravitz et al., 2010). However, recent studies on animals suggest that both direct and indirect pathways are active during the initiation, execution and termination of action sequences, which indicate that the basal ganglia circuits may have a more complex functional organization (Jin et al., 2014; Cui et al., 2013). The hyperdirect pathway (Nambu, Tokuno & Takada, 2002) consists of glutamatergic excitatory neurons that transmit signals quickly from the cerebral cortex to SNr/GPi via the STN, producing a net effect of motor inhibition. It has been proposed that the major role of the STN is behavioural switching (Aron & Poldrack, 2006; Isoada & Hikosaka, 2008; Hikosaka & Isoda, 2010), which suggests that the STN activity is associated with supressing automatic and fast actions to initiate controlled and slow actions. Moreover, inactivation of the STN ameliorates some of the motor deficits observed in PD patients (Limousin et al., 1995, 1998).

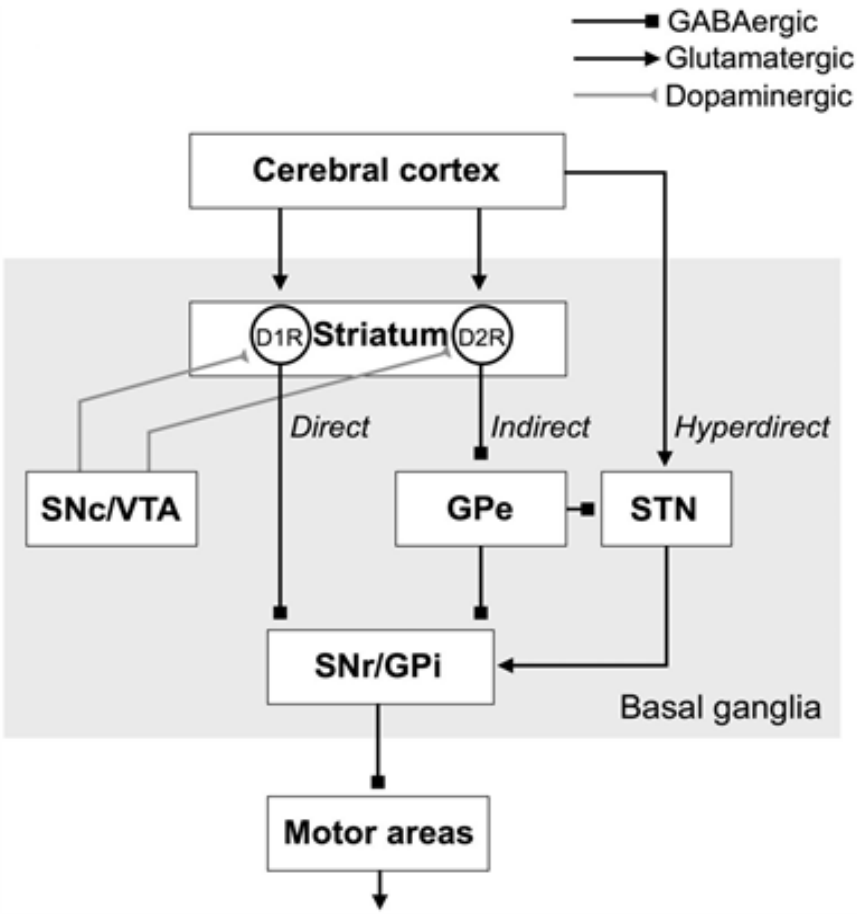

Figure 1.11 Direct, indirect and hyperdirect pathways. The striatum receives inputs mainly from the cerebral cortex. D1R-expressing neurons in the striatum connect to SNr/GPi directly (direct pathway). D2R-expressing neurons connect to SNr/GPi indirectly through GPe and STN (indirect pathway). STN receives inputs directly from the cerebral cortex and send outputs to SNr/GPi (hyperdirect pathway). Dopaminergic neurons in SNc/VTA heavily innervate the striatum. D1R = dopamine receptor D1; D2R = dopamine receptor D2. Figure and caption from Kim & Hikosaka (2015).

Together with the striatum, the STN is the principle input nucleus of the basal ganglia. It receives afferents from the cerebral cortex, the thalamus and the limbic system

(Gurney, Prescott & Redgrave, 2001). It has been proposed that the STN has a role in processing the conflict between evidence for different decision/action options (Frank, 2006; Bogacz, 2007; Gurney, Humphries, Wood, Prescott & Redgrave, 2004; Herz et al., 2014). Studies have been proposed to support the role of the STN in inter-related processes including: switching from automatic to controlled processing (Isoda & Hikosaka, 2008), slowing down when encountering surprising events (Wessel et al., 2016; Wessel & Aron, 2017), inhibitory and executive control (Frank, 2006; Frank et al., 2007) and adjusting response thresholds during speed and accuracy trade-offs (Bogacz et al., 2010). By recording the local field potentials of STN activity in PD patients, Herz, Zavala, Bogacz & Brown (2016) showed that STN low-frequency oscillations modulates decision threshold, and that the relationship between the STN activity and decision threshold modulation is context dependent. Furthermore, it has been shown that the cortico-basal ganglia networks modulate the speed and accuracy trade-offs during decision-making (Herz et al., 2017). On the other hand, Isoda & Hikosaka (2008) reported more phasic change in the neural activity of the STN during the inhibition of automatic inappropriate actions compared to the facilitation of controlled actions, indicating a role of the STN in behavioural switching. The findings of neural activity recordings are in consistent with the functional imaging study of Aron & Poldrack (2006), which has shown a role of the STN in the stop-signal paradigm (details in Figure 1.12). The studies thus suggest that STN plays a crucial role in all three basic executive functions.

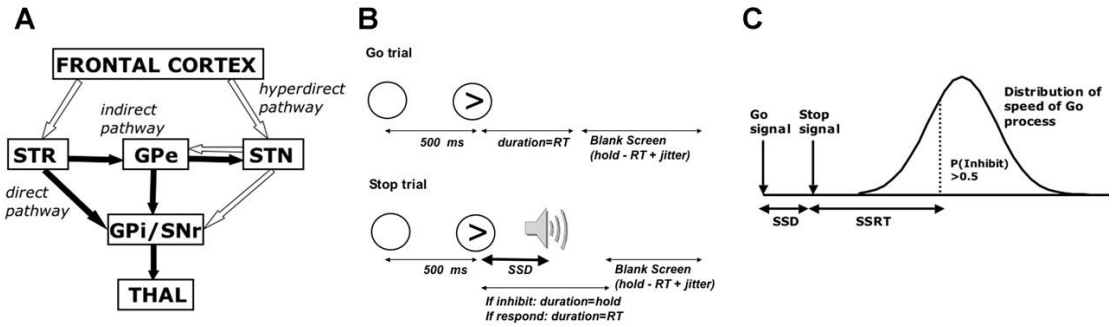

Figure 1.12 A basal-ganglia model and the Stop-signal paradigm. A. An influential model proposes three pathways through the basal ganglia (direct, indirect, and hyperdirect). SNr, Substantia nigra; THAL, thalamus; STR, striatum. Open arrows are excitatory (glutamatergic); filled arrows are inhibitory (GABAergic). Figure adapted from Nambu et al. (2002). B. The Stop-signal paradigm consists of Go- and Stop-signal trials. On Go trials, the subject has 1 s (the hold period) to make a left or right button press in response to the stimulus. As soon as the subject responds (reaction time), the stimulus is replaced by a blank screen for a variable period of time (1 s − RT = jitter time, where jitter ranges between 0.5 and 4 s, mean of 1 s). On a Stop trial, a tone is played at some delay (SSD) after the arrow stimulus. If the response is inhibited, the arrow remains for 1 s, followed by the blank screen jitter period; if the subject does not inhibit (i.e., responds), then the timing is the same as the Go trial. SSD changes dynamically throughout the experiment to produce a 50% inhibition rate. C. Stop-signal reaction time (SSRT) is estimated using the race model (Logan & Cowan, 1984). This assumes that Go and Stop processes are in a race and are independent of each other. The independence assumption implies that the distribution of Go processes on Stop trials (whether a response is made or not) is the same as the observed distribution of Go responses (when there is no Stop signal). On

Stop trials, a tone occurs at some delay, the SSD after the Stop signal. If this delay is short, then P (inhibit) is high and this is likely to be a Stop-Inhibit trial; if the delay is long, then P (inhibit) is low and this is likely to be a Stop-Respond trial. If SSD is varied so that P (inhibit)=0.5, then SSRT can be estimated by subtracting the SSD from the median value of the Go distribution. Figure and caption from Aron & Poldrack (2006).

1-2-3. The basal ganglia circuits for conflict monitoring and action selection

To make an appropriate response in the visual environment requires the accumulation of external information and the internal information about current behavioural needs. An agent is required to activate the collection of signals and inhibit the influence of noise in the environment and concurrently in the meantime balance the speed and accuracy of responding before producing a response. The characteristics of such ability involve context monitoring, inhibitory control and action selection.

Botvinick, Braver, Barch, Carter & Cohen (2001) have proposed that there exists a conflict monitoring system, potentially involving the anterior cingulate cortex (ACC) of the human frontal lobe, which monitors for the occurrence of conflict in information processing. In other words, this conflict monitoring system evaluates current levels of conflict and passes the information to control centres, which eventually trigger the centres to adjust the strength of their influence on processing (Botvinick et al., 2001). Frontal-basal ganglia circuits have been proposed to be involved in conflict resolution and controlling the execution of actions (Aron, Robbins & Poldrack, 2004; Frank, 2005; Aron & Poldrack, 2006; Aron, 2007; van den Wildenberg et al., 2006; Wylie et al., 2009). According to the response selection hypothesis, the cortex sends excitatory signals that represent response commands elicited by cognitive computations carried out at the cortical level to the basal ganglia, which suggests that the basal ganglia are involved in response selection (Brown & Marsden, 1998; Robbins & Brown, 1990; Wylie, Stout & Bashore, 2005; Mink, 1996; Redgrave et al, 1999). Traditional theories of motor control regard it as the output end

of a serial process that includes perceptual, cognitive and executive processes (Cisek, 2005). It has been proposed that planning and execution are distinct processes separated by neural representation of a 'desired trajectory' (Abend, Bizzi & Morasso, 1982). However, Cisek (2005) has argued that, based on the neural data obtained from studies of the activity of the primary motor cortex (Scott & Kalaska, 1997; Sergio & Kalaska, 2003) and muscle activity (Karst & Hasan, 1991; Gordon, Ghilardi, Cooper & Ghez, 1993), behaviour may instead be viewed as parallel processes that specify the potential actions currently made possible by the environment and processes that select one of those actions for execution. Furthermore, Cisek (2007) has proposed an 'affordance competition hypothesis', which suggested that sensory information received from the environment is continuously processed, while other kinds of information are also collected in order to select a single action from several potential actions. The term 'affordance' defined by Gibson (2014) regards the behaviour as a competition between internal representations of the potential actions. In other words, the process of action selection and the specification of an action occur simultaneously and continue even during the performance of movements (Cisek, 2007). Note that only currently available actions are specified in this manner and selective attentional mechanisms can eliminate many alternative actions during the process of transforming sensory information into representations of action. The concept is consistent with one of the key roles of precision of the active inference model proposed by Friston et al (2013) as precision modulates the biased competition among future control states. Action selection is modulated by the biasing inputs from various areas that support potential actions in a competition.

The basal ganglia through the direct and indirect pathways have been suggested to selectively execute one action command while suppressing the other alternatives (Mink, 1996; Redgrave, Prescott & Gurney, 1999; Frank, Samanta, Moustafa & Sherman, 2007; Cisek, 2007). In addition, the basal ganglia exhibit activity that is related to movement parameters (Alexander & Crutcher, 1990) and decision variables such as reward (Schultz, 1998) and expectations (Lauwereyns, Watanabe, Coe & Hikosaka, 2002). Theoretically it has been proposed that the connectivity between the basal ganglia potentially bias the competition between potential actions represented in the fronto-parietal system (Cisek, 2007). Building on previous work, the latest model proposed by Thura & Cisek (2017) suggested that instead of contributing to the choice between potential movements, the basal ganglia actually provide a time-dependent signal that controls the urgency to commit to a choice, which could lead to the adjustment of the speed and accuracy trade-off when making decisions (Thura, Cos, Trung & Cisek, 2014; Thura & Cisek, 2016). In this 'urgency-gating model', the cortical regions are hypothesised to the selection of optimal action choices whereas the basal ganglia are hypothesised to control the speed-accuracy trade-off between committing to a choice versus continuing the selection (Thura & Cisek, 2017). An animal study showed that the STN activity is triggered in association with presentation of a stop cue during action cancellation; in particular, the STN transmits the stop cue information to SNr before the increased striatal input creates action suppression (Schmidt, Leventhal, Mallet, Chen & Berke, 2013). The results of this study supported the idea of a race between a go and a stop process, with the outcome

of this race determining the success or failure of motor inhibition on each trial. Furthermore, another major function of the hyperdirect pathway seems to be behavioural switching as it suppresses quick and automatic movements to switch to more controlled processing (Aron & Poldrack, 2006; Isoda & Hikasoka, 2008). Despite the urgency gating model proposing that the basal ganglia do not contribute to which actions to select but the urgency of committing to the responses intended by the cortical areas, studies in PD patients treated with STN DBS have shown that the STN plays a role in integrating sensory information during decision-making (Frank et al., 2007; Frank, 2011; Green et al., 2013). In summary, while the involvement of the basal ganglia in the processes of information accumulation remains debatable, the above evidence suggests that the basal ganglia play an important role in action selection and inhibitory control.

1-3. Parkinson's disease (PD)

The pathological hallmark of PD is the degeneration of dopamine neurons in the substantia pars compacta of the basal ganglia; which results in dopamine depletion in the nigro-striatal pathway. PD therefore provides an ideal human model to investigate the effect of basal ganglia dysfunction and dopamine depletion on motor and cognitive function. In this section I will briefly review the motor and non-motor symptoms in PD from early stage to advanced PD, and the neural mechanisms underlying these motor and cognitive deficits.

Table 1.2 lists the most frequent clinical features associated with PD. The loss of the nigrostriatal dopaminergic neurons and the presence of intraneuronal proteinacious cytoplasmic inclusions termed “Lewy Bodies” (LBs) are the main pathological hallmarks of PD (Dauer & Przedborski, 2003). The dopamine neurons in the substantia nigra compacta that degenerate, primarily project to the putamen. It is generally agreed that dopaminergic cell death of the neostriatum results in the motor abnormalities of hypokinesia/bradykinesia, rigidity and tremor that are observed as the primary symptoms of PD patients (Olanow, Stern & Sethi, 2009; Crossman, 1990). Dopamine deficiency in the basal ganglia causes excessive thalamic inhibition that suppresses the cortical motor system, which potentially results in akinesia (DeLong, 1990), rigidity and tremor, whereas the abnormalities of gait and posture may be attributed to inhibitory descending projections (Lang & Lozano, 1998). In addition to the core motor symptoms, PD is associated with a host of other motor and non-motor symptoms (Jankovic, 2008). Table 1.2 lists the motor and non-motor symptoms in PD.

Table 1.2 Parkinson’s disease symptoms

Motor symptoms	Non-motor symptoms
Tremor, bradykinesia, rigidity, postural instability	Cognitive impairment, bradyphrenia, tip-of-the-tongue (word finding) phenomenon
Hypomimia, dysarthria, dysphagia, sialorrhoea	Depression, apathy, anhedonia, fatigue, other behavioural and psychiatric problems
Decreased arm swing, shuffling gait, festination difficulty arising from chair, turning in bed	Sensory symptoms: anosmia, ageusia, pain (shoulder, back), paresthesias
Micrographia, cutting food, feeding, hygiene, slow activities of daily living	Dysautonomia (orthostatic hypotension, constipation, urinary and sexual dysfunction, abnormal sweating, seborrhoea), weight loss
Glabellar reflex, blepharospasm, dystonia, striatal deformity, scoliosis, camptocormia	Sleep disorders (REM behaviour disorder, vivid dreams, daytime drowsiness, sleep fragmentation, restless legs syndrome)

Table from Jankovic (2008).

While motor symptoms have been the major focus in treating PD, cognitive dysfunction has gained much attention in recent years. Studies have shown the occurrence of cognitive deficits in patients with PD including attention and executive dysfunction from the early stages of the illness (Dubois & Pillon, 1996; Brown & Marsden, 1998; Dirnberger & Jahanshahi, 2013) and dementia in the later stages (Gratwicke, Jahanshahi & Foltynie, 2015). In addition, dopaminergic medication, particularly dopaminergic agonists used to ameliorate the motor symptoms of PD may potentially introduce side effects such as impulsivity in PD patients presenting as impulse control disorders (ICDs), it has been suggested that up to 25% of patients treated with dopaminergic agonists may experience an ICD (Weintraub, David, Evans, Grant & Stacy, 2015). Non-motor symptoms such as depression, anxiety, apathy, hallucinations and fatigue are also common features in PD (Aarsland, Brønnick, Larsen, Tysnes & Alves, 2009).

1-3-1. Non-motor symptoms in PD: impaired executive functions, mild cognitive impairment, deficits in decision-making

The neuropsychological deficits in PD range from mild executive dysfunction in the early stages to mild cognitive impairment and dementia in later stage (Litvan et al., 2012; Dirnberger & Jahanshahi, 2013). As previously discussed, EFs can be defined broadly and variously, generally they refer to complex cognitive processes such as goal formulation, planning and action execution that are required to reach a certain goal (Kudlicka, Clare & Hindle, 2011). Table 1.3 presents a list of standardized tests commonly used for the neuropsychological assessment of executive deficits in PD (Dirnberger & Jahanshahi, 2013).

Table 1.3 List of standardized tests commonly used for the neuropsychological assessment of executive deficits in PD

Test	Creators	Procedure	Processes involved
Wisconsin Card Sorting Test (WCST)	Nelson, 1976	To learn and classify different cards to the same categories	Cognitive flexibility Inhibition
Stroop interference task	Stroop, 1935	To name the incongruent ink colour of the printed colour words as fast as and as accurate as possible	Inhibition Cognitive flexibility
Trail Making	Reitan, 1958	To trace a number sequence (e.g. 1-2-3...) or a number-letter sequence (e.g.	Inhibition Cognitive flexibility

Test		1-A-2-B...) with a pen or pencil on the test sheet	
Word fluency	Benton, 1968	To produce as many words as possible that begins with a particular letter (phonemic) or belonging to a particular category (semantic) in 60 seconds	Inhibition Cognitive flexibility Context Monitoring
Digit Span Backwards	Wechsler, 1984	To repeat sequences of numbers of increasing length (2-9 items) in the reverse order of presentation by the examiner	Working memory
Tower of London test	Owen et al., 1992	To move coloured balls across different-sized pegs to match a target configuration in as minimal moves as possible. Only one ball is allowed to move at a time	Planning Inhibition
Hayling Sentences Completion Task	Burgess & Shallice 1997	To complete incomplete sentences in (1) with highly associated missing words to make sentence meaningful and (2) with words completely unconnected with the meaning of the sentence	Inhibition
Random Generation of Numbers	Spatt & Goldenberg , 1993	To generate a random sequence of number	Context monitoring Inhibition

Kudlicka et al (2011) conducted a meta-analysis and systemic review of the pattern of

executive impairment in early-stage PD, the results showed consistent evidence for cognitive difficulties across five executive function tests including verbal fluency, digit span backward, Wisconsin Card Sorting Test (WCST), Stroop test and Trail Making Test (TMT). These tests assess a broad range of executive functions including cognitive flexibility (verbal fluency), set switching (TMT, WCST), selection attention/working memory (digit span backward), and concept formation (WCST) (Kudlicka et al., 2011). The results of the meta-analysis provide consistent evidence for cognitive deficits in PD patients. Frank (2005) has proposed that cognitive deficits in PD patients can be categorised into two classes: one that requires the attentional process or working memory (Partiot et al., 1996; Gotham et al., 1988; Dubois et al., 1994; Woodward, Bub & Hunter, 2002; Henik, Singh, Beckley & Rafal, 1993; Rogers et al., 1998), which is believed to be associated with frontal cortex connection; whereas the other one involves implicit learning and probabilistic classification (Jackson, Jackson, Harrison, Henderson & Kennard, 1995; Ashby, Noble, Filoteo, Waldron & Ell, 2003; Maddox, Ashby & Bohil, 2003). Evidence has suggested that patients with PD showed inability to plan motor tasks and mental inflexibility (Taylor, Saint-Cyr & Lang, 1986; Brown & Marsden, 1998; Berardelli, Accornero, Argenta, Meco & Manfredi, 1986). Such impairment in executive functions may be viewed as deficits in behaviours that are based on updating information continuously, which is potentially caused by dopamine degeneration (Nieoullon, 2002).

In addition to executive dysfunctions, mild cognitive impairment is also a common feature in PD and is associated with higher risk to develop dementia (Litvan et al.,

2011, 2012; Janvin, Larsen, Aarslan & Hugdahl, 2006). Different criteria in defining mild cognitive impairment have been proposed, for example, Petersens (2004) suggested the criteria for amnestic mild cognitive impairment include (1) memory complaint usually corroborated by an informant; (2) objective memory impairment for age; (3) essentially preserved general cognitive function; (4) largely intact functional activities and (5) not demented. Moreover, Aarsland et al (2009) investigated mild cognitive impairment in non-demented, drug-naïve patients with PD. The results showed that patients are significantly impaired on all neuropsychological tests compared to healthy controls, the largest effect sizes were found for verbal memory and psychomotor speed. A total of 18.9% of the patients with PD were classified as having mild cognitive impairment, among these patients two-thirds of them had a non-amnestic subtype and one-third had an amnestic subtype (Aarsland et al., 2009). By using fMRI techniques, Beyer, Janvin, Larsen & Aarsland (2007) showed that PD patients with mild cognitive impairment had reduced grey matter in the left frontal and both temporal lobes. The Movement Disorder Society commissioned a task forced to mark the edge of diagnostic criteria for mild cognitive impairment in PD, of which the results show a significant heterogeneity within PD mild cognitive impairment in the number and types of cognitive domain impairments (Litvan et al., 2011)

Moreover, a number of studies have demonstrated that PD patients show deficits in decision-making when performing gambling tasks compared to age-matched healthy controls. One of the commonly used gambling tasks on investigating decision-making

and strategies is the Game of Dice Task. GDT is a gambling task based on the concept of Iowa Gambling Task (IGT) of Bechara, Damasio, Damasio & Anderson (1994). GDT requires participants to predict which number will be face upwards after rolling a dice, whereas IGT asks the participants to choose from four decks of cards to gain the maximum gain. Participants will be provided with a starting capital and the goals for both tasks are to increase the capital and avoid losing. The difference between the GDT and the IGT is that in the GDT, rules and the amounts of gains and losses are explicitly presented on the computer screen; participants will also be informed of the actual number of the bets they have to make. Whereas for the IGT, participants have to implicitly learn from the outcome of each selection to develop the best strategy as to choose the decks of cards with small reward but even smaller losses, rather than the decks of cards with large rewards but even larger losses. The core difference between the GDT and the IGT can therefore categorise the GDT as decision-making under 'risk', and the IGT as decision-making under 'ambiguity'. Euteneuer et al (2009) investigated the performance of PD patients on both the IGT and the GDT, the results showed that PD patients were impaired in the GDT but not the IGT, which is consistent with some previous studies that found no significant difference between PD patients and healthy controls on the performance of the IGT (Mimura, Oeda & Kawamura, 2006; Stout, Rodawalt & Siemers, 2001; Czernecki et al., 2002), but is inconsistent with other studies that showed impairments of PD patients on the IGT (Pagonabarraga et al., 2007; Kobayakawa, Koyama, Mimura & Kawamura, 2008; Perretta, Pari & Beninger, 2005; Thiel et al., 2003). The altered decision-making was not associated with age of onset, duration of PD and motor severity (Czernecki et al.,

2002; Perretta et al., 2005; Mimura et al., 2006; Pagonabarraga et al., 2007).

The tendency to risky choices observed in PD patients on the IGT has been proposed to be related to the dysfunction of the amygdala, which is known to be involved in risk evaluation (Kobayakawa et al., 2008). It has been suggested that impaired executive functions are associated with poorer GDT performance, which is modulated by the dorsolateral prefrontal loop (Brand et al., 2006; Euteneuer et al., 2009). On the other hand, the limbic loop has been shown to play a major role in the IGT performance (Bechara et al., 1994; Thiel et al., 2003; Lawrence, Jollant, O'daly, Zelaya & Phillips, 2008). The contradictory findings suggest that depending on the stage of illness of the patients in the various samples, the limbic loop might not be principally affected in PD patients to a degree that is sufficient to affect the IGT performance substantially (Euteneuer et al., 2009). Labudda et al (2010) investigated the performance of the GDT on PD patients with fMRI techniques. While behaviourally the patients showed impairments in making profitable decisions, on the fMRI version of the task that did not include a feedback component, PD patients showed no difference compared to healthy controls. PD patients and healthy controls had similar behavioural patterns in the fMRI task but patients exhibited reduced parietal activation, which potentially indicate different strategy application when using explicit information for the decision process (Labudda et al., 2010). In general, most studies showed that PD patients have impairment in selecting profitable choices; such impairment is linked to executive functions and feedback processing, which is potentially due to dorsolateral prefrontal loop dysfunction and/or dopaminergic

medication. Taken together, clinical studies have found that in addition to motor symptoms, non-motor symptoms including executive dysfunctions, mild cognitive impairments, and impaired decision-making.

1-3-2. Neural network model of dopamine in Parkinsonism

Following the loss of dopamine neurons and cognitive dysfunctions in Parkinsonism, Frank (2005) has proposed a neural network model (Figure 1.13) about the dynamic dopamine modulation of basal ganglia to account for the cognitive deficits, which involves deficits in attentional processes, working memory and implicit learning, in PD patients. The model suggests that reduced dynamic range of the dopamine signal affects the modulation of Go/NoGo representations in the direct and indirect pathways of the basal ganglia that facilitate or suppress a response. Furthermore, phasic dopamine release during error feedback is critical for the implicit learning of stimulus-reward-response contingencies as in probabilistic classification and reversal tasks, which provides a mechanistic description of how dopaminergic medication may lead to reversal impairments that is generally consistent with the 'overdose hypothesis' (Frank, 2005; Gotham et al., 1988; Cools et al., 2001; Swainson et al, 2000). The loss of dopamine neurons in the dorsal striatum in PD thus leads to cognitive deficits in reinforcement learning and potentially information updating, which are also associated with context monitoring.

The neural mechanisms of dopamine release can be viewed as the expression of two

dopamine subgroups of receptors: D1 and D2. The D1 receptor is predominately expressed in the direct 'Go' pathway that promotes the repeat of an action and favoured outcomes, whereas the D2 group is mainly expressed in the indirect 'No Go' pathway, which supresses an action to avoid negative outcomes (Keefe & Gerfen, 1995; Gerfen, 2000; Frank, 2005). The increase of dopamine levels thus activates the D1 group and the direct 'GO' pathway, meanwhile inhibiting NoGo activity via D2 receptors, leading to repeated actions. The balance of activity between the direct and indirect pathways is altered and the resulting disruption in GPi/SNr output may lead to abnormalities in movements featured in basal ganglia disorders (DeLong, 1990; Albin et al., 1989). Dysfunction of such a system thus may account for the motor deficits in patients with PD. Without enough dopamine release, the brain is constantly in the state of NoGo due to the overly active indirect pathway that inhibits motor execution (Frank, 2005). Dopaminergic medication ameliorates the motor symptoms by elevating dopamine levels in the depleted areas, activating the D1 receptors and Go activity. However, it has been suggested that dopaminergic medications may impair the ability to learn from negative outcomes in PD patients, leading to impulsive behaviours (Frank, Seeberger & O'reilly, 2004; Cools, Altamirano & D'Esposito, 2006). Figure 1.13B shows the dopamine modulation effect on the Go and NoGo pathways.

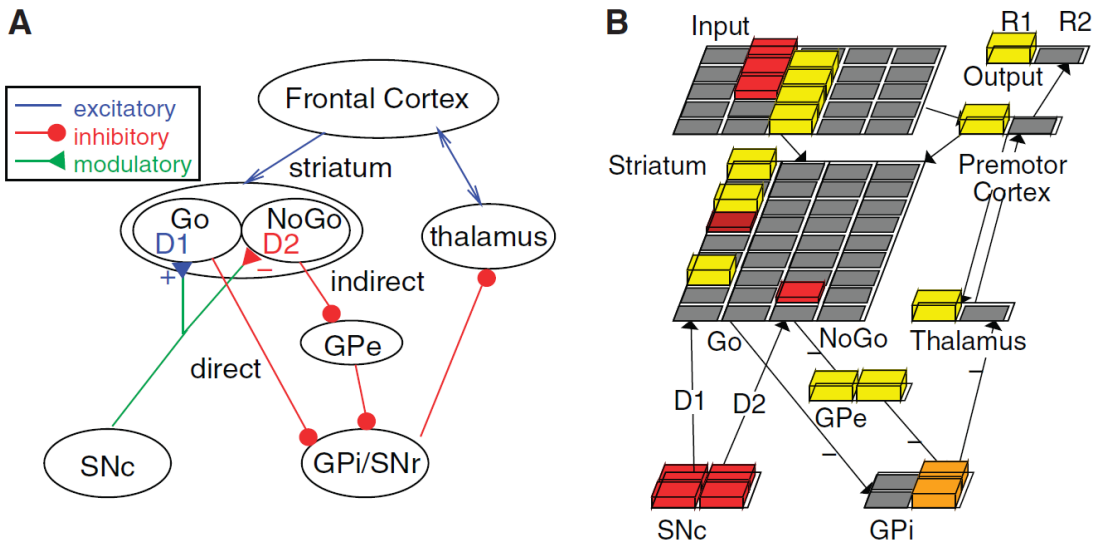

Figure 1.13 (A) The cortico-striato-thalamo-cortical loops, including the direct (Go) and indirect (NoGo) pathways of the basal ganglia. The Go cells disinhibit the thalamus via the internal segment of the globus pallidus (GPi) and thereby facilitate the execution of an action. The NoGo cells conversely increase the inhibition of the thalamus that supresses actions. Dopamine from the substantia nigra pars compacta (SNc) projects to the dorsal striatum, exciting Go cells via D1 receptors and inhibiting NoGo cells via D2 receptors. GPe: external segment of globus pallidus; SNr: substantia nigra pars reticulate. (B) The Frank neural network of the basal ganglia circuit (squares represent units, with height and colour reflecting neural activity; yellow means most active, red means less active and grey means not active). The premotor cortex selects an output response via direct projections from the thalamus. Go units are in the left half of the striatum layer whereas the NoGo units are in the right half, with separate columns for the two responses [Response 1(R1, left button), Response 2 (R2, right button)]. In this example, the Go pathway is stronger than the NoGo for R1, which inhibits the GPi and disinhibits the thalamus that facilitates the execution of an action in the cortex. A tonic level of dopamine is shown in the SNc.

Figure from Frank et al (2007).

The circuitry that implements such a selection function involves the striatum, which receives inputs from multiple cortical areas and projects outputs to the GPi and SNr to the thalamus, eventually projecting back to the cortical areas (Frank, 2005). In addition, the anterior cingulate cortex (ACC) projections to the ventro-medial striatum mediate different aspects of reward-based behaviours, whereas the dorsal premotor cortex projections to the dorsal striatum/putamen and the lateral caudate nucleus are suggested to play an important role in monitoring and planning action (Hadland, Rushworth, Gaffan & Passingham, 2003; Roesch & Olson, 2004; Haber & Calzavara, 2009). Therefore, the degenerated nigrostriatal pathway in patients with PD may not only cause motor symptoms but also account for the non-motor symptoms. The amount of medication necessary to increase the dopamine-depleted areas in PD such as the dorsal striatum might overdose the relatively intact ventral striatum in early PD (Frank, 2005). Dopamine has long been identified to be a core neurotransmitter in reinforcement learning processes (Schultz, Apicella & Ljungberg, 1993). In addition, the basal ganglia have been proposed to be involved in reinforcement learning (Frank et al., 2004; Bayer & Glimcher. 2005). Based on reinforcement learning theory, Frank et al (2004) investigated the role of dopamine in leaning from positive and negative outcomes by testing PD patients on and off medication on two cognitive procedural learning tasks. The results showed that when off medication, patients were better at learning from negative outcomes, conversely, when on medication, patients learned better from positive outcomes (Frank et al., 2004). The observation was consistent

with the model of the direct and indirect pathways that separate 'GO' and 'NoGo' responses modulated by differential signals of positive and negative outcomes, which suggest that dopamine burst increase activity in the 'Go' pathway in the basal ganglia circuit and therefore reinforce choices from good outcomes. Conversely, dopamine dips lead to the activation of the 'NoGo' pathway that facilitates the avoidance of negative outcomes (Hikosaka, 1989; Frank et al, 2004). Frank (2005) has also suggested that the basal ganglia and specifically the STN can act as a temporary brake to raise response thresholds to prevent premature responses and allow time for information accumulation to enable selection of that is able to execute the most appropriate motor command during the competition between motor actions represented in the motor or the premotor cortex. In particular, the STN receives direct projections from the pre-SMA and cingulate cortex regions (Parent & Hazrati, 1995) which allows it to fulfil these proposed roles.

1-3-3. Dopamine Overdose Hypothesis

Since the establishment of dopaminergic depletion as the pathophysiological basis of PD, dopamine substitutions such as levodopa and dopamine agonists have been widely used pharmacotherapies in treating PD patients (Vaillancourt et al., 2013). While dopamine medication has been proven to be effective in ameliorating motor symptoms of PD, an increasing number of studies have been suggesting that dopaminergic medication may improve cognitive functions in some patients but impair them in others (Gotham et al., 1988; Cools et al., 2001; Dirnberger &

Jahanshahi, 2013). Gotham et al (1988) showed that PD patients exhibited improved verbal fluency but impaired performance in an associative conditional learning task and a subjective-ordered pointing task when on medication. The findings led to the formulation of 'dopamine overdose hypothesis'. The dopamine overdose hypothesis proposed by Cools et al (2001) states that, the administration of dopamine medication to PD patients may replete dopamine-depleted regions such as the dorsal, rostral head of the caudate nucleus and the putamen, but may overstimulate relatively intact regions such as the ventral striatum in early PD, leading to poorer performance on tasks mediated through these circuits such as reversal learning (Cools et al, 2001), conditional associative learning (Gotham et al, 1998), complex discrimination learning (Swainson et al, 2000), and probabilistic classification learning (Jahanshahi et al 2010). This overdose hypothesis is consistent with the proposal of an 'inverted U' relationship between dopamine levels and cognitive performance (Figure 1.14; Cools et al., 2001; Cools, 2006).

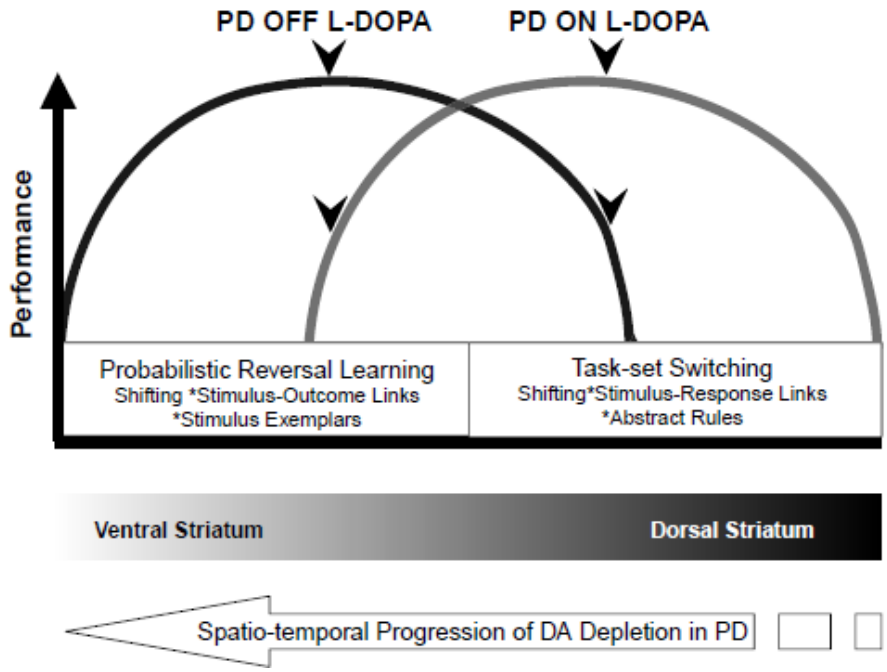

Figure 1.14 Schematic of the 'L-DOPA over-dose' hypothesis in PD. The black 'Inverted-U-shaped' curve refers to the finding that performance on the probabilistic reversal learning task, associated with the ventral striatum, is intact in patients OFF medication (PD OFF L-DOPA) but impaired in the same patients ON medication as the left black arrows shown. The grey 'Inverted-U-shaped' curve refers to the finding that performance on the switching task, associated with the dorsal striatum, is intact in patients ON medication (PD ON L-DOPA) but impaired in the same patients OFF medication. Figure from Cools (2006).

Empirical studies have revealed inconsistent results on the effects of dopamine medication on task performance. While some studies found that PD patients performed worse om sequential learning tasks when being ON medication than OFF medication (Feigin et al., 2003; Kwak, Muller, Bohnen, Dayalu, & Seidler, 2010, 2012; Muslimovic et al., 2007), other studies have shown no such effects of

medication on sequential learning task performance (Pascual-Leone et al., 1993; Ghilardi et al., 2007). Kwak et al (2010, 2012) suggest that such inconsistent results may be due to the differential effects of dopamine medication on early versus later stage of sequence learning processes. The early phase of sequence learning has been hypothesised to be associated with ventral striatum, whereas the later phase of sequence learning is more closely related to activity in the dorsal striatum (Doyon, Penhune, Ungerleider, 2003; Lehericy et al., 2005; Miyachi, Hikosaka, & Lu, 2002). In consistent with the hypothesis, Kwak et al (2010) observed that PD patients OFF medication as well as healthy controls showed better performance on sequence learning compared to PD patients ON medication. Moreover, PD patients OFF medication and healthy controls have been found to show activity in the ventral striatum during early sequence learning but not observed in PD patients ON medication (Kwak et al., 2012). In addition to the differential involvement of striatal functions in sequence learning, factors such as stage of disease, striatal structure used in the task, and genotype for genetic polymorphisms may also play a role in dopaminergic metabolism in striatum and prefrontal cortex, thus contribute to the inconsistent results on the effects of dopamine medication (Vaillancourt et al., 2013).

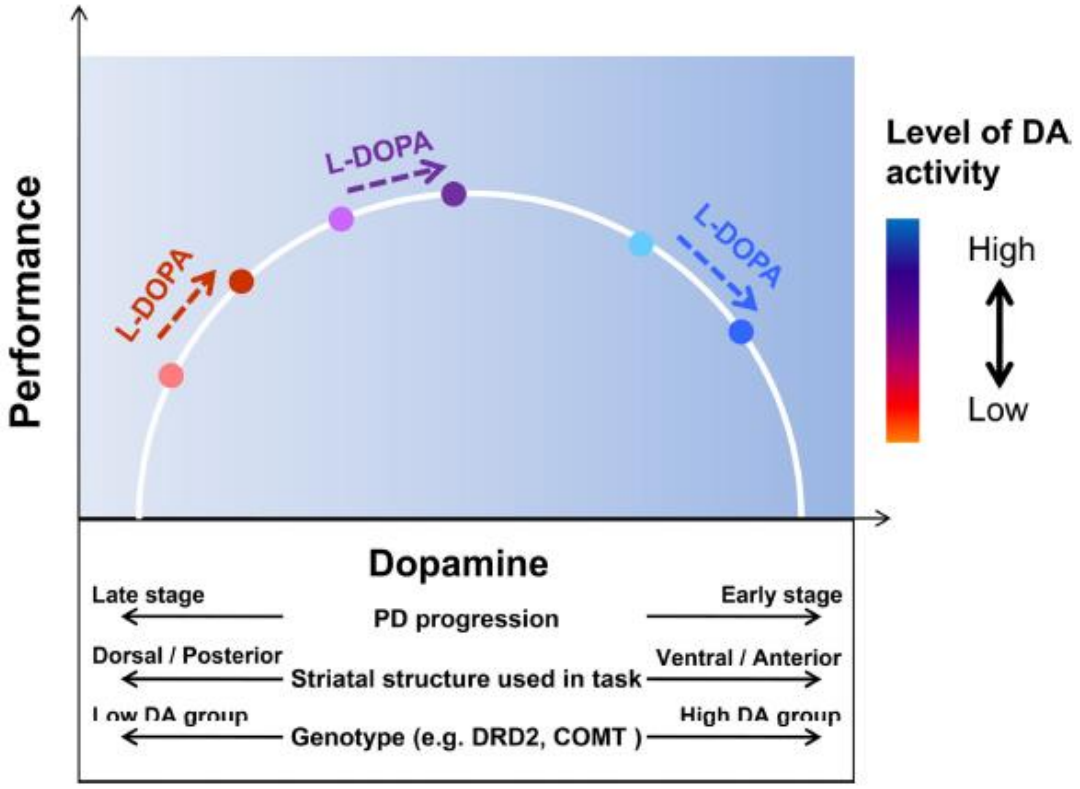

Figure 1.15 Factors such as genetic polymorphisms, striatal structure used in the task, disease progression may collectively contribute to each patient's starting location on the inverted-U shaped function describing the association between dopamine and task performance, which in turn determines whether performance will worsen, improve, or show no change with dopaminergic medications. Figure from Vaillancourt et al (2013).

1-3-4. The computational role of the subthalamic nucleus (STN) in inhibitory control

In addition to degeneration of dopamine neurons, another pathological feature of PD is the overactivity of the STN and GPi. It has been suggested that the excessive

inhibitory output from the GPi and SNr to the thalamus and underactivation of cortical areas contributes to akinesia and bradykinesia in PD (DeLong, 1990; Albin et al, 1989). In animal studies, lesions of the STN lead to involuntary movements, which can resemble the dyskinesias observed in Parkinson's disease (PD) patients and hemiballism (Crossman, Sambrook & Jackson, 1984). On the other hand, lesions of the STN has also been found to alleviate akinetic-rigid syndromes in parkinsonian monkeys (Aziz et al., 1992; Aziz, Peggs, Sambrook & Crossman, 1991; Bergman, Wichmann & DeLong, 1990), providing a potential treatment for motor deficits related to rigidity in PD patients. In human studies, inactivation of the STN have also been found to ameliorate some of the motor deficits observed in PD patients (Limousin et al., 1995, 1998)

As discussed in Chapter 1-2-2, the hyperdirect pathway in the basal ganglia consists of glutamatergic excitatory neurons that transmit signals quickly from the cerebral cortex to SNr/GPi via the STN, producing a net effect of motor inhibition (Nambu, Tokuno & Takada, 2002). In addition to motor inhibition, it has been proposed that the STN also plays an important role in cognitive flexibility (Aron & Poldrack, 2006; Isoada & Hikosaka, 2008; Hikosaka & Isoda, 2010), which suggests that the STN activity is associated with supressing automatic and fast actions to initiate controlled and slow actions. Frank (2006) has proposed a computational role of the STN in dynamically controlling the threshold for executing a response, which is fundamentally modulated by the intensity of competing possible actions. In other words, STN is essential to integrate all information before action selection, thereby

prevents premature responses especially in high-conflict situations. Studies have shown that high-frequency stimulation induced impairments during decision-making when decision conflict was presented in PD patients (Frank et al., 2007; Green et al., 2013). One potential hypothesis for the impairment could be the stimulation-induced disruption of the activity of the limbic circuit between the anterior cingulate cortex (ACC) and the ventral striatum as revealed by the imaging study of Schroeder et al. (2002). As previously discussed, the ACC has been proposed to modulate the conflict monitoring system that detect and integrate response conflict, and send signals to the basal ganglia to control the execution of actions (Botvinick, Nystrom, Fissell, Carter & Cohen, 1999). In particular, the STN receives direct projections from the pre-supplementary motor area (pre-SMA) and cingulate cortex that compose conflict monitoring systems, which allows the STN to implement cognitive control by sending NoGo signals via diffuse excitatory projections to basal ganglia output nuclei (Mink, 1996; Parent & Hazrati, 1995; Frank et al., 2007). Consistent with the proposed computational role of the STN, Cavanagh et al (2011) showed that mPFC activity increased and decision threshold decreased with STN DBS on during decision conflict. Figure 1.16 illustrates the computational role of the STN in action selection during decision conflict.

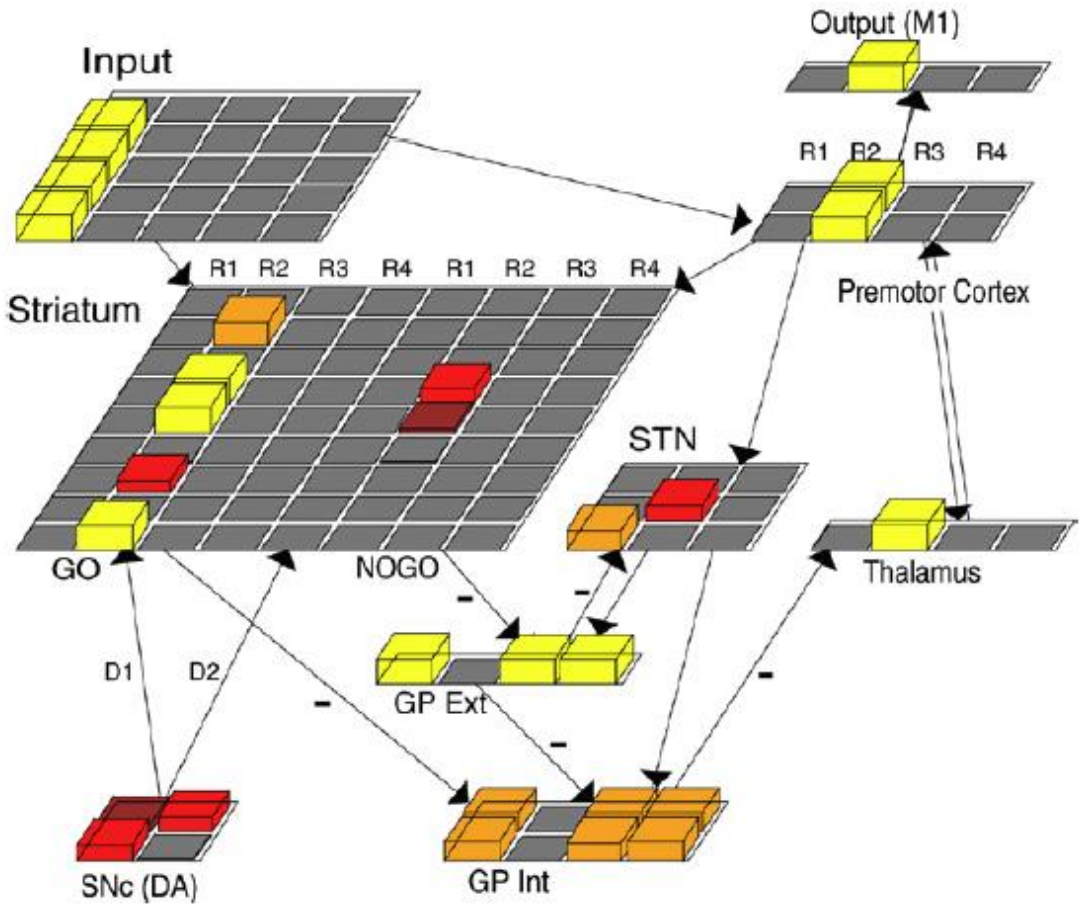

Figure 1.16 The subthalamic nucleus is incorporated into a scaled-up model that includes four competing responses (R1–R4). The STN receives excitatory projections from pre/motor cortex in the "hyperdirect pathway" and excites both GPi and GPe; GPe provides inhibitory feedback on STN activity. Figure and caption from Frank (2006).

Bogacz et al (2010) have proposed that the STN is essential in balancing the competing demands of response speed and response accuracy (i.e. the speed-accuracy trade-off), especially under accuracy emphasis the STN receives additional excitatory inputs and such increased STN activity produces slower and more accurate decisions/actions. Moreover, Green et al (2013) showed that PD patients OFF

stimulation exhibited reduced reaction time under high decision conflict on a moving dots task, and conversely, the effect of high conflict declined when PD patients were ON stimulation. Individual data sets are described by two models: when PD patients were OFF stimulation, the fast-diffusion model best described the behavioural data, while on stimulation, the race model accounted better for the behaviour under DBS (Green et al., 2013). The fast-diffusion model applied to two alternative choices tasks indicates that the information favouring each of the two alternative options is integrated over each trial and that a decision is reached when the accumulated information exceeds a critical threshold (Bogacz, Brown, Moehlis, Holmes & Cohen, 2006), whereas the race model indicated that sensory information for the two alternatives are integrated independently (Bogacz & Gurney, 2007). In other words, the results of the Green et al (2013) study have provided evidence supporting that cortico-basal ganglia networks implement system-level computations that optimise decision-makings and potentially further action selection. Figure 1.17 illustrates the computational architectures for models of binary decision making.

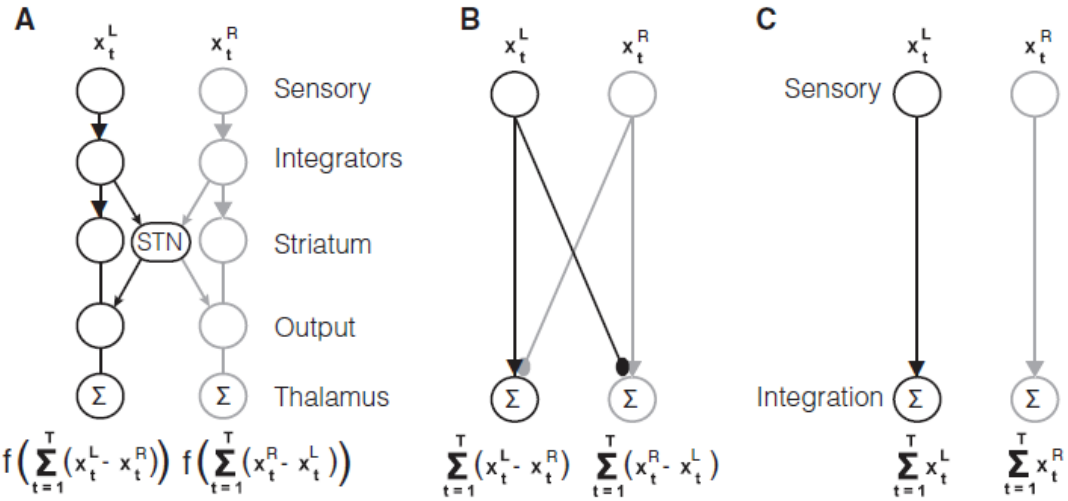

Figure 1.17 (A) A network model implementing the multihypothesis sequential probability ratio test. The black and gray circles denote neural populations selective for movement toward the left and right, respectively. Labels next to the populations denote the brain areas where they are located (‘‘Integrators’’ denotes cortical integrator neurons, and ‘‘Output’’ denotes the output nuclei of the BG: the internal segment of the globus pallidus and the substantia nigra pars reticulata). The arrows denote excitatory connections, and the lines ending with circles denote inhibitory connections. The labels above and below the models indicate the values of inputs and outputs, respectively. The labels x_t^L and x_t^R denote the activities of sensory neurons selective for motion toward the left and right, respectively, at the current time T. f is a monotonic function equal to $f(s) = -\log[1 + \exp(2gs)]$, where g is a positive model parameter and s the sum of the difference between both alternatives for each output unit. (B) In the diffusion model, the difference between sensory inputs for the two alternative choices is integrated. A choice is made once this integrated difference exceeds a decision threshold. Only the difference between sensory inputs affects the values of the integrators. (C) The simplest model of binary choice is the race model. Two independent integrators accumulate sensory evidence supporting each of the two choice alternatives (here, motion to the left or right). A choice is made once the activity of any integrator exceeds a fixed threshold. Figure and captions from Green et al (2013).

In addition to decision conflict, Pote et al (2016) found that when decision conflict was set at a constant 50% coherence for the moving dots task, patients with STN DBS

on responded faster but made more errors and had reduced decision thresholds under speed instructions, suggesting that STN DBS induced impulsive responses under speed pressure. Together, the results support the imaging studies that suggest the STN is involved in the modulation of SAT through the adjustments of response thresholds during decision-making (Forstmann et al., 2008; van Veen et al., 2008; Ivanoff et al., 2008; Domenech & Dreher, 2010). In addition, by recording local field potentials (LFP) from the STN DBS electrodes while performing a moving dots task in PD patients, Zavala et al (2014) demonstrated that dynamic coupling of neural activity between midline frontal cortex and the STN is dominated by information flow from the cortex to the STN, and that the elevated STN theta activity is specific to conflict. The results thus provide robust support for the hypothesis that the connections between the STN and the mPFC modulate decision thresholds during decision conflict in decision-making (Zavala et al., 2014). Moreover, Leimbach et al (2018) showed that when reward, decision conflict and/or time pressure to make decisions were absent during the decision-making processes, the STN plays no critical role in modulating the decision threshold.

1-3-5 Deep brain stimulation (DBS) of the subthalamic nucleus (STN)

Once levodopa induced complications such as dyskinesias or on-off fluctuations develop, patients are considered appropriate potential candidates for deep-brain stimulation (Okun, Fernandez, Rodriguez, Foote, 2007). The selection criteria for DBS surgery include: motor symptoms that are dopamine responsive, aged below 70

or 80 (this varies across centres), no evidence of brain atrophy on MRI, no dementia, no major psychiatric illness, no other major physical illness which would be a contra-indication for surgery. Deep brain stimulation is a surgical technique in which one or more electrodes attached to leads are implanted in specific regions of the brain, the STN or GPi that are hyperactive in PD (Figure 1.18) (Okun, 2012).

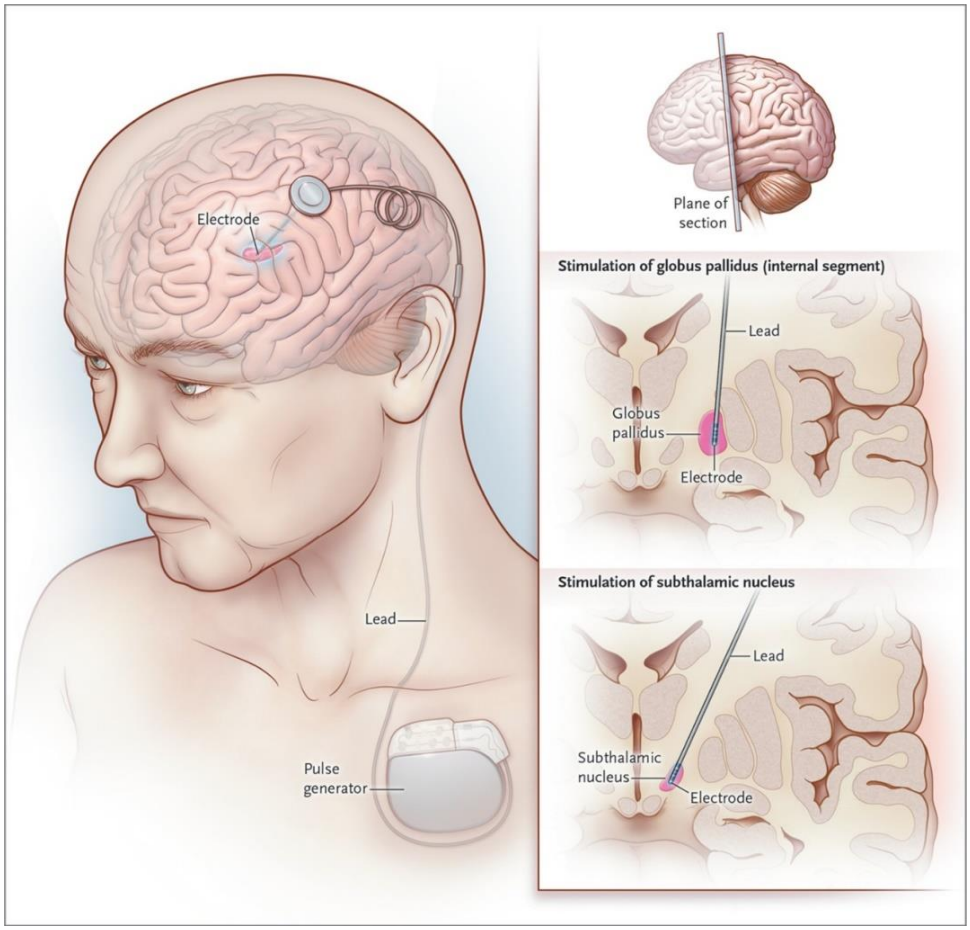

Figure 1.18 Electrode Implantation for Deep-Brain Stimulation. The electrode for deep-brain stimulation is implanted in either the subthalamic nucleus or the internal segment of the globus pallidus. The lead passes through a burr hole in the skull. Attached to the lead is a connecting wire, which is tunneled under the skin of the scalp and neck to the anterior chest wall, where it is connected to an impulse

generator. Figure from Okun (2012).

Furthermore, it has been sown in rodent studies that STN high-frequency stimulation (HFS) could increase striatal dopamine release and metabolism (Bruet et al., 2001; Meissner et al., 2003; Lacombe et al., 2007; Zhao et al., 2009; Pazo, Hocht, Barcelo, Fillipini & Lomastro, 2010), such increase is thought to account for the improvement of parkinsonian symptoms in animal models of PD. Glutaminergic output on the dopaminergic neurons of the SNc from the STN is believed to be involved in the degeneration of dopamine neurons, STN-HSF may slow down such neurodegeneration process by decreasing glutamate output (Benabid, Chabardes, Mitofanis & Pollak, 2009). The clinical observations on PD patients have shown that STN DBS is effective against levodopa sensitive motor symptoms (Benabid et al., 1998; Moro et al., 1999) and it is generally observed that patients reduce dopaminergic medication after surgery (Krack et al., 2003; Kleiner-Fisman et al., 2003), it has therefore been proposed that STN DBS has an effect on increasing striatal dopamine release. However, human imaging studies of STN DBS have found no evidence supporting the hypothesis that STN DBS is associated with striatal dopamine release (Hilker et al., 2003; Strafella, Sadikot & Dagher, 2003; Nozaki et al., 2013; Thobois et al, 2003). For example, Hilker et al (2003) has found no correlation between the changes of dopamine radioligand binding and the simulation amplitudes in a positron emission tomography (PET) study.

Despite the growing clinical practice of STN-HFS, the underlying mechanisms of

DBS STN remains undetermined (Meissner et al., 2005; Montgomery & Gale, 2008; McIntyre & Hahn, 2010). Two general theories have been strongly debated regarding the effects of STN DBS: (1) DBS suppresses or inhibits the stimulated nucleus that mimics the effects of ablation; (2) DBS results in activation of the stimulated nucleus that is transmitted throughout the network (McIntyre, Savasta, Goff & Vitek, 2004). Nevertheless, lesions or DBS of the STN in primates reduce the symptoms of parkinsonism in MPTP-treated monkeys (Bergman et al., 1990; Benazzouz et al., 1993). Moreover, DBS of the STN has been shown to remarkably improve the motor impairments in PD as now established in randomized clinical trials (Deuschl et al, 2006; Weaver et al, 2012; Follett & Torres-Russotto, 2012; Williams et al, 2010). A few experimental studies have shown that STN-HFS reduces the activity of STN neurons (Benazzouz, Gross, Feger, Boraud, & Bioulac, 1993; Benazzouz et al., 2004; Salin, Manrique, Forni, & Goff, 2002; Tai et al., 2003). Studies have shown that in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-(MPTP)-lesioned non-human primates, STN-HFS increases the mean firing rate of GPi neurons and modifies the spontaneously irregular firing pattern into regular firing pattern (Bergman, Wichmann, Karmon, & DeLong, 1994; Hashimoto, Elder, Okun, Patrick, & Vitek, 2003). Electrophysiological recordings of local field potentials and unit activity in human STN suggest that increased oscillatory activity in beta frequency band may contribute to parkinsonian pathophysiology (Brown et al., 2001; Levy et al., 2002; Brown, 2003; Kuhn et al, 2004). Moreover, studies have shown that DBS attenuate oscillatory beta activity in PD patients, which may result in motor improvement (Kuhn et al., 2008; Bronte-Stewart et al., 2009; Giannicola et al., 2010).

In addition, studies have found that deep brain stimulation of the STN and GPi are equally effective in improving motor deficits in PD (Anderson, Burchiel, Hogarth, Favre & Hammerstad, 2005; Follett et al., 2010). More reports on the mood, behavioural and cognitive side-effects associated with STN DBS than GPi DBS stimulation have been found, potentially due to higher STN implantation rate; however the relatively smaller size and anatomical location of the STN may also account for the effect (Walter & Vitek, 2004). Combs et al (2015) conducted a meta-analysis to compare the cognitive, behavioural and mood symptoms between the two targets. The results showed that GPi DBS produced relatively fewer neurocognitive declines than STN DBS. While the former resulted in a small decline in attention and a small-moderate decline in verbal fluency; the latter produced small declines in psychomotor speed, memory, attention, executive functions, and overall cognition, and also moderate declines in both semantic and phonemic fluency (Combs et al., 2015). In addition, in a recent review of the cognitive literature and the available meta-analyses of this literature; Troster et al (2017) concluded that bilateral STN DBS is reasonably cognitively safe except for decrements in verbal fluency and on the Stroop task.

1-4. The effect of acute manipulations of treatments on cognitive functions associated with context monitoring in PD patients

One of the goals of the present PhD thesis is to investigate the acute effects of treatments (i.e. dopamine medication and STN DBS) on cognitive functions associated with context monitoring in PD patients. In the present section I will selectively review studies that manipulated acute effects of either of these treatments on cognitive functions in PD patients.

1-4-1 The acute effects of dopaminergic medication on executive functions in PD patients

Progressive degeneration of dopaminergic neurons in the SNc is the main feature of PD. The most common therapeutic strategy is dopaminergic medication including dopamine precursors such as levodopa and dopaminergic agonists. While both types of medication significantly ameliorate motor deficits in PD patients, as discussed in Chapter 1-2-4, dopamine overdose effect on aspects of cognitive function and neuropsychological and psychiatric side effects have also been reported for patients in the early stages of PD treated with medication (Saint-Cyr, Taylor & Lang, 1993). As briefly mentioned in previous sections, Frank et al (2004) have proposed a computational model of basal ganglia-dopamine interactions in cognition, which predicts that PD patients are impaired in learning form positive feedback and have enhanced learning from negative feedback when being OFF medication due to the reduced level of dopamine; whereas when being ON medication, PD patients would have sufficient dopamine to learn from positive feedback but relatively impaired at

learning from negative feedback. The proposed model may provide explanations on the observation that dopaminergic medication alleviates some cognitive deficits but impairs other cognitive functions that are associated with the intact basal ganglia regions (due to dopamine overdose hypothesis, which was discussed in Chapter 1-3-3) (Frank, 2005).

The early stages of PD are associated more with nigrostriatal dopamine depletion and to a lesser extent associated with mesocorticolimbic dopamine depletion. The impairment of PD on the performance of gambling tasks is often reflected as impulsive choices that lead to large losses. In addition, it has been shown that PD patients treated with dopaminergic medication, especially dopaminergic agonists, potentially develop impulse control disorders (ICDs) (Voon & Fox, 2007; Wu, Politis & Piccini, 2009; Weintraub et al., 2015). ICDs are defined as behaviours that are performed repetitively, excessively, and compulsively to a degree that greatly interferes with major aspects of daily life (Grant, Schreiber, & Odlaug, 2011). In addition to pathological gambling, shopping, hypersexuality and binge eating, other impulsive-compulsive behaviours including punding, hobbyism, walk-about and hoarding have also been described in PD (Weintraub et al., 2015). Molina et al (2000) first reported the association between PD and pathological gambling, potentially due to the pharmacological treatment. Dodd et al (2005) assessed 11 PD patients who developed pathological disorders and their medical therapy, showing a correlation between dopaminergic agonists and the development of pathological gambling. Weintraub et al (2010) conducted a cross-sectional study of 3090 patients in America

and Canada, which showed that 13.6% of patients developed one risk, and 3.9% had 2 or more ICDs. ICDs were more common in patients treated with dopamine agonists, showing a 2-3.5 fold increased odds of inducing ICDs for dopamine agonist treatment (Weintraub et al., 2010).

Dopamine-receptor binding profiles may provide a neurobiological explanation for the association between dopamine agonist treatment and ICDs. 93 % of the prescribed dopamine agonists that were associated with ICDs were relatively selective for the dopamine D3 receptors (Dodd et al., 2005). D3 receptors are proposed to be abundant in the ventral striatum (Gurevich & Joyce, 1999), which is also a brain region that is associated with the hedonic response to amphetamine, addictions and impulsivity (Drevets et al., 2001; Lee et al., 2009). In addition to dopaminergic medication, factors such as male gender, younger age at PD onset, being single, higher novelty seeking personality, and personal or family history of substance abuse are factors relevant to development of ICDs in PD (Voon et al., 2007; Weintraub et al., 2010, 2015). The association of ICDs with other risk factors may suggest involvement of a complicated network in human impulsivity and compulsivity. In addition, studies have shown that PD patients without ICDs and PD patients with ICDs showed different behavioural patterns in decision-making (Djamshidian et al., 2010; Djamshidian et al., 2012). While all PD patients showed reflection impulsivity as reflected by less information sampled before making a decision, PD patients without ICDs showed a behavioural pattern similar to pathological gamblers, whereas PD patients with ICDs exhibited a pattern resembling more to substance users

(Djamshidian et al., 2012). Moreover, PD patients without ICDs performed worse on working memory tests (Djamshidian et al., 2012). The results suggest that tasks investigating evidence accumulation might be powerful for detecting impulsive-compulsive behaviours in PD. Studies in rodents showed that blockade of dopamine receptors reduces preference to wait longer or work harder to obtain large rewards (Cardinal, Robbins & Everitt, 2000; Salamone, Wisniecki, Carlson & Correa, 2001). Drugs increasing dopamine transmission such as amphetamine can exert differential effects on decision-making, while lower doses of amphetamine enhances tolerance for delays to reward delivery. These results suggest that acute manipulation of dopaminergic transmission is involved in cost/benefit decision-making. In addition to the acute effects, chronic administration of drugs, especially dopaminergic agonists, has been demonstrated to impair inhibitory control and decision-making (Everitt & Robbins, 2005).

In the review that discussed chronic dopaminergic stimulation in PD patients on inducing motor and behavioural side-effects, Voon et al (2009) suggested that chronic dopaminergic medication (both levodopa and dopaminergic agonists) seems to alter presynaptic dopamine transmission that leads to both levodopa-induced dyskinesias and ICDs. In addition, never-medicated PD patients showed impaired stimulus-response learning ability compared to healthy controls (Nagy et al., 2007). Ryterska, Jahanshahi & Osman (2013) conducted a meta-analysis in an attempt to determine the motor and cognitive factors that determined impairment of decision-making in PD patients. The results revealed two key predictors of

decision-making impairment in PD: (1) the feedback structure of the decision-making task and (2) the medication status of patients while performing the task. Behavioural studies on patients with PD tested on and off medication have shown the effects of acute dopaminergic medication on probabilistic classification learning, perceptual decision-making and action selection (Czernecki et al., 2002; Shohamy, Myers, Geghman, Sage, & Gluck, 2006; Frank et al., 2007; Moustafa, Sherman & Frank, 2008; Jahanshahi, Wilkinson, Gahir, Dharminda & Lagnado, 2010; Galea, Bestmann, Beigi, Jahanshahi & Rothwell., 2012; Huang et al., 2015). For example, Moustafa et al (2008) have shown that PD patients both on and off medication showed attentional shifting deficits in an information updating related task, but for different reasons. Moreover, medication seemed to improve working memory. More specifically, unmedicated PD patients showed deficits in updating attentional set, whereas medicated PD patients were impaired in ignoring distractors that were previously relevant to the task (Moustafa et al., 2008). Jahanshahi et al (2010) suggested that PD patients on medication performed worse on than off medication and healthy controls on a probabilistic classification learning task. On a moving dots task, Huang et al (2015) have shown that dopaminergic medication did not induce impulsivity when acting under time pressure or in situations of decision conflict; instead it impaired the ability to extract sensory information in PD patients, resulting in patients making more errors in a perceptual decision-making task when faced with decision conflict. In contrast, Castrioto et al (2015) showed no effect of acute manipulation of dopaminergic medication on the IGT scores, however, PD patients off medication showed significantly worse performance compared to age-matched healthy controls.

While the acute manipulation of dopaminergic medication may improve working memory and the subjective evaluation of motivation, it may also impair attentional shifting and perceptual decision-making. The results suggest that dopaminergic medication is effective in reducing the negative symptoms caused by the loss of dopamine neurons in multiple neural mechanisms that involved dopamine transmission. Timmer, Sescousse, Esselink, Piray & Cools (2018) showed that dopaminergic medication increased a value-dependent gambling bias in non-depressed PD patients, which is associated with the dopamine overdose hypothesis (Cools et al., 2006). In contrast to previous studies reporting dopaminergic medication inducing impulsive decisions in PD, Foerde et al (2016) showed that PD patients (who did not have ICDs) tested on medication made more farsighted choices, which suggests that dopamine influences the evaluation of larger later rewards. Note that the Foerde et al (2016) study investigated different groups of PD patients when ON versus OFF medication, individual differences in levels of dopamine deficiency and in making intertemporal decisions should also be taken into account in future studies.

In summary, despite a few studies suggesting that dopamine medication used in treating PD produced no side effects in patients, most studies have found that dopamine medication induced side effects such as executive dysfunctions, impaired decision-making and potential development of ICDs in PD patients.

1-4-2. The acute effects of STN-DBS on executive functions in PD

In addition to dopamine medication, STN DBS is also a common treatment for PD. As previously discussed, the exact mechanism of STN DBS and how specifically it improves the motor symptoms pf in PD remains unclear (Montgomery & Gale, 2008; McIntyre & Hahn, 2010). Moreover, experimental studies have shown inconsistent results on the effects of acute manipulation of STN DBS on executive functions in PD patients.

While STN DBS has been clinically demonstrated to alleviate tremor, rigidity, bradykinesia, and levodopa-induced dyskinesias, its effects on cognition are less clear and depend on the cognitive domains under consideration (Parsons, Rogers, Braaten, Woods & Tröster, 2006; Woods, Fields & Troster, 2002; Comb et al, 2015; Jahanshahi, 2013). Woods et al (2002) concluded in a critical review that most common findings for the effects of STN DBS, in addition to improving the motor deficits, are improvements in self-reported symptoms of depression and diminished verbal fluency. Consistent with this conclusion, Funkiewiez et al (2004) investigated 77 PD patients before, 1 and 3 years after surgery and found that STN stimulation did not lead to global cognitive deterioration however, verbal fluency was found to worsen. Such verbal fluency decline has been related to apathy and a decrease in self activation (Funkiewiez et al., 2004). A meta-analysis study of 28 neuropsychological cohort studies published between 1999 and 2006 including 612 patients revealed significant but small declines in executive functions, vernal learning and memory in PD patients treated with STN DBS (Parsons et al., 2006). Table 1.4 shows the average weighted effect sizes, standard errors of the effect sizes and confidence limit. The

neuroanatomical and cognitive mechanisms underlying the negative effect of STN DBS on verbal fluency are not mutually exclusive. Intraoperative electrical stimulation studies suggested that the striatum might have dissociable roles in the motor and cognitive control of language (Robles, Gatignol, Capelle, Mitchell & Duffau, 2005). In addition to the effects of STN DBS on neuropsychological tests, it has been suggested that DBS of the STN has an impact on executive control or inhibition of prepotent responses (Jahanshahi, 2013).

Table 1.4 Random effect sizes for the neuropsychological domains

	Average random effect size	Effect size variance	95% CI
Cognitive screening	0·04	0·001	−0·05 to 0·12
Attention and concentration	0·02	0·001	−0·08 to 0·12
Executive functions	0·08*	0·001	−0·03 to 0·20
Psychomotor speed	0·22	0·020	−0·02 to 0·54
Verbal functions	0·21*	0·020	−0·04 to 0·46
Visual functions	0·06	0·010	−0·16 to 0·27
Verbal fluency	0·64*	0·030	0·32 to 0·96
Phonemic fluency	0·51*	0·080	−0·05 to 1·08
Semantic fluency	0·73*	0·030	0·41 to 1·04

Table from Parsons, Rogers, Braaten, Woods & Tröster, 2006.

To investigate the dynamic role of the STN in modulating decision thresholds in proportion to reinforcement and decision conflict, Frank et al (2007) administrated computerized decision-making tasks to PD patients treated with DBS of the STN in different sessions (i.e. ON and OFF). The results showed that patients on stimulation failed to slow down with increased decision conflict, supporting the hypothesis that the STN provides a control signal that prevents premature responses depending on decision conflict (Frank, 2006; Frank et al, 2007). Moreover, Green et al (2013) have demonstrated that PD patient with STN DBS ON made more fast and incorrect responses during the modulation of SAT (i.e. speed-accuracy trade-off) when making decisions compared to PD patients OFF stimulation and age-matched healthy controls. Together the results thus suggest that the STN is involved in information integration during decision making and/or action selection.

In addition to its role in information integration, the STN is proposed to be involved in the accumulation of probabilistic information (Bogacz & Gurney, 2007). Coulthard et al (2012) showed that DBS of the STN impairs response choice requiring information integration and induces failures to slow down to incorporate new information before making a decision in PD patients. Studies investigating the effect of DBS of the STN on the Iowa Gambling task (IGT) report no significant difference in overall performance between ON and OFF sessions 2-4 weeks or 10 months after surgery (Oyama et al., 2011; Czernecki et al., 2005). Evens, Hoefler, Biber, & Lueken (2016) showed that acute DBS of the STN increased risky choices in the IGT. However, DBS of the STN had no effect on incentive salience attribution or the

evaluation of delayed rewards. In contrast, Brandt et al (2015) showed that stimulation of the STN tempered risk-seeking behaviours in PD patients, additionally the stimulation made patients more risk-aversive in ambiguous-risk situations. While results on experimental tasks suggest that in general DBS of the STN causes little to no negative effect on decision-making (Czernecki et al., 2005; Yugeta et al., 2010; Swann et al., 2011; Torta et al., 2012; Boller et al., 2014; Fumagalli et al 2015; Brandt et al., 2015), Smeding et al (2007) have suggested that pathological gambling is related to a combination of STN stimulation and treatment with dopamine agonists based on a case report. Consistent with this hypothesis, Castrioto et al (2015) reported that patients after surgery improved performance on the IGT due to the reduction of the dopaminergic medication. By contrast, Rogers et al (2011) showed that DBS of the STN enhanced loss-chasing behaviours on the Cambridge gambling task. In contrast with the previous findings, Torta et al (2012) revealed no such effects, instead patients reported being more impulsive subjectively during off stimulation periods.

Neuropsychological tests have shown inconsistent results regarding the effects of STN DBS on inhibitory control related EFs in PD patients. To examine the effect of STN DBS in PD on controlling inhibition, the stop-signal paradigm and the estimation of stop-signal reaction time (SSRT) based on the horse race model (Logan & Cowan, 1984) have been used in several studies (van den Wildenberg et al., 2006; Swann et al., 2011; Mirabella et al., 2011; Greenhouse et al, 2011; Ray et al, 2009; Obeso et al, 2013). A few studies have shown prolonged SSRTs in patients ON compared to OFF stimulation, indicating that STN DBS impairs inhibitory control in

PD patients (Ray et al, 2009; Ballanger, Poisson, Broussolle, & Thobois, 2012; Obeso et al, 2013). However, three studies that investigated the effect of STN DBS SSRT have reported significantly shorter SSRTs in PD patients with stimulation ON than OFF, suggesting that DBS of the STN improves inhibitory control on the stop signal task (van den Wildenberg et al., 2006; Swann et al., 2011; Mirabella et al., 2011). Moreover, other studies using different tasks such as a cue-target detection task and a Status quo task also showed behavioural improvements for PD patients on tasks involving proactive inhibition (Favre et al., 2013; Zaehle et al., 2017). In addition to SSRT, Go/NoGo task has also been widely used to assess inhibitory control. While most studies suggested that STN DBS impaired inhibitory control on the Go/NoGo task performance (Hershey et al., 2004; Ballanger et al., 2009; Hershey et al., 2010), one study showed that STN DBS improved action execution when rewards were anticipated (Wagenbreth et al., 2015). Moreover, Georgiev et al (2016) showed that STN DBS selectively decreased discriminability on tasks with high probability but not low probability of GO stimuli. Factors such as medication state when performing the behavioural tasks, disease duration, the difference of the SSRT tasks used, baseline SSRTs in PD patients relative to healthy controls, the exact location of the stimulating electrode in the STN and surgical procedure variations may contribute to the inconsistency in these results. Despite these studies provide contrary results, the results of these studies suggest a direct involvement of the STN in inhibitory and executive control (Table 1.5).

Table 1.5 Studies investigating the effects of STN DBS on inhibitory control and

cognitive flexibility			
Task used	Impaired by STN DBS	Enhanced by STN DBS	Related executive functions
SSRT (Stop-signal reaction time)	Jahanshahi et al (2000) Schroeder et al (2002) Ray et al (2009) Obeso et al (2013)	Van den Wildenberg et al (2006) Greenhouse et al (2011) Swann et al (2011) Mirabella et al (2011)	Inhibition
Go/NoGo task	Hershey et al (2004) Ballanger et al (2009) Hershey et al (2010) Wagenbreth et al (2015) Georgiev et al (2016)	Wagenbreth et al (2015)	Inhibition
Stroop interference task/ Simon	Jahanshahi et al (2000) Schroeder et al		Cognitive flexibility Inhibition

task	(2002) Witt et al (2008) Wylie et al (2010)		

1-5. General Aims, hypotheses and methodology

The general aims of the present thesis were to investigate the acute effects of dopamine and STN DBS on basic executive functions such as shifting, updating and inhibition. PD patients are recruited as a human model of dopamine depletion. Dopaminergic medication and STN DBS are used to further investigate how these treatments both ameliorate motor deficits and affect executive functions in PD. Behavioural performance on computerised tasks on/off medication or on/off stimulation is compared for each patient. In addition, performance of PD patients was compared to age-matched healthy controls (HCs). On one hand, in accordance with the 'dopamine overdose hypothesis' (Cools et al., 2006), PD patients would have poorer performance on probabilistic learning tasks, which involves the presentation of one discrimination to learn at a time, when being ON medication than OFF medication, due to medication overstimulates dopamine-intact ventral striatum in PD patients. On the other hand, based on the theories of STN DBS in inhibitory control and previous results observed in PD patients, it is hypothesised that STN DBS would impair the basic EFs including shifting, updating and inhibition in PD patients, resulting in poorer performance on behavioural tasks when being ON stimulation.

1-5-1. Computerised tasks

In the present section I introduce the computerised tasks used in the present PhD thesis in detail.

Moving dots tasks: Speed/Accuracy trade-off and Difficulty

The 'speed-accuracy' moving-dots task (Britten, Shadlen, Newsome & Movshon, 1992) required participants to decide whether a cloud of dots moved to the left or the right of the screen. Out of 120 dots, 50% moved coherently in one direction and the remaining 50% moved randomly. Each dot consisted of three pixels, and the diameter of the entire cloud of dots was 250 pixels. At the beginning of each trial, a written cue (i.e. FAST for speed and ACCURATE for accuracy) was presented, instructing participants to adopt different levels of cautiousness. Participants would decide the direction of the dots by pressing one of two buttons with either their left (for dots moving left) or right (for dots moving right) index finger. The cues were pseudo-randomly intermixed and there were equal numbers of FAST and ACCURATE cues in a block of 200 trials. At the end of each trial, participants received feedback, which depended on the previously presented cue. Under speed conditions, whenever participants exceeded the reaction time criterion of 500 ms, a "too slow" feedback was presented. If participants responded within the time criterion for the speed condition, they received the feedback "in time." At the end of the accuracy trials, participants were presented with an "incorrect" or "correct" feedback, depending on whether they had made an error or provided a correct response. The negative feedbacks were presented in red, while the positive feedbacks appeared in

green. Feedback provided an additional incentive for participants to adopt different levels of caution in response to the different cues.

The ‘difficulty’ moving-dots task also required participants to decide the direction in which a cloud of dots moved. No cues for Speed or Accuracy were used in this task. The coherence of moving dots ranged from 5%, 10%, 15%, 25%, 35% to 50%, respectively making it harder (5%) or easier (50%) to decide the direction of the moving dots. The higher the coherence was, the easier it was to judge the direction of the moving cloud of dots, thus leading to faster responses. Conversely, the lower the coherence was, the more difficult it was to decide the direction of the moving dots and therefore leading to slower response time. At the end of each trial, participants received “incorrect”, “correct” or “no response” feedbacks depending on their responses (Figure 1.9).

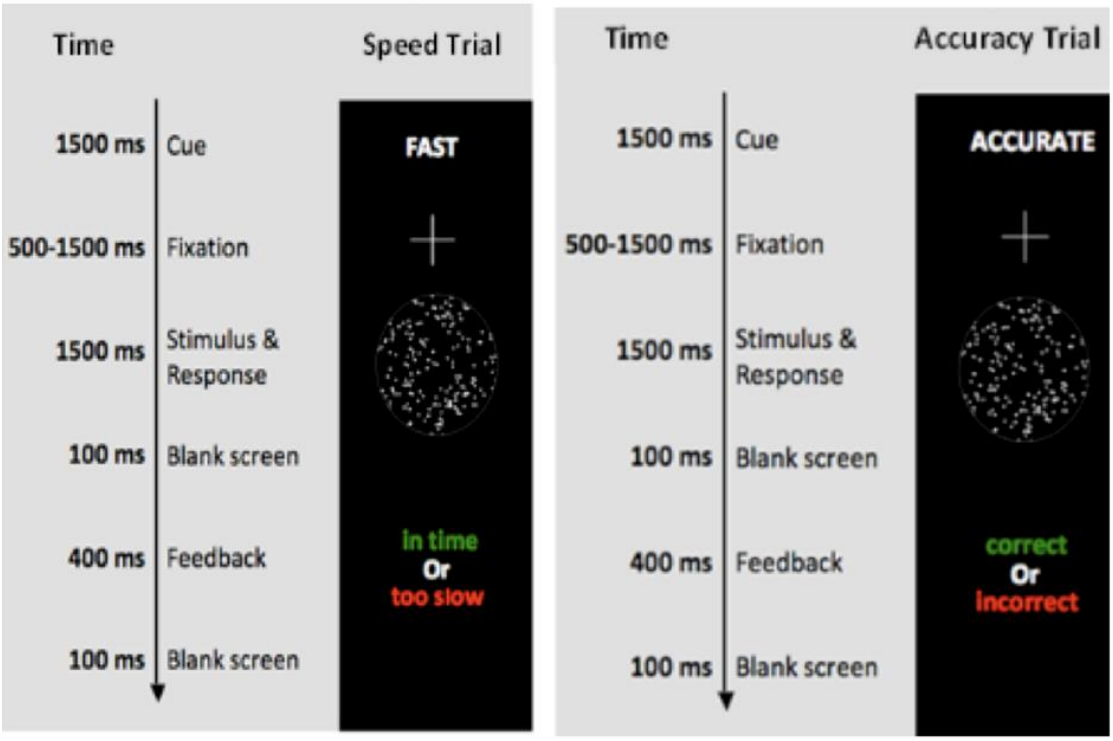

Figure 1.19 The speed–accuracy version of the moving dots task. The task difficulty version of the task was similar but without the speed/accuracy instructions and the coherence of the dots varied from5%, 10%, 15%, 25%, 35% to 50%.

Block-designed moving dots task

A block-designed moving dots task was used which consisted of two kinds of blocks: controlled blocks and automatic blocks to investigate the role of the STN in switching between different tasks. At the same time the moving dots paradigm also allow the study of how DBS STN may affect the modulation of the SAT during perceptual decision-making under various moving dots coherence.

The “automatic” (100% coherence) blocks required participants to decide whether a cloud of dots moved to the left or the right of the screen. All the dots moved coherently in the same direction. The participants were given two different

instructions before every trial: FAST (for speed) and ACCURATE (for accuracy), while the level of coherence being kept constantly at 100%. The participants then decided on the direction of the moving dots by pressing one of two buttons with either their left (for dots moving left) or right (for dots moving right) index finger. in accordance to the instruction. The cues were pseudo-randomly intermixed and there were equal numbers of FAST and ACCURATE cues in 2 blocks of 60 trials, which made it a total of 120 trials. At the end of each trial, participants received feedback, which depended on the previously presented cue. In the speed condition, whenever the participants made a response within 500 ms, the feedback 'in time' was presented, otherwise a 'too slow' feedback. In the accuracy condition, participants received the feedback 'correct' or 'incorrect' depending on their responses. 'No response' was presented on the screen if the participants failed to make any response on the trial within a time-frame of 1500ms. In the "controlled" blocks, the participants were also required to decide the direction in which a cloud of dots moved. They were instructed to do the task as fast and as accurately as possible. Cues for speed or accuracy were also used in this version of the task, as outlined above. The coherence ("difficulty") level of the moving dots were set at 5%, 10%, 15%, 25%, 35% and 50%, making it harder (5%) or easier (50%) to decide the direction of the moving dots, since the higher the level of coherence was, the easier it was to judge the direction of the moving cloud of dots, thus leading to faster responses. In each block, there were equal numbers of trials at each level of coherence, pseudo-randomally mixed, with half presented under 'speed' and half under 'accuracy' instructions. At the end of each trial, participants received the feedback "in time", "too slow" or "no response"

depending on their responses, as outlined above. The numbers of trials were selected to obtain reliable measures of perceptual decision-making while at the same time avoiding causing fatigue for the patients (Lerche, Voss & Nagler, 2017)

The probabilistic RT Task

The probabilistic RT task requires participants to learn the association between the presented imperative stimuli (IS) and specific finger presses (Galea et al., 2012) (Figure 1.20 a). The order of the IS can be predictable or unpredictable (Figure 1.20 b&c).

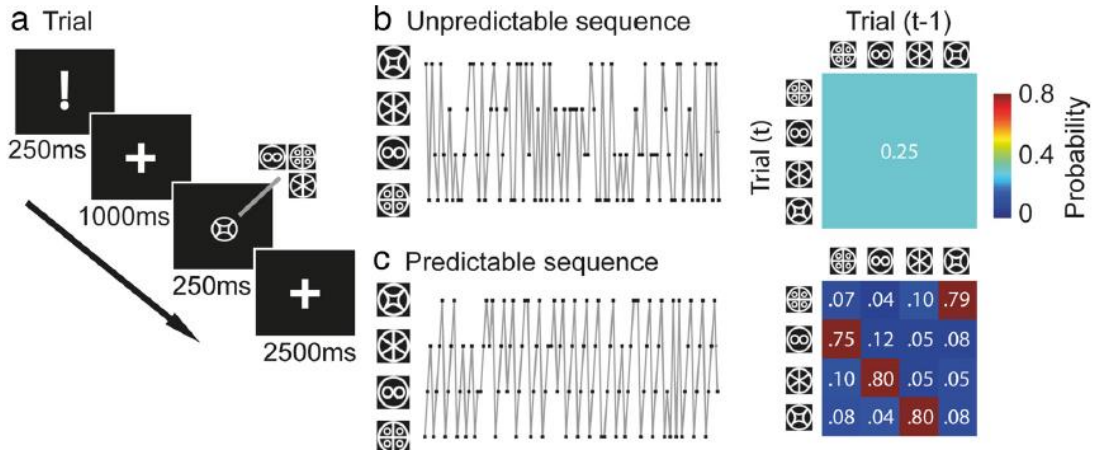

Figure 1.20 The probabilistic reaction time task. ***a***, Schematic representation of a single trial. A visual warning sign is presented followed by a fixation cross. One of the four novel IS is then presented and participants are required to respond as fast and accurate as possible when the next fixation cross is presented; ***b*** and ***c*** show that the order of the visual stimuli can either be predictable or unpredictable. Predictable sequences were generated from a first-order Markov sequence in which there are 16 combinations that determined the relationship between the IS on trial *t* and on trial *t*-1.

Numbers within the probability matrices represent the transition probabilities. The overall probability of each IS on trial *t* was equal across all blocks. Figure adapted from Galea et al., (2012).

Participants sit in front of a computer screen 30 cm away. A custom button box with four buttons is placed in front of the dominant hand. The participants are instructed to place each one of their fingers on each of the four buttons and to maintain this position throughout the task. Initially, an un-informative warning cue ("!") was displayed for 250 ms. Then a fixation cross was presented for 1000 ms, one of the four IS was shown in the centre of the screen for 250 ms. The fixation cross then reappeared during the response period (2500 ms). During this time, the participant was required to respond to the IS as fast as possible but not at the expense of accuracy. Each IS image is associated with pressing a specific button. The task is divided into 4 blocks, with block 1 and 4 being unpredictable conditions, block 2 and 3 being predictable conditions. No explicit information about the underlying patterns in each block is provided to participants. Participants were simply instructed to react with speed and accuracy. During the main experiment, error feedback is removed, and participants conduct four blocks of 100 trials with short rest periods between blocks. In the first and last blocks, stimuli sequences are unpredictable with a 0.25 probability of each IS being presented on trial *t* (Figure 1.20b). Conversely, in the middle of the two blocks, the IS is drawn from a predictable first-order Markov sequence. The design creates a structure that the probability of the current stimuli *t* is conditionally dependent on the stimulus of the previous trial *t*-1. There are 16 possible

combinations that determine the relationship between the IS on trial *t* and on trial *t*-1. Importantly, the overall probability of each IS is equal across all blocks. For all correct responses, RT is calculated as the time between IS onset and the subsequent button press. Moreover, the RT in predictable conditions is further compared between probable and improbable trials. The predictability of the current trial is also quantified, t_i, based on the IS presented on the previous trial, t_i -1, given by the mutual information (MI) between consecutive IS (Harrison et al., 2006). MI is the reduction in uncertainty of the IS on the current trial *t* as a result of the knowledge of the IS on the previous trial t_i -1.

1-5-2. Computational Models

Hierarchical Drift Diffusion Model

Based on the concept of the drift diffusion model (detail in previous section), Voss & Voss (2007) proposed a fast-dm software for the parameter estimation, which provides a novel and flexible tool for fast and precise diffusion model by using partial differential equation method and Kolmogorov-Smirnov statistic for the optimisation of the parameters, which was used to apply to the behavioural data (Lerche et al., 2017).

While the drift diffusion model is a powerful tool to infer the latent psychological processes underlying simple choice decision-making, studies investigated neural mechanisms associated with evidence accumulation and decision threshold modulation often have low trial numbers in each condition, making it difficult to

estimate model parameters. Wiecki, Sofer & Frank (2013) have developed a Python-based toolbox, which uses hierarchical Bayesian parameter estimation methods to allow simultaneous estimation of individual subjective parameters and the group distribution that the parameters are drawn from, while also providing measures of uncertainty in these parameters in the posterior distribution. Figure 1.21 illustrates the framework of hierarchical drift diffusion model.

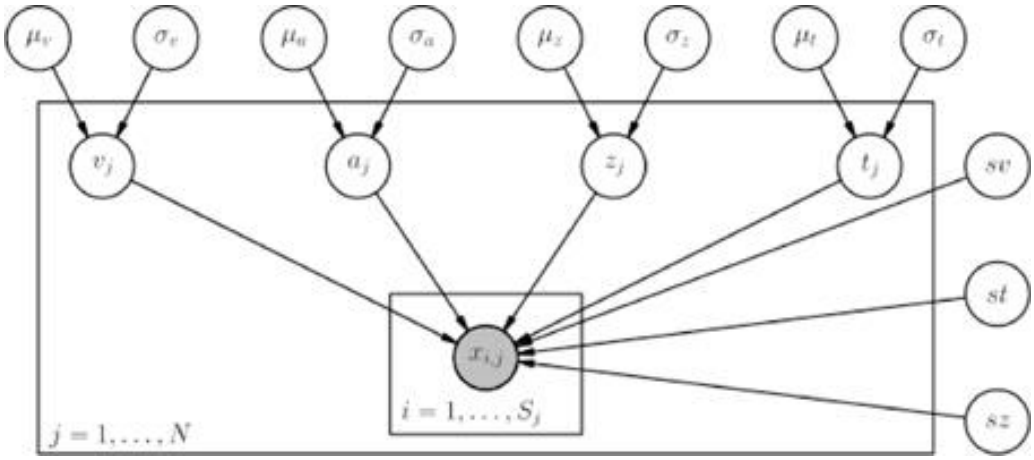

Figure 1.21 Basic graphical hierarchical model implemented by HDDM for estimation of the drift-diffusion model. Round nodes represent random variables. Shaded nodes represent observed data. Directed arrows from parents to children visualize that parameters of the child random variable are distributed according to its parents. Plates denote that multiple random variables with the same parents and children exist. The outer plate is over subjects while the inner plate is over trials. Figure from Wiecki, T., Sofer, I., and Frank, M. (2013).

Machine learning frameworks

It has been proposed that PD patients with and without ICDs showed distinct behavioural patterns that may shed lights on explaining why some patients would

develop the impulsive behaviours and the others would not (Djamshidian et al., 2012, 2014). The distinct behavioural patterns may thus be used as a factor in building predictive models that could serve as a screening tool for PD patient who are at high risk of developing ICDs as the disease progresses or induced by inappropriate treatments (e.g. high dosage of dopamine agonists). As previously discussed, PD patients have been reported to exhibit impaired perceptual decision-making processes and such impairment may lead to the onset of ICDs. To examine the potentiality of using behavioural patterns on a perceptual decision-making framework in predicting impulsive behaviours in PD patients, algorithms from the field of machine learning were used to construct predictive models. Figure 1.22 shows a general diagram for using machine learning in predictive modelling.

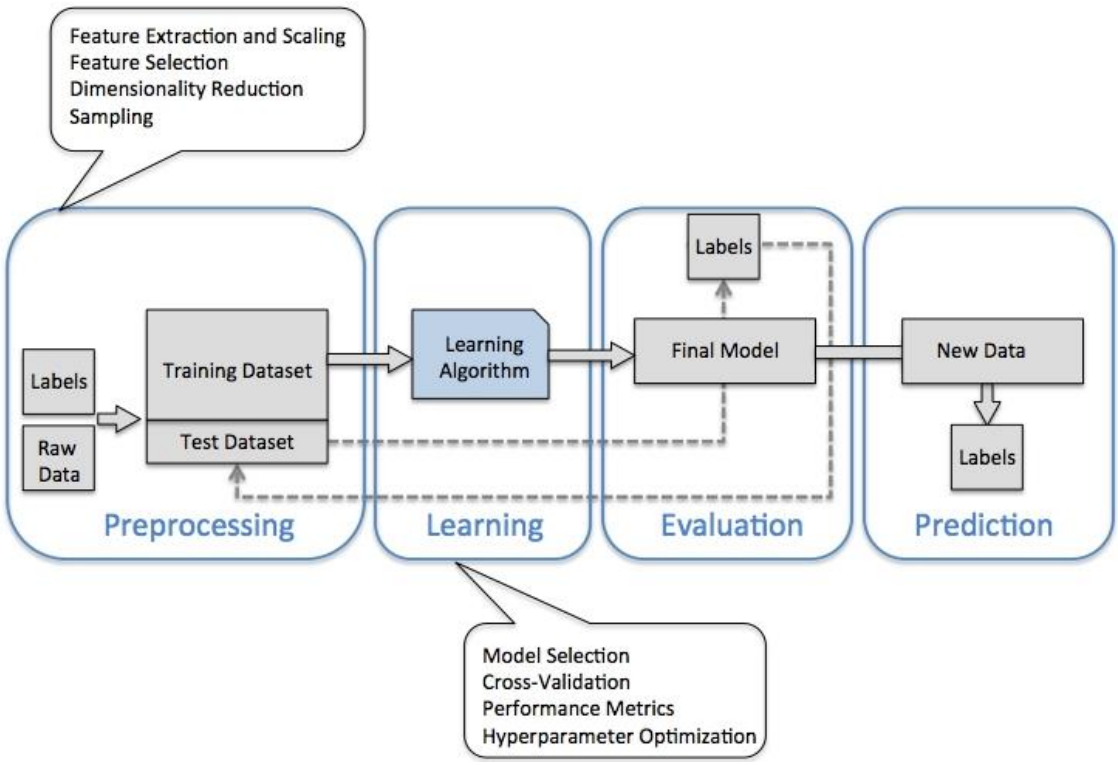

Figure 1.22 A typical workflow diagram for using machine learning in predictive

modelling. Figure from Raschka (2015).

1-5-3. Samples

All PD patients recruited for the studies had a clinical diagnosis of idiopathic Parkinson's disease according to the Parkinson's Disease UK Brain Bank criteria (Hughes, Daniel, Kilford & Lees, 1992). The severity of patients' motor symptoms and their stage of illness were rated on the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987) and the Hoehn & Yahr (1967) scale respectively. The Mini Mental State Examination (MMSE, Folstein et al, 1975) and the Beck Depression Inventory (BDI, Beck, Steer & Brown, 1996) and the Starkstein Apathy Scale (Starkstein, 2012) were respectively used to ensure that the patients are not suffering from dementia or depression or apathy at the time of assessment. Age-matched healthy controls were recruited from among the spouses and friends of the patients and through local advertising. All age-matched healthy controls did not have any neurological, psychiatric illness, history of head injury, drug or alcohol abuse.

Information from previous studies was used to measure the sample sizes necessary to obtain a statistically significant effect. For all study, the sample sizes were based on previous studies that investigated similar effects of dopaminergic medication or effects of STN DBS on perceptual decision-making processes/probabilistic reaction time task in PD patients (Galea et al., 2012; Green et al., 2013; Huang et al., 2015).

Effect sizes were reported for all the significant results to present the magnitude of the significant effects in a standardized metric that allow the practical significance, which represents the practical consequences of the findings for daily life (Lakens, 2013). The following formula provides calculation for effect size of between-subject design (given as Cohen's *d*, Cohen, 1992):

$$d = \frac{(\mu 1 - \mu 2)}{\sigma}$$

Where $\mu 1$ represents the mean of group 1, $\mu 2$ represents the mean of group 2. σ1 represents the standard deviation of group 1, whereas σ2 represents the standard deviation of group 2, and σ represents the pooled standard deviation of the two groups.

$$\sigma = \sqrt{[(\sigma 1^2 + \sigma 2^2)/2]}$$

For within-subject design, the dependence among means must be corrected; therefore the correlation between the two means needs to be considered during calculation (Morris & DeShon, 2002). Due to small sample sizes (n < 20) in all studies, Cohen's *d* may be biased in giving estimate of the population effect size, therefore the corrected effect size (Lakens, 2013), also known as Hedge's *g* (Hedges & Olkin, 1985) was reported for all the significant results:

$$\text{Hedge's } g = Cohen's\ d \times \left(1 - \frac{3}{4(n1 + n2) - 9}\right)$$

1-5-4. Ethics approval

All studies have the approval of the Joint Ethics Committee of the Institute of Neurology and The National Hospital for Neurology and Neurosurgery, London. The

ethics approval number for the project is 01/N040. All participants were provided with an information sheet and encouraged to ask questions about the procedures of the study before participation. Written informed consent was obtained from each participant prior to the investigation.

1-5-5. Statistical Analysis:

Programming languages R and relevant packages (R Core Team, 2013), Python and relevant toolboxes (Oliphant, 2007; Millman & Aivazis, 2011; Walt, Colbert & Varoquaux, 2011) and IBM SPSS 20 software were used to analyse the data and construct needed models. A mixed repeated measures design combined with a between groups design to compare patients with age-matched controls is used in most studies. For statistical analyses, reaction times (RTs) and response accuracy were measured for each participant. Multiple measurements per subjects were taken due to the repeated-measure experimental design, which violates the assumption of linear model that requires data to be independent from each other. The visual stimuli in all studies of the thesis were randomly presented to each participant and each participant performed the task repeatedly, the dependent variables thus have two forms of dependencies: for subjects and for conditions.

For the error data that were non-normally distributed and unbalanced experimental design (i.e. PD patients tested twice for OFF/ON medication or stimulation states and HCs tested only once), generalized linear mixed models (GLMM) and linear mixed model (LMM) were used to analyse the behavioural data. In addition, the models

allow the consideration of random effect such as individual difference to be taken account for. To select the best fitted model, the Akaike information criterion (AIC) was used during model selection (Bozdogan, 1987).

To determine whether PD patients and healthy controls are matched, independent t-tests were used for age, global cognition measured on MMSE, depression and apathy scores on the Beck Depression Inventory-II (DBS-II) and the Starkstein Apathy Scale (SAS). Paired t-tests were used to compare UPDRS scores OFF versus ON medication or with STN-DBS OFF versus ON stimulation for patients to determine the effect of medication or STN DBS on ameliorating motor symptoms in PD. Where necessary, a Bonferroni correction was used to adjust the p value for multiple comparisons. Due to the relatively small sample sizes in the studies, for all the differences (between- and within-subjects) that reach a significant level, the effect size was calculated to emphasise the size of the differences using Hedges' *g* as previously introduced.

Chapter 2 The acute manipulation of dopaminergic medication did not induce impaired context monitoring on a moving dots task in Parkinson's disease patients with impulse control disorders history

2-1 Abstract

To investigate the 'dopamine overdose hypothesis', which suggests that dopamine medication may induce side effects on executive functions (EFs) in PD patients, the present study tested 11 patients with Parkinson's disease (PD) who had been clinically diagnosed with impulse control disorders (ICDs) ON and OFF dopaminergic medication, and compared their performance to 14 age-matched healthy controls (HCs). Two versions of a moving dots task were used, one manipulated speed and accuracy instructions to assess the modulation of Speed and Accuracy trade-off (SAT), which is associated with the ability to dynamically switch between mental sets. The other manipulated the level of coherence (i.e. task difficulty) of the task, which are considered to be associated with information accumulation and updating in the present study. Both versions of task require abilities of 'context monitoring'. The hierarchical drift diffusion model (HDDM) was fitted to the behavioural data to further analyse the underlying mental processes related to the basic EFs during the task. The results showed that acute manipulation of dopamine medication did not have significant effects on the performance of PD patients. From the behavioural point of view, PD patients both ON and OFF dopamine medication were able to perform the task as well as age-matched healthy controls in terms of reaction time (RT) and response accuracy. Likewise, the application of HDDM to the behavioural data showed no differences between PD patients with ICD history and age-matched HCs. Taken together, the acute manipulation of dopamine medication did not induce negative effects in PD patients with ICD history. The results may be due to the ceiling effect of the task as both groups of participants showed high response accuracy and fast RTs. In addition, scores from the neuropsychological tests shows that reducing dopamine agonists in long term care for PD patients who had developed ICDs, which is a common clinical approach for treating ICDs, does not induce negative effects on cognitive function in PD patients.

2-2 Introduction

Impulse control disorders (ICDs) such as pathological gambling, shopping, binge eating, and hypersexuality involve "behaviours that are performed repetitively, excessively, and compulsively to an extent that interferes with major daily functioning" (Grant et al., 2011). In recent years, there has been increasing evidence suggesting that patients with Parkinson's disease (PD) treated with dopaminergic medication are at increased risk of developing one or more ICDs (Voon & Fox, 2007; Weintraub et al., 2015). In a cross-sectional study of 3,090 patients, the use of dopamine agonists in the treatment of the motor symptoms of PD has been shown to be associated to with 2- to 3.5- fold increased odds of developing an ICD (Weintraub et al., 2010). Such an association between dopamine agonists and the onset of ICDs is now well-established (Voon et al., 2006; Voon & Fox, 2007, Weintraub et al., 2015).

As discussed in Chapter 1, the dopamine overdose hypothesis proposed by Cools et al (2001) states that, the administration of dopamine medication to PD patients may replete dopamine-depleted regions such as the dorsal, rostral head of the caudate nucleus and the putamen, but may overstimulate relatively intact regions such as the ventral striatum in early PD, leading to poorer performance on tasks mediated through these circuits such as reversal learning (Cools et al, 2001), conditional associative learning (Gotham et al, 1988), complex discrimination learning (Swainson et al, 2000), and probabilistic classification learning (Jahanshahi et al 2010). In addition, acute manipulation of medication state in PD patients has revealed that, PD patients tested ON medication are impaired in learning from negative feedback, and fail to

make profitable decisions on certain gambling or decision-making tasks (Frank et al., 2007; Djamshidian et al., 2010; Mimura et al., 2006; Pagonabarraga et al., 2007; Euteneuer et al., 2009; Huang et al., 2015), suggesting that dopaminergic medication may interfere with basic executive functions (EFs) such as shifting (i.e. switching flexibly between tasks and/or mental sets) and updating (i.e. constant monitoring and modifying working memory contents based on sampled information) in PD. It has been proposed that the deficit in learning from negative feedback other cognitive functions may relate to dopaminergic medication masking dips in dopamine release following negative feedback (Schultz, 2007; Frank, 2005), thus the development of ICDs in PD patients has been associated with the impaired cognitive functions induced by dopamine overdose. Imaging studies that investigated the mechanisms of ICDs in PD have revealed that compared to patients without ICDs, patients with ICDs such as pathological gambling show different patterns of brain activation in brain areas implicated in inhibition and impulse control (van Eimeren et al, 2009; 2010; Wu et al, 2013), particularly in response to dopaminergic medication (van Eimeren et al 2010). Dopaminergic medication resulted in differential patterns of activation in the lateral orbitofrontal cortex, rostral cingulate, amygdala and external segment of the globus pallidus (GPe), with decreased dopamine-induced activation observed in PD patients with pathological gambling in contrast to increased dopamine-induced activation in these areas in patients without pathological gambling (van Eimeren et al, 2010). Furthermore, chronic treatment with dopaminergic medication can interfere with the phasic and tonic activity of dopaminergic neurons, which could be associated with long-term neuro-adaptation including regulation of receptor and transporter

density (Voon et al., 2017). Reduced concentrations of striatal dopamine transporter (Smith, Xie, & Weintraub, 2016; Voon et al., 2014; Vriend et al., 2014), and altered striatal and cortical dopamine homeostasis (Rao et al., 2010; Ray et al., 2012) may potentially contribute to the development of ICDs.

The ability to control behaviours in order to perform more context-appropriate actions is referred to as 'context monitoring', which requires the basic EFs such as information updating and the ability to adapt to the dynamically changing environment (i.e. shifting) (Chatham et al., 2012). While a number of studies have investigated the association between dopaminergic medication, inhibitory control and reward sensitivity as potential mechanisms of PD patients with ICDs (Rossi et al., 2010; Bentivoglio et al., 2013; Djamshidian et al., 2010; Pineau et al., 2016; Voon et al., 2010, 2011; Housden et al., 2010; Leroi et al., 2013), the aim of the present study is to investigate the acute effect of dopaminergic medication on basic EFs associated with 'context monitoring' in PD patients with ICDs, using a moving dots task. In the present thesis, context monitoring was viewed as two components: (1) speed and accuracy (SAT) modulation that is considered to be associated with shifting between different mental sets (external drives to be fast or to be accurate), and (2) the rate of information accumulation, which is viewed as a type of updating ability. When making binary decisions in such tasks, an agent must gather perceptual information until a boundary separation (in the model this boundary separation is referred to as 'boundary separation') is reached for one of the two options, then execute the action which is appropriate for that selected option.

In the present study, to determine how dopamine medication affects these two components in context monitoring in PD patients with ICDs, we used two versions of the 'moving dots' task and tested patients ON and OFF their medication. In one version, which was termed as the 'SAT' version, before each trial instructions would be presented so that the participants would be asked to either be fast or be accurate for the trial, the moving dots stimuli was set at a constant 50% coherence for all trials. In another version, we manipulated the level of coherence of the moving dots to modify the degree of decision conflict (i.e. task difficulty) so that the information needed to make responses differ between trials. A hierarchical drift diffusion model (HDDM) was fitted to the behavioural data (Wiecki et al., 2013), which enabled estimation of boundary separation, drift rate and non-decision time within a hierarchical Bayesian framework. The STA version of the task was used to investigate the ability to adapt to dynamically changing mental sets (i.e. to be fast or to be accurate), whereas the 'Difficulty' version manipulated different was used to investigate the ability to sample and update sensory information from the stimuli presented when the level of coherence/task difficulty/degree of conflict was experimentally manipulated. It was hypothesised that PD patients with ICDs would show faster reaction times and lower response accuracy when tested ON medication than OFF medication due to 'dopamine overdose hypothesis', and when compared to age-matched healthy controls (HCs). Furthermore, in a previous study we found that dopaminergic medication impaired evidence accumulation in PD patients without ICDs, particularly in the presence of decision conflict (Huang et al., 2015). On the basis of these results,

it was predicted that compared to the OFF medication state, being ON medication would influence information accumulation in high conflict (i.e. low coherence) conditions, such that the patients with ICDs would make more incorrect responses with increasing task difficulty/lower coherence versions of the task.

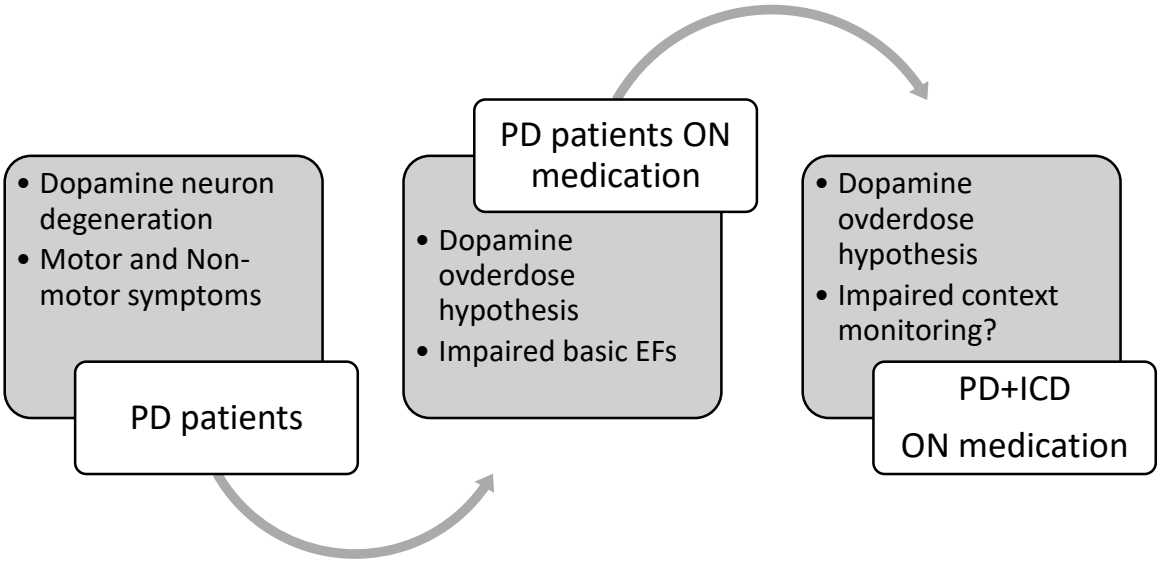

Figure 2.1 A schematic framework on the hypothesis of the present study. For Parkinson's disease (PD) patients, due to dopamine neuron degeneration, patients exhibited motor and non-motor symptoms. For PD patients ON medication, based on dopamine overdose hypothesis, patients showed impairments on basic executive functions (EFs) such as shifting, updating and inhibition. For PD patients with impulse control disorder (ICD), the development on the impulsive symptoms may be due to impaired EFs and/or abnormal reward sensitivity.

2-3 Material and methods

Participants

Eleven patients (3 females) with Parkinson's disease who had been clinically diagnosed with impulse control disorders (PD ICDs) and 14 age-matched healthy controls (HCs) (6 females) were recruited. PD patients had a clinical diagnosis of idiopathic Parkinson's disease according to the Parkinson's Disease UK Brain Bank criteria (Hughes et al., 1992). All patients had been additionally diagnosed as suffering from ICDs by a neurologist (average 6 years since last demonstrated active ICD symptoms). The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease (QUIP) was used to screen for current or past impulsive behaviours for the ICD patients (Weintraub et al., 2009; Weintraub, et al., 2012). The Mini-Mental State Examination (cut-off score of 26; Folstein et al., 1975) was used to screen for cognitive impairment/dementia and the Beck Depression Inventory-II (BDI-II, Beck et al., 1996) was used to screen for depression (cut-off score of 24). None of the patients had cognitive impairment/dementia or clinical depression. None of the healthy controls had any neurological or psychiatric illness, head injury or drug or alcohol abuse. Patients were examined by a neurologist, both OFF and ON medication, and the severity of their motor symptoms and their stage of illness were rated on the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987). Self-reported QUIP scores showed that among the eleven patients, ICDs consisted of both hypersexuality and compulsive shopping in 3, binge eating and compulsive shopping in 2, hypersexuality in 2, binge eating in 2 and repetitive punding behaviours in 2. All patients were currently on levodopa medication, with the mean levodopa equivalent dose presented in Table 2.1. Most patients reported to have previously taken the dopamine agonist Ropinirole, three were still taking the drug but

at a reduced dosage. All participants had normal or corrected-to-normal vision. The demographic and clinical details of the participants are presented in Table 2.1.

Table 2.1. Demographic and clinical details of the sample. Table shows means and in brackets standard deviations.

	HC	**PD patients with ICDs**	***P***
Age	66.79(10.46)	59.91(7.57)	p =.08
MMSE	29.43(0.64)	29.18(1.08)	p =.484
BDI-II	6.46(5.09)	15.33(1.61)	p =.001* +[1]
Digit Span	17.93(3.89)	18.18(4.17)	p =.877
UPDRS-III		OFF: 28.00 (8.56) ON: 13.67 (7.65)	p <.0001* +[2]
Onset age		49.22(8.23)	
LEDD		950.45 (383.63)	
Disease Duration		8.78 years (5.78)	
QUIP		2.27 (2.20)	

PD=Parkinson's disease; ICDs=impulse control disorders; MMSE=Mini Mental State Examination; BDI=Beck Depression Inventory; UPDRS=Unified Parkinson's Disease Rating Scale; LEDD=L-Dopa Equivalent Daily Dose; N/A=Not Applicable; NS=not significant; "*" = significant difference between groups (BDI) or ON vs. OFF medication for patients (UPDRS); +[1]= Effect size of BDI-II: Hedge's g= 2.561; +[2] = Effect size of UPDRS score III: paired sample Hedge's g= 3.824

Design & Procedure

A repeated measures design was used. All participants (patients and healthy controls) performed two versions of the moving dots task, which manipulated either speed versus accuracy instructions or level of coherence. Both tasks were performed by all participants in two testing sessions on the same day. For practical reasons, patients were first tested in the "OFF" state, after overnight withdrawal of dopaminergic medication for approximately 12–16 h. After finishing the session off medication they took their dopaminergic medication and were tested in the "ON" medication state at least one hour later. The ON an OFF medication states were confirmed by the UPDRS III ratings by a neurologist, which indicated that the motor symptoms of PD patients were significantly improved when they took their dopaminergic medication compared to the OFF state ($t(10)=8.39$, $p<.001$). The study was approved by the joint ethics committee of the UCL Institute of Neurology and the National Hospital for Neurology & Neurosurgery. Informed consent was obtained from all participants.

The moving dots task

In each session participants performed two versions of the moving dots task.

The "speed–accuracy" version of the moving-dots task (Britten et al., 1992) required participants to decide whether a cloud of dots moved to the left or the right of the screen. The participants were given one of two different instructions before every trial: FAST (for speed) and ACCURATE (for accuracy), while the level of coherence was kept constant at 50%, that is half of the 120 dots moved coherently in the same direction, while the remainder moved randomly. The participants then decided on

the direction of the moving dots by pressing one of two buttons with either their left (for dots moving left) or right (for dots moving right) index finger according to the instruction. The cues were pseudo-randomly intermixed and there were equal numbers of FAST and ACCURATE cues in a block of 100 trials. At the end of each trial, participants received feedback, which depended on the previously presented cue. When Speed was emphasized, whenever the participants made a response within 500 ms, the feedback 'in time' was presented, otherwise a 'too slow' feedback. When Accuracy was emphasized, participants received the feedback 'correct' or 'incorrect' depending on their responses. 'No response' was presented on the screen if the participants failed to make any response on the trial within a time-frame of 1500ms.

In the "task difficulty" version of the moving-dots, the participants were also required to decide the direction in which a cloud of dots moved. They were instructed to do the task as fast and as accurately as possible. No cues for speed or accuracy were used in this task. The coherence ("difficulty") level of the moving dots were set at 5%, 10%, 15%, 25%, 35% and 50%, making it harder (5%) or easier (50%) to decide the direction of the moving dots, since the higher the level of coherence was, the easier it was to judge the direction of the moving cloud of dots, thus leading to faster responses. At the end of each trial, participants received the feedback "incorrect", "correct" or "no response" depending on their responses.

The speed and accuracy version of the task contained two blocks with 100 trials each, whereas the difficulty version of the task contained one block with 120 trials. For

each of the two tasks, the numbers of trials were selected to obtain reliable measures of perceptual decision-making while at the same time avoiding causing fatigue for the patients. Figure 2.2 illustrates the speed and accuracy version of the task.

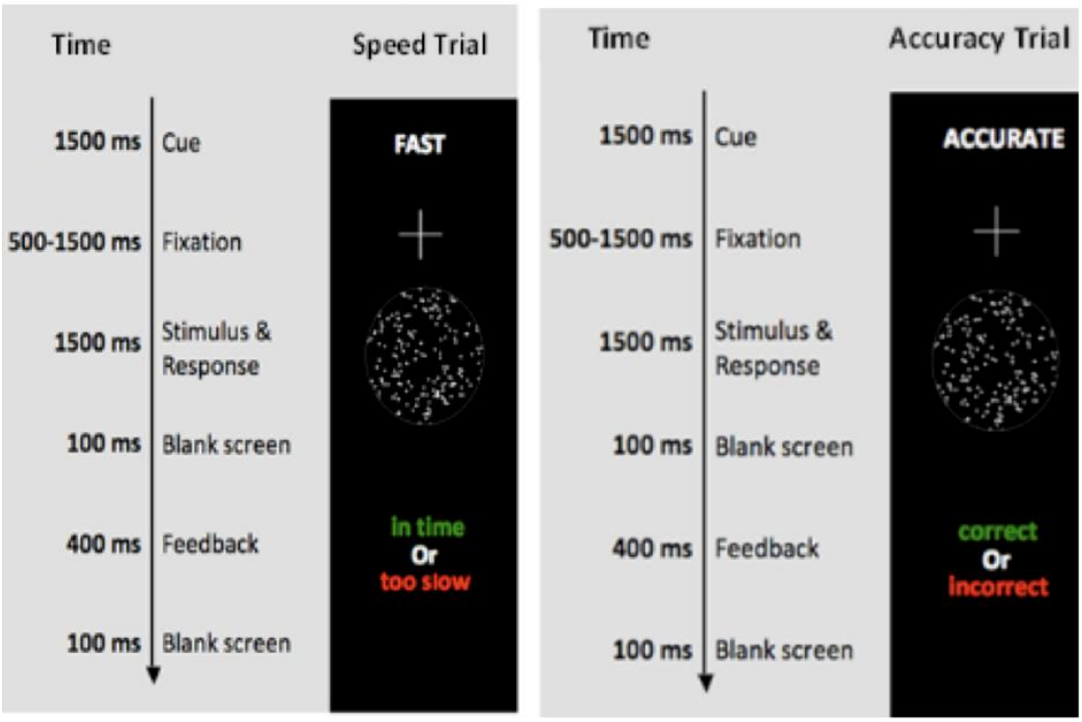

Figure 2.2 The speed–accuracy version of the moving dots task. The task difficulty version of the task was similar but without the speed/accuracy instructions and the coherence of the dots varied from 5%, 10%, 15%, 25%, 35% to 50%.

Data Analysis

R (R Core Team, 2013) and IBM SPSS software were used to analyze the data. Reaction times (RTs) to the nearest s and response accuracy were measured as dependent variables. A linear mixed model (LMM) was used to fit reaction time with group (HC versus PD ICD), time (T1/OFF versus T2/ON), Type (i.e. different instructions, for Speed version of the task) or coherence (for Difficulty version of the

task) as fixed effects. Subject was assigned as a random effect to account for subject-by-subject variation in overall RTs. In addition to a random intercept, a random slope in Type (for Speed version of the task) or Coherence (for Difficulty version of the task) has also been added into the model, which means that the rate at which individuals made decisions based on the Speed/Accuracy instructions or the coherence of moving dots is different from person to person. Assuming the fixed effect of Coherence being positive, if an individual has a positive random effect, it suggests that the individual made responses more quickly with higher coherence level, while a negative random effect means that an individual would make slower responses with higher coherence level. Log base 10 transformation was performed to reduce the skewness of the data. To construct the mixed model, R package lme4 (Bates, Maechler & Bolker, 2012) was used. The Maximum Llikelihood (ML) approach was used for parameter estimation. The Likelihood Ratio Test was used as a mean to attain p-values of the fixed effects, which compared models with full factors and reduced factors to determine the significance of a fixed effect.

A generalized linear mixed model was used to fit the response accuracy data due to the data being non-normal. For the present data a binomial distribution with a logistic link was selected to construct the model, at the same time it was specified that the response accuracy could vary randomly across subjects. ML approach with Laplace approximation was used for parameter estimation. Group (HC versus PD ICD), time (T1/OFF versus T2/ON), instruction for Speed version of the task and coherence for Difficulty version of the task were assigned as fixed effects. Subject was assigned as a

random effect to account for by-subject variation in overall response accuracy. $p<.05$ was used as a criterion for statistical significance. The Akaike information criterion (AIC), which estimates the relative quality of a statistical model given a specified data set, was used for model selection (Bozdogan, 1987). The relative quality of the model is indicated by the calculated information loss, therefore the model that has the minimised AIC would be chosen as the most fitted model given the specified dataset.

Hierarchical Drift Diffusion Model

The diffusion model has been widely used in investigating perceptual decision-making processes especially two-forced-choice tasks (Voss & Voss, 2007; Voss, Voss, & Lerche, 2015; Ratcliff, 1978; Ratcliff & McKoon, 2008). In the diffusion model, three variables were calculated and discussed: the boundary separation, the non-decision time and the drift rate. The boundary separation (a) represents the response threshold to reach a decision. Figure 2.3 illustrates the change of boundary separation in SAT. The longer the distance between the starting point and boundary separation, the longer the response time is and the longer it takes to make a decision, and fewer errors are likely to occur. Conversely, the shorter the distance between the starting point and the boundary separation, the faster a decision would be made, but the person is more likely to make errors. The decision-making process is defined as having three phases: perceptual processing (processing the stimulus) with a certain duration, decision phase with a certain duration and response phase with a certain duration. The non-decision time (t0) is defined as the sum of the perceptual

processing time plus the response time. Drift rate (v) represents the speed of the information accumulation process which begins from the starting point till one of the two decision boundaries is met. For the current experiment it represents the certainty/confidence to distinguish between noise and signal. A higher drift rate suggests a higher certainty/confidence to distinguish noise and signal and faster rate of information accumulation, which should be the case on easier higher coherence trials; whereas a lower drift rate at lower levels of coherence reflects a lower certainty/confidence to distinguish between noise and signal and to choose the direction of the moving dots on the harder trials and hence a slower rate of information accumulation.

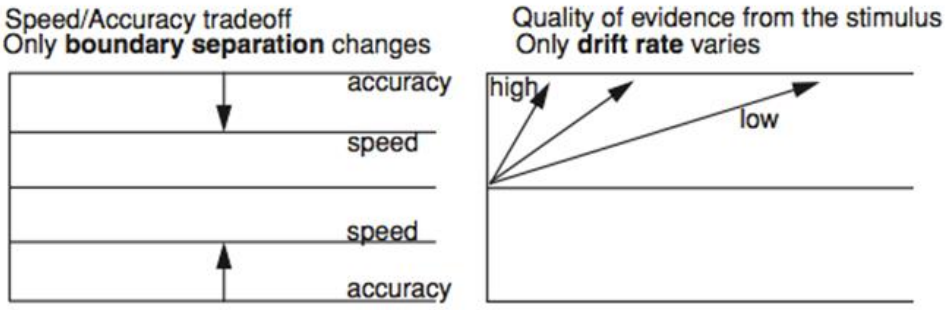

Figure 2.3 Simulated diffusion processes. The Left Panel: boundary separation changes with speed versus accuracy instructions. The Right Panel: drift rate varies with difficulty in stimulus discrimination and level of coherence. Figure from Ratcliff, R. and McKoon, G. (2008).

To quantitatively fit the diffusion model to the behavioural data, a Python-based

hierarchical drift diffusion model (HDDM) toolbox (Wiecki et al., 2013) was used. HDDM uses hierarchical Bayesian parameter estimation methods for simultaneous estimation of subject parameters and the group distribution from which they are drawn, at the same time providing measures of uncertainty in the posterior distribution (Figure 2.4). In addition, HDDM requires less data per subject/condition than the non-hierarchical method, is able to deal with outliers and it allows for Bayesian data analysis. HDDM includes a regression model that allows estimation of trial-by-trial influences of a covariate onto model parameters. In the present study, HDDM was fitted to the behavioural data using the 'HDDMRegressor' function, which allows individual parameters to be described by a linear model specification. One of the benefits of estimating a model in a Bayesian framework is that significant testing can be directly performed on the posterior rather than relying on frequentist statistics. The Bayesian approach uses probability to quantify uncertainty and makes more precise probability statements about the state of the system by calculating the probability of a model given collected data (i.e. P(model | data)) (Puga, Krzywinski & Altman, 2015).

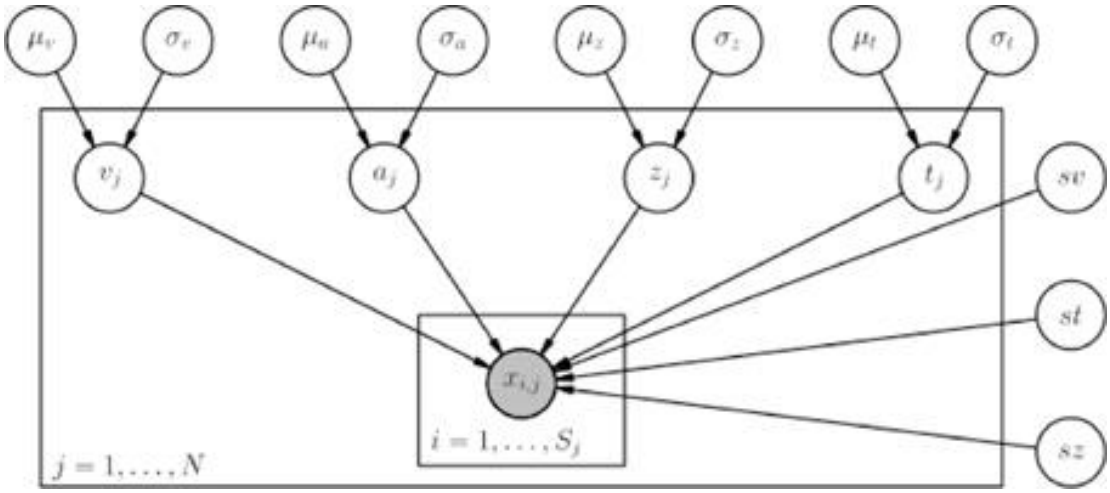

Figure 2.4 Basic graphical hierarchical model implemented by HDDM for estimation of the drift-diffusion model. Round nodes represent random variables. Shaded nodes represent observed data. Directed arrows from parents to children visualize that parameters of the child random variable are distributed according to its parents. Plates denote that multiple random variables with the same parents and children exist. The outer plate is over subjects while the inner plate is over trials. Figure from Wiecki, T., Sofer, I., and Frank, M. (2008).

In addition, the HDDM uses Markov-Chain Monte Carlo (MCMC) to estimate the joint posterior distribution of all model parameters, which requires the chains of the model to have properly converged. When using the MCMC sampling, it is critical to examine the convergence of the model to make sure that the modelling is sampling from the actual posterior distribution. While there is no 100% fool-proof method to assess whether the chains are converged, one of the methods is to look at the traces of the posteriors. To visually examine the convergence of the model constructed for the study, the trace, the autocorrelation and the marginal posteriors were plotted. A

converged chain would have a stationary trace, low auto-correlation and normally distributed subject and group mean posteriors, while group variability posteriors are Gamma distributed. For brevity the figures examining the convergence of the created model were not shown here-please see Appendix A for the figures and the codes for creating the HDDMs. The models created in the present study seemed to be well-converged.

2-4 Results

Dopaminergic medication produced a significant improvement of the motor symptoms of PD, as reflected by a reduction of the UPDRS-III ratings ($t(10)=8.39$, $p<.0001$, paired sample Hedge's $g= 3.824$; see Table 2.2).

2-4.1 The analysis of data from the Speed/Accuracy version of the task

Analysis of the Behavioural data for the Speed/Accuracy version of the task

A LMM was used to analyse RTs of correct trials, which specified Group (HC/ PD ICD), Time (T1/OFF medication, T2/ON medication) and Type of instruction (Speed/ Accuracy) specified as the fixed effects and the subject specified as a random effect with Type as a random slope. In the LMM model contrast, all levels of the categorical variables are compared to the base level (reference category). Here the base levels are: HC (for Group), T1/OFF medication (for Time) and Accuracy (for Type). All effects are estimated with respect to the base levels.

The model showed that all participants had faster RTs when Speed was emphasised

than when Accuracy was emphasised (t(9957)=-15.09, p<.0001, Hedge's g=1.08). There was no difference on RTs for PD patients with ICD history ON versus OFF medication (t(9957)=-1.32, p=0.187) or for PD patients versus age-matched HCs (t(26)=0.15, p=0.881). RTs did not differ for age-matched HCs for the Time 1 versus Time 2 assessments (t(9957)=-0.66, p=0.527). No significant interactions were found. Figure 2.4 illustrates the results. Together the results suggest that (1) all participants adjusted responses with SAT, reflected as faster RTs when Speed was emphasized, (2) there was no effect of acute manipulation of dopaminergic medication on RTs for PD patients with ICD history and (3) PD patients with ICD history were able to perform the task as fast as age-matched HCs.

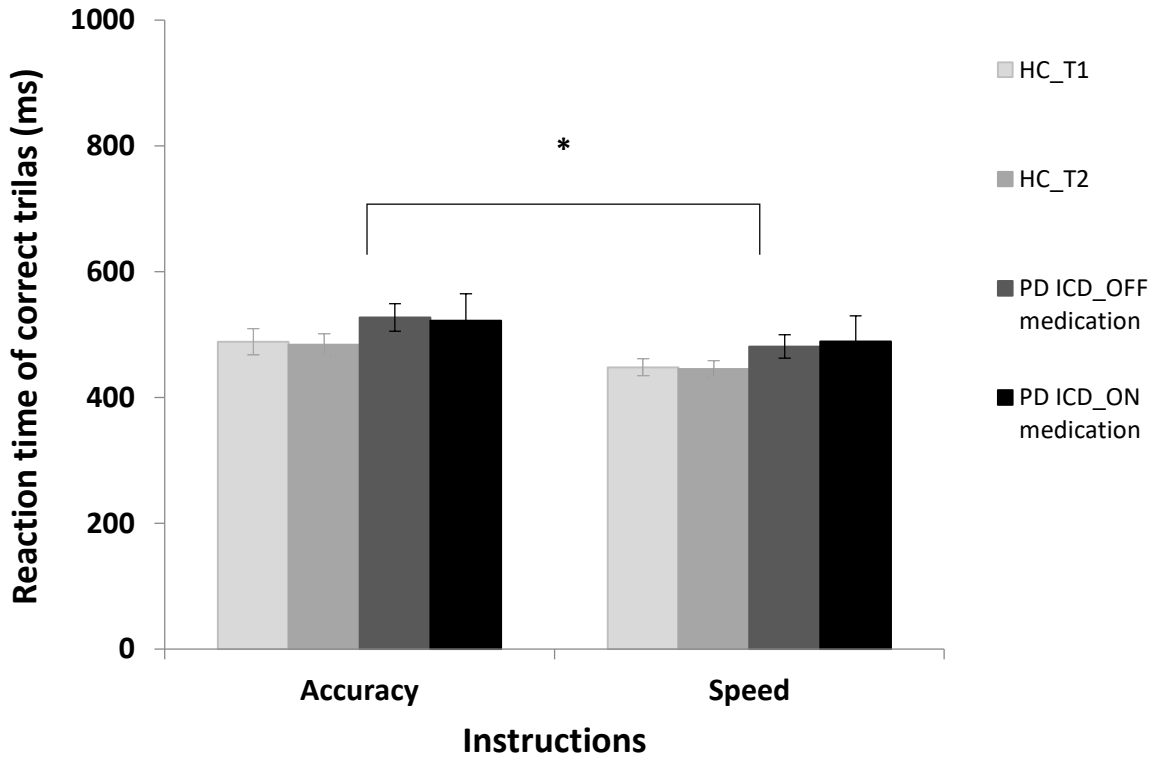

Figure 2.5 Reaction time (s) for PD patients with ICD history tested ON versus

OFF medication and age-matched healthy controls (HCs) assessed twice (T1 versus T2) under Speed and Accuracy instructions. Error bars are the standard error of the means. The asterisk symbols denote statistically significant differences. T1=Time 1, T2= Time 2.

A GLMM was used to analyse response accuracy, which specified Group (HC/ PD ICD), Time (T1/OFF medication, T2/ON medication) and Type of instruction (Speed/ Accuracy) specified as the fixed effects and the subject was specified as a random effect using binomial distribution. The model showed that all participants had higher response accuracy when Accuracy was emphasised than when Speed was emphasised (Z=-3.09, p=0.002, Hedge's *g*= 0.72). There was no difference in response accuracy between PD patients with ICD history and age-matched HCs (Z=0.04, p=0.968). No difference was found in response accuracy between PD patients with ICD history ON versus OFF medication (Z=-0.01, p=0.990). Age-matched HCs performed equally accurately at Time 1 versus Time 2 (Z=-0.25, p=0.801). No interactions were found. Figure 2.5 illustrates the results. Taken together, the results suggest that (1) all participants modulated response accuracy according to SAT, reflecting a lower accuracy when Speed was emphasized, (2) there was no effect of acute manipulation of dopaminergic medication on response accuracy for PD patients with ICD history or repeated assessment for HCs and (3) PD patients with ICD history performed the task as accurately as age-matched HCs.

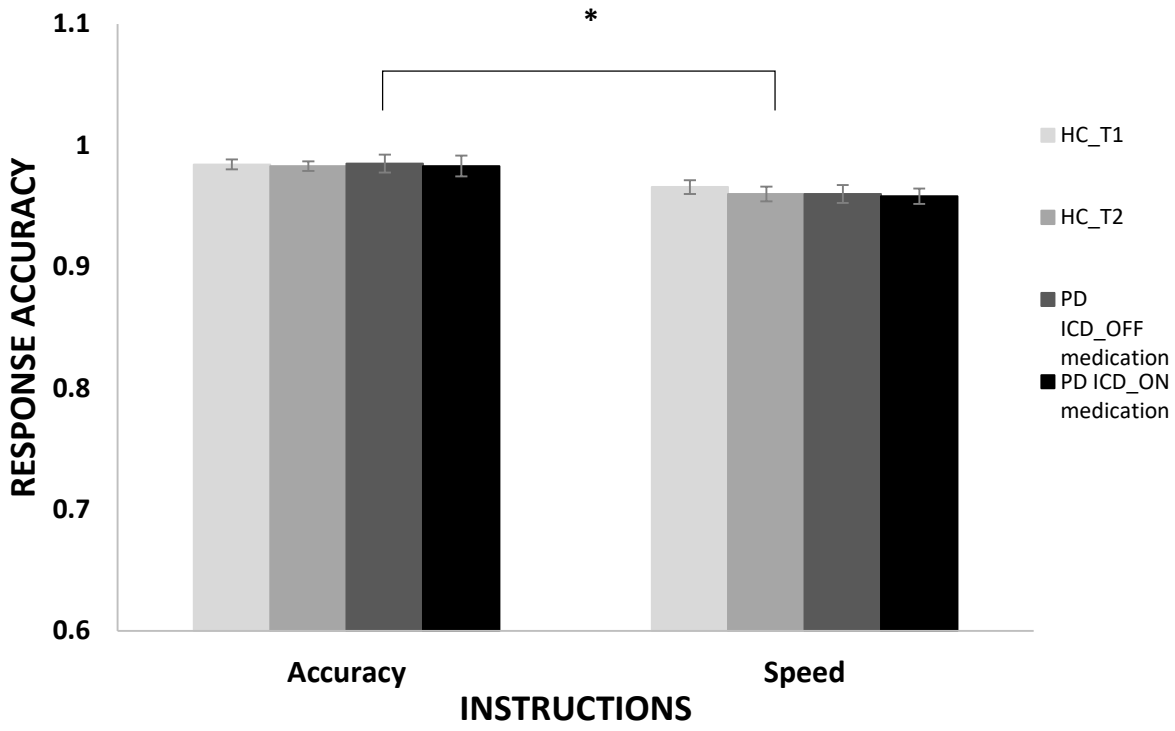

Figure 2.6 Response accuracy between PD patients with ICD history (ON versus OFF medication) and age-matched healthy controls (HCs) (T1 versus T2) under Speed and Accuracy instructions. Standard error means are presented as the error bars. The asterisk symbols denote statistically significant difference. T1=Time 1, T2= Time 2.

Hierarchical drift diffusion model (HDDM) fitted to the behavioural data of the Speed-Accuracy trade-off (SAT) version of the task

The above results show that Speed and Accuracy instructions had a strong impact on RTs and response accuracy for both PD patients with ICD history and age-matched HCs. However, no acute effect of dopaminergic medication was found on the behavioural data and no difference was found between PD patients and HCs.

To investigate how experimental manipulations affect the underlying mental processes of moving dots tasks, the HDDM was used to fit the behavioural data. In the HDDM, the posterior distributions of three model parameters (i.e. the boundary separation, the non-decision time and the drift rate) were estimated as a function of task manipulations and their interactions. In the SAT version of the task, drift rate was considered to be unaffected by the Speed/Accuracy instructions because it was hypothesised that the drift rate was mainly associated with the quality of sensory evidence provided (e.g. coherence level, as manipulated in the Difficulty version of the task discussed in later sections). Three main factors were considered for behavioural switching in the model: Type of Instruction (Speed/ Accuracy), Time (T1 (OFF medication)/ T2(ON medication)), and Group (HC/ PD ICD). Here an HDDM was constructed assuming that the boundary separation (a) and non-decision time (t), would be affected by all three factors, whereas drift rate (v) would be affected by factors Time and Group. As noted above, the boundary separation determines when to make responses, whereas non-decision time represents the time for non-decision processes such as stimulus encoding and response execution, and drift rate indicates

the rate of information accumulation among participants. The effects of factors are expressed relative to the intercept conditions. The base levels for the categorical variables are HCs (for Group), T1/OFF medication (for Time) and Accuracy (for Type).

The main three goals of the SAT version of the task were to determine (1) whether the boundary separation for Speed instruction is lower than for Accuracy instruction that leads to faster but error-prone decisions, (2) whether the acute manipulation of dopaminergic medication would decrease the boundary separation for PD patients with ICD history (particularly when Speed was emphasized) and (3) whether the boundary separation for PD patients with ICD history is lower than for HCs. The HDDM showed that all participants had lower boundary separation when Speed was emphasised than when Accuracy was emphasised as most of the regression coefficients were smaller than zero. No difference on boundary separation was found between T1/OFF medication and T2/ON medication as the regression coefficient overlaps with zero. In addition, for all participants the effect of Speed instruction on decreasing boundary separation was enhanced during Time 2 as most of the regression coefficients were smaller than zero. There was no difference in boundary separation between PD patients with ICD history and age-matched HCs, as the regression coefficient overlaps with zero. Moreover, the HDDM showed a trend that PD patients with ICD history had lower drift rate than age-matched HCs as the regression coefficient is mostly smaller than zero, which suggests that PD patients with ICD history had a tendency to have lower drift rate when during information

accumulation. No significant interactions were found. The details of the created HDDM were presented in Appendix A.

Taken together, the results showed that (1) all participants had lower boundary separations when Speed was emphasised than when Accuracy was emphasised, (2) the acute manipulation of dopaminergic medication did not produce negative effect on boundary separation modulation for PD patients with ICD history, (3) PD patients and age-matched HCs did not differ in boundary separation modulation during Speed/Accuracy trade-off.

2-4.2 The analysis of data from the Difficulty version of the task

Analysis of the Behavioural data from the Difficulty version of the task

In the present section data from the Difficulty version of the task were analysed and presented. A LMM was used for analysing the RTs, with Group (HC/ PD ICD), Time (T1/OFF, T2/ON) and coherence Level (5%, 10%, 15%, 25%, 35% and 50%) specified as the fixed effect and the subject was specified as a random effect with Coherence as a random slope (Figure 2.11). The base levels of the categorical variables are HC (for Group), 5% (for Level) and T1/OFF medication (for Time). All levels of a factor are compared to the base level. All effects are estimated with respect to the base levels.

The model showed that RTs were significantly decreased as coherence level increased (10%: t(5373)=-3.67, p<.0001, Hedge's *g*=; 15%: t(5373)=-5.53, p<.0001, Hedge's

g=; 25%: t(5373)=-12.33, p<.0001; Hedge's *g*=, 35%: t(5373)=-14.22, p<.0001, Hedge's *g*=; 50%: t(5373)=-15.70, p<.0001, Hedge's *g*=). There was no difference in RTs for PD patients with ICD history ON versus OFF medication (t(5373)=-0.82, p=0.413). In addition, there was no difference in RTs between PD patients with ICD history and age-matched HCs (t(34)=0.01, p=0.990). No significant interaction was found. Figure 2.7 illustrates the results. Together the results suggest that (1) all participants responded equally well to different coherence levels, reflected as faster RTs during high coherence trials, (2) the acute manipulation of dopaminergic medication did not have any effect on RTs for PD patients with ICD history, and (3) PD patients were able to perform the task as fast as age-matched HCs.

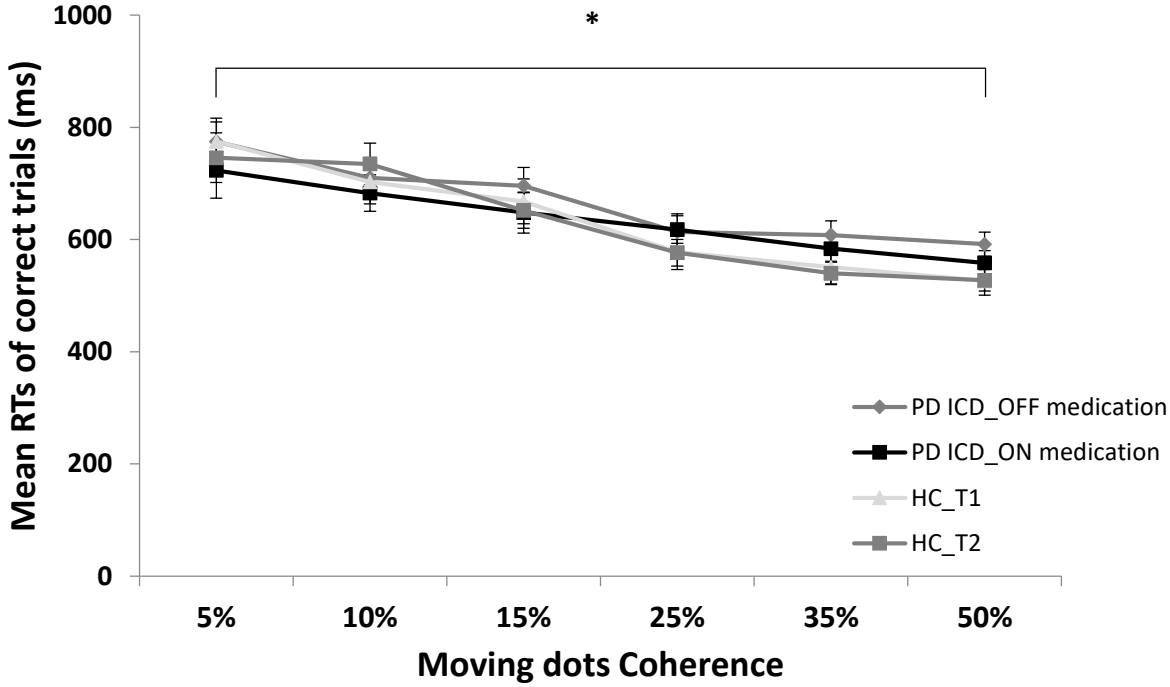

Figure 2.7 Reaction times in seconds (s) for PD patients with ICD history (ON versus OFF medication) and age-matched healthy controls (HCs) (T1 versus T2)

under different coherence levels of the moving dots. The error bars are standard error of the mean. The asterisk symbols denote significant differences as a function of level of coherence. T1=Time 1, T2= Time 2.

A GLMM was used for analysing response accuracy, with Group (HC/ PD ICD), Time (T1/OFF, T2/ON) and Level (5%/ 10%/ 15%/ 25%/ 35%/ 50%) specified as the fixed effect and the subject was specified as a random effect with Coherence as a random slope. The base levels of the categorical variables are HC (for Group), 5% (for Level) and T1/OFF medication (for Time). All levels of a factor are compared to the base level. All effects are estimated with respect to the base levels. The model showed that response accuracy was significantly increased as coherence level increased (10%: Z=3.80, p<.0001, Hedge's *g*=0.41; 15%: Z=6.48, p<.0001, Hedge's *g*=0.56; 25%: Z=6.16, p<.0001; Hedge's *g*=0.64, 35%: Z=-5.88, p<.0001, Hedge's *g*=0.89; 50%: Z=5.89, p<.0001, Hedge's *g*=1.04). There was no difference in response accuracy for PD patients with ICD history ON versus OFF medication (Z=-1.49, p=0.136). In addition, there was no difference in response accuracy between PD patients with ICD history and age-matched HCs (Z=-0.23, p=0.819). No significant interactions were found. Figure 2.8 illustrates the results of the model. Together the results suggest that (1) all participants responded equally well to the coherence levels, reflected as higher response accuracy during high coherence level trials, (2) the acute manipulation of dopaminergic medication did not have any effect on response accuracy for PD patients with ICD history, and (3) PD patients were able to perform the task as well as age-matched HCs.

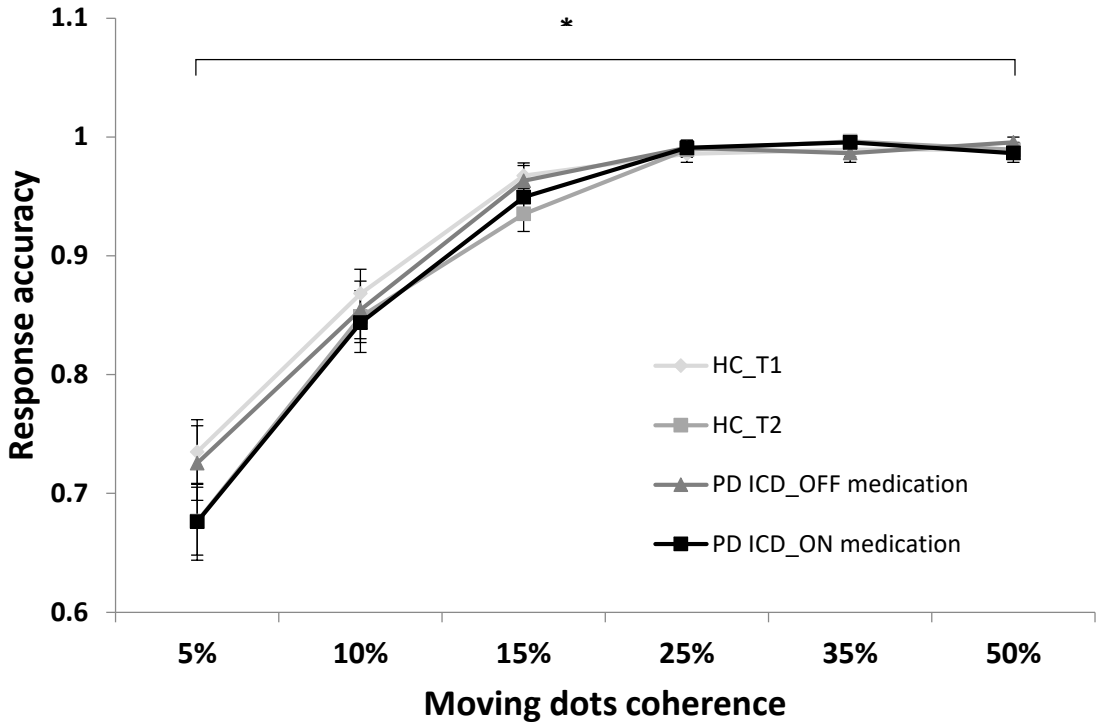

Figure 2.8 Response accuracy for PD patients with ICD history (ON versus OFF medication) and age-matched healthy controls (HCs) (T1 versus T2) under different coherence levels of the moving dots. The error bars are standard error of the mean. The asterisk symbols denote significant differences. T1=Time 1, T2= Time 2.

Hierarchical drift diffusion model fitted to the behavioural data of the Difficulty version of the task

As previously introduced, in the HDDM, three model parameters: the boundary separation (a), the non-decision time (t) and the drift rate (v) were estimated under the effects and the interactions of experimental manipulations. In the Difficulty version of the task, drift rate was considered to be associated with the ability of extracting sensory information in guiding perceptual decision-making. Such an ability is hypothesised to be associated with the quality of sensory information (i.e. Coherence levels). In addition, boundary separation and non-decision time were considered unaffected by the Coherence level because it was hypothesised that both factors are mainly associated with the Speed/Accuracy trade-offs (as manipulated in the SAT version of the task discussed in the previous section).

Here the main three goals of the Difficulty version of the task were to assess (1) how decisions conflict/level of task difficult/coherence affects sensory evidence accumulation - i.e. if drift rate would be higher when the coherence levels were higher, leading to more accurate and faster RTs, (2) how drift rate differs between PD patients with ICD history when ON versus OFF medication, and (3) how drift rate differs between PD patients with ICD history and age-matched HCs. Three main factors were considered in the model: Level (as in coherence levels) (10%/ 15%/ 25%/ 35%/ 50%), Time (T1/ T2), and Group (PD ICD/ HC). Here an HDDM was constructed assuming that the boundary separation (a) and non-decision time (t), of which the former determines when to make responses whereas the later represents time for non-decision

processes such as stimulus encoding and response execution, would be affected by factors Time and Group, whereas drift rate (v) was considered to be affected by all factors.

The model shows that all participants had higher drift rate when coherence level was high as the regression coefficient was larger than zero. There was no difference in drift rate between PD patients with ICD history and HCs as the regression coefficient overlaps with zero. For all participants, boundary separation was lower during Time 2 than Time 1 as most of the regression coefficients were smaller than zero. There was no difference in boundary separation between PD patients with ICD history and age-matched HCs as the regression coefficient overlaps with zero. In addition, for all participants non-decision time was higher during Time 2 than Time 1 as most of the regression coefficient were larger than zero. There was no difference in non-decision time between PD patients with ICD history and age-matched HCs as the regression coefficient overlaps with zero. The details of the created HDDM were presented in Appendix A. Table 2.2 summarises the findings of the study.

Table 2.2 The main findings of the effect of speed-accuracy instructions and task difficulty on the different variables of the moving dots task

	Speed/Accuracy version of the task	**Difficulty version of the task**
Behavioural data (RTs, Response Accuracy)	➢ All participants had faster RTs and lower response accuracy when Speed was emphasized. ➢ The acute manipulation of dopaminergic medication had no effects on the behavioural data. ➢ There was no difference between PD patients with ICD history and age-matched HCs.	➢ All participants had faster RTs and higher response accuracy when coherence level was high. ➢ The acute manipulation of dopaminergic medication had no effects on the behavioural data. ➢ There was no difference between PD patients with ICD history and age-matched HCs.
Parameters derived from the HDDMs (boundary separation, drift rate and non-decision time)	➢ For all participants, boundary separation was lower when Speed was emphasized than when Accuracy was emphasized. ➢ For all participants, non-decision time was lower when Speed was emphasized than when Accuracy was emphasized. ➢ PD patients with ICD history had a tendency to have lower drift rate than age-matched HCs.	➢ For all participants, boundary separation was lower during T2/ON medication than T1/OFF medication. ➢ For all participants, non-decision time was higher during T2/ON medication than T1/OFF medication. ➢ For all participants, drift rate was higher during T2/ON medication and when coherence levels were high.

RTs= reaction times, HDDM= hierarchical drift diffusion model, T2= Time 2, HCs= healthy controls

Correlational analysis with levodopa-equivalent dose and Power analysis

Because of the relatively small number of participants (n=11 for PD ICDs; n=14 for HCs), a power analysis was performed on the findings between PD patients ON versus OFF medication, and between PD patients and age-matched HCs. For behavioural comparison between PD patients ON versus OFF medication, the effect sizes were all below 0.05 (Hedge's g <0.05), and the statistical power equates to 0.05. To increase the power up to 0.95, more than 10000 participants would be needed for each group, which suggests that the non-significant results between PD patients with ICD history ON versus OFF medication are reliable. Moreover, for behavioural data compared between PD patients with ICD history and HCs, the effect sizes were all below 0.05 (Hedge's g <0.05), and the statistical power equates to 0.05. To increase the power up to 0.95, at least 10375 participants would be needed for each group, the analysis thus suggests that the non-significant results between PD patients with ICD history and age-matched HCs are reliable. In addition, seven of the PD ICD patients were on dopamine agonists in addition to levodopa. As expected, the levodopa equivalent daily dose was significantly higher in those who took both dopamine agonists and levodopa compared to those who took levodopa only ($t(9)=-3.97$, $p=.003$). However, when the results of the patients with or without additional dopamine agonist medication were analyzed, there were no differences on any of the behavioural measures. The correlation of the levodopa equivalent daily dose was examined for each patient with the RT measures. None of these correlations were of notable magnitude or significant.

2-5 Discussion

Behaviourally, the results showed that when under Speed instruction, all participants had lower response accuracy and faster RTs, which suggest that all participants demonstrated SAT when making perceptual decisions. On the other hand, when coherence level was high, participants had faster RTs and better response accuracy, indicating that extent of task difficulty/decision conflict (i.e. the quality of the sensory information) plays an important role in guiding behaviours. These significant effects of task manipulation indicated that the two versions of the task were reliable in assessing the mental processes of SAT modulation and information accumulation across the two groups, and that all participants had been able to follow the instructions. Moreover, for the SAT version of the task all participants had faster RTs (< 500 ms), whereas for the Difficulty version of the task even for the same dots coherence (50%), RTs were slower (> 500 ms). This could reflect as the task-induced context for performing the two tasks: as the SAT version of the task introduced the speed pressure when making responses, participants would hold the information in mind therefore overall the RTs were faster in the STA version task than the Difficulty version of the task (without the demand to make faster responses). Contrary to predictions, no acute effect of medication was found on task performance for PD patients with ICD history. Surprisingly, no difference was found between PD patients with ICD history and age-matched HCs.

Potential reasons for the contrary-to-prediction results

Despite the fact that sample size was relatively small in the present study, power

analysis has shown that the non-significant behavioural results were reliable. A few reasons may contribute to the non-significant results of the present study: firstly, despite the significant effects of task manipulations such as coherence and SAT instructions, the tasks selected may have a ceiling effect. As the behavioural data shown, the response accuracy for all participants were more than 50% even for the difficult trails, and for the SAT version of the task both groups had a response accuracy as high as more than 95%, suggesting that the task may not be challenging enough to reflect the effects of medication, as well as the difference between patient group and age-matched healthy control group. Secondly, in the current study the recruited PD ICD patients did not have active ICD symptoms. Due to difficulties in recruiting for PD patients with active ICD symptoms, we recruited PD patients with ICD history instead. Reducing or withdrawing dopamine agonist intake, which is a common clinical treatment for PD ICD, may have contributed to the non-significant effect of the medication in the present study. PD patients recruited for the study had received adjustment on their medication to treat ICDs, therefore their current medication treatments may be unlikely to induce side effects on EFs. Although a study has demonstrated that treated PD patients without clinically apparent ICDs still exhibited impairments in subjectively accumulating sufficient information when making decisions in a beads task (Djamshidian et al., 2012), in the present study we did not find difference on task performance between the two groups. Thirdly, due to practical reasons, PD ICD patients were assessed first then ON medication. Such an experimental design prevented the separation between medication effects and practice effects. Results from the HDDMs revealed some effects of Time (practice) on

boundary separation, drift rate and non-decision time even though there was no difference between T1/OFF medication and T2/ON medication on the behavioural data (RTs and response accuracy). The results thus indicate that practice effects influence the underlying mental processes when making performing the moving dots tasks. Future studies attempt to examine the medication effects should introduce a counter-balanced task design. Fourthly, the present study is consistent with previous studies showing that PD patients with active ICDs did not show deficits in tasks that manipulate decision conflict such as the Simon task (Wylie et al., 2012) and the Stroop interference task (Djamshidian et al., 2011). Fifthly, the moving dots paradigm has been proposed to be related to motor inhibition (Eagle, Bari, & Robbins, 2008; Djamshidian et al., 2014; Sharma, Markon, & Clark, 2014), the present results are consistent with previous studies in showing that PD patients with active ICD symptoms/ICD history have no deficits on motor inhibition (Claassen et al., 2015; Leroi et al., 2013). In spite of the negative results, the present study could be further discussed in two ways: (1) from the dopamine medication point of view and (2) from PD patients who developed ICDs point of view.

Dopamine overdose hypothesis

In the present study, the acute manipulation of dopamine medication did not produce any effects (neither negative nor positive effects) on task performance, which may result from the ceiling effect of the tasks being not challenging enough to reflect any difference (i.e. response accuracy higher than 95% for both groups). However, a pervious study using the exact same task procedure has found a significant negative

effect of medication on overall response accuracy in PD patients without ICD history compared to age-matched HCs (Huang et al., 2015). Such an inconsistent result may be due to (1) individual variance on task performance, (2) different statistical analysis methods, and (3) PD patients with ICD history (average age: 59.91) were younger compared to those who did not have ICD history recruited in previous study (average age: 61.62; Huang et al., 2015). In addition to the ceiling effect, the results may suggest that the moving dots tasks are suboptimal in examining dopamine overdose hypothesis. As discussed previously, PD patients treated with dopamine medication may show deficits on reversal learning (Cools et al, 2001), conditional associative learning (Gotham et al, 1988), complex discrimination learning (Swainson et al, 2000), probabilistic classification learning (Jahanshahi et al 2010), learning from negative feedback, and fail to make profitable decisions on certain gambling or decision-making tasks (Frank et al., 2007; Djamshidian et al., 2010; Mimura et al., 2006; Pagonabarraga et al., 2007; Euteneuer et al., 2009). All of the above tasks consist of the element of learning, which involves more complex processes than the basic EFs. The role of dopamine and reinforcement learning have been well-established (Hollerman & Schultz, 1998; Holroyd & Coles, 2002; Montague, Dayan, & Sejnowski, 1996). As discussed in Chapter 1, the neural mechanisms of dopamine release can be viewed as the expression of two dopamine subgroups of receptors: D1 and D2. The D1 receptor is predominately expressed in the direct 'Go' pathway that promotes the repeat of an action and favoured outcomes, whereas the D2 group is mainly expressed in the indirect 'No Go' pathway, which supresses an action to avoid negative outcomes (Keefe & Gerfen, 1995; Gerfen, 2000; Frank, 2005). The

dopamine over dose hypothesis is also supported by computational models (Frank, 2005) and dopamine synthesis studies using animal models (Sawaguchi, Matsumura, & Kutoba, 1990; Wang & Goldman-Rakic, 2004; Williams & Goldman-Rakic, 1995; Seamans, Durstewitz, Christie, Stevens, & Sejnowski, 2001). In addition, a pharmacological study in healthy human subjects has shown that participants with high baseline striatal dopamine synthesis would be overstimulated by D2 receptor agonist, leading to impaired reversal leaning performance when being on drug (Cools et al., 2009). Moreover, D2 receptors have been suggested to be more abundant in the basal ganglia, which supports the hypothesis that the basal ganglia may serve as a dynamic gating mechanism for updating working memory in the frontal cortex (Frank, Loughry, & O'Reilly, 2001).

Furthermore, impulsivity and impaired reward processing have also been associated with dopamine overdose hypothesis (Robert et al., 2009; Wiecki & Frank, 2010), of which the present study did not investigate. The development of ICD in PD patients has been suggested to be closely associated with pharmacological treatment (Molina et al., 2010; Dodd et al., 2005). In addition, studies have shown that PD patients ON medication showed deficits when performing gambling tasks (Shohamy et al., 2006; Perretta, Pari, & Beninger, 2005; Pagonabarraga et al., 2007; Kobayakawa, Koyama, Mimura, & Kawamura, 2008; Sáez-Francàs et al., 2014, 2016; Mapelli, Rosa, Cavalletti, Schiff, & Tamburin, 2014; Xi et al., 2015; Kobayakawa, Tsuruya, & Kawamura, 2010; Evens, Hoefler, Biber, & Lueken, 2016). The impairment of PD on the performance of gambling tasks is often reflected as impulsive choices that lead to

large losses. Furthermore, it has been shown that PD patients treated with dopaminergic medication, especially dopaminergic agonists, increases risk of developing ICDs (Voon & Fox, 2007; Wu, Politis & Piccini, 2009; Weintraub et al., 2015). Dopamine-receptor binding profiles may provide a neurobiological explanation for the association between dopamine agonist treatment and ICDs. It has been shown that 93 % of the prescribed dopamine agonists that were associated with ICDs were relatively selective for the dopamine D3 receptors (Dodd et al., 2005). D3 receptors are proposed to be abundant in the ventral striatum (Gurevich & Joyce, 1999), which is also a brain region that is associated with the hedonic response to amphetamine, addictions and impulsivity (Drevets et al., 2001; Lee et al., 2009). Taken from the above studies, future studies investigating the effect of dopaminergic medication in PD patients with ICDs should focus on the relationships between dopamine, learning and impulsivity, which involve prospect of reward sensitivity, and the related neural mechanisms.

PD patients with ICD

In addition to behavioural results, psychological measures such as the random number task and MMSE have revealed no difference between PD patient group and age-matched HC group. Moreover, scores from the UPDRS-III tested ON versus OFF medication showed that dopamine medication significantly improves motor symptoms in PD patients. Together these results may suggest that (1) long term reducing/withdrawing from dopamine agonists does not induce negative effects on cognitive function in PD patients with ICDs, and (2) motor improvement induced by

medication did not sacrifice after medication adjustment. Although PD patients showed significantly higher scores in BDI-II, suggesting that patients had mild depression compared to age-matched HCs, such an observation may be related to the disease itself instead of the pure effects of dopamine medication. The relationships between depression and PD have been extensively discussed in other studies (Cummings, 1992; Reijnders, Ehrt, Weber, Aarsland, & Leentjens, 2008; Aarsland, Pahlhagen, Ballard, Ehrt, & Svenningsson, 2012).

In recent years, more awareness has been made on the risk of PD patients developing ICDs that may lead to devastating consequences such as financial loss, divorce, career crisis, and increased health risk (Weintraub et al., 2015). Moreover, ICDs are associated with low quality of life (Phu et al., 2014), increased caregiver burden (Leroi, McDonald, Pantula, & Harbishettar, 2012) and greater functional impairment (Voon et al., 2011). It has been suggested that up to 25% of PD patients treated with minimally therapeutic dosage of dopamine agonist may experience an ICD (Hassan et al., 2011; Weintraub et al., 2015). The DOMINION study reported a prevalence of 17.1% in treated PD patients that received dopamine agonist treatment, whereas a prevalence of 6.9% was found in PD patients who did not receive dopamine agonist treatment (Weintraub et al., 2010). In the review that discussed chronic dopaminergic stimulation in PD patients on inducing motor and behavioural side-effects, Voon et al (2009) suggested that chronic dopaminergic medication (both levodopa and dopaminergic agonists) seems to alter presynaptic dopamine transmission that leads to both levodopa-induced dyskinesias and ICDs. In addition to dopamine medication,

factors such as personal or family history of alcoholism or gambling; younger age; impulsive or novelty-seeking traits; gender (male for hypersexuality, female for binge eating and pathological shopping); early onset of PD; being unmarried; depressive symptoms, and past or current cigarette smoking can all be associated with the development of ICDs in PD (Voon & Fox, 2007; Weintraub et al., 2010; Joutsa, Martikainen, Vahlberg, Voon, & Kaasinen, 2012; Weintraub et al., 2015). The association of ICDs with other risk factors may suggest the involvement of a complicated network in human impulsivity and compulsivity.

In addition, studies have shown that PD patients with and without ICDs showed different behavioural patterns in decision-making even after PD patients with ICDs are treated, which may suggest that PD patients who are at risk of developing ICDs show difference on certain functions that could be predictable prior to medication administration (Djamshidian et al., 2010; Djamshidian et al., 2012). While all PD patients showed impairments on updating information before making a decision, PD patients without ICDs showed a behavioural pattern similar to pathological gamblers, whereas PD patients with ICDs exhibited a pattern resembling more to substance users (Djamshidian et al., 2012). In addition, PD patients with behavioural addictions are impaired in generating useful beliefs that would predict future outcomes with the accumulated information (Averbeck et al., 2013). The studies are in consistent with the hypothesis that PD patients with ICDs are less able to update stimulus value through negative prediction errors in reinforcement learning models (Voon et al., 2010b; Piray et al., 2014). Conversely, PD patients without ICDs performed worse on

working memory tests (Djamshidian et al., 2012) Moreover, it has also been shown that PD patients are unable to combine previously learned information with current sensory information to guide behaviours (Perugini, Ditterich & Basso, 2016; Herz, Bogacz & Brown, 2016). These studies thus suggest that PD patients with and without ICDs show different behavioural patterns that may provide certain insights on predicting those who are prone to develop ICDs.

Summary

In terms of the clinical implications of these results for the management of ICDs, the present study showed that long term withdrawal/reducing dopamine agonists (due to the fact that the patients recruited were not actively showing ICD symptoms) did not induce impairments on cognition and motor functions when performing a moving dots task in PD. Future studies investigating the effects of dopaminergic medication on inducing impulsivity in PD patients with ICDs should focus on the relationships between dopamine and reward sensitivity. On the other hand, despite the present results showed no significant difference when directly comparing task performance between PD patients with ICD history and age-matched HCs, studies have suggested that PD patients with and without ICDs may be distinguishable by using classification predictive modelling on certain task performance patterns, therefore my next study would be building predictive models to investigate such hypothesis.

Chapter 3 Using the performance on a moving dots task to classify the membership between PD patients with and without impulse control disorders (ICDs) within a machine-learning framework

3-1 Abstract

Following previous results, it is hypothesised that behavioural data from moving dots tasks may be used to build classification predictive models to distinguish PD patients with impulse control disorders (ICDs) from PD patients without ICDs. Such an approach may potentially help finding a tool to predict vulnerability to develop impulsivity in PD patients. The present study attempted to use the behavioural performance on two types of moving dots tasks, one of which manipulated different instructions (i.e. Speed and Accuracy) with constant coherence level, whereas the other one manipulated task difficulty (i.e. 5% dots coherence), as one of the input factors to predict the membership between PD patients who developed impulse control disorders (ICDs) and PD patients who did not develop the ICDs. Machine learning algorithms were used to find patterns and make predictive models given the input variables. Models that produced the highest accuracy in making predictions on the membership would be selected for further validation. Factors such as reaction times (RTs) during incorrect trials, age when being assessed, age of PD onset and averaged levodopa daily dose were taken as input variables to train the predictive models. The results showed that the behavioural patterns, such as RTs of incorrect trials under Speed instruction and under 5% dots coherence, had high accuracy in correctly classifying membership between PD patients with and without ICDs, using a classification and regression tress algorithm. The present study thus supports that tasks require speed and accuracy trade-off modulation and/or sensory information integration may be suitable for screening for vulnerability to develop ICDs in PD patients.

3-2 Introduction

Impulsive control disorders (ICDs) in patients with Parkinson's disease (PD) have been recognised to be a psychiatric complication that would lead to devastating consequences not only for the patients but also the caregivers (Weintraub et al., 2015; Antonini et al., 2016).

As discussed in previous chapter, ICDs involve "behaviours that are performed repetitively, excessively, and compulsively to an extent that interferes with major daily functioning" such as pathological gambling, shopping, binge eating, and hypersexuality (Grant, Schreiber, & Odlaug, 2011). PD patients developing ICDs may lead to devastating consequences such as financial loss, divorce, career crisis, and increased health risk (Weintraub et al., 2015). Moreover, ICDs are associated with low quality of life (Phu et al., 2014), increased caregiver burden (Leroi et al., 2012) and greater functional impairment (Voon et al., 2011). The onset of ICDs in PD patients had been closely associated with the use of dopamine agonist (Cools et al., 2003; Voon et al., 2006; Voon & Fox, 2007, Voon et al., 2010; Weintraub et al., 2015; Antonini et al., 2016). It has been suggested that therapeutic dosage of dopamine agonist may be a risk factor in PD patients to develop ICDs (Weintraub et al., 2010; Hassan et al., 2011; Weintraub et al., 2015). While dopamine agonist is closely associated with the onset of ICDs in PD patients, recent studies have also suggested that deep brain stimulation (DBS) of the subthalamic nucleus (STN) might induce impulsivity in treated PD patients (Frank et al., 2007; Lu, Bharmal, & Suchowersky, 2006; Smeding et al., 2007; Halbig et al., 2009; Moum et al., 2012). These studies

together suggest that treatments for PD, be it dopaminergic medication or DBS, could potentially induce the onset of ICDs. Therefore, it is important for preventive strategies to early identify risk factors before performing any treatments on PD patients to avoid the onset of ICDs (Halbig et al., 2009).

Risk factors such as personal or family history of alcoholism or gambling; younger age; impulsive or novelty-seeking personality traits; gender (male for hypersexuality, female for binge eating and pathological shopping); early onset of PD; being unmarried; and past or current cigarette smoking have all been identified to be associated with the development of ICDs in PD (Voon & Fox, 2007; Weintraub et al., 2010; Weintraub et al., 2015). It has been proposed that purely cognitive measures of executive functions can predict individual difference in clinically behaviours (Friedman et al., 2007; Friedman, Miyake, Robinson, & Hewitt, 2011; Young et al., 2009). Following such hypothesis, it is possible that cognitive measures could be used to predict future behaviours, even predicting the likelihood of developing certain disorders. In line with the hypothesis, a study has shown that treated PD+ICD patients showed distinguishable task performance compared to PD patients without ICDs on a beads task (Djamshidian et al., 2012). The beads task assesses how much information participants would gather before making a decision, while both groups of PD patients sampled significantly less information, the researchers found that PD patients with ICDs showed behavioural patterns similar to substance users, whereas PD patients without ICDs showed behavioural patterns that were more closely resembled substance users (Djamshidian et al., 2012). In addition, an opposite interaction

between medication state and learning was found on PD patients with ICDs compared to PD patients without ICDs, which suggests that when being OFF medication, PD patients with ICDs showed decreased learning from negative feedback and increased learning from positive feedback (Djamshidian et al., 2011). These studies therefore indicate that PD patients with and without ICDs have distinguishable traits that could be identified. Moreover, previous studies have associated impaired perceptual decision-making processes to the development of impulsive behaviour in PD patients (Frank et al., 2007; Green et al., 2013; Djamshidian et al., 2012; Huang et al., 2015; Zaehle et al., 2017). Performance on the moving dots paradigm, which is considered to be a perceptual decision-making task, may thus be used as model inputs in building predictive models, leading to a potential screen tool for possible development of impulsive behaviours that could lead to the onset of ICDs for PD patients.

The era of big data has arrived with recent rapid increase on the generation of digital data and rapid development of computer science that provides efficient methods to extract new insights from massive datasets (Lee & Yoon, 2017). In the healthcare area, predictive models have been used for diagnostic and prognostic tasks (Dreiseitl & Ohno-Machado, 2002; Martin et al., 2009; Rosenfeld & Breslow, 2008; Masood & Al-Jumaily, 2013). Data acquired from actual cases could be used to build these models with machine learning algorithms. Big data enable the identification of health intervention targets through the analysis of high volume and high variety datasets, and the refinement of the ensuing interventions using high velocity feedback mechanisms (Mooney, Westreich & El-Sayed, 2015). Machine learning is defined as a set of

methods that can automatically detect patterns in data, use the uncovered patterns to predict future data, or to perform decision-making under uncertainty (Murphy, 2014). Machine learning can be divided into three types: supervised, unsupervised and reinforcement learning.

For the supervised learning approach, which is the most common type of machine learning, the goal is to use the algorithm to find the most optimal mapping function between a given input and output. Such a mapping function would be accurate in predicting future outputs. Supervised learning receives its name because the process of the algorithms learning from a training dataset can be thought of as a teacher supervising the learning process in which correct answers are known. Learning would stop when the algorithm reaches a certain degree of performance (i.e. accurately predicting the outputs). For example, the algorithm that could be used for Spam detection in current e-mail systems, certain characters (e.g. the word 'discount' or 'great offer' in the subject title) of the e-mail would lead to being labelled as Spam and other characters such as the word 'meeting' may be labelled as important. There are correct answers when learning the patterns of the dataset in this example. Unsupervised learning, on the other hand, is referred to when there exist only input data but no corresponding outputs. Unlike supervised leaning, there are no correct answers and no supervision. The algorithms have to find the structure of the input data relying on their own computational ability. For example, an on-line recommendation system could categorize different groups of customers based on their purchasing behaviour (i.e. preference), clustering similar data and provide future

recommendations. There are no correct answers given in this situation. Lastly, the reinforcement learning approach takes into account how to maximise the accumulated reward in guiding the learning process. The machine using the reinforcement learning approach is allowed to learn the most optimal behaviour that maximises the reward based on feedback. In handling large amount of data, machine learning is therefore a powerful approach to find patterns and provide future predictions in guiding behaviours.

The present study thus attempted to use performance of individual participants on two versions of a moving dots task to predict impulsivity in PD patients using algorithms from the field of machine learning for data classification. In addition, behavioural data from two versions of the moving dots were selected: speed and accuracy trade-off (SAT) version and the 'Difficulty' version. The former manipulated speed and accuracy instructions to motivate participants to make fast or accuracy responses whereas the later manipulated dots coherence to introduce task difficulty. Reaction times (RTs) of incorrect trials collected from the moving dots task were used to classify group membership between PD patients with (PD+ICD) and without ICD history (PD-ICD). To be more precise, six sets of data were selected as model inputs: RTs of incorrect trials under Speed instruction for PD patients ON medication and OFF medication, RTs of incorrect trials under Accuracy instruction for PD patients ON medication and OFF medication, and RTs of incorrect trials under 5% dots coherence ON medication and OFF medication. The data were selected based on the following hypotheses: PD patients with ICD history may show different behavioural

patterns compared to PD patients without ICD history when acting under (1) speed pressure, (2) the need to be accurate and (3) high decision conflict. Moreover, previous studies have demonstrated that medication state plays an important role in controlling behaviours in PD patients, therefore medication state has also been taken into account in selecting model inputs. In addition to the behavioural data, age when being assessed, PD onset age and averaged levodopa daily dose (LEDD) were also included in the model as input variables.

3-3 Methods

Dataset & programming language libraries

The behavioural data were taken from thirteen PD-ICD (Huang et al, 2015) and eleven PD+ICD patients (Chapter 2) from previous studies. Demographic details of the patients are presented in Table 3.1. Python and SciPy platform were used for the classification of the data (Millman & Aivazis, 2011; Jones, Oliphant, & Peterson, 2001). The data collected from the Speed and Accuracy trade-off (SAT) version and Difficulty version of the moving dots tasks were used as input variables. RTs during incorrect trials were used and separated between Speed instruction and Accuracy instruction. Behavioural data were also compared for different medication states. The aim of the study is to identify the difference between PD+ICD group and PD-ICD group when making decisions under SAT and when decision conflict was presented, during ON medication state and OFF medication state. Moreover, using the identified behavioural parameter to predict future possibility of PD patients developing ICDs. The python codes for performing data classification were modified from Brownlee

(2016) (Please see Appendix for the codes and outputs). The SAT version of the moving dots task consisted of 100 trials, which asked participants to make perceptual decisions on the direction (left or right) of a cloud of moving dots based on instructions given before the appearance of sensory stimuli. Coherence of the moving dots was fixed at a constant 50% level. The instructions either emphasised Speed (i.e. Fast) or Accuracy (i.e. Accurate). Participants were instructed to make response in accordance to the given instruction. On the other hand, for the Difficulty version of the task, dots coherence was manipulated to vary from 5%, 10% 15%, 25%, 35% and 50%. There were no Speed or Accuracy instructions presented before each trial for this version of the task. RTs of incorrect trials of the 5% dots coherence were selected as model inputs due to the hypothesis that PD patients with ICD may show impaired EFs associated with updating information under high decision conflict. For the details of the moving dots task please refer to previous chapters.

Table 3.1 Demographic details of PD-ICD and PD+ICD patients.

	Gender	Age when being assessed	Age of PD onset	LEDD (Levodopa Daily Dose)		Gender	Age when being assessed	Age of PD onset	LEDD (Levodopa Daily Dose)
PD-ICD 01	m	71	64	600	**PD+ICD 01**	m	54	50	300
PD-ICD 02	m	69	69	900	**PD+ICD 02**	m	58	50	600
PD-ICD 03	m	67	60	500	**PD+ICD 03**	m	70	57	700
PD-ICD 04	f	42	37	850	**PD+ICD 04**	m	56	47	800
PD-ICD 05	f	60	50	1431	**PD+ICD 05**	f	57	54	825
PD-ICD 06	m	86	83	300	**PD+ICD 06**	m	60	52	880
PD-ICD 07	f	68	51	810	**PD+ICD 07**	m	57	35	960
PD-ICD 08	m	52	45	1530	**PD+ICD 08**	f	45	38	1000

PD-ICD 09	f	43	38	910	**PD+ICD 09**	f	67	65	1390
PD-ICD 10	m	67	55	980	**PD+ICD 10**	m	70	62	1400
PD-ICD 11	f	58	48	650	**PD+ICD 11**	m	65	60	1600
PD-ICD 12	m	77	75	600					
PD-ICD 13	m	41	32	750					
Mean (SD)		61.62 (13.96)	54.38 (15.31)	831.62 (344.02)	Mean (SD)		59.91 (7.57)	51.82 (9.38)	950.45 (383.63)

Data Classification

The supervised machine learning approach can be further categorised into regression and classification. The main goal of the regression approach is to predict a continuous numerical variable, whereas the aim of the classification approach is to identify to which category an object belongs. Here in the present study a classification approach was used to identify different groups of PD patients (i.e. PD+ICD and PD-ICD) based on age when being assessed, PD onset age, mean LEDD and RTs on incorrect trials of the moving dots task. The aim of classifying data is to decide the class membership (y') of an unknown input (x') based on a dataset consists of data items x_i with known class membership y_i. The input variables are often multi-dimensional vectors. There are two different approaches for data classification: the first considers only the distinction between the two classes and labels either 1 or 0 to an unknown input variable; the second approach models the probabilistic posterior distribution $P(y|x)$, which not only provides a class label for each input variable but also a probability of class membership (Dreiseitl & Ohno-Machad, 2002). Due to small sample sizes in the studies, the RTs of incorrect trials were seen as indepent examples for each class. There are only 4 attributes and less than 400 rows, suggesting that the data set is small and relatively simple. The aim of the study is to examine the hypothesis of whenther it is possible to use behavioural data as predictors in making predictions, it is not the main focus to find the best algorithm in fitting all types of data, therefore the models are created using the simplest techniques.

Six different algorithms including logistic regression (LR), linear discriminant analysis (LDR), K-nearest neighbors (KNN), classification and regression tress (CART), Gaussian

naive Bayes (NB) and support vector machines (SVM) were evaluated to select the model with best performance (Bishop, 2006; Browlee, 2016). Among the six algorithms logistic regression and linear discriminant analysis are linear algorithms and the other four are non-linear. The results were directly comparable because the models created using the six algorithms used the exact same data splits during elevation. Models with the highest accuracy score were selected. Two methods were used to test the accuracy of the selected models: the hold-out method and cross validation. The hold-out method splits the data into two groups: training set is used to train the classifier whereas the test set is used to estimate the error rate of the trained claddifier. The amount of data required for building predictive models depends on many factors such as the complexity of questions of interest and the complexity of the learning algorithm and is thus unknowable (Brownlee, 2017). The present study used 70% of the dataset as the training set and 30% of it as the testing set (Gholami, Chau, Fadaee, Torkaman, & Ghaffari, 2015). In addition, K-fold cross validation (conventionally K=10) was also used to estimate accuracy of the model. The validation dataset was to prevent errors during the training processes such as overfitting to the training set or a data leak, which would negatively affect the accuracy of the model.

Logistic Regression (LR)

Logistic regression, borrowed from the field of statistics by machine learning, uses the logistic function (also referred to as Sigmoid function), which is the inverse form of the logit function, to solve linear and binary classification problems. Despite the name, logistic regression is a model for classification rather than regression (Raschka, 2015). In general, a logistic regression model predicts the probability of certain samples belonging to one of the

two categories (labelled with value 1 in the model) in the data set:

$$P(1|x,\alpha) = \frac{1}{1+e^{-(\alpha \cdot x)}}$$

, where x represents the data items and α represents the parameter vector. The probability for the other class (labelled with value 0) would thus be calculated as $P(0|\, x,\, \alpha) = 1 - P(1|\, x,\, \alpha)$ (Dreiseitl & Ohno-Machado, 2002). Figure 3.1 illustrates the general concept of logistic regression: the algorithm receives the inputs of a sample **X** and combined with the weights **W** to compute the net input, which would be passed onto the activation function (here the sigmoid function) for the prediction of class membership (Raschka, 2015).

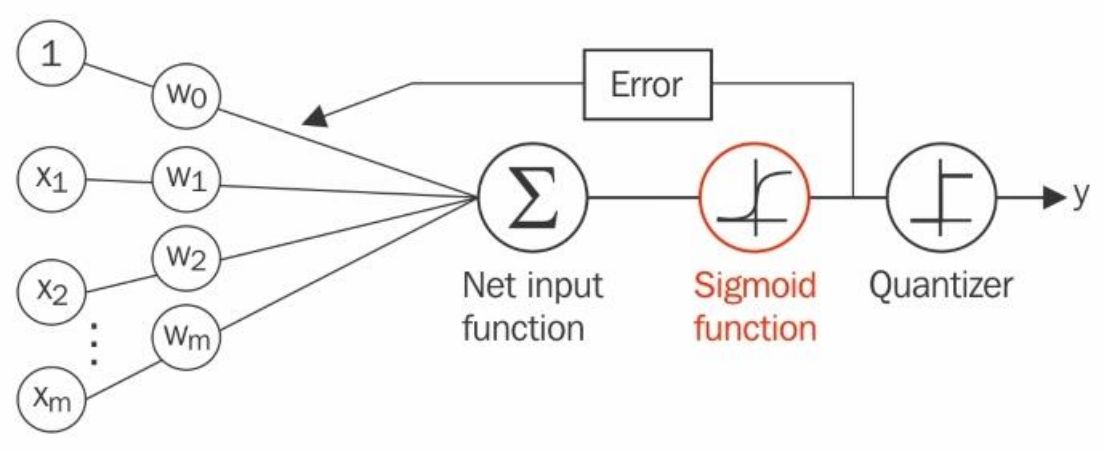

Figure 3.1 The general concept of logistic regression. The output produced by the sigmoid function is interpreted as the probability of certain sample belonging to one of the two classes, given the features parameterized by the weights. The predicted probability is converter into a binary outcome via a quantizer. Figure from Raschka, (2015).

Linear Discriminant Analysis (LDA)

Linear discriminant analysis (LDA) was proposed by R. Fischer in 1936, which consists in finding the projection hyperplane that minimizes the interclass variance and maximized the

distance between the projected means of the classes (Xanthopoulos, Pardalos & Trafalis, 2013). The general concept behind the LDA is to find the feature subspace that optimizes class separability (Raschka, 2015). One assumption in the LDA is that the data is normally distributed, in addition, it is assumed that the classes have identical covariance matrices and that the features are statistically independent of each other. However, in dimensionality reducntion and classification tasks, LDA may still work reasonally well even if the above assumptions are violated (Duda, Hart, & Stork, 2012). Figure 3.2 illustrates the concept of LDA for a two-class data classification.

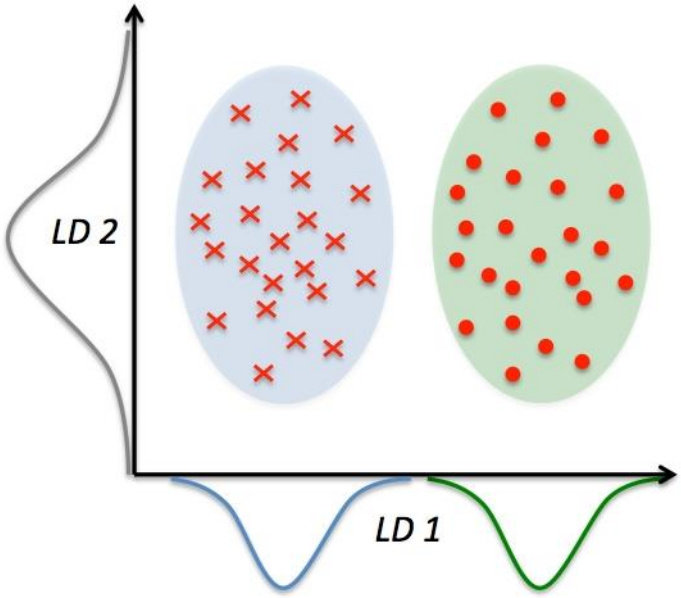

Figure 3.2 The concept of linear discriminant analysis (LDA) for a two-class data classification. Samples from class 1 are shown as crosses whereas samples from class 2 are shown as circles. The linear discriminant 1 (LD 1) on the x-axis separates the two normally distributed classes. The linear discriminant 2 (LD 2) on the y-axis, while captures the general variance in the dataset, would not be an ideal linear discriminant as is does not capture any of the information that discriminates the two classes. Figure from Raschka, (2015).

K-nearest neighbours (KNN)

The K-nearest neighbours (KNN) algorithm classifies each unlabelled example by the majority label among its k-nearest neighbours in the training dataset (Weinberger, Blitzer & Saul, 2006). Instead of learning a discriminative function from the training datamm, the KNN algorithm memorizes the training dataset. Namelym the KNN finds the k samples in the training dataset that are closest (or most similar) to the point that is to be classifies, the class of the point is then determined by a majority vote among the k nearest neighbours (Raschka, 2015). KNN is considered a nonparametric model that uses memory-based approach. Such an approach may work more optimally when the dataset has very few dimentions because the computational complexity for classifying new samples grows linearly with the increasing number of samples in the training dataset (Friedman, Bentley, & Finkel, 1976). As Figure 5.3 shows, the data point "?" is classified as triangle class label based on the k (in this example, 5) nearest neighbours of the sample.

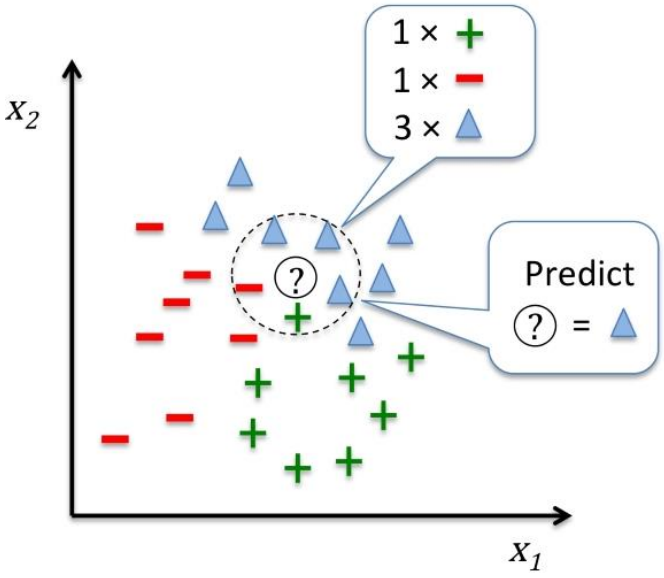

Figure 3.3 The concept of the k-nearest neighbour classifier (KNN). The question mark "?"represents the data point that is to be classified. The three symbols (triangle, the plus sign

and the minus sign) indicate different class labels. Based on the majority vote of the 5 nearest (k=5) neighbours, the data point is therefore classified as class triangle. Figure from Raschka, (2015).

Classification and regression trees (CART)

For classification and regression tree methods, the models are constructed by recursively partitioning the data space and fitting a simple prediction model within each partition (Loh, 2011). The partitioning can be graphically presented as a decision tree classifier, which can be thought of as breaking down the data by making decisions based on asking a series of questions. Namely, the deicison tree model learns a series of questions to infer the class lables of the samples (Raschka, 2015). Classification trees are designed for inputs that take a finite number of unordered values, with misclassification cost measured as prediction error. (Loh, 2011). Regression trees, on the other hand are designed for inputs that take continuous or ordered discrete values, with the squared difference between the observed and predicted values measured as prediction error (Loh, 2011). The approach in practice may reasly lead to overfitting as the decision tree grows deeper, therefore it is better to set a limit for the maximal depth of the decision tree. Figure 3.4 illustrates an example of a one-day activity being decided within the decision tree framework.

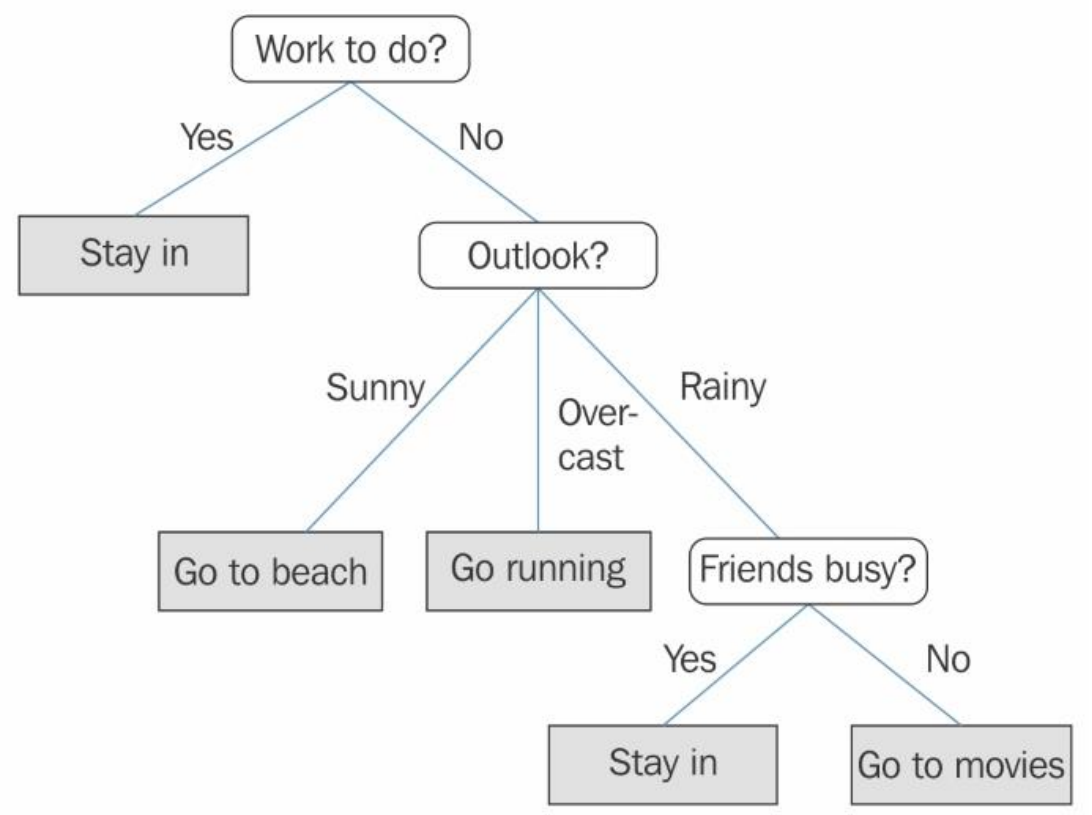

Figure 3.4 An example of decision tree deciding upon an activity on a particular day. While the figure illustrates the concepts of decision tree based on categorical labels, the same concepts applies for numerical datasets. Figure from Raschka, (2015).

Gaussian Naïve Bayes (GNB)

Naïve Bayes is a linear classifier that can be effectively applied to high-dimensional datasets, which predicts the probability of each class based on the feature vector for given continuous big data with a prior distribution of the probability. The naive aspect of the algorithms is that it assumes all of the input dimensions are independent from each other (Raizada & Lee, 2013). Gaussian Naïve Bayes (GNB) classifier referred to Naïve Bayes classifier that considers the bid data is generated through a Gaussian process with normal distribution, which allows the z-score distance to be converted into a p-value. Figure 3.5 illustrates the

concept of GNB, showing that the z-score distance of each data point x was calculated

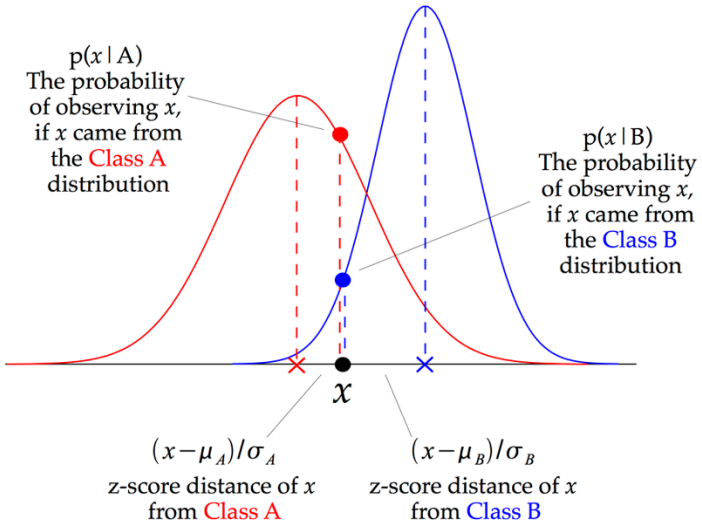

Figure 3.5 The concept of Gaussian Naïve Bayes (GNB) classifier. The distance between the data point x and the class mean divided by the standard deviation of the class is the z-score distance of x. Because the model assumes the data to be normally distributed, each z-score distance is allowed to be converted directly into a p-value. Figure from Raizada & Lee (2013).

Support vector machines (SVM)

The SVM algorithms are the most representatives of the data classification approach that considers only a dichotomous difference between the two classes. A support vector machine classified the input variables by finding the hyperplane that maximizes the margin (i.e. the distance between the optimal hyperplane and input data points) between the two classes. The SVM concerns the problem of constructing consistent estimators from data, namely, how to estimate the model performance on an unknown dataset, given the characteristic of the model and its performance on a training dataset (Dreiseitl & Ohno-Machado, 2002).

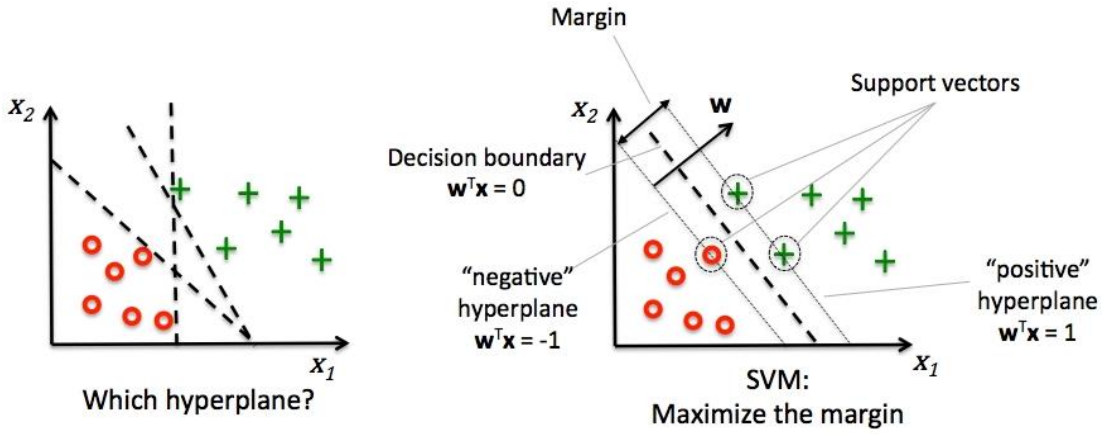

Figure 3.6. The support vector machine (SVM). The aim of the SVM is to find a hyperplane that optimally separate the two classes. The optimization is to maximize the margin, which is defined as the distance between the separating hyperplane (decision boundary) and the training samples that are closest to this hyperplane, which are the co-called support vectors. Figure from Raschka, (2015).

3-4 Results

RTs from incorrect trials under Accuracy instruction (ON/OFF medication) to predict PD+ICD/PD-ICD membership

Six models were created using six different algorithms discussed in the previous section. For the codes and figures please refer to the Appendix. The metric of accuracy was used to evaluate the models. Figure 3.7 illustrates the spread and the mean accuracy of each model. Each algorithm was evaluated 10 times with the 10-fold cross validation, thus each model had a population of accuracy measures. As shown in the figure, the spread of the samples indicates that many samples reached 100% accuracy in model CART, whereas the other five models had less accuracy in predicting the classification of the data.

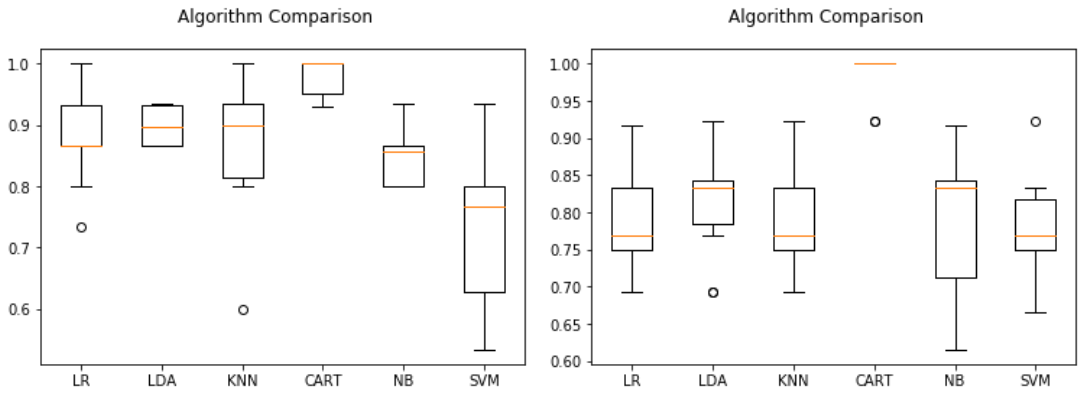

Figure 3.7 Model evaluation results that compare the spread and the mean accuracy of each model created with different algorithms. The left figure represents the results from models using OFF medication data set, whereas the right figure represents the results from models using ON medication data set. LR= logistic regression, LDA= linear discriminant analysis, KNN= K-Nearest Neighbors, CART= Classification and Regression Trees, NB= Gaussian Naive Bayes, SVM = Support Vector Machines.

The score of accuracy represented the ratio of the number of correctly predicted cases divided by the total number of cases in the database. The results showed that the model created with classification and regression tree algorithm had the highest accuracy score. Table 3.2 shows the estimated accuracy score for each model.

Table 3.2 Estimated accuracy score for each model using data of incorrect responses funder Accuracy instructions

	Models	**LR**	**LDA**	**KNN**	**CART**	**NB**	**SVM**
OFF	Mean	0.89	0.90	0.87	0.98	0.84	0.74

medication data set	Estimated Accuracy	(0.08)	(0.03)	(0.11)	(0.03)	(0.04)	(0.12)
ON medication data set	Mean Estimated Accuracy	0.79 (0.07)	0.82 (0.08)	0.79 (0.08)	0.98 (0.03)	0.79 (0.09)	0.78 (0.07)

LR= logistic regression, LDA= linear discriminant analysis, KNN= K-Nearest Neighbors, CART= Classification and Regression Trees, NB= Gaussian Naive Bayes, SVM = Support Vector Machines. The estimated accuracy score was given as the mean with the standard deviation in parentheses.

The CART algorithm was the most accurate model among the six models created and tested. The validation dataset was used to further examine the accuracy of the selected model. The results showed a 97% precision in making predictions on the validation dataset. Table 3.3 shows the classification report of the models, which indicates how well the models worked. The uneven number of each class may contribute to the high precision of the model, therefore a confusion matrix was calculated to see the types of the errors the model made when making predictions.

Table 3.3 The classification report of the classification and regression tree (CART) models created with OFF/ON medication under Accuracy instruction data sets

OFF medication data set				
	Precision	Recall	F1-Score	Support
PD+ICD	1.00	0.86	0.92	14
PD-ICD	0.92	1.00	0.96	23

Avg. /Total	0.95	0.95	0.94	37
ON medication data set				
	Precision	Recall	F1-Score	Support
PD+ICD	0.88	0.88	0.88	8
PD-ICD	0.96	0.96	0.96	24
Avg. /Total	0.94	0.94	0.94	32

Precision: precision in successfully classifying each case; Recall: accuracy in predicting the classes for each case; F1-Score: a weighted average of the precision and recall; Support: number of cases given by the validation dataset.

As shown in Table 3.4, for the OFF medication data set, the type of the error appeared in two cases when two PD+ICD data points were misclassified as PD-ICD, whereas PD-ICD data were all accurately classified. The Table showed that there were 14 cases in class PD+ICD and 24 cases in class PD-ICD. 2 of the 14 cases in the class PD+ICD were correctly classified (recall: 12/14=0.86) whereas all the cases in the class PD-ICD were correctly classified (recall: 23/23=1.00). For the 12 cases classified as class PD+ICD in the model, all of them were actually labelled as PD+ICD, leading to the 1.00 precision (12/12=1.00). On the other hand, for the 25 cases classified as PD-ICD in the model, only 23 of them actually belonged to the PD-ICD class, the precision was therefore calculated as 23/25= 0.92. On the other hand, for the ON medication data set, the type of the error appeared in one case when a PD+ICD data point was misclassified as PD-ICD, and when a PD-ICD data point was misclassified as PD+ICD. The Table showed that there were 8 cases in class PD+ICD and 24 cases in class PD-ICD. 7 of the 8 cases in the class PD+ICD were correctly classified (recall: 7/8=0.88)

whereas 23 out of the 24 cases in the class PD-ICD were correctly classified (recall: 23/24=0.96). For the 8 cases classified as class PD+ICD in the model, 7 of them were accurately labelled as PD+ICD, leading to the 0.88 precision (7/8=0.88). On the other hand, for the 24 cases classified as PD-ICD in the model, only 23 of them actually belonged to the PD-ICD class, the precision was therefore calculated as 23/24= 0.96.

Table 3.4 The confusion matrix of the classification and regression tree (CART) models

OFF medication data set			
	PD+ICD (Predicted)	PD-ICD (Predicted)	Total
PD+ICD (Input)	12	2	14
PD-ICD (Input)	0	23	23
ON medication data set			
	PD+ICD (Predicted)	PD-ICD (Predicted)	Total
PD+ICD (Input)	7	1	8
PD-ICD (Input)	1	23	24

RTs from incorrect trials under Speed instruction (ON/OFF medication) to predict PD+ICD/PD-ICD membership

Likewise, here six models were created using six different algorithms using data sets of Speed instructions. For the codes and figures please refer to Appendix C. The metric of accuracy was used to evaluate the models. Figure 3.8 illustrates the spread and the mean accuracy of each model. Each algorithm was evaluated 10 times with the 10-fold cross

validation, thus each model had a population of accuracy measures. As shown in the figure, the spread of the samples indicates that many samples reached 100% accuracy in model CART, whereas the other five models had less accuracy in predicting the classification of the data.

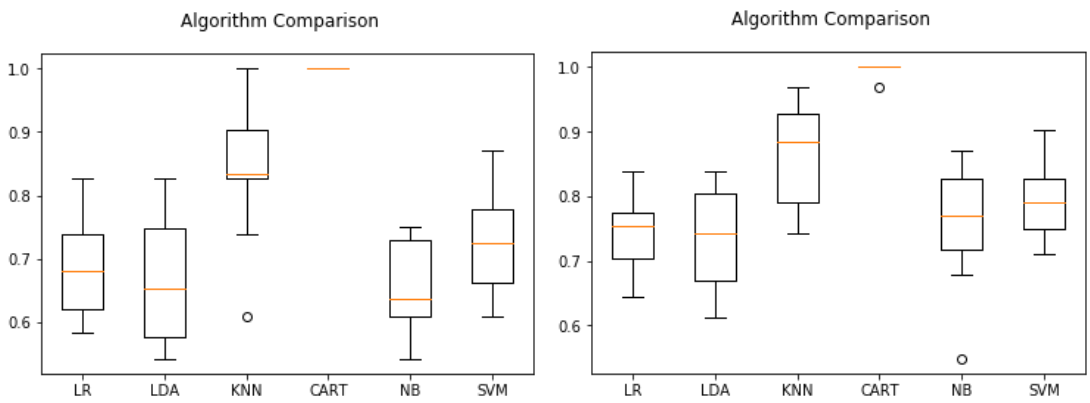

Figure 3.8 Model evaluation results that compare the spread and the mean accuracy of each model created with different algorithms. The left figure represents the results from models using OFF medication data set, whereas the right figure represents the results from models using ON medication data set. LR= logistic regression, LDA= linear discriminant analysis, KNN= K-Nearest Neighbors, CART= Classification and Regression Trees, NB= Gaussian Naive Bayes, SVM = Support Vector Machines.

The score of accuracy represented the ratio of the number of correctly predicted cases divided by the total number of cases in the database. The results showed that the model created with classification and regression tree algorithm had the highest accuracy score. Table 3.5 shows the estimated accuracy score for each model.

Table 3.5 Estimated accuracy score for each model

	Models	LR	LDA	KNN	CART	NB	SVM
OFF medication data set	Mean Estimated Accuracy	0.69 (0.08)	0.67 (0.10)	0.84 (0.10)	1.00 (0.00)	0.65 (0.07)	0.73 (0.09)
ON medication data set	Mean Estimated Accuracy	0.74 (0.06)	0.73 (0.07)	0.87 (0.08)	0.99 (0.01)	0.76 (0.09)	0.79 (0.06)

LR= logistic regression, LDA= linear discriminant analysis, KNN= K-Nearest Neighbors, CART= Classification and Regression Trees, NB= Gaussian Naive Bayes, SVM = Support Vector Machines. The estimated accuracy score was given as the mean with the standard deviation in parentheses.

The CART algorithm was the most accurate model among the six models created and tested. The validation dataset was used to further examine the accuracy of the selected model. The results showed a 100% precision in making predictions on the validation dataset. Table 3.6 shows the classification report of the models, which indicates how well the models worked. The uneven number of each class may contribute to the high precision of the model, therefore a confusion matrix was calculated to see the types of the errors the model made when making predictions.

Table 3.6 The classification report of the classification and regression tree (CART) models created with OFF/ON medication under Speed instruction data sets

OFF medication data set				
	Precision	Recall	F1-Score	Support
PD+ICD	1.00	1.00	1.00	12
PD-ICD	1.00	1.0	1.00	47
Avg. /Total	1.00	1.00	1.00	59
ON medication data set				
	Precision	Recall	F1-Score	Support
PD+ICD	1.00	1.00	1.00	21
PD-ICD	1.00	1.00	1.00	56
Avg. /Total	1.00	1.00	1.00	77

Precision: precision in successfully classifying each case; Recall: accuracy in predicting the classes for each case; F1-Score: a weighted average of the precision and recall; Support: number of cases given by the validation dataset.

As shown in Table 3.7, for both ON and OFF medication data sets, PD+ICD and PD-ICD data points were all accurately classified. The Table showed that for OFF medication data set, there were 12 cases in class PD+ICD and 59 cases in class PD-ICD. All 12 cases in the class PD+ICD were correctly classified (recall: 12/12=1.00). Similarly, all the cases in the class PD-ICD were correctly classified (recall: 47/47=1.00). For the 12 cases classified as class PD+ICD in the model, all of them were actually labelled as PD+ICD, leading to the 1.00 precision (12/12=1.00). In addition, for the 47 cases classified as PD-ICD in the model, all 47

cases actually belonged to the PD-ICD class, the precision was therefore calculated as 47/47= 1.00. For the ON medication data set, all data points were correctly classified. The Table showed that there were 21 cases in class PD+ICD and 56 cases in class PD-ICD. All 21 of the 21 cases in the class PD+ICD were correctly classified (recall: 21/21=1.00). Moreover, all 56 cases in the class PD-ICD were correctly classified (recall: 56/56=1.00). For the 21 cases classified as class PD+ICD in the model, all 21 of them were accurately labelled as PD+ICD, leading to the 1.00 precision (21/21=1.00). For the 56 cases classified as PD-ICD in the model, all 56 of them actually belonged to the PD-ICD class, the precision was therefore calculated as 56/56= 1.00.

Table 3.7 The confusion matrix of the classification and regression tree (CART) models

OFF medication data set			
	PD+ICD (Predicted)	PD-ICD (Predicted)	Total
PD+ICD (Input)	12	0	12
PD-ICD (Input)	0	47	59
ON medication data set			
	PD+ICD (Predicted)	PD-ICD (Predicted)	Total
PD+ICD (Input)	21	0	21
PD-ICD (Input)	0	56	56

RTs from incorrect trials under 5% dots coherence (ON/OFF medication) to predict PD+ICD/PD-ICD membership

Six models were created using six different algorithms discussed in the previous section. For the codes and figures please refer to Appendix C. The metric of accuracy was used to evaluate the models. Figure 3.9 illustrates the spread and the mean accuracy of each model. Each algorithm was evaluated 10 times with the 10-fold cross validation, thus each model had a population of accuracy measures. As shown in the figure, the spread of the samples indicates that many samples reached 100% accuracy in model CART, whereas the other five models had less accuracy in predicting the classification of the data.

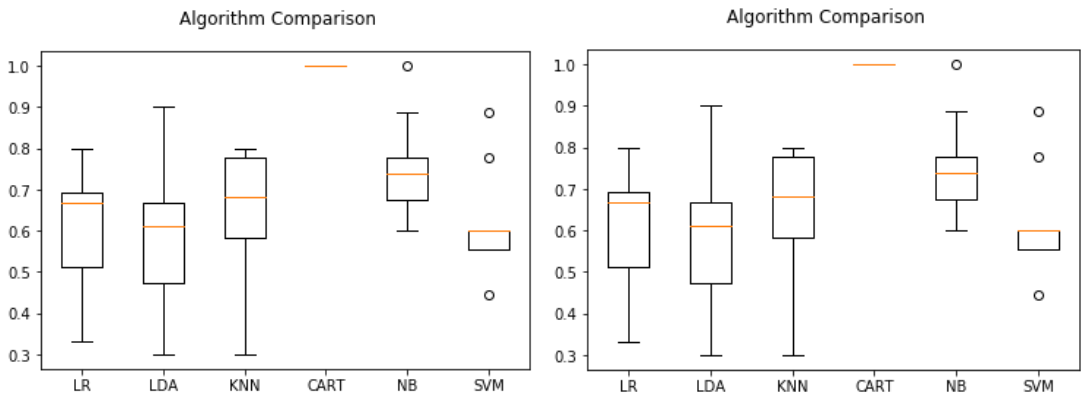

Figure 3.9 Model evaluation results that compare the spread and the mean accuracy of each model created with different algorithms. The left figure represents the results from models using OFF medication data set, whereas the right figure represents the results from models using ON medication data set. LR= logistic regression, LDA= linear discriminant analysis, KNN= K-Nearest Neighbors, CART= Classification and Regression Trees, NB= Gaussian Naive Bayes, SVM = Support Vector Machines.

The score of accuracy represented the ratio of the number of correctly predicted cases divided by the total number of cases in the database. The results showed that the model created with classification and regression tree algorithm had the highest accuracy score. Table 3.8 shows

the estimated accuracy score for each model.

Table 3.8 Estimated accuracy score for each model

	Models	LR	LDA	KNN	CART	NB	SVM
OFF medication data set	Mean Estimated Accuracy	0.61 (0.15)	0.59 (0.16)	0.64 (0.16)	1.00 (0.00)	0.76 (0.11)	0.62 (0.12)
ON medication data set	Mean Estimated Accuracy	0.54 (0.10)	0.53 (0.10)	0.70 (0.13)	0.98 (0.03)	0.64 (0.13)	0.56 (0.12)

LR= logistic regression, LDA= linear discriminant analysis, KNN= K-Nearest Neighbors, CART= Classification and Regression Trees, NB= Gaussian Naive Bayes, SVM = Support Vector Machines. The estimated accuracy score was given as the mean with the standard deviation in parentheses.

The CART algorithm was the most accurate model among the six models created and tested. The validation dataset was used to further examine the accuracy of the selected model. The results showed a 100% precision in making predictions on the validation dataset. Table 3.9 shows the classification report of the models, which indicates how well the models worked. The uneven number of each class may contribute to the high precision of the model, therefore a confusion matrix was calculated to see the types of the errors the model made when making predictions.

Table 3.9 The classification report of the classification and regression tree (CART) models created with OFF/ON medication under 5% dots coherence data sets

OFF medication data set				
	Precision	Recall	F1-Score	Support
PD+ICD	1.00	1.00	1.00	8
PD-ICD	1.00	1.0	1.00	16
Avg. /Total	1.00	1.00	1.00	24
ON medication data set				
	Precision	Recall	F1-Score	Support
PD+ICD	1.00	1.00	1.00	11
PD-ICD	1.00	1.00	1.00	27
Avg. /Total	1.00	1.00	1.00	38

Precision: precision in successfully classifying each case; Recall: accuracy in predicting the classes for each case; F1-Score: a weighted average of the precision and recall; Support: number of cases given by the validation dataset.

As shown in Table 3.10, for both ON and OFF medication data sets, PD+ICD and PD-ICD data points were all accurately classified. The Table showed that for OFF medication data set there were 8 cases in class PD+ICD and 16 cases in class PD-ICD. All 8 cases in the class PD+ICD were correctly classified (recall: 8/8=1.00). Similarly, all the cases in the class PD-ICD were correctly classified (recall: 16/16=1.00). For the 8 cases classified as class PD+ICD in the model, all of them were actually labelled as PD+ICD, leading to the 1.00 precision (8/8=1.00). In addition, for the 16 cases classified as PD-ICD in the model, all 16

cases actually belonged to the PD-ICD class, the precision was therefore calculated as 16/16= 1.00. For the ON medication data set, all data points were correctly classified. The Table showed that there were 11 cases in class PD+ICD and 27 cases in class PD-ICD. All 11 of the 11 cases in the class PD+ICD were correctly classified (recall: 11/11=1.00). Moreover, all 27 cases in the class PD-ICD were correctly classified (recall: 27/27=1.00). For the 11 cases classified as class PD+ICD in the model, all 11 of them were accurately labelled as PD+ICD, leading to the 1.00 precision (11/11=1.00). For the 27 cases classified as PD-ICD in the model, all 27 of them actually belonged to the PD-ICD class, the precision was therefore calculated as 27/27= 1.00.

Table 3.10 The confusion matrix of the classification and regression tree (CART) models

OFF medication data set			
	PD+ICD (Predicted)	PD-ICD (Predicted)	Total
PD+ICD (Input)	8	0	8
PD-ICD (Input)	0	16	16
ON medication data set			
	PD+ICD (Predicted)	PD-ICD (Predicted)	Total
PD+ICD (Input)	11	0	11
PD-ICD (Input)	0	27	27

3-5 Discussion

In the present study, the results showed that RTs from incorrect trials of a moving dots

paradigm, especially RTs of incorrect trials under Speed instruction and under 5% dots coherence, could be used to classify the membership between PD+ICD and PD-ICD groups in PD patients. While all constructed models had high accuracy in making predictions, the models created with different datasets (i.e. one used incorrect trials under Speed instruction whereas the other one used incorrect trails under Accuracy instruction) were not comparable because they were created from different datasets. Therefore, it is difficult to directly compare the performance of the models with regard to data classification. However, the total classes of the models indicate that RTs on incorrect trials under Speed instruction may provide better predictions for data classification on categorising the PD+ICD/PD-ICD membership.

Predictive modelling approach in the field of health care and limitations of the present study

The present results suggest a possibility to use behavioural data as a predictor in predicting the vulnerability in developing ICDs in PD aptients. To develop the best/most suitable predictive model is not the main research interest of the study. In recent years, predictive modelling approaches have been received much attention in the field of health care (Choi et al., 2016; Hatzmann, Maurice-Stam, Heymans, & Grootenhuis, 2009), such as in gene expression analysis (Shi et al., 2010). However, few studies discuss the possibility to use behavioural data as screening tool in disease prevention.

The quality of a predictive model depends on three factors: the quality of the input data in building the model, the caution when choosing the adjustable parameters, and evaluation criteria when reporting the results of model processing. Given the current dataset the CART

model was selected for the best performance in making predictions on the classification. Despite the results suggest a possibility to use the behavioural data in predicting PD patients prone to develop ICDs, there are a few limitations of the present study should be acknowledged. First, while the dataset consists of 24 patients and up to 389 response trials, it was a relatively small sample size. Second, due to the small sample size, each response trial as considered as a dependent data point, which may have produced bias in the dataset when estimating the accuracy of the model. Third, the models created in the present study were designed in the simplest manner to avoid too much noise in the data, however this may result in high accuracy but less interoretability (Hall, 2016). Fourthly, the classification approach used in the present study requires numeric input variable thus other predictive factors that were associated with the development of PD ICD such as gender (binary vector), marital status, and personal/family history experience of using psychostimulants (Weintraub et al., 2015) were not included in the models. Approaches that are able to construct models with more input variables from multiple dimensions may be more informative on screening for the development of ICDs in PD patients in future studies. For such models, which are far more complicated that the ones constructed in current study, algorithms such sequential backward selection (SBS) could be used to select the most important features at the same time maintain the accuracy of the model. While the accuracy in making predictions on the membership of PD patients is high given the present data, future studies are required to further investigate the reliability and validity of using behavioural patterns in a moving dots task as a clinical screening tool to predict impulsive behaviours in PD patients. As previously discussed, ICDs in PD patients would cause devastating consequences to patients and the caregivers (Weintraub et al., 2015; Phu et al., 2014; Leroi et al., 2012; Voon et al., 2011), and that the

onset of the ICDs is likely to be induced by treatments such as dopaminergic medication (especially dopamine agonist) (Cools et al., 2003; Voon et al., 2007, 2011; Weintraub et al., 2010, 2015) and STN DBS (Hälbig et al., 2009; Moum et al., 2012). The behavioural tasks can therefore be administered on untreated PD patients and the data can be used for building predictive models that help guiding further treatment to prevent the onset of the ICDs.

Note that in the present study it is not the main purpose to determine which input variable in the model had the most impact on making the predictions, because impulsivity is not a unitary construct and the onset of a disease or a disorder is hardly determined by only one factor. The aim of the models is to use the input variables (e.g. behavioural patterns and factors such as age) in making predictions on PD patients that may potentially develop ICDs in the future, rather than finding the potential factors that may be the cause of the development of the ICDs. Such concept is supported by the idea of the big data, which focus on temporal stability of the association, rather than on causal relationship (Lee & Yoon, 2017). Moreover, PD+ICD patients recruited in the study were not actively showing symptoms of ICDs, yet the patients still showed different behavioural patterns compared to PD-ICD patients. The results are in line with previous study in suggesting that PD+ICD and PD-ICD patients had distinct behavioural pattern, which may shed insights on why some PD patients developed ICDs and the others did not (Djamshidian et al., 2012, 2014).

Behavioural classification in PD patients with and without ICDs

Previously, Djamshidian et al (2012) have used a linear discriminant analysis to classify PD patients with and without ICDs using the performance on a beads task. The beads task

requires participants to decide from which of the two cups coloured beads were being drawn. The cups differed in the proportion of blue and green beads they contained (e.g. one cup is 80% Green and 20% Blue whereas the other cup contains 20% Green and 80% Blue). Participants were first shown a bead draw, which was either blue or green. Then the participants could choose between drawing another bead and guessing from which cup the bead was drawing from. Participants are allowed to draw as many beads as they need to make decisions. The number of draws is associated with the subjective certainty of making the decision. The essence of the beads task is that participants are allowed to gather as much information as subjectively needed. During ambiguous trials, participants would gather more information to guide the decision. Conversely, participants would gather less information during trials that are much clearer. The number of beads draws therefore represents the amount of information gathered before making optimal decisions. Both PD-ICD and PD+ICD patients have been shown to draw significantly less beads compared to age-matched healthy controls, indicating that PD patients showed reflection impulsivity when making decisions (Djamshidian et al., 2012). Furthermore, the authors used the data in the 80/20 condition to predict the class membership of PD-ICD and PD+ICD patients by using the number of draws in the 80/20 condition to predict group membership between different groups of patients, which produced a 96% accuracy in making predictions on the membership of PD patients. Djamshidian et al (2012) thus proposed that the behavioural patterns for the beads task were a powerful tool to screen for impulsive behaviours in PD patients. The present results were in line with the study in showing that PD patients with and without ICDs have different behavioural patterns, and that tools may be developed to screen for PD patient that are vulnerable to develop ICDs based on such difference.

Summary

In summary, the results suggest that by using data classification methods, it may be possible to classify PD patients into PD+ICD and PD-ICD groups with certain behavioural tasks, which could further be used as a clinical assessment in unmedicated PD patients to reduce the chance of ICD onset. Here in the present study, it is shown that tasks manipulated speed pressure and decision conflict may be suitable for screening vulnerability to develop ICDs in PD patients. Future studies are in need to further investigate the type of measures and develop more proper models and algorithms in predicting ICDs onset in PD patients before treatment.

Chapter 4 The acute effects of deep brain stimulation of the subthalamic nucleus on task-switching within the framework of moving dots paradigm in PD patients

4-1 Abstract

Conflict monitoring during the information processes is one of the key characteristics of task switching. Evidence has shown that deep brain stimulation (DBS) of the subthalamic nucleus (STN) would induce deficits by disrupting the normal function of the STN on information processing during task switching in patients with Parkinson's disease (PD). To investigate such a hypothesis, ten PD patients treated with bilateral STN DBS were recruited to perform on a block-designed moving dots task, where parts of the task consisted of 100% dot coherence blocks (i.e. automatic behaviours) and other parts consisted of various coherence levels (5%-50%) (i.e. controlled behaviours). The beahavioural performance of PD patients was compared to twelve age-matched healthy controls (HC). The results show that the acute manipulation of STN DBS did not induce deficits on task switching for PD patients, instead STN DBS improved the performance on the moving dots task. However, PD patients with STN DBS ON did show impairments on the Inhibition/Switching section of Colour Word Interference Test, which supports the negative effect induced by STN DBS in PD patients. The evidence suggests that task-switching may involve fundamentally different but related cognitive processes, which are controlled by distinct brain areas. Moreover, the above results are in line with the hypothesis that the reliability of sensory information plays an important role on modulating SAT. Furthermore, PD patients still showed subtle difference on underlying cognitive components under the effects of DBS, which supports a role of the STN on modulating boundary separation and sensory information integration during task performance.

4-2 Introduction

Most daily behaviours are well-learned routines that evoke the same actions, from time to time decisions must be made to switch from the habitual/automatic behaviour to controlled behaviour in order to adjust to the changes. Such a process requires context monitoring and the control of motor inhibition to supress an intended/initiated action in order to activate an alternative action that is more context appropriate.

The subthalamic nucleus (STN) has been proposed to play an important role in motor control. As discussed in Chapter 1, the hyperdirect pathway of the basal ganglia (Nambu, Tokuno & Takada, 2002) consists of glutamatergic excitatory neurons that transmit signals quickly from the cerebral cortex to the substantia nigra pars compacta (SNr)/ the internal segment of the globus pallidus (GPi) via the STN, producing a net effect of motor inhibition, and that lesions of the STN induced involuntary movements in rodents (Crossman et al., 1984) and alleviated akinetic-rigid syndromes in parkinsonian monkeys (Aziz et al., 1992; Aziz, Peggs, Sambrook & Crossman, 1991; Bergman et al., 1990). In a primate study Isoda & Hikosaka (2008) found that the STN neurons showed activation during task switching. Moreover, the activation of the STN neurons was similar but slightly slower that the activation of the pre-SMA neurons, which supports the hypothesis that the STN receives signals regarding behaviour switching from the pre-SMA and activates its function of motor inhibition to supress the old ongoing but invalid actions in order to execute new adaptive actions (Hikosaka & Isoda, 2010). In addition to motor inhibition, it has been proposed that the STN also plays an important role in cognitive flexibility (Aron & Poldrack, 2006; Isoada & Hikosaka, 2008; Hikosaka & Isoda, 2010), which suggests that the STN activity is associated with supressing automatic and fast

actions to initiate controlled and slow actions. In particular, the STN receives direct projections from the pre-SMA and cingulate cortex that compose conflict monitoring systems, which allows the STN to implement cognitive control by sending NoGo signals via diffuse excitatory projections to basal ganglia output nuclei (Mink, 1996; Parent & Hazrati, 1995; Frank et al., 2007). Frank (2006) has proposed a computational role of the STN in dynamically controlling the threshold for executing a response, which is fundamentally modulated by the intensity of competing possible actions. In other words, STN is essential to integrate all information before action selection, thereby prevents premature responses especially in high-conflict situations. Studies have shown that high-frequency stimulation induced impairments during decision-making when decision conflict was presented in PD patients (Frank et al., 2007; Green et al., 2013). One potential hypothesis for the impairment could be the stimulation-induced disruption of the activity of the limbic circuit between the ACC and the ventral striatum as revealed by the imaging study of Schroeder et al. (2002). Consistent with the proposed computational role of the STN, Cavanagh et al (2011) showed that mPFC activity increased and decision threshold decreased with STN DBS on during conflict. In line with the above hypothesis, PD patients treated with deep brain stimulation (DBS) of the STN have been found to be impaired in slowing down when facing high decision conflict (Frank et al., 2007; Wylie et al., 2010; Green et al., 2013) and task switching during a Stroop interference task, where participants are required to supress the habit of saying the names of colours (automatic behaviours) and say the ink colour of the name printed instead (controlled behaviour) (Jahanshahi et al., 2000; Schroeder et al., 2002; Witt et al., 2008).

Here the present study used a block-designed moving dots task including automatic blocks and controlled blocks, which attempted to not only study behavioural switching but also simulate the dynamic environment during action selection (implemented by varied coherences of the moving dots and the explicit instructions on informing participants to be fast or accurate) in PD patients. Acute manipulation of STN DBS was adopted to assess the effect of STN DBS on behaviours in PD patients. Moreover, performance of PD patients was compared to age-matched healthy controls (HCs). In addition to behavioural switching, the moving dots paradigm also allows the investigation on the acute effect of STN DBS on mental processes associated with speed/accuracy trade-off (SAT) and information integration, which in the present PhD thesis are considered to be associated with the basic executive functions including switching, shifting and inhibition. Two studies examining the acute effects of STN DBS on the same moving dots paradigm have found that (1) STN DBS significantly influenced task performance especially under high decision conflict (i.e. high task difficulty) when accuracy was emphasized, indicating that stimulation reduced the effects of task difficulty/level of coherence of the moving dots on reaction times (RTs) (Green et al., 2013), and (2) when coherence level was kept constant at a relatively easy level, STN DBS had a stronger impact on moving dots task performance when speed was emphasized that led to fast and incorrect responses (Pote et al., 2016). Both studies suggest a role of the STN in and that STN DBS would induce negative impact on inhibitory control in PD patients. Following results from the above studies, it is hypothesised that when being ON stimulation PD patients would have impaired task switching, resulting in faster reaction time (RT) and more incorrect responses. Computational models were applied to the behavioural data to further study the underlying mental processes of SAT modulation and sensory information

integration. Three parameters including boundary separation, drift rate and non-decision time would be derived from the model. It is predicted that PD patients ON stimulation would have lower boundary separation and lower drift rate that are associated with impaired abilities of cognitive flexibility on the task.

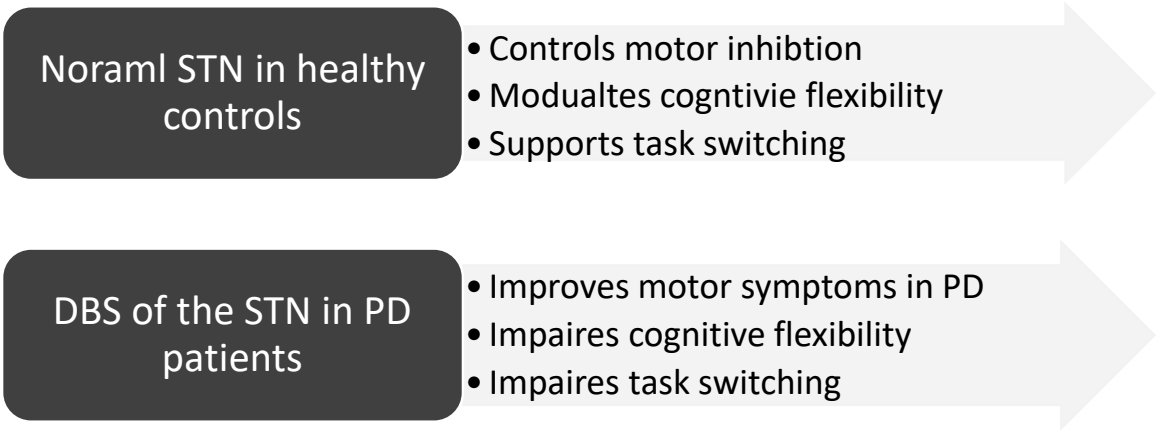

Figure 4.1 Difference between Parkinson's disease (PD) patients treated with deep brain stimulation (DBS) of subthalamic nucleus (STN) and healthy controls on the functions of the STN.

4-3 Material and methods

Participants

Ten patients (2 females) with Parkinson's disease treated with bilateral STN DBS at least 6 months or longer after surgery and twelve age-matched healthy controls (HCs) (5 females) were recruited. PD patients had a clinical diagnosis of idiopathic Parkinson's disease according to the Parkinson's Disease UK Brain Bank criteria (Hughes et al., 1992). The Mini

Mental State Examination (cut-off score of 26; Folstein et al., 1975) was used to screen for dementia. The Starkstein Apathy Scale (SAS) was used to screen for apathy symptoms (cut-off score of 14; Starkstein et al., 1992). The Beck Depression Inventory II (BDI-II, Beck et al., 1996) was used to screen for depression (cut-off score of 24). None of the patients had dementia or clinical depression. Even though the patients had significantly higher levels of apathy than the controls on the SAS, none had clinical levels/diagnosis of apathy. None of the healthy controls had any neurological or psychiatric illness, head injury or drug or alcohol abuse. Patients were examined by a neurologist, both ON and OFF stimulation, the severity of their motor symptoms and their stage of illness were rated on the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987). All participants had normal or corrected-to-normal vision. The clinical details of all participants are presented in Table 4.1, whereas the clinical data of patients with Parkinson's disease are listed in Table 4.2.

Table 4.1. Demographic and clinical details of the participants. Table shows means with standard deviations in parenthesis.

	PD (n=10)	**HC (n=12)**	***p* value**
Handedness (RH:LH)	10:0	12:0	N/A
Mini Mental State Examination	29.10 (1.10)	29.82 (0.39)	*p*=.070
Beck Depression Inventory	8.45 (5.54)	6.91 (5.80)	*p*=.542
Starkstein Apathy Scale	12.83 (4.34)	8.71 (3.25)	*p*=.141
Barratt Impulsivity Scale	65.4 (10.98)	57.27 (8.87)	*p*=.085
Digit Span forward and backwards total score	17.8 (3.85)	20.55 (3.50)	*p*=.103
Trail Making Test-part A Completion time (seconds)	52.5 (22.96)	45.1 (10.27)	*p*=.270
Trail Making Test-part B Completion time (seconds)	90.5 (30.63)	82.27 (24.22)	*p*=.358

Colour Word Interference Test-colour naming			
Errors	0.9 (1.10)	0.36 (0.65)	*p*=.178
Completion Time (seconds)	36.1 (7.74)	31.91 (4.83)	*p*=.110
Colour Word Interference Test-word reading			
Errors	0.5 (0.53)	0.00 (0.00)	*p*=.006* +[1]
Completion Time (seconds)	24.4 (4.25)	22.82 (4.29)	*p*=.253
Colour Word Interference Test-Inhibition			
Errors	2.2 (2.74)	1.18 (1.38)	*p*=.660
Completion Time (seconds)	65.1 (12.93)	61.09 (13.36)	*p*=.376
Colour Word Interference Test-Inhibition/Switching			
Errors	4.00 (2.49)	1.00 (0.82)	*p*=.002* +[2]
Completion Time (seconds)	81.9 (22.97)	58.09 (8.79)	*p*=.008* +[3]
Age of onset (years)	46.6 (8.44)	N/A	N/A
Disease duration (years)	14.9 (5.30)	N/A	N/A
UPDRS score III			
PD STN-DBS ON	15.6 (7.14)	N/A	*p*=.018*+[4]
PD STN-DBS OFF	29.5 (16.77)		

UPDRS= Unified Parkinson's Disease Rating Scale, PD = Parkinson's disease, STN-DBS = Deep brain stimulation of the subthalamic nucleus, N/A= Not Applicable, *= Statistically significant differences between groups

+[1]= Effect size of Errors of Colour Word Interference Test-word reading: Hedge's *g*= -1.817

+[2]= Effect size of Errors of Colour Word Interference Test-Inhibition/Switching: Hedge's *g* = -1.753

+[3]= Effect size of Completion Time of Colour Word Interference Test-Inhibition/Switching: Hedge's *g* = -1.444

+[4]= Effect size of UPDRS score III: paired sample Hedge's *g* = -2.504

Design and Procedure

A repeated measures design was used. All patients performed two blocks (i.e. auto and control blocks) of the moving dots task twice (in total four blocks), once ON stimulation and once OFF stimulation, with the order counterbalanced between participants. Due to the moving dots stimui were presented psudo-randomly, it was assumed that no here were no

learning/practice effects on the task performance. In addition, a study using the same task paradigm has suggested that there were no learning/practice effects on the behavioural parameters for the moving dots task (Huang et al., 2015), therefore the healthy controls performed the task once. In addition, it should affect the behavioural parameters for PD patients whether they were tested ON then OFF stimulation or OFF then ON stimulation. The task and all the questionnaires were performed by all participants on the same day. The study was approved by the joint ethics committee of the UCL Institute of Neurology and the National Hospital for Neurology & Neurosurgery. Informed consent was obtained from all participants. Clinical data of PD patients were shown in Table 4.2.

Table 4.2 Clinical data of patients with Parkinson's disease.

Subject	Gender/Age (years)	Disease Duration (years)	UPDRS (ON Med/OFF Stim)	UPDRS (ON Med/ON Stim)	DBS parameters	Years after DBS operation	L-Dopa Daily Dosage (LEDD)
01	m/68	26	30	13	L: 2-, 3.0V, 60 µs, 160Hz R: 9-, 3.0V, 60 µs, 160Hz	2.5 years	460
02	m/67	17	27	15	L:1-, 2.9V, 60µs, 130Hz R:9-, 2.9V, 60 µs, 130Hz	2 years	900
03	m/62	15	17	11	L:2-, 1.2V, 60 µs, 160Hz R: 2-,1.2V,60 µs ,160Hz	2 years	1060
04	m/68	9	27	21	L:1-, 2.3V, 60 µs, 180Hz R: 9-, 3.0V, 60 µs, 180Hz	2 years	960
05	f/69	16	16	11	L: 1-, 1.75V, 60 µs, 150Hz R: 9-, 1.65V, 60 µs, 150Hz	1 year	870
06	m/69	12	36	16	L: 1-, 2.6V, 60 µs 130Hz R :8-, 2.5V, 60 µs, 130Hz	1 year	500
07	m/54	14	67	14	L: 1-, 2.3V, 60 µs, 180Hz R: 9-, 3.0V, 60 µs, 180Hz	2.5 years	500
08	m/69	14	5	7	L: 2-, 1.2V, 62 µs, 130Hz R: 3-, 3.5V, 62 µs, 130Hz	2 years	700
09	f/45	7	41	33	L: 1-, 3.0V, 60 µs, 125Hz R: 9-, 2.0V, 60 µs, 125Hz/8-, 3.00V, 60 µs, 125Hz	2 years	700
10	m/44	12	29	15	L: 1-, 0.9V, 60 µs, 130Hz R:9-, 2.0V, 60 µs, 130Hz	2 years	150

The moving dots task

In the present study, a moving dots task paradigm (Britten et al., 1992) with block design was used to assess the task switching behaviour. As introduced in previous Chapters, the moving dots paradigm requires participants to decide the direction of a cloud of moving dots on a computer screen. The coherence levels of the moving dots may be manipulated for experimental purpose. For the 'Automatic' blocks, all trials contained moving dots with 100% coherence, which makes it very easy for the participants to decide the direction of the moving dots. For the 'Controlled' blocks, the dots coherence varied from 5% to 50% (including 5%, 10%, 15%, 25%, 35% and 50%), which required participants to decide under conflicts that would take more cognitive processing to make correct responses. All participants went through the order of 'Auto block- Control block- Auto block' to investigate task switching behaviours. In addition to the task switching behaviour, the moving dots paradigm also provides a chance to investigate the modulation of SAT and the ability to sample and integrate sensory information in guiding responses. The numbers of trials in for each block were selected to obtain reliable parameter estimation in diffusion modelling while at the same time avoiding fatigue for the patients (Lerche et al., 2017).

Data Analysis

R (R Core Team, 2013) and IBM SPSS software were used to analyze the data. Reaction times (RTs) of correct trials and response accuracy were measured as dependent variables. Linear mixed model (LMM) was used to fit reaction time with DBS (DBS ON/ DBS OFF/ HC), and Blocks (B1/ B2/ B3) as fixed effects. Subject was assigned as a random effect to account for subject-by-subject variation in overall RTs. In addition to a random intercept, a random slope in Type has also been added

into the model, which means that the rate at which individuals made decisions based on the Speed/Accuracy instructions is different from person to person.

To construct the mixed model, R package *lme4* (Bates, Maechler & Bolker, 2012) was used. The Maximum Llikelihood (ML) approach was used for parameter estimation. The Likelihood Ratio Test was used as a mean to attain p-values of the fixed effects, which compared models with full factors and reduced factors to determine the significance of a fixed effect. Moreover, a generalized linear mixed model (GLMM) was used to fit the response accuracy data due to the data being non-normal. For the present data a binomial distribution with a logistic link was selected to construct the model, at the same time it was specified that the response accuracy could vary randomly across subjects. ML approach with Laplace approximation was used for parameter estimation. DBS (DBS ON/ DBS OFF/ HC), and Blocks (B1/ B2/ B3) were assigned as fixed effects. Subject was assigned as a random effect to account for by-subject variation in overall response accuracy. $p<.05$ was used as a criterion for statistical significance. The Akaike information criterion (AIC), which estimates the relative quality of a statistical model given a specified data set, was used for model selection (Bozdogan, 1987). The relative quality of the model is indicated by the calculated information loss, therefore the model that has the minimised AIC would be chosen as the most fitted model given the specified dataset.

Hierarchical Drift Diffusion Model (HDDM)

In addition to the behavioural measurement, computational model was applied to derived underlying cognitive mechanisms during SAT modulation and sensory information integration. The diffusion model has been widely used in investigating underlying cognitive processes especially for two-forced-choice tasks (Voss & Voss,

2007; Voss et al., 2015; Ratcliff, 1978; Ratcliff & McKoon, 2008). In the diffusion model, three variables were calculated and discussed: the boundary separation, the non-decision time and the drift rate. The boundary separation (a) represents the response threshold to reach a decision/response. The longer the distance between the starting point and boundary threshold, the longer the response time is and the longer it takes to make a decision/response, and lesser errors are likely to occur. Conversely, the shorter the distance between the starting point and the boundary ` threshold, the faster a decision would be made, but the person is more likely to make errors. The components of the process are defined as having three phases: perceptual processing (processing the stimulus) with a certain duration, decision phase with a certain duration and response phase with a certain duration. The non-decision time (t0) is defined as the sum of the perceptual processing time plus the response time. Drift rate (v) refers to as the as the speed of the information accumulation process which leads to one of the two decision boundaries, for the current experiment it represents the certainty/confidence to distinguish between noise and signal. A higher drift rate suggests a higher certainty/confidence to distinguish noise and signal, which should be the case on easier higher coherence trials, whereas a lower drift rate at lower levels of coherence reflects a lower certainty/confidence to distinguish between noise and signal and to choose the direction of the moving dots on the harder trials.

To quantitatively fit the diffusion model to the behavioural data, a Python-based hierarchical drift diffusion model (HDDM) toolbox (Wiecki et al., 2013) was used. HDDM uses hierarchical Bayesian parameter estimation methods for simultaneous estimation of subject parameters and the group distribution from which they are drawn, at the same time providing measures of uncertainty in the posterior distribution (Figure 4.2). In addition, HDDM requires less data per subject/condition

than the non-hierarchical method, is able to deal with outliers and it allows for Bayesian data analysis. HDDM includes a regression model that allows estimation of trial-by-trial influences of a covariate onto model parameters. In the present study, HDDM was fitted to the behavioural data using the 'HDDMRegressor' function, which allows individual parameters to be described by a linear model specification. One of the benefits of estimating a model in a Bayesian framework is that significant testing can be directly performed on the posterior rather than relying on frequentist statistics. The Bayesian approach uses probability to quantify uncertainty and makes more precise probability statements about the state of the system by calculating the probability of a model given collected data (i.e. P(model | data)) (Puga et al., 2015).

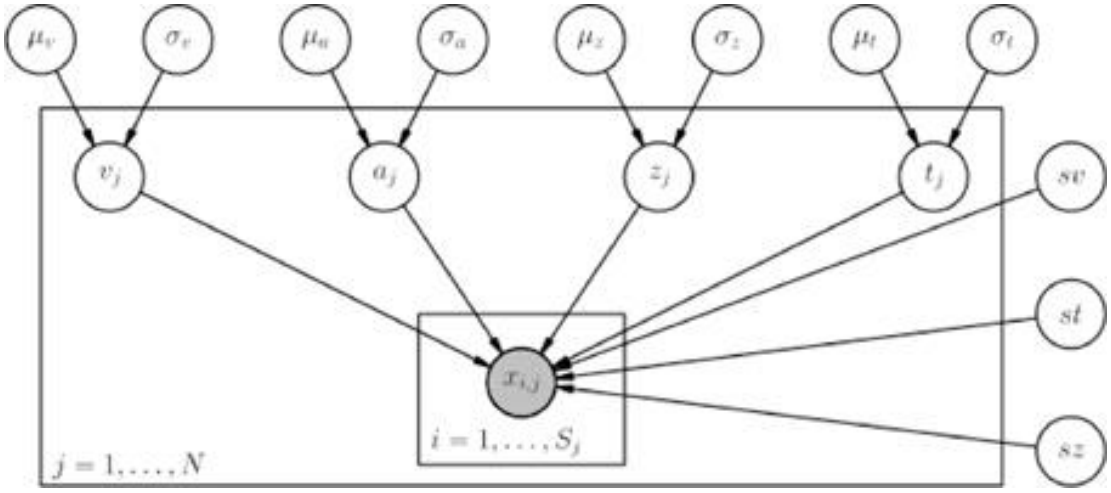

Figure 4.2 Basic graphical hierarchical model implemented by HDDM for estimation of the drift-diffusion model. Round nodes represent random variables. Shaded nodes represent observed data. Directed arrows from parents to children visualize that parameters of the child random variable are distributed according to its parents. Plates denote that multiple random variables with the same parents and children exist. The outer plate is over subjects while the inner plate is over trials. Figure from Wiecki, T., Sofer, I., and Frank, M. (2013).

4-4. Results

The results are presented form three perspectives: (1) behavioural data from task switching and moving dots task (SAT modulation and sensory information integration) points of view, (2) application of computational model on the behavioural data, and (3) comparisons between current and previous studies using the same moving dots task.

4-4-1 The analyses of the behavioural data

Response accuracy and RTs during task switching

Firstly, to examine how well participants performed the task, a GLMM was created using response accuracy as the dependent variable, with DBS (STN DBS ON/ DBS OFF/ HC) and Block (Block 1/ Block 2/ Block 3) set as fixed effects and subject as a random effect. For the variable 'Block', Block 1 represents the first block that was an Auto block with 100% dot coherence, following by a Control block (Block 2) with varied dots coherence and finally another Auto block (Block 3). Such order of blocks includes both switching from automatic behaviour to control behaviour, and switching from controlled behaviour to automatic behaviour. Note that the effects of all factors are expressed relative to the intercept conditions, which were set as the baselines. Here STN DBS ON was set as the intercept condition for DBS factor, whereas Block 1 was set as the intercept condition for Block.

The model showed a significant difference on response accuracy between Block 1 and Block 2 ($Z=-4.348$, $p<.0001$), suggesting that for all participants the performance on Block 1 (automatic block) was significantly better than on Block 2 (controlled block), which is in line with predictions. In addition, for PD patients ON stimulation, there is a possible negative trend on response accuracy between Block 3 and Block 1 ($Z=-1.705$, $p=0.088$), suggesting that PD patients with STN DBS ON had a trend to

have worse performance during Block 3 than Block 1. Both Block 3 and Block 1 were Auto blocks with 100% dot coherence; such a negative trend may potentially be the results of impaired task switching induced by DBS interrupting the function of STN on proactive switching in PD patients. However, the effect size of the trend is considered small (Hedge's g = 0.216). There was no difference on response accuracy (Z=-0.387, p=0.699) between PD patients ON versus OFF stimulation. In contrast, there is a significant difference on response accuracy between PD patients with STN DBS ON and age-matched HCs (Z=3.169, p=0.002), indicating that HCs had better performance than PD patients during Block 1. The effect size for the difference on response accuracy between PD patients with STN DBS ON during Block 1 is medium (Hedge's g = 0.568). Moreover, the two-factor interaction Block x DBS showed a significant difference (Z=-3.244, p=0.001), which suggested that the difference on response accuracy for the two blocks was larger for HCs than for PD patients with STN DBS ON. The effect size of difference between Block 1 and Block 2 for HCs is large (Hedge's g = 1.003) and the effect size of difference between Block 1 and Block 2 for PD patients with STN DBS ON is medium (Hedge's g = 0.561). As shown in Figure 4.3, such a difference was reflected by the significantly better performance for HCs during automatic blocks.

The results together suggest that (1) all participants had higher response accuracy during Auto blocks than Control blocks; (2) the acute manipulation of STN DBS had no effects on response accuracy, and (3) PD patients were able to perform the Control blocks as well as age-matched HCs, however during Auto blocks PD patients across both stimulation states had significantly lower response accuracy than HCs. Figure 4.3 illustrates the response accuracy during task switching for all participants.

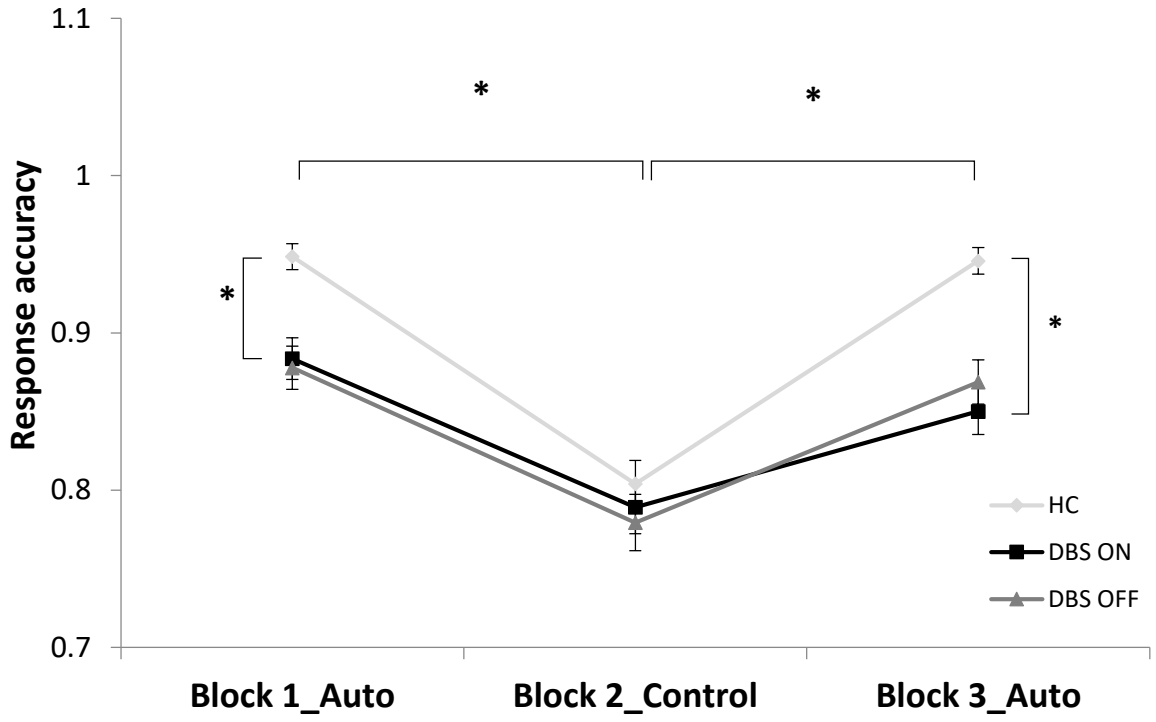

Figure 4.3 Response accuracy during task switching. Standard error means are presented as the error bars. The asterisk symbols denote statistically significant difference.

To further examine how the participants perform the behavioural task, reaction times (RTs) of correct trials were analysed with linear mixed models (LMMs). The LMM took RTs of correct trials as the dependent variable, with DBS (STN DBS ON/ STN DBS OFF/ HC) and Block (Block 1/ Block 2/ Block 3) set as the fixed effects and subject as the random effect. Note that the effects of all factors are expressed relative to the intercept conditions, which were set as the baselines. Here STN DBS ON was set as the intercept condition for DBS factor, whereas Block 1 was set as the intercept condition for Block.

The model showed that there was a significant difference on RTs between Block 2 and

Block 1 for PD patients ON stimulation (t=9.561, p<.0001), indicating that RTs during Block 2 RTs were significantly slower (higher) than during Block 1, which is in line with the prediction that RTs during Control blocks would be higher than during Auto blocks. The effect size of the significant effect of Block on RTs for PD patients with STN DBS ON is larger (Hedge's *g* = -1.107). There was no difference between Block 1 and Block 3 for PD patients ON stimulation (t=-1.279, p=0.201), indicating that PD patients ON stimulation had faster RTs when switching from controlled behaviour to automatic behaviour. During Block 1, there was no difference between PD patients ON stimulation and age-matched HCs (t=-1.245, p=0.224). There was a significant two-factor interaction between Block x DBS (t=2.895, p=0.004), showing that the difference on RTs between the two blocks are higher for HCs than for PD patients ON stimulation. In addition, the effect size of difference between Block 1 and Block 2 for HCs is larger (Hedge's *g* = -1.720) than the effect size of difference between Block 1 and Block 2 for PD patients with STN DBS ON (Hedge's *g*= -1.107), which suggests that the difference is larger for HCs than for PD patients with STN DBS ON. Together the results suggest that HCs were actually more sensitive during task switching compared to PD patients with STN DBS ON. In summary the results indicate that (1) all participants had successful task-switching behaviour reflecting as significantly higher (slower) RTs during Control blocks than Auto blocks, (2) STN DBS improved the RTs of PD patients to a degree that were as fast as age-matched HCs, and (3) however, PD patients ON stimulation had different behavioural patterns than OFF stimulation and age-matched HCs. Surprisingly the different behavioural patterns mainly occurred during Auto blocks when sensory information was sufficient (Table 4.3). Figure 4.4 illustrates the RTs of correct trials during task witching for all participants.

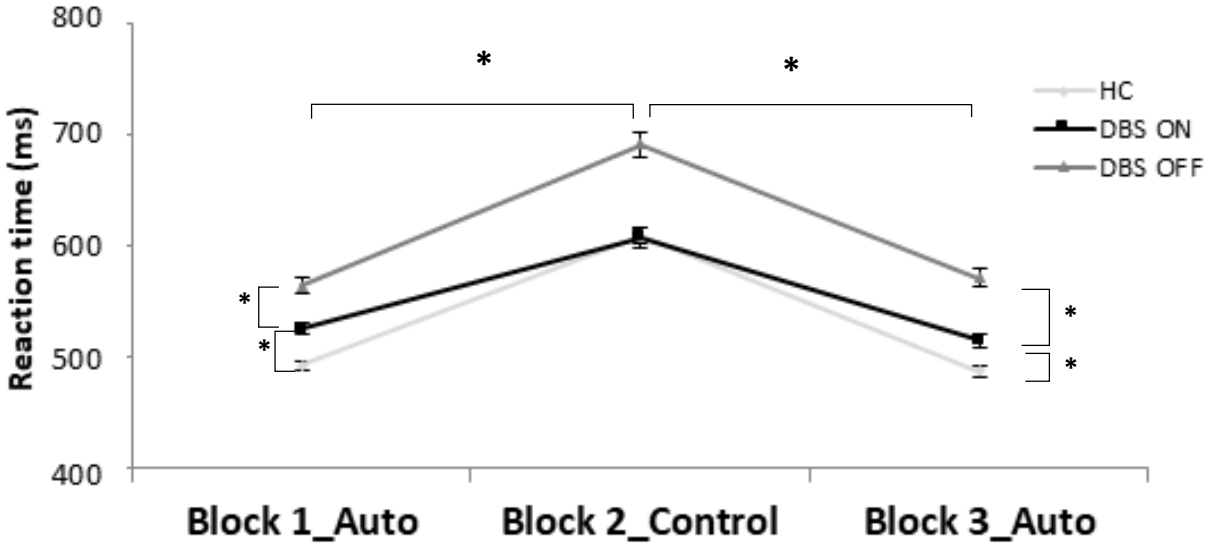

Figure 4.4 RTs of correct trials for PD patients with STN DBS ON and OFF stimulation and for healthy controls (HC). Standard error means are presented as the error bars. The asterisk symbols denote statistically significant difference. Visually the slopes of DBS OFF and HC seem to be parallel, however the slop of DBS ON seems to be steeper, indicating a trend of different behavioural pattern for PD patients ON stimulation.

Table 4.3 Summary of main findings of the behavioural data.

	Task switching from Auto blocks to Control blocks
Response accuracy	➢ All participants had successful task switching behaviour reflecting as better task performance during Auto blocks than Control blocks. ➢ The acute manipulation of STN DBS had no effects on response accuracy. ➢ PD patients were able to perform the Control blocks as well as age-matched HCs, however during Auto blocks PD patients had significantly lower response accuracy than HCs.
RTs of correct trials	➢ All participants had faster RTs during Auto blocks than Control blocks. ➢ Acute manipulation of STN DBS improved RTs for PD patients. ➢ PD patients ON stimulation showed different behavioural patterns

	compared to age-matched HCs and when being OFF stimulation.

Response accuracy and RTs under the effects of Speed/Accuracy instructions and dots coherence

Response accuracy

In addition to task switching, behavioural data were also analysed under the effects of Speed/Accuracy instructions and dots coherence to study the potential effects of STN DBS on the underlying mental processes of SAT modulation and information integration. Initially data analyses were performed using factors Type (Speed/ Accuracy), Level (5%/ 10%/ 15%/ 25%/ 35%/ 50%/ 100%) and DBS (STN DBS ON/STN DBS OFF/ HC) on dependent variables response accuracy and RTs (the results are shown in the Appendix B). However, such a procedure raised a problem that each coherence level may contain too small of trial numbers comparing to the 100% moving dots trials therefore decreases the power of the model. To decrease this difference on the trial number, instead of comparing each individual coherence level, the various coherence levels were divided into three groups: Low coherence levels (5%, 10%, 15%), High coherence levels (25%, 35%, 50%) and 100% coherence level (automatic behaviour). To examine how participants performed the task as a function of Speed/Accuracy instructions and dots coherence, a GLMM was created using response accuracy as the dependent variable, with Type (Speed/ Accuracy), Coherence (Low coherence/ High coherence/ 100% coherence) and DBS (STN DBS ON/STN DBS OFF/ HC) set as fixed effects and subject as a random effect. all levels of the categorical variables are compared to the base level (reference category). Here the base levels are: Accuracy (Type), 100% coherence (for Coherence) and STN DBS

ON (for DBS).

The model shows that all participants had higher response accuracy when Accuracy was emphasized (Z=-4.27, p<.0001, Hedge's g = 0.55). The effect of Type on response accuracy was significantly reversed during Low coherence trials (Z=2.06, p=0.039, Hedge's g =0.04) suggesting that when sensory information was insufficient, SAT had less impact on task performance for all participants. In addition, age-matched HCs had higher response accuracy than PD patients ON/OFF stimulation (Z=3.46, p<.0001, Hedge's g =0.37) during 100% coherence trials. PD patients (both ON and OFF stimulation) had higher response accuracy during 100% than Low coherence trials (Z=-5.4, p<.0001, Hedge's g = 0.4), however, response accuracy did not differ between 100% coherence trials and High coherence trials (Z=0.60, p=0.546) for PD patients. On the other hand, task performance of age-matched HCs was significantly related to dots coherence as response accuracy was significantly lower for High coherence trials (Z=-2.7, p=0.007, Hedge's g =0.44) and for Low coherence trials (Z=-3.2, p=0.001, Hedge's g =1.54) compared to 100% coherence trials. No other significant interaction was found. The results showed that (1) all participants had higher response accuracy when Accuracy was emphasized during 100% coherence and High coherence trials but not Low coherence trials, (2) the acute manipulation of STN DBS did not produce negative effects on response accuracy for PD patients, (3) age-matched HCs had higher response accuracy than PD patients when dots coherence was 100%, and (4) age-matched HCs had higher response accuracy as the dots coherence increased. However, for PD patients both ON and OFF stimulation, such an effect of dots coherence on response accuracy was only observed between Low coherence trials and 100% coherence trials but not between High coherence trials and 100% trials. Figure 4.5 illustrates the above results.

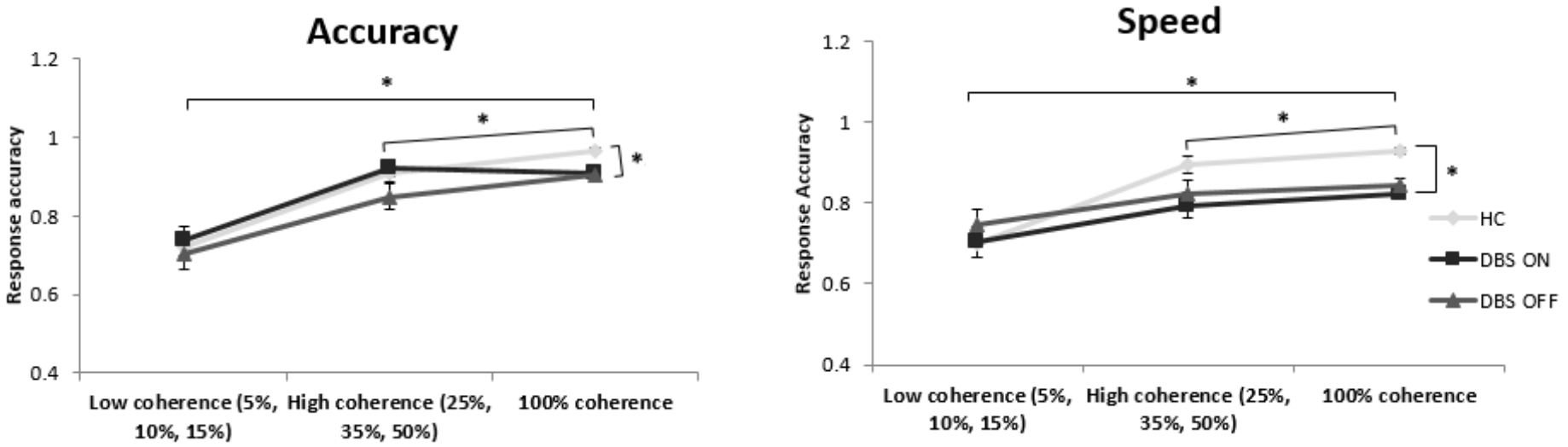

Figure 4.5 Response accuracy under the effects of Accuracy and Speed instructions and various dots coherence for PD patients with STN DBS ON (DBS ON), STN DBS OFF (DBS OFF) and age-matched healthy controls (HCs). Data of PD patients ON stimulation are presented in colour red, data of PD patients OFF stimulation are presented in colour blue, and HCs are presented in colour green. The standard error of the mean presented as the error bars. The asterisk symbols denote statistically significant differences.

Reaction Times

Furthermore, to examine how participants performed the task as a function of Speed/Accuracy instructions and dots coherence, a LMM was created using RTs of correct responses as the dependent variable, with Type (Speed/ Accuracy), Coherence (Low coherence/ High coherence/ 100% coherence) and DBS (STN DBS ON/ DBS OFF/ HC) set as fixed effects and subject as a random effect. All levels of the categorical variables are compared to the base level (reference category). Here the base levels are: Accuracy (Type), 100% coherence (for Coherence) and STN DBS ON (for DBS).

The model shows that all participants had faster RTs when Speed was emphasized ($t(4823)=-5.99$, $p<.0001$, Hedge's $g = 0.32$) for all coherence trials, except for the 100% coherence trials such an effect of Speed instruction was significantly reversed for age-matched HCs ($t(4823)=2.75$, $p=0.006$, Hedge's $g =0.30$), which means that for HCs there was no effect of Speed/Accuracy instructions on RTs during 100% coherence. All participants had faster RTs when dots coherence was 100% compared to High coherence trials ($t(4823)=3.04$, $p=0.002$, Hedge's $g =0.50$) and compared to Low coherence trials ($t(4823)=11.11$, $p<.0001$, Hedge's $g =0.86$). PD patients had faster RTs when ON than OFF stimulation ($t(4823)=4.86$, $p<.0001$, Hedge's $g =0.66$). No difference was found in RTs between PD patients ON stimulation and age-matched HCs ($t(26)=-1.69$, $p=0.104$). No other significant interactions were found. The results showed that (1) all participants had faster RTs when Speed was emphasized, except for when dots coherence was 100%, such an effect of Speed instruction was eliminated for age-matched HCs, (2) all participants had faster RTs when decision conflicts were low (i.e. when dots coherence was high), (3) the acute

manipulation of STN DBS significantly decreased RTs for PD patients to the level of the RTs of HCs.

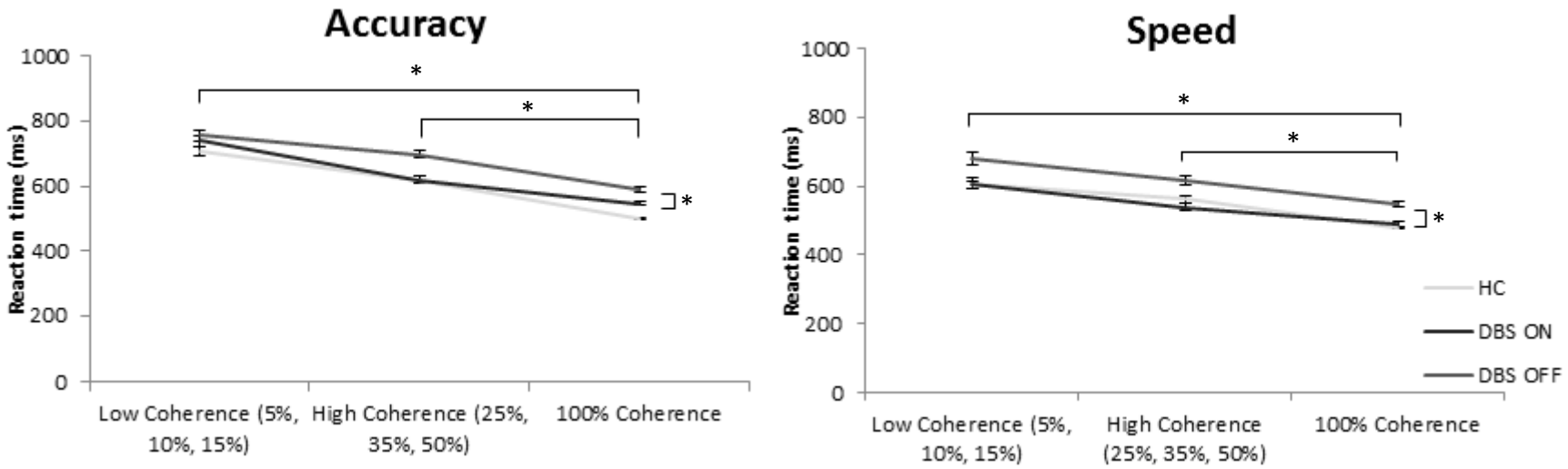

Figure 4.6 Reaction time of correct trials under the effects of Accuracy and Speed instructions and various dots coherence (Low coherence/ High coherence/ 100% coherence) for PD patients with STN DBS ON (DBS ON), STN DBS OFF (DBS OFF) and age-matched healthy controls (HCs). Data of PD patients ON stimulation are presented in colour red, data of PD patients OFF stimulation are presented in colour blue, and HCs are presented in colour green. Standard error of the mean is presented as the error bars. The asterisk symbols denote statistically significant differences.

4-4-2 The application of the Hierarchical drift diffusion model (HDDM) to the behavioural data of task switching

HDDM fitted to the behavioural data for task switching

The above results show that PD patients with STN DBS ON had different behavioural patterns during task switching compared to when being OFF stimulation and age-matched HCs, which is in line with the hypothetical role of the STN on proactive switching and the hypothesis that DBS of the STN interrupts such role that leads to impaired task switching in PD patients.

As discussed in previous chapter, the application of the HDDM allows the study of how task manipulations affect the underlying cognitive processes when performing the task for all participants. In the HDDM, the posterior distribution of three model parameters (i.e. the decision threshold, the non-decision time and the drift rate) was estimated under the effects of task manipulations and their interactions. Two main factors were considered for behavioural switching in the model: DBS (BDS ON/ DBS OFF/ HC) and Block (Block 1/ Block 2/ Block 3). Here an HDDM was constructed assuming that the decision threshold (a) and non-decision time (t), of which the former determines when to make responses whereas the later represents time for non-decision processes such as stimulus encoding and response execution, would vary between participants (i.e affected by the factor DBS) but would not be affected by the factor Block. In addition, the model considered drift rate (v) to vary under the effects of both DBS and Block, the former indicates difference on the ability of information accumulation among different participants and the later indicates the difference on the quality of sensory information provided by different blocks. For brevity the figures of the model are

not shown here, please refer to Appendix B. In summary the results from HDDMs show that (1) overall HCs had lower decision threshold, higher non-decision time and higher drift rate than PD patients, and (2) all participants had higher drift rate during Block 1 and lower drift rate during Block 2 (potentially due to task manipulations on moving dots coherence), however PD patients with STN DBS ON were less influenced by the switching of blocks on drift rate compared to being STN DBS OFF and age-matched HCs.

HDDM fitted to the behavioural data under the effects of speed/accuracy instructions and dots coherence

In previous HDDMs, the models were constructed using factors DBS and Block to assess the underlying cognitive components. To look into the data from the perceptual decision-making point of view, an HDDM using DBS (STN DBS ON/ STN DBS OFF/ HC), Type (i.e. type of the instruction: Speed/Accuracy) and Coherence (Low coherence/ High coherence/ 100% coherence) as fixed factors were further created. Here the HDDM was constructed assuming that the decision threshold (a) would vary between participants (DBS), different types of instructions (Type) and the quality of sensory evidence (Coherence). In addition, the model considered drift rate (v) to vary under the effects of DBS and Coherence but unaffected by Type. Non-decision time was eliminated from the model due to failed convergence of the model.

Table 4.4 The effect of Speed instructions on decreasing boundary separation (a) for all participants

The effect of Speed instructions on decreasing boundary separation (a)

	Low Coherence	High Coherence	100% Coherence
STN DBS ON	O	O	O
STN DBS OFF	—	+	—
HC	O	O	—

'O'= the effect of Speed instructions occurred, '—'= the effect of Speed instructions decreased, '+'= the effect of Speed instructions increased. Note that in the model data from STN DBS ON were set as the reference level for comparison.

Taken together, the HDDM shows that (1) all participants had higher decision threshold and lower drift rate when moving dots coherence decreased, (2) PD patients with STN DBS ON had lower decision threshold and lower drift rate than age-matched HCs but higher decision threshold and higher drift rate than being STN DBS OFF, (3) the acute manipulation of STN DBS had impacts on how PD patients performed the moving dots task under the effects of moving dots coherence and Speed/Accuracy instructions (Table 4.5).

Table 4.5 Summary of the behavioural data and the application of hierarchical drift diffusion model (HDDM) on the behavioural data

	Task manipulation	The acute manipulation of STN DBS	Comparison between PD patients and age-matched HCs
Behavioural results	➢ When sensory information was sufficient (100% and High coherence trials), all participants displayed SAT reflecting as faster RTs and more incorrect responses ➢ For all participants there was no effect of Speed/Accuracy instructions on behaviour during Low coherence trials	➢ STN DBS decreased overall RTs but did not render negative effect on response accuracy ➢ STN DBS did not affect how PD patients reacted to Speed/Accuracy instructions along with various dots coherence	➢ PD patients with STN DBS ON were able to perform as fast as HCs ➢ HCs had higher response accuracy than PD patients when dots coherence was 100% ➢ As the dots coherence increased, HCs had better response accuracy
Results derived from the HDDM	➢ When decision conflict was relatively low (i.e. High dot coherence), Speed/Accuracy instructions had an impact on modulating decision thresholds for all participants ➢ The modulation of decision threshold was dependent on both SAT and dots coherence simultaneously	➢ PD patients ON stimulation had lower decision threshold than OFF stimulation for all coherence and both instructions ➢ For 100% dots coherence, decision threshold modulation was unaffected by Speed/Accuracy instructions for PD patients ON stimulation ➢ For Low coherence trials, decision threshold modulation was unaffected by Speed/Accuracy instructions for PD patients OFF stimulation	➢ HCs had higher decision threshold and higher drift rate than PD patients ON/OFF stimulation ➢ Unlike HCs, drift rate did not differ between High coherence trials and 100% coherence trails for PD patients

SAT=Speed and Accuracy trade-off; RTs= reaction times; PD=Parkinson's disease; HCs=heanthy controls

4-4-3 Comparison between previous and present studies

In addition to behavioural data analysis and application of computational model, to see whether current data replicated the results of Green et al (2013) study or the Pote et al (2016) study, the data were further analysed as following.

Comparing to Green et al (2013) study

First the trials from the controlled blocks (of which the coherence levels ranged from 5%, 10%, 15%, 25%, 35% to 50%) were analysed. A GLMM was created using response accuracy as the dependent variable, with Type (Speed/ Accuracy), Coherence (5%/ 10%/ 15%/ 25%/ 35%/ 50%) and DBS (STN DBS ON/ DBS OFF/ HC) set as fixed effects and subject as a random effect. All levels of the categorical variables are compared to the base level (reference category). Here the base levels are: Accuracy (for Type), 5% coherence (for Coherence) and STN DBS ON (for DBS). For brevity the output of the GLMM is not shown. Figure 3.4 illustrates the results of the model. Type of instruction had no effects on response accuracy for all participants (PD patients with DBS ON: Z= -0.01, p=0.992; PD patients with DBS OFF: Z=0.35, p=0.726; HCs: Z=0.93, p=0.354), suggesting that Speed/Accuracy instruction had limited influence on response accuracy. For all participants, as the coherence level increased response accuracy also significantly increased (15%: Z=2.56, p=0.011, Hedge's g= 0.27; 25%: Z=4.02, p<.0001, Hedge's g=0.43; 35%: Z=4.41, p<.0001, Hedge's g=0.54; 50%: Z=4.41, p<.0001, Hedge's g=0.60), indicating that response accuracy was closely related to the quality of sensory information. There was no difference in response accuracy between PD patients ON versus OFF stimulation (Z=0.93, p=0.354) or between PD

patients ON/OFF stimulation and HCs (Z=0.35, p=0.726). No significant interactions were found.

Second, a LMM was created using RTs as the dependent variable, with Type (Speed/ Accuracy), Coherence (5%/ 10%/ 15%/ 25%/ 35%/ 50%) and DBS (STN DBS ON/ DBS OFF/ HC) set as fixed effects and subject as a random effect. All levels of the categorical variables are compared to the base level (reference category). Here the base levels are: Accuracy (for Type), 5% coherence (for Coherence) and STN DBS ON (for DBS). For brevity the output of the LMM is not shown. Figure 3.5 illustrates the results of the model. Type had a significant effect on RTs for all participants (t(3693)=-4.88, p<.0001, Hedge's g=0.40), suggesting that all participants responded faster when Speed was emphasised. Moreover, for all participants RTs decreased/became faster as the dots coherence increased (25%: t(3638)=-4.30, p<.0001, Hedge's g=0.38; 35%: t(3639)=-5.92, p<.0001, Hedge's g=0.50; 50%: t(3638)=5.31, p<.0001, Hedge's g=0.53), indicating that when sensory information was sufficient (i.e. higher dots coherence), all participants made responses faster. There was no differences in RTs between PD patients ON versus OFF stimulation (t(3638)=1.55, p=0.122) or between PD patients ON/OFF stimulation and HCs (t(58)=-0.52, p=0.803). No significant interaction was found. The results showed that, contrary to the Green et al study, which found that STN DBS reduced the effect of the present data did not find that acute manipulation of STN DBS had no significant effect when making decisions under conflict for PD patients. Figure 4.7 illustrates the above results.

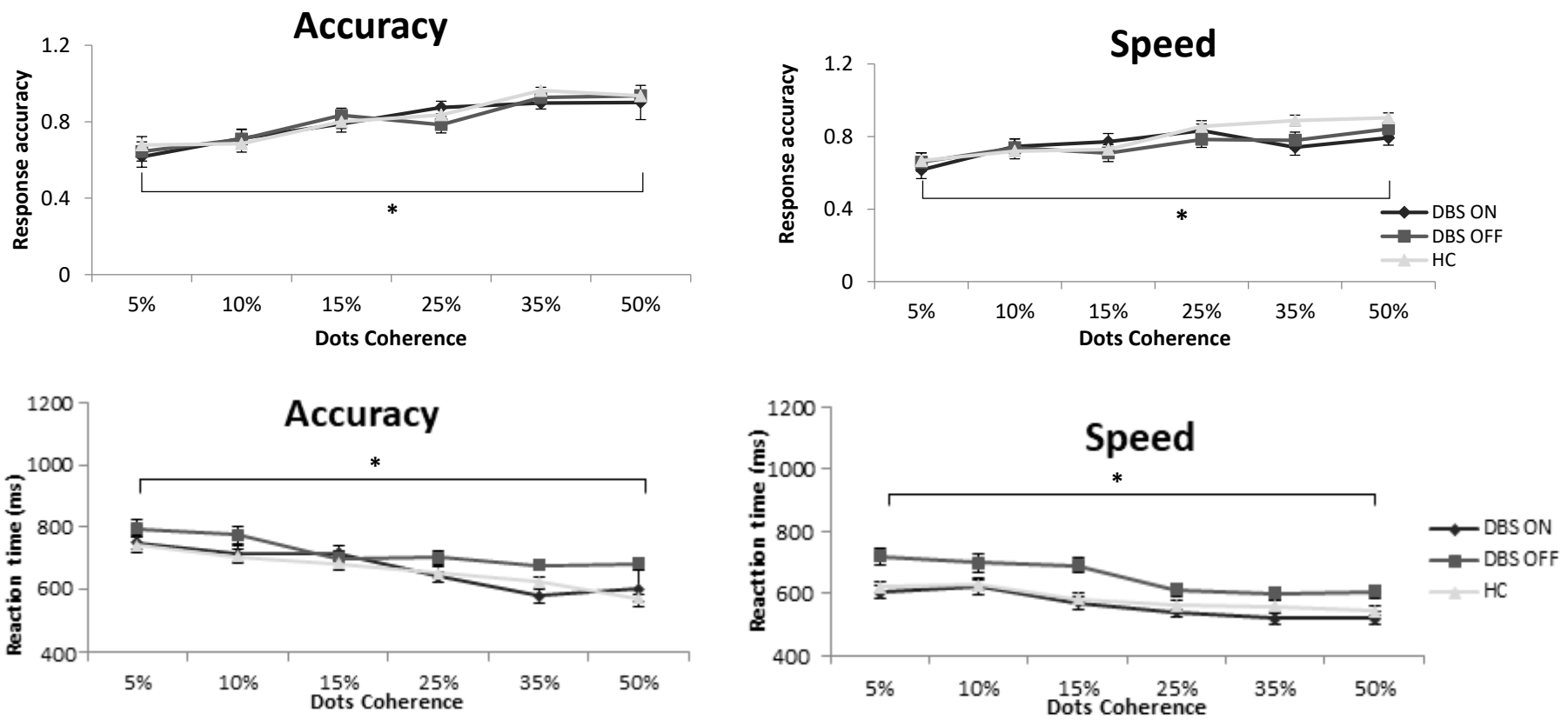

Figure 4.7 Response accuracy and Reaction time (ms) under the effects of Speed (SP)/Accuracy (AC) instructions and dots coherence from 5% to 50% for PD patients with STN DBS ON (DBS ON), STN DBS OFF (DBS OFF) and age-matched healthy controls (HCs). Data of PD patients ON stimulation are presented in colour red, data of PD patients OFF stimulation are presented in colour blue, and HCs are presented in colour green. The standard error of the mean is presented as the error bars. The asterisk symbols denote statistically significant differences.

Comparing to Pote et al (2016) study

To further compare current data with the Pote et al (2016) study, behavioural parameters from 50% trials (derived from the various coherence blocks) and automatic blocks (constant 100% dots coherence) were analyzed with GLMM and LMM. Type (Speed/ Accuracy) and DBS (STN DBS ON/ DBS OFF/ HC) were set as fixed effects and subject was set as a random effect. All levels of the categorical variables are compared to the base level (reference category). Here the base levels are: Accuracy (for Type) and STN DBS ON (for DBS). For brevity the outputs of the models are not shown. Figure 3.6 & Figure 3.7 illustrates the results of the models.

For 50% dots coherence trials, all participants responded faster ($t(593)=-3.14$, $p=0.002$, Hedge's $g=0.24$) and made more errors ($Z=-2.18$, $p=0.029$, Hedge's $g=0.33$) when Speed was emphasised. There was no difference in response accuracy between PD patients ON versus OFF stimulation ($Z=0.86$, $p=0.389$) and no difference in response accuracy between PD patients and age-matched HCs ($Z=0.78$, $p=0.437$). PD patients made faster responses when ON stimulation than OFF stimulation ($t(593)=3.36$, $p=0.001$, Hedge's $g=0.28$). There was no difference on RTs between PD patient with DBS ON stimulation and age-matched HCs ($t(41)=-0.81$, $p=0.422$). No significant interaction was found. Figure 3.6 illustrates the behavioural results of 50% dots coherence trials. The results from 50% trials suggest that the acute manipulation of STN DBS did not specifically induce faster RTs especially when Speed instruction was emphasised for PD patients. Instead, PD patients with STN DBS ON were able to perform as fast as age-matched HCs and did not sacrifice the accuracy, which may suggest an improvement on motor function produced by STN DBS. However, note that the

data from 50% trials were derived from a block with various dots coherence therefore the trail numbers are small, and that the various coherence was presented pseudo-randomly, therefore it is not possible to neglect the effect of coherence order. These two confounding factors may interfere with drawing a concrete conclusion on the effect of STN DBS and Speed/Accuracy instruction on making perceptual decisions for PD patients independently of task difficulty, if by simply looking at data from the 50% coherence trials. The results from 100% coherence blocks were therefore analysed to provide more evidence on how STN DBS and Speed/Accuracy instruction affect decision-making under conditions which decision conflicts were absent. For 100% dots coherence blocks, all participants had higher response accuracy when Accuracy was emphasised ($Z=-4.25$, $p<.0001$, Hedge's $g=0.2$). No difference was found between PD patients ON versus OFF stimulation in response accuracy ($Z=-0.35$, $p=0.724$). Age-matched HCs had higher response accuracy than PD patients ($Z=3.27$, $p=0.001$, Hedge's $g=0.28$). No significant interactions were found for response accuracy. Moreover, during 100% coherence trials PD patients ON stimulation had faster RTs than OFF stimulation ($t(3756)=5.35$, $p<.0001$, Hedge's $g=0.37$). Age-matched HCs did not have faster RTs when Speed was emphasised during the 100% dots coherence trials due to the effect of Speed was significantly reversed for HCs ($t(3756)=3.39$, $p=0.001$, Hedge's $g=0.21$), which suggests that during 100% coherence the effect of Speed/Accuracy instructions was eliminated for HCs but not to a degree that RTs were faster under Accuracy instructions (Figure 3.7). There was no difference on RTs between PD patients ON stimulation and HCs ($t(24)=-1.38$, $p=0.180$). No other significant interaction was found. Figure 3.7 illustrates the behavioural results of 100% dots coherence trials. By showing that PD patients with STN DBS ON had faster RTs along with making more incorrect responses than being OFF

stimulation especially under speed pressure, Pote et al (2016) suggested that STN stimulation induced impulsive actions in patients when acting under speed pressure independently of task difficulty. However, in the present study PD patients with STN DBS ON did not make more errors despite having in general faster RTs compared to being OFF stimulation when dots coherence was 100%. The decrease in RTs for PD patients ON stimulation was not induced by the speed pressure, but could likely be a result of the benefits of STN DBS on motor function, when performing moving dots task without decision conflicts. Therefore, the results showed that the acute manipulation of STN DBS in the present study did not induce impulsive behaviours (faster RTs along with more incorrect responses) when under Speed pressure during a constant dots coherence or 50% dots coherence. Figure 4.8 illustrates the above results.

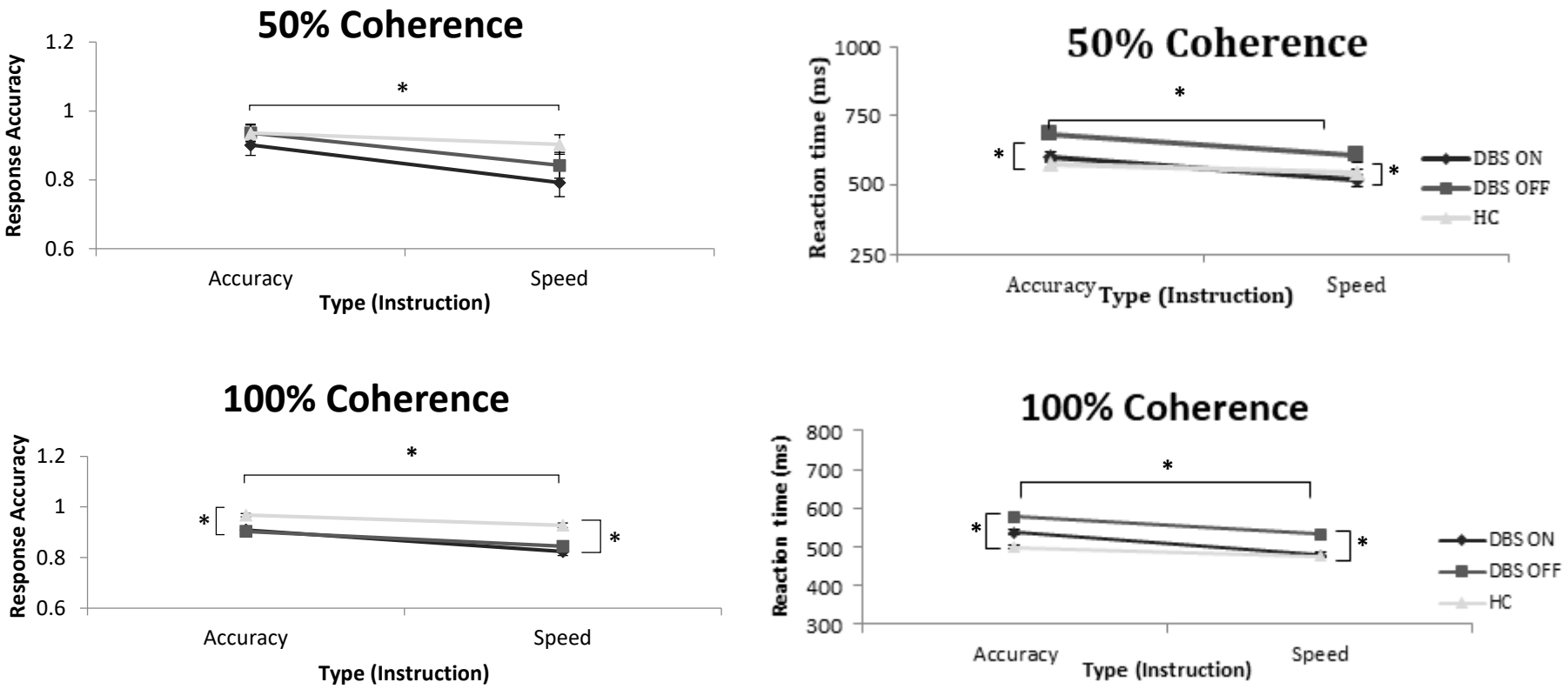

Figure 4.8 Response accuracy and Reaction time (ms) under the effects of Speed (SP)/Accuracy (AC) instructions and dots coherence from 5% to 50% for PD patients with STN DBS ON (DBS ON), STN DBS OFF (DBS OFF) and age-matched healthy controls (HCs). Data of PD patients ON stimulation are presented in colour red, data of PD patients OFF stimulation are presented in colour blue, and HCs are presented in colour green. The standard error of the mean is presented as the error bars. The asterisk symbols denote statistically significant differences.

4-5 Discussion

The present study investigated the acute manipulation of STN DBS in PD patients on task switching. In addition, by using a block-design moving dots task that also manipulated Speed/Accuracy instructions and various moving dots coherence, the acute effects of STN DBS on SAT modulation and sensory information integration were analysed as well. The main findings of the above results are: (1) from task switching point of view, the acute manipulation of STN DBS did not significantly induce deficits on behaviours for PD patients, (2) from the SAT modulation and sensory information integration point of view, acute effects of STN DBS improved RTs and underlying cognitive components (i.e. drift rate and boundary separation) but impaired making responses during 100% coherence trials in PD patients, and (3) the acute manipulation of STN DBS had impacts on behavioural patterns for PD patients. Similar to the results section, the following discussion is presented from three aspects: (1) the effects of STN DBS on behavioural switching, (2) the effects of STN DBS on SAT modulation and sensory information integration, and (3) comparison between present and previous results using similar moving dots tasks.

The effects of STN DBS on behavioural switching

The results from the present behavioural task did not show that the acute manipulation of STN DBS had significant influences on behavioural switching from Auto blocks to Control blocks in PD patients. Instead, both behavioural data and computational parameters suggest that PD patients had impaired mental processes during Auto blocks, which would be further discussed in the next section. PD patients with STN DBS ON had a possible negative trend to have worse performance during Block 3 than Block 1. Since both Block 3 and Block 1 were

Auto blocks with 100% dot coherence; such a negative trend may potentially be the results of impaired task switching induced by DBS interrupting the function of STN on proactive switching in PD patients. However no acute effect of STN DBS was found on behavioural switching from Auto blocks to Control blocks in PD patients. A few reasons may contribute to the non-significant results on task switching: firstly, the attentional demands of the Control blocks were within the available resources of PD patients. Brown & Marsden (1988) proposed a hypothesis that the locus of attentional control is an important aspect in determining the presence and/or the magnitude of cognitive deficits in PD patients, which suggests that PD patients may not show deficits performing that task if the demands of the task are within the available attentional resource. The results are in line with the hypothesis showing that performance of PD patients during the Control blocks maintained despite the increased task demands. Secondly, previous studies have shown that PD patients with STN DBS ON had impairments on performing Stroop interference task, which requires participants to withhold a predominant/automatic response (i.e. word reading) and activate a more controlled one (i.e. reading ink colour instead of word) (Combs et al., 2015; Troster, Jankovic, Tagliati, Peichel, & Okun, 2017). In the present study, the automatic behaviours were defined as responding to 100% of the dots moving to the same direction, which is not as predominantly encoded in the brain as word reading. Suck task difference may contribute to the non-significant results.

Despite the behavioural results showing no significant negative effects on task switching, the psychological tests showed that PD patients with STN DBS ON had robustly slower RTs and lower response accuracy than age-matched HCs on the Colour Word Interference

Test-Inhibition/Switching (i.e. Stroop interference task, see Table 4.1). The test requires participants to say the ink colours of the printed colour words but when encountering a certain cue (e.g. when the printed word was in a rectangular text box), participants are instructed to say the printed colour words instead of the ink colours. Note that PD patients only performed the task once (when being STN DBS ON), therefore it is unknown that whether such deficits were induced by the acute effect of STN DBS. Nevertheless, the results from this task indicate that PD patients with STN DBS ON had impaired behavioural/mental set switching. This is consistent with previous studies showing that PD patients were impaired in performing tasks that require mental sets/rules switching (Combs et al., 2015; Troster et al., 2017). In addition to the role of STN, behavioural and imaging studies show that patients who suffered from frontal lobe damage showed deficits in task switching (Owen et al., 1993; Holroyd & Coles, 2002; Rushworth et al., 2004; Botvinick et al., 2004; Sakai, 2008), which may indicate that the cortico-basal ganglia loops are closely involved in controlling task switching. Together the evidence suggests that task-switching may involve fundamentally different but related cognitive processes, which are controlled by distinct brain areas. Future studies are required to investigate these different connections on controlling task switching.

Modulation of SAT requires the optimal estimation on the precision of the sensory input

The results reported above show that Speed and Accuracy instructions had stronger impacts on behavioural data especially during high coherence level trials but not when coherence levels were low, which indicates that the modulation of boundary separation and potentially SAT requires the reliability of the sensory evidence to be known. In the theoretical

frameworks of a two-alternative-forced-choice task such as the diffusion model, the optimal decision-making processes are described as information integration to a threshold (Gold & Shadlen, 2002; Ratcliff & McKoon, 2008). However, Deneve (2012) proposed that such analogy hides a problem that to know how much information to be accumulated and set the optimal decision threshold, firstly the reliability of the sensory evidence must be known. Under the Bayesian framework, the modulation of decision threshold is thus associated with the reliability of sensory evidence and the inner drive to be fast/accurate. The present results not only support the involvement of the reliability of sensory information on drift rate, but also support the role of the reliability of sensory information on modulating decision threshold that affects the accuracy of the decisions.

Interestingly, the above results show that during Control blocks PD patients were able to react as well as age-matched HCs, however during Auto blocks, PD patients not only had poorer performance and slower RTs, but also had lower drift rate and higher decision threshold compared to age-matched HCs. Moreover, PD patients with STN DBS ON had different behavioural patterns compared to being OFF stimulation and compared to age-matched HCs, reflecting as both HCs and PD patients with STN DBS OFF had bigger difference on RTs between Auto blocks and Control blocks, however for PD patients with STN DBS ON such a difference was significantly smaller (Figure 4.4). The results indicate that PD patients with STN DBS ON were slow in making decisions when sensory information was sufficient. Moreover, the application of the HDDM showed that PD patients with STN DBS ON, though had higher decision threshold, were less influenced by task switching on drift rate. One of the possible reasons may be the involvement of the Speed/Accuracy instructions that interrupted

the decision-making processes for PD patients with STN DBS ON. As shown in Table 4.4, for PD patients with STN DBS ON only, the modulation of decision threshold was influenced by Speed/Accuracy instructions during 100% coherence trials. For age-matched HCs and PD patients with STN DBS OFF, when sensory information was sufficient, the high reliability of the sensory information increased confidence in making decisions and surpassed the effect of Speed/Accuracy instructions on processing the decisions. However, for PD patients with STN DBS ON, even when the reliability of the sensory information was high, the effect of Speed/Accuracy instructions remained strongly on modulating decision threshold, resulting in slower RTs.

Bogacz (2010) proposed four theories that explain the part of the cortico-basal ganglia circuit that modulates the Speed/Accuracy trade-off, including 'cortical', 'striatal', 'STN' and 'synaptic' theories. All of the four theories are based on the mechanism that the Speed instructions increase the baseline of cortical integrators and cause changes in one of the four circuits. However these theories neglected the potential effect of the reliability of the sensory information, which in the present study has been shown to be important when making perceptual decisions. Future studies are in need to investigate (1) how normal STN activity modulates decision thresholds when simultaneously taking into accounts of the reliability of the sensory information, and (2) how DBS of the STN would affect this process in PD patients that lead to impairments when performing tasks require sensory information integration.

Comparison between previous and present studies

As shown in introduction, two studies examining the acute effects of STN DBS on moving dots tasks found that (1) STN DBS induced significantly lower response accuracy and faster RTs under high decision conflict (1.6%, 4.8%, 8.0%) especially when accuracy was emphasized, indicating that stimulation reduced the effect of task difficulty/level of coherence of the moving dots on reaction times (RTs) (Green et al., 2013), and (2) when coherence level was kept constant at a relatively easy level (50%), STN DBS induced faster RTs and lower response accuracy for PD patients when Speed was emphasised (Pote et al., 2016). Contrary to the Green et al (2013) study, the present study did not find an effect of STN DBS on reducing the effects of dot coherence, which potentially results from the fact that even the low coherence trials (5%, 10%, 15%) had higher coherence levels compared to the Green et study (2013) (1.6%, 4.8%, 8.0%). On the other hand, the present study showed that PD patients with STN DBS ON had significantly lower response accuracy when Speed was emphasised during High coherence trials but no significant difference on RTs compared to when being STN DBS OFF, which did not fully support the hypothesis that Speed pressure induces fast and low response accuracy in PD patients. Such an observation could result from the complex design of the current experiment, which may not be optimal in terms of studying the impulsive behaviours induced by STN DBS in PD. In addition, the Green et al (2013) study tested PD patients ON versus OFF stimulation OFF dopamine medication, whereas Pote et al (2016) study tested PD patients ON dopamine medication, therefore the effects of dopamine medication could not ne neglected. Despite the different procedures and behavioural results, the previous two studies and the present study all suggest a role of the STN and effects of DBS on affecting SAT, and modulating boundary threshold potentially via encoding the reliability of sensory information that is associated with the dots coherence.

Future studies are required to further investigate the effects of STN DBS on affecting SAT modulation, the direction of such effects, and the possibility of inducing negative effects on behaviours in PD patients.

Table 4.6 Behavioural data comparison between previous studies and the present result

Comparing to Green et al study (2013)		Comparing to Pote et al study (2016)	
Results from the Green et al (2013) study	Present Study	Results from the Pote et al (2016) study	Present results
➢ PD patients with STN DBS ON had faster RTs and lower response accuracy than when OFF stimulation when Accuracy was emphasised during high decision conflicts (low dots coherence: 1.6%, 4.8%, 8.0%)	➢ STN DBS did not induce faster RTs and higher error rate under Accuracy instructions during high decision conflicts (low coherence level: 5%, 10%, 15%) for PD patients	➢ PD patients with STN DBS ON had faster RTs along with higher error rate than when OFF stimulation under Speed pressure during a constant 50% dots coherence	➢ STN DBS decreased overall RTs but did not induce faster RTs along with higher error rates especially under Speed instructions during 50% coherence for PD patients ➢ STN DBS decreased overall RTs but did not induce faster RTs along with higher error rates especially under Speed instructions during 100% coherence for PD patients

Summary

The present study shows no negative effect on task switching behaviours induced by the acute manipulations of STN DBS on a block-designed moving dots task. However, PD patients with STN DBS ON did show deficits on task switching during the Inhibition/Switching part of the Colour Word Interference Test compared to age-matched HCs. The evidence suggests that task-switching may involve fundamentally different but related cognitive processes, which are controlled by distinct brain areas. Moreover, the above results are in line with the hypothesis that the reliability of sensory information plays an important role on modulating SAT. Furthermore, PD patients still showed subtle difference on underlying cognitive components under the effects of DBS, which supports a role of the STN on SAT and sensory information integration. To further investigate how DBS may affect STN function on cognitive and motor control, in the next chapter I would study PD patients with STN DBS using a behavioural task that manipulated unexpected sensroy events which leads to 'action reprogramming'.

Chapter 5 The effect of deep brain stimulation of the subthalamic nucleus on action reprogramming when encountering unexpected events

5-1. Abstract

Following previous results indicating that the deep brain stimulation (DBS) of the subthalamic nucleus (STN) may disrupt the role of the STN in inhibition in Parkinson's disease (PD) patients, the present study aimed to investigate the potential effect of DBS STN on reprogramming actions when facing unexpected sensory events. The STN has been proposed to play a prominent role in motor inhibition, reprogramming planned actions and is involved in interruption of cognitive functions and attentional reorientation when encountering unexpected sensory events. To investigate such a role of the STN, ten patients with Parkinson's disease (PD) treated with bilateral deep brain stimulation (DBS) of the STN were recruited to participate in the study using a probabilistic reaction time (RT) task. PD patients performed the task twice, once ON stimulation and once OFF stimulation, with a counterbalanced design. The performance of PD patients was also compared to twelve age-matched healthy controls (HCs). The results show that all participants were able to react fast during Predictable blocks/Probable trials than Unpredictable blocks/Improbable trials. In addition, response accuracy did not differ between Predictable and Unpredictable blocks for all participants, but for HCs response accuracy was higher during Probable trials than Improbable trials, such a difference was not observed in PD patients across stimulation states. Furthermore, PD patients exhibited robust speed and accuracy trade-offs when performing the probabilistic RT task, which may indicate that PD patients, especially PD patients OFF stimulation, were predominately aiming to act fast therefore sacrificed response accuracy. The results thus indicate that PD patients with STN DBS OFF could act as fast as age-matched HCs, however such fast responses would cost response accuracy. The present study did not show an effect of DBS on inducing impaired action reprogramming, however it did not rule out the the possibility of STN DBS to impaire motor/cognition control through inhibiton in PD patients. Moreover, in the present study PD patients treated with STN DBS were assessed ON medication, which may be the reason why the results did not reflect the hypothetical effects of DBS on interrupting the role of STN in cognitive and motor control.

5-2 Introduction

Facing unexpected events is inevitable in daily life, which may lead to slowness in movement and cognitive distraction. When facing a surprising or an unexpected event, the brain has to inhibit the execution of a planned action, gather more information and generate a new action in order to reach a better outcome given the changed circumstance. Such a process of action adjustment is referred to as 'action reprogramming' (Mar, Piekema, Coles, Hulstijn, & Toni, 2007).

A significant feature of action reprogramming is the slowness in reaction time (RT) when encountering unexpected events. Such slowness has been associated with a global mechanism of motor inhibition via the frontal-basal ganglia connections (Wessel & Aron, 2013, 2015). In addition, evidence has shown that multiple routes are involved in an interaction between the primary motor area and the frontal cortex to mediate action inhibition during action reprogramming: a direct cortical route and a subcortical route via the basal ganglia, including the subthalamic nucleus (STN) (Neuber, Mars, Buch, Olivier, & Rushworth, 2010). Local field potential recordings on Parkinson's disease (PD) patients undergoing DBS revealed that elevated STN activity is associated with post-error slowing of RTs, which suggests a role for the STN in motor adjustments following errors (Siegert et al., 2014). It has been well-established that the STN is involved in motor inhibition (Aron & Poldrack, 2006; van den Wildenberg et al., 2006; Kim & Hikosaka, 2015; Alegre et al, 2013; Obeso et al, 2014). Human imaging studies also provide evidence supporting the prominent role of the STN in suppressing an ongoing movement, and that decreasing STN activity releases the brain from inhibition (Aron &Poldrack, 2006; Aron, Behrens, Smith, Frank, & Poldrack, 2007; Li et al, 2008; Forstmann et al, 2010). Such a mechanism is possibly through the 'hyperdirect' pathway in which the STN receives signals from the cerebral cortex and projects to the SNr/GPi (Nambu, Tokuno, & Takada, 2002; Kim & Hikosaka, 2015). Furthermore, in primate studies, the STN has been shown to mediate the control signals from cortex and implement action switching from automatic to controlled behaviours via its connections with the basal ganglia output nuclei (Isoda & Hikosaka, 2008; Hikosaka & Isoda, 2010). The STN has also been proposed to serve as a brake to allow more information to be integrated before making an optimal response, which is believed to be relevant to its role in motor inhibition (Frank, 2006). Moreover, computational models of the basal ganglia have suggested that the degree of decision conflict dynamically modulates STN activity, which contributes to optimally delaying action selection in a given situation in order to decrease the uncertainty

when making decisions (Frank, 2006; Bogacz & Gurney, 2007; Bogacz, Wagenmakers, Forstmann, & Nieuwenhuis, 2010). In addition, a recent study of local filed potentials from the STN in deep brain stimulation (DBS) treated PD patients has shown that encountering unexpected events increases STN activity, which leads to the decrement of verbal working memory, and is related to attentional reorientation (Wessel et al., 2016). Wessel et al (2016) further proposed that surprise (i.e. unexpectedness) interrupts cognition via the same fronto-basal ganglia mechanism that interrupts action, which may lead to a new theory of distraction that involves a cortico-basal ganglia network that underlies motor suppression but also affects cognitive function. These studies together suggest that the STN, being part of the global suppressive mechanism of the basal ganglia, also participates in mediating cognitive functions such as making decisions under decision conflict and/or in response to encountering unexpected events. In line with such a hypothesis, the STN may potentially be involved in controlling action reprogramming.

STN DBS is an effective procedure for treating the motor symptoms in patients with Parkinson's disease (PD) (Deuschl et al, 2006; Weaver et al., 2012; Williams et al, 2010). It has been hypothesised that high-frequency stimulation of the STN supresses the over enhancement of oscillatory β activity in PD patients, which is closely associated with the deterioration of flexible behavioural and cognitive control (Engel & Fries, 2010), therefore is associated with the therapeutic motor improvement of DBS in PD patients (Kühn et al., 2008). Consistent with the hypothesised computational role of the STN, DBS of the STN has been shown to induce faster reaction times (RT) during high-conflict decision contexts in PD patients, potentially due to stimulation of the STN interfering with the normal STN activity on inhibiting premature responses (Jahanshahi et al, 2000; Witt et al, 2006; Frank et al., 2007; Green et al., 2013; Pote et al, 2016). While the exact mechanism underlying the beneficial effects of STN DBS on the motor symptoms of PD remains unknown (Vitek, 2002; McIntyre, Savasta, Kerkerian-Le Goff, & Vitek, 2004), it is hypothesised that high frequency stimulation decreased STN activity, which releases the brain from motor inhibition. Furthermore, PD patients treated with DBS of the STN have been shown to have impairments in response inhibition (Hershey et al., 2004, 2010; Ballanger et al., 2009; Favre et al., 2013; Obeso et al., 2013; Georgiev et al, 2016; Williams et al, 2015) and making accurate decisions under decision conflict ON stimulation compared to OFF stimulation (Jahanshahi et al., 2000; Schroeder et al., 2002; Frank et al, 2007; Witt et al., 2008; Wylie et al., 2010). To examine the hypothesis that STN modulates reactions to unexpected events, a probabilistic RT task

created by Galea et al (2012) was used to assess the effect of STN DBS on perceiving unexpected sensory events and action reprogramming on PD patients. PD patients receiving both STN DBS and dopaminergic medication and age-matched healthy controls were recruited for the study. Patients were tested OFF and ON stimulation ON their usual dopaminergic medication. The probabilistic RT task used a predictable first-order Markov sequence to generate order of stimulus presentation, which enabled the participants to predict the stimulus in current trial based on what appeared in the previous trial. Trials that violated the expectedness/prediction were defined as improbable and thus created a sense of unexpectedness.

Thus two kinds of blocks were included in the behavioural task: one was unpredictable and the other was predictable. Within the predictable trials there were probable trials and improbable trials, which were designed to create the sense of unexpectedness. The sense of unexpectedness is quantified by the frequency of stimulus appearance. Unexpected events, as Wessel & Aron (2017) categorised in their review, can be of three different types: (1) action error, (2) unexpected action outcome and (3) unexpected perceptual events. The unexpected events manipulated in the present study were unexpected perceptual events. In addition, the unexpectedness of the sensory event in the present task was task relevant as participants had to make responses in accordance to the presented imperative stimulus (IS), which may not only affect the interruption of behaviour but also involve interrupting cognition. While there may exist different underlying neural mechanisms in the brain that would be triggered by the three different types of unexpected events, Wessel & Aron (2017) further proposed a unified theory on how these unexpected events affect motor and cognitive functions. Namely, when unexpected events activate the fronto-basal ganglia network that modulates suppression of ongoing motor function, cognitive functions (e.g. verbal working memory) at the same time will be interrupted by the activation of the same network, involving the pre-SMA/right inferior frontal cortex and the STN. It is hypothesised that the STN would ordinarily be involved in perceiving surprising events via the same mechanism as motor inhibition, and that STN DBS which reduces STN hyperactivity in PD would interfere with this 'unexpected' function such that when tested ON STN DBS, PD patients would have overall faster RTs but impaired action reprogramming relative to DBS OFF, which leads to more incorrect responses during the improbable trials.

5-3 Materials and Methods

Participants

Ten PD patients (2 females) treated with Parkinson's disease treated with bilateral STN DBS at least 6 months or longer after surgery and twelve age-matched healthy controls (HCs) (5 females) were recruited for the study. All patients met the United Kingdom Brain Bank criteria for idiopathic PD (Hughes, Daniel, Kilford, & Lees, 1992). For all participants, there was no history of any other neurological disease, head injury, psychiatric illness, or drug/alcohol abuse. The Mini Mental State Examination (cut-off score of 26; Folstein, Folstein, & McHugh, 1975) was used to screen for dementia and the Beck Depression Inventory (Beck, Steer, & Brown, 1996) was used to screen for depression (cut-off score of 24). None of the patients had dementia or clinical depression. Patients were examined by a neurologist, both ON and OFF stimulation, and the severity of their motor symptoms and their stage of illness were rated on the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987). All participants had normal or corrected-to-normal vision. The clinical details of all participants are presented in Table 5.1. Demographic information and clinical data of patients with Parkinson's disease are listed in Table 5.2.

Table 5.1. Demographic and clinical details of the participants. Table shows means with standard deviations in parenthesis.

	PD (n=10)	**HC (n=12)**	***p* value**
Age (years)	61.5 (10.10)	68.17 (9.47)	*p*=.107
Handedness (RH:LH)	10:0 (100% RH)	12:0 (100% RH)	N/A
Mini Mental State Examination	29.10 (1.10)	29.82 (0.39)	*p*=.070
Beck Depression Inventory-II	8.45 (5.54)	6.91 (5.80)	*p*=.542
Starkstein Apathy Scale	12.83 (4.34)	8.71 (3.25)	*p*=.141
Barratt Impulsivity Scale	65.4 (10.98)	57.27 (8.87)	*p*=.085
Digit Span forward and backwards total score	17.8 (3.85)	20.55 (3.50)	*p*=.103
Trail Making Test-part A			
Completion time (seconds)	52.5 (22.96)	45.1 (10.27)	*p*=.270
Trail Making Test-part B			
Completion time (seconds)	90.5 (30.63)	82.27 (24.22)	*p*=.358
Colour Word Interference Test-colour naming	0.9 (1.10)	0.36 (0.65)	*p*=.178
Errors	36.1 (7.74)	31.91 (4.83)	*p*=.110
Completion Time (seconds)			
Colour Word Interference Test-word reading			
Errors	0.5 (0.53)	0.00 (0.00)	*p*=.006*
Completion Time (seconds)	24.4 (4.25)	22.82 (4.29)	+[1] *p*=.253

Colour Word Interference Test-Inhibition			
Errors	2.2 (2.74)	1.18 (1.38)	*p*=.660
Completion Time (seconds)	65.1 (12.93)	61.09 (13.36)	*p*=.376
Colour Word Interference			
Test-Inhibition/Switching	4.00 (2.49)	1.00 (0.82)	*p*=.002*
Errors	81.9 (22.97)	58.09 (8.79)	+[2]
Completion Time (seconds)			*p*=.008* +[3]
Age of onset (years)	46.6 (8.44)	N/A	N/A
Disease duration (years)	14.9 (5.30)	N/A	N/A
UPDRS score III			
PD STN-DBS ON	15.6 (7.14)	N/A	*p*=.018*
PD STN-DBS OFF	29.5 (16.77)		+[4]

RH= right handed, LH= left handed, UPDRS= Unified Parkinson's Disease Rating Scale, PD = Parkinson's disease, STN-DBS = Deep brain stimulation of the subthalamic nucleus, N/A= Not Applicable, *= Statistically significant differences between groups

+[1]= Effect size of Errors of Colour Word Interference Test-word reading: Hedge's *g* = -1.89

+[2]= Effect size of Errors of Colour Word Interference Test-Inhibition/Switching: Hedge's *g* = -1.81

+[3]= Effect size of Completion Time of Colour Word Interference Test-Inhibition/Switching: Hedge's *g* = -1.50

+[4]= Effect size of UPDRS score III: Hedge's *g* = -2.60

Table 5.2 Clinical data of patients with Parkinson's disease.

Subject	Gender/Age (years)	Disease Duration (years)	UPDRS (ON Med/OFF Stim)	UPDRS (ON Med/ON Stim)	DBS parameters	Years after DBS operation	L-Dopa Daily Dosage (LEDD)
01	m/68	26	30	13	L: 2-, 3.0V, 60 µs, 160Hz R: 9-, 3.0V, 60 µs, 160Hz	2.5 years	460
02	m/67	17	27	15	L:1-, 2.9V, 60µs, 130Hz R:9-, 2.9V, 60 µs, 130Hz	2 years	900
03	m/62	15	17	11	L:2-, 1.2V, 60 µs, 160Hz R: 2-,1.2V,60 µs ,160Hz	2 years	1060
04	m/68	9	27	21	L:1-, 2.3V, 60 µs, 180Hz R: 9-, 3.0V, 60 µs, 180Hz	2 years	960
05	f/69	16	16	11	L: 1-, 1.75V, 60 µs, 150Hz R: 9-, 1.65V, 60 µs, 150Hz	1 year	870
06	m/69	12	36	16	L: 1-, 2.6V, 60 µs 130Hz R :8-, 2.5V, 60 µs, 130Hz	1 year	500
07	m/54	14	67	14	L: 1-, 2.3V, 60 µs, 180Hz R: 9-, 3.0V, 60 µs, 180Hz	2.5 years	500
08	m/69	14	5	7	L: 2-, 1.2V, 62 µs, 130Hz R: 3-, 3.5V, 62 µs, 130Hz	2 years	700
09	f/45	7	41	33	L: 1-, 3.0V, 60 µs, 125Hz R: 9-, 2.0V, 60 µs, 125Hz/8-, 3.00V, 60 µs, 125Hz	2 years	700
10	m/44	12	29	15	L: 1-, 0.9V, 60 µs, 130Hz R:9-, 2.0V, 60 µs, 130Hz	2 years	150

Behavioural Task

PD patients completed two sessions on the same day: once ON stimulation and once OFF stimulation, with breaks in between as the participants needed. The session order was counterbalanced across patients. Control participants completed the session once. The unbalanced experimental design of the present study was in reference to the experimental design of the Galea et al (2012) study, which compared the effect of dopaminergic medication on PD patients. Originaly the age-matched HCs were designed to perform the task twice (the same as PD patients for comparison), however some participants declined to perform the task for the second time because they thought it was too time-consuming for them and make them tired. In addition, since there was no monetary reimbursement, the participantion rate was low. Therefore, for practical reasons such as saving time and increasing willingness for HCs to participate in the study, age-matched HCs was asked to perform the task once. To reduce the disadvantage of such unbalanced design, generalized linear mixed models (GLMM) and linear mixed model (LMM) were used to analyse the behavioural data. In addition, because of the probabilistic nature of the behaviourla task, it is assumed that there are no practice effects for performing the task.

The behavioural task was introduced to the participants on a computer with a custom button box with four buttons. The participants were instructed to place each one of their fingers on each of the four buttons and to maintain this position throughout the task. Initially, an un-informative warning cue ("!") was displayed for 250 ms. After a fixation cross was presented for 1000 ms, one of the four imperative stimuli (IS) was shown in the centre of the screen for 250 ms. The fixation cross then reappeared during the response period (2500 ms).

During this time, the participants were required to respond to the IS as fast and as accurately as possible. Each IS image was associated with pressing a specific button. The stimulus-response mapping was acquired through trial and error. During the training session composed of 200 trials, feedback either 'correct!!!' or 'wrong', was presented after each response, indicating whether the participants had selected the correct response associated with the particular stimulus.

During the main experiment, the feedback was removed. The task was divided into 4 blocks, with block 1 and 4 being unpredictable conditions where the probability of each IS being presented at trail *t* equals to 0.25. On the other hand, blocks 2 and 3 were designed as predictable conditions, where the IS was drawn from a predictable first-order Markov sequence. Each block contained 100 trials. This design created predictable sequences that the current stimulus on trial *t* was conditionally dependent on the stimulus of the previous trial, *t*-1. In other words, the type of IS on previous trials *t*-1 provides information to predict the type of IS on the current trial *t*. The distribution specified in the transition matrix quantified the dependence among consecutive stimuli, which generated the predictable sequences in which IS order 1-2-3-4 occurred with high probability (Figure 5.1 C). There were 16 possible combinations that determined the relationship between the IS on trial *t* and on trial *t*-1. The overall probability of each IS should be equal across all blocks. The experimental design provided a probabilistic context that allowed participants to reduce uncertainty before an event occurred (Harrison et al, 2006). Because of the probabilistic nature of the generated sequences, occasionally unexpected (surprising) stimuli would appear that was not expected based on the predictability of the sequence. When these unexpected (surprising) stimuli were

presented, participants would need to inhibit the planned response based on prior expectations about the forthcoming stimuli. It is important to note that no explicit information about the underlying patterns in each block was provided to participants. Participants were simply instructed to react with speed and accuracy.

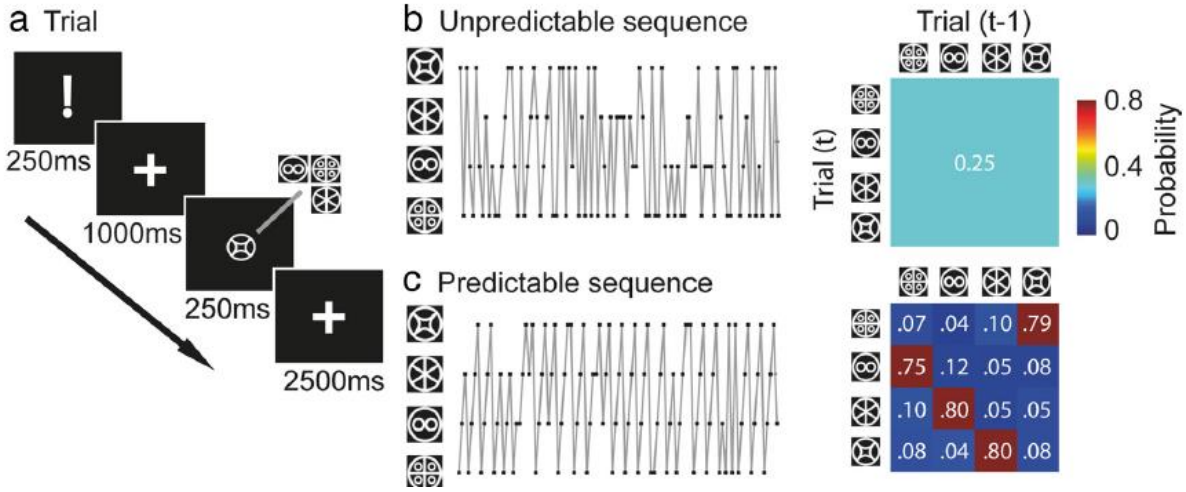

Figure 5.1 Experimental design. (A) Schematic representation of a single trial. A visual warning signal was followed by one of four novel IS. Participants were told to react as fast as possible to the IS. The order of the visual stimuli could either be unpredictable (B: blocks 1, 4) or predictable (C; blocks 2, 3). Predictable sequences were generated from a first-order Markov sequence in which there were 16 combinations that determined the relationship between the IS on trial *t* and on trial *t*-1. Numbers within the probability matrices represent the transition probabilities. The overall probability of each IS on trial t was equal across all blocks. Figure and caption from Galea et al., (2012).

Data Analysis

R (R Core Team, 2013) and IBM SPSS software were used to analyze the data. Reaction

times (RTs) and response accuracy were measured as dependent variables. For all correct responses, RTs were calculated as the time between IS onset and the subsequent button press. Moreover, RTs in predictable conditions were further compared between probable and improbable trials. A simple linear mixed model (LMM) was used to fit RTs with Group (HC versus PD), Stimulation (DBS OFF versus ON), Response Accuracy (Correct responses versus Incorrect responses) and Probability (Improbable versus Unpredictable, Improbable versus Probable) as fixed effects. Subject was assigned as a random effect to account for by-subject variation in overall RTs. Log base 10 transformation was performed to reduce the skewness of the data.

Generalized linear mixed models (GLMM) were used to fit the response accuracy data due to the data being non-normal. For the present data a binomial distribution with a logistic link was selected to construct the model, at the same time it was specified that the response accuracy could vary randomly across subjects. A simple GLMM that defined Group (HC versus PD), Stimulation (DBS OFF versus ON), Probability (Improbable versus Unpredictable, Improbable versus Probable) as fixed effects was fitted to the behavioural data. ML approach with Laplace approximation was used for parameter estimation. $p<.05$ was used as a criterion for statistical significance. The Akaike information criterion (AIC), which estimates the relative quality of a statistical model given a specified data set, was used for model selection (Bozdogan, 1987). The relative quality of the model is indicated by the calculated information loss, therefore the model that has the minimised AIC would be chosen as the most fitted model given the specified dataset.

R package *lme4* (Bates, Maechler & Bolker, 2012) was used to construct the LMMs and the

GLMMs. Maximum likelihood (ML) approach was used for parameter estimation for the LMMs. Likelihood Ratio Test was used as a mean to attain p-values of the fixed effects, which compared models with full factors and reduced factors to determine the significance of a fixed effect. For all the significant results, the effect sizes were given as Hedge's *g*.

5-4 Results

Effects of Predictability on response accuracy and reaction time of correct trials

A GLMM was created to examine how well participants performed the task. Two main factors were considered to affect response accuracy in the model: Predictability (Predictable/ Unpredictable) and DBS (DBS ON/ DBS OFF/ HC). In the GLMM, all levels of the categorical variables are compared to the base level (reference category). Here the base levels are: Predictable (for Predictability) and DBS ON (for DBS). All effects are estimated with respect to the base levels. The model showed that age-matched HCs had higher response accuracy than PD patients with stimulation ON ($Z=2.88$, $p=0.004$, Hedge's $g=0.32$), whereas PD patients with STN DBS ON had higher response accuracy than OFF stimulation ($Z=-3.85$, $p<.0001$, Hedge's $g=0.27$). For all participants, response accuracy did not differ between Predictable and Unpredictable blocks ($Z=-0.52$, $p=0.602$). The results suggest that (1) all participants performed equally well for Predictable and Unpredictable blocks, (2) PD patients with STN DBS ON had better performance than when OFF stimulation, however the small effect size shows that the significant difference on response accuracy between PD patients ON versus OFF STN DBS was not very robust, and (3) age-matched HCs had better response accuracy than PD patients (both ON and OFF stimulation), but again the small effect size suggest that such a difference was not very robust. Figure 5.2 illustrates the above

results.

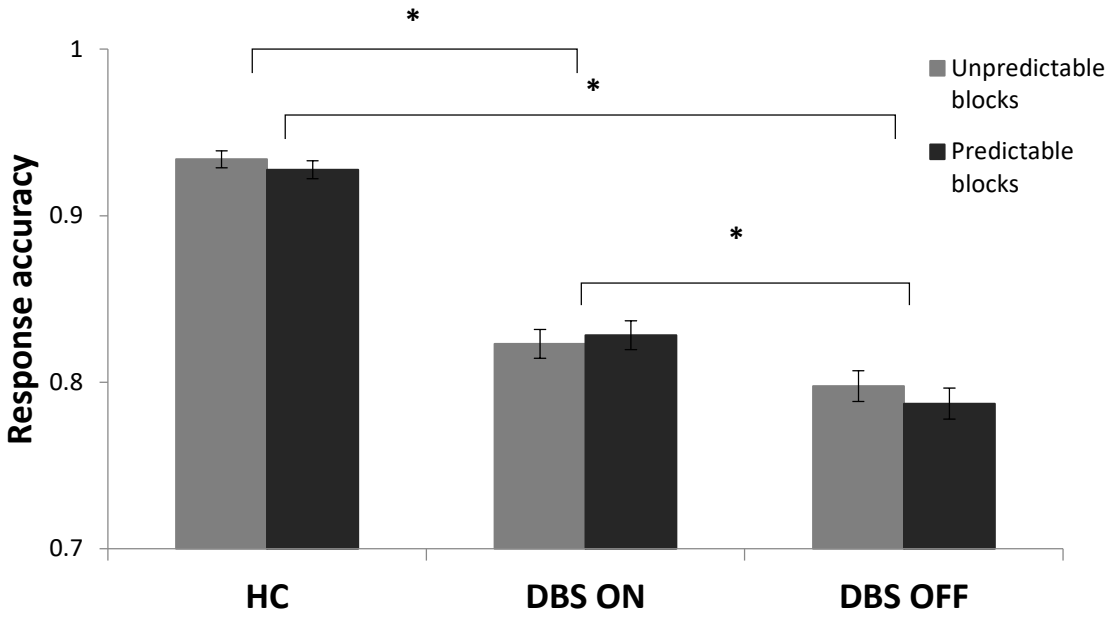

Figure 5.2 Response accuracy for Unpredictable (light grey bar) and Predictable (dark grey bar) for healthy control (HC), PD patients with deep brain stimulation (DBS) ON (DBS ON) and OFF (DBS OFF). Standard error of the mean is set as the error bars. The asterisk symbols denote the statistical significance.

A LMM was created using RTs as the dependent variable. Two main factors were considered to affect response accuracy in the model: Predictability (Predictable/ Unpredictable) and DBS (DBS ON/ DBS OFF/ HC). In the model contrast of the LMM, all levels of the categorical variables are compared to the base level (reference category). Here the base levels are: Predictable (for Predictability) and DBS ON (for DBS). All effects are estimated with respect to the base levels. For all participants, RTs were faster during Predictable blocks ($t(10610)=6.63$, $p<.0001$, Hedge's $g= 0.41$). There was no difference on RTs between PD patients ON versus OFF stimulation ($t(10310)=-0.67$, $p=0.505$). Age-matched HCs had faster RTs during Predictable trials than PD patient with STN DBS ON ($t(10610)=2023$, $p=0.003$,

Hedge's *g*= 0.41) but not during Unpredictable trials (t(23)=-0.52, p=0.606). The results suggest that (1) all participants performed equally fast for Unpredictable blocks but HCs were the fastest during Predictable blocks, and (2) the acute manipulation of STN DBS did not have effects on RTs for PD patients. Figure 5.3 illustrates the above results.

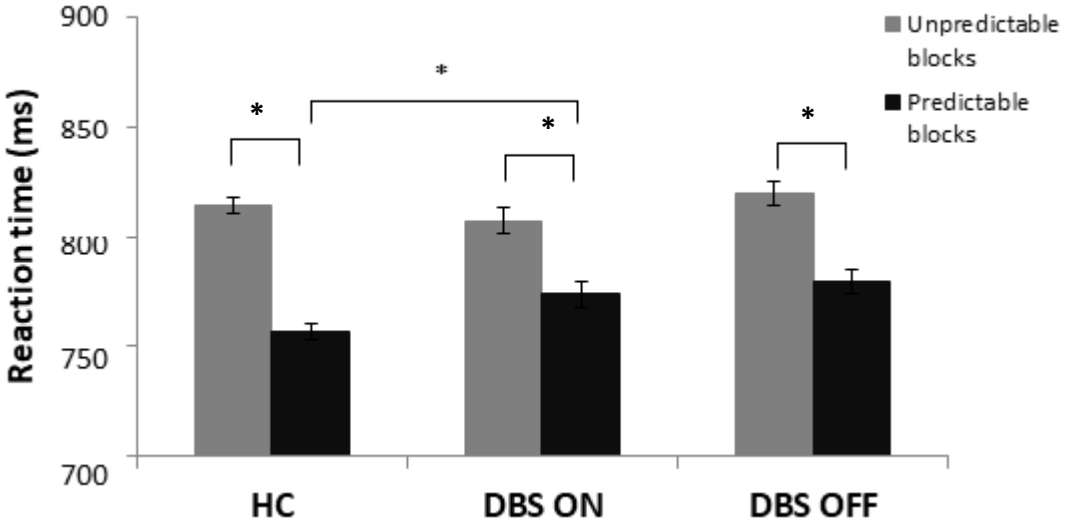

Figure 5.3 RTs of correct trials during Predictable and Unpredictable blocks for PD patients with STN DBS ON (DBS ON) and OFF (DBS OFF), and for healthy controls (HC). Standard error of the mean is presented as the error bars. The asterisk symbols denote statistically significant differences. As shown in the figures, all participants had similar behavioural patterns when responding to Predictable/Unpredictable blocks. The main difference is that age-matched HCs were much faster than PD patients (both ON/OFF stimulation) when responding to Predictable blocks.

Effects of Trial type on response accuracy and reaction times (RTs) of correct trials

Figure 4.4 shows the average RT for each of the 16 possible combinations of IS on the previous and the current trial, during predictable blocks. Due to the probabilistic nature of the task, some participants may not experience all 16 combinations. Therefore, these data were

not suitable to be statistically analysed. However, from a pure observational point of view, in general there seems to be little difference between HCs and PD patients in both stimulation states. As shown by faster RTs to the highly probable combinations, it is clear that HCs were able to learn the relative probabilities between consecutive IS. For PD patients both ON and OFF stimulation, RTs for some combinations were faster despite the lower relative probabilities but does not seem to differ robustly between HCs (Figure 5.4).

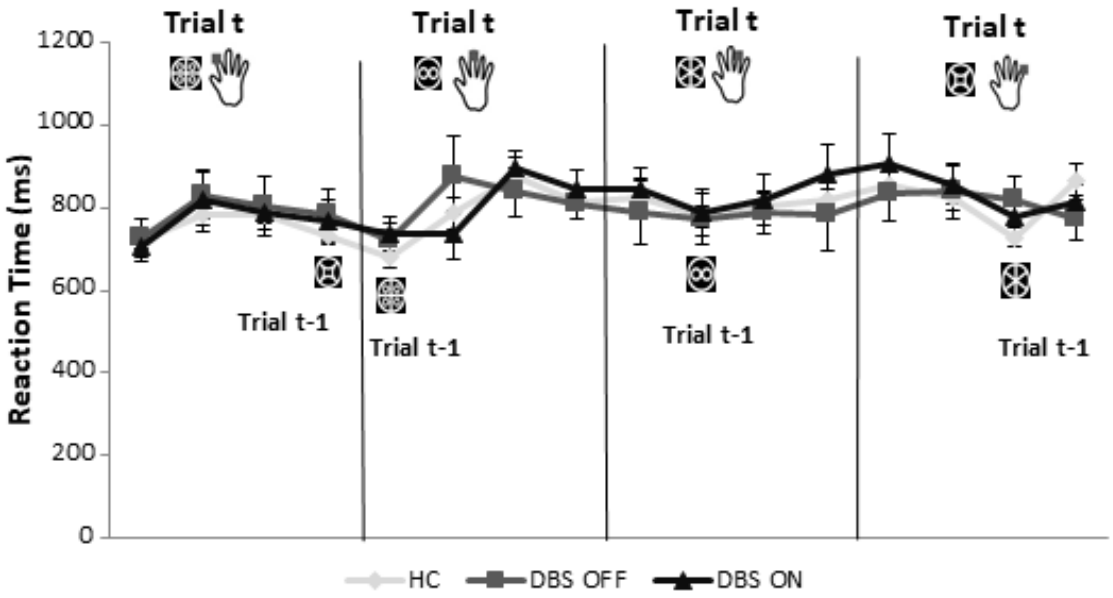

Figure 5.4 Average ± SEM group reaction times (RTs) for each of the 16 possible imperative stimulus (IS) combinations between the IS on trial *t* and *t-1* for all three groups Healthy controls (HC) Parkinson's disease patients (PD) with stimulation OFF (PD OFF) or ON (PD ON).

To further investigate how participants responded to Probable and Improbable trials in Predictable blocks, behavioural data was analysed with GLMM and LMM. Here a GLMM was creased using response accuracy as the dependent variable, with Probability (Improbable/Probable) and DBS (DBS ON/ DBS OFF/ HC) set as the fixed effects and subject as a random effect. The base levels in the present GLMM are Improbable (for Probability) and DBS ON (for DBS). All levels of the categorical variables are compared to the base level (reference category). Across Probable and Improbable trials, for PD patients, response accuracy was higher when ON stimulation than OFF stimulation (Z=-2.26, p=0.024, Hedge's *g*= 0.22). PD patients did not differ in response accuracy between Probable and Improbable trials ON (Z=0.29, p=0.769) or OFF stimulation (Z=0.37, p=0.713). In addition, age-matched HCs had higher response accuracy than PD patients (Z=-2.90, p=0.004, Hedge's *g*= 0.32). Taken together, the results indicate that (1) HCs had significantly higher response accuracy than PD patients, (2) PD patients with STN DBS ON had higher response accuracy than STN DBS OFF, despite the fact that effect sizes showed that such differences on task performance on probable vs improbable trials may not be robust across Probable and Improbable trial, and (3) age-matched HCs were more sensitive in reacting to Probable/Improbable trials. Figure 5.5 illustrates the above results.

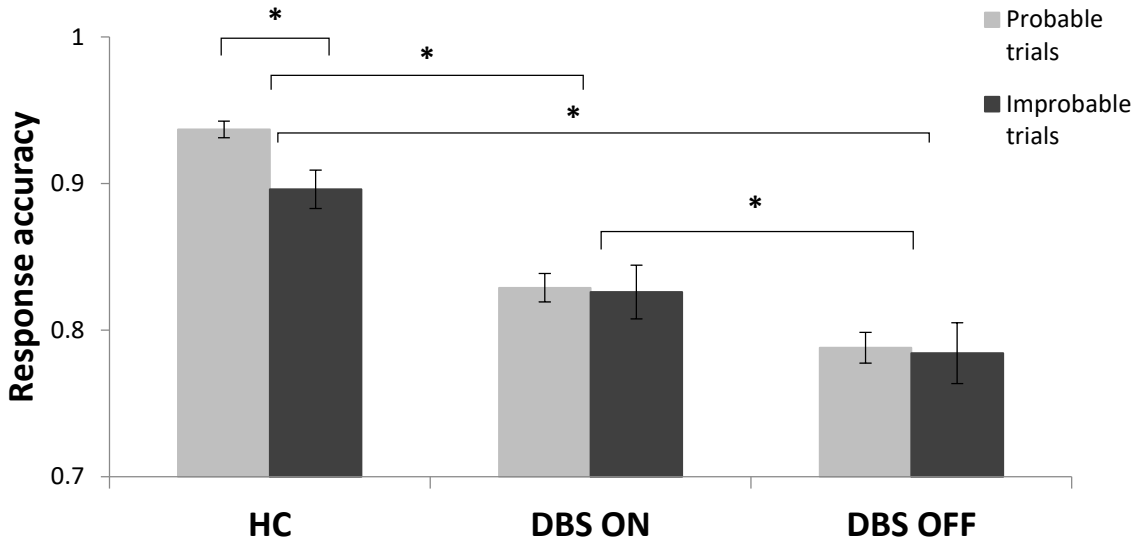

Figure 5.5 Response accuracy for healthy controls (HCs), Parkinson's disease patients with deep brain stimulation (DBS) of subthalamic nucleus (STN) OFF (DBS OFF) and ON (DBS ON). The error bars are standard error of the mean. The asterisk symbols denote the statistical significance.

Moreover, a LMM was created using RTs of correct trials as the dependent variable, with Probability (Improbable/Probable) and DBS (DBS ON/ DBS OFF/ HC) set as the fixed effects and subject as a random effect. The base levels in the present LMM are Improbable (for Probabiliy) and DBS ON (for DBS). All levels of the categorical variables are compared to the base level (reference category). For all participants, RTs were faster for Probable than Improbable trials ($t(6203)=-6.78$, $p<.0001$, Hedge's $g= 0.82$). PD patients did not differ on RTs between DBS ON versus OFF during Probable ($t(6204)=-1.73$, $p=0.083$) and Improbable trials ($t(6203)=-1.75$, $p=0.080$). There was no difference on RTs between PD patients and age-matched HCs ($t(25)=-0.07$, $p=0.941$). Taken together, the results indicate that (1) all participants had faster RTs during Probable trials than Improbable trials, (2) the acute manipulation of STN DBS did not affect RTs, and (3) there was no difference on RTs

between PD patients and age-matched HCs. Figure 5.6 illustrates the above results.

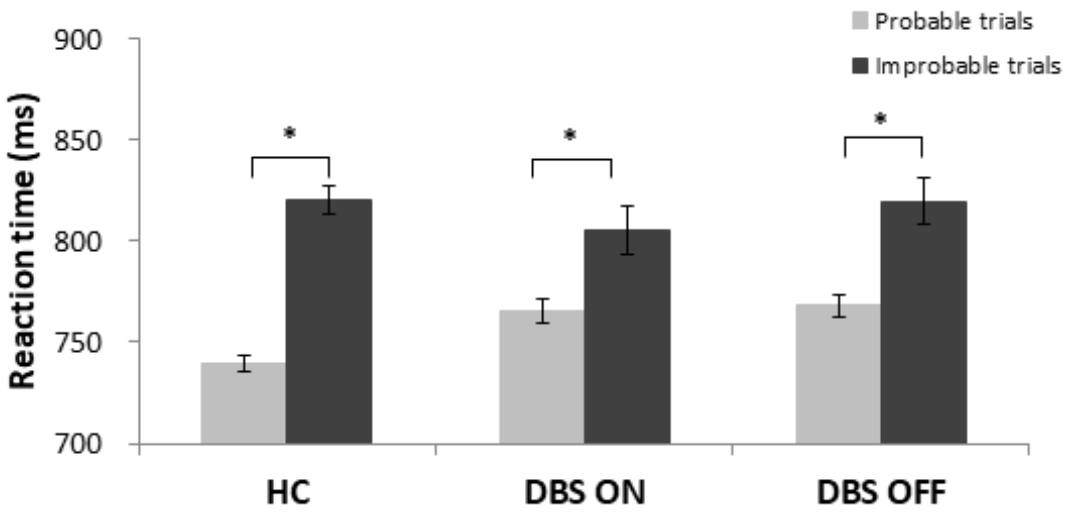

Figure 5.6 RTs of correct trials during Probable and Improbable trials of Predictable blocks for PD patients with STN DBS ON and OFF, and for healthy controls (HC). Standard error of the mean is presented as the error bars. The asterisk symbols denote statistically significant differences. As shown in the figures, all participants had similar behavioural patterns when responding to Probable/Improbable trials. The main difference is that age-matched HCs were much faster than PD patients (both ON/OFF stimulation) when responding to Probable trials.

Table 5.3 Summary of the main findings of the behavioural data.

	Predictable versus Unpredictable blocks	Probable versus Improbable trials of Predictable blocks
Response accuracy	➢ All participants performed equally well on Predictable and Unpredictable blocks.	➢ HCs had better performance on Probable trials than Improbable trials, but not PD patients.
	➢ PD patients had better performance ON than OFF stimulation ➢ HCs had better performance than PD patients (both ON and OFF stimulation).	
RTs	➢ All participants responded faster to Predictable blocks/Probable trials than Unpredictable blocks/Improbable trials. ➢ The acute manipulation of STN DBS did not affect RTs for PD patients. ➢ All participants reacted equally fast when performing the task.	

5-5. Discussion

The above analysis examined the effects of Predictability of blocks and Trial type (probable vs improbable) on response accuracy and RTs of correct trials. In terms of task manipulation, all participants had faster RTs during Predictable blocks and slower RTs for Improbable trials, which indicates that the task was reliable in examining action reprogramming (i.e. slowness after encountering surprising events). From a behavioural point of view, the results show that (1) all participants had faster RTs during Predictable blocks than Unpredictable blocks, and that the predictability did not make different on response accuracy for all participants, (2) the acute manipulation of STN DBS did not have effects on RTs but significantly improved task performance, and (3) PD patients were able to respond as fast as age-matched HCs however

the response accuracy was sacrificed, resulting in a behavioural speed and accuracy trade-off.

The effects of STN DBS on action reprogramming

Contrary to expectation, the acute manipulation of STN DBS did not render negative effects on decreasing RTs and/or producing more incorrect responses when trial types were improbable. Instead PD patients with STN DBS ON had higher overall response accuracy than when being OFF stimulation, although the effect sizes for the singifcant results were small (around 0.2). The hypothesis of the present study was that DBS of the STN would impaire inhibition when encountering unexpected sensory events (potentially by decreasing STN-beta power), resulting in faster RTs when encountering unexpected events. One possible factor may contribute to the observed results: for the current study PD patients were assessed ON medication to reduce discomfort, therefore the effects of medication may interfere with the effects of STN DBS. Moerover, unlike age-matched HCs, response accuracy did not differ between Probable and Improbable trials for PD patients, which may suggest that patients had certain difference in processing Probable versus Improbable events. Previous studies have shown that the sense of 'Surprise' or unexpectedness is closely related to prediction errors and thus may be associated with the level of dopamine in the brain (Bestmann et al., 2008; Galea et al., 2012; Shomaker & Meeker, 2015). On the other hand, the results may also suggest that the behavioural task requires certain improvements, as the results showed, PD patietns reacted to Improbable trials as fast as age-matched HCs. The difference seemed to appear when reacting to Probable trials, where age-matched HCs responded significantly faster than patients. This may suggest that the Improbable trials in the present study did not properly reflect the unexpectedness that would create robust action

reprogramming that was intended to study. Despite in the present study the results did not show speficits effects of STN DBS on action reprogramming, pervious studies have shown that the STN plays a major role in motor inhibition (Nambu et al., 2002; Aron &Poldrack, 2006; Aron, Behrens, Smith, Frank, & Poldrack, 2007; Li et al, 2008; Forstmann et al, 2010; Kim & Hikosaka, 2015) and that DBS of the STN may interrupt such functions that leads to impaired inhibiton resulting in cognitive side effects in PD patients (Hershey et al., 2004, 2010; Ballanger et al., 2009; Favre et al., 2013; Obeso et al., 2013; Georgiev et al, 2016; Williams et al, 2015). The inconsistent results of effects of STN DBS on behavioural data in PD patients may results from confounding factors such as individual difference, tasks used, experimental design, disease duration, and surgical procedures.

Speed and Accuracy trade-offs (SAT) potentially affected task performance in PD patients

For PD patients with both STN DBS ON and OFF, there was no effect of Probable/Improbable trials nor effect of Predictable/Unpredictable blocks on response accuracy. On the other hand, for age-matched HCs there were significant effects of these manipulations of probabilities on response accuracy. Furthermore, in the present studies PD patients were able to made responses as fast as HCs. However, PD patients both OFF and ON stimulation had lower response accuracy than HCs. Such an observation could potentially result from the SAT for PD patients, namely, in order to act fast the accuracy was sacrificed when performing the task. The inner drive to perform fast prevailed over performing accurately for PD patients.

Four theories have been proposed to account for the underlying neural mechanisms of such a

trade-off: the cortical theory, the striatal theory, the STN theory and the synaptic theory, which stand for different circuits that modulate the balance between making a fast or making an accurate response (for details please see the review of Bogacz, 2010). The present study supports the striatal theory, which proposed that when speed is emphasised during decision-making (to select and make a response), the striatum receives excitatory signals from the cortical area that releases the inhibitory function of the basal ganglia, thus facilitates faster RTs but may lead to premature responses. Since PD patients in the current study were tested ON medication state, the SAT may thus be associated with dopaminergic medication increasing the activity of the striatum. On the other hand, in the present study acute manipulation on the effect of STN DBS increased the response accuracy but did not alter the RTs in PD patients, which in a sense may also be consistent with the STN theory, which suggests that in order to make accurate responses, the increased activity STN produced slow but accurate responses. Grossly speaking the effect of DBS is theoretically assumed to reduce the STN activity, such improvement on the task performance may be due to the optimal balance between dopaminergic medication and the STN DBS. Moreover, in the current study participants did not receive feedback after making responses therefore were unable to adjust decisions based on feedback. The potential effect of forgetting the stimulus-response mapping may also have contributed to the lower response accuracy for PD patients.

In addition, PD patients with STN DBS ON had better response accuracy than when STN DBS was OFF, which may be hypothetically associated with the benefits of the treatment. The shift of attention is closely related to cognitive control and post-error slowing (Notebaert et al., 2009). It has been proposed that the basal ganglia play a role in focusing, which has

further suggested that dopamine suppresses the unwanted expected action and facilitates the initiation of the unexpected action (Redgrave et al., 199l; Cools et al., 2001; Frank, 2005; Isoda & Hikosaka, 2007; Hikosaka & Isoda, 2010). The ON medication state of PD patients in the present study therefore potentially facilitated the RTs when responding to Unpredictable/Predictable blocks and Probable/Improbable trials.

Non-DBS treated PD patients had prolonged RTs in reacting to surprising events when OFF medication

The occurrence of unexpected events and the need of action reprogramming can be seen as reflecting the sensorimotor system having issued a prediction error (Bestmann et al., 2008; Galea et al., 2012). Making decisions requires a certain degree of confidence, which represents the graded beliefs of the likelihood about the desired outcomes. Such confidence in making decisions could be derived from a mapping between the decision variables (i.e. accumulated sensory evidence) and the probability that the decision based on these decision variables is correct and leads to the desired outcome (Zylberberg et al., 2016; Kiani et al., 2014). A previous study using the same probabilistic RT task as the present study had shown that non-DBS treated PD patients tested OFF dopaminergic medication had impaired action reprogramming, which demonstrates that prediction error, which relates to dopamine levels, modulates the action reprogramming deficits in PD patients (Galea et al., 2012). Moreover, in such a framework PD patients OFF medication have low dopamine levels and are less confident about the new sensory evidence thus are more reliant on top-down predictions, which results in prolonged RTs when prediction error occurs for PD patients OFF medication (Galea et al., 2012). Furthermore, dopamine is considered to reflect the precision or reliability

of sensory information. Computational studies have proposed a role of dopamine in encoding the precision of prediction errors that generate actions by simulating dopaminergic neurotransmission at a different level of a hierarchical mode (Friston et al., 2012; FitzGerald, Schwartenbeck, Moutoussis, Dolan, & Friston., 2015). Together, evidence from previous studies suggests that dopamine plays a major role in encoding the precision of prediction error and the confidence in updating prior beliefs with accumulated sensory information, therefore controls action reprogramming. PD patients in the present study were assessed ON medication, which potentially contributes to the non-sifnificant results of acute manipulations of STN DBS.

To ameliorate the motor deficits in PD patients, clinically DBS STN and dopaminergic medication are combined depending on each patient's motor symptoms. Many studies have been conducted separately in examining the effects of STN DBS and the effects of dopamine medication (Frank et al., 2007; Galea et al., 2012; Green et al., 2013; Djamshidian et al., 2012, 2014; Huang et al., 2015; Pote et al., 2016) on cognition and motor function, however, for PD patients treated with both DBS and medication, it may not be easy to disentangle the effects of one treatment from the other even with acute manipulation of ON or OFF these treatments. It remains unclear how the relationship between dopaminergic medication and the STN together affect the motor and cognitive function in PD patients. Novel approaches should be developed in assessing the effects of both treatments for PD in order to reach better disease management for patients and carers and provide insights on the brain networks in future.

Summary

To sum up, the results show that the acute manipulation of STN DBS did not render negative effects on RTs during action reprogramming. In addition, PD patients exhibited a robust SAT when performing the probabilistic task. However, it is not to say that DBS of STN would not interfere with the STN functions on inhibition and cognitive/motor control that may result in side effects in PD patients. Future studies are required to (1) investigate the role of STN on interrupting cognition such as working memory after encountering unexpected events, and (2) the connections between dopaminergic medication and STN DBS on modulating SAT in PD patients.

Chapter 6 General Discussion

6-1 Main findings from each study

Evidence from previous studies, as discussed in Chapter 1, has suggested that treatments for Parkinson's disease (PD) such as dopamine medication and deep brain stimulation (DBS) of the subthalamic nucleus (STN) would induce side effects on basic executive functions (EFs) including abilities of shifting, updating and cognitive flexibility in patients, possibly due to the 'dopamine overdose hypothesis' and the hypothetical effects of DBS on the role of the STN in inhibitory control and sensory information integration, leading to impairments on performing certain behavioural tasks. Studies in the present PhD thesis thus focused on assessing the acute effects of both treatments (i.e. dopamine medication and STN DBS) for PD patients on behaviours associated with speed and accuracy trade-off (SAT) modulation and sensory information sampling and updating, using behavioural tasks such as a moving dots task and a probabilistic reaction time (RT) task. The studies assessed how PD patients perform the behavioural tasks ON versus OFF treatments in relative to age-matched healthy controls (HC). In addition, hierarchical drift diffusion models (HDDM) were applied to the behavioural data to further derive the underlying cognitive components during task performance. In general, there were no robustly negative effects induced by acute manipulation of both treatments on behavioural data. Despite the limitations of the task design, the behavioural results combining psychological test scores suggest that while some evidence shows that medical and surgical treatments can induce negative side effects on cognition for PD patients, such side effects may be small and specific to individuals, indicating that both treatments are safe and reliable procedures in ameliorating motor symptoms of PD without inducing negative side-effects on cognitive functions.

However, while the acute manipulations of both treatments produced no significantly negative effects on general task performance, PD patients were found to show subtle defects on cognitive components involving the ability to update and sample the environmental sensory information, which may further lead to the subtle impairments on the modulation of SAT. In Chapter 2, the results showed that PD patients who had been clinically diagnosed with impulse control disorders (ICD) were able to perform the moving dots tasks as well as age-matched healthy controls (HC) in terms of RTs and response accuracy. A ceiling effect may exist for the selected moving dots task as most participants had response accuracy as high as more than 95%, therefore the task may not be challenging enough to reflect the effects of medication, as well as the difference between patient group and age-matched healthy control group. Nevertheless, the results indicate that the clinical approaches on reducing dopamine agonist to treat impulsive behaviour did not induce any negative side effects on motor or cognitive functions for PD patients who developed with ICDs. Despite showing no significant acute effects of dopamine medication, PD patients with ICD history and PD patients without ICDs showed different behavioural patterns on the same moving dots task (Huang et al., 2015). The results are in line with previous studies showing that PD patients with and without ICDs showed different behavioural patterns in decision-making even after PD patients with ICDs are treated, which may suggest that PD patients who are at risk of developing ICDs show difference on certain functions that could be predictable prior to medication administration (Djamshidian et al., 2010; Djamshidian et al., 2012). Chapter 3 thus introduced a study using behavioural data collected from the moving dots tasks to build classification predictive models, in order to investigate the hypothesis on PD patients with

and without ICDs may be distinguishable by building classification predictive modelling with certain task performance patterns. The results show that difference on performance of certain tasks between PD patients who developed ICDs and PD patients who did not have ICDs is distinguishable using a machine learning algorithm. Such distinct behavioural pattern could therefore be used as a screen tool to predict PD patients who have high risk to develop ICDs thus preventing the onset of the disorders. Moreover, previous evidence suggests that PD patients with ICDs showed different behavioural patterns on a task required sensory information updating compared to PD patients without ICDs (Djamshidian et al., 2012). Together, the results suggest that tasks involving information updating and SAT modulation may be powerful in predicting vulnerability to develop ICDs in PD patients.

In addition to the effects of dopamine medication on behaviours in PD patients, the present thesis also aimed to investigate the effects of STN DBS PD in PD patients. In Chapter 4, a block-designed moving dots task was used to investigate the hypothesis on PD patients with STN DBS may show deficits on task switching. In addition, the nature of moving dots task could provide a chance to study the effects of STN DBS on SAT modulation and sensory information updating. The results show that the acute manipulation of STN DBS did not induce deficits on task switching for PD patients in a block-desinged moving dots task. However, PD patients with STN DBS ON did show impairments on a psychological test assessing the ability of task switching, which supports that DBS of the STN impairs certain task-swithcing abilities in PD patients. The evidence suggests that task-switching may involve fundamentally different but related cognitive processes, which are controlled by distinct brain areas. Moreover, the above results are in line with the hypothesis that the

reliability of sensory information plays an important role on modulating SAT. Moreover, PD patients still showed subtle difference on underlying cognitive components under the effects of DBS, which supports a role of the STN on modulating SAT and sensory information integration during task performance. To further investigate on how STN DBS may affect the function of STN on imformation updating and inhibitory control, a probabilistic RT task was used to assess the effect of STN DBS on reprogramming actions when encountering unexpected sensory events in PD patients. The results show that the acute manipulation of STN DBS did not induce negative effects on the probabilistic RT task for PD patients. The results may be due to the task design not properly inducing the unexpectedness that would create robust action reprogramming that was intended to study. In addition, PD patients exhibited robust SAT when performing the probabilistic RT task, which may indicate that PD patients were predominately aiming to act fast therefore sacrificed response accuracy. Moverover, PD patients treated with STN DBS were assessed ON medication, which may be the reason why the results did not reflect the hypothetical effects of DBS on interrupting the role of STN in motor control that induce fast RTs and more incorrect responses in PD patients.

6-2 Clinical and theoretical implications

The present thesis investigated the acute effect of dopamine medication and STN DBS on EFs in PD patients by assessing PD patients ON versus OFF treatments with behavioural tasks associated with the abilities of updating, shifting and inhibition, therefore may shed lights on the role of dopamine medication and DBS of the STN on motor inhibition and cognitive control in patients with PD. Overall speaking, in the studies of present PhD thesis

both dopaminergic medication and STN DBS were effective in ameliorating motor deficits in PD patients and produced no significantly negative effects on behaviours. Moreover, PD patients did not show significantly negative effects on most of the psychological tests compared to age-matched HCs, except for affective psychiatric tests such as depression inventory scores and apathy scale. Combining the previous and present results, both dopamine medication and STN DBS are considered to be safe and effective methods in treating PD. Despite the results showing no significant side effects produced by the acute manipulations of both treatments, it is not to say that long term administration of both treatments would not induce side effects in PD patients.

As discussed in Chapter 1, the dopamine overdose hypothesis proposed by Cools et al (2001) states that, the administration of dopamine medication to PD patients may replete dopamine-depleted regions such as the dorsal, rostral head of the caudate nucleus and the putamen, but may overstimulate relatively intact regions such as the ventral striatum in early PD, leading to poorer performance on tasks mediated through these circuits such as reversal learning (Cools et al, 2001), conditional associative learning (Gotham et al, 1998), complex discrimination learning (Swainson et al, 2000), and probabilistic classification learning (Jahanshahi et al 2010). In addition, Weintraub et al (2010) proposed that ICDs were more common in patients treated with dopamine agonists, showing higher probabilities of inducing ICDs for dopamine agonist treatment. In the present study the acute manipulation of dopamine medication did not affect task performance but did improve motor functions in PD patients with ICD history, which may result from (1) in the present study the recruited PD patients were not early PD, therefore the ventral striatum may be dopamine depleted as the

disease progressed and that medication would not overstimulate the area, (2) the dopamine overdoes hypothesis does not apply to treated PD+ICD patiens as their medication treamtents have been adjusted to a level that no signifricant behavioural impairments would be observed, and (3) the dopamine overdoes hypopthesis does not apply to the processes of the moving dots tasks performance. It is difficult to determine how disease progress affects the degeneration of dopamine neurons in different striatal regions in different PD patients, and how dopamine medication stimulate or overstimulate certain regions in treating PDs. However, the results of Chapter 3 provide a possibility that the onset of PD+ICD may be predictable by analysing performance on behavioural tasks associated with EFs.

In addition to dopamine overdose hypothesis, it has been suggested that dopamine agnosit is closely related to the onset of ICDs (Voon & Fox, 2007; Weintraub et al., 2015). Moreover, it has been suggested that obsessive-compulsiveness is closely related to impulsivity in individuals (Li & Chen, 2007; Isaias et al., 2008). Impulsivity is not a unitary phenomenon and has several distinct components (Evenden, 1999; Dalley, Everitt, & Robbins, 2011). First, delayed motor inhibition (‘impulsive action’). Second, a failure to take time to reflect and adequately sample evidence before making a decision (‘reflection impulsivity’). Third, an inability to delay gratification shown as a tendency to accept small immediate rewards over larger delayed rewards (‘impulsive choice’). Fourth, engagement in risky behaviours such as gambling. Different experimental tasks tap different components of impulsivity. Table 6.1 summarises the studies that have used different behavioural tasks to examine the four components of impulsivity in PD patients with ICDs. In general, most of the behavioural studies showed that PD patients with ICDs made more impulsive and risky choices on

behavioural tasks except for one study that found no difference between PD patients with or without ICDs (Pineau et al., 2016) (see Table 6.1). Furthermore, PD patients with ICDs were not impaired on motor inhibition assessed on the stop signal task (Claassen et al,2015; Leroi et al, 2013). Also, hasty decisions under conflict on tasks such as the Simon task (Wylie et al., 2012) or the Stroop interference test (Djamshidian et al., 2011) were not observed in PD patients with ICDs, such results are in line with results from Chapter 2. Thus, the available evidence suggests that PD patients with ICDs exhibit specific forms of impulsivity and do not have a generalized deficit in inhibitory control. These results contradict with the hypothesis that PD patients with impaired EFs such as motor inhibition are more prone to develop ICDs (Weintraub et al., 2010, 2015).

Table 6.1. Behavioural studies examining different aspects of impulsivity in non-surgically treated patients with Parkinson's disease (PD) who developed impulse control disorders (ICDs).

Type of Impulsivity Assessed	**Authors**	**Behavioural Tasks**	**Main findings**
Impulsive Action (failure of motor inhibition)	Claassen et al (2015) Leroi et al (2013)	Stop Signal Task	PD+ICD patients did not show impulsive action.
Reflection Impulsivity (Sample less information before making decisions)	Djamshidian et al (2012) Wylie et al (2012) Djamshidian et al (2011)	Beads Task Simon Conflict Task Stroop Task	All PD patients (PD+ICD patients and PD-ICD patients) had similar performance on all behavioural tasks
	Djamshidian et al (2014)	Simple Reaction time task/ Perceptual decision-making task	PD+ICDs had faster RTs on the simple reaction time task, and had fastest RTs on incorrect trials on perceptual decision-making task
Impulsive Choice (choose small but immediate reward over large but delayed rewards)	Voon et al (2010) Voon et al (2011) Leroi et al (2013)	Discounting Task Risk task	PD+ICD patients made more risky choices and had impaired EFs with greater anterior insular activity compared to PD-ICD patients
	Housden et al (2010)	self-rated Kirby delay discounting questionnaire /Delay Discounting Task	PD+ICD patients showed highly elevated delay discounting than PD-ICD patients

Risky Behaviour (on gambling tasks)	Bentivoglio et al (2013) Rossi et al (2009) Pineau et al (2016)	Iowa Gambling Task	PD+ICD patients showed a statistical trend to make more risky choices than PD-ICD patients
	Djamshidian et al (2010)	Gambling Task	PD+ICD patients were more risk prone than PD-ICD patients

PD+ICD: Parkinson's disease patients with impulse control disorders; PD-ICD: Parkinson's disease patients without impulse control disorders; HCs: healthy controls; PD+DA: Parkinson's disease patients treated with dopamine agonists; PD-DA: Parkinson's disease patients treated without dopamine agonist.

In the present thesis, the acute manipulation of STN DBS did not render significant negative effects on task performance. The results are consistent with previous follow-up studies showing that STN DBS produced no negative effects on global motor and cognitive functions (Funkiewiez et al., 2004; Temel et al., 2006; Schüpbach et al., 2005; Troster et al., 2017). However, It remains unclear how exactly DBS affects the STN functions, the studies have suggested that DBS of the STN decreases beta-band oscillations that leads to motor improvement in PD patients (Kuhn, Kupsch, Schneider, & Brown., 2006; Kuhn et al., 2008). Moreover, the effect of DBS on the STN in PD patients is hypothesised to interrupt with the theoretical role of the STN on information integration and serving as a brake in the brain comes from its involvement in global motor inhibition via the hyperdirect pathway, leading to impaired inhibition and motor/cognitive control.

On the other hand, previous studies have shown that the STN plays a role in information integration when decision conflicts are presented, leading PD patients with DBS ON to have impulsive decisions/behaviours (Frank et al., 2007; Green et al., 2013). Computational models of decision-making hypothesise that the STN mediates the function of slowing down when facing difficult decisions by elevating decision thresholds so that more evidence could be sampled before making an optimal response (Bogacz & Gurney, 2007; Frank, 2005; Frank et al., 2007; Bogacz, 2010; Mansfield, Karayanidis, Jamadar, Heathcote, & Forstmann, 2011; Cavanagh et al., 2011; Green et al., 2013). In addition, the present thesis also supports the 'urgency-gating model' proposed by Thura & Cisek (2017), which suggest that the basal ganglia are hypothesised to control the SAT between committing to a choice versus continuing the selection. However, Thura & Cisek (2017) suggested that instead of contributing to the choice between potential movements, the basal ganglia

actually provide a time-dependent signal that controls the urgency to commit to a choice, which could lead to the adjustment of the SAT when making decisions. In the present study it is not determined whether the STN is involved in providing such time-dependent signal. Future studies are in need to investigate on how the STN is involved within the urgency-gating model.

Taken together, studies in the present thesis showed that (1) while dopamine medication is closely related to the onset of ICDs, it is possible to identify PD patients who may be prone to develop ICDs before medication treatments, which could have clinical benefits for desease prevention, and that (2) in both studies PD patients treated with STN DBS were assessed ON medication, which may be the reason why the results did not reflect the hypothetical effects of DBS on interrupting the role of STN in cognitive and motor control. It may be hypothesised that the impaired inhibitory control could be diminished by dopamine medication. In addition, DBS of the STN may not induce impaired inhibitory control in all conditions, however the rpesent studies did not rule out the the possibility of STN DBS to impaire motor/cognition control in PD patients. It requires more studies on determining the distinct effects of dopamine medication and STN DBS on these functions in PD patients, which may also shed lights on the normal functions of dopamine and the STN on cognitive functions.

6-4 Limitations

There are a few limitations of the studies, some of which have been addressed in each experimental chapter. In this section I will briefly review these limitations and provide potential ways to improve these flaws for future studies.

Firstly, the design of the chosen behavioural tasks in the present studies appeared to be suboptimal in examing the executive functions interested of topic. For example, the moving dots task used in Chapter 2 seemed to have a ceiling effect. In addition, contrary to previous studies showing that treatments of PD have effects on the task performance (Frank et al., 2007; Green et al., 2013; Pote et al., 2016; Galea et al., 2012), the present studies revealed no robust effects of acute manipulations of treatments. The inconsistent results may be due to difference on task design (such as the dots coherence in the Green study and present study being different), experimental procedure and individual difference. Approches should be developed in account for the potential effects of the above confounding factors (Whitsett & Shoda, 2014; Hayward, 2007).

Secondly, small sample sizes have been a general issue in all studies due to difficulties in recruiting participants that would be discussed later. To diminish the disadvantages of small sample sizes, effect sizes were calculated for each significant effect of treatment manipulation and each significant difference between groups using Hedges' *g*. For moderate to large effect sizes, it suggests that the effects are robust despite the small sample sizes. For the present studies, although most of the effect sizes reported were small to moderate effect sizes, due to the participants being patient groups, small effect sizes may still indicate beneficial improvements or noticeable impairments that are worth investigating. One of the reasons for the small sample sizes in the present thesis was because the experimental design of all behavioural studies was to examine the acute effects of treatments on cognitive and motor functions. Patients were therefore required to be OFF treatment for at least 2-3 hours to assess the behavioural data. This was a great concern for most patients therefore many of them refused to participate in studies because they did not want to be OFF treatments. In addition, the

participation of the study was purely voluntary, which means that the participants received no monetary reimbursement. This drawback could make it less motivated for patients to participate in the studies. To reduce the difficulties in recruiting patients to participate in behavioural studies, better communication should be formed between patients and experimenters. The experimenters have the responsibilities to make the experiments clear and relevant to the patients in order to increase their willingness to take parts in by carefully designing the experiments and explaining the aims in details to the patients. During the process of designing the experimental tasks, most concerns have been put onto the convenience of the experimenters. It should be considered with more carefulness the balance between the aims of the research, the procedures of the experiments and how it would affect the patients. For example, being OFF treatments would no doubt cause discomforts to patients therefore it is understandable why patients would refuse to participate in the studies. It is therefore important to consider if the acute manipulation of treatments is a necessary design to achieve the aims of the research. If it is necessary for the purpose of the study, the experimenters should be dedicated to make the experimental environment trustworthy and somehow closer to comfortable for patients to be willing to participate in the study. These important issues should be carefully considered when designing experimental procedures especially for recruiting the patient groups as experimental participants.

Third and correspondingly, due to the difficulties in recruiting PD participants, same patients have been repeatedly calling back to do other studies. Bias may occur such as patients who are willingly to participant in scientific research repeatedly have certain personality traits that may potentially affect behaviours. The results collected from the same group of patients may therefore not be robust in representing larger patient population. For future studies, it is therefore important to increase sample sizes and

PD patient group. This could be achieved by spreading news via social media pages (e.g. Twitter, Facebook and Instagram) and charity foundation (e.g. Parkinson's UK) so that more PD patients would know about the study therefore increasing the probability of participation.

Fourthly, ICD patients were treated OFF medication than ON medication for practical reasons, practice effect thus could not be distinct from the effect of medication. In order to make certain that the effect of dopaminergic medication was completely OFF when testing patients for OFF session, it is required for patients to have an overnight withdrawal (approximately 12-16 hours) from their normal medication prior to testing. Previous study has shown no practice effect for age-matched HCs on the moving dots task therefore when designing the experiment it did not strike me as a problem. However, the present results proved that there was a practice effect for HCs and the effect of dopaminergic medication could therefore not be ruled out for PD patients. In order to prevent such misunderstanding, it is recommended to assess the effect of dopaminergic medication in a counter-balanced design in the future. In addition, in the present studies the tasks seem to have a ceiling effect as both patient group and healthy control groups had more than 95% response accuracy. The task difficulty should also be carefully designed in future studies to investigate proposed hypotheses. Fourth, PD patients treated with bilateral STN DBS were assessed ON medication state. The effects of dopaminergic medication (especially dopamine agonists) could therefore not be ruled out. In animal studies, STN high-frequency stimulation (HFS) has been demonstrated to increase striatal dopamine release and metabolism (Bruet et al., 2001; Meissner et al., 2003; Lacombe et al., 2007; Zhao et al., 2009; Pazo, Hocht, Barcelo, Fillipini and Lomastro, 2010), such increase is hypothesised to cause the improvement of movement deficits in PD. However, human studies on DBS-STN

have found no evidence supporting the hypothesis that DBS-STN increase the striatal dopamine level (Hilker et al., 2003; Strafella, Sadikot & Dagher, 2003; Nozaki et al., 2013). Clinical observations on PD patients have shown that patients treated with STN DBS decrease the intake of dopamine medication. Nevertheless, the interactions between STN DBS and dopaminergic medication and the underlying neural mechanisms on improving motor and (possibly) cognitive functions remain unclear. Future studies are in need to shed lights on the connections between the treatments and the way they work in better understanding PD and how to treat the symptoms.

6-5 Direction for future research

The present thesis provides several different directions for the future studies.

In terms of the effects of dopamine medication, Chapter 2 suggests that in line with previous studies, PD patients with ICD history were able to perform as well as age-matched HCs on a moving dots task manipulating decision conflict, and that the acute effect of medication did not produce negative influences on task performance. Voon et al (2017) proposed that chronic treatment with dopamine medication can interfere with the phasic and tonic activity of dopaminergic neurons, which could be associated with long-term neuro-adaptation including regulation of receptor and transporter density. It has also been suggested that reduced concentrations of striatal dopamine transporter (Smith et al., 2016; Voon et al., 2014; Vriend et al., 2014), and altered striatal and cortical dopamine homeostasis (Rao et al., 2010; Ray et al., 2012) may potentially contribute to the development of ICDs. Moreover, factors such as personal or family history of alcoholism or gambling; younger age; impulsive or novelty-seeking traits; gender (male for hypersexuality, female for binge eating and pathological shopping); early onset of PD; being unmarried; and past or current

cigarette smoking can all be associated with the development of ICDs in PD (Voon & Fox, 2007; Weintraub et al., 2010; Weintraub et al., 2015). Future studies should therefore focus on the chronic effects of dopamine medication, especially dopamine agonist, and identify risky factors on inducing risky behaviours and choices in PD patients, in order to prevent the onset of ICDs in patients, which may also shed lights on the underlying neural mechanisms. The effects of dopamine agonist on inducing impulsive choices may also provide insights on how abnormal dopamine transmission would lead to pathological gambling and addiction. Future studies investigating the development of ICDs in PD patients should focus on impulsive choices and risky behaviour that involve rewarding effect and corresponding neural mechanisms such as the mesolimbic dopaminergic pathways. On the other hand, the present thesis indicates PD patients developed ICDs may potentially be identified before medication treatment through tasks associated with EFs

In addition, dopamine has been well established to be involved in major cognitive functions such as reinforcement learning, decision-making and motor/cognitive control. Most of the dopamine neurons reside in the midbrain and form three cell groups: (1) the retrorubral nucleus (RRN, cell group A8 in the rat); (2) the substantia nigra pars compacta (SNpc, A9) and (3) the ventral tegmental area (VTA, A10) (Daw & Tobler, 2014). Over the past several decades, two aspects have been proposed to be the major functions of dopamine in the striatum: (1) movement control and (2) modulating motivation and reward. The majority of studies have been focused on how the brain resolves the reinforcement learning problem via the midbrain dopamine neurons (Glimcher, 2011; Niv, 2009; Daw & Tobler, 2014; Schultz, Dayan & Montague, 1997). Besides the reinforcement learning framework in explaining learning and decision-making, Friston, Daunizeau & Kiebel (2009) have proposed

that optimal behaviours could be guided by the adjustment of the agents' internal states and external sampling of sensory evidence to minimise free energy, which discard the notion of reward, value or utility. Such framework is termed as 'active inference' (Friston et al., 2009). It has been suggested that the brain can be regarded as an inference machine, which governs the processes involved in accumulation of sensory information and making inference about the external world (Helmholtz, 1866; Gregory, 1980; Rao & Ballard, 1995; Friston et al., 2005; Friston, 2010). Friston et al (2012) have considered dopamine neurotransmission as an integral part of Bayes-optimal perception and sensorimotor integration that responds to the perceptual cues in an environment with a fixed level of uncertainty. In active inference, behaviour emerges as a natural consequence of high-level sensorimotor representations that are maintained by bottom-up prediction errors in both sensory and motor modalities (Friston, Daunizeau, Kilner & Kiebel, 2010; Friston et al., 2013; Friston & Kiebel, 2009). In other words, dopamine is involved in selecting the proprioceptive (motor) and exteroceptive (sensory) signals (prediction errors) that compete for higher level explanation by controlling their precision, which means that dopamine is in a position to select an attribute of a probabilistic representation that determines the confidence about what is presented (Friston et al., 2012). Moreover, confidence in making a decision can be associated with decision itself (i.e. to obtain more information and/or prediction of a reward) and a link between previous decision outcomes and the strategy on guiding the following decisions (van den Berg et al., 2016a). Confidence, choice and RTs are further proposed to be elements in a bounded evidence accumulation process (van den Berg et al., 2016b). Together previous studies have suggested an important role of dopamine in reinforcement learning and making inference, how dopamine depletion may affect these functions in PD patients could therefore bring insights on the supporting the hypothetical role of dopamine in the

brain.

Following the results of Chapter 2, the machine learning study described in Chapter 3 suggests that it is possible to use behavioural pattern as an input factor in building predictive models that serve as a screening tool to distinguish patients who may be more likely to develop ICDs in the future. Previous studies have also suggested the existence of pre-motor markers that may predict high risk in developing PD for some people (Chaudhuri & Schapira, 2009; Büttner et al., 1995; Postuma et al., 2006). Moreover, the application of machine learning on clinical data may also be powerful and useful to monitor disease progress for patients with long-term diseases such as PD. Diseases are not caused by one single factor but various factors interacting on various levels. Interdisciplinary research programmes are needed to better monitor the progress of chronic diseases. In 2014, New York University's Institute for the Study of Decision Making and the Kavli Foundation have initiated an interdisciplinary research platform named The HUMAN Projects (URL: https://www.thehumanproject.org/), which attempts to link the connections between human minds, bodies and environment to build a comprehensive understanding of the factors and the interactions between these factors that shape how people live and affect their health and well-being (Azmak et al., 2015). These factors and the interactions between the factors may further help to form new theories, therapeutics and policies that improve the quality of life. Chronic diseases such as PD and Alzheimer's disease result from interactions between many different factors on various levels, and the disease progress also highly correlated with theses interactions. If similar research platform could be built for patients who have chronic diseases, clinicians, caregivers and patients themselves could benefit from the data and be more efficient in monitoring the disease progress. Smartphone applications can be used to

help track each patient's individual data on various levels such as medication intake, food intake, mood, and the amount of exercise... etc. These data could be further analysed and used for building customized models that help to improve the quality of live for both patients and caregivers, especially for long-term degenerative diseases such as Parkinson's disease.

On the other hand, Chapter 4 supports the hypothesis that the STN plays a role in task switching. Moreover, the evidence suggests that task-switching may involve fundamentally different but related cognitive processes, which are controlled by distinct brain areas. The results are also in line with the hypothesis that the reliability of sensory information plays an important role on modulating SAT (Devene, 2012). Furthermore, PD patients still showed subtle difference on underlying cognitive components under the effects of DBS, which supports a role of the STN on modulating boundary separation and sensory information integration. While some studies suggest that when decision conflict was presented, PD patients with STN DBS ON would show impulsive behaviours when response accuracy was emphasised (Bogacz & Gurney, 2007; Frank, 2005; Frank et al., 2007; Bogacz, 2010; Mansfield et al., 2011; Cavanagh et al., 2011; Green et al., 2013), one suggested that speed pressure without decision conflict could induce impulsive behaviours (Pote et al., 2016), and others proposed that the inability to slow down when making decisions during high decision conflict conditions and the exhibition of reflection impulsivity by PD patients who had undergone functional neurosurgery was associated with dopamine agonists rather than with DBS (Djamshidian et al., 2013; Djamshidian et al., 2014). Future studies are needed to determine how these multiple factors (i.e. STN DBS, dopamine agonist, decision conflict and SAT) and their interactions affect PD patients when making perceptual decisions. Moreover, future studies may be

developed to investigate how the STN is involved in modulating decision thresholds during value-based decision making, which may provide insights on how cortico-basal ganglia circuits participate in the computation of the associations between action and outcome, and the evaluation of the rewards that are associated with the different outcomes.

Moreover, Chapter 5 shows that the acute manipulation of STN DBS improved task performance on the probabilistic RT task for PD patients. The observation indicates that PD patients with STN DBS ON slowed down when encountering surprising events but not to a degree that would induce abnormally slowed behaviours. Such an observation contradicts the hypothesis that DBS in PD patients would disrupt the function of the STN in serving as a brake in the brain that would allow more information to be accumulated during ambiguous conditions, resulting in impulsive decisions/actions and impaired action reprogramming (Frank et al., 2007; Green et al., 2013). Future studies are therefore required to determine the role of the STN in making decisions under ambiguity. Moreover, PD patients exhibited a robust SAT when performing the probabilistic task. Four theories have been proposed to account for the underlying neural mechanisms of such a trade-off: the cortical theory, the striatal theory, the STN theory and the synaptic theory, which stand for different circuits that modulate the balance between making a fast or making an accurate response (for details please see the review of Bogacz, 2010). The present results support both striatal and the STN theory on modulating the SAT. Future studies may be developed to determine the underlying neural mechanisms.

In addition, Wessel et al (2016) found that encountering unexpected events increases STN activity, which leads to the decrement of verbal working memory, and is related

to attentional reorientation. The authors therefore proposed that encountering surprising events would interrupt cognition via the same fronto-basal ganglia mechanism that interrupts action, which may lead to a new theory of distraction that involves a cortico-basal ganglia network that underlies motor suppression but also affects cognitive function (Wessel et al., 2016). Studies are in need to investigate the role of STN on interrupting cognition such as working memory after encountering unexpected events, and the connections between dopaminergic medication.

Overall speaking, the present PhD thesis suggests that both STN DBS and dopamine medication are effective in treating motor dysfunction in PD and the potential siede effects induced by treatments may be specific to individuals under certain coditions. However, the results do not rule out the potential side effects thay may be induced by treatments which would result in devastating consequnces to certain patients and their families. As prevention is better than cure, it is useful to further explore the possibilities of developing screening tools to identify risk factors for developing other disorders such as ICDs and dementia in individual patients, in order to reach better patient-centered care, which focuses on the individual's particular health care needs.

References

Aarsland, D., Brønnick, K., Larsen, J., Tysnes, O., Alves, G., & Group, N. P. S. (2009). Cognitive impairment in incident, untreated Parkinson disease the Norwegian ParkWest study. *Neurology, 72*(13), 1121-1126.

Aarsland, D., Påhlhagen, S., Ballard, C. G., Ehrt, U., & Svenningsson, P. (2012). Depression in Parkinson disease—epidemiology, mechanisms and management. *Nature Reviews Neurology, 8*(1), 35.

Albin, R. L., Young, A. B., & Penney, J. B. (1989). The functional anatomy of basal ganglia disorders. *Trends in neurosciences, 12*(10), 366-375.

Alegre, M., Lopez-Azcarate, J., Obeso, I., Wilkinson, L., Rodriguez-Oroz, M. C., Valencia, M., . . . Jahanshahi, M. (2013). The subthalamic nucleus is involved in successful inhibition in the stop-signal task: a local field potential study in Parkinson's disease. *Experimental neurology, 239*, 1-12.

Alexander, G. E., & Crutcher, M. D. (1990). Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends in neurosciences, 13*(7), 266-271.

Anderson, V. C., Burchiel, K. J., Hogarth, P., Favre, J., & Hammerstad, J. P. (2005). Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease. *Archives of Neurology, 62*(4), 554-560.

Antonini, A., Chaudhuri, K., Boroojerdi, B., Asgharnejad, M., Bauer, L., Grieger, F., & Weintraub, D. (2016). Impulse control disorder related behaviours during long-term rotigotine treatment: a post hoc analysis. *European Journal of Neurology, 23*(10), 1556-1565.

Aron, A. R., Behrens, T. E., Smith, S., Frank, M. J., & Poldrack, R. A. (2007). Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. *Journal of Neuroscience, 27*(14), 3743-3752.

Aron, A. R., & Poldrack, R. A. (2006). Cortical and subcortical contributions to stop signal response inhibition: role of the subthalamic nucleus. *Journal of Neuroscience, 26*(9), 2424-2433.

Ashby, F. G., Noble, S., Filoteo, J. V., Waldron, E. M., & Ell, S. W. (2003). Category learning deficits in Parkinson's disease. *Neuropsychology, 17*(1), 115.

Aziz, T. Z., Peggs, D., Agarwal, E., Sambrook, M. A., & Crossman, A. R. (1992). Subthalamic nucleotomy alleviates parkinsonism in the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-exposed primate. *British journal of neurosurgery, 6*(6), 575-582.

Aziz, T. Z., Peggs, D., Sambrook, M., & Crossman, A. (1991). Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1, 2, 3, 6-

tetrahydropyridine (MPTP)-induced parkinsonism in the primate. *Movement disorders: official journal of the Movement Disorder Society, 6*(4), 288-292.

Azmak, O., Bayer, H., Caplin, A., Chun, M., Glimcher, P., Koonin, S., & Patrinos, A. (2015). Using Big data to understand the human condition: the kavli HUMAN project. *Big data*, *3*(3), 173-188.

Ballanger, B., Poisson, A., Broussolle, E., & Thobois, S. (2012). Functional imaging of non-motor signs in Parkinson's disease. *J Neurol Sci, 315*(1-2), 9-14. doi:10.1016/j.jns.2011.11.008

Ballanger, B., van Eimeren, T., Moro, E., Lozano, A. M., Hamani, C., Boulinguez, P., . . . Strafella, A. P. (2009). Stimulation of the subthalamic nucleus and impulsivity: release your horses. *Ann Neurol, 66*(6), 817-824. doi:10.1002/ana.21795

Bates, D., Maechler, M., & Bolker, B. (2012). lme4: linear mixed-effects models using S4 classes. R package version 0.999375-42. 2011. *Google Scholar*.

Bayer, H. M., & Glimcher, P. W. (2005). Midbrain dopamine neurons encode a quantitative reward prediction error signal. *Neuron, 47*(1), 129-141.

Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition, 50*(1-3), 7-15.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Beck depression inventory-II. *San Antonio, 78*(2), 490-498.

Benabid, A., Benazzouz, A., Hoffmann, D., Limousin, P., Krack, P., & Pollak, P. (1998). Long-term electrical inhibition of deep brain targets in movement disorders. *Movement Disorders, 13*(S3), 119-125.

Benabid, A. L., Chabardes, S., Mitrofanis, J., & Pollak, P. (2009). Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. *The Lancet Neurology, 8*(1), 67-81.

Benazzouz, A., Gross, C., Féger, J., Boraud, T., & Bioulac, B. (1993). Reversal of rigidity and improvement in motor performance by subthalamic high-frequency stimulation in MPTP-treated monkeys. *European Journal of Neuroscience, 5*(4), 382-389.

Benazzouz, A., Tai, C. H., Meissner, W., Bioulac, B., Bezard, E., & Gross, C. (2004). High-frequency stimulation of both zona incerta and subthalamic nucleus induces a similar normalization of basal ganglia metabolic activity in experimental parkinsonism. *The FASEB journal, 18*(3), 528-530.

Bentivoglio, A. R., Baldonero, E., Ricciardi, L., De Nigris, F., & Daniele, A. (2013). Neuropsychological features of patients with Parkinson's disease and impulse control disorders. *Neurological Sciences, 34*(7), 1207-1213.

Benton, A. L. (1968). Differential behavioral effects in frontal lobe disease. *Neuropsychologia, 6*(1), 53-60.

Berardelli, A., Accornero, N., Argenta, M., Meco, G., & Manfredi, M. (1986). Fast complex arm movements in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 49*(10), 1146-1149.

Bergman, H., Wichmann, T., & DeLong, M. R. (1990). Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. *Science, 249*(4975), 1436-1438.

Bergman, H., Wichmann, T., Karmon, B., & DeLong, M. (1994). The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. *Journal of neurophysiology, 72*(2), 507-520.

Bestmann, S., Harrison, L. M., Blankenburg, F., Mars, R. B., Haggard, P., Friston, K. J., & Rothwell, J. C. (2008). Influence of uncertainty and surprise on human corticospinal excitability during preparation for action. *Current Biology, 18*(10), 775-780.

Beyer, M. K., Janvin, C. C., Larsen, J. P., & Aarsland, D. (2007). A magnetic resonance imaging study of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel-based morphometry. *Journal of Neurology, Neurosurgery & Psychiatry, 78*(3), 254-259.

Bogacz, R., Brown, E., Moehlis, J., Holmes, P., & Cohen, J. D. (2006). The physics of optimal decision making: a formal analysis of models of performance in two-alternative forced-choice tasks. *Psychological review, 113*(4), 700.

Bogacz, R., & Gurney, K. (2007). The basal ganglia and cortex implement optimal decision making between alternative actions. *Neural computation, 19*(2), 442-477.

Bogacz, R., Wagenmakers, E.-J., Forstmann, B. U., & Nieuwenhuis, S. (2010). The neural basis of the speed–accuracy tradeoff. *Trends in neurosciences, 33*(1), 10-16.

Boller, J. K., Barbe, M. T., Pauls, K. A. M., Reck, C., Brand, M., Maier, F., . . . Kalbe, E. (2014). Decision-making under risk is improved by both dopaminergic medication and subthalamic stimulation in Parkinson's disease. *Experimental neurology, 254*, 70-77.

Botvinick, M., Nystrom, L. E., Fissell, K., Carter, C. S., & Cohen, J. D. (1999). Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature, 402*(6758), 179.

Bozdogan, H. (1987). Model selection and Akaike's information criterion (AIC): The general theory and its analytical extensions. *Psychometrika, 52*(3), 345-370.

Brand, M., Labudda, K., & Markowitsch, H. J. (2006). Neuropsychological correlates

of decision-making in ambiguous and risky situations. *Neural Networks, 19*(8), 1266-1276.

Brandt, J., Rogerson, M., Al-Joudi, H., Reckess, G., Shpritz, B., Umeh, C. C., . . . Mari, Z. (2015). Betting on DBS: Effects of subthalamic nucleus deep brain stimulation on risk taking and decision making in patients with Parkinson's disease. *Neuropsychology, 29*(4), 622.

Britten, K. H., Shadlen, M. N., Newsome, W. T., & Movshon, J. A. (1992). The analysis of visual motion: a comparison of neuronal and psychophysical performance. *J Neurosci, 12*(12), 4745-4765.

Bronte-Stewart, H., Barberini, C., Koop, M. M., Hill, B. C., Henderson, J. M., & Wingeier, B. (2009). The STN beta-band profile in Parkinson's disease is stationary and shows prolonged attenuation after deep brain stimulation. *Experimental neurology, 215*(1), 20-28.

Brown, P. (2003). Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. *Movement disorders: official journal of the Movement Disorder Society, 18*(4), 357-363.

Brown, P., & Marsden, C. (1998). What do the basal ganglia do? *The Lancet, 351*(9118), 1801-1804.

Brown, P., Oliviero, A., Mazzone, P., Insola, A., Tonali, P., & Di Lazzaro, V. (2001). Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *Journal of Neuroscience, 21*(3), 1033-1038.

Brownlee, J. (2016, 10th, June). Your First Machine Learning Project in Python Step-By-Step [Blog Post]. Retrieved from https://machinelearningmastery.com/machine-learning-inpython-step-by-step/

Brownlee, J. (2017, 24th, July). How Much Training Data is Required for Machine Learning? [Blog Post]. Retrieved from https://machinelearningmastery.com/much-training-data-required-machine-learning/

Bruet, N., Windels, F., Bertrand, A., Feuerstein, C., Poupard, A., & Savasta, M. (2001). High frequency stimulation of the subthalamic nucleus increases the extracellular contents of striatal dopamine in normal and partially dopaminergic denervated rats. *Journal of Neuropathology & Experimental Neurology, 60*(1), 15-24.

Büttner, T., Kuhn, W., Müller, T., Patzold, T., & Przuntek, H. (1995). Color vision in Parkinson's disease: Missing influence of amantadine sulphate. *Clinical neuropharmacology*.

Burgess, P. W., & Shallice, T. (1997). The hayling and brixton tests.

Cardinal, R. N., Robbins, T. W., & Everitt, B. J. (2000). The effects of

d-amphetamine, chlordiazepoxide, α-flupenthixol and behavioural manipulations on choice of signalled and unsignalled delayed reinforcement in rats. *Psychopharmacology, 152*(4), 362-375.

Castrioto, A., Funkiewiez, A., Debû, B., Cools, R., Lhommée, E., Ardouin, C., . . . Pollak, P. (2015). Iowa gambling task impairment in Parkinson's disease can be normalised by reduction of dopaminergic medication after subthalamic stimulation. *J Neurol Neurosurg Psychiatry, 86*(2), 186-190.

Cavanagh, J. F., Wiecki, T. V., Cohen, M. X., Figueroa, C. M., Samanta, J., Sherman, S. J., & Frank, M. J. (2011). Subthalamic nucleus stimulation reverses mediofrontal influence over decision threshold. *Nature neuroscience, 14*(11), 1462.

Chatham, C. H., Claus, E. D., Kim, A., Curran, T., Banich, M. T., & Munakata, Y. (2012). Cognitive control reflects context monitoring, not motoric stopping, in response inhibition. *PloS one, 7*(2), e31546.

Chaudhuri, K. R., Healy, D. G., & Schapira, A. H. (2006). Non-motor symptoms of Parkinson's disease: diagnosis and management. *The Lancet Neurology, 5*(3), 235-245.

Chaudhuri, K. R., & Schapira, A. H. (2009). Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *The Lancet Neurology, 8*(5), 464-474.

Choi, E., Bahadori, M. T., Sun, J., Kulas, J., Schuetz, A., & Stewart, W. (2016). Retain: An interpretable predictive model for healthcare using reverse time attention mechanism. In *Advances in Neural Information Processing Systems* (pp. 3504-3512).

Cisek, P. (2007). Cortical mechanisms of action selection: the affordance competition hypothesis. *Philosophical Transactions of the Royal Society of London B: Biological Sciences, 362*(1485), 1585-1599.

Claassen, D. O., van den Wildenberg, W. P., Harrison, M. B., van Wouwe, N. C., Kanoff, K., Neimat, J. S., & Wylie, S. A. (2015). Proficient motor impulse control in Parkinson disease patients with impulsive and compulsive behaviors. *Pharmacology Biochemistry and Behavior, 129*, 19-25.

Cohen, J. (1992). A power primer. *Psychol Bull, 112*(1), 155-159.

Combs, H. L., Folley, B. S., Berry, D. T., Segerstrom, S. C., Han, D. Y., Anderson-Mooney, A. J., . . . van Horne, C. (2015). Cognition and depression following deep brain stimulation of the subthalamic nucleus and globus pallidus pars internus in Parkinson's disease: a meta-analysis. *Neuropsychology review, 25*(4), 439-454.

Cools, R. (2006). Dopaminergic modulation of cognitive function-implications for

l-DOPA treatment in Parkinson's disease. *Neuroscience & Biobehavioral Reviews, 30*(1), 1-23. doi:https://doi.org/10.1016/j.neubiorev.2005.03.024

Cools, R., Altamirano, L., & D'esposito, M. (2006). Reversal learning in Parkinson's disease depends on medication status and outcome valence. *Neuropsychologia, 44*(10), 1663-1673.

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001). Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cerebral cortex, 11*(12), 1136-1143.

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2003). L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia, 41*(11), 1431-1441.

Cools, R., Frank, M. J., Gibbs, S. E., Miyakawa, A., Jagust, W., & D'Esposito, M. (2009). Striatal dopamine predicts outcome-specific reversal learning and its sensitivity to dopaminergic drug administration. *Journal of Neuroscience, 29*(5), 1538-1543.

Crossman, A. (1990). A hypothesis on the pathophysiological mechanisms that underlie levodopa-or dopamine agonist-induced dyskinesia in Parkinson's disease: implications for future strategies in treatment. *Movement disorders: official journal of the Movement Disorder Society, 5*(2), 100-108.

Crossman, A., Sambrook, M., & Jackson, A. (1984). Experimental hemichorea/hemiballismus in the monkey: studies on the intracerebral site of action in a drug-induced dyskinesia. *Brain, 107*(2), 579-596.

Cummings, J. L. (1992). Depression and Parkinson's disease: a review. *The American journal of psychiatry, 149*(4), 443.

Czernecki, V., Pillon, B., Houeto, J., Pochon, J., Levy, R., & Dubois, B. (2002). Motivation, reward, and Parkinson's disease: influence of dopatherapy. *Neuropsychologia, 40*(13), 2257-2267.

Czernecki, V., Pillon, B., Houeto, J., Welter, M., Mesnage, V., Agid, Y., & Dubois, B. (2005). Does bilateral stimulation of the subthalamic nucleus aggravate apathy in Parkinson's disease? *Journal of Neurology, Neurosurgery & Psychiatry, 76*(6), 775-779.

Dalley, J. W., Everitt, B. J., & Robbins, T. W. (2011). Impulsivity, compulsivity, and top-down cognitive control. *Neuron*, *69*(4), 680-694.

Dauer, W., & Przedborski, S. (2003). Parkinson's disease: mechanisms and models. *Neuron, 39*(6), 889-909.

Daw, N. D., & Tobler, P. N. (2014). Value learning through reinforcement: the basics of dopamine and reinforcement learning *Neuroeconomics (Second Edition)*

(pp. 283-298): Elsevier.

DeLong, M. R. (1990). Primate models of movement disorders of basal ganglia origin. *Trends in neurosciences, 13*(7), 281-285.

Deneve, S. (2012). Making decisions with unknown sensory reliability. *Frontiers in neuroscience, 6*, 75.

D'esposito, M., Detre, J. A., Alsop, D. C., Shin, R. K., Atlas, S., & Grossman, M. (1995). The neural basis of the central executive system of working memory. *Nature, 378*(6554), 279.

Deuschl, G., Schade-Brittinger, C., Krack, P., Volkmann, J., Schäfer, H., Bötzel, K., . . . Eisner, W. (2006). A randomized trial of deep-brain stimulation for Parkinson's disease. *New England Journal of Medicine, 355*(9), 896-908.

Diamond, A. (2013). Executive functions. *Annual review of psychology, 64*, 135-168.

Dirnberger, G., & Jahanshahi, M. (2013). Executive dysfunction in P arkinson's disease: A review. *Journal of neuropsychology, 7*(2), 193-224.

Djamshidian, A., Jha, A., O'sullivan, S. S., Silveira-Moriyama, L., Jacobson, C., Brown, P., . . . Averbeck, B. B. (2010). Risk and learning in impulsive and nonimpulsive patients with Parkinson's disease. *Movement Disorders, 25*(13), 2203-2210.

Djamshidian, A., O'Sullivan, S. S., Lawrence, A. D., Foltynie, T., Aviles-Olmos, I., Magdalinou, N., . . . Averbeck, B. B. (2014). Perceptual decision-making in patients with Parkinson's disease. *Journal of psychopharmacology, 28*(12), 1149-1154.

Djamshidian, A., O'Sullivan, S. S., Lees, A., & Averbeck, B. B. (2011). Stroop test performance in impulsive and non impulsive patients with Parkinson's disease. *Parkinsonism & related disorders, 17*(3), 212-214.

Djamshidian, A., O'sullivan, S. S., Sanotsky, Y., Sharman, S., Matviyenko, Y., Foltynie, T., . . . Doherty, K. M. (2012). Decision making, impulsivity, and addictions: do Parkinson's disease patients jump to conclusions? *Movement Disorders, 27*(9), 1137-1145.

Dodd, M. L., Klos, K. J., Bower, J. H., Geda, Y. E., Josephs, K. A., & Ahlskog, J. E. (2005). Pathological gambling caused by drugs used to treat Parkinson disease. *Archives of Neurology, 62*(9), 1377-1381.

Domenech, P., & Dreher, J.-C. (2010). Decision threshold modulation in the human brain. *Journal of Neuroscience, 30*(43), 14305-14317.

Doyon, J., Penhune, V., & Ungerleider, L. G. (2003). Distinct contribution of the cortico-striatal and cortico-cerebellar systems to motor skill learning. *Neuropsychologia, 41*(3), 252-262.

Dreiseitl, S., & Ohno-Machado, L. (2002). Logistic regression and artificial neural

network classification models: a methodology review. *Journal of biomedical informatics*, *35*(5-6), 352-359.

Drevets, W. C., Gautier, C., Price, J. C., Kupfer, D. J., Kinahan, P. E., Grace, A. A., . . . Mathis, C. A. (2001). Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biological psychiatry*, *49*(2), 81-96.

Dubois, B., Malapani, C., Verin, M., Rogelet, P., Deweer, B., & Pillon, B. (1994). Cognitive functions and the basal ganglia: the model of Parkinson disease. *Revue neurologique*, *150*(11), 763-770.

Dubois, B., & Pillon, B. (1996). Cognitive deficits in Parkinson's disease. *Journal of neurology*, *244*(1), 2-8.

Duda, R. O., Hart, P. E., & Stork, D. G. (2012). *Pattern classification*. John Wiley & Sons.

Eagle, D. M., Bari, A., & Robbins, T. W. (2008). The neuropsychopharmacology of action inhibition: cross-species translation of the stop-signal and go/no-go tasks. *Psychopharmacology*, *199*(3), 439-456.

Engel, A. K., & Fries, P. (2010). Beta-band oscillations—signalling the status quo? *Current opinion in neurobiology*, *20*(2), 156-165.

Engle, R. W., & Kane, M. J. (2004). Executive attention, working memory capacity, and a two-factor theory of cognitive control. *Psychology of learning and motivation*, *44*, 145-200.

Euteneuer, F., Schaefer, F., Stuermer, R., Boucsein, W., Timmermann, L., Barbe, M. T., . . . Kalbe, E. (2009). Dissociation of decision-making under ambiguity and decision-making under risk in patients with Parkinson's disease: a neuropsychological and psychophysiological study. *Neuropsychologia*, *47*(13), 2882-2890.

Evenden, J. L. (1999). Varieties of impulsivity. *Psychopharmacology*, *146*(4), 348-361.

Evens, R., Hoefler, M., Biber, K., & Lueken, U. (2016). The Iowa Gambling Task in Parkinson's disease: A meta-analysis on effects of disease and medication. *Neuropsychologia*, *91*, 163-172.

Everitt, B. J., & Robbins, T. W. (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nature neuroscience*, *8*(11), 1481.

Fahn, S., & Elton, R. (1987). Members of the UPDRS development committee. *Recent developments in Parkinson's disease, 2*(J), 153.

Feigin, A., Ghilardi, M., Carbon, M., Edwards, C., Fukuda, M., Dhawan, V., . . . Eidelberg, D. (2003). Effects of levodopa on motor sequence learning in

Parkinson's disease. *Neurology, 60*(11), 1744-1749.

FitzGerald, T. H., Schwartenbeck, P., Moutoussis, M., Dolan, R. J., & Friston, K. (2015). Active inference, evidence accumulation, and the urn task. *Neural computation*, *27*(2), 306-328.

Foerde, K., Figner, B., Doll, B. B., Woyke, I. C., Braun, E. K., Weber, E. U., & Shohamy, D. (2016). Dopamine modulation of intertemporal decision-making: Evidence from Parkinson disease. *Journal of cognitive neuroscience, 28*(5), 657-667.

Follett, K. A., & Torres-Russotto, D. (2012). Deep brain stimulation of globus pallidus interna, subthalamic nucleus, and pedunculopontine nucleus for Parkinson's disease: which target? *Parkinsonism & related disorders, 18*, S165-S167.

Follett, K. A., Weaver, F. M., Stern, M., Hur, K., Harris, C. L., Luo, P., . . . Moy, C. (2010). Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *New England Journal of Medicine, 362*(22), 2077-2091.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research, 12*(3), 189-198.

Forstmann, B. U., Anwander, A., Schäfer, A., Neumann, J., Brown, S., Wagenmakers, E.-J., . . . Turner, R. (2010). Cortico-striatal connections predict control over speed and accuracy in perceptual decision making. *Proceedings of the National Academy of Sciences, 107*(36), 15916-15920.

Forstmann, B. U., Dutilh, G., Brown, S., Neumann, J., Von Cramon, D. Y., Ridderinkhof, K. R., & Wagenmakers, E.-J. (2008). Striatum and pre-SMA facilitate decision-making under time pressure. *Proceedings of the National Academy of Sciences, 105*(45), 17538-17542.

Frank, D. N., Amand, A. L. S., Feldman, R. A., Boedeker, E. C., Harpaz, N., & Pace, N. R. (2007). Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proceedings of the National Academy of Sciences, 104*(34), 13780-13785.

Frank, M. J. (2005). Dynamic dopamine modulation in the basal ganglia: a neurocomputational account of cognitive deficits in medicated and nonmedicated Parkinsonism. *Journal of cognitive neuroscience, 17*(1), 51-72.

Frank, M. J. (2006). Hold your horses: a dynamic computational role for the subthalamic nucleus in decision making. *Neural Networks, 19*(8), 1120-1136.

Frank, M. J. (2011). Computational models of motivated action selection in corticostriatal circuits. *Current opinion in neurobiology, 21*(3), 381-386.

Frank, M. J., Loughry, B., & O'Reilly, R. C. (2001). Interactions between frontal

cortex and basal ganglia in working memory: a computational model. *Cognitive, Affective, & Behavioral Neuroscience, 1*(2), 137-160.

Frank, M. J., Samanta, J., Moustafa, A. A., & Sherman, S. J. (2007). Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. *Science, 318*(5854), 1309-1312.

Frank, M. J., Seeberger, L. C., & O'reilly, R. C. (2004). By carrot or by stick: cognitive reinforcement learning in parkinsonism. *Science, 306*(5703), 1940-1943.

Friedman, J. H., Bentley, J. L., & Finkel, R. A. (1976). An algorithm for finding best matches in logarithmic time. *ACM Trans. Math. Software*, *3*(SLAC-PUB-1549-REV. 2), 209-226.

Friedman, N. P., Haberstick, B. C., Willcutt, E. G., Miyake, A., Young, S. E., Corley, R. P., & Hewitt, J. K. (2007). Greater attention problems during childhood predict poorer executive functioning in late adolescence. *Psychological science, 18*(10), 893-900.

Friedman, N. P., Miyake, A., Robinson, J. L., & Hewitt, J. K. (2011). Developmental trajectories in toddlers' self-restraint predict individual differences in executive functions 14 years later: A behavioral genetic analysis. *Developmental psychology, 47*(5), 1410.

Friston, K. (2010). The free-energy principle: a unified brain theory? *Nature Reviews Neuroscience, 11*(2), 127.

Friston, K., & Kiebel, S. (2009). Predictive coding under the free-energy principle. *Philosophical Transactions of the Royal Society of London B: Biological Sciences, 364*(1521), 1211-1221.

Friston, K., Schwartenbeck, P., FitzGerald, T., Moutoussis, M., Behrens, T., & Dolan, R. J. (2013). The anatomy of choice: active inference and agency. *Frontiers in human neuroscience, 7*, 598.

Friston, K. J. (2005). Hallucinations and perceptual inference. *Behavioral and Brain Sciences, 28*(6), 764-766.

Friston, K. J., Daunizeau, J., Kilner, J., & Kiebel, S. J. (2010). Action and behavior: a free-energy formulation. *Biological cybernetics, 102*(3), 227-260.

Friston, K. J., Shiner, T., FitzGerald, T., Galea, J. M., Adams, R., Brown, H., . . . Bestmann, S. (2012). Dopamine, affordance and active inference. *PLoS computational biology, 8*(1), e1002327.

Fumagalli, M., Marceglia, S., Cogiamanian, F., Ardolino, G., Picascia, M., Barbieri, S., . . . Priori, A. (2015). Ethical safety of deep brain stimulation: A study on moral decision-making in Parkinson's disease. *Parkinsonism Relat Disord, 21*(7), 709-716. doi:10.1016/j.parkreldis.2015.04.011

Funkiewiez, A., Ardouin, C., Caputo, E., Krack, P., Fraix, V., Klinger, H., . . . Pollak, P. (2004). Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 75*(6), 834-839.

Galea, J. M., Bestmann, S., Beigi, M., Jahanshahi, M., & Rothwell, J. C. (2012). Action reprogramming in Parkinson's disease: response to prediction error is modulated by levels of dopamine. *Journal of Neuroscience, 32*(2), 542-550.

Georgiev, D., Dirnberger, G., Wilkinson, L., Limousin, P., & Jahanshahi, M. (2016). In Parkinson's disease on a probabilistic Go/NoGo task deep brain stimulation of the subthalamic nucleus only interferes with withholding of the most prepotent responses. *Exp Brain Res, 234*(4), 1133-1143. doi:10.1007/s00221-015-4531-2

Gerfen, C. R. (2000). Dopamine-mediated gene regulation in models of Parkinson's disease. *Annals of neurology, 47*(4 Suppl 1), S42-50; discussion S50-42.

Ghilardi, M. F., Feigin, A. S., Battaglia, F., Silvestri, G., Mattis, P., Eidelberg, D., & Di Rocco, A. (2007). L-Dopa infusion does not improve explicit sequence learning in Parkinson's disease. *Parkinsonism & related disorders, 13*(3), 146-151.

Gholami, V., Chau, K. W., Fadaee, F., Torkaman, J., & Ghaffari, A. (2015). Modeling of groundwater level fluctuations using dendrochronology in alluvial aquifers. *Journal of hydrology*, *529*, 1060-1069.

Giannicola, G., Marceglia, S., Rossi, L., Mrakic-Sposta, S., Rampini, P., Tamma, F., . . . Priori, A. (2010). The effects of levodopa and ongoing deep brain stimulation on subthalamic beta oscillations in Parkinson's disease. *Experimental neurology, 226*(1), 120-127.

Gotham, A., Brown, R., & Marsden, C. (1988). 'Frontal'cognitive function in patients with Parkinson's disease 'on'and 'off'levodopa. *Brain, 111*(2), 299-321.

Grant, J. E., Schreiber, L., & Odlaug, B. L. (2011). Impulse control disorders: updated review of clinical characteristics and pharmacological management. *Frontiers in psychiatry, 2*, 1.

Gratwicke, J., Jahanshahi, M., & Foltynie, T. (2015). Parkinson's disease dementia: a neural networks perspective. *Brain, 138*(6), 1454-1476.

Green, N., Bogacz, R., Huebl, J., Beyer, A.-K., Kühn, A. A., & Heekeren, H. R. (2013). Reduction of influence of task difficulty on perceptual decision making by STN deep brain stimulation. *Current Biology, 23*(17), 1681-1684.

Gregory, R. L. (1980). Perceptions as hypotheses. *Phil. Trans. R. Soc. Lond. B, 290*(1038), 181-197.

Gurevich, E. V., & Joyce, J. N. (1999). Distribution of dopamine D3 receptor

expressing neurons in the human forebrain: comparison with D2 receptor expressing neurons. *Neuropsychopharmacology, 20*(1), 60-80.

Haber, S. N., & Calzavara, R. (2009). The cortico-basal ganglia integrative network: the role of the thalamus. *Brain research bulletin, 78*(2-3), 69-74.

Hadland, K., Rushworth, M., Gaffan, D., & Passingham, R. (2003). The anterior cingulate and reward-guided selection of actions. *Journal of neurophysiology, 89*(2), 1161-1164.

Hälbig, T., Tse, W., Frisina, P., Baker, B., Hollander, E., Shapiro, H., . . . Olanow, C. (2009). Subthalamic deep brain stimulation and impulse control in Parkinson's disease. *European Journal of Neurology, 16*(4), 493-497.

Hall, P. (2016, February 11). Predictive modeling: Striking a balance between accuracy and interpretability. Retrived from https://www.oreilly.com/ideas/predictive-modeling-striking-a-balance-between-accuracy-and-interpretability

Harrison, L. M., Duggins, A., & Friston, K. J. (2006). Encoding uncertainty in the hippocampus. *Neural Netw, 19*(5), 535-546. doi:10.1016/j.neunet.2005.11.002

Hashimoto, T., Elder, C. M., Okun, M. S., Patrick, S. K., & Vitek, J. L. (2003). Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. *Journal of Neuroscience, 23*(5), 1916-1923.

Hassan, A., Bower, J., Kumar, N., Matsumoto, J., Fealey, R., Josephs, K., & Ahlskog, J. (2011). Dopamine agonist-triggered pathological behaviors: surveillance in the PD clinic reveals high frequencies. *Parkinsonism & related disorders, 17*(4), 260-264.

Hayward, D. K. R. (2007). When Averages Hide Individual Differences in Clinical Trials: Analyzing the results of clinical trials to expose individual patient's risks might help doctors make better treatment decisions. *American Scientist*, *95*(1), 60-68.

Hedges, L., & Olkin, I. (1985). Statistical models for meta-analysis: New York: Academic Press.

Helmholtz, H. v. (1866). Concerning the perceptions in general. *Treatise on physiological optics*.

Henik, A., Singh, J., Beckley, D. J., & Rafal, R. D. (1993). Disinhibition of automatic word reading in Parkinson's disease. *Cortex, 29*(4), 589-599.

Hershey, T., Black, K. J., Hartlein, J., Braver, T. S., Barch, D. M., Carl, J. L., & Perlmutter, J. S. (2004). Dopaminergic modulation of response inhibition: an fMRI study. *Brain Res Cogn Brain Res, 20*(3), 438-448. doi:10.1016/j.cogbrainres.2004.03.018

Hershey, T., Campbell, M. C., Videen, T. O., Lugar, H. M., Weaver, P. M., Hartlein,

J., . . . Perlmutter, J. S. (2010). Mapping Go-No-Go performance within the subthalamic nucleus region. *Brain, 133*(Pt 12), 3625-3634. doi:10.1093/brain/awq256

Hikosaka, O. (1989). Role of basal ganglia in initiation of voluntary movements *Dynamic interactions in neural networks: Models and data* (pp. 153-167): Springer.

Hikosaka, O., & Isoda, M. (2010). Switching from automatic to controlled behavior: cortico-basal ganglia mechanisms. *Trends in cognitive sciences, 14*(4), 154-161.

Hilker, R., Voges, J., Ghaemi, M., Lehrke, R., Rudolf, J., Koulousakis, A., . . . Heiss, W. D. (2003). Deep brain stimulation of the subthalamic nucleus does not increase the striatal dopamine concentration in parkinsonian humans. *Movement disorders: official journal of the Movement Disorder Society, 18*(1), 41-48.

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: onset, progression and mortality. *Neurology, 17*(5), 427-442.

Hollerman, J. R., & Schultz, W. (1998). Dopamine neurons report an error in the temporal prediction of reward during learning. *Nature neuroscience, 1*(4), 304.

Holroyd, C. B., & Coles, M. G. (2002). The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychological review, 109*(4), 679.

Housden, C. R., O'sullivan, S. S., Joyce, E. M., Lees, A. J., & Roiser, J. P. (2010). Intact reward learning but elevated delay discounting in Parkinson's disease patients with impulsive-compulsive spectrum behaviors. *Neuropsychopharmacology, 35*(11), 2155.

Huang, Y.-T., Georgiev, D., Foltynie, T., Limousin, P., Speekenbrink, M., & Jahanshahi, M. (2015). Different effects of dopaminergic medication on perceptual decision-making in Parkinson's disease as a function of task difficulty and speed–accuracy instructions. *Neuropsychologia, 75*, 577-587.

Hughes, A. J., Daniel, S. E., Kilford, L., & Lees, A. J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *Journal of Neurology, Neurosurgery & Psychiatry, 55*(3), 181-184.

Isaias, I. U., Siri, C., Cilia, R., De Gaspari, D., Pezzoli, G., & Antonini, A. (2008). The relationship between impulsivity and impulse control disorders in Parkinson's disease. *Movement disorders: official journal of the Movement Disorder Society*, *23*(3), 411-415.

Isoda, M., & Hikosaka, O. (2008). Role for subthalamic nucleus neurons in switching from automatic to controlled eye movement. *Journal of Neuroscience*, *28*(28),

7209-7218.

Ivanoff, J., Branning, P., & Marois, R. (2008). fMRI evidence for a dual process account of the speed-accuracy tradeoff in decision-making. *PloS one, 3*(7), e2635.

Jackson, G. M., Jackson, S. R., Harrison, J., Henderson, L., & Kennard, C. (1995). Serial reaction time learning and Parkinson's disease: Evidence for a procedural learning deficit. *Neuropsychologia, 33*(5), 577-593.

Jahanshahi, M. (2013). Effects of deep brain stimulation of the subthalamic nucleus on inhibitory and executive control over prepotent responses in Parkinson's disease. *Frontiers in systems neuroscience, 7*, 118.

Jahanshahi, M., Ardouin, C., Brown, R., Rothwell, J., Obeso, J., Albanese, A., . . . Pollak, P. (2000). The impact of deep brain stimulation on executive function in Parkinson's disease. *Brain, 123*(6), 1142-1154.

Jahanshahi, M., Jones, C. R., Zijlmans, J., Katzenschlager, R., Lee, L., Quinn, N., . . . Lees, A. J. (2010). Dopaminergic modulation of striato-frontal connectivity during motor timing in Parkinson's disease. *Brain, 133*(3), 727-745.

Jahanshahi, M., Wilkinson, L., Gahir, H., Dharminda, A., & Lagnado, D. A. (2010). Medication impairs probabilistic classification learning in Parkinson's disease. *Neuropsychologia, 48*(4), 1096-1103.

Jankovic, J. (2008). Parkinson's disease: clinical features and diagnosis. *Journal of Neurology, Neurosurgery & Psychiatry, 79*(4), 368-376.

Janvin, C. C., Larsen, J. P., Aarsland, D., & Hugdahl, K. (2006). Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. *Movement disorders: official journal of the Movement Disorder Society, 21*(9), 1343-1349.

Jones, E., Oliphant, T., & Peterson, P. (2014). {SciPy}: open source scientific tools for {Python}.

Joutsa, J., Martikainen, K., Vahlberg, T., Voon, V., & Kaasinen, V. (2012). Impulse control disorders and depression in Finnish patients with Parkinson's disease. *Parkinsonism & related disorders, 18*(2), 155-160.

Keefe, K., & Gerfen, C. (1995). D1–D2 dopamine receptor synergy in striatum: effects of intrastriatal infusions of dopamine agonists and antagonists on immediate early gene expression. *Neuroscience, 66*(4), 903-913.

Kim, H. F., & Hikosaka, O. (2015). Parallel basal ganglia circuits for voluntary and automatic behaviour to reach rewards. *Brain, 138*(7), 1776-1800.

Kleiner-Fisman, G., Fisman, D. N., Sime, E., Saint-Cyr, J. A., Lozano, A. M., & Lang, A. E. (2003). Long-term follow up of bilateral deep brain stimulation of the subthalamic nucleus in patients with advanced Parkinson disease. *Journal of*

neurosurgery, 99(3), 489-495.

Kobayakawa, M., Koyama, S., Mimura, M., & Kawamura, M. (2008). Decision making in Parkinson's disease: Analysis of behavioral and physiological patterns in the Iowa gambling task. *Movement Disorders, 23*(4), 547-552.

Kobayakawa, M., Tsuruya, N., & Kawamura, M. (2010). Sensitivity to reward and punishment in Parkinson's disease: an analysis of behavioral patterns using a modified version of the Iowa gambling task. *Parkinsonism & related disorders, 16*(7), 453-457.

Krack, P., Batir, A., Van Blercom, N., Chabardes, S., Fraix, V., Ardouin, C., . . . LeBas, J. F. (2003). Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *New England Journal of Medicine, 349*(20), 1925-1934.

Kudlicka, A., Clare, L., & Hindle, J. V. (2011). Executive functions in Parkinson's disease: Systematic review and meta-analysis. *Movement Disorders, 26*(13), 2305-2315.

Kühn, A. A., Kempf, F., Brücke, C., Doyle, L. G., Martinez-Torres, I., Pogosyan, A., . . . Hariz, M. I. (2008). High-frequency stimulation of the subthalamic nucleus suppresses oscillatory β activity in patients with Parkinson's disease in parallel with improvement in motor performance. *Journal of Neuroscience, 28*(24), 6165-6173.

Kühn, A. A., Kupsch, A., Schneider, G. H., & Brown, P. (2006). Reduction in subthalamic 8–35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease. *European Journal of Neuroscience*, *23*(7), 1956-1960.

Kühn, A. A., Williams, D., Kupsch, A., Limousin, P., Hariz, M., Schneider, G. H., . . . Brown, P. (2004). Event-related beta desynchronization in human subthalamic nucleus correlates with motor performance. *Brain, 127*(4), 735-746.

Kwak, Y., Peltier, S., Bohnen, N., Müller, M., Dayalu, P., & Seidler, R. D. (2010). Altered resting state cortico-striatal connectivity in mild to moderate stage Parkinson's disease. *Frontiers in systems neuroscience*, *4*, 143.

Kwak, Y., Peltier, S., Bohnen, N., Müller, M., Dayalu, P., & Seidler, R. D. (2012). L-DOPA changes spontaneous low-frequency BOLD signal oscillations in Parkinson's disease: a resting state fMRI study. *Frontiers in systems neuroscience, 6*, 52.

Labudda, K., Brand, M., Mertens, M., Ollech, I., Markowitsch, H. J., & Woermann, F. G. (2010). Decision making under risk condition in patients with Parkinson's disease: a behavioural and fMRI study. *Behavioural neurology, 23*(3), 131-143.

Lacombe, E., Carcenac, C., Boulet, S., Feuerstein, C., Bertrand, A., Poupard, A., &

Savasta, M. (2007). High-frequency stimulation of the subthalamic nucleus prolongs the increase in striatal dopamine induced by acute l-3, 4-dihydroxyphenylalanine in dopaminergic denervated rats. *European Journal of Neuroscience, 26*(6), 1670-1680.

Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Frontiers in psychology, 4*, 863.

Lang, A. E., & Lozano, A. M. (1998). Parkinson's disease. *New England Journal of Medicine, 339*(16), 1130-1143.

Lauwereyns, J., Watanabe, K., Coe, B., & Hikosaka, O. (2002). A neural correlate of response bias in monkey caudate nucleus. *Nature, 418*(6896), 413.

Lawrence, N. S., Jollant, F., O'daly, O., Zelaya, F., & Phillips, M. L. (2008). Distinct roles of prefrontal cortical subregions in the Iowa Gambling Task. *Cerebral cortex, 19*(5), 1134-1143.

Lee, B., London, E. D., Poldrack, R. A., Farahi, J., Nacca, A., Monterosso, J. R., . . . Mukherjee, J. (2009). Striatal dopamine d2/d3 receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. *Journal of Neuroscience, 29*(47), 14734-14740.

Lee, C. H., & Yoon, H.-J. (2017). Medical big data: promise and challenges. *Kidney research and clinical practice, 36*(1), 3.

Lehéricy, S., Bardinet, E., Tremblay, L., Van de Moortele, P.-F., Pochon, J.-B., Dormont, D., . . . Ugurbil, K. (2005). Motor control in basal ganglia circuits using fMRI and brain atlas approaches. *Cerebral cortex, 16*(2), 149-161.

Lehto, J. E., Juujärvi, P., Kooistra, L., & Pulkkinen, L. (2003). Dimensions of executive functioning: Evidence from children. *British Journal of Developmental Psychology, 21*(1), 59-80.

Leimbach, F., Georgiev, D., Litvak, V., Antoniades, C., Limousin, P., Jahanshahi, M., & Bogacz, R. (2018). Deep Brain Stimulation of the Subthalamic Nucleus Does Not Affect the Decrease of Decision Threshold during the Choice Process When There Is No Conflict, Time Pressure, or Reward. *Journal of cognitive neuroscience, 30*(6), 876-884.

Lerche, V., Voss, A., & Nagler, M. (2017). How many trials are required for parameter estimation in diffusion modeling? A comparison of different optimization criteria. *Behavior research methods, 49*(2), 513-537.

Leroi, I., Barraclough, M., McKie, S., Hinvest, N., Evans, J., Elliott, R., & McDonald, K. (2013). Dopaminergic influences on executive function and impulsive behaviour in impulse control disorders in Parkinson's disease. *Journal of neuropsychology, 7*(2), 306-325.

Leroi, I., McDonald, K., Pantula, H., & Harbishettar, V. (2012). Cognitive impairment in Parkinson disease: impact on quality of life, disability, and caregiver burden. *Journal of geriatric psychiatry and neurology*, *25*(4), 208-214.

Levy, R., Ashby, P., Hutchison, W. D., Lang, A. E., Lozano, A. M., & Dostrovsky, J. O. (2002). Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. *Brain*, *125*(6), 1196-1209.

Li, C. S. R., & Chen, S. H. (2007). Obsessive–compulsiveness and impulsivity in a non-clinical population of adolescent males and females. *Psychiatry research*, *149*(1-3), 129-138.

Li, C.-s. R., Huang, C., Yan, P., Paliwal, P., Constable, R. T., & Sinha, R. (2008). Neural correlates of post-error slowing during a stop signal task: a functional magnetic resonance imaging study. *Journal of cognitive neuroscience*, *20*(6), 1021-1029.

Limousin, P., Krack, P., Pollak, P., Benazzouz, A., Ardouin, C., Hoffmann, D., & Benabid, A.-L. (1998). Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *New England Journal of Medicine*, *339*(16), 1105-1111.

Limousin, P., Pollak, P., Benazzouz, A., Hoffmann, D., Le Bas, J.-F., Perret, J. E., . . . Broussolle, E. (1995). Effect on parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *The Lancet*, *345*(8942), 91-95.

Litvan, I., Aarsland, D., Adler, C. H., Goldman, J. G., Kulisevsky, J., Mollenhauer, B., . . . Weintraub, D. (2011). MDS Task Force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. *Movement Disorders*, *26*(10), 1814-1824.

Litvan, I., Goldman, J. G., Tröster, A. I., Schmand, B. A., Weintraub, D., Petersen, R. C., . . . Emre, M. (2012). Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Movement Disorders*, *27*(3), 349-356. doi:10.1002/mds.24893

Logan, G. D., & Cowan, W. B. (1984). On the ability to inhibit thought and action: A theory of an act of control. *Psychological review*, *91*(3), 295.

Loh, W. Y. (2011). Classification and regression trees. *Wiley Interdisciplinary Reviews: Data Mining and Knowledge Discovery*, *1*(1), 14-23.

Lu, C., Bharmal, A., & Suchowersky, O. (2006). Gambling and Parkinson disease. *Archives of Neurology*, *63*(2), 298-298.

Maddox, W. T., Ashby, F. G., & Bohil, C. J. (2003). Delayed feedback effects on rule-based and information-integration category learning. *Journal of experimental psychology: learning, memory, and cognition*, *29*(4), 650.

Mansfield, E. L., Karayanidis, F., Jamadar, S., Heathcote, A., & Forstmann, B. U. (2011). Adjustments of response threshold during task switching: a model-based functional magnetic resonance imaging study. *Journal of Neuroscience*, *31*(41), 14688-14692.

Mapelli, D., Di Rosa, E., Cavalletti, M., Schiff, S., & Tamburin, S. (2014). Decision and dopaminergic system: an ERPs study of Iowa gambling task in Parkinson's disease. *Frontiers in psychology*, *5*, 684.

Mars, R. B., Piekema, C., Coles, M. G., Hulstijn, W., & Toni, I. (2007). On the programming and reprogramming of actions. *Cerebral cortex*, *17*(12), 2972-2979.

Martin, L. T., Ruder, T., Escarce, J. J., Ghosh-Dastidar, B., Sherman, D., Elliott, M., . . . Culbert, A. (2009). Developing predictive models of health literacy. *Journal of general internal medicine*, *24*(11), 1211.

Masood, A., & Ali Al-Jumaily, A. (2013). Computer aided diagnostic support system for skin cancer: a review of techniques and algorithms. *International journal of biomedical imaging*, *2013*.

McIntyre, C. C., & Hahn, P. J. (2010). Network perspectives on the mechanisms of deep brain stimulation. *Neurobiology of disease*, *38*(3), 329-337.

McIntyre, C. C., Savasta, M., Kerkerian-Le Goff, L., & Vitek, J. L. (2004). Uncovering the mechanism (s) of action of deep brain stimulation: activation, inhibition, or both. *Clinical neurophysiology*, *115*(6), 1239-1248.

Meissner, W., Harnack, D., Reese, R., Paul, G., Reum, T., Ansorge, M., . . . Kupsch, A. (2003). High-frequency stimulation of the subthalamic nucleus enhances striatal dopamine release and metabolism in rats. *Journal of neurochemistry*, *85*(3), 601-609.

Meissner, W., Leblois, A., Hansel, D., Bioulac, B., Gross, C. E., Benazzouz, A., & Boraud, T. (2005). Subthalamic high frequency stimulation resets subthalamic firing and reduces abnormal oscillations. *Brain*, *128*(10), 2372-2382.

Millman, K. J., & Aivazis, M. (2011). Python for scientists and engineers. *Computing in Science & Engineering*, *13*(2), 9-12.

Mimura, M., Oeda, R., & Kawamura, M. (2006). Impaired decision-making in Parkinson's disease. *Parkinsonism & related disorders*, *12*(3), 169-175.

Mink, J. W. (1996). The basal ganglia: focused selection and inhibition of competing motor programs. *Progress in neurobiology*, *50*(4), 381-425.

Miyachi, S., Hikosaka, O., & Lu, X. (2002). Differential activation of monkey striatal neurons in the early and late stages of procedural learning. *Experimental brain research*, *146*(1), 122-126.

Miyake, A., & Friedman, N. P. (2012). The nature and organization of individual

differences in executive functions: Four general conclusions. *Current directions in psychological science, 21*(1), 8-14.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive psychology, 41*(1), 49-100.

Molina, J. A., Sáinz-Artiga, M. J., Fraile, A., Jiménez-Jiménez, F. J., Villanueva, C., Ortí-Pareja, M., & Bermejo-P, F. (2000). Pathologic gambling in Parkinson's disease: a behavioral manifestation of pharmacologic treatment? *Movement Disorders, 15*(5), 869-872.

Montague, P. R., Dayan, P., & Sejnowski, T. J. (1996). A framework for mesencephalic dopamine systems based on predictive Hebbian learning. *Journal of Neuroscience, 16*(5), 1936-1947.

Montgomery Jr, E. B., & Gale, J. T. (2008). Mechanisms of action of deep brain stimulation (DBS). *Neuroscience & Biobehavioral Reviews, 32*(3), 388-407.

Mooney, S. J., Westreich, D. J., & El-Sayed, A. M. (2015). Epidemiology in the era of big data. *Epidemiology (Cambridge, Mass.), 26*(3), 390.

Moro, E., Scerrati, M., Romito, L., Roselli, R., Tonali, P., & Albanese, A. (1999). Chronic subthalamic nucleus stimulation reduces medication requirements in Parkinson's disease. *Neurology, 53*(1), 85-85.

Morris, S. B., & DeShon, R. P. (2002). Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. *Psychol Methods, 7*(1), 105-125.

Moum, S. J., Price, C. C., Limotai, N., Oyama, G., Ward, H., Jacobson, C., . . . Okun, M. S. (2012). Effects of STN and GPi deep brain stimulation on impulse control disorders and dopamine dysregulation syndrome. *PloS one, 7*(1), e29768.

Moustafa, A. A., Sherman, S. J., & Frank, M. J. (2008). A dopaminergic basis for working memory, learning and attentional shifting in Parkinsonism. *Neuropsychologia, 46*(13), 3144-3156.

Murphy, K. P. (2014). Machine learning: a probabilistic perspective. 2012. *Cité en*, 117.

Muslimović, D., Post, B., Speelman, J. D., & Schmand, B. (2007). Motor procedural learning in Parkinson's disease. *Brain, 130*(11), 2887-2897.

Nagy, H., Kéri, S., Myers, C. E., Benedek, G., Shohamy, D., & Gluck, M. A. (2007). Cognitive sequence learning in Parkinson's disease and amnestic mild cognitive impairment: Dissociation between sequential and non-sequential learning of associations. *Neuropsychologia, 45*(7), 1386-1392.

Nambu, A., Tokuno, H., & Takada, M. (2002). Functional significance of the cortico–subthalamo–pallidal 'hyperdirect'pathway. *Neuroscience research, 43*(2), 111-117.

Nassery, A., Palmese, C. A., Sarva, H., Groves, M., Miravite, J., & Kopell, B. H. (2016). Psychiatric and cognitive effects of deep brain stimulation for parkinson's disease. *Current neurology and neuroscience reports*, *16*(10), 87.

Nelson, H. E. (1976). A modified card sorting test sensitive to frontal lobe defects. *Cortex, 12*(4), 313-324.

Neubert, F.-X., Mars, R. B., Buch, E. R., Olivier, E., & Rushworth, M. F. (2010). Cortical and subcortical interactions during action reprogramming and their related white matter pathways. *Proceedings of the National Academy of Sciences, 107*(30), 13240-13245.

Nieoullon, A. (2002). Dopamine and the regulation of cognition and attention. *Progress in neurobiology, 67*(1), 53-83.

Nozaki, T., Sugiyama, K., Yagi, S., Yoshikawa, E., Kanno, T., Asakawa, T., . . . Ouchi, Y. (2013). Effect of subthalamic nucleus stimulation during exercise on the mesolimbocortical dopaminergic region in Parkinson's disease: a positron emission tomography study. *Journal of Cerebral Blood Flow & Metabolism, 33*(3), 415-421.

Obeso, I., Wilkinson, L., Casabona, E., Speekenbrink, M., Luisa Bringas, M., Alvarez, M., . . . Macías, R. (2014). The subthalamic nucleus and inhibitory control: impact of subthalamotomy in Parkinson's disease. *Brain, 137*(5), 1470-1480.

Obeso, I., Wilkinson, L., Rodriguez-Oroz, M. C., Obeso, J. A., & Jahanshahi, M. (2013). Bilateral stimulation of the subthalamic nucleus has differential effects on reactive and proactive inhibition and conflict-induced slowing in Parkinson's disease. *Exp Brain Res, 226*(3), 451-462. doi:10.1007/s00221-013-3457-9

Okun, M. S. (2012). Deep-brain stimulation for Parkinson's disease. *New England Journal of Medicine, 367*(16), 1529-1538.

Okun, M. S., Fernandez, H. H., Rodriguez, R. L., & Foote, K. D. (2007). Identifying candidates for deep brain stimulation in Parkinson's disease. *Geriatrics, 62*(5), 18-24.

Olanow, C. W., Stern, M. B., & Sethi, K. (2009). The scientific and clinical basis for the treatment of Parkinson disease (2009). *Neurology, 72*(21 Supplement 4), S1-S136.

Oliphant, T. E. (2007). Python for scientific computing. *Computing in Science & Engineering, 9*(3).

Owen, A., James, M., Leigh, P., Summers, B., Marsden, C., Quinn, N. a., . . . Robbins,

T. (1992). Fronto-striatal cognitive deficits at different stages of Parkinson's disease. *Brain, 115*(6), 1727-1751.

Oyama, G., Shimo, Y., Natori, S., Nakajima, M., Ishii, H., Arai, H., & Hattori, N. (2011). Acute effects of bilateral subthalamic stimulation on decision-making in Parkinson's disease. *Parkinsonism & related disorders, 17*(3), 189-193.

Pagonabarraga, J., García-Sánchez, C., Llebaria, G., Pascual-Sedano, B., Gironell, A., & Kulisevsky, J. (2007). Controlled study of decision-making and cognitive impairment in Parkinson's disease. *Movement Disorders, 22*(10), 1430-1435.

Parent, A., & Hazrati, L.-N. (1995). Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. *Brain Research Reviews, 20*(1), 91-127.

Parsons, T. D., Rogers, S. A., Braaten, A. J., Woods, S. P., & Tröster, A. I. (2006). Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. *The Lancet Neurology, 5*(7), 578-588.

Partiot, A., Verin, M., Pillon, B., Teixeira-Ferreira, C., Agid, Y., & Dubois, B. (1996). Delayed response tasks in basal ganglia lesions in man: further evidence for a striato-frontal cooperation in behavioural adaptation. *Neuropsychologia, 34*(7), 709-721.

Pascual-Leone, A., Grafman, J., Clark, K., Stewart, M., Massaquoi, S., Lou, J. S., & Hallett, M. (1993). Procedural learning in Parkinson's disease and cerebellar degeneration. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 34*(4), 594-602.

Pazo, J. H., Höcht, C., Barceló, A. C., Fillipini, B., & Lomastro, M. J. (2010). Effect of electrical and chemical stimulation of the subthalamic nucleus on the release of striatal dopamine. *Synapse, 64*(12), 905-915.

Perretta, J. G., Pari, G., & Beninger, R. J. (2005). Effects of Parkinson disease on two putative nondeclarative learning tasks: probabilistic classification and gambling. *Cognitive and Behavioral Neurology, 18*(4), 185-192.

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of internal medicine, 256*(3), 183-194.

Phu, A. L., Xu, Z., Brakoulias, V., Mahant, N., Fung, V. S., De Moore, G., . . . Krause, M. (2014). Effect of impulse control disorders on disability and quality of life in Parkinson's disease patients. *Journal of Clinical Neuroscience, 21*(1), 63-66.

Pineau, F., Roze, E., Lacomblez, L., Bonnet, A.-M., Vidailhet, M., Czernecki, V., & Corvol, J.-C. (2016). Executive functioning and risk-taking behavior in Parkinson's disease patients with impulse control disorders. *Journal of neural transmission, 123*(6), 573-581.

Postuma, R. B., Lang, A. E., Massicotte-Marquez, J., & Montplaisir, J. (2006). Potential early markers of Parkinson disease in idiopathic REM sleep behavior disorder. *Neurology*, *66*(6), 845-851.

Pote, I., Torkamani, M., Kefalopoulou, Z.-M., Zrinzo, L., Limousin-Dowsey, P., Foltynie, T., . . . Jahanshahi, M. (2016). Subthalamic nucleus deep brain stimulation induces impulsive action when patients with Parkinson's disease act under speed pressure. *Experimental brain research, 234*(7), 1837-1848.

Puga, J. L., Krzywinski, M., & Altman, N. (2015). Points of Significance. Bayesian networks. *Nat Methods, 12*(9), 799-800.

Raizada, R. D., & Lee, Y.-S. (2013). Smoothness without smoothing: why Gaussian naive Bayes is not naive for multi-subject searchlight studies. *PloS one, 8*(7), e69566.

Rao, H., Mamikonyan, E., Detre, J. A., Siderowf, A. D., Stern, M. B., Potenza, M. N., & Weintraub, D. (2010). Decreased ventral striatal activity with impulse control disorders in Parkinson's disease. *Movement Disorders, 25*(11), 1660-1669.

Rao, R. P., & Ballard, D. H. (1995). An active vision architecture based on iconic representations. *Artificial intelligence, 78*(1-2), 461-505.

Raschka, S. (2015). *Python machine learning*: Packt Publishing Ltd.

Ratcliff, R. (1978). A theory of memory retrieval. Psychological review, 85(2), 59

Ratcliff, R., & McKoon, G. (2008). The diffusion decision model: theory and data for two-choice decision tasks. *Neural Comput, 20*(4), 873-922. doi:10.1162/neco.2008.12-06-420

Ratcliff, R., & Smith, P. L. (2004). A comparison of sequential sampling models for two-choice reaction time. *Psychol Rev, 111*(2), 333-367. doi:10.1037/0033-295X.111.2.333

Ray, N. J., Jenkinson, N., Brittain, J., Holland, P., Joint, C., Nandi, D., . . . Aziz, T. Z. (2009). The role of the subthalamic nucleus in response inhibition: evidence from deep brain stimulation for Parkinson's disease. *Neuropsychologia, 47*(13), 2828-2834. doi:10.1016/j.neuropsychologia.2009.06.011

Ray, N. J., Miyasaki, J. M., Zurowski, M., Ko, J. H., Cho, S. S., Pellecchia, G., . . . Strafella, A. P. (2012). Extrastriatal dopaminergic abnormalities of DA homeostasis in Parkinson's patients with medication-induced pathological gambling: a [11C] FLB-457 and PET study. *Neurobiology of disease, 48*(3), 519-525.

Redgrave, P., Prescott, T. J., & Gurney, K. (1999). The basal ganglia: a vertebrate solution to the selection problem? *Neuroscience, 89*(4), 1009-1023.

Reijnders, J. S., Ehrt, U., Weber, W. E., Aarsland, D., & Leentjens, A. F. (2008). A

systematic review of prevalence studies of depression in Parkinson's disease. *Movement Disorders*, *23*(2), 183-189.

Reitan, R. M. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and motor skills*, *8*(3), 271-276.

Robert, G., Drapier, D., Verin, M., Millet, B., Azulay, J. P., & Blin, O. (2009). Cognitive impulsivity in Parkinson's disease patients: assessment and pathophysiology. *Movement disorders*, *24*(16), 2316-2327.

Robles, S. G., Gatignol, P., Capelle, L., Mitchell, M., & Duffau, H. (2005). The role of dominant striatum in language: a study using intraoperative electrical stimulations. *Journal of Neurology, Neurosurgery & Psychiatry*, *76*(7), 940-946.

Roesch, M. R., & Olson, C. R. (2004). Neuronal activity related to reward value and motivation in primate frontal cortex. *Science*, *304*(5668), 307-310.

Rogers, R., Sahakian, B., Hodges, J., Polkey, C., Kennard, C., & Robbins, T. (1998). Dissociating executive mechanisms of task control following frontal lobe damage and Parkinson's disease. *Brain: A Journal of Neurology*, *121*(5), 815-842.

Rogers, R. D., Wielenberg, B., Wojtecki, L., Elben, S., Campbell-Meiklejohn, D., & Schnitzler, A. (2011). Deep brain stimulation of the subthalamic nucleus transiently enhances loss-chasing behaviour in patients with Parkinson's disease. *Exp Neurol, 231*(1), 181-189. doi:10.1016/j.expneurol.2011.06.007

Rosenfeld, B. A., & Breslow, M. (2008). Using predictive models to continuously update a treatment plan for a patient in a health care location: Google Patents.

Rossi, M., Gerschcovich, E. R., De Achaval, D., Perez-Lloret, S., Cerquetti, D., Cammarota, A., . . . Leiguarda, R. (2010). Decision-making in Parkinson's disease patients with and without pathological gambling. *European Journal of Neurology*, *17*(1), 97-102.

Ryterska, A., Jahanshahi, M., & Osman, M. (2013). What are people with Parkinson's disease really impaired on when it comes to making decisions? A meta-analysis of the evidence. *Neuroscience & Biobehavioral Reviews*, *37*(10), 2836-2846.

Sáez-Francàs, N., Andrés, G. M., Ramírez, N., de Fàbregues, O., Álvarez-Sabín, J., Casas, M., & Hernández-Vara, J. (2016). Clinical and psychopathological factors associated with impulse control disorders in Parkinson's disease. *Neurología (English Edition)*, *31*(4), 231-238.

Sáez-Francàs, N., Hernández-Vara, J., Corominas-Roso, M., Alegre, J., Jacas, C., & Casas, M. (2014). Relationship between poor decision-making process and fatigue perception in Parkinson's disease patients. *Journal of the neurological*

sciences, 337(1-2), 167-172.

Saint-Cyr, J., Taylor, A., & Lang, A. (1993). Neuropsychological and psychiatric side effects in the treatment of Parkinson's disease. *Neurology*.

Salamone, J., Wisniecki, A., Carlson, B., & Correa, M. (2001). Nucleus accumbens dopamine depletions make animals highly sensitive to high fixed ratio requirements but do not impair primary food reinforcement. *Neuroscience, 105*(4), 863-870.

Salin, P., Manrique, C., Forni, C., & Kerkerian-Le Goff, L. (2002). High-frequency stimulation of the subthalamic nucleus selectively reverses dopamine denervation-induced cellular defects in the output structures of the basal ganglia in the rat. *Journal of Neuroscience, 22*(12), 5137-5148.

Sawaguchi, T., Matsumura, M., & Kubota, K. (1990). Catecholaminergic effects on neuronal activity related to a delayed response task in monkey prefrontal cortex. *Journal of neurophysiology, 63*(6), 1385-1400.

Schmidt, R., Leventhal, D. K., Mallet, N., Chen, F., & Berke, J. D. (2013). Canceling actions involves a race between basal ganglia pathways. *Nature neuroscience, 16*(8), 1118.

Schomaker, J., & Meeter, M. (2015). Short-and long-lasting consequences of novelty, deviance and surprise on brain and cognition. *Neuroscience & Biobehavioral Reviews*, *55*, 268-279.

Schroeder, U., Kuehler, A., Haslinger, B., Erhard, P., Fogel, W., Tronnier, V., . . . Ceballos-Baumann, A. (2002). Subthalamic nucleus stimulation affects striato-anterior cingulate cortex circuit in a response conflict task: a PET study. *Brain, 125*(9), 1995-2004.

Schultz, W. (1998). Predictive reward signal of dopamine neurons. *Journal of neurophysiology, 80*(1), 1-27.

Schultz, W. (2007). Behavioral dopamine signals. *Trends in neurosciences, 30*(5), 203-210.

Schultz, W., Apicella, P., & Ljungberg, T. (1993). Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. *Journal of Neuroscience, 13*(3), 900-913.

Seamans, J. K., Durstewitz, D., Christie, B. R., Stevens, C. F., & Sejnowski, T. J. (2001). Dopamine D1/D5 receptor modulation of excitatory synaptic inputs to layer V prefrontal cortex neurons. *Proceedings of the National Academy of Sciences, 98*(1), 301-306.

Sharma, L., Markon, K. E., & Clark, L. A. (2014). Toward a theory of distinct types of "impulsive" behaviors: A meta-analysis of self-report and behavioral measures. *Psychological bulletin, 140*(2), 374.

Shi, L., Campbell, G., Jones, W. D., Campagne, F., Wen, Z., Walker, S. J., ... & Shaughnessy Jr, J. D. (2010). The MicroArray Quality Control (MAQC)-II study of common practices for the development and validation of microarray-based predictive models. *Nature biotechnology*, *28*(8), 827.

Shohamy, D., Myers, C. E., Geghman, K. D., Sage, J., & Gluck, M. A. (2006). L-dopa impairs learning, but spares generalization, in Parkinson's disease. *Neuropsychologia*, *44*(5), 774-784.

Siegert, S., Ruiz, M. H., Brücke, C., Huebl, J., Schneider, G.-H., Ullsperger, M., & Kühn, A. A. (2014). Error signals in the subthalamic nucleus are related to post-error slowing in patients with Parkinson's disease. *Cortex, 60*, 103-120.

Smeding, H., Goudriaan, A., Foncke, E., Schuurman, P., Speelman, J., & Schmand, B. (2007). Pathological gambling after bilateral STN stimulation in Parkinson disease. *Journal of Neurology, Neurosurgery & Psychiatry*.

Smith, K. M., Xie, S. X., & Weintraub, D. (2016). Incident impulse control disorder symptoms and dopamine transporter imaging in Parkinson disease. *J Neurol Neurosurg Psychiatry, 87*(8), 864-870.

Spatt, J., & Goldenberg, G. (1993). Components of random generation by normal subjects and patients with dysexecutive syndrome. *Brain and Cognition, 23*(2), 231-242.

Starkstein, S. E. (2012). Apathy in Parkinson's disease: diagnostic and etiological dilemmas. *Movement Disorders, 27*(2), 174-178.

Stout, J. C., Rodawalt, W. C., & Siemers, E. R. (2001). Risky decision making in Huntington's disease. *Journal of the International Neuropsychological Society, 7*(1), 92-101.

Strafella, A. P., Sadikot, A. F., & Dagher, A. (2003). Subthalamic deep brain stimulation does not induce striatal dopamine release in Parkinson's disease. *Neuroreport, 14*(9), 1287-1289.

Strange, B. A., Duggins, A., Penny, W., Dolan, R. J., & Friston, K. J. (2005). Information theory, novelty and hippocampal responses: unpredicted or unpredictable? *Neural Networks, 18*(3), 225-230.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of experimental psychology, 18*(6), 643.

Swainson, R., Rogers, R., Sahakian, B., Summers, B., Polkey, C., & Robbins, T. (2000). Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. *Neuropsychologia, 38*(5), 596-612.

Swann, N., Poizner, H., Houser, M., Gould, S., Greenhouse, I., Cai, W., . . . Aron, A. R. (2011). Deep brain stimulation of the subthalamic nucleus alters the cortical

profile of response inhibition in the beta frequency band: a scalp EEG study in Parkinson's disease. *Journal of Neuroscience, 31*(15), 5721-5729.

Tai, C.-h., Boraud, T., Bezard, E., Bioulac, B., Gross, C., & Benazzouz, A. (2003). Electrophysiological and metabolic evidence that high-frequency stimulation of the subthalamic nucleus bridles neuronal activity in the subthalamic nucleus and the substantia nigra reticulata. *The FASEB journal, 17*(13), 1820-1830.

TAYLOR, A. E., Saint-Cyr, J., & Lang, A. (1986). Frontal lobe dysfunction in Parkinson's disease: The cortical focus of neostriatal outflow. *Brain, 109*(5), 845-883.

Team, R. C. (2013). R: A language and environment for statistical computing.

Thiel, A., Hilker, R., Kessler, J., Habedank, B., Herholz, K., & Heiss, W.-D. (2003). Activation of basal ganglia loops in idiopathic Parkinson's disease: a PET study. *Journal of neural transmission, 110*(11), 1289-1301.

Thobois, S., Fraix, V., Savasta, M., Costes, N., Pollak, P., Mertens, P., . . . Broussolle, E. (2003). Chronic subthalamic nucleus stimulation and striatal D2 dopamine receptors in Parkinson's disease. *Journal of neurology, 250*(10), 1219-1223.

Thura, D., & Cisek, P. (2016). Modulation of premotor and primary motor cortical activity during volitional adjustments of speed-accuracy trade-offs. *Journal of Neuroscience, 36*(3), 938-956.

Thura, D., & Cisek, P. (2017). The basal ganglia do not select reach targets but control the urgency of commitment. *Neuron, 95*(5), 1160-1170. e1165.

Thura, D., Cos, I., Trung, J., & Cisek, P. (2014). Context-dependent urgency influences speed–accuracy trade-offs in decision-making and movement execution. *Journal of Neuroscience, 34*(49), 16442-16454.

Timmer, M. H., Sescousse, G., Esselink, R. A., Piray, P., & Cools, R. (2018). Mechanisms underlying dopamine-induced risky choice in Parkinson's disease with and without depression (history). *Computational Psychiatry, 2*, 11-27.

Torta, D. M., Vizzari, V., Castelli, L., Zibetti, M., Lanotte, M., Lopiano, L., & Geminiani, G. (2012). Impulsivities and Parkinson's disease: delay aversion is not worsened by deep brain stimulation of the subthalamic nucleus. *PloS one, 7*(9), e43261.

Tröster, A. I., Jankovic, J., Tagliati, M., Peichel, D., & Okun, M. S. (2017). Neuropsychological outcomes from constant current deep brain stimulation for Parkinson's disease. *Movement Disorders, 32*(3), 433-440.

Vaillancourt, D. E., Schonfeld, D., Kwak, Y., Bohnen, N. I., & Seidler, R. (2013). Dopamine overdose hypothesis: evidence and clinical implications. *Movement Disorders, 28*(14), 1920-1929.

van den Wildenberg, W. P., van Boxtel, G. J., van der Molen, M. W., Bosch, D. A.,

Speelman, J. D., & Brunia, C. H. (2006). Stimulation of the subthalamic region facilitates the selection and inhibition of motor responses in Parkinson's disease. *Journal of cognitive neuroscience, 18*(4), 626-636.

van Eimeren, T., Monchi, O., Ballanger, B., & Strafella, A. P. (2009). Dysfunction of the default mode network in Parkinson disease: a functional magnetic resonance imaging study. *Archives of Neurology, 66*(7), 877-883.

van Eimeren, T., Pellecchia, G., Cilia, R., Ballanger, B., Steeves, T. D., Houle, S., . . . Strafella, A. P. (2010). Drug-induced deactivation of inhibitory networks predicts pathological gambling in PD. *Neurology, 75*(19), 1711-1716.

Van Veen, V., Krug, M. K., & Carter, C. S. (2008). The neural and computational basis of controlled speed-accuracy tradeoff during task performance. *Journal of cognitive neuroscience, 20*(11), 1952-1965.

Vitek, J. L. (2002). Mechanisms of deep brain stimulation: excitation or inhibition. *Movement disorders: official journal of the Movement Disorder Society, 17*(S3), S69-S72.

Voon, V., Fernagut, P.-O., Wickens, J., Baunez, C., Rodriguez, M., Pavon, N., . . . Bezard, E. (2009). Chronic dopaminergic stimulation in Parkinson's disease: from dyskinesias to impulse control disorders. *The Lancet Neurology, 8*(12), 1140-1149.

Voon, V., & Fox, S. H. (2007). Medication-related impulse control and repetitive behaviors in Parkinson disease. *Archives of Neurology, 64*(8), 1089-1096.

Voon, V., Gao, J., Brezing, C., Symmonds, M., Ekanayake, V., Fernandez, H., . . . Hallett, M. (2011). Dopamine agonists and risk: impulse control disorders in Parkinson's; disease. *Brain, 134*(5), 1438-1446.

Voon, V., Hassan, K., Zurowski, M., De Souza, M., Thomsen, T., Fox, S., . . . Miyasaki, J. (2006). Prevalence of repetitive and reward-seeking behaviors in Parkinson disease. *Neurology, 67*(7), 1254-1257.

Voon, V., Mole, T. B., Banca, P., Porter, L., Morris, L., Mitchell, S., . . . Potenza, M. N. (2014). Neural correlates of sexual cue reactivity in individuals with and without compulsive sexual behaviours. *PloS one, 9*(7), e102419.

Voon, V., Napier, T. C., Frank, M. J., Sgambato-Faure, V., Grace, A. A., Rodriguez-Oroz, M., . . . Fernagut, P.-O. (2017). Impulse control disorders and levodopa-induced dyskinesias in Parkinson's disease: an update. *The Lancet Neurology, 16*(3), 238-250.

Voon, V., Reynolds, B., Brezing, C., Gallea, C., Skaljic, M., Ekanayake, V., . . . Hallett, M. (2010). Impulsive choice and response in dopamine agonist-related impulse control behaviors. *Psychopharmacology, 207*(4), 645-659.

Voss, A., & Voss, J. (2007). Fast-dm: a free program for efficient diffusion model

analysis. *Behav Res Methods, 39*(4), 767-775.

Voss, A., Voss, J., & Lerche, V. (2015). Assessing cognitive processes with diffusion model analyses: a tutorial based on fast-dm-30. *Front Psychol, 6*, 336. doi:10.3389/fpsyg.2015.00336

Vriend, C., Nordbeck, A. H., Booij, J., van der Werf, Y. D., Pattij, T., Voorn, P., . . . Berendse, H. W. (2014). Reduced dopamine transporter binding predates impulse control disorders in Parkinson's disease. *Movement Disorders, 29*(7), 904-911.

Wagenbreth, C., Zaehle, T., Galazky, I., Voges, J., Guitart-Masip, M., Heinze, H. J., & Duzel, E. (2015). Deep brain stimulation of the subthalamic nucleus modulates reward processing and action selection in Parkinson patients. *J Neurol, 262*(6), 1541-1547. doi:10.1007/s00415-015-7749-9

Walt, S. v. d., Colbert, S. C., & Varoquaux, G. (2011). The NumPy array: a structure for efficient numerical computation. *Computing in Science & Engineering, 13*(2), 22-30.

Walter, B. L., & Vitek, J. L. (2004). Surgical treatment for Parkinson's disease. *The Lancet Neurology, 3*(12), 719-728.

Wang, Y., & Goldman-Rakic, P. S. (2004). D2 receptor regulation of synaptic burst firing in prefrontal cortical pyramidal neurons. *Proceedings of the National Academy of Sciences, 101*(14), 5093-5098.

Weaver, F. M., Follett, K. A., Stern, M., Luo, P., Harris, C. L., Hur, K., . . . Moy, C. (2012). Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. *Neurology, 79*(1), 55-65.

Wechsler, D. (1984). *WMS-R: Wechsler memory scale-revised: manual*: Psychological Corporation.

Weinberger, K. Q., Blitzer, J., & Saul, L. K. (2006). *Distance metric learning for large margin nearest neighbor classification*. Paper presented at the Advances in neural information processing systems.

Weintraub, D. (2009). Impulse control disorders in Parkinson's disease: prevalence and possible risk factors. *Parkinsonism Relat Disord, 15 Suppl 3*, S110-113. doi:10.1016/S1353-8020(09)70794-1

Weintraub, D., David, A. S., Evans, A. H., Grant, J. E., & Stacy, M. (2015). Clinical spectrum of impulse control disorders in Parkinson's disease. *Movement Disorders, 30*(2), 121-127.

Weintraub, D., Koester, J., Potenza, M. N., Siderowf, A. D., Stacy, M., Voon, V., . . . Lang, A. E. (2010). Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Archives of Neurology, 67*(5), 589-595.

Wessel, J. R., & Aron, A. R. (2013). Unexpected events induce motor slowing via a

brain mechanism for action-stopping with global suppressive effects. *Journal of Neuroscience, 33*(47), 18481-18491.

Wessel, J. R., & Aron, A. R. (2015). It's not too late: The onset of the frontocentral P 3 indexes successful response inhibition in the stop-signal paradigm. *Psychophysiology, 52*(4), 472-480.

Wessel, J. R., Ghahremani, A., Udupa, K., Saha, U., Kalia, S. K., Hodaie, M., . . . Chen, R. (2016). Stop-related subthalamic beta activity indexes global motor suppression in Parkinson's disease. *Movement Disorders, 31*(12), 1846-1853.

Whitsett, D. D., & Shoda, Y. (2014). An approach to test for individual differences in the effects of situations without using moderator variables. *Journal of experimental social psychology*, *50*, 94-104.

Wiecki, T. V., Sofer, I., & Frank, M. J. (2013). HDDM: hierarchical bayesian estimation of the drift-diffusion model in python. *Frontiers in neuroinformatics, 7*, 14.

Williams, A., Gill, S., Varma, T., Jenkinson, C., Quinn, N., Mitchell, R., . . . Daniels, J. (2010). Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *The Lancet Neurology, 9*(6), 581-591.

Williams, G. V., & Goldman-Rakic, P. S. (1995). Modulation of memory fields by dopamine Dl receptors in prefrontal cortex. *Nature, 376*(6541), 572.

Witt, K., Daniels, C., Reiff, J., Krack, P., Volkmann, J., Pinsker, M. O., . . . Schnitzler, A. (2008). Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. *The Lancet Neurology, 7*(7), 605-614.

Witt, K., Kopper, F., Deuschl, G., & Krack, P. (2006). Subthalamic nucleus influences spatial orientation in extrapersonal space. *Movement Disorders, 21*(3), 354-361.

Woods, S. P., Fields, J. A., & Tröster, A. I. (2002). Neuropsychological sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a critical review. *Neuropsychology review, 12*(2), 111-126.

Woodward, T. S., Bub, D. N., & Hunter, M. A. (2002). Task switching deficits associated with Parkinson's disease reflect depleted attentional resources. *Neuropsychologia, 40*(12), 1948-1955.

Wu, K., Politis, M., & Piccini, P. (2009). Parkinson disease and impulse control disorders: a review of clinical features, pathophysiology and management. *Postgraduate medical journal, 85*(1009), 590-596.

Wu, M., Giel, K. E., Skunde, M., Schag, K., Rudofsky, G., de Zwaan, M., . . . Friederich, H. C. (2013). Inhibitory control and decision making under risk in

bulimia nervosa and binge-eating disorder. *International Journal of Eating Disorders, 46*(7), 721-728.

Wylie, S. A., Ridderinkhof, K. R., Elias, W. J., Frysinger, R. C., Bashore, T. R., Downs, K. E., . . . van den Wildenberg, W. P. (2010). Subthalamic nucleus stimulation influences expression and suppression of impulsive behaviour in Parkinson's disease. *Brain, 133*(Pt 12), 3611-3624. doi:10.1093/brain/awq239

Wylie, S. A., van den Wildenberg, W., Ridderinkhof, K. R., Claassen, D. O., Wooten, G. F., & Manning, C. A. (2012). Differential susceptibility to motor impulsivity among functional subtypes of Parkinson's disease. *J Neurol Neurosurg Psychiatry*, jnnp-2012-303056.

Xanthopoulos, P., Pardalos, P. M., & Trafalis, T. B. (2013). Linear discriminant analysis *Robust data mining* (pp. 27-33): Springer.

Xi, C., Zhu, Y., Mu, Y., Chen, B., Dong, B., Cheng, H., . . . Wang, K. (2015). Theory of mind and decision-making processes are impaired in Parkinson's disease. *Behavioural brain research, 279*, 226-233.

Young, S. E., Friedman, N. P., Miyake, A., Willcutt, E. G., Corley, R. P., Haberstick, B. C., & Hewitt, J. K. (2009). Behavioral disinhibition: Liability for externalizing spectrum disorders and its genetic and environmental relation to response inhibition across adolescence. *Journal of abnormal psychology, 118*(1), 117.

Yugeta, A., Terao, Y., Fukuda, H., Hikosaka, O., Yokochi, F., Okiyama, R., . . . Hanajima, R. (2010). Effects of STN stimulation on the initiation and inhibition of saccade in Parkinson disease. *Neurology, 74*(9), 743-748.

Zaehle, T., Wagenbreth, C., Voges, J., Heinze, H.-J., & Galazky, I. (2017). Effects of deep brain stimulation of the subthalamic nucleus on perceptual decision making. *Neuroscience, 343*, 140-146.

Zavala, B. A., Tan, H., Little, S., Ashkan, K., Hariz, M., Foltynie, T., . . . Brown, P. (2014). Midline frontal cortex low-frequency activity drives subthalamic nucleus oscillations during conflict. *Journal of Neuroscience, 34*(21), 7322-7333.

Zhao, X.-d., Cao, Y.-q., Liu, H.-h., Li, F.-q., You, B.-m., & Zhou, X.-p. (2009). Long term high frequency stimulation of STN increases dopamine in the corpus striatum of hemiparkinsonian rhesus monkey. *Brain research, 1286*, 230-238.

Appendices

In [5]:
```
#plot the figures to examine the convergence of the model
m_Speed.plot_posteriors()
plt.show()
```

```
Plotting a_Intercept
Plotting a_C(type)[T.SP]
Plotting a_C(time)[T.T2]
Plotting a_C(Group)[T.PD ICD]
Plotting a_C(type)[T.SP]:C(time)[T.T2]
Plotting a_C(type)[T.SP]:C(Group)[T.PD ICD]
Plotting a_C(time)[T.T2]:C(Group)[T.PD ICD]
Plotting a_C(type)[T.SP]:C(time)[T.T2]:C(Group)[T.PD ICD]
Plotting v_Intercept
Plotting v_C(time)[T.T2]
Plotting v_C(Group)[T.PD ICD]
Plotting v_C(time)[T.T2]:C(Group)[T.PD ICD]
Plotting t_Intercept
Plotting t_C(type)[T.SP]
Plotting t_C(time)[T.T2]
Plotting t_C(Group)[T.PD ICD]
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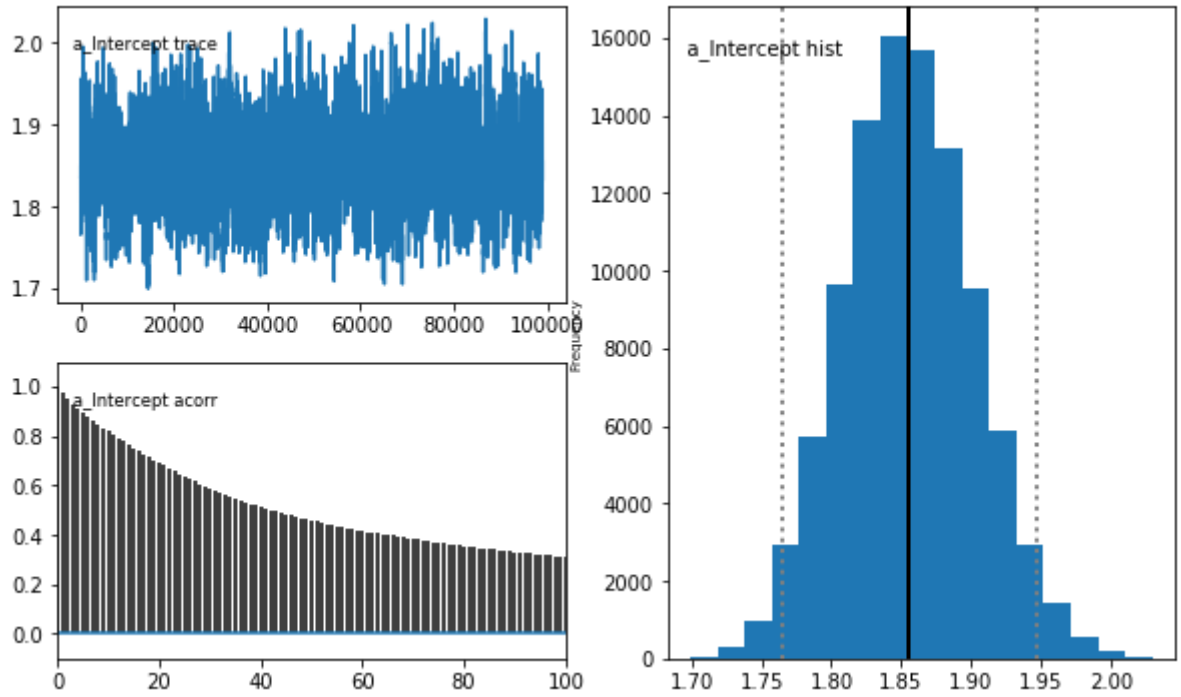

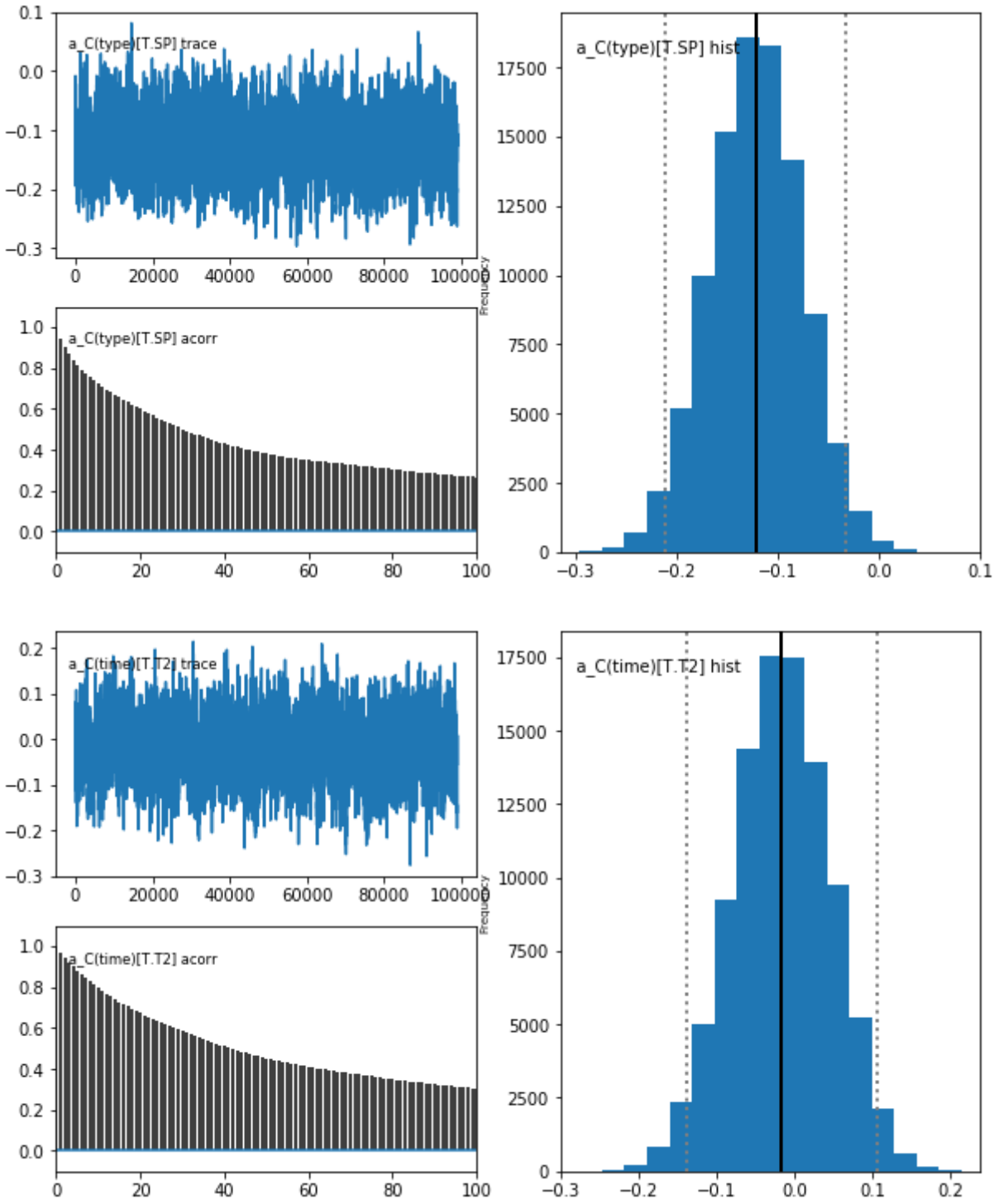
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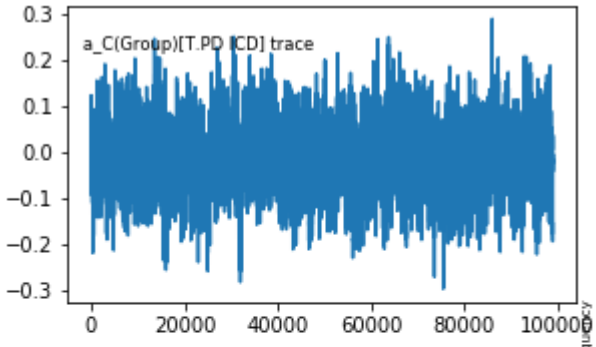
Frequency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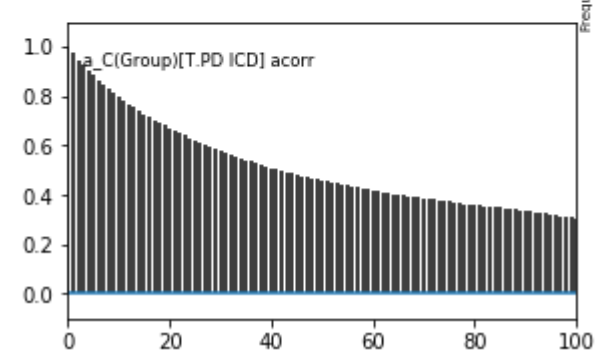
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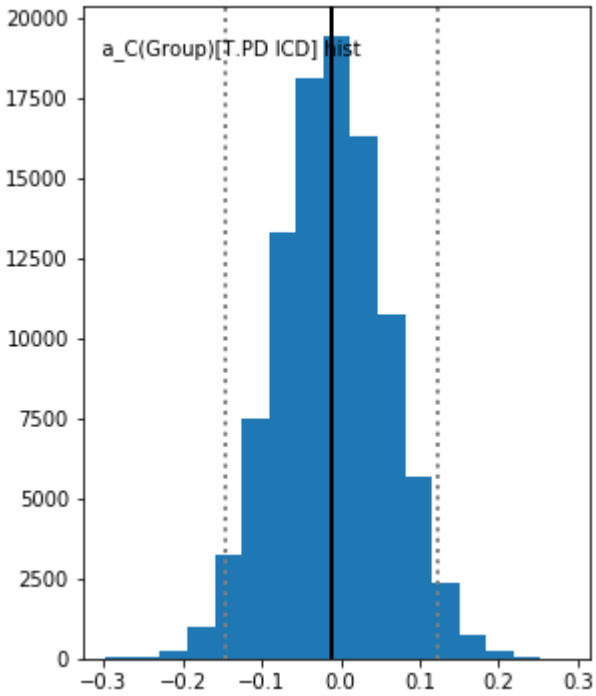
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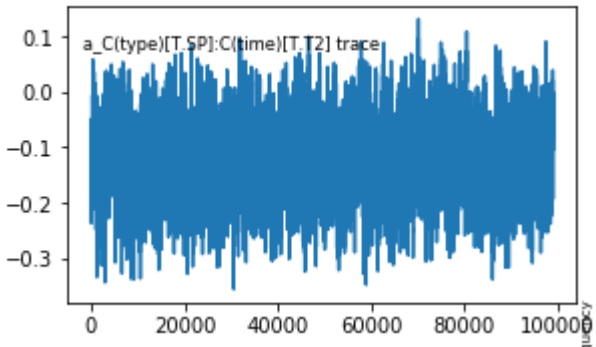
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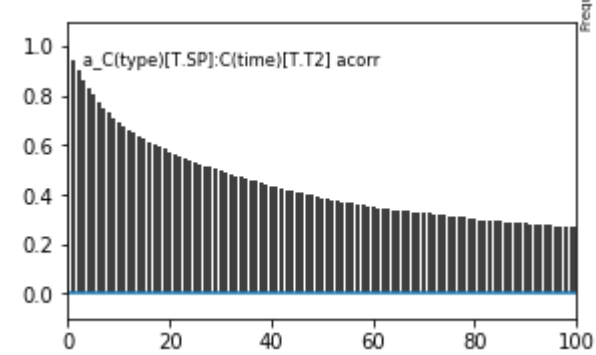
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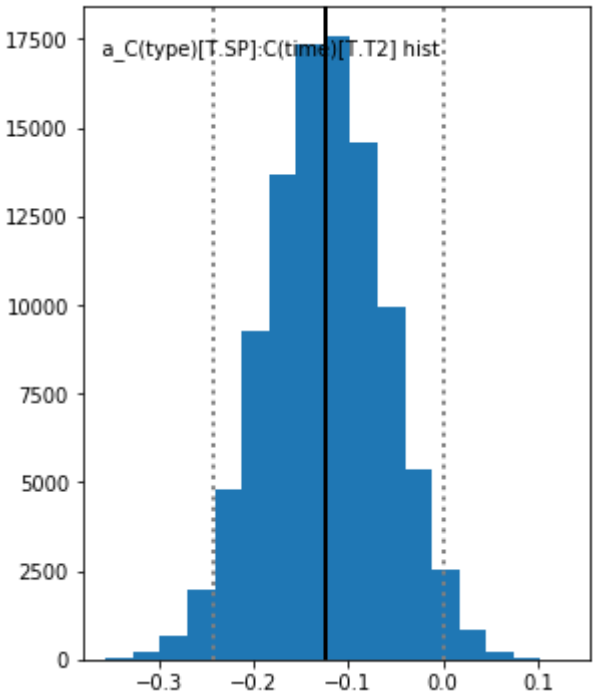
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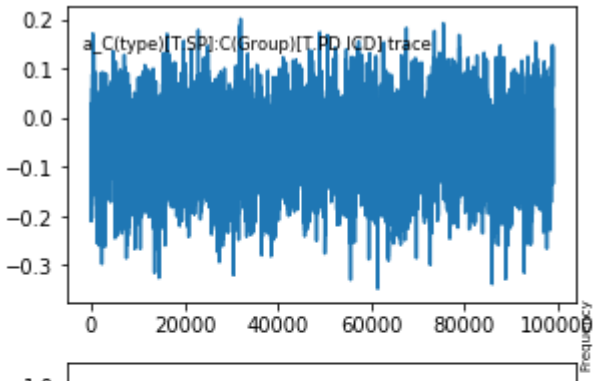
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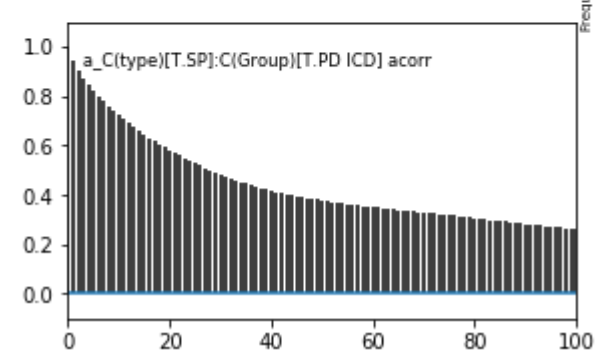
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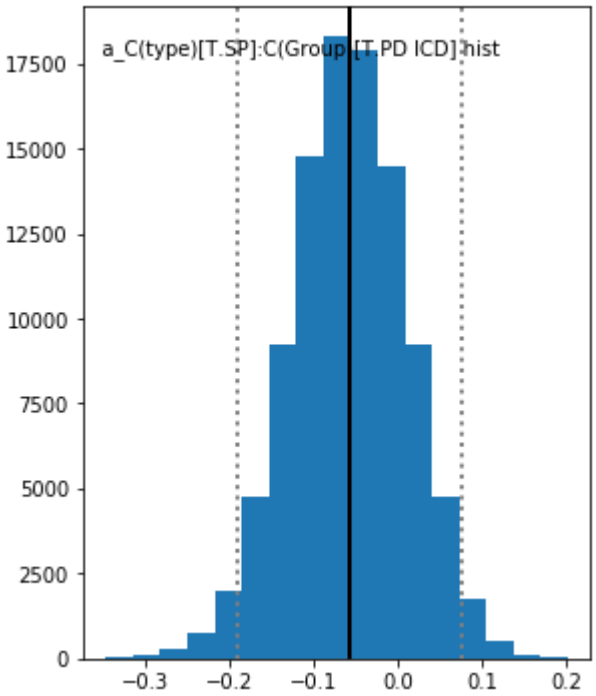
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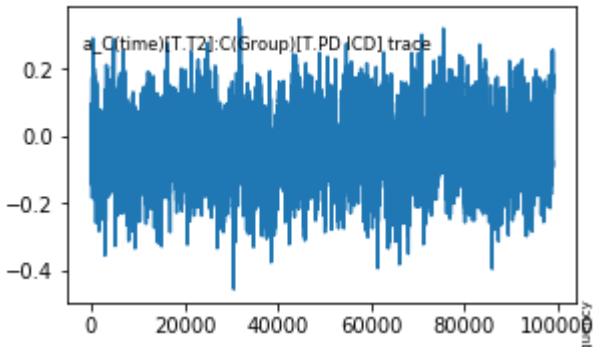
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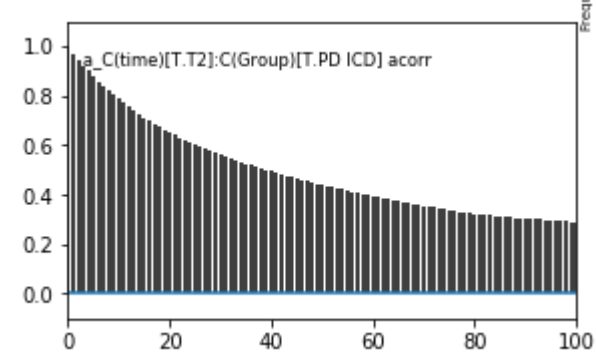
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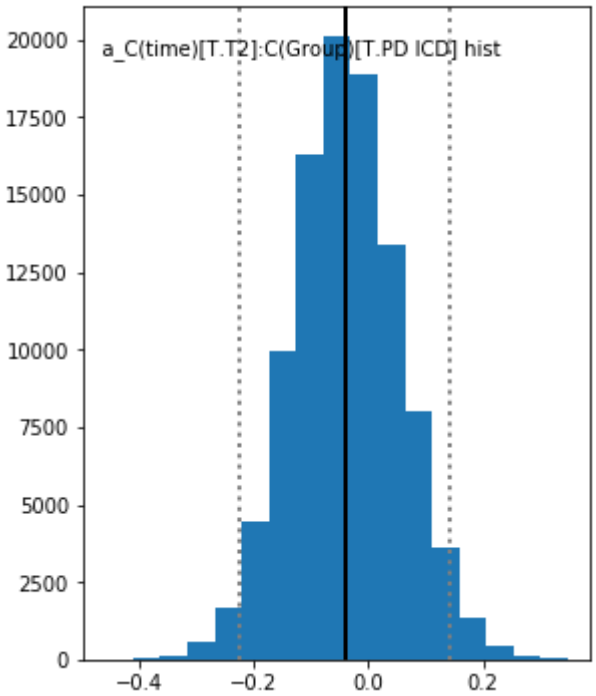
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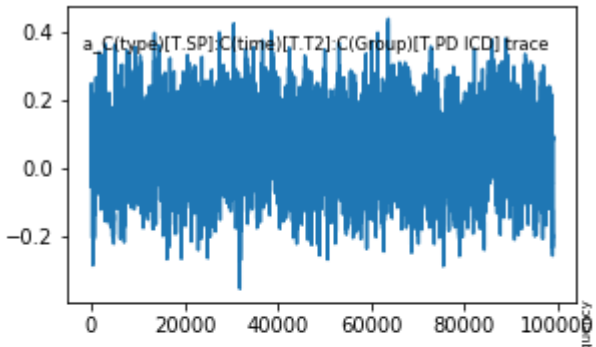
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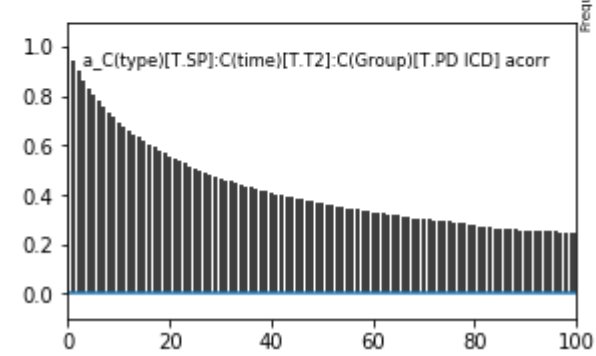
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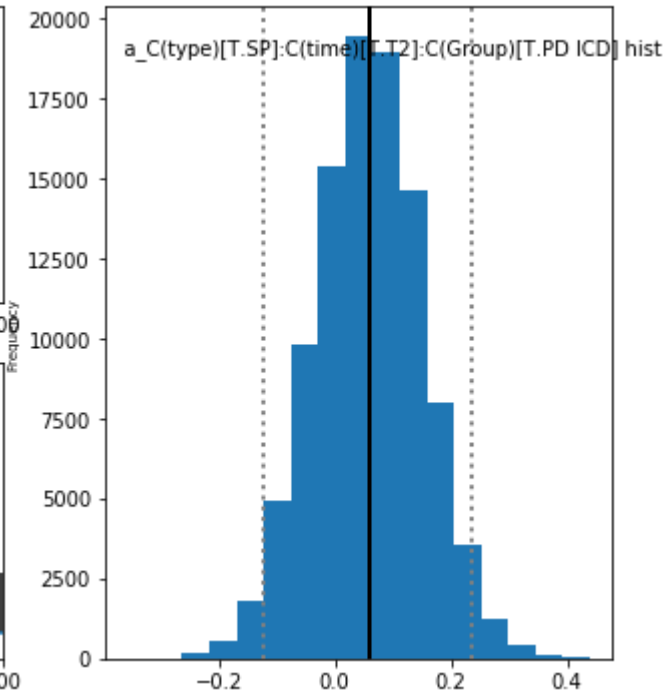
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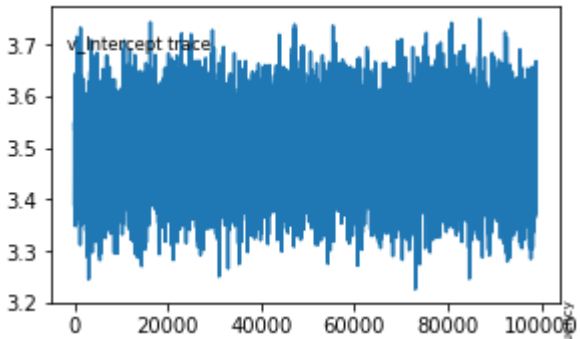
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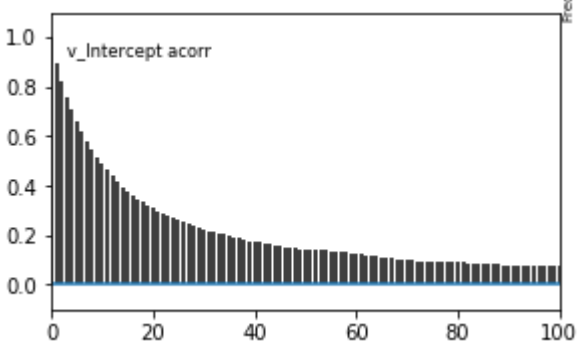
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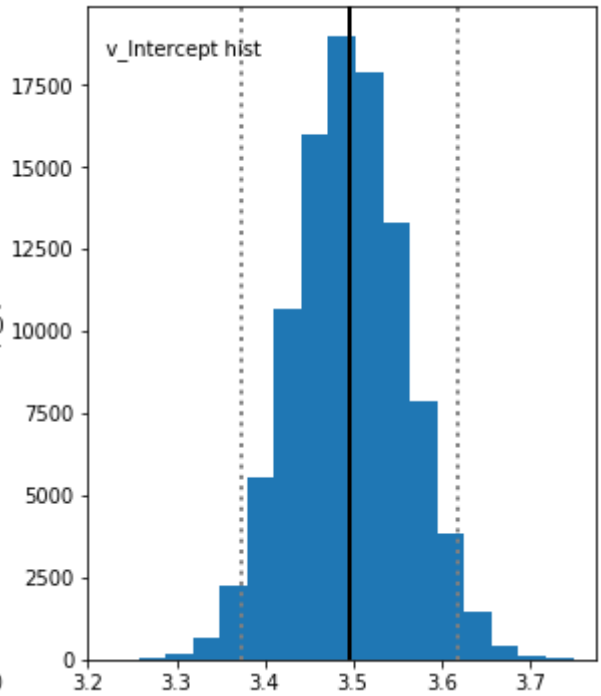
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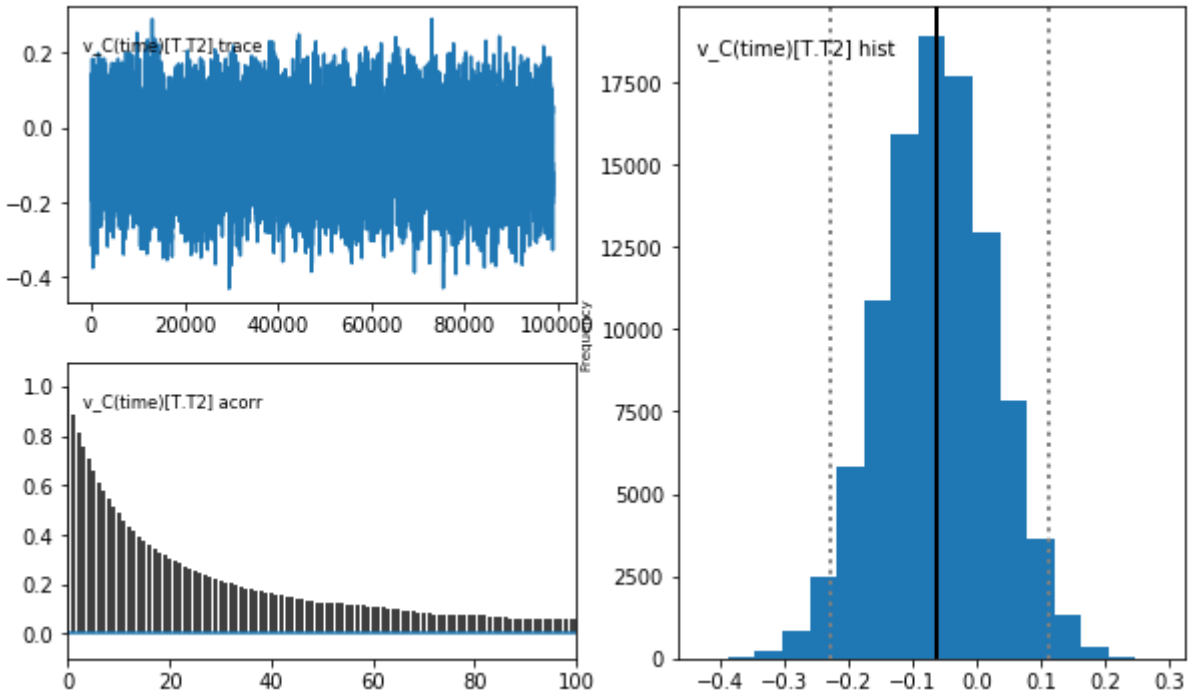
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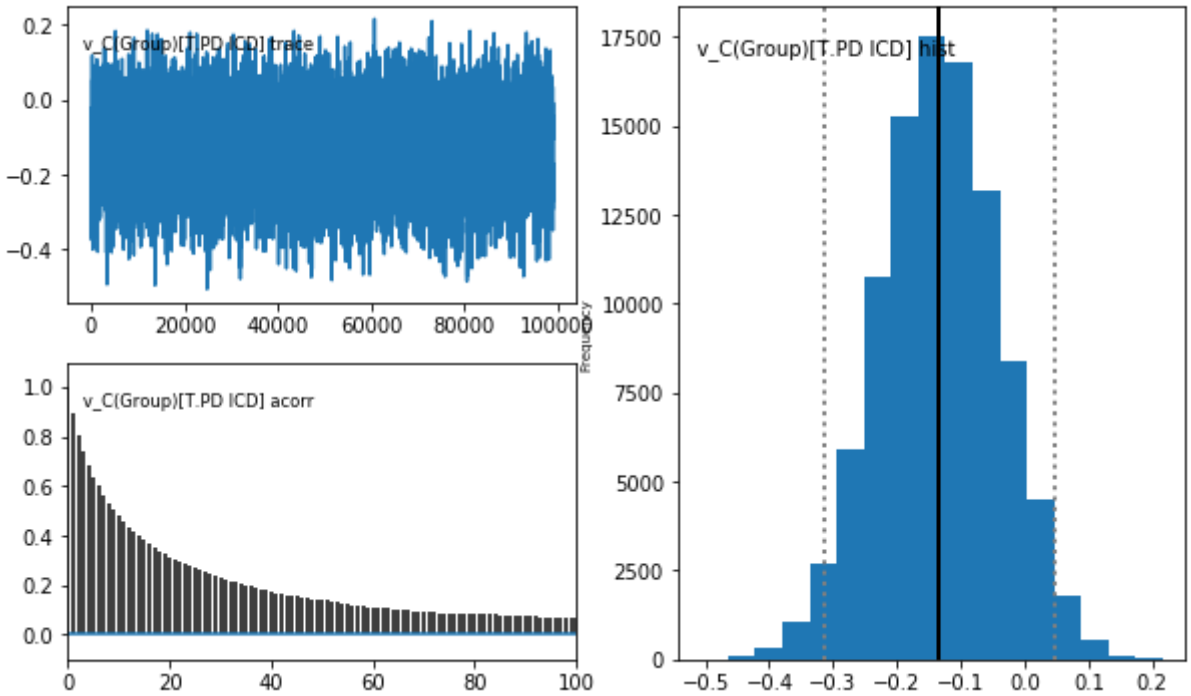
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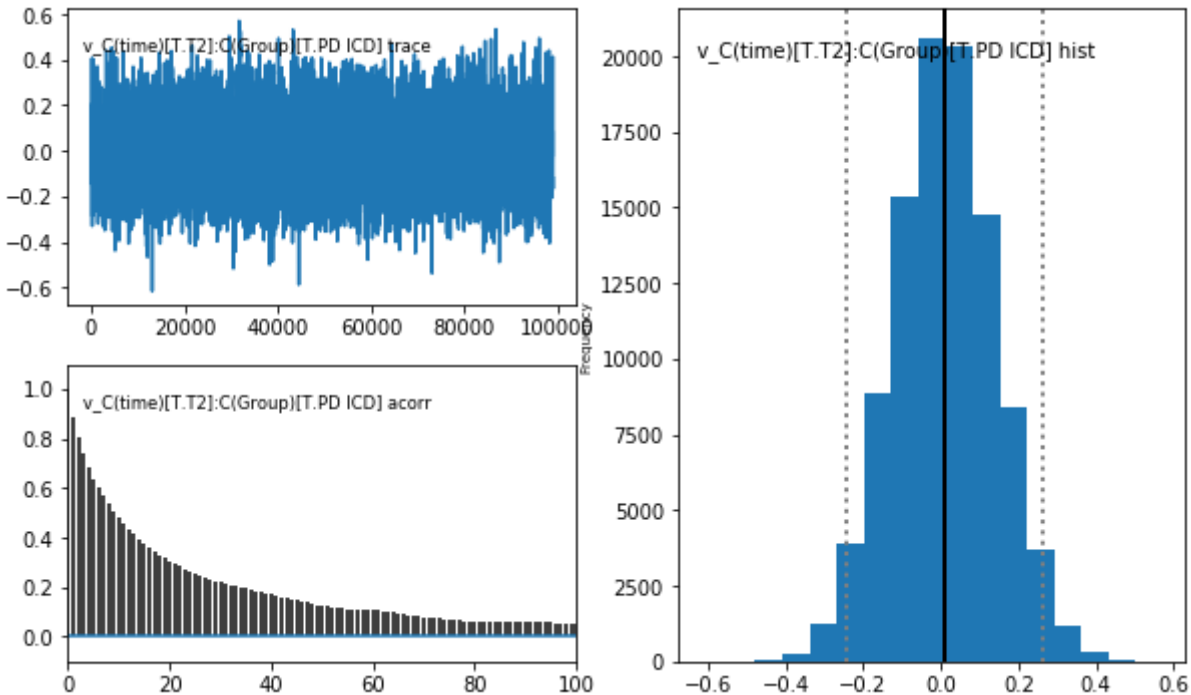
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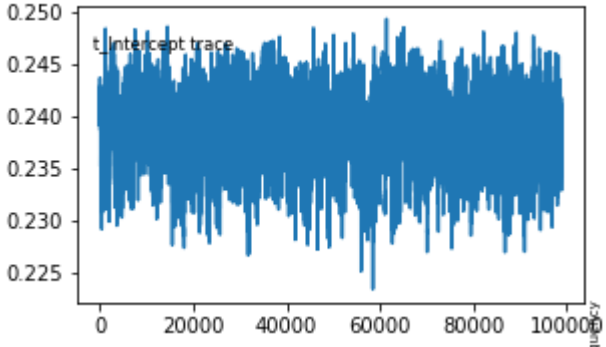
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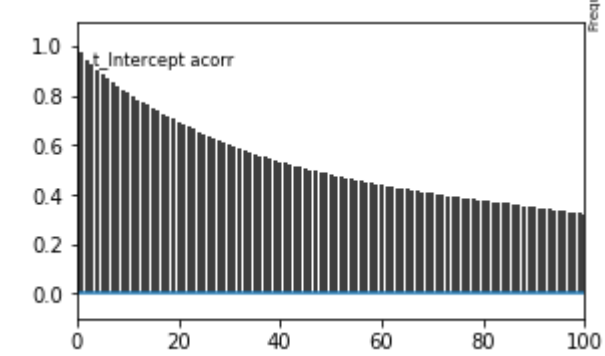
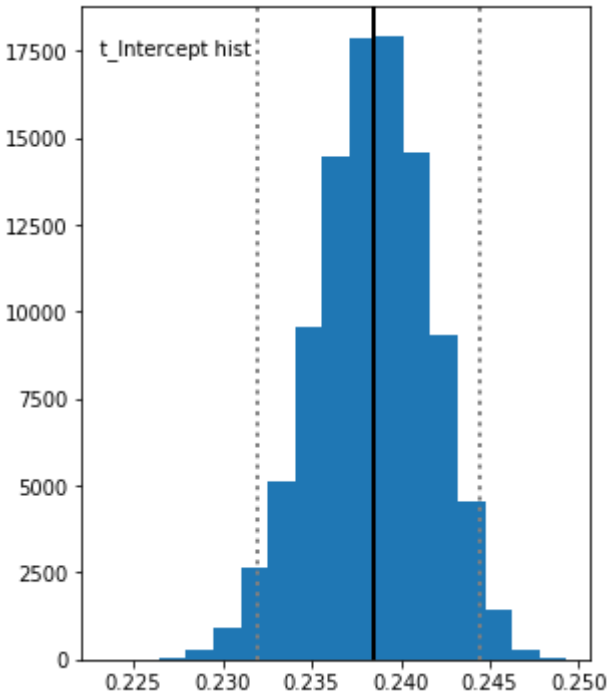
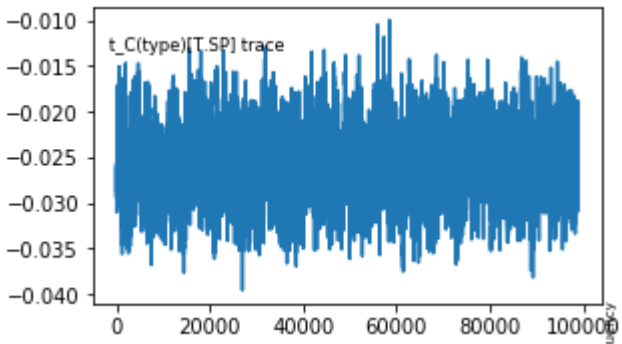
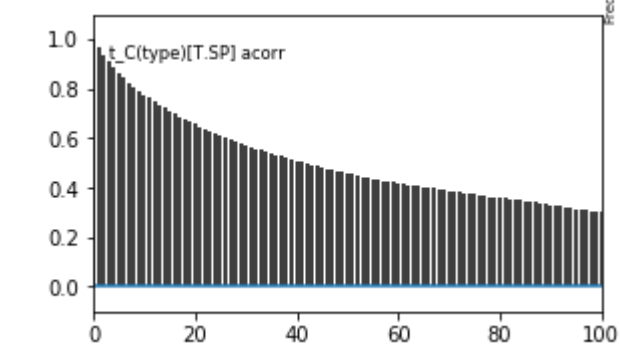
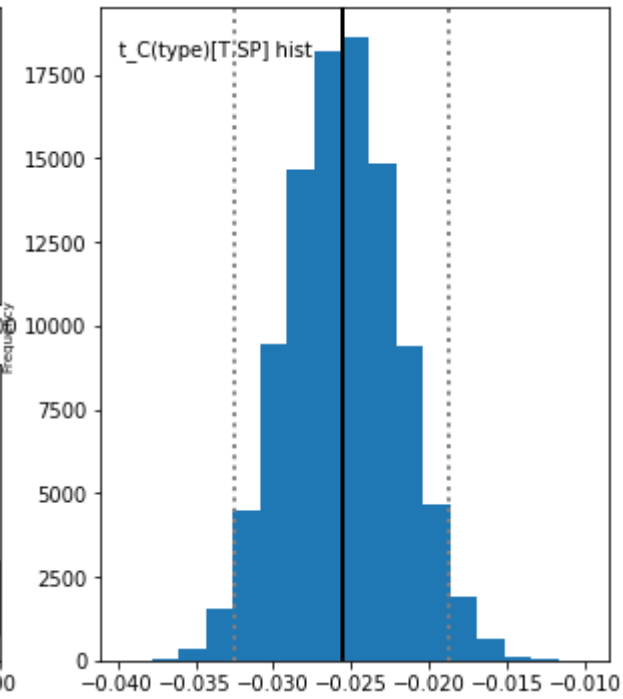
80000
100000

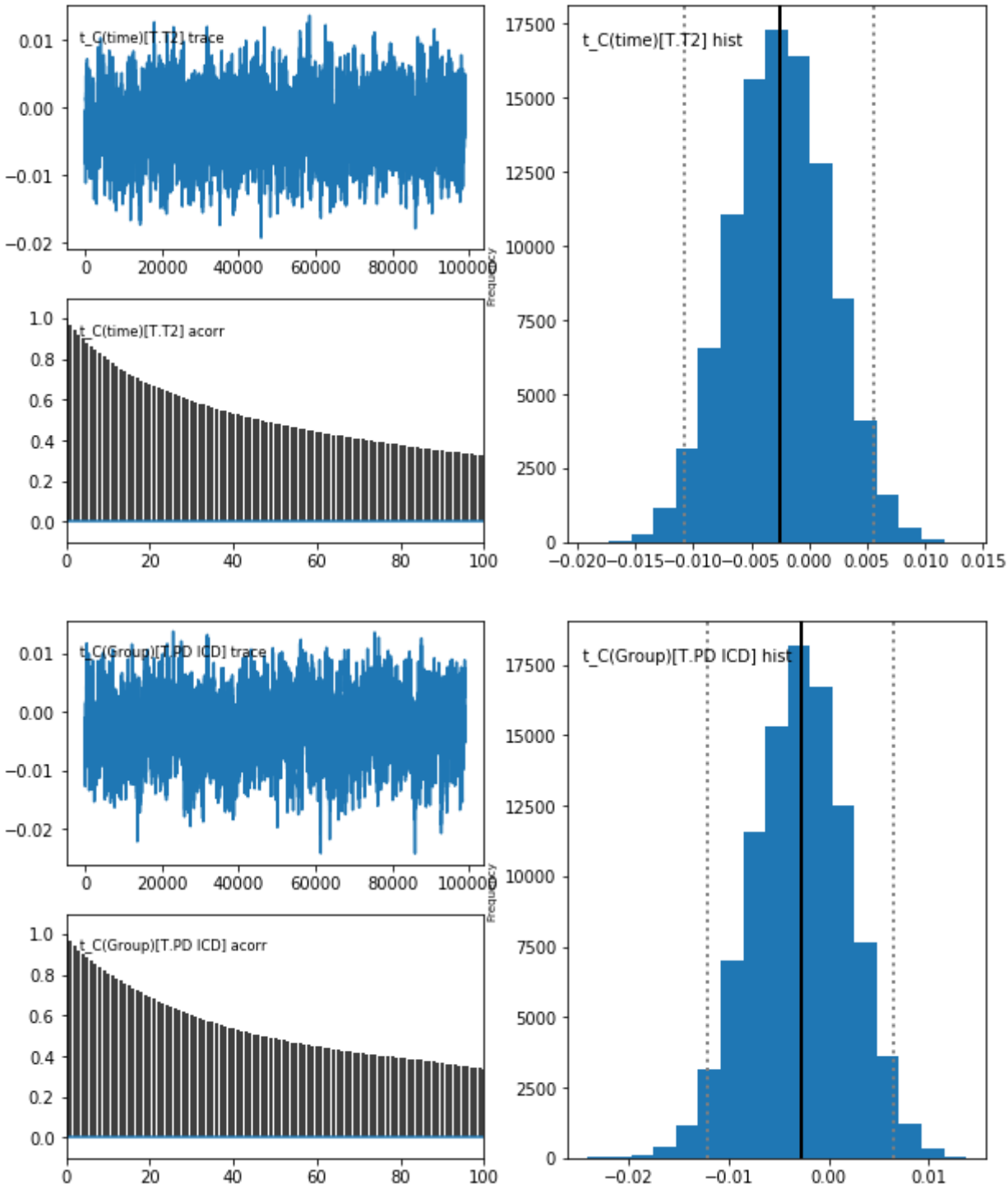

t_Intercept acorr
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100

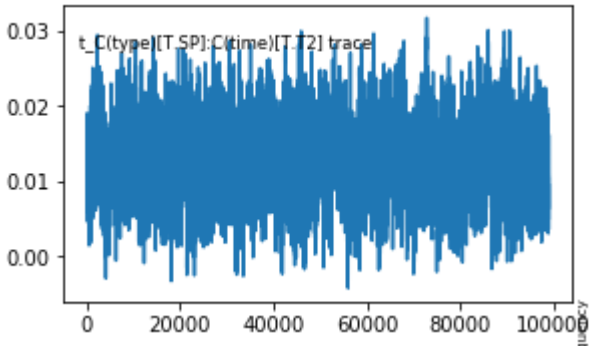

t_Intercept hist
Frequency
17500
15000
12500
10000
7500
5000
2500
0
0.225
0.230
0.235
0.240
0.245
0.250

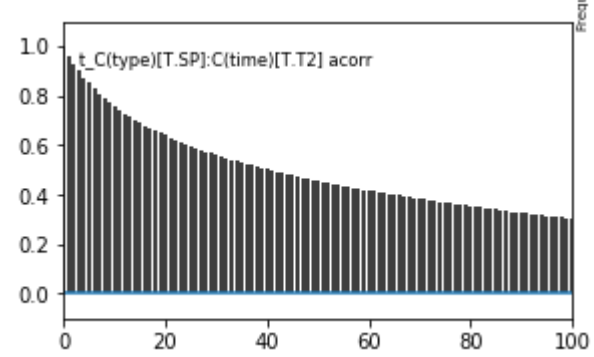

t_C(type)[T.SP] trace
−0.010
−0.015
−0.020
−0.025
−0.030
−0.035
−0.040
0
20000
40000
60000
80000
100000

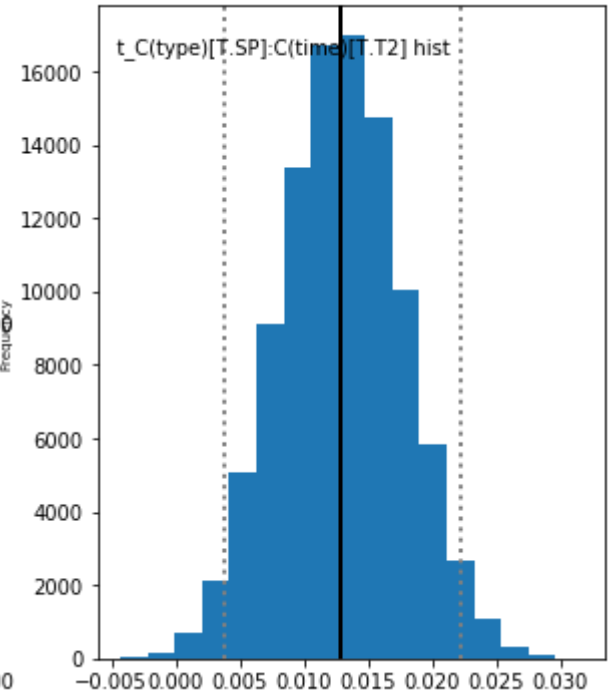

t_C(type)[T.SP] acorr
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100

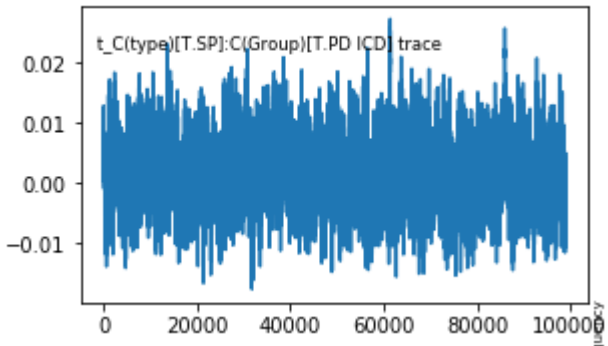

t_C(type)[T.SP] hist
Frequency
17500
15000
12500
10000
7500
5000
2500
0
−0.040
−0.035
−0.030
−0.025
−0.020
−0.015
−0.010

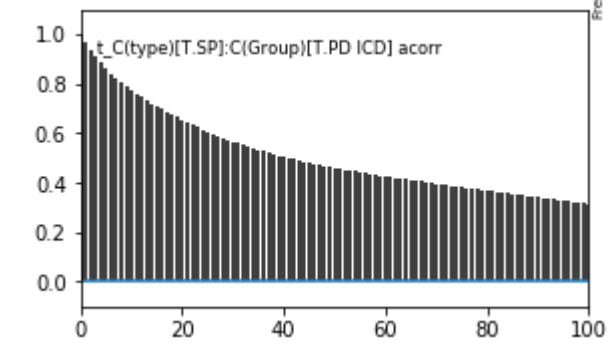

t_C(time)[T.T2] trace
t_C(time)[T.T2] hist
t_C(time)[T.T2] acorr
t_C(Group)[T.PD ICD] trace
t_C(Group)[T.PD ICD] hist
t_C(Group)[T.PD ICD] acorr
Frequency

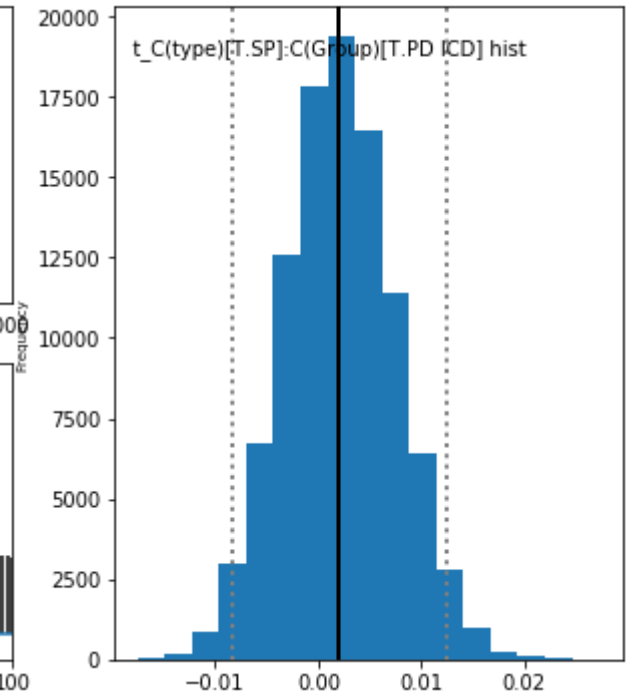

t_C(type)[T.SP]:C(time)[T.T2] trace
0.03
0.02
0.01
0.00
0
20000
40000
60000
80000
100000


t_C(type)[T.SP]:C(time)[T.T2] acorr
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100

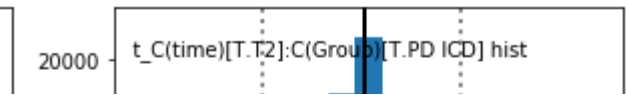

t_C(type)[T.SP]:C(time)[T.T2] hist
Frequency
16000
14000
12000
10000
8000
6000
4000
2000
0
−0.005
0.000
0.005
0.010
0.015
0.020
0.025
0.030

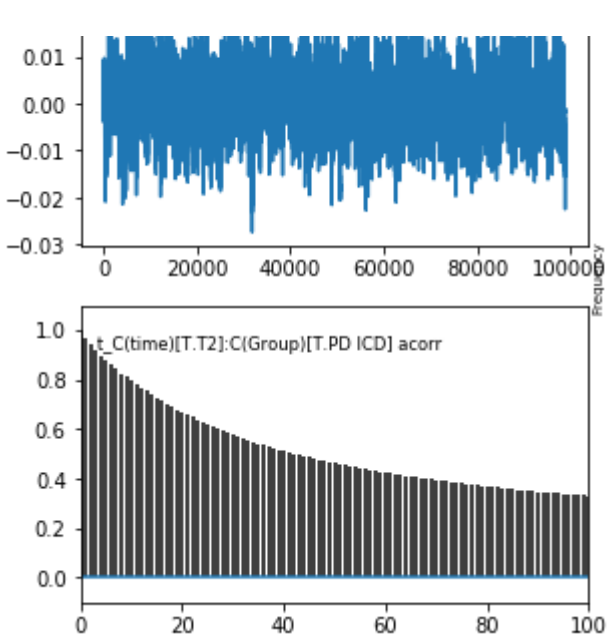

t_C(type)[T.SP]:C(Group)[T.PD ICD] trace
0.02
0.01
0.00
−0.01
0
20000
40000
60000
80000
100000

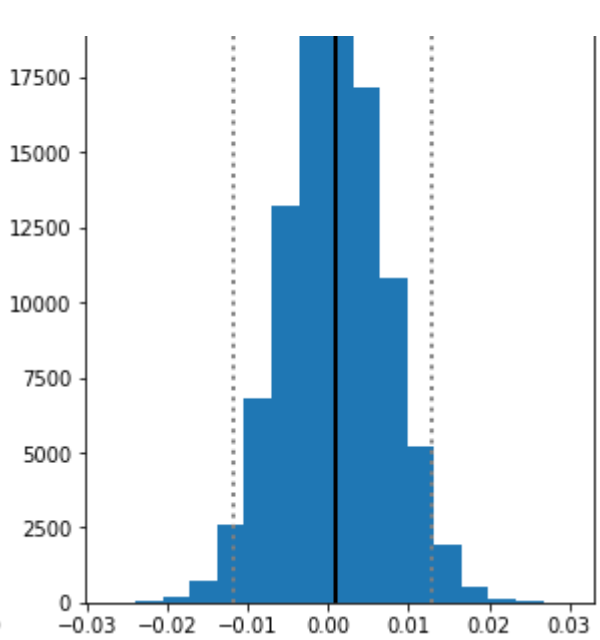

t_C(type)[T.SP]:C(Group)[T.PD ICD] acorr
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100

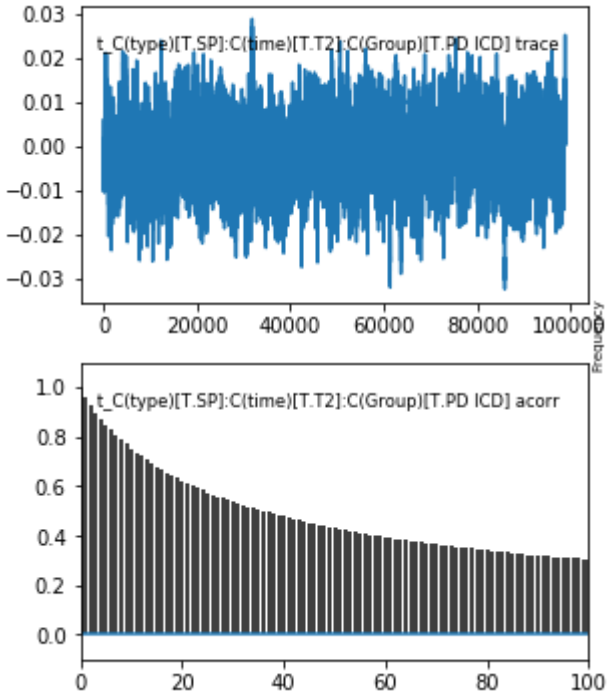

t_C(type)[T.SP]:C(Group)[T.PD ICD] hist
Frequency
20000
17500
15000
12500
10000
7500
5000
2500
0
−0.01
0.00
0.01
0.02

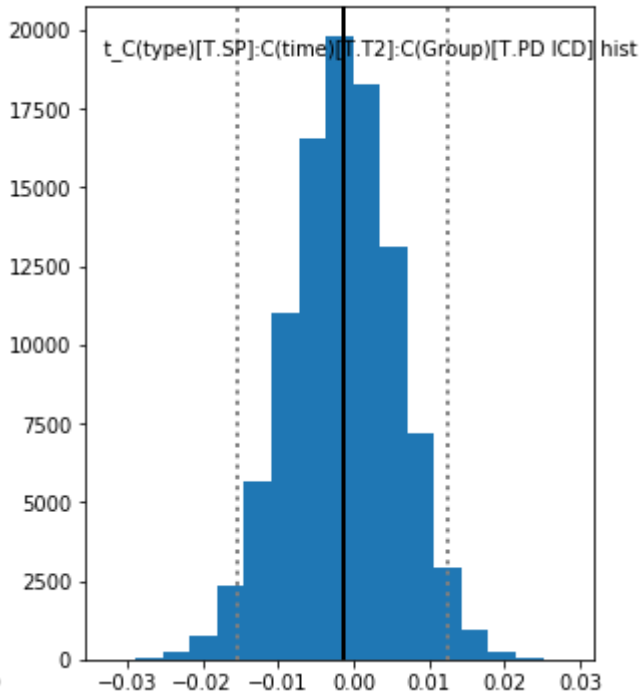

t_C(time)[T.T2]:C(Group)[T.PD ICD] trace
0.03
0.02


t_C(time)[T.T2]:C(Group)[T.PD ICD] hist
20000


t_C(time)[T.T2]:C(Group)[T.PD ICD] acorr


Frequency


t_C(type)[T.SP]:C(time)[T.T2]:C(Group)[T.PD ICD] trace
t_C(type)[T.SP]:C(time)[T.T2]:C(Group)[T.PD ICD] acorr


t_C(type)[T.SP]:C(time)[T.T2]:C(Group)[T.PD ICD] hist
Frequency

In [6]:
```
a_Intercept, a_Group, a_Time, a_Type, a_Group_Time, a_Group_Type, a_Time_Type, a_

#Plot the posterior distribution of decision threshold (a) under the influence o
hddm.analyze.plot_posterior_nodes([a_Group])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(a_Group < 0)=", (a_Group.trace() < 0).mean()

#Plot the posterior distribution of decision threshold (a) under the influence o
hddm.analyze.plot_posterior_nodes([a_Time])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(a_Time < 0)=", (a_Time.trace() < 0).mean()

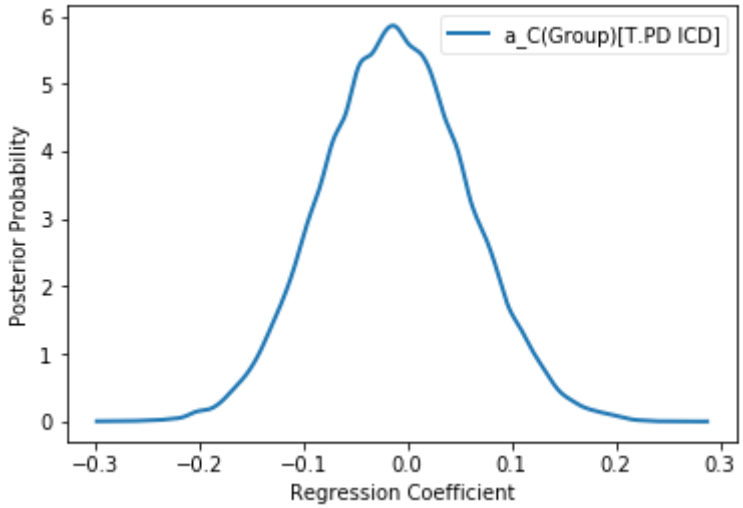
#Plot the posterior distribution of decision threshold (a) under the influence o
hddm.analyze.plot_posterior_nodes([a_Type])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(a_Type < 0)=", (a_Type.trace() < 0).mean()

#Plot the posterior distribution of decision threshold (a) under the inflence of
hddm.analyze.plot_posterior_nodes([a_Group_Time])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(a_Time_Group < 0)=", (a_Group_Time.trace() < 0).mean()

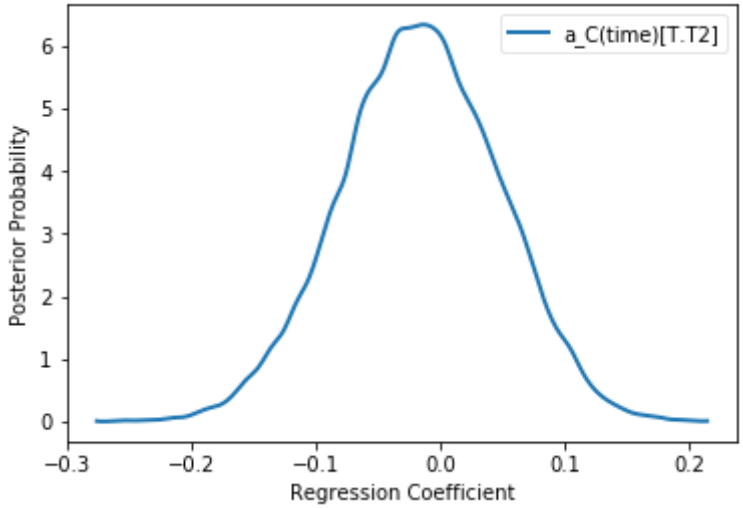
#Plot the posterior distribution of decision threshold (a) under the influence o
hddm.analyze.plot_posterior_nodes([a_Group_Type])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(a_Type_Group < 0)=", (a_Group_Type.trace() < 0).mean()

#Plot the posterior distribution of decision threshold (a) under the influence o
hddm.analyze.plot_posterior_nodes([a_Time_Type])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(a_Type_Time < 0)=", (a_Time_Type.trace() < 0).mean()

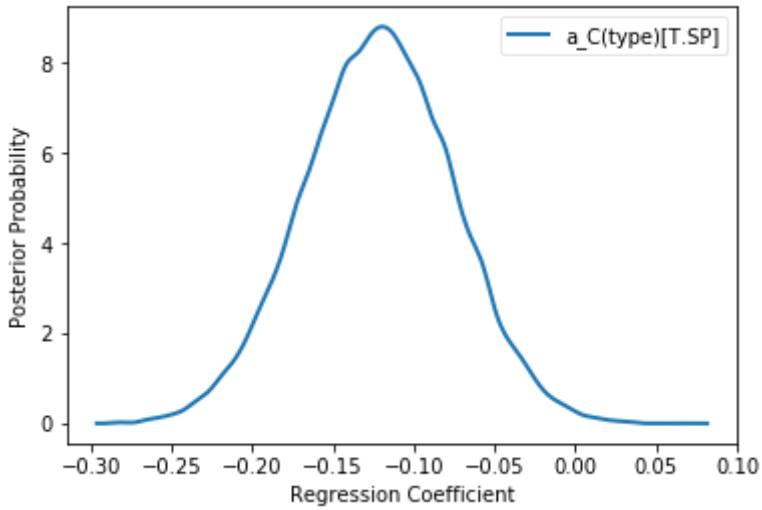
#Plot the posterior distribution of decision threshold (a) under the influence o
hddm.analyze.plot_posterior_nodes([a_Group_Time_Type])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(a_Type_Time_Group < 0)=", (a_Group_Time_Type.trace() < 0).mean()
```



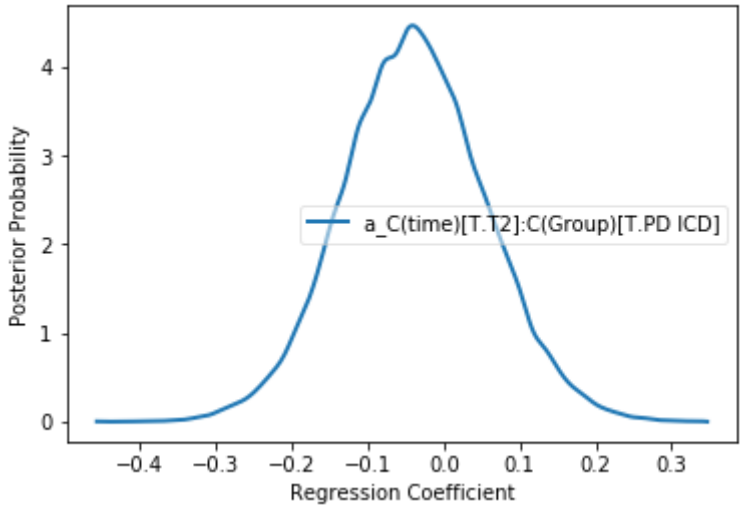
P(a_Group < 0)= 0.56797979798



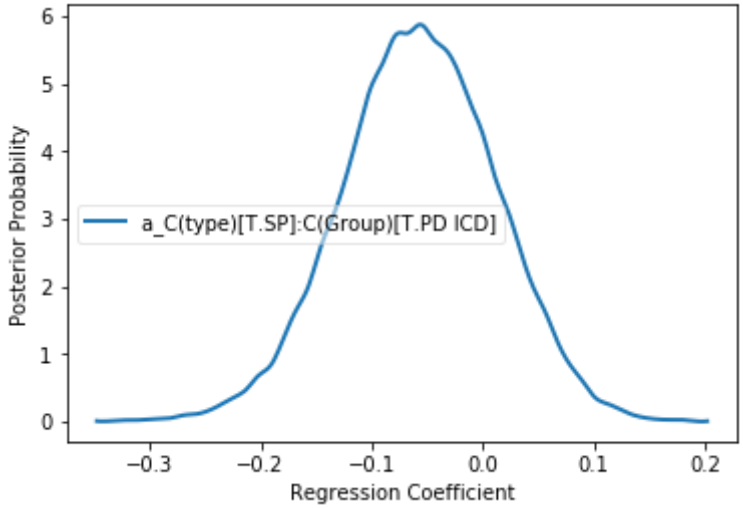
P(a_Time < 0)= 0.602616161616



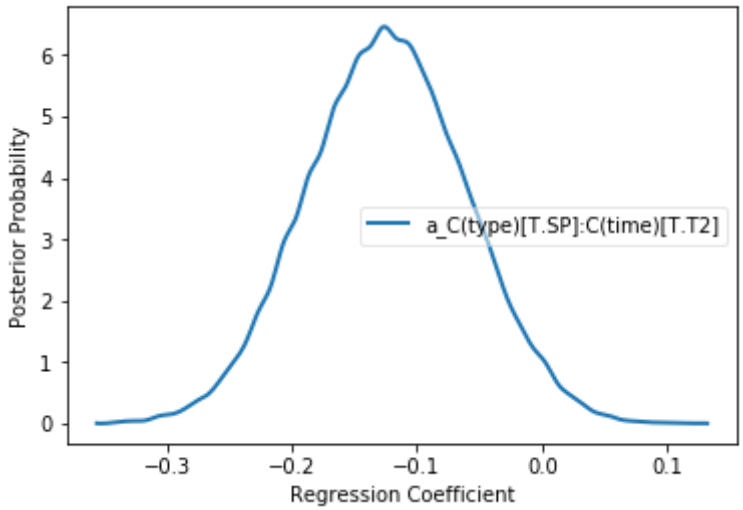
P(a_Type < 0)= 0.996454545455



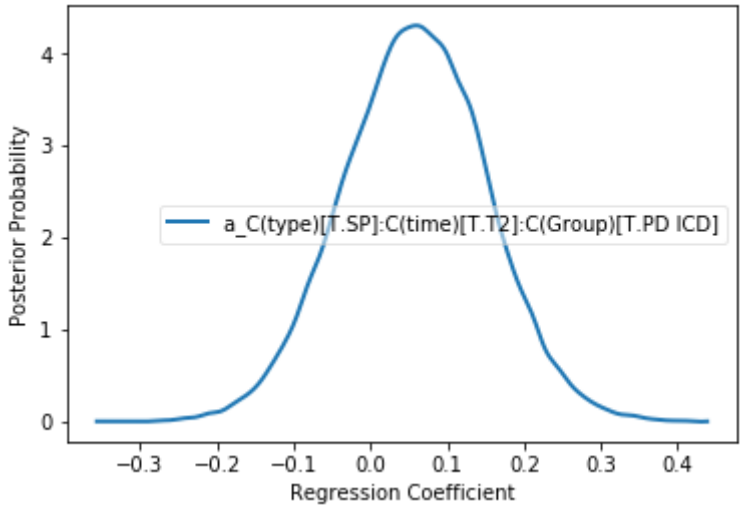
P(a_Time_Group < 0)= 0.668545454545



P(a_Type_Group < 0)= 0.801767676768



P(a_Type_Time < 0)= 0.976848484848



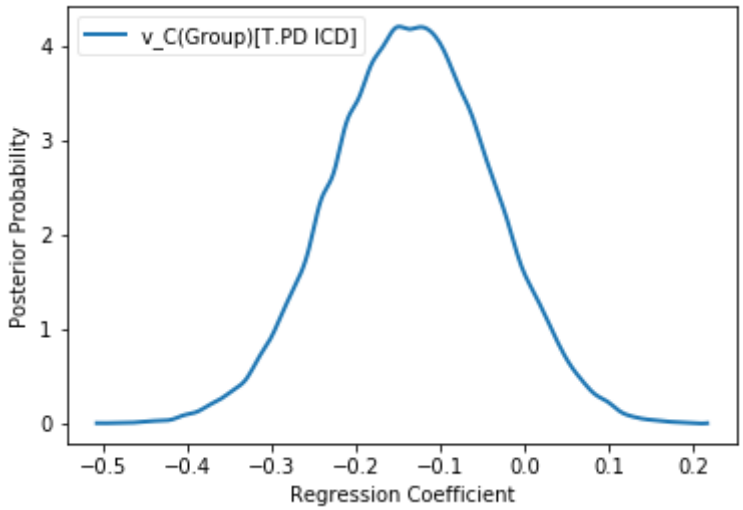
P(a_Type_Time_Group < 0)= 0.265282828283

In [7]:
```
v_Intercept, v_Group, v_Time, v_Group_Time = m_Speed.nodes_db.loc[['v_Intercept'

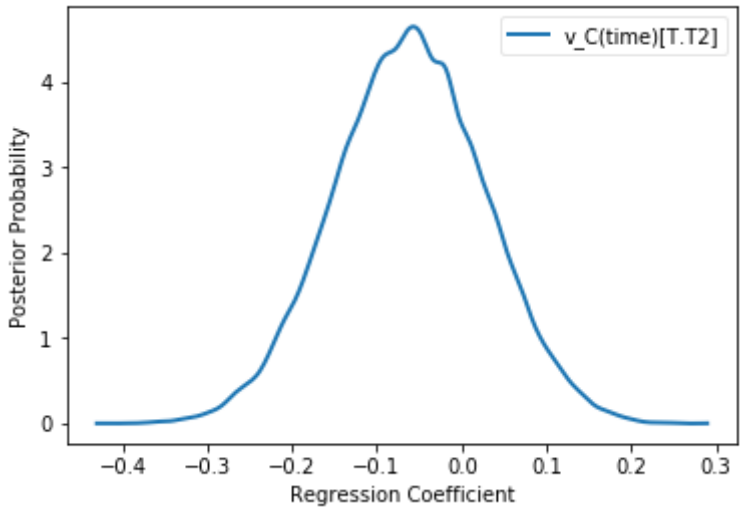
#Plot the posterior distribution of drift rate (v) under the influence of group
hddm.analyze.plot_posterior_nodes([v_Group])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(v_Group < 0)=", (v_Group.trace() < 0).mean()

#Plot the posterior distribution of drift rate (v) under the influence of time (
hddm.analyze.plot_posterior_nodes([v_Time])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(v_Time < 0)=", (v_Time.trace() < 0).mean()

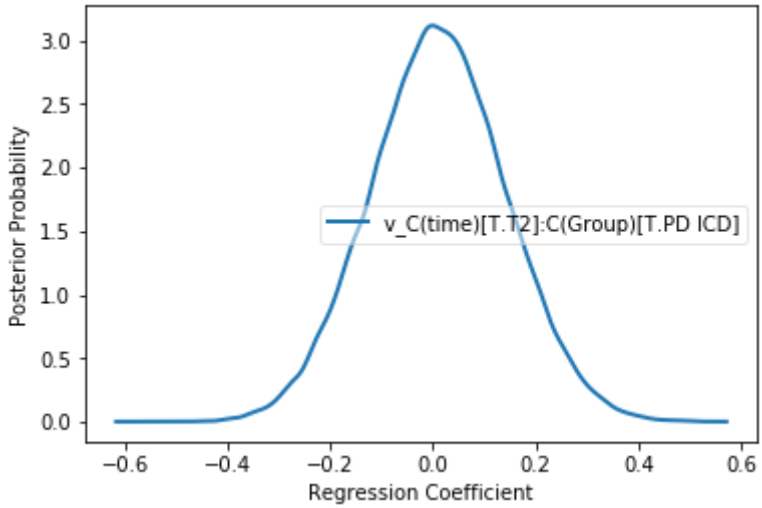
#Plot the posterior distribution of drift rate (v) under the influence of group*
hddm.analyze.plot_posterior_nodes([v_Group_Time])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(v_Time_Group < 0)=", (v_Group_Time.trace() < 0).mean()
```




```
P(v_Group < 0)= 0.924080808081
```




```
P(v_Time < 0)= 0.759595959596
```



P(v_Time_Group < 0)= 0.470424242424

In [8]:
```
t_Intercept, t_Group, t_Time, t_Type, t_Group_Time, t_Group_Type, t_Time_Type, t_

#Plot the posterior distribution of non-decision time (t) under the influence of
hddm.analyze.plot_posterior_nodes([t_Group])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(t_Group < 0)=", (t_Group.trace() < 0).mean()

#Plot the posterior distribution of non-decision time (t) under the influence of
hddm.analyze.plot_posterior_nodes([t_Time])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(t_Time < 0)=", (t_Time.trace() < 0).mean()

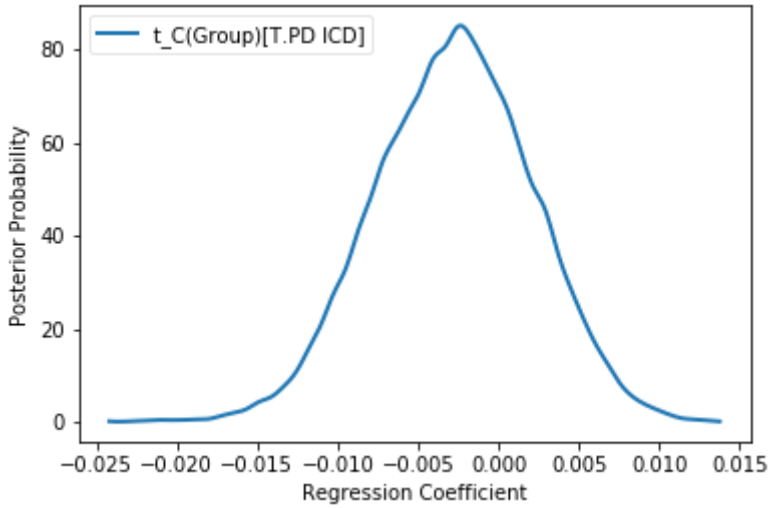
#Plot the posterior distribution of non-decision time (t) under the influence of
hddm.analyze.plot_posterior_nodes([t_Type])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(t_Type < 0)=", (t_Type.trace() < 0).mean()

#Plot the posterior distribution of non-decision time (t) under the inflence of
hddm.analyze.plot_posterior_nodes([a_Group_Time])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(a_Time_Group < 0)=", (a_Group_Time.trace() < 0).mean()

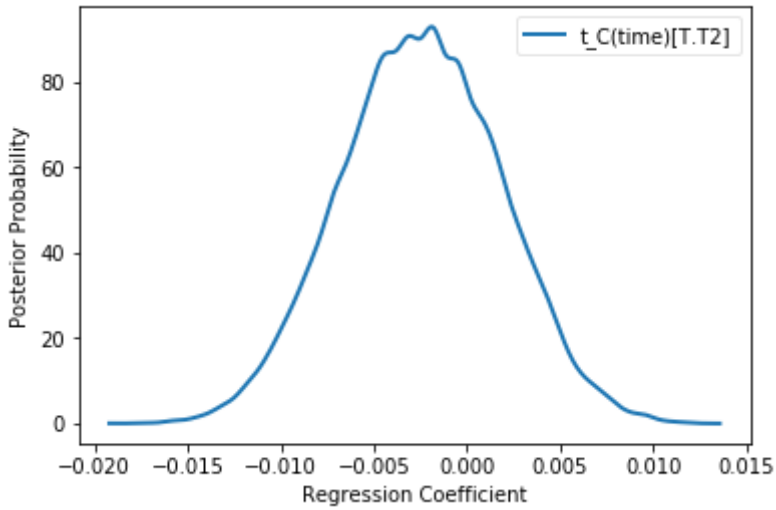
#Plot the posterior distribution of non-decision time (t) under the influence of
hddm.analyze.plot_posterior_nodes([t_Group_Type])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(t_Type_Group < 0)=", (t_Group_Type.trace() < 0).mean()

#Plot the posterior distribution of non-decision time (t) under the influence of
hddm.analyze.plot_posterior_nodes([t_Time_Type])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(t_Type_Time < 0)=", (t_Time_Type.trace() < 0).mean()

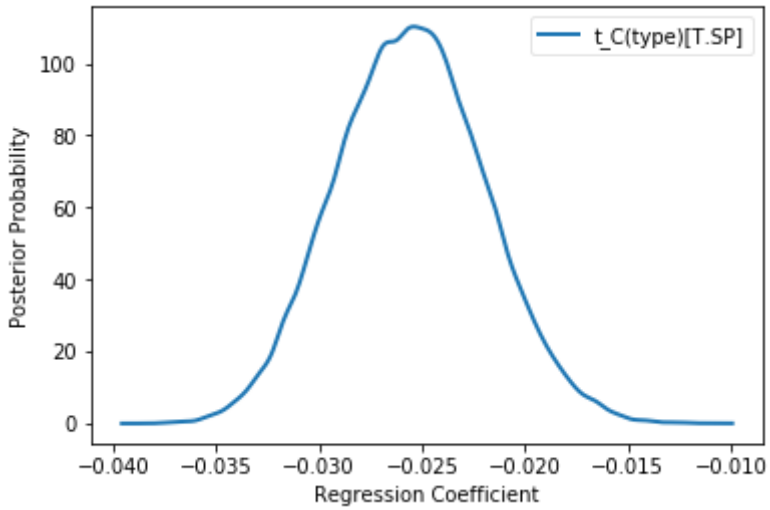
#Plot the posterior distribution of non-decision time (t) under the influence of
hddm.analyze.plot_posterior_nodes([t_Group_Time_Type])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(t_Type_Time_Group < 0)=", (t_Group_Time_Type.trace() < 0).mean()
```



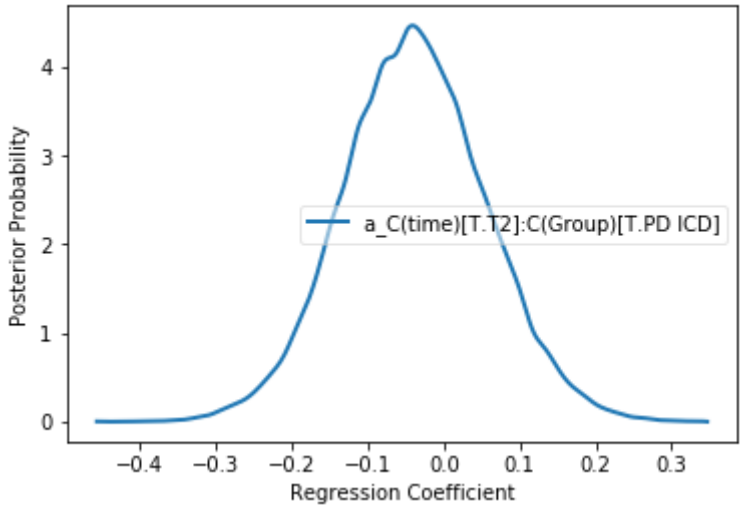
P(t_Group < 0)= 0.71904040404



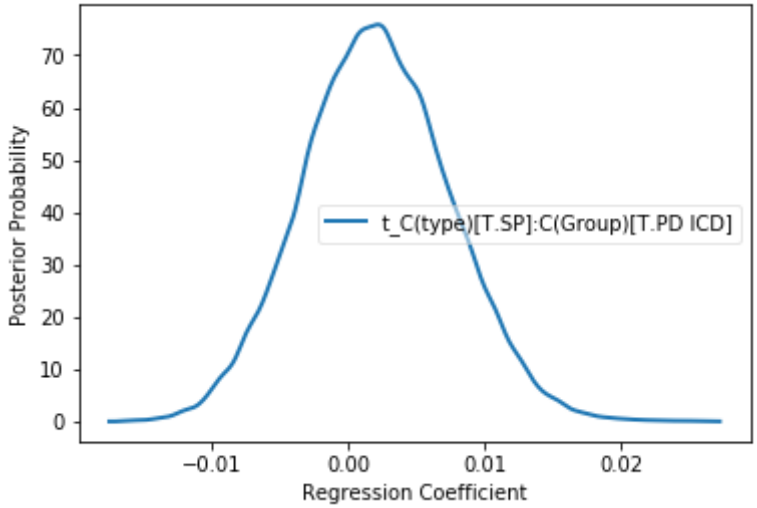
P(t_Time < 0)= 0.718494949495



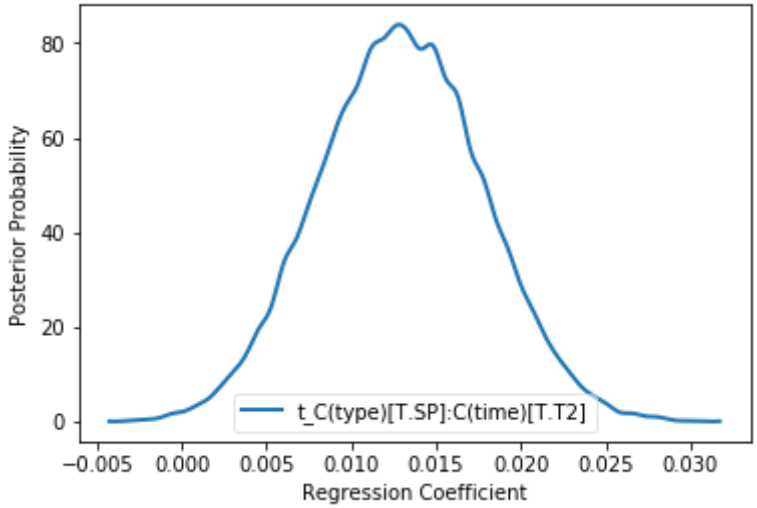
P(t_Type < 0)= 1.0



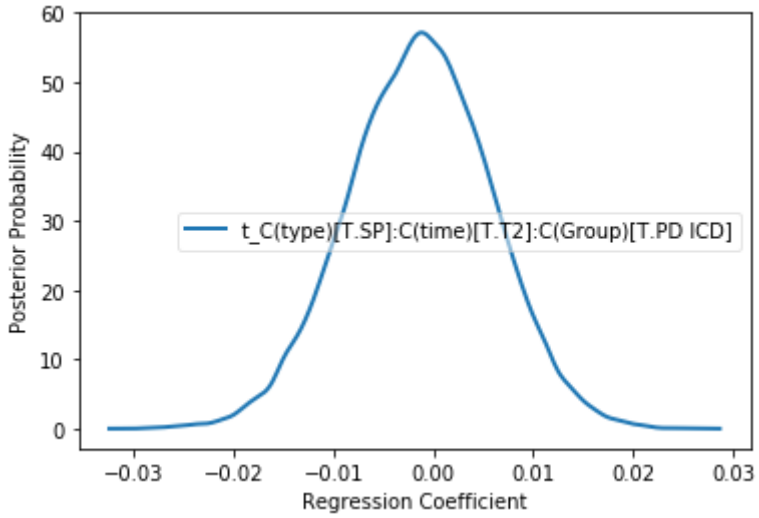
P(a_Time_Group < 0)= 0.668545454545



P(t_Type_Group < 0)= 0.350101010101



P(t_Type_Time < 0)= 0.00207070707071



P(t_Type_Time_Group < 0)= 0.573404040404

Appendix - Programming codes for Chapter 2

In [1]:
```
#import the related toolboxes
import hddm
import pandas as pd
import matplotlib.pyplot as plt
```

```
/Users/Nicole/anaconda2/lib/python2.7/site-packages/IPython/parallel.py:13: Sh
imWarning: The `IPython.parallel` package has been deprecated. You should impo
rt from ipyparallel instead.
  "You should import from ipyparallel instead.", ShimWarning)
```

In [5]:
```
#import the data
Difficulty = hddm.load_csv('/Users/Nicole/Desktop/HDDM_DotsPD/Difficulty.csv')
```

In [6]:
```
#Instead of estimating one static threshold per subject across trials, this mode
m_Difficulty = hddm.HDDMRegressor(Difficulty, ["a ~ C(Time)*C(Group)","v ~ C(Lev
```

```
Adding these covariates:
['a_Intercept', 'a_C(Time)[T.T2]', 'a_C(Group)[T.PD ICD]', 'a_C(Time)[T.T2]:C
(Group)[T.PD ICD]']
Adding these covariates:
['v_Intercept', 'v_C(Level)[T.L2]', 'v_C(Level)[T.L3]', 'v_C(Level)[T.L4]', 'v
_C(Level)[T.L5]', 'v_C(Level)[T.L6]', 'v_C(Time)[T.T2]', 'v_C(Group)[T.PD IC
D]', 'v_C(Level)[T.L2]:C(Time)[T.T2]', 'v_C(Level)[T.L3]:C(Time)[T.T2]', 'v_C
(Level)[T.L4]:C(Time)[T.T2]', 'v_C(Level)[T.L5]:C(Time)[T.T2]', 'v_C(Level)[T.
L6]:C(Time)[T.T2]', 'v_C(Level)[T.L2]:C(Group)[T.PD ICD]', 'v_C(Level)[T.L3]:C
(Group)[T.PD ICD]', 'v_C(Level)[T.L4]:C(Group)[T.PD ICD]', 'v_C(Level)[T.L5]:C
(Group)[T.PD ICD]', 'v_C(Level)[T.L6]:C(Group)[T.PD ICD]', 'v_C(Time)[T.T2]:C
(Group)[T.PD ICD]', 'v_C(Level)[T.L2]:C(Time)[T.T2]:C(Group)[T.PD ICD]', 'v_C
(Level)[T.L3]:C(Time)[T.T2]:C(Group)[T.PD ICD]', 'v_C(Level)[T.L4]:C(Time)[T.T
2]:C(Group)[T.PD ICD]', 'v_C(Level)[T.L5]:C(Time)[T.T2]:C(Group)[T.PD ICD]',
'v_C(Level)[T.L6]:C(Time)[T.T2]:C(Group)[T.PD ICD]']
Adding these covariates:
['t_Intercept', 't_C(Time)[T.T2]', 't_C(Group)[T.PD ICD]', 't_C(Time)[T.T2]:C
(Group)[T.PD ICD]']
```

In [7]:
```
#Start drawing 10000 samples and discarding 1000 as burn-in
m_Difficulty.sample(10000, burn=1000)
```

```
 [-----------------100%-----------------] 10001 of 10000 complete in 20136.0 s
ec
```

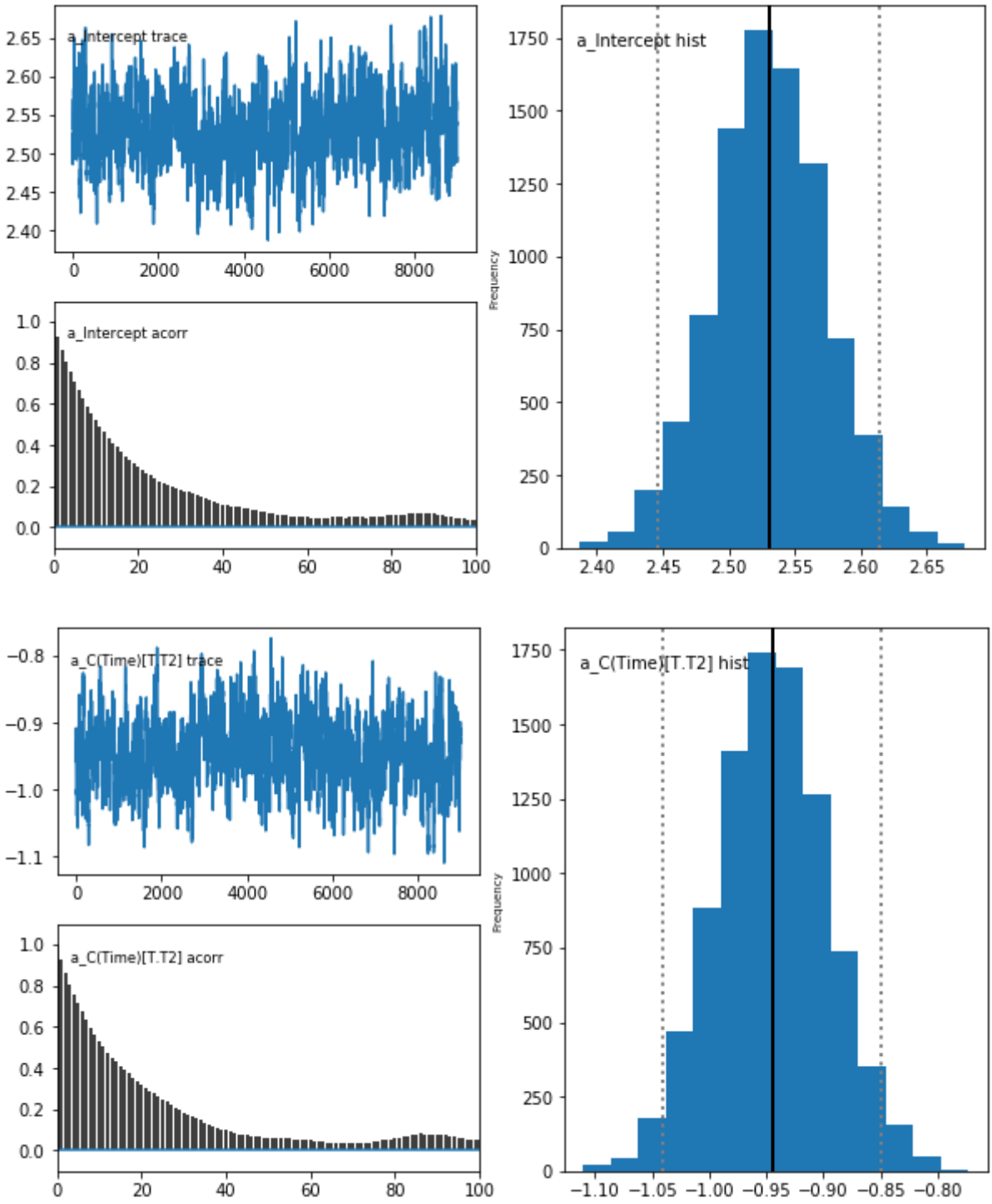
Out[7]:
```
<pymc.MCMC.MCMC at 0x11f1925d0>
```

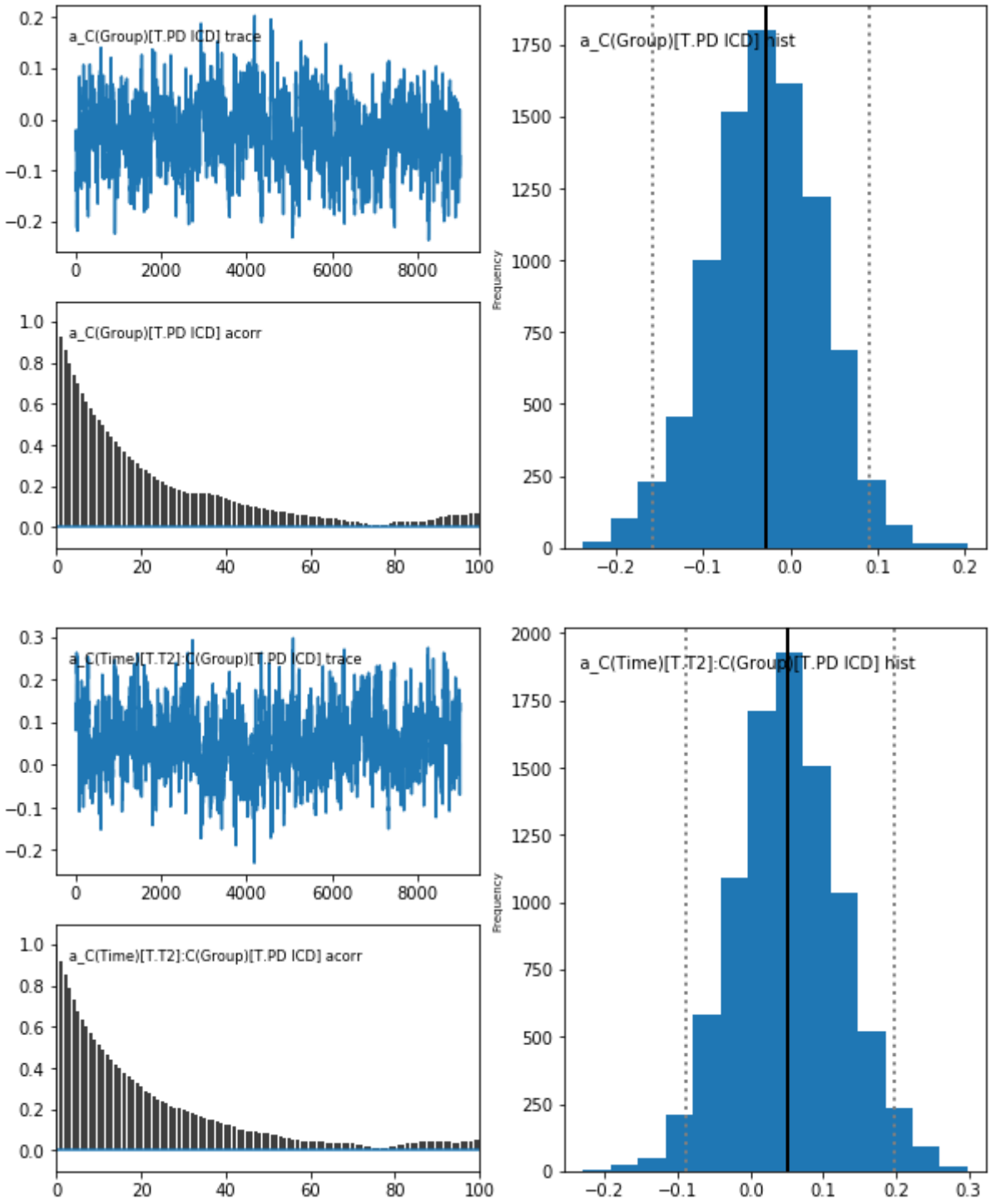
In [8]:
```
#plot the figures to examine the convergence of the model
m_Difficulty.plot_posteriors()
plt.show()
#As the figure shown, the model seems to be well-converged
```

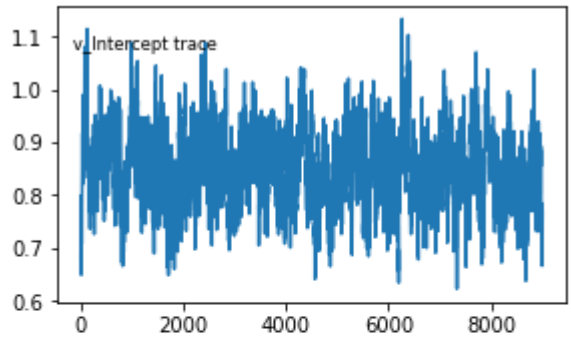
```
Plotting a_Intercept
Plotting a_C(Time)[T.T2]
Plotting a_C(Group)[T.PD ICD]
Plotting a_C(Time)[T.T2]:C(Group)[T.PD ICD]
Plotting v_Intercept
Plotting v_C(Level)[T.L2]
Plotting v_C(Level)[T.L3]
Plotting v_C(Level)[T.L4]
Plotting v_C(Level)[T.L5]
Plotting v_C(Level)[T.L6]
Plotting v_C(Time)[T.T2]
Plotting v_C(Group)[T.PD ICD]
Plotting v_C(Level)[T.L2]:C(Time)[T.T2]
Plotting v_C(Level)[T.L3]:C(Time)[T.T2]
Plotting v_C(Level)[T.L4]:C(Time)[T.T2]
Plotting v_C(Level)[T.L5]:C(Time)[T.T2]
Plotting v_C(Level)[T.L6]:C(Time)[T.T2]
Plotting v_C(Level)[T.L2]:C(Group)[T.PD ICD]
Plotting v_C(Level)[T.L3]:C(Group)[T.PD ICD]
Plotting v_C(Level)[T.L4]:C(Group)[T.PD ICD]
Plotting v_C(Level)[T.L5]:C(Group)[T.PD ICD]
```

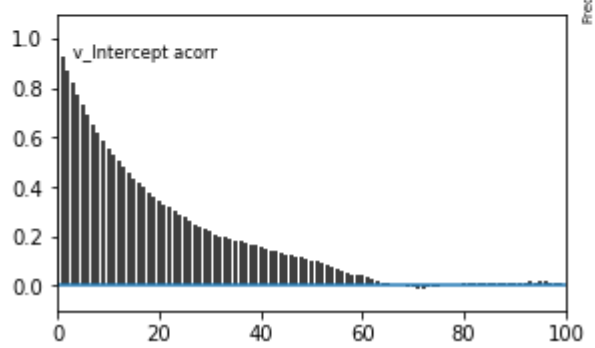
```
/Users/Nicole/anaconda2/lib/python2.7/site-packages/matplotlib/pyplot.py:524:
RuntimeWarning: More than 20 figures have been opened. Figures created through
the pyplot interface (`matplotlib.pyplot.figure`) are retained until explicitl
y closed and may consume too much memory. (To control this warning, see the rc
Param `figure.max_open_warning`).
  max_open_warning, RuntimeWarning)
```

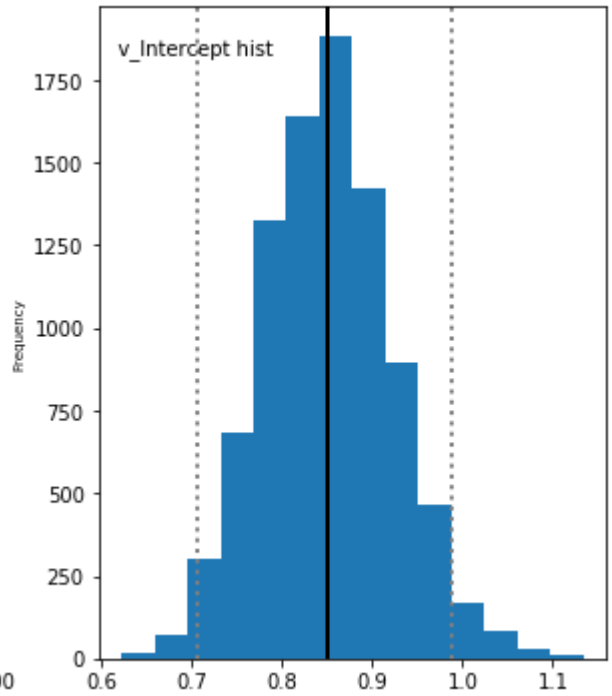
```
Plotting v_C(Level)[T.L6]:C(Group)[T.PD ICD]
Plotting v_C(Time)[T.T2]:C(Group)[T.PD ICD]
Plotting v_C(Level)[T.L2]:C(Time)[T.T2]:C(Group)[T.PD ICD]
Plotting v_C(Level)[T.L3]:C(Time)[T.T2]:C(Group)[T.PD ICD]
Plotting v_C(Level)[T.L4]:C(Time)[T.T2]:C(Group)[T.PD ICD]
Plotting v_C(Level)[T.L5]:C(Time)[T.T2]:C(Group)[T.PD ICD]
Plotting v_C(Level)[T.L6]:C(Time)[T.T2]:C(Group)[T.PD ICD]
Plotting t_Intercept
Plotting t_C(Time)[T.T2]
Plotting t_C(Group)[T.PD ICD]
Plotting t_C(Time)[T.T2]:C(Group)[T.PD ICD]
```

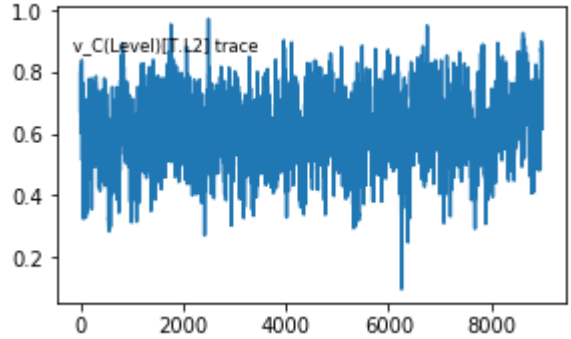

a_Intercept trace
a_Intercept acorr
a_Intercept hist
Frequency
a_C(Time)[T.T2] trace
a_C(Time)[T.T2] acorr
a_C(Time)[T.T2] hist
Frequency

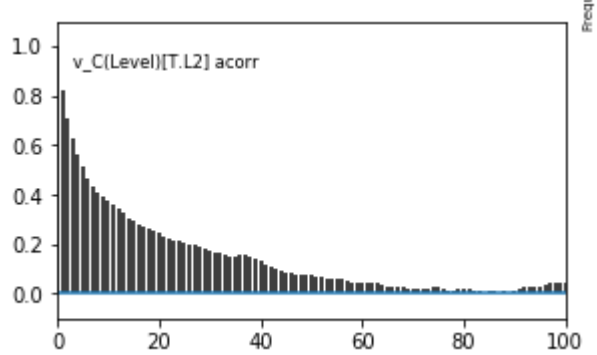

a_C(Group)[T.PD ICD] trace
a_C(Group)[T.PD ICD] acorr
a_C(Group)[T.PD ICD] hist
Frequency
a_C(Time)[T.T2]:C(Group)[T.PD ICD] trace
a_C(Time)[T.T2]:C(Group)[T.PD ICD] acorr
a_C(Time)[T.T2]:C(Group)[T.PD ICD] hist
Frequency

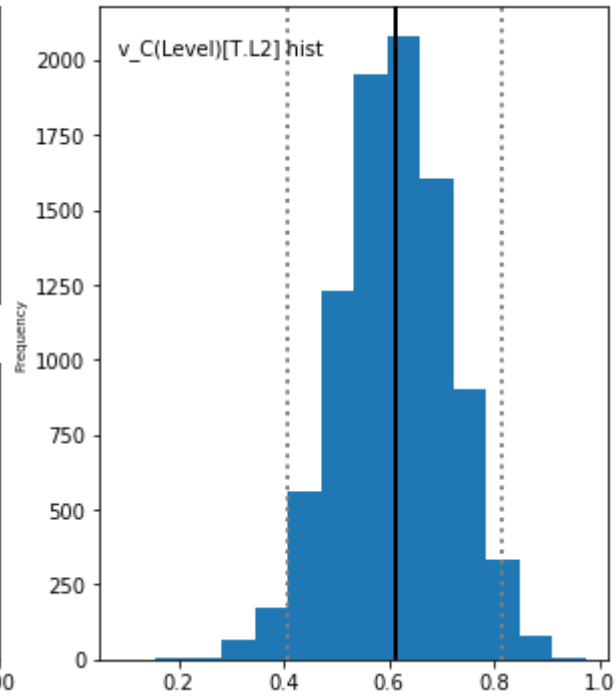

v_Intercept trace
1.1
1.0
0.9
0.8
0.7
0.6
0
2000
4000
6000
8000

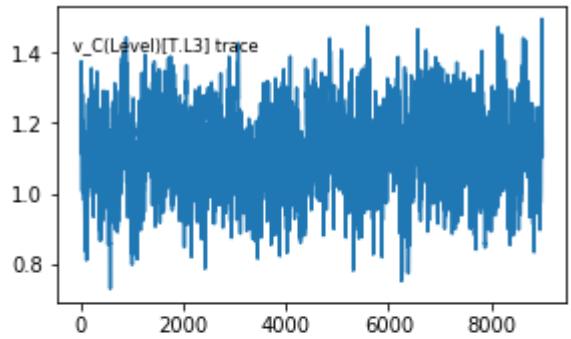

v_Intercept acorr
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100

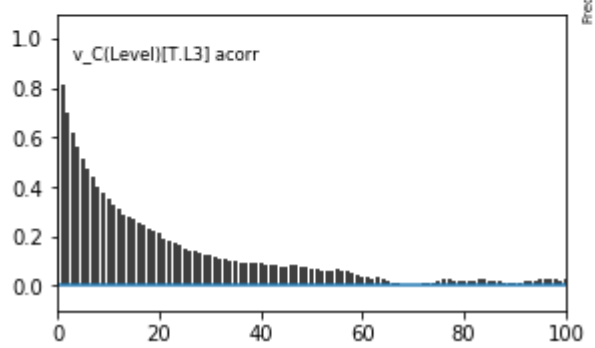

v_Intercept hist
Frequency
1750
1500
1250
1000
750
500
250
0
0.6
0.7
0.8
0.9
1.0
1.1

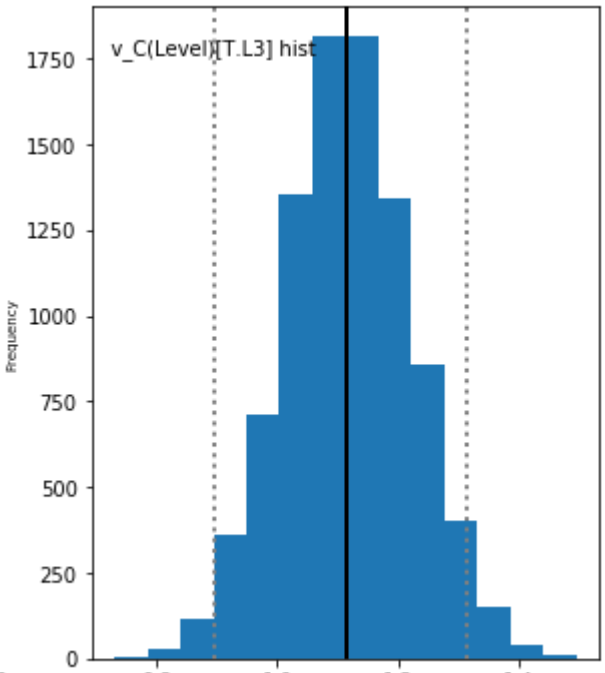

v_C(Level)[T.L2] trace
1.0
0.8
0.6
0.4
0.2
0
2000
4000
6000
8000

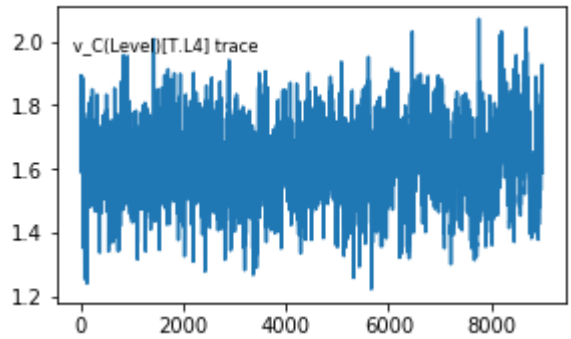

v_C(Level)[T.L2] acorr
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100

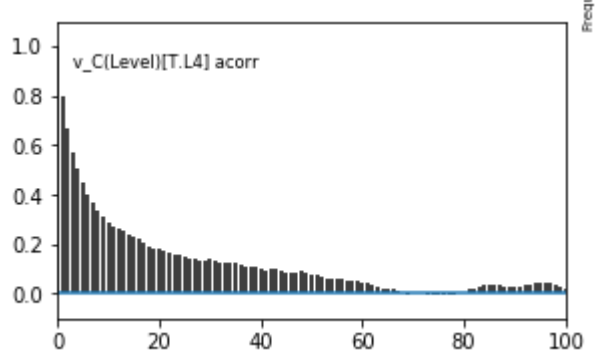

v_C(Level)[T.L2] hist
Frequency
2000
1750
1500
1250
1000
750
500
250
0
0.2
0.4
0.6
0.8
1.0

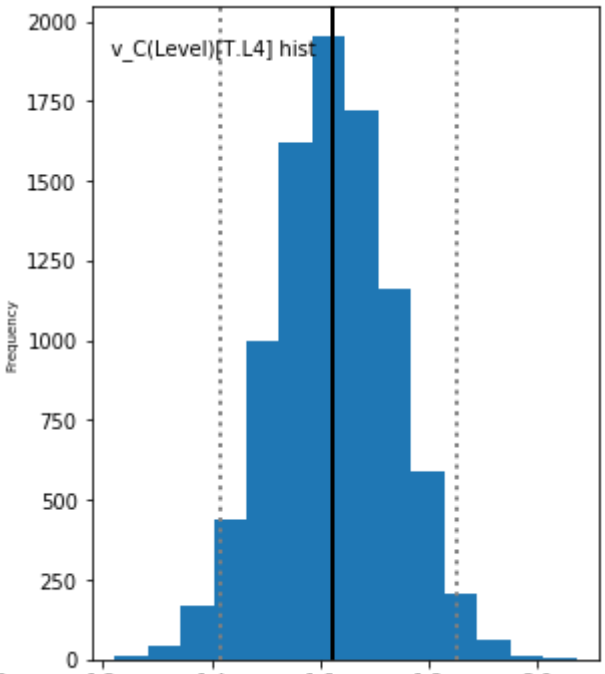

v_C(Level)[T.L3] trace

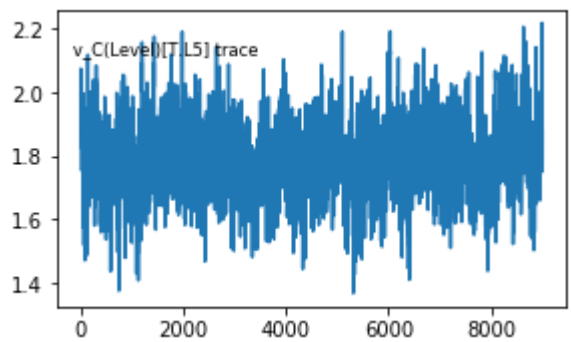

v_C(Level)[T.L3] acorr

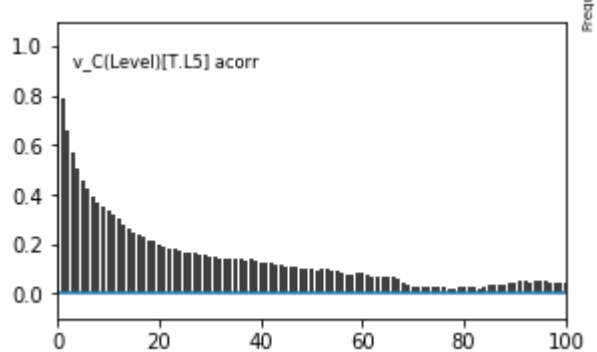

v_C(Level)[T.L3] hist
Frequency

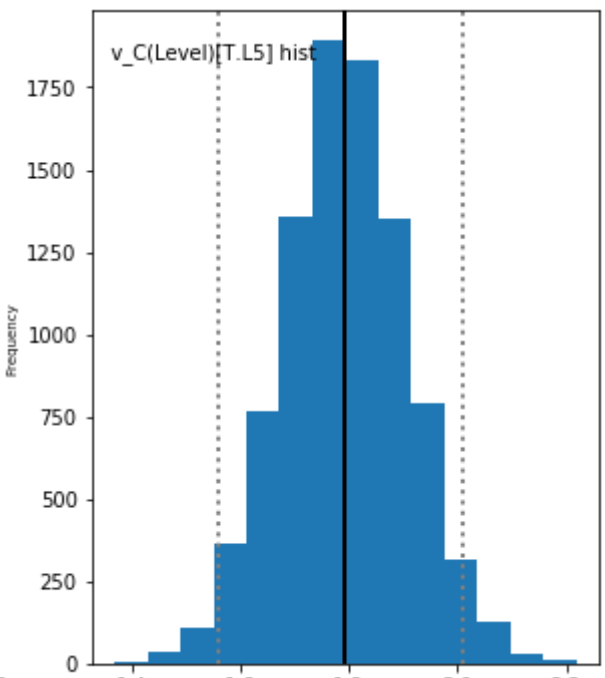

v_C(Level)[T.L4] trace

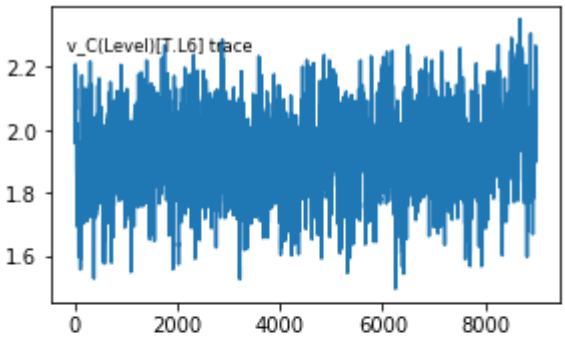

v_C(Level)[T.L4] acorr

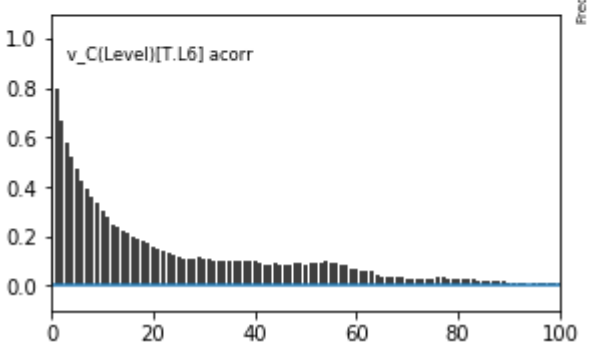

v_C(Level)[T.L4] hist
Frequency

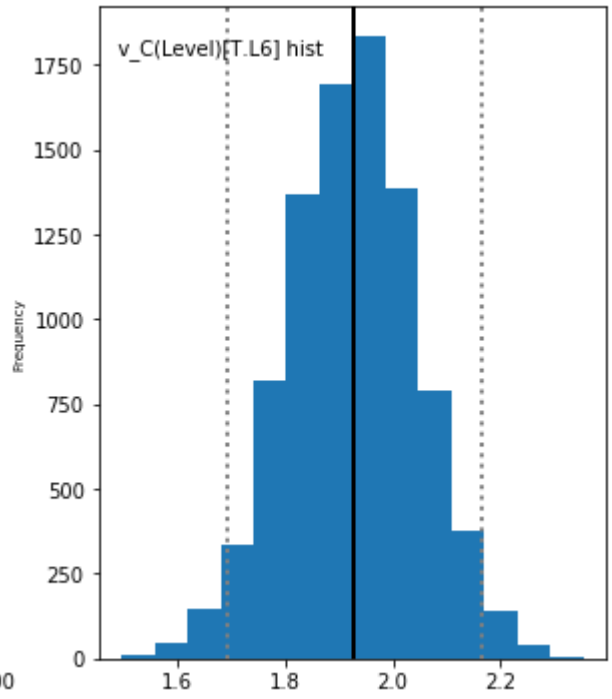

v_C(Level)[T.L5] trace

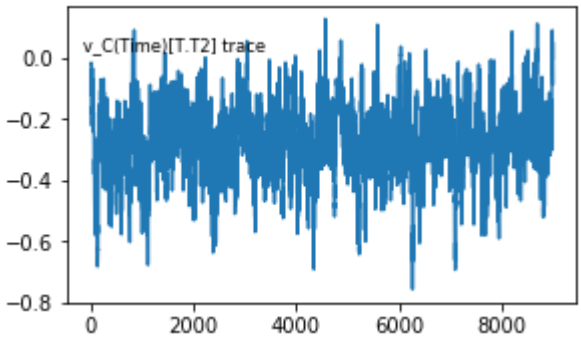

v_C(Level)[T.L5] acorr

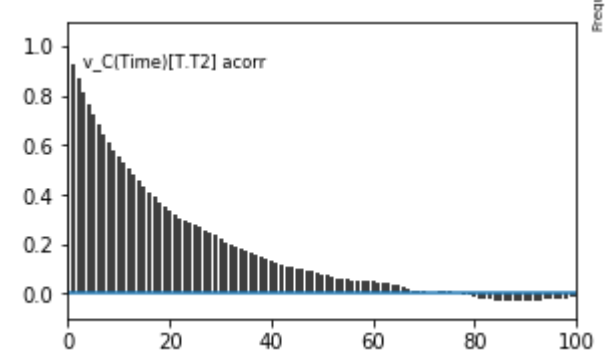

v_C(Level)[T.L5] hist
Frequency

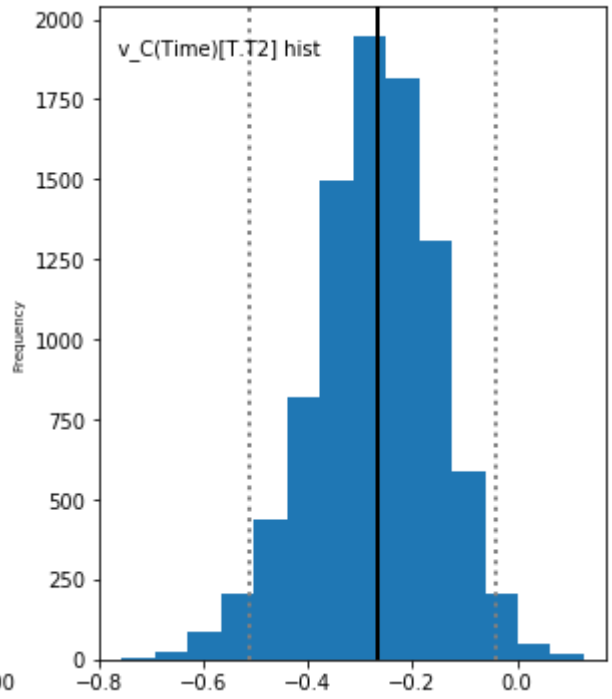

v_C(Level)[T.L6] trace
2.2
2.0
1.8
1.6
0
2000
4000
6000
8000

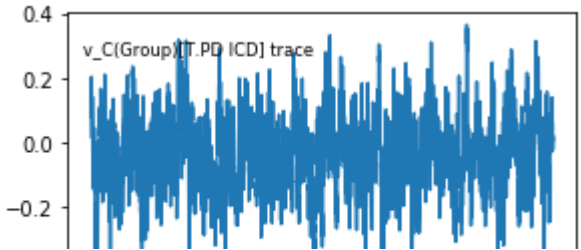

v_C(Level)[T.L6] acorr
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100

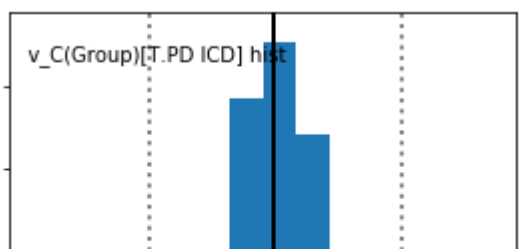

v_C(Level)[T.L6] hist
Frequency
1750
1500
1250
1000
750
500
250
0
1.6
1.8
2.0
2.2

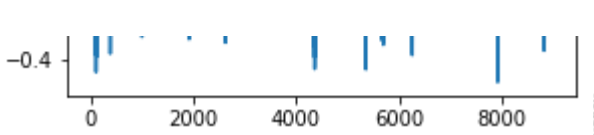

v_C(Time)[T.T2] trace
0.0
−0.2
−0.4
−0.6
−0.8
0
2000
4000
6000
8000

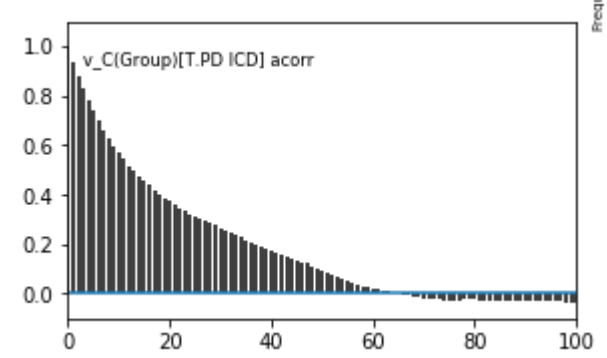

v_C(Time)[T.T2] acorr
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100

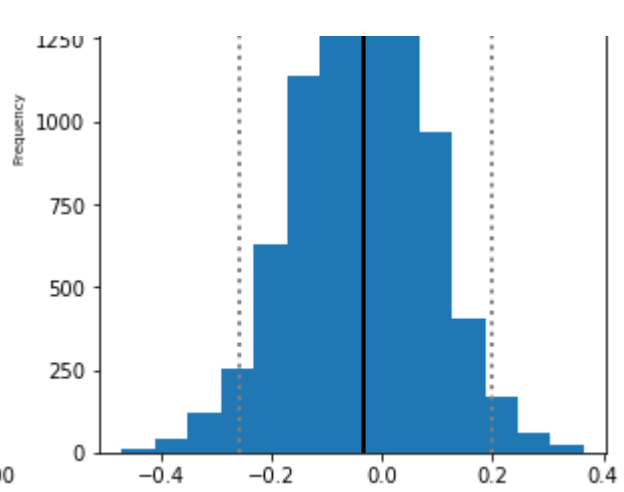

v_C(Time)[T.T2] hist
Frequency
2000
1750
1500
1250
1000
750
500
250
0
−0.8
−0.6
−0.4
−0.2
0.0

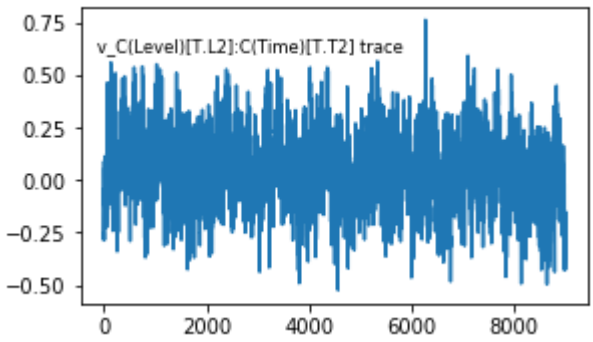

v_C(Group)[T.PD ICD] trace
0.4
0.2
0.0
−0.2

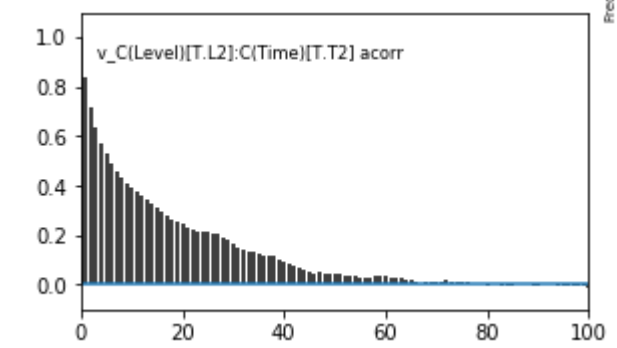

v_C(Group)[T.PD ICD] hist
1750
1500

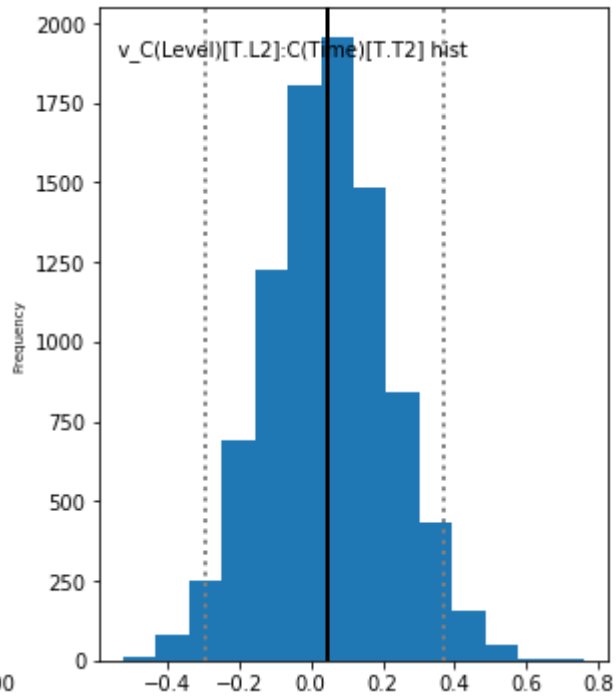



v_C(Group)[T.PD ICD] acorr


Frequency


v_C(Level)[T.L2]:C(Time)[T.T2] trace


v_C(Level)[T.L2]:C(Time)[T.T2] acorr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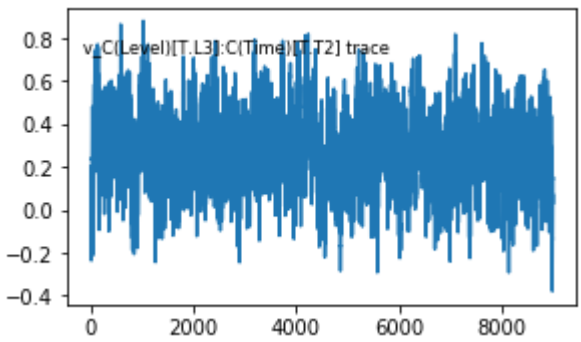
Frequency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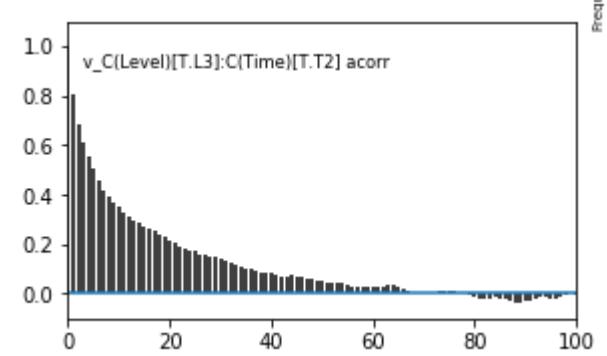
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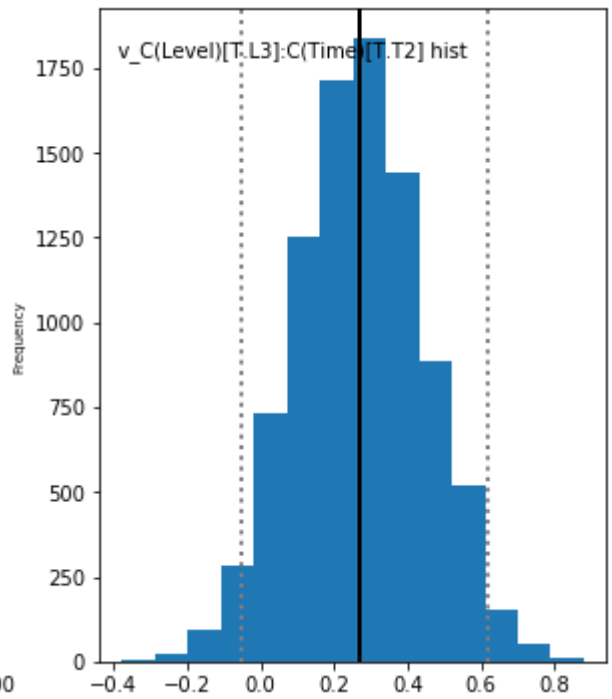
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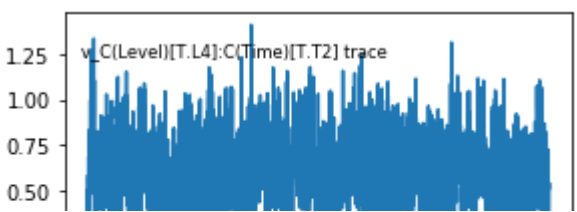
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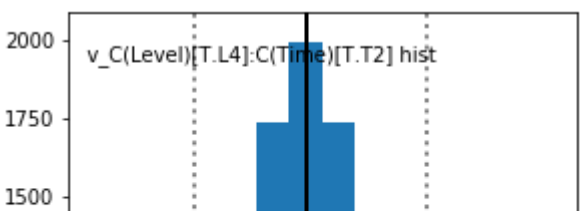
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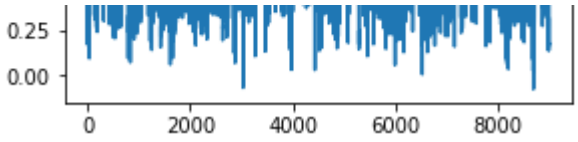
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0.00
0
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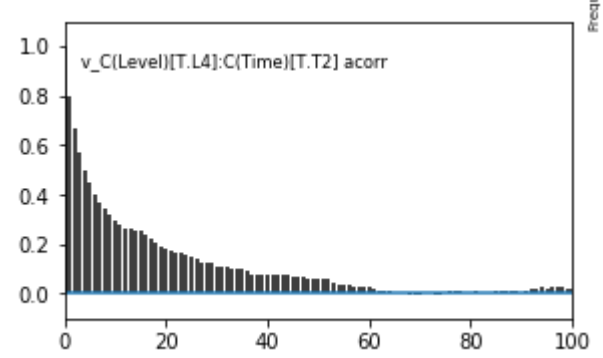
4000
6000
8000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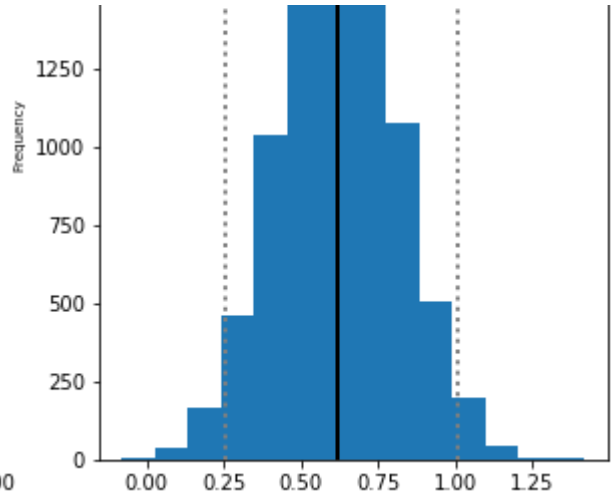
0.6
0.4
0.2
0.0
0
20
40
60
80
100


Frequency
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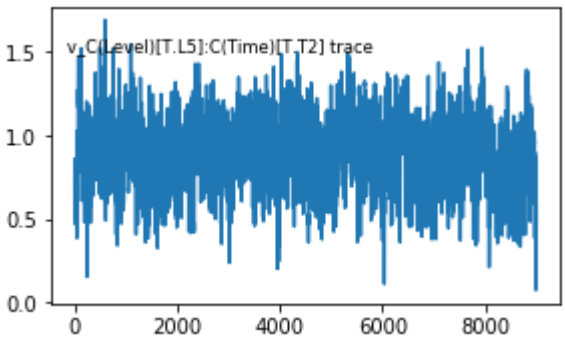
1000
750
500
250
0
0.00
0.25
0.50
0.75
1.00
1.25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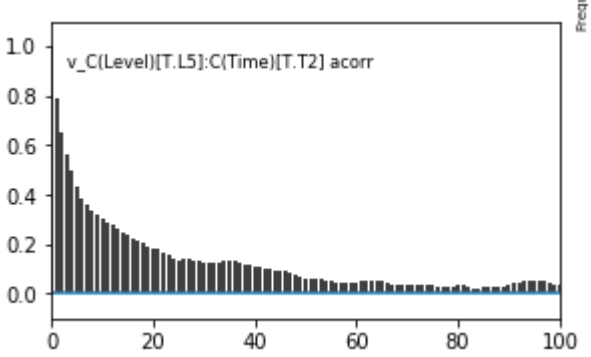
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80
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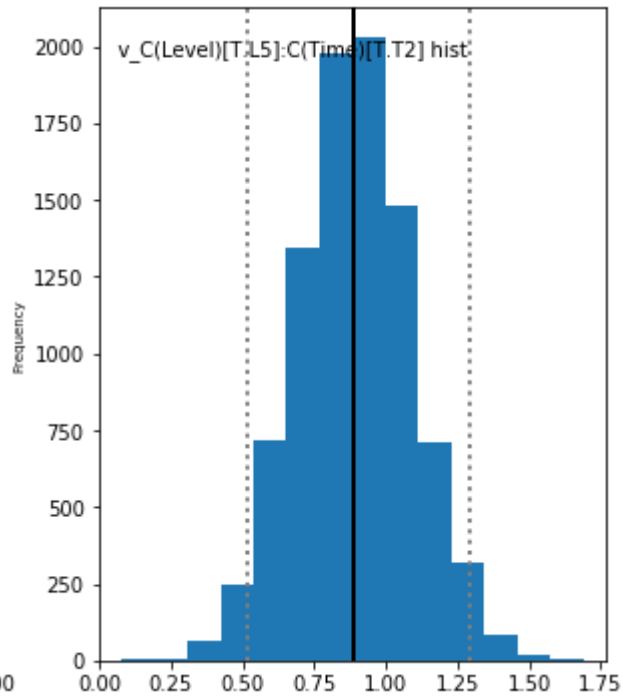
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Frequency
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0.75
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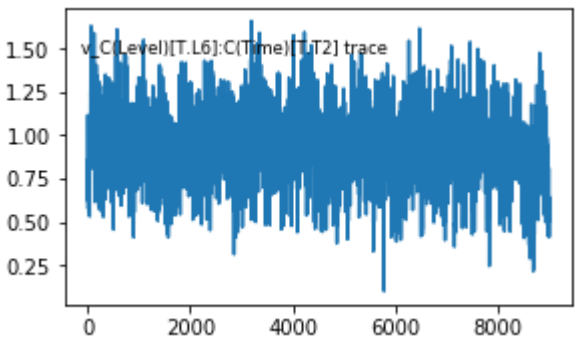
1.75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0.50
0.25
0
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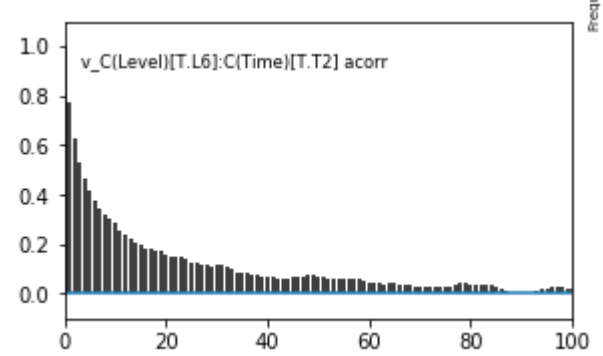
6000
8000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0
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40
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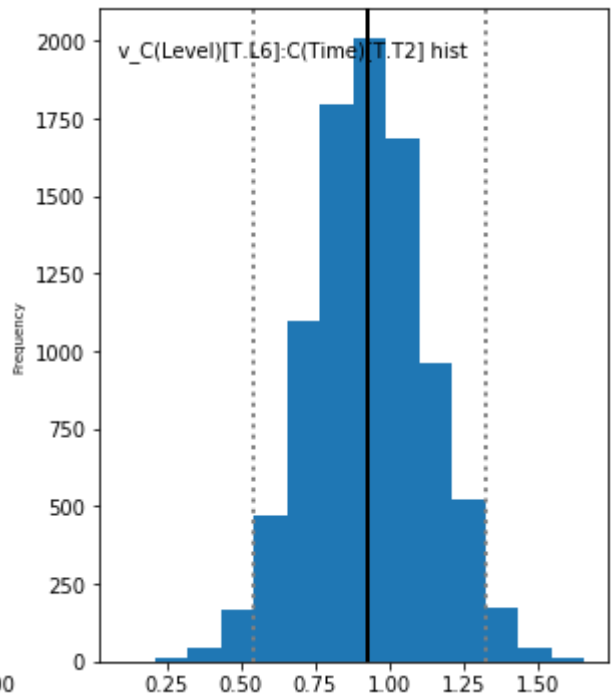
80
100


v_C(Level)[T.L6]:C(Time)[T.T2] hist
Frequency
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1750
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1250
1000
750
500
250
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0.50
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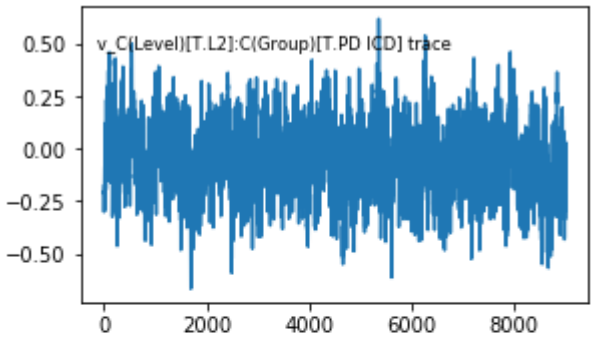
1.00
1.25
1.50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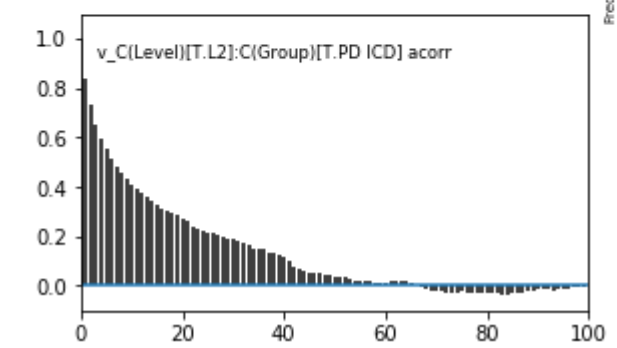
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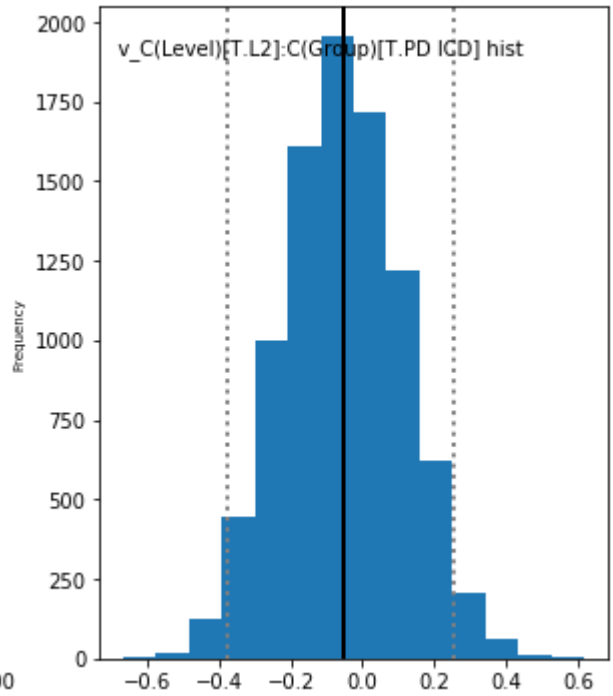
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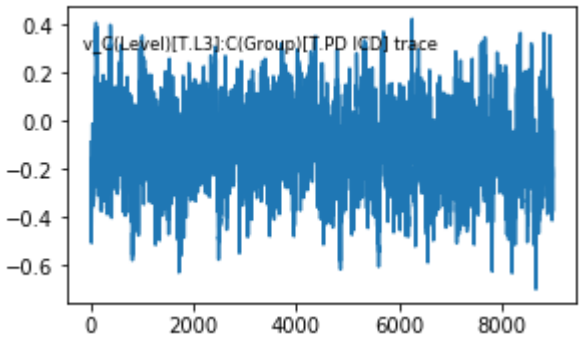
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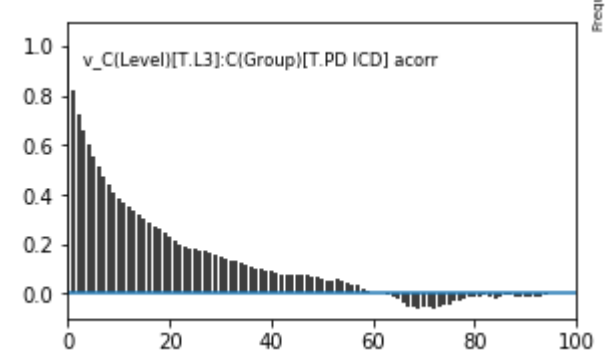
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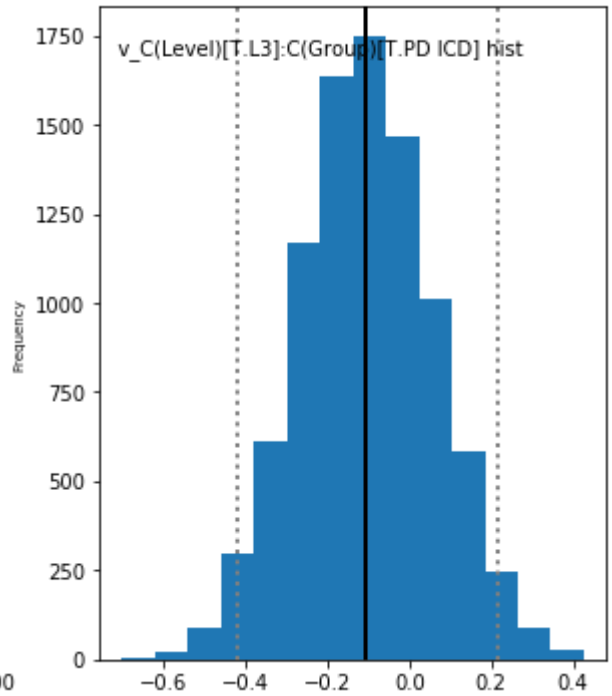
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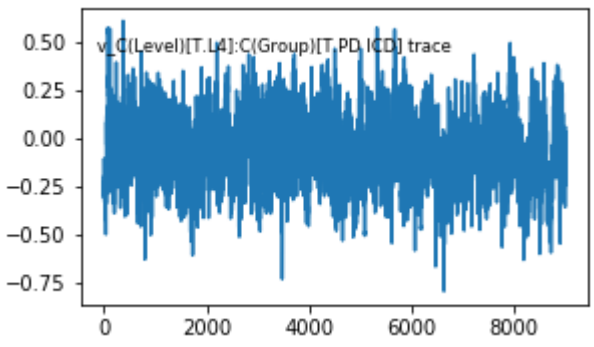
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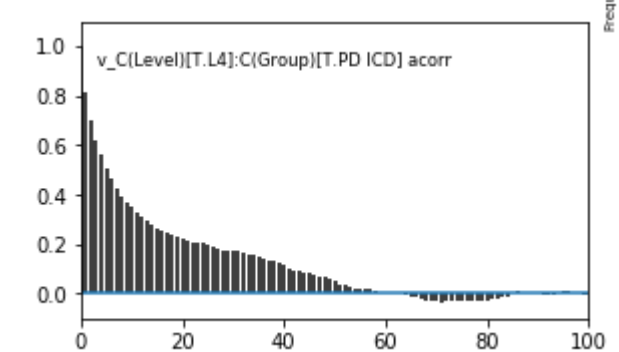
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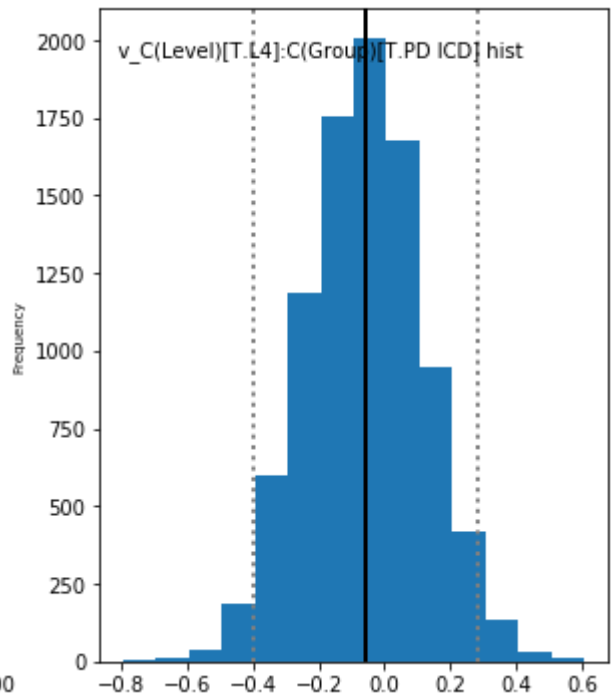
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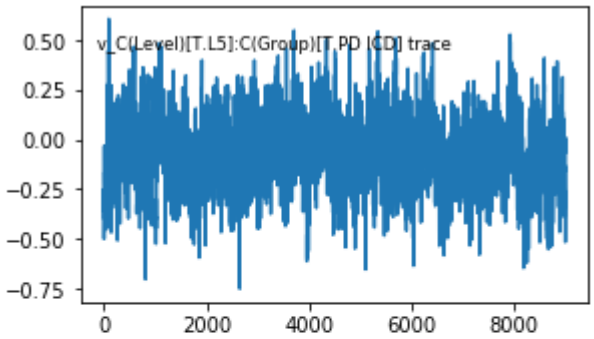
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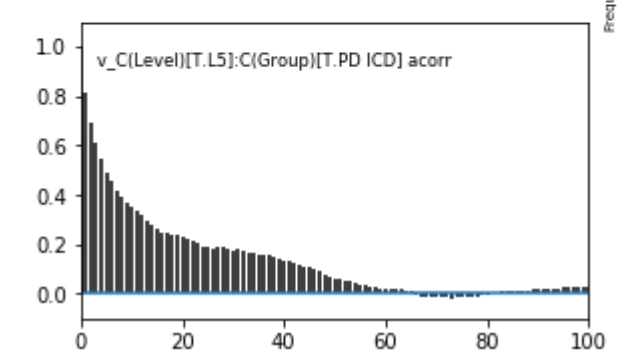
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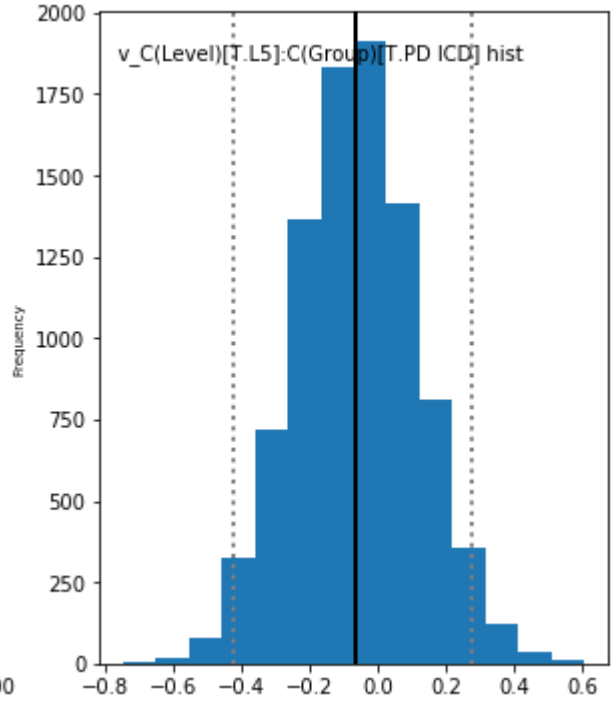
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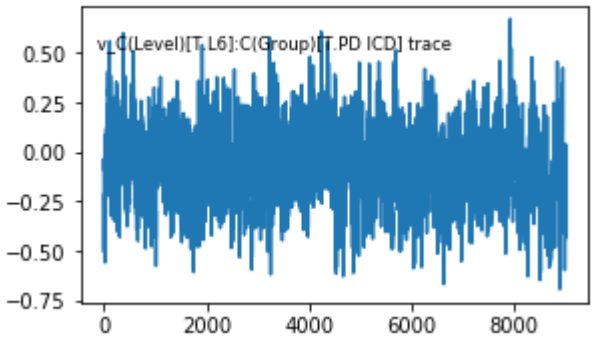
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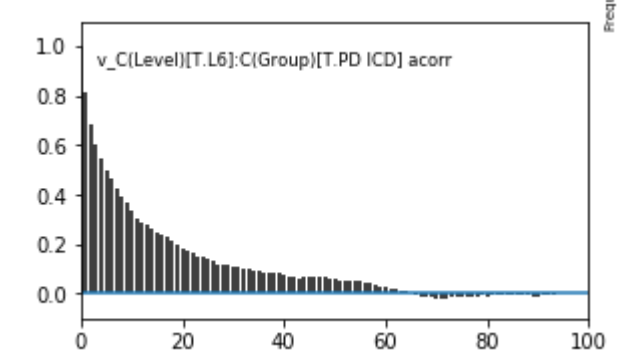
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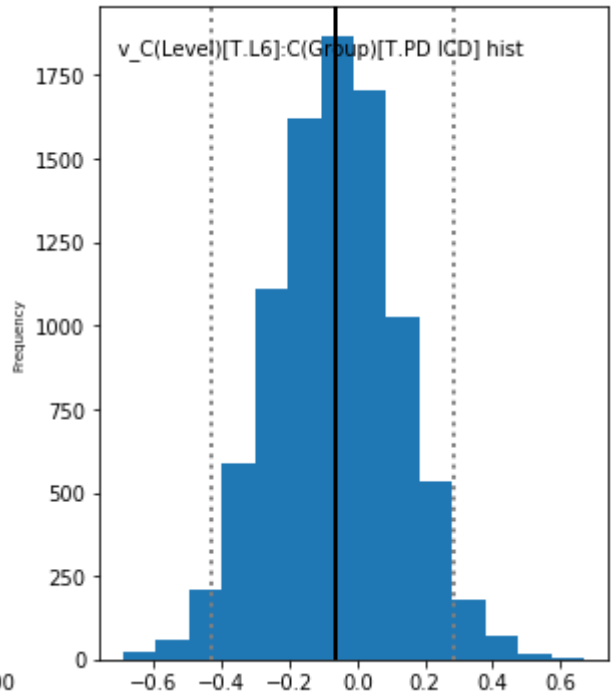
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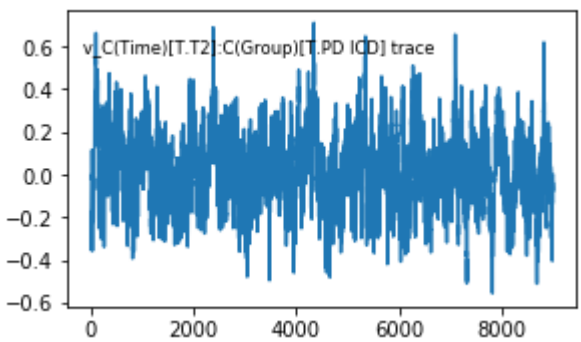
Frequency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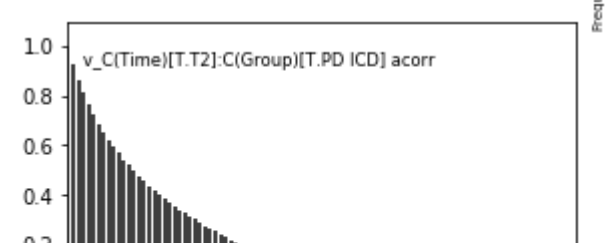
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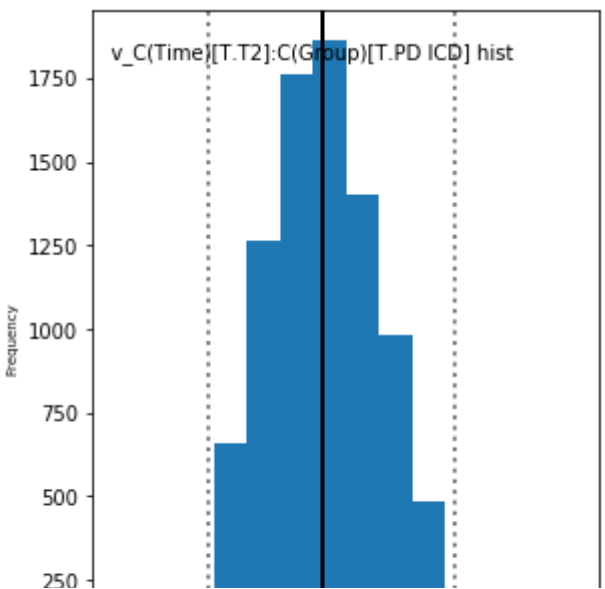
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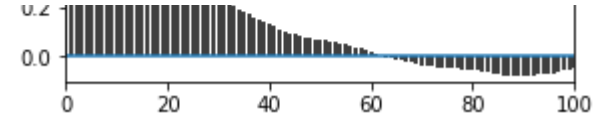

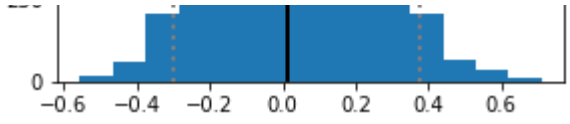

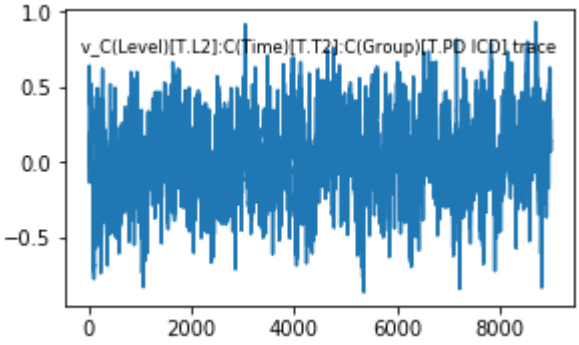
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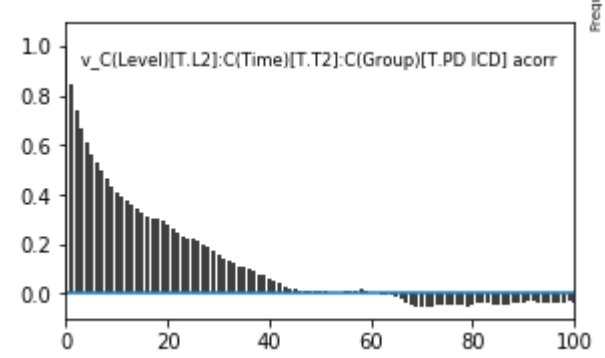
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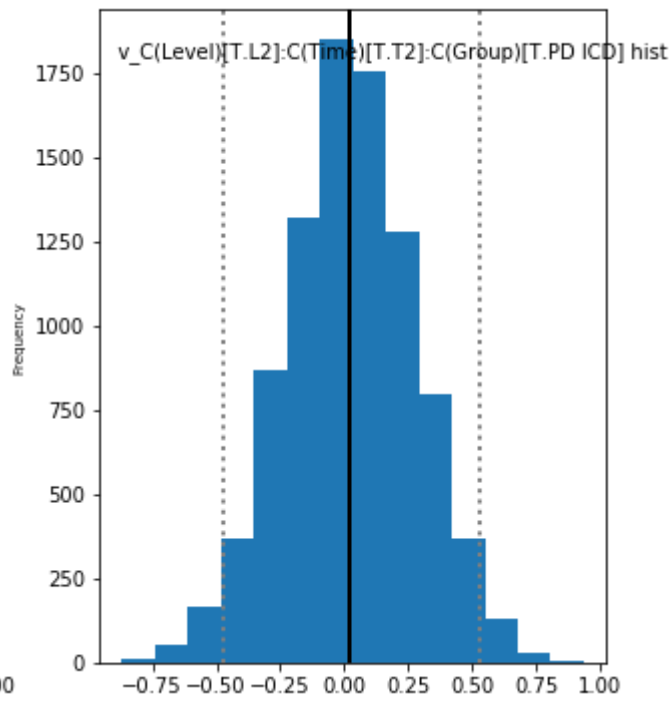
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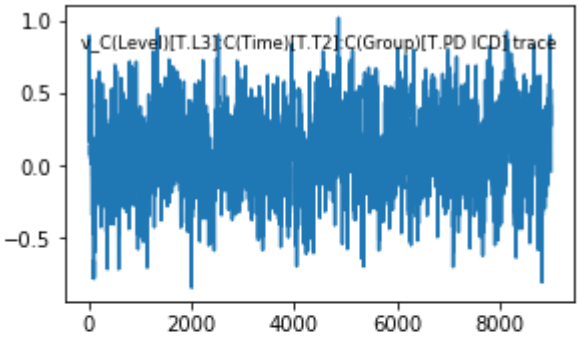
Frequency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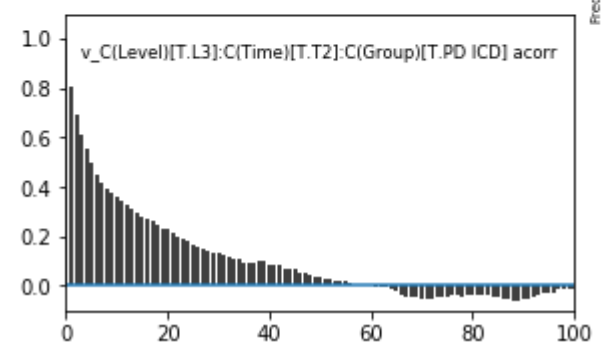
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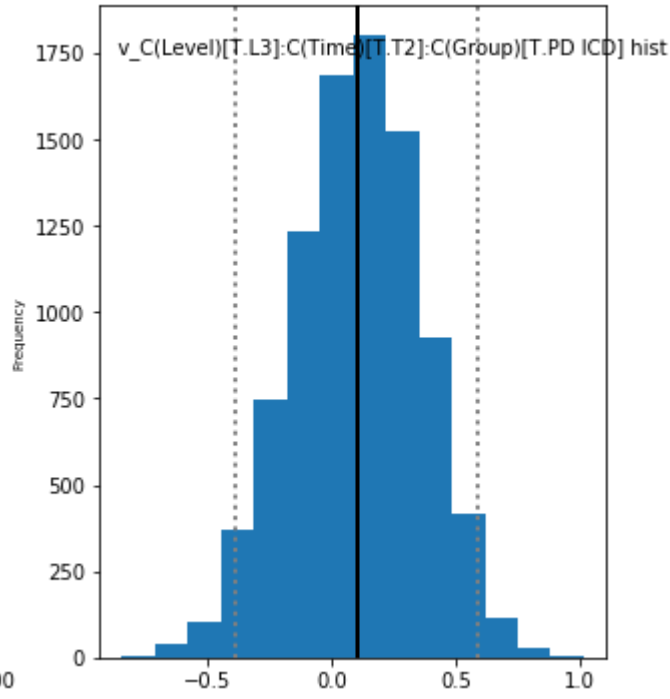
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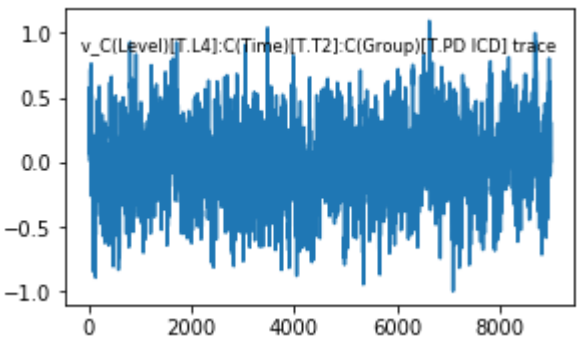
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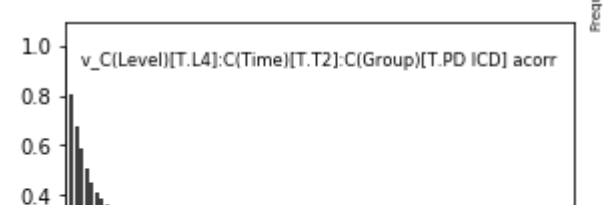
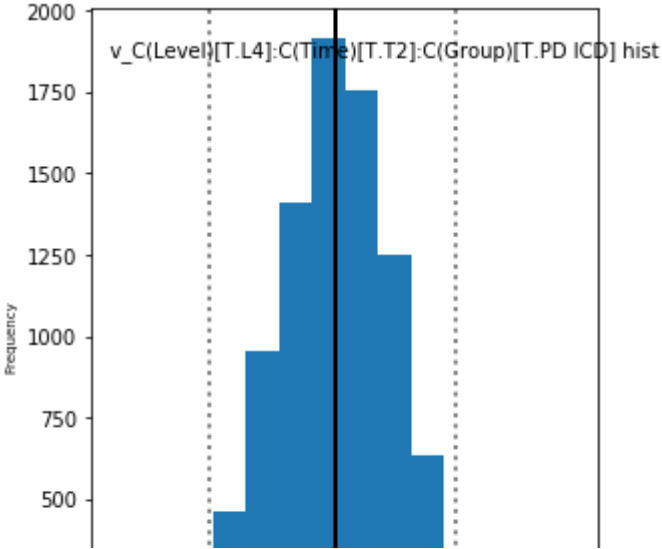
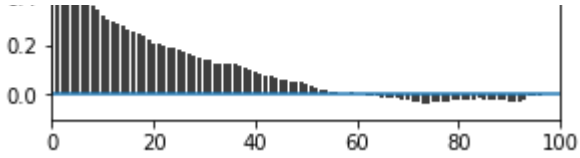
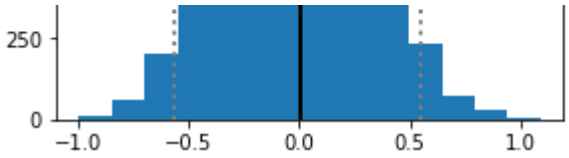
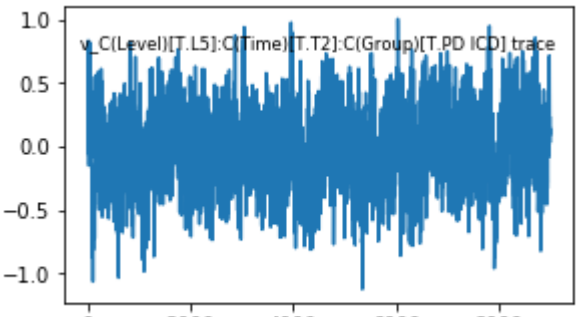
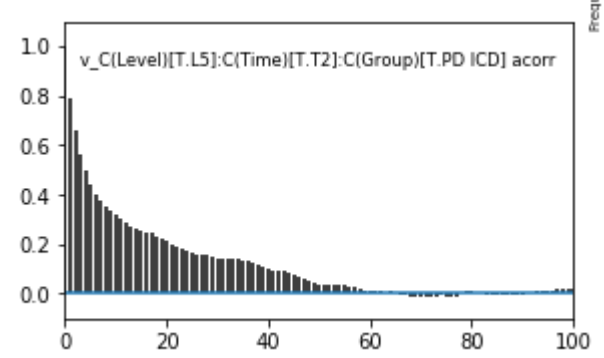

v_C(Level)[T.L4]:C(Time)[T.T2]:C(Group)[T.PD ICD] acorr

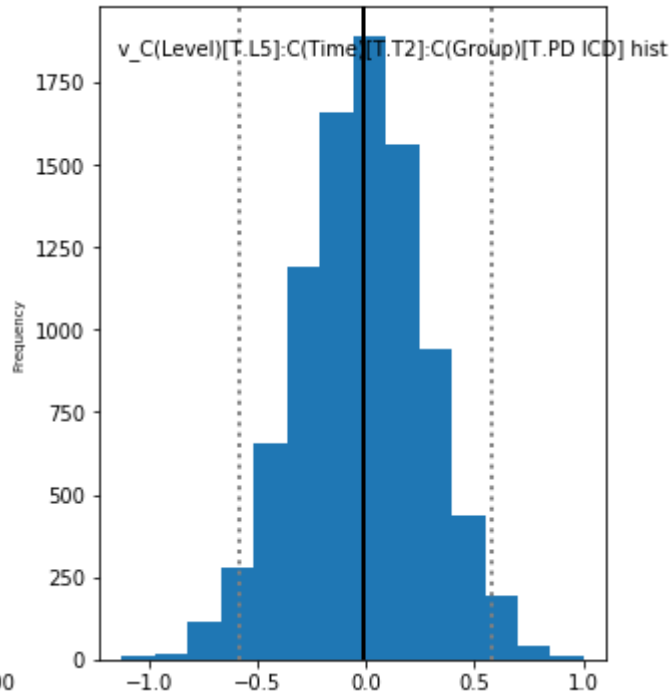

v_C(Level)[T.L4]:C(Time)[T.T2]:C(Group)[T.PD ICD] hist
Frequency

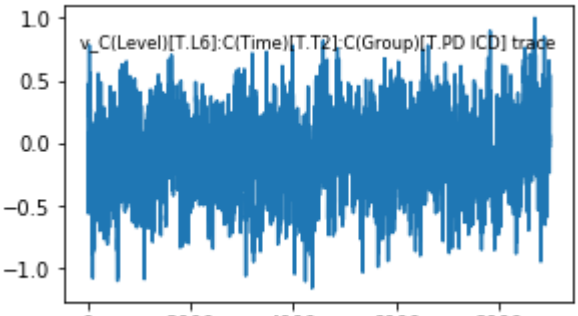


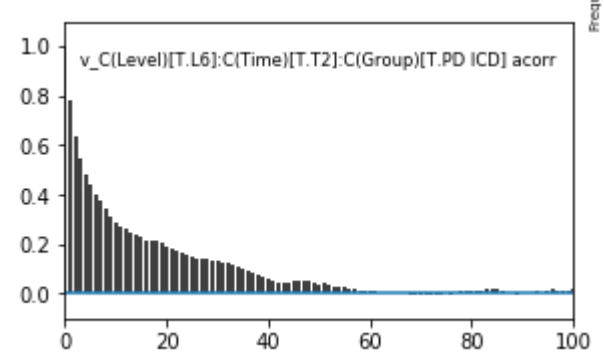


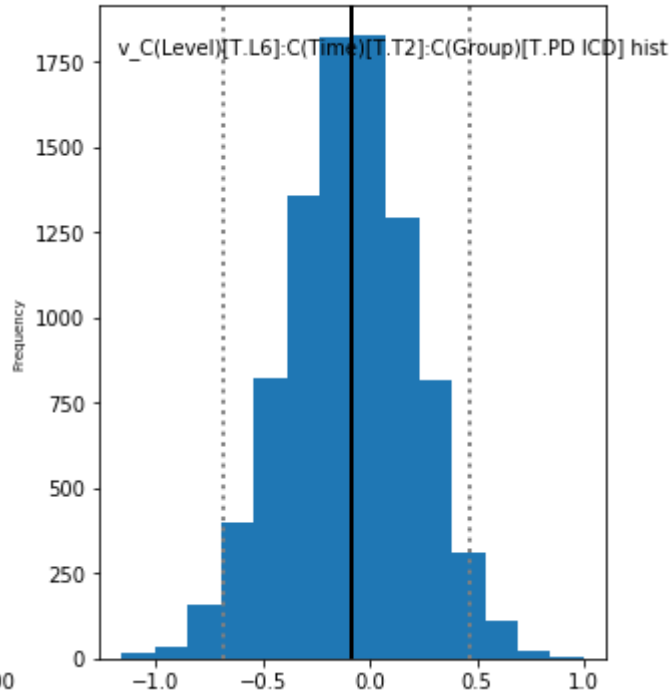

v_C(Level)[T.L5]:C(Time)[T.T2]:C(Group)[T.PD ICD] trace

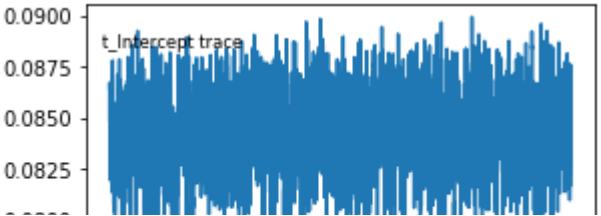

v_C(Level)[T.L5]:C(Time)[T.T2]:C(Group)[T.PD ICD] acorr

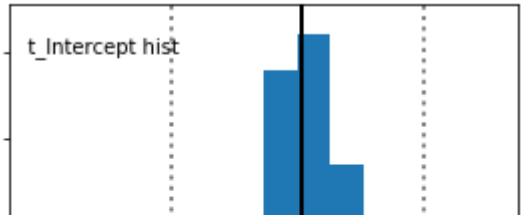

v_C(Level)[T.L5]:C(Time)[T.T2]:C(Group)[T.PD ICD] hist
Frequency

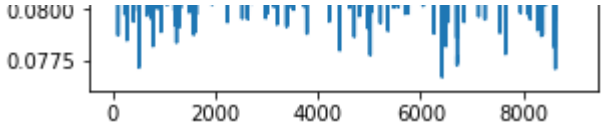

v_C(Level)[T.L6]:C(Time)[T.T2]:C(Group)[T.PD ICD] trace

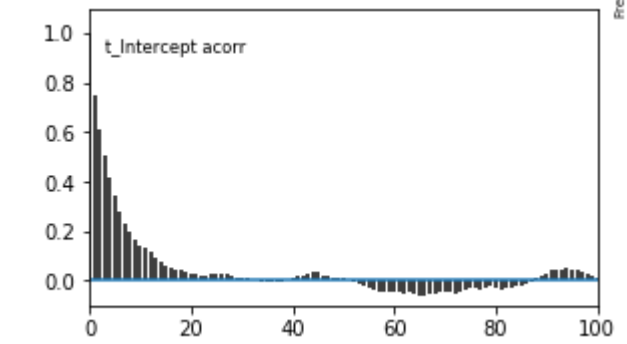

v_C(Level)[T.L6]:C(Time)[T.T2]:C(Group)[T.PD ICD] acorr

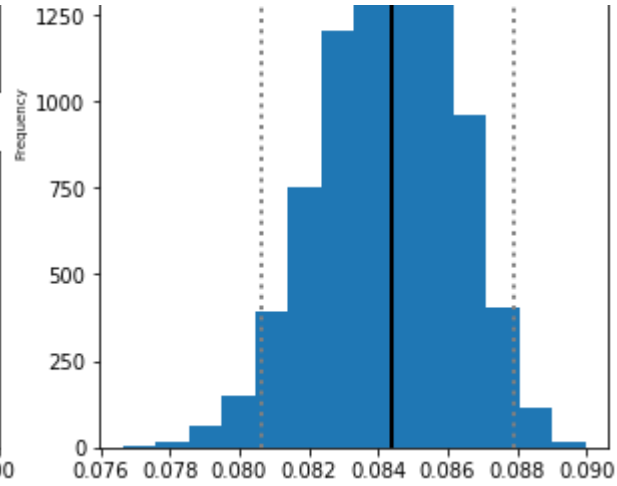

v_C(Level)[T.L6]:C(Time)[T.T2]:C(Group)[T.PD ICD] hist
Frequency

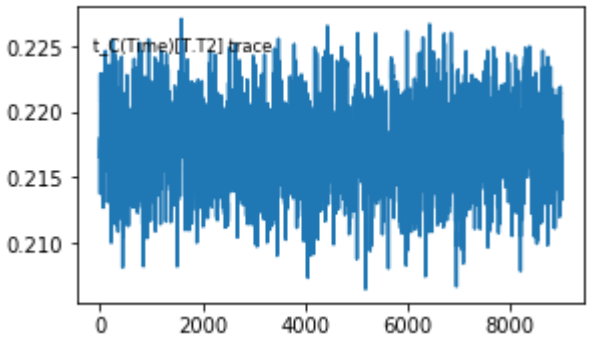

t_Intercept trace

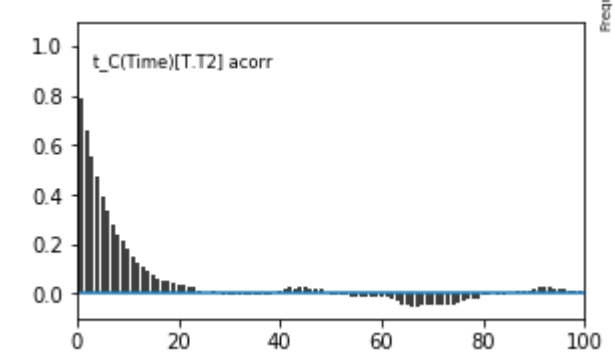

t_Intercept hist

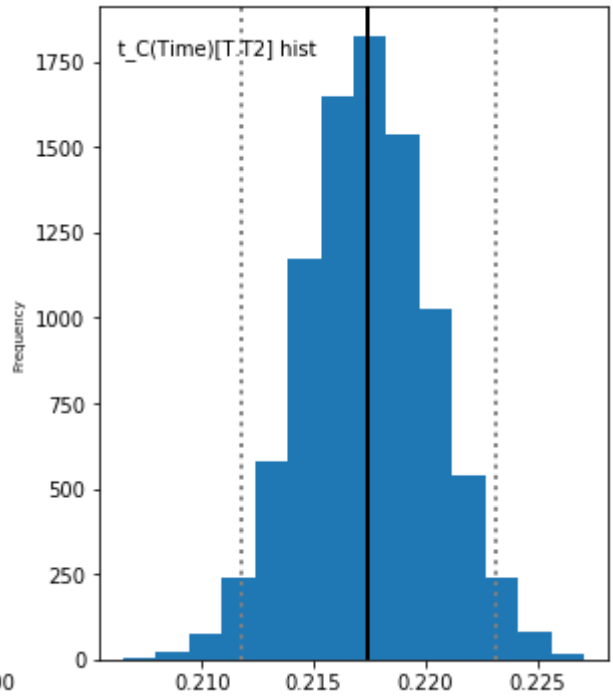

0.0800
0.0775
0
2000
4000
6000
8000

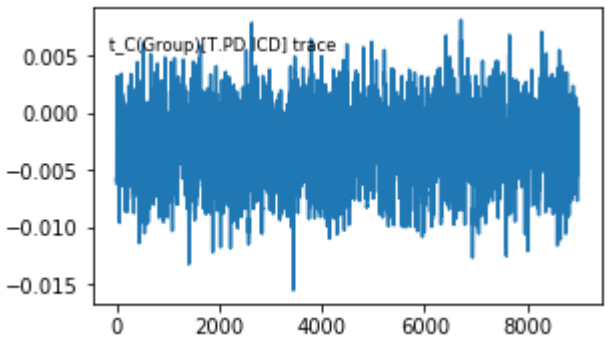

t_Intercept acorr
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100

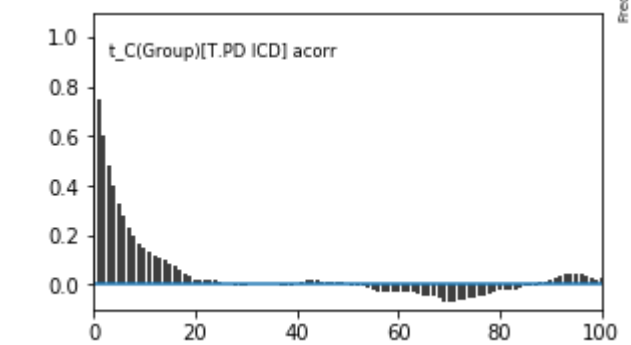

Frequency
1250
1000
750
500
250
0
0.076
0.078
0.080
0.082
0.084
0.086
0.088
0.090

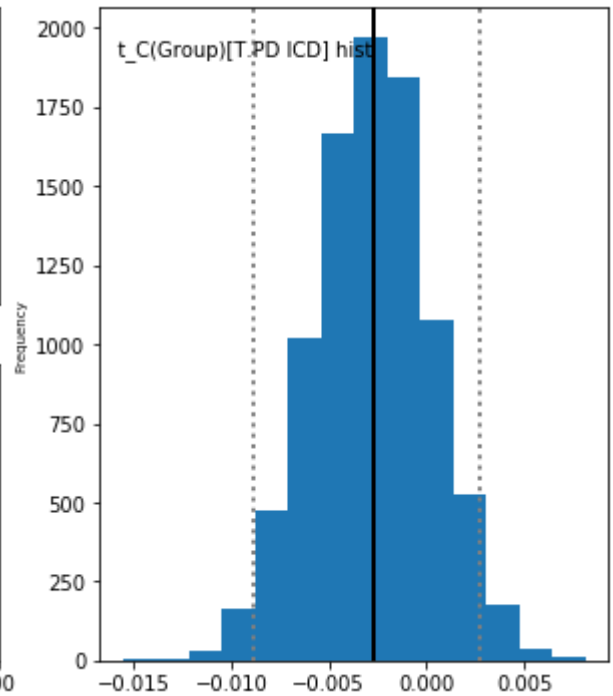

t_C(Time)[T.T2] trace
0.225
0.220
0.215
0.210
0
2000
4000
6000
8000

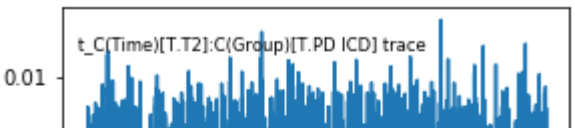

t_C(Time)[T.T2] acorr
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100

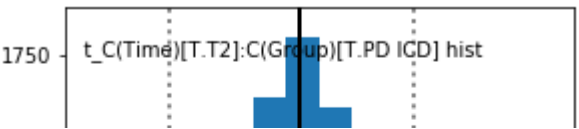

t_C(Time)[T.T2] hist
Frequency
1750
1500
1250
1000
750
500
250
0
0.210
0.215
0.220
0.225

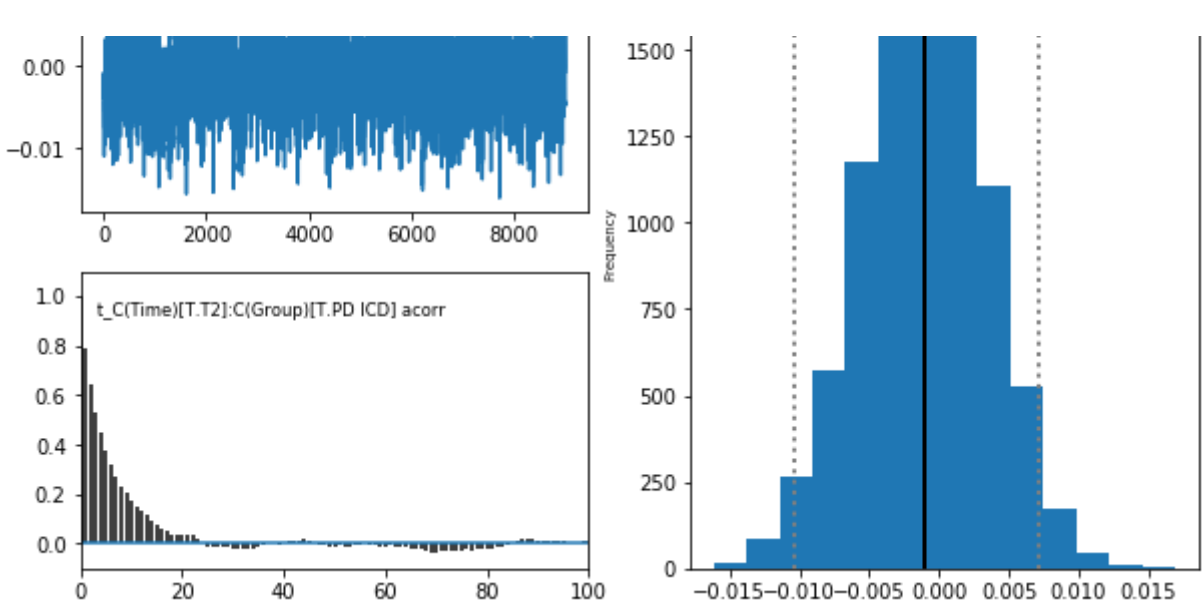

t_C(Group)[T.PD ICD] trace
0.005
0.000
−0.005
−0.010
−0.015
0
2000
4000
6000
8000


t_C(Group)[T.PD ICD] acorr
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100


t_C(Group)[T.PD ICD] hist
Frequency
2000
1750
1500
1250
1000
750
500
250
0
−0.015
−0.010
−0.005
0.000
0.005


t_C(Time)[T.T2]:C(Group)[T.PD ICD] trace
0.01

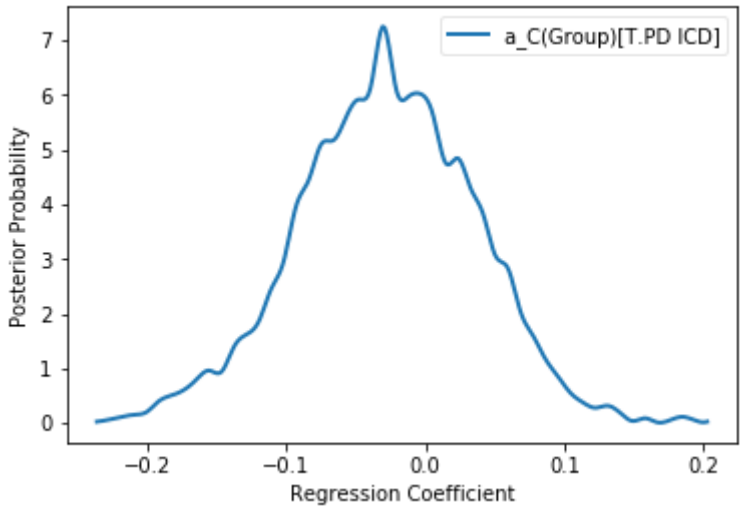

t_C(Time)[T.T2]:C(Group)[T.PD ICD] hist
1750


0.00
−0.01
0
2000
4000
6000
8000
t_C(Time)[T.T2]:C(Group)[T.PD ICD] acorr
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
Frequency
1500
1250
1000
750
500
250
0
−0.015
−0.010
−0.005
0.000
0.005
0.010
0.015

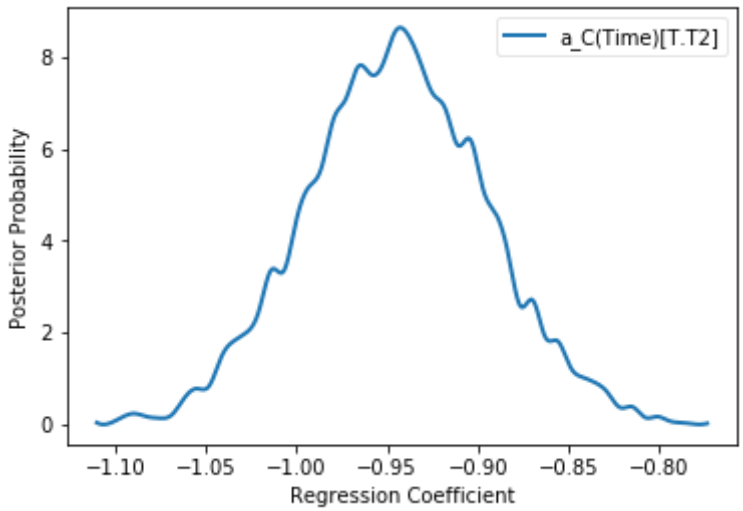
In [9]:
```
#Extract the posterior distribution of decision threshold (a) under the effects
a_Intercept, a_Group, a_Time, a_Group_Time = m_Difficulty.nodes_db.loc[['a_Inter
#Plot the posterior distribution of decision threshold (a) under the influence o
hddm.analyze.plot_posterior_nodes([a_Group])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(a_Group < 0)=", (a_Group.trace() < 0).mean()
#As the figure shown, the regression coefficient overlaps with zero, indicating

#Plot the posterior distribution of decision threshold (a) under the influence o
hddm.analyze.plot_posterior_nodes([a_Time])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(a_Time < 0)=", (a_Time.trace() < 0).mean()
#The regression coefficient is negative with more than 99% of it being begative,

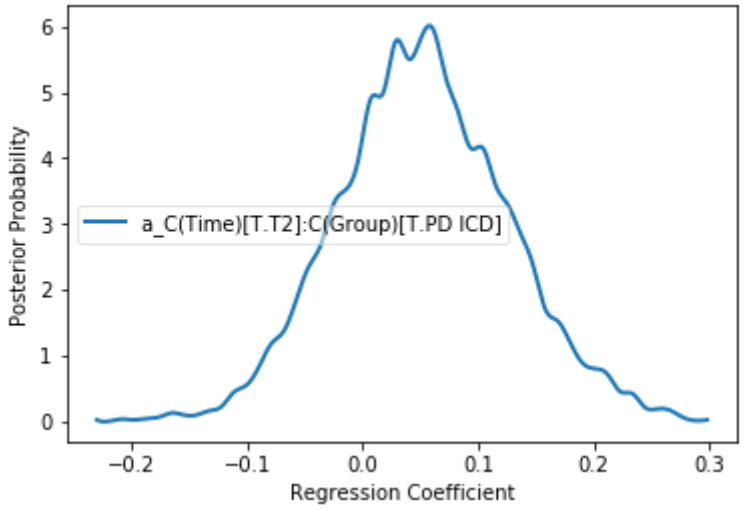
#Plot the posterior distribution of decision threshold (a) under the influence o
hddm.analyze.plot_posterior_nodes([a_Group_Time])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(a_Time_Group < 0)=", (a_Group_Time.trace() < 0).mean()
#The regression coefficient overlaps with zero, showing no effect of the Group*T
```




```
P(a_Group < 0)= 0.670666666667
```




```
P(a_Time < 0)= 1.0
```



P(a_Time_Group < 0)= 0.233

In [22]:

```
#Extract the posterior distribution of each parameter under the effects of diffe
v_Intercept, v_Group, v_Time, v_L2, v_L3, v_L4, v_L5, v_L6 = m_Difficulty.nodes_
#Plot the posterior distribution of drift rate (v) under the influence of the gr
hddm.analyze.plot_posterior_nodes([v_Group])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(v_Group < 0)=", (v_Group.trace() < 0).mean()
# As the figure and the probability shown, the regression coefficient overlaps w

#Plot the posterior distribution of drift rate (v) under the influence of the ti
hddm.analyze.plot_posterior_nodes([v_Time])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(v_Time < 0)=", (v_Time.trace() < 0).mean()
#The regression coefficient was zero with more than 99% of it being negative, in

#Plot the posterior distribution of drift rate (v) under the influence of the Co
hddm.analyze.plot_posterior_nodes([v_L2, v_L3, v_L4, v_L5, v_L6])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(v_L2 < 0)=", (v_L2.trace() < 0).mean()
print "P(v_L3 < 0)=", (v_L3.trace() < 0).mean()
print "P(v_L4 < 0)=", (v_L4.trace() < 0).mean()
print "P(v_L5 < 0)=", (v_L5.trace() < 0).mean()
print "P(v_L6 < 0)=", (v_L6.trace() < 0).mean()
#The regression coefficient of all coherence level is positive and more than 99%

#Extract the posterior distribution of drift rate (v) under the effects of diffe
v_Group_Time, v_Group_L2, v_Group_L3, v_Group_L4, v_Group_L5, v_Group_L6 = m_Dif
#Plot the posterior distribution of drift rate (v) under the influence of the gr
hddm.analyze.plot_posterior_nodes([v_Group_Time])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(v_Time_Group < 0)=", (v_Group_Time.trace() < 0).mean()
#The regression coefficient overlaps with zero, indicating that the Group*Time i

#Plot the posterior distribution of drift rate (v) under the influence of the gr
hddm.analyze.plot_posterior_nodes([v_Group_L2, v_Group_L3, v_Group_L4, v_Group_L
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(v_L2_Group < 0)=", (v_Group_L2.trace() < 0).mean()
print "P(v_L3_Group < 0)=", (v_Group_L3.trace() < 0).mean()
print "P(v_L4_Group < 0)=", (v_Group_L4.trace() < 0).mean()
print "P(v_L5_Group < 0)=", (v_Group_L5.trace() < 0).mean()
print "P(v_L6_Group < 0)=", (v_Group_L6.trace() < 0).mean()
#The regression coefficient overlaps with zero, indicating that the Group*Cohere


#Extract the posterior distribution of drift rate (v) under the effects of diffe
v_Time_L2, v_Time_L3, v_Time_L4, v_Time_L5, v_Time_L6 = m_Difficulty.nodes_db.lo
#Plot the posterior distribution of drift rate (v) under the influence of the ti
hddm.analyze.plot_posterior_nodes([v_Time_L2, v_Time_L3, v_Time_L4, v_Time_L5, v
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(v_L2_Time < 0)=", (v_Time_L2.trace() < 0).mean()
print "P(v_L3_Time < 0)=", (v_Time_L3.trace() < 0).mean()
print "P(v_L4_Time < 0)=", (v_Time_L4.trace() < 0).mean()
print "P(v_L5_Time < 0)=", (v_Time_L5.trace() < 0).mean()
```

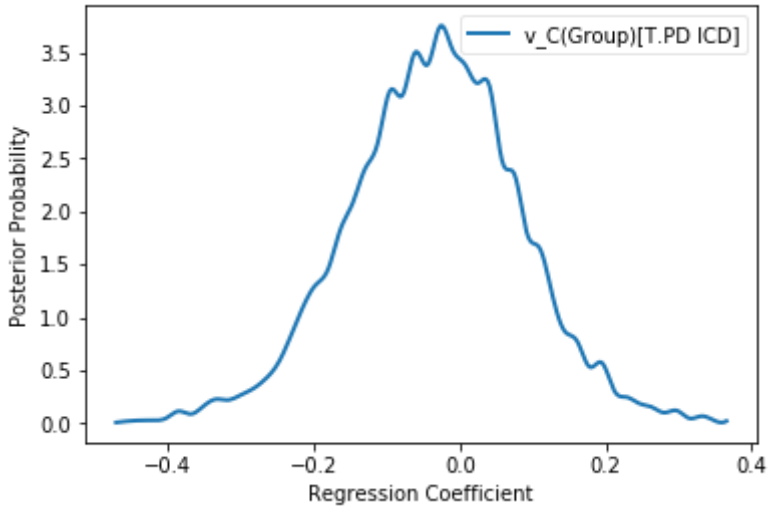
```
print "P(v_L6_Time < 0)=", (v_Time_L6.trace() < 0).mean()
#As the figure and the probability shown, as the Coherence level increases, the



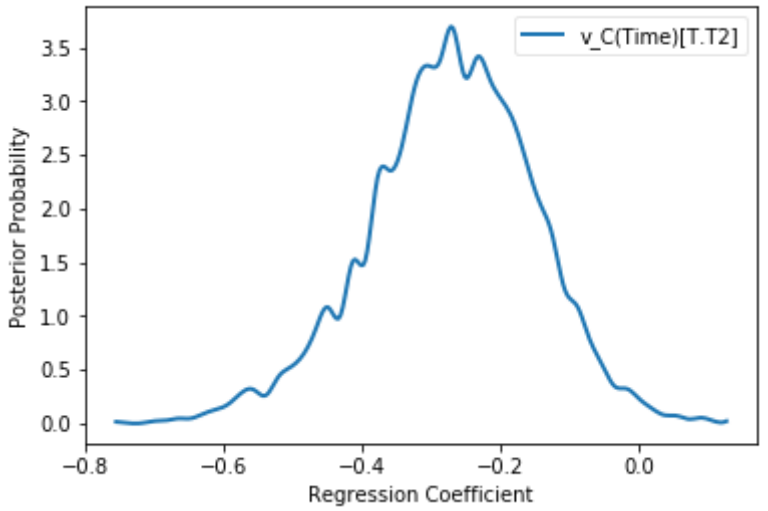
#Extract the posterior distribution of drift rate (v) under the effects of diffe
v_Group_Time_L2, v_Group_Time_L3, v_Group_Time_L4, v_Group_Time_L5, v_Group_Time_
#Plot the posterior distribution of drift rate (v) under the influence of the gr
hddm.analyze.plot_posterior_nodes([v_Group_Time_L2, v_Group_Time_L3, v_Group_Tim
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(v_L2_Time_Group < 0)=", (v_Group_Time_L2.trace() < 0).mean()
print "P(v_L3_Time_Group < 0)=", (v_Group_Time_L3.trace() < 0).mean()
print "P(v_L4_Time_Group < 0)=", (v_Group_Time_L4.trace() < 0).mean()
print "P(v_L5_Time_Group < 0)=", (v_Group_Time_L5.trace() < 0).mean()
print "P(v_L6_Time_Group < 0)=", (v_Group_Time_L6.trace() < 0).mean()
#The regression coefficient overlaps with zero, indicating that the Group*Time*C
```

```
<matplotlib.figure.Figure at 0x1282a3c10>
```

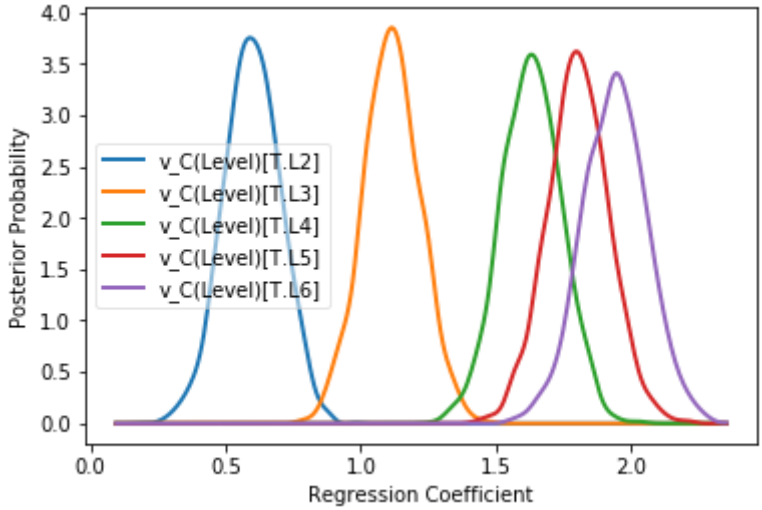
```
<matplotlib.figure.Figure at 0x128a3da50>
```



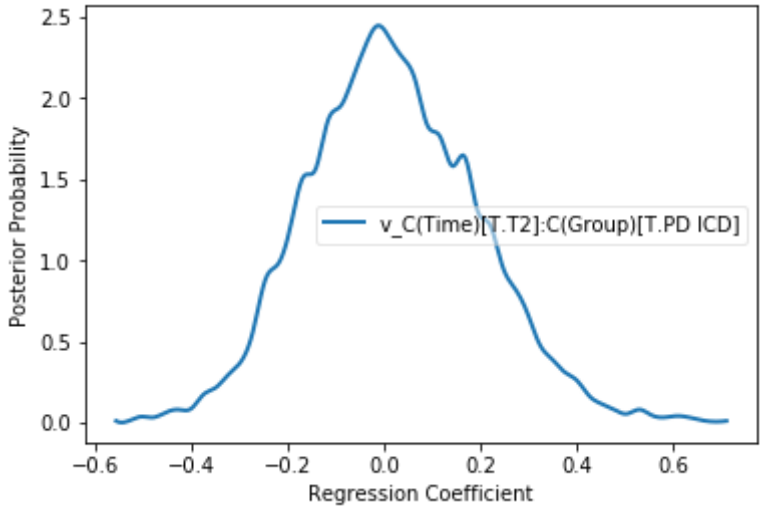

```
P(v_Group < 0)= 0.619666666667
```



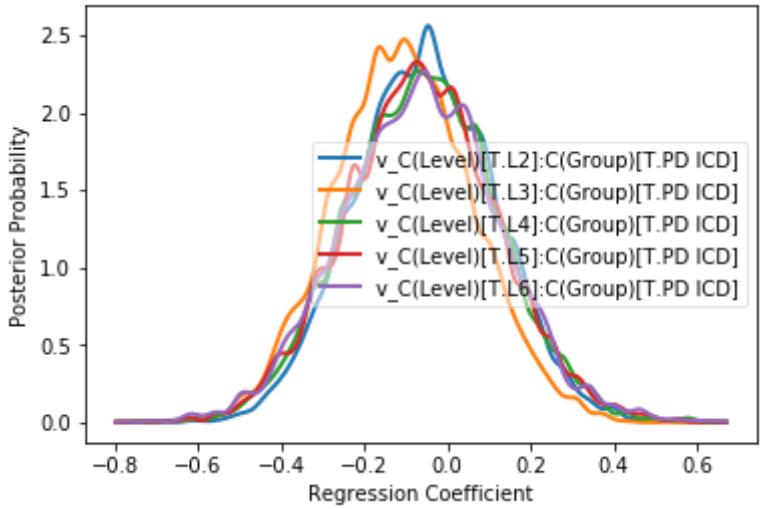

```
P(v_Time < 0)= 0.992444444444
```



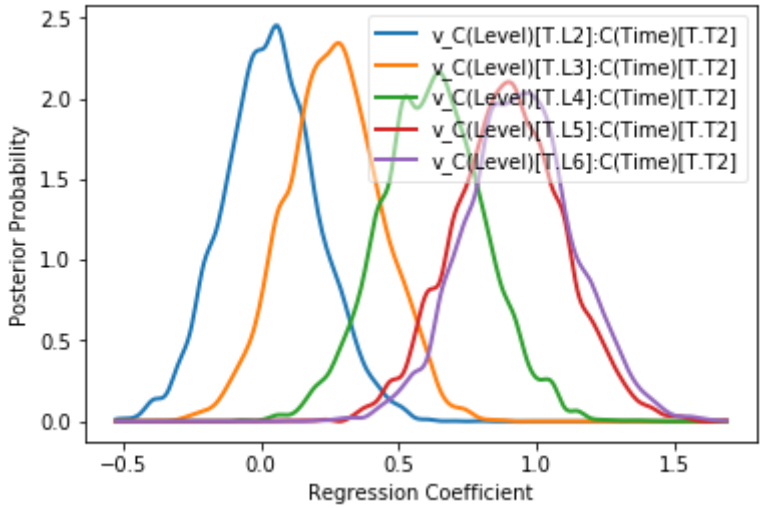

```
P(v_L2 < 0)= 0.0
P(v_L3 < 0)= 0.0
P(v_L4 < 0)= 0.0
P(v_L5 < 0)= 0.0
P(v_L6 < 0)= 0.0
```



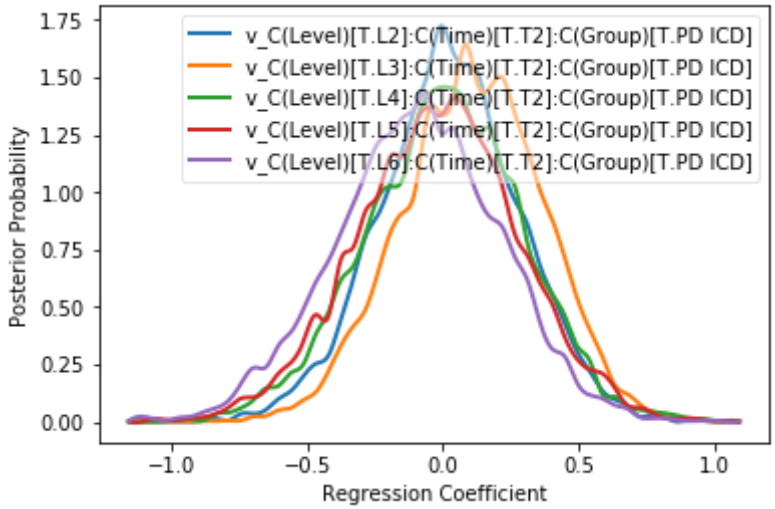

```
P(v_Time_Group < 0)= 0.473222222222
```




```
P(v_L2_Group < 0)= 0.631444444444
P(v_L3_Group < 0)= 0.742111111111
P(v_L4_Group < 0)= 0.629666666667
P(v_L5_Group < 0)= 0.638555555556
P(v_L6_Group < 0)= 0.631666666667
```




```
P(v_L2_Time < 0)= 0.392111111111
P(v_L3_Time < 0)= 0.0556666666667
P(v_L4_Time < 0)= 0.000333333333333
P(v_L5_Time < 0)= 0.0
P(v_L6_Time < 0)= 0.0
```

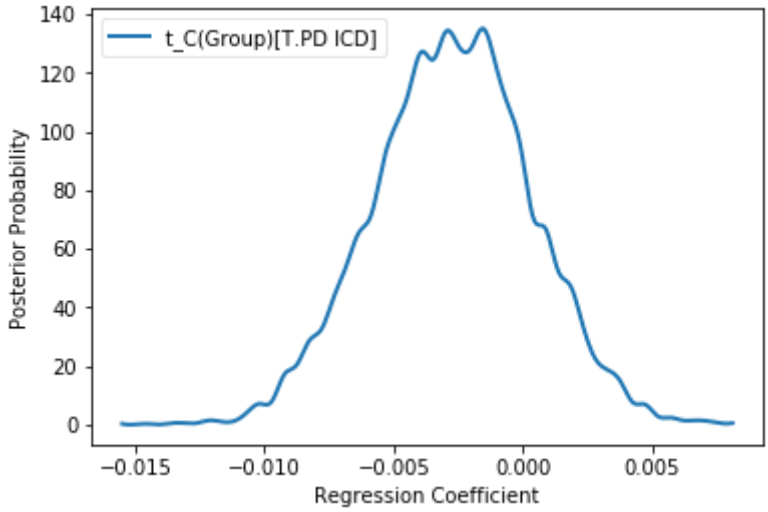



```
P(v_L2_Time_Group < 0)= 0.460444444444
P(v_L3_Time_Group < 0)= 0.340666666667
P(v_L4_Time_Group < 0)= 0.485111111111
P(v_L5_Time_Group < 0)= 0.520777777778
P(v_L6_Time_Group < 0)= 0.62
```

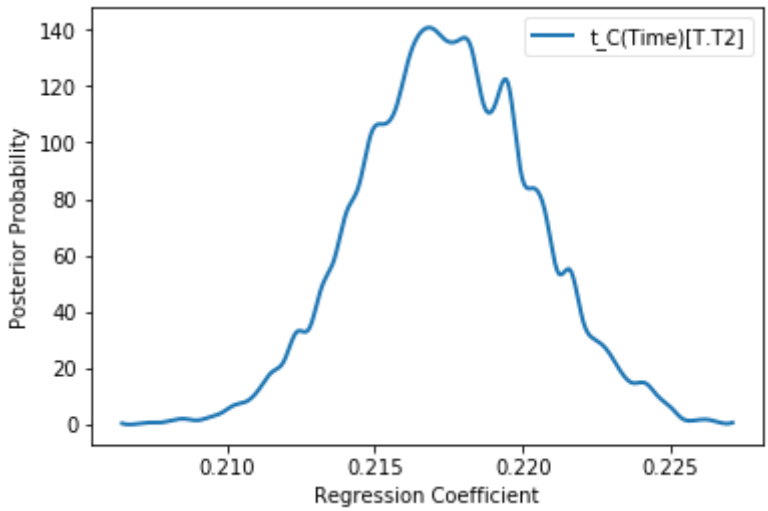
In [23]:
```
#Extract the posterior distribution of non-decision time (t) under the effects o
t_Intercpet, t_Group, t_Time, t_Group_Time = m_Difficulty.nodes_db.loc[['t_Inter
#Plot the posterior distribution of non-decision time (t) under the influence of
hddm.analyze.plot_posterior_nodes([t_Group])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(t_Group < 0)=", (t_Group.trace() < 0).mean()
#The regression coefficient overlaps with zero, indicating that the Group*Time*C

#Plot the posterior distribution of non-decision time (t) under the influence of
hddm.analyze.plot_posterior_nodes([t_Time])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(t_Time < 0)=", (t_Time.trace() < 0).mean()
#The regression coefficient is positive with more than 99% of it being larger th

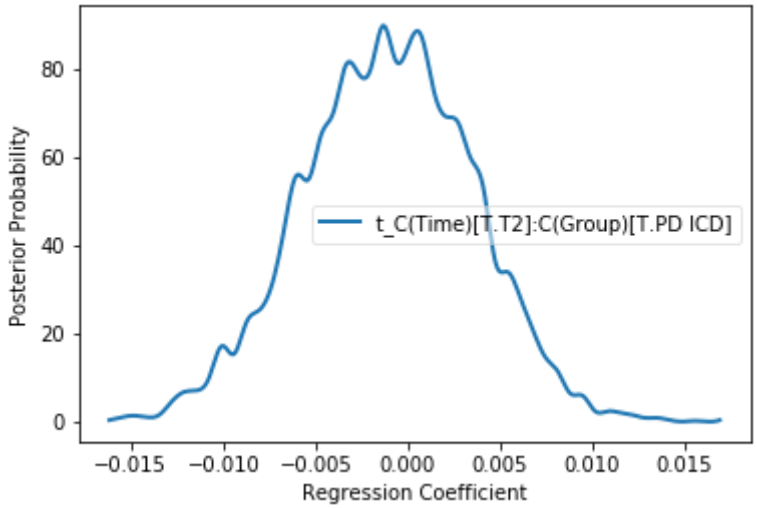
#Plot the posterior distribution of non-decision time (t) under the influence of
hddm.analyze.plot_posterior_nodes([t_Group_Time])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(t_Time_Group < 0)=", (t_Group_Time.trace() < 0).mean()
#The regression coefficient overlaps with zero, indicating that the Group*Time i
```




```
P(t_Group < 0)= 0.828111111111
```




```
P(t_Time < 0)= 0.0
```




```
P(t_Time_Group < 0)= 0.582777777778
```

In [ ]:

Appendix - Programming codes for Chapter 3

In [149]:
```
import pandas as pd
import scipy
import matplotlib.pyplot as plt
import numpy as np
import sklearn
from pandas.tools.plotting import scatter_matrix
from sklearn import model_selection
from sklearn.metrics import classification_report
from sklearn.metrics import confusion_matrix
from sklearn.metrics import accuracy_score
from sklearn.linear_model import LogisticRegression
from sklearn.tree import DecisionTreeClassifier
from sklearn.neighbors import KNeighborsClassifier
from sklearn.discriminant_analysis import LinearDiscriminantAnalysis
from sklearn.naive_bayes import GaussianNB
from sklearn.svm import SVC
```

In [150]:
```
#Create predictive model with RTs of incorrect trials under Accuracy i
#Input variables: age (when being assessed), onset age, LEDD, RTs of i
path = "/Users/yu-tinghuang/Documents/ML_Data/ML_AC_OFF.csv"
names = ['Age', 'Age of PD onset', 'LEDD', 'RT' ,'class']
dataset = pd.read_csv(path, names=names)

y = dataset.iloc[0:128, 4].values
y = np.where(y== 'PD-ICD', -1, 1)
X = dataset.iloc[0:185, [2, 3]].values
plt.scatter(X[:128,0], X[:128, 1], color='blue', marker='x', label='PD
plt.scatter(X[128:185,0], X[128:185, 1], color='red', marker='o', label
plt.xlabel('LEDD')
plt.ylabel('RT')
plt.legend(loc='upper left')
plt.show()
y = dataset.iloc[0:128, 4].values
y = np.where(y== 'PD-ICD', -1, 1)
X = dataset.iloc[0:185, [1, 3]].values
plt.scatter(X[:128,0], X[:128, 1], color='blue', marker='x', label='PD
plt.scatter(X[128:185,0], X[128:185, 1], color='red', marker='o', label
plt.xlabel('Age of PD onset')
plt.ylabel('RT')
plt.legend(loc='upper left')
plt.show()
y = dataset.iloc[0:128, 4].values
y = np.where(y== 'PD+ICD', -1, 1)
X = dataset.iloc[0:185, [1, 3]].values
plt.scatter(X[:128,0], X[:128, 1], color='blue', marker='x', label='PD
plt.scatter(X[128:185,0], X[128:185, 1], color='red', marker='o', label
plt.xlabel('Age')
plt.ylabel('RT')
plt.legend(loc='upper left')
plt.show()

#box and whisker plots
```

```
#box and whisker plots
dataset.plot(kind='box', subplots=True, layout=(2,2), sharex=False, sha
plt.show()

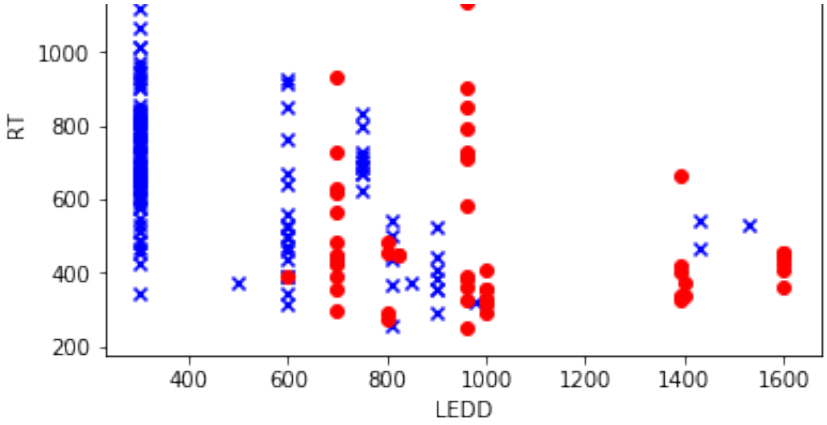
#scatter plot matrix
scatter_matrix(dataset)
plt.show()

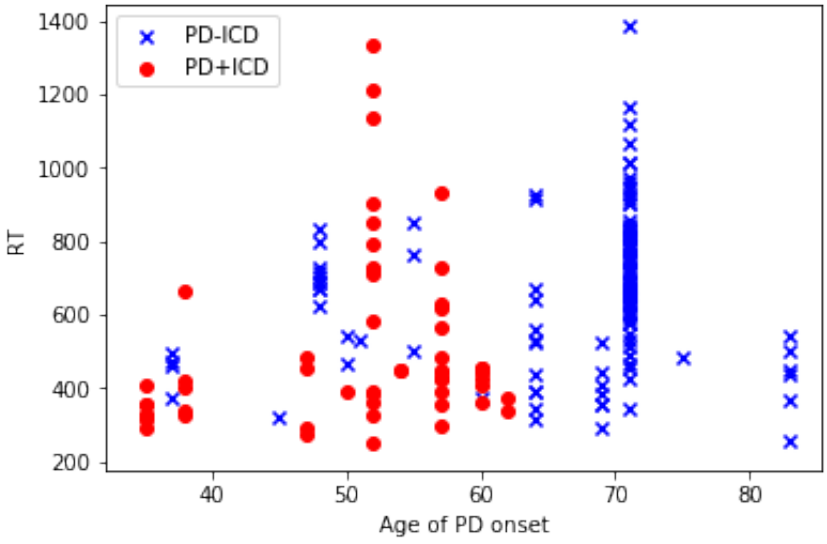
#Split-out validation dataset
array = dataset.values
X = array[:,0:4]
Y = array[:,4]
validation_size = 0.20
seed = 7
X_train, X_validation, Y_train, Y_validation = model_selection.train_t

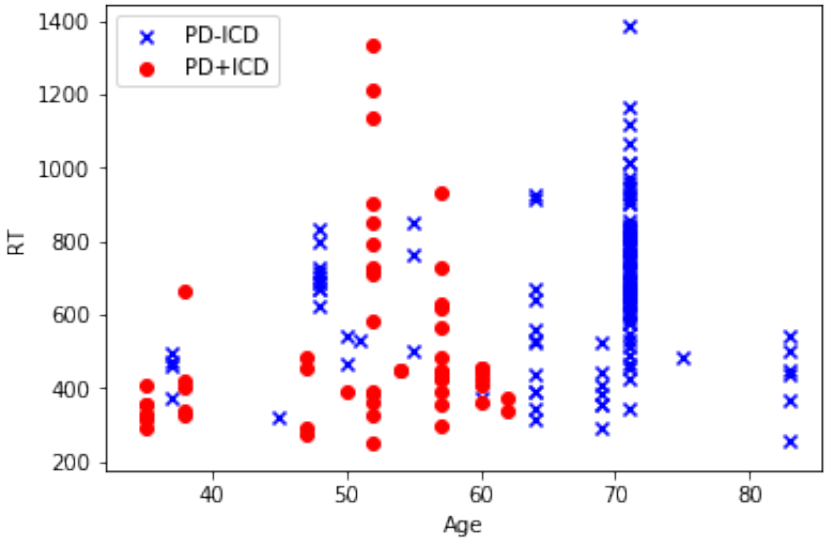
# Spot Check Algorithms
models = []
models.append(('LR', LogisticRegression()))
models.append(('LDA', LinearDiscriminantAnalysis()))
models.append(('KNN', KNeighborsClassifier()))
models.append(('CART', DecisionTreeClassifier()))
models.append(('NB', GaussianNB()))
models.append(('SVM', SVC()))
# evaluate each model in turn
results = []
names = []
for name, model in models:
    kfold = model_selection.KFold(n_splits=10, random_state=seed)
    cv_results = model_selection.cross_val_score(model, X_train, Y_tra
    results.append(cv_results)
    names.append(name)
    msg = "%s: %f (%f)" % (name, cv_results.mean(), cv_results.std())
    print(msg)

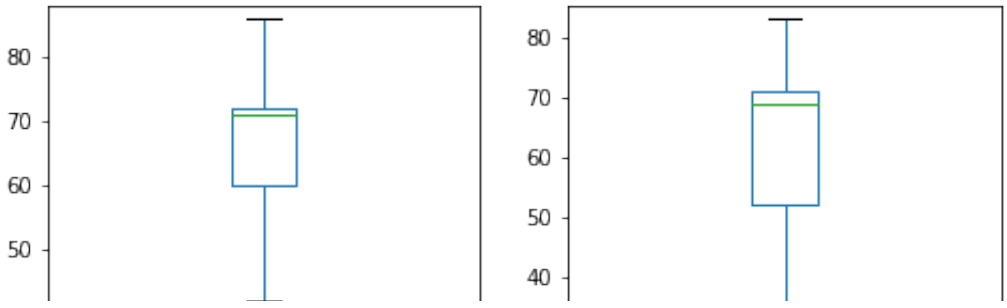
#Compare Algorithms
fig = plt.figure()
fig.suptitle('Algorithm Comparison')
ax = fig.add_subplot(111)
plt.boxplot(results)
ax.set_xticklabels(names)
plt.show()

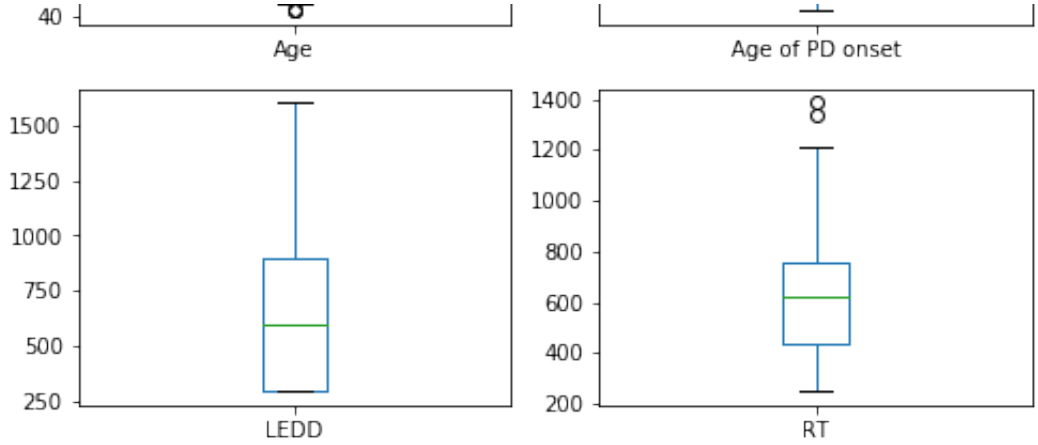
# Make predictions on validation dataset
cart = DecisionTreeClassifier()
cart.fit(X_train, Y_train)
predictions = cart.predict(X_validation)
print(accuracy_score(Y_validation, predictions))
print(confusion_matrix(Y_validation, predictions))
print(classification_report(Y_validation, predictions))
```


RT
LEDD
1000
800
600
400
200
400
600
800
1000
1200
1400
1600

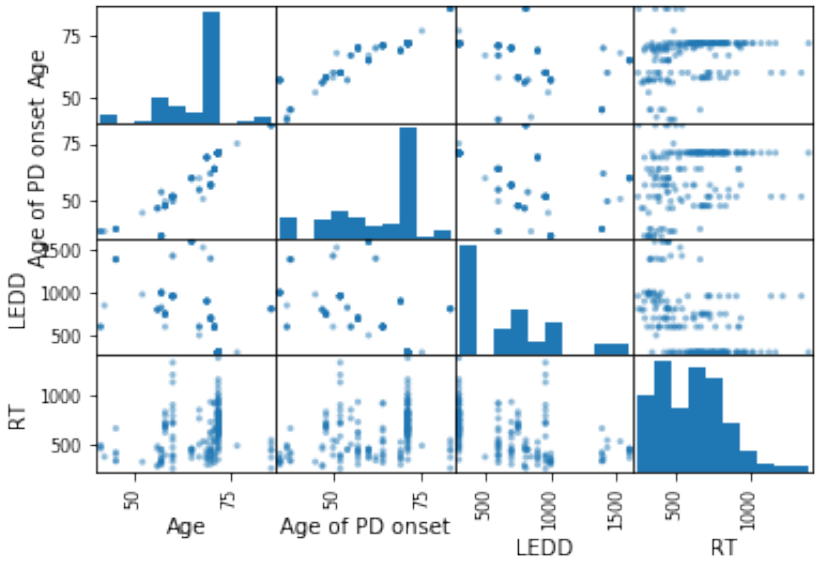

PD-ICD
PD+ICD
RT
Age of PD onset
1400
1200
1000
800
600
400
200
40
50
60
70
80


PD-ICD
PD+ICD
RT
Age
1400
1200
1000
800
600
400
200
40
50
60
70
80

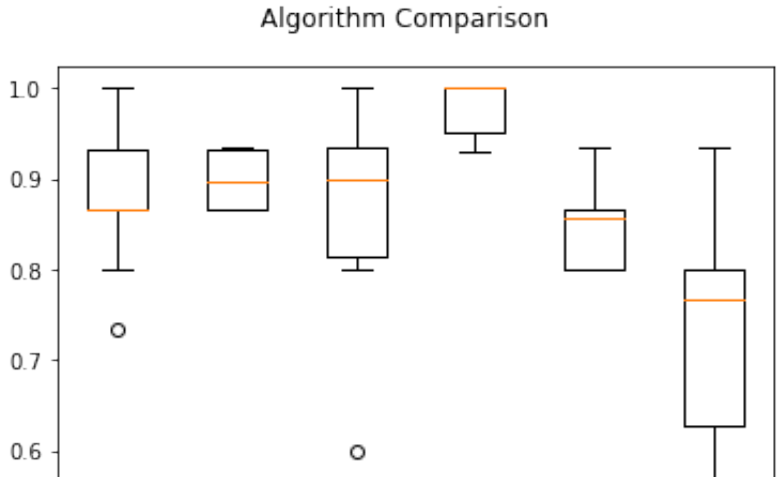

80
70
60
50
80
70
60
50
40

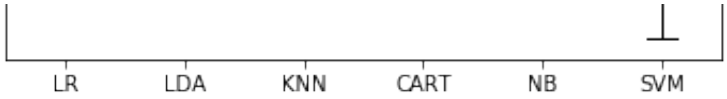



```
/anaconda3/lib/python3.6/site-packages/ipykernel_launcher.py:40: Fut
ureWarning: 'pandas.tools.plotting.scatter_matrix' is deprecated, im
port 'pandas.plotting.scatter_matrix' instead.
```




```
LR: 0.886190 (0.078894)
LDA: 0.899048 (0.032423)
KNN: 0.865714 (0.107535)
CART: 0.979524 (0.031302)
NB: 0.844762 (0.041959)
SVM: 0.737143 (0.120181)
```






```
0.9459459459459459
[[12  2]
 [ 0 23]]
             precision    recall  f1-score   support

     PD+ICD       1.00      0.86      0.92        14
     PD-ICD       0.92      1.00      0.96        23

avg / total       0.95      0.95      0.94        37
```

In [151]:

```
#Create predictive model with RTs of incorrect trials under Accuracy i
#Input variables: age (when being assessed), onset age, LEDD, RTs of i
path = "/Users/yu-tinghuang/Documents/ML_Data/ML_AC_ON.csv"
names = ['Age', 'Age of PD onset', 'LEDD', 'RT' ,'class']
dataset = pd.read_csv(path, names=names)
y = dataset.iloc[0:121, 4].values
y = np.where(y== 'PD-ICD', -1, 1)
X = dataset.iloc[0:157, [2, 3]].values
plt.scatter(X[:121,0], X[:121, 1], color='blue', marker='x', label='PD
plt.scatter(X[121:157,0], X[121:157, 1], color='red', marker='o', label
plt.xlabel('LEDD')
plt.ylabel('RT')
plt.legend(loc='upper left')
plt.show()
y = dataset.iloc[0:121, 4].values
y = np.where(y== 'PD-ICD', -1, 1)
X = dataset.iloc[0:157, [1, 3]].values
plt.scatter(X[:121,0], X[:121, 1], color='blue', marker='x', label='PD
plt.scatter(X[121:157,0], X[121:157, 1], color='red', marker='o', label
plt.xlabel('Age of PD onset')
plt.ylabel('RT')
plt.legend(loc='upper left')
plt.show()
y = dataset.iloc[0:121, 4].values
y = np.where(y== 'PD+ICD', -1, 1)
X = dataset.iloc[0:157, [1, 3]].values
plt.scatter(X[:121,0], X[:121, 1], color='blue', marker='x', label='PD
plt.scatter(X[121:157,0], X[121:157, 1], color='red', marker='o', label
plt.xlabel('Age')
plt.ylabel('RT')
plt.legend(loc='upper left')
plt.show()

#box and whisker plots
dataset.plot(kind='box', subplots=True, layout=(2,2), sharex=False, sha
plt.show()

#scatter plot matrix
scatter matrix(dataset)
```

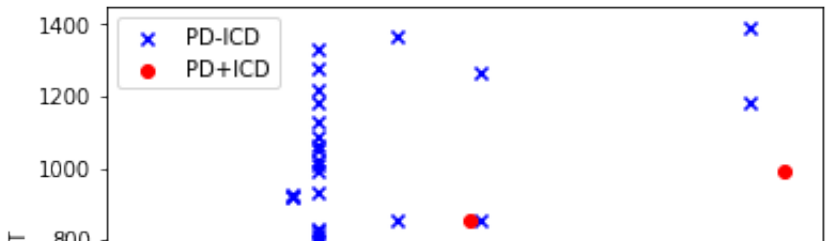
```
plt.show()

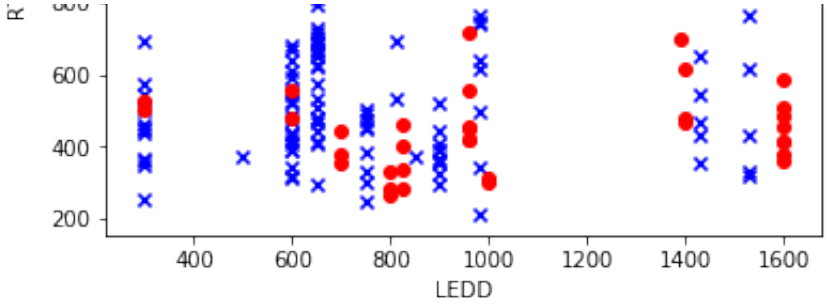

#Split-out validation dataset
array = dataset.values
X = array[:,0:4]
Y = array[:,4]
validation_size = 0.20
seed = 7
X_train, X_validation, Y_train, Y_validation = model_selection.train_t

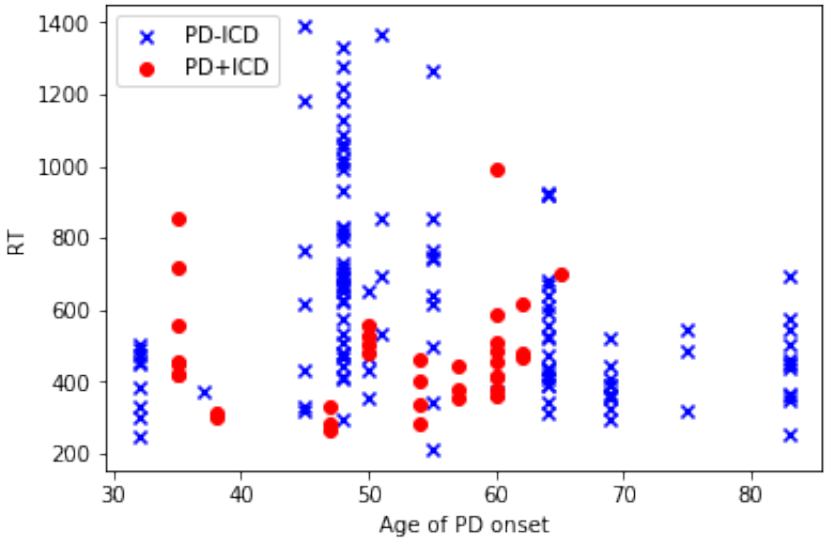
# Spot Check Algorithms
models = []
models.append(('LR', LogisticRegression()))
models.append(('LDA', LinearDiscriminantAnalysis()))
models.append(('KNN', KNeighborsClassifier()))
models.append(('CART', DecisionTreeClassifier()))
models.append(('NB', GaussianNB()))
models.append(('SVM', SVC()))
# evaluate each model in turn
results = []
names = []
for name, model in models:
    kfold = model_selection.KFold(n_splits=10, random_state=seed)
    cv_results = model_selection.cross_val_score(model, X_train, Y_tra
    results.append(cv_results)
    names.append(name)
    msg = "%s: %f (%f)" % (name, cv_results.mean(), cv_results.std())
    print(msg)

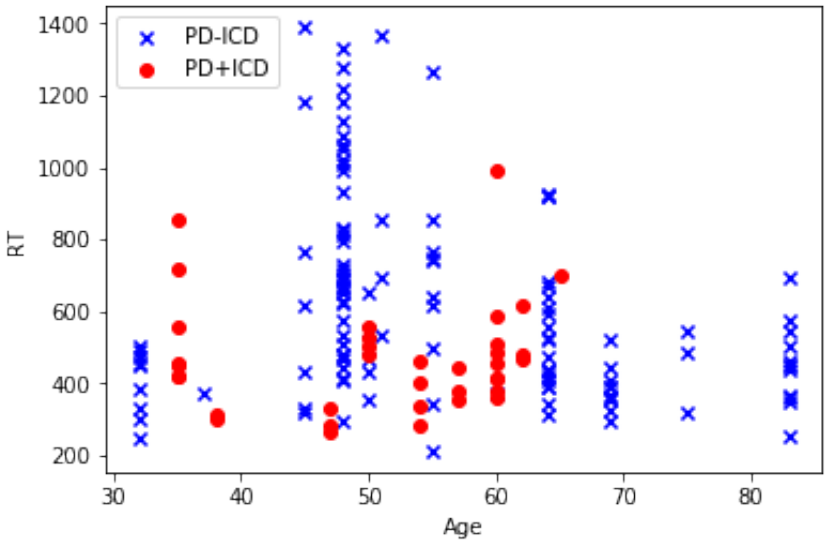
#Compare Algorithms
fig = plt.figure()
fig.suptitle('Algorithm Comparison')
ax = fig.add_subplot(111)
plt.boxplot(results)
ax.set_xticklabels(names)
plt.show()

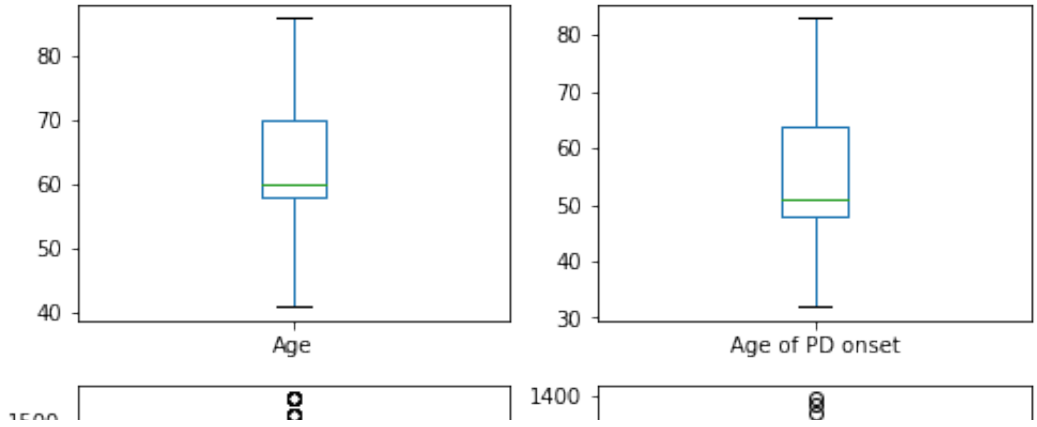
# Make predictions on validation dataset
cart = DecisionTreeClassifier()
cart.fit(X_train, Y_train)
predictions = cart.predict(X_validation)
print(accuracy_score(Y_validation, predictions))
print(confusion_matrix(Y_validation, predictions))
print(classification_report(Y_validation, predictions))
```

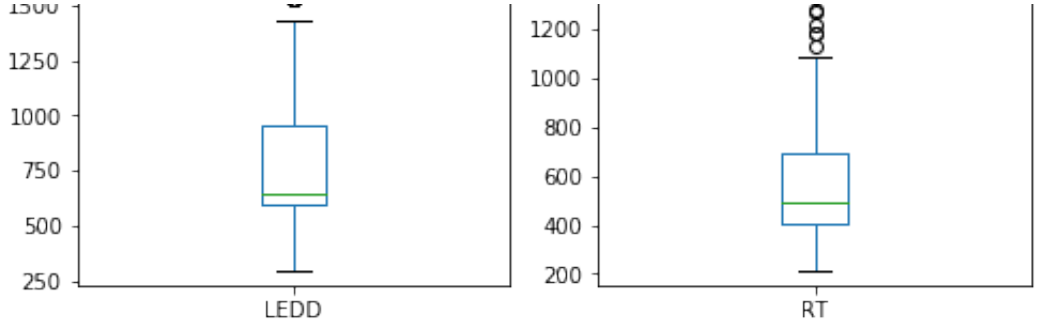



600
400
200
400
600
800
1000
1200
1400
1600
LEDD

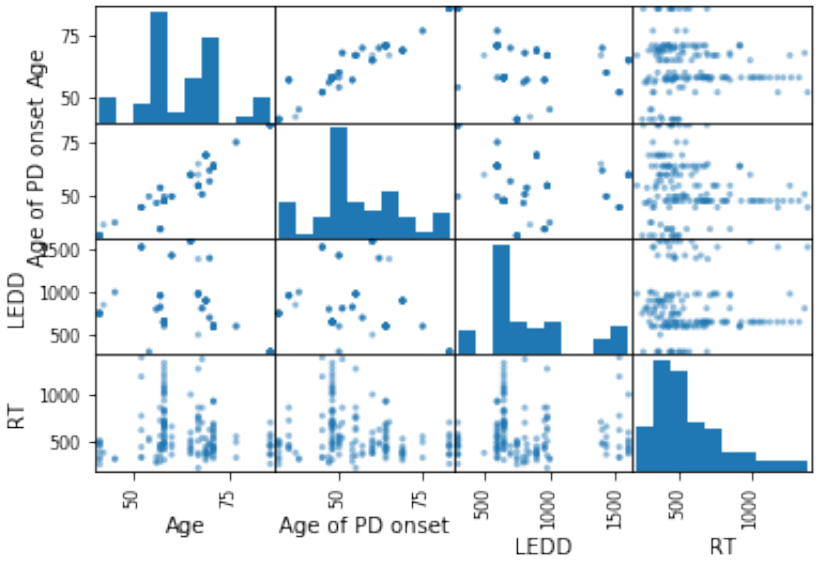

PD-ICD
PD+ICD
RT
1400
1200
1000
800
600
400
200
30
40
50
60
70
80
Age of PD onset


PD-ICD
PD+ICD
RT
1400
1200
1000
800
600
400
200
30
40
50
60
70
80
Age

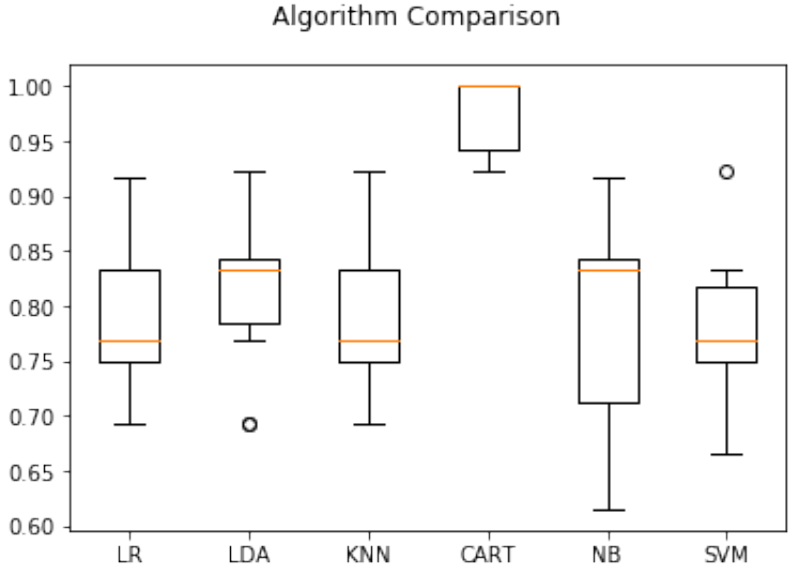

80
70
60
50
40
Age
80
70
60
50
40
30
Age of PD onset
1400




```
/anaconda3/lib/python3.6/site-packages/ipykernel_launcher.py:39: Fut
ureWarning: 'pandas.tools.plotting.scatter_matrix' is deprecated, im
port 'pandas.plotting.scatter_matrix' instead.
```




```
LR: 0.785256 (0.067734)
LDA: 0.817308 (0.075153)
KNN: 0.792949 (0.077829)
CART: 0.976923 (0.035251)
NB: 0.785256 (0.091343)
SVM: 0.775641 (0.069751)
```



```
0.9375
[[ 7  1]
 [ 1 23]]
             precision    recall  f1-score   support

     PD+ICD       0.88      0.88      0.88         8
     PD-ICD       0.96      0.96      0.96        24

avg / total       0.94      0.94      0.94        32
```

In [153]:

```
#Create predictive model with RTs of incorrect trials under Speed inst
#Input variables: age (when being assessed), onset age, LEDD, RTs of i
path = "/Users/yu-tinghuang/Documents/ML_Data/ML_SP_OFF.csv"
names = ['Age', 'Age of PD onset', 'LEDD', 'RT' ,'class']
dataset = pd.read_csv(path, names=names)

y = dataset.iloc[0:215, 4].values
y = np.where(y== 'PD-ICD', -1, 1)
X = dataset.iloc[0:292, [2, 3]].values
plt.scatter(X[:215,0], X[:215, 1], color='blue', marker='x', label='PD
plt.scatter(X[215:292,0], X[215:292, 1], color='red', marker='o', label
plt.xlabel('LEDD')
plt.ylabel('RT')
plt.legend(loc='upper left')
plt.show()
y = dataset.iloc[0:215, 4].values
y = np.where(y== 'PD-ICD', -1, 1)
X = dataset.iloc[0:292, [1, 3]].values
plt.scatter(X[:215,0], X[:215, 1], color='blue', marker='x', label='PD
plt.scatter(X[215:292,0], X[215:292, 1], color='red', marker='o', label
plt.xlabel('Age of PD onset')
plt.ylabel('RT')
plt.legend(loc='upper left')
plt.show()
y = dataset.iloc[0:215, 4].values
y = np.where(y== 'PD-ICD', -1, 1)
X = dataset.iloc[0:292, [1, 3]].values
plt.scatter(X[:215,0], X[:215, 1], color='blue', marker='x', label='PD
plt.scatter(X[215:292,0], X[215:292, 1], color='red', marker='o', label
plt.xlabel('Age')
plt.ylabel('RT')
plt.legend(loc='upper left')
plt.show()

#box and whisker plots
dataset.plot(kind='box', subplots=True, layout=(2,2), sharex=False, sh
plt.show()

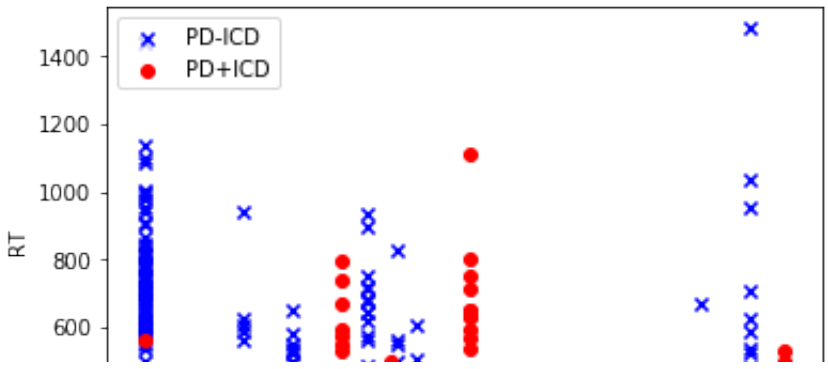
#scatter plot matrix
scatter_matrix(dataset)
plt.show()
```

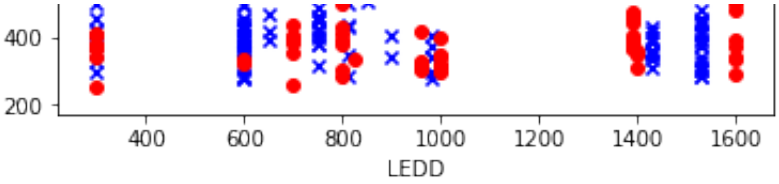
```
#Split-out validation dataset
array = dataset.values
X = array[:,0:4]
Y = array[:,4]
validation_size = 0.20
seed = 7
X_train, X_validation, Y_train, Y_validation = model_selection.train_t

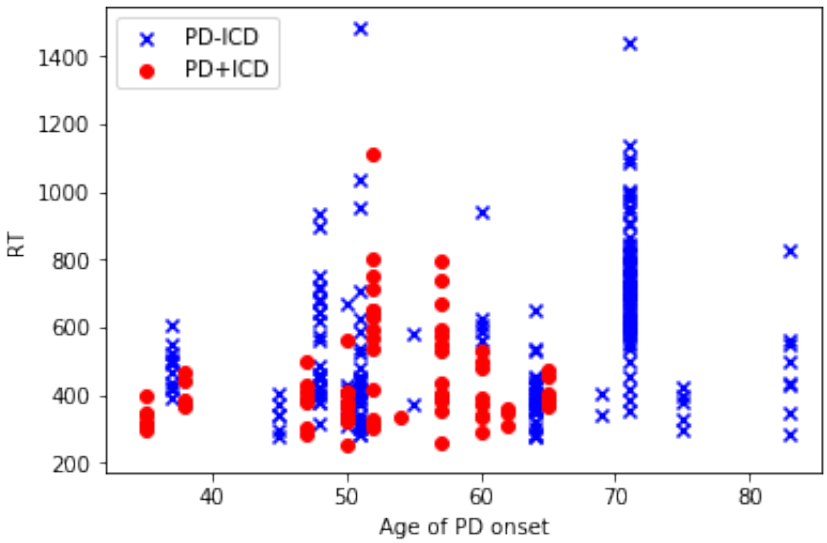
#Spot Check Algorithms
models = []
models.append(('LR', LogisticRegression()))
models.append(('LDA', LinearDiscriminantAnalysis()))
models.append(('KNN', KNeighborsClassifier()))
models.append(('CART', DecisionTreeClassifier()))
models.append(('NB', GaussianNB()))
models.append(('SVM', SVC()))
# evaluate each model in turn
results = []
names = []
for name, model in models:
    kfold = model_selection.KFold(n_splits=10, random_state=seed)
    cv_results = model_selection.cross_val_score(model, X_train, Y_tra
    results.append(cv_results)
    names.append(name)
    msg = "%s: %f (%f)" % (name, cv_results.mean(), cv_results.std())
    print(msg)

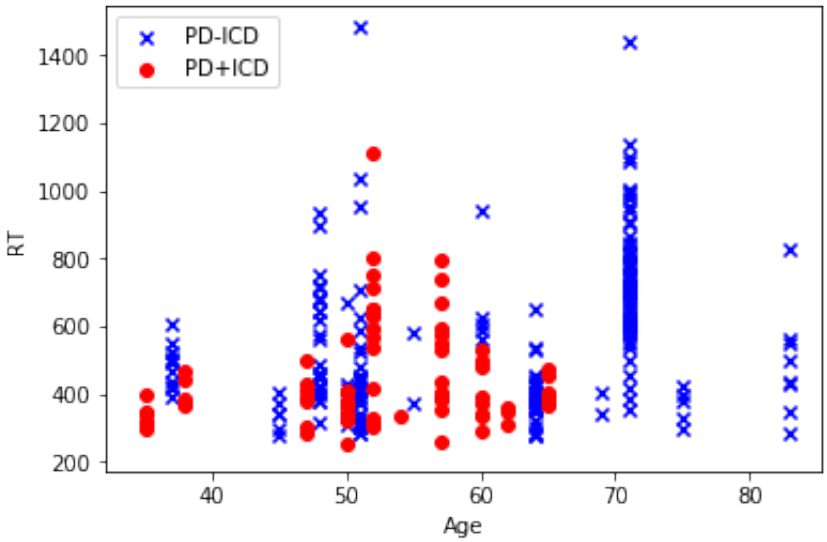

#Compare Algorithms
fig = plt.figure()
fig.suptitle('Algorithm Comparison')
ax = fig.add_subplot(111)
plt.boxplot(results)
ax.set_xticklabels(names)
plt.show()

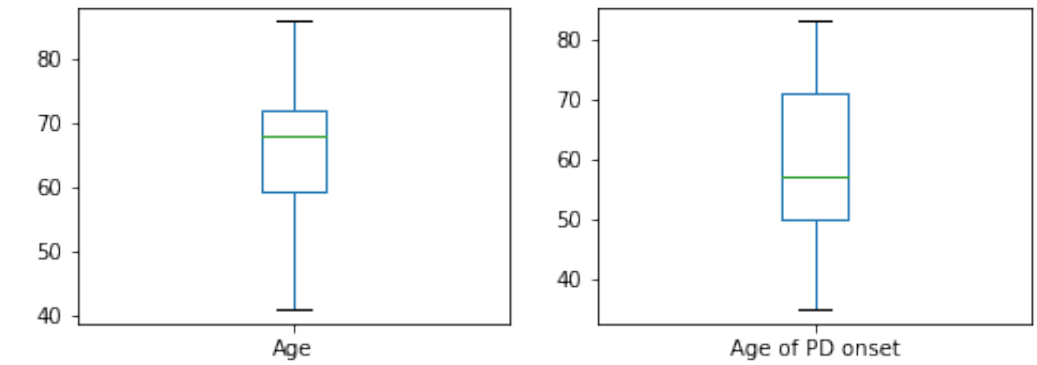
# Make predictions on validation dataset
cart = DecisionTreeClassifier()
cart.fit(X_train, Y_train)
predictions = cart.predict(X_validation)
print(accuracy_score(Y_validation, predictions))
print(confusion_matrix(Y_validation, predictions))
print(classification_report(Y_validation, predictions))
```

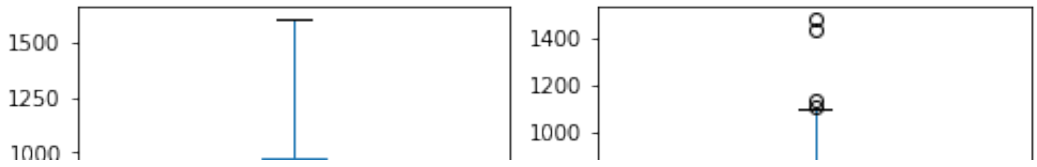


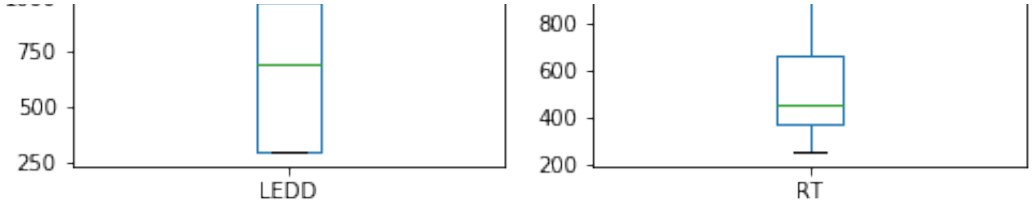

400
200
400
600
800
1000
1200
1400
1600
LEDD


PD-ICD
PD+ICD
RT
Age of PD onset

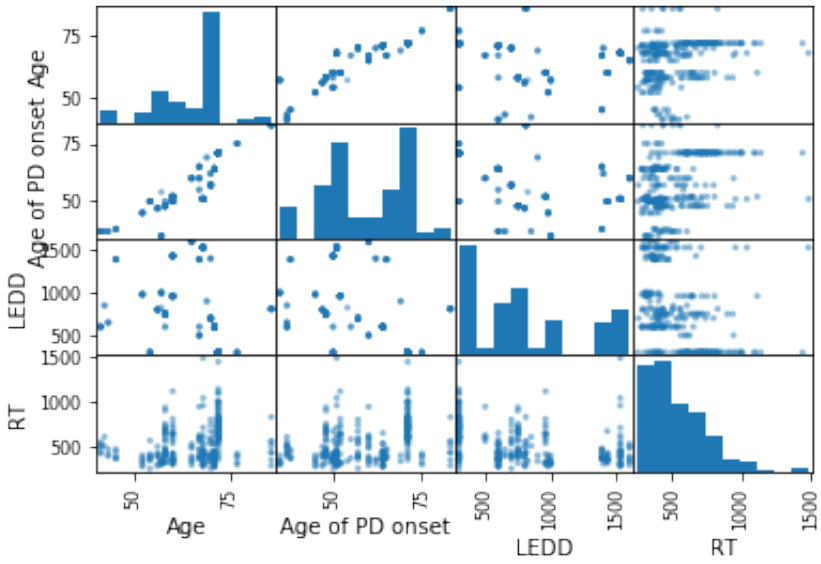

PD-ICD
PD+ICD
RT
Age


Age
Age of PD onset

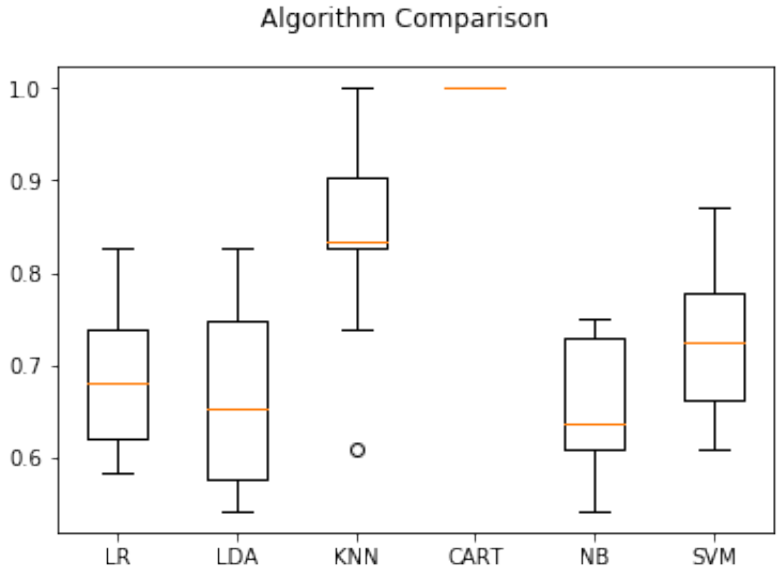

1500
1250
1400
1200
1000




```
/anaconda3/lib/python3.6/site-packages/ipykernel_launcher.py:40: Fut
ureWarning: 'pandas.tools.plotting.scatter_matrix' is deprecated, im
port 'pandas.plotting.scatter_matrix' instead.
```




```
LR: 0.690942 (0.078403)
LDA: 0.669203 (0.096520)
KNN: 0.840580 (0.104659)
CART: 1.000000 (0.000000)
NB: 0.652355 (0.072275)
SVM: 0.729891 (0.087391)
```




```
1.0
[[12  0]
```

```
 [ 0 47]]
             precision    recall  f1-score   support

     PD+ICD       1.00      1.00      1.00        12
     PD-ICD       1.00      1.00      1.00        47

avg / total       1.00      1.00      1.00        59
```

In [154]:
```
#Create predictive model with RTs of incorrect trials under Speed inst
#Input variables: age (when being assessed), onset age, LEDD, RTs of i
path = "/Users/yu-tinghuang/Documents/ML_Data/ML_SP_ON.csv"
names = ['Age', 'Age of PD onset', 'LEDD', 'RT' ,'class']
dataset = pd.read_csv(path, names=names)

y = dataset.iloc[0:295, 4].values
y = np.where(y== 'PD-ICD', -1, 1)
X = dataset.iloc[0:385, [2, 3]].values
plt.scatter(X[:295,0], X[:295, 1], color='blue', marker='x', label='PD
plt.scatter(X[295:385,0], X[295:385, 1], color='red', marker='o', label
plt.xlabel('LEDD')
plt.ylabel('RT')
plt.legend(loc='upper left')
plt.show()
y = dataset.iloc[0:295, 4].values
y = np.where(y== 'PD-ICD', -1, 1)
X = dataset.iloc[0:385, [1, 3]].values
plt.scatter(X[:295,0], X[:295, 1], color='blue', marker='x', label='PD
plt.scatter(X[295:385,0], X[295:385, 1], color='red', marker='o', label
plt.xlabel('Age of PD onset')
plt.ylabel('RT')
plt.legend(loc='upper left')
plt.show()
y = dataset.iloc[0:295, 4].values
y = np.where(y== 'PD+ICD', -1, 1)
X = dataset.iloc[0:385, [1, 3]].values
plt.scatter(X[:295,0], X[:295, 1], color='blue', marker='x', label='PD
plt.scatter(X[295:385,0], X[295:385, 1], color='red', marker='o', label
plt.xlabel('Age')
plt.ylabel('RT')
plt.legend(loc='upper left')
plt.show()

#box and whisker plots
dataset.plot(kind='box', subplots=True, layout=(2,2), sharex=False, sha
plt.show()

#scatter plot matrix
scatter_matrix(dataset)
plt.show()

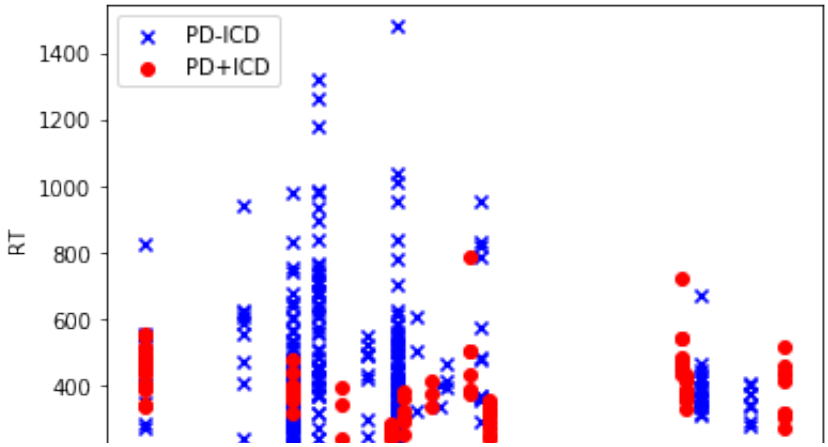
#Split-out validation dataset
array = dataset.values
X = array[:,0:4]
```

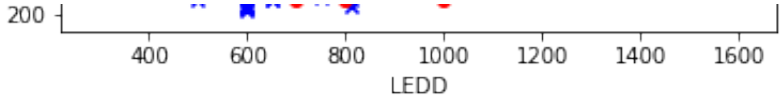
```
X = array[:,0:4]
Y = array[:,4]
validation_size = 0.20
seed = 7
X_train, X_validation, Y_train, Y_validation = model_selection.train_t

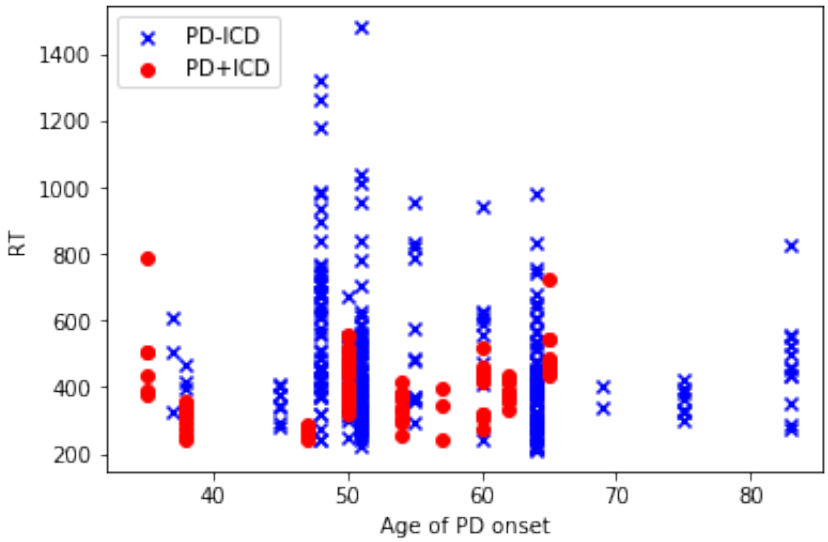
# Spot Check Algorithms
models = []
models.append(('LR', LogisticRegression()))
models.append(('LDA', LinearDiscriminantAnalysis()))
models.append(('KNN', KNeighborsClassifier()))
models.append(('CART', DecisionTreeClassifier()))
models.append(('NB', GaussianNB()))
models.append(('SVM', SVC()))
# evaluate each model in turn
results = []
names = []
for name, model in models:
    kfold = model_selection.KFold(n_splits=10, random_state=seed)
    cv_results = model_selection.cross_val_score(model, X_train, Y_tra
    results.append(cv_results)
    names.append(name)
    msg = "%s: %f (%f)" % (name, cv_results.mean(), cv_results.std())
    print(msg)

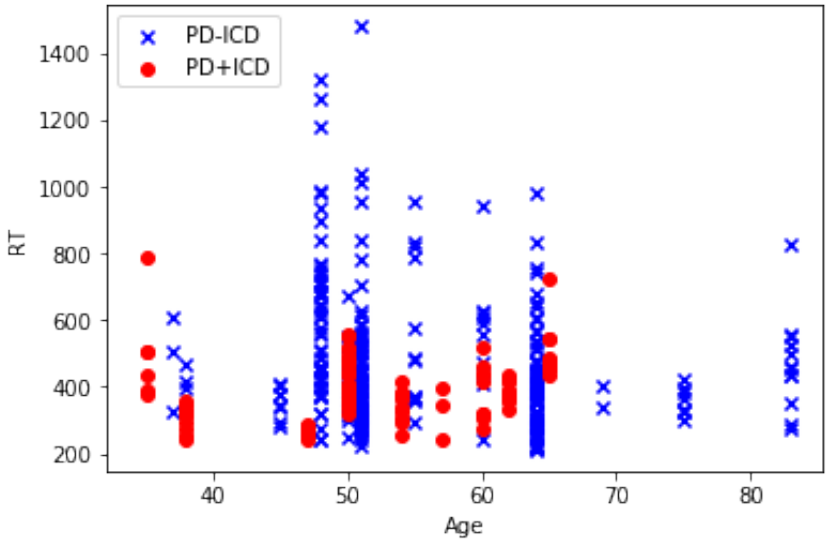
#Compare Algorithms
fig = plt.figure()
fig.suptitle('Algorithm Comparison')
ax = fig.add_subplot(111)
plt.boxplot(results)
ax.set_xticklabels(names)
plt.show()

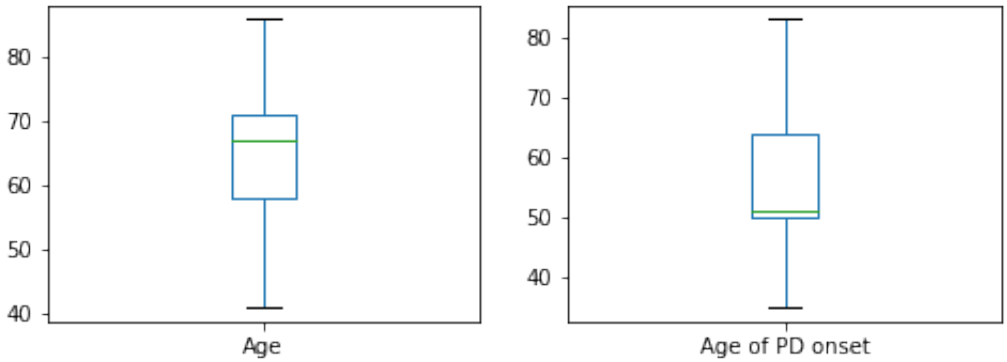
# Make predictions on validation dataset
cart = DecisionTreeClassifier()
cart.fit(X_train, Y_train)
predictions = cart.predict(X_validation)
print(accuracy_score(Y_validation, predictions))
print(confusion_matrix(Y_validation, predictions))
print(classification_report(Y_validation, predictions))
```

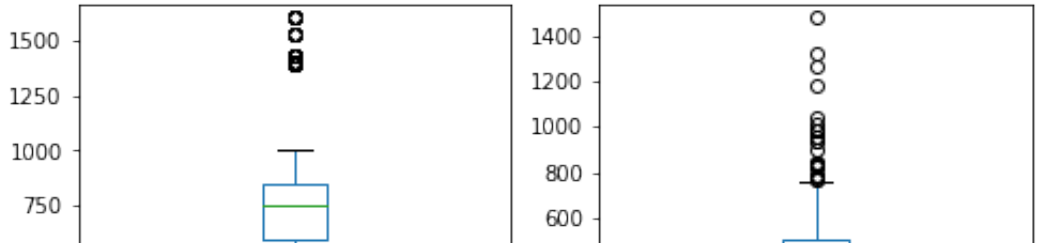


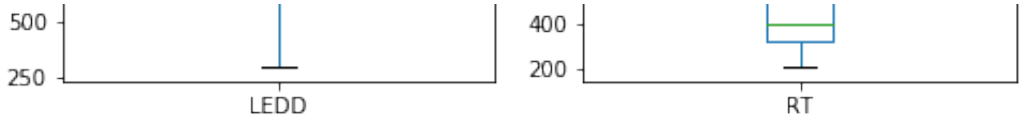

200
400
600
800
1000
1200
1400
1600
LEDD


PD-ICD
PD+ICD
RT
Age of PD onset

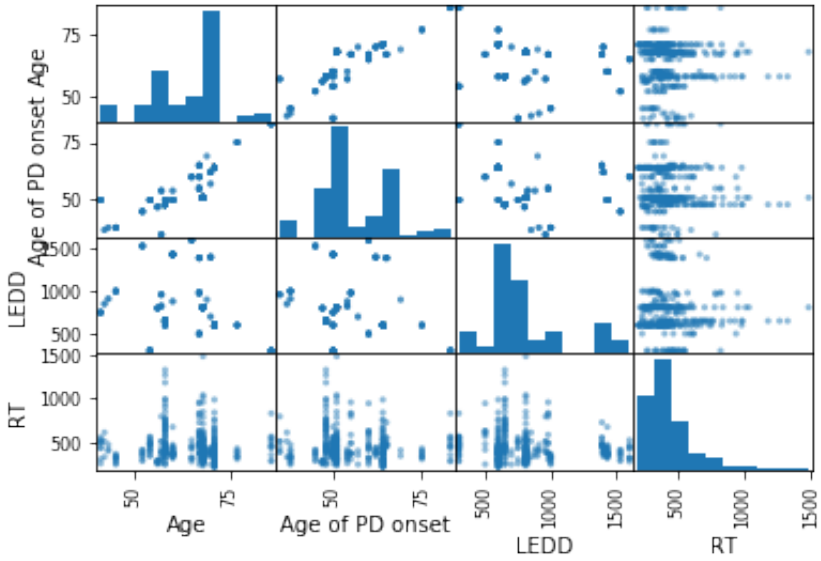

PD-ICD
PD+ICD
RT
Age


Age
Age of PD onset

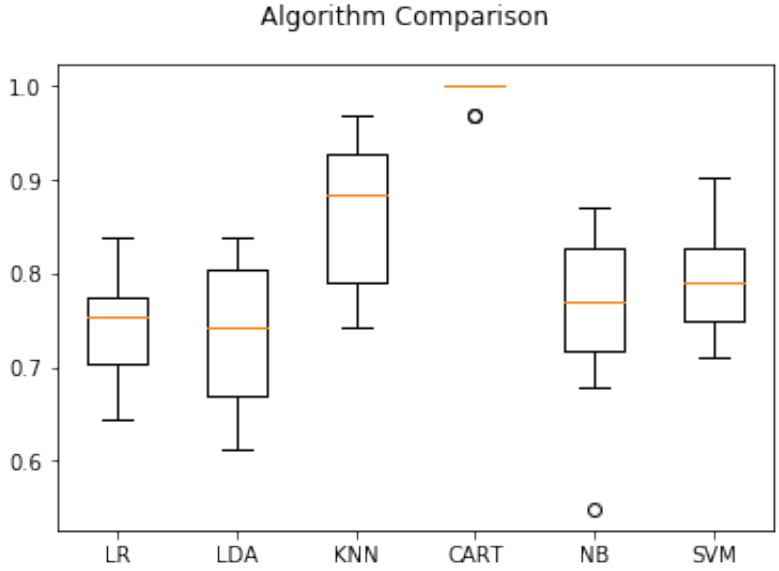





```
/anaconda3/lib/python3.6/site-packages/ipykernel_launcher.py:40: Fut
ureWarning: 'pandas.tools.plotting.scatter_matrix' is deprecated, im
port 'pandas.plotting.scatter_matrix' instead.
```




```
LR: 0.743441 (0.057030)
LDA: 0.733763 (0.074991)
KNN: 0.866989 (0.078139)
CART: 0.993548 (0.012903)
NB: 0.760000 (0.093203)
SVM: 0.789032 (0.057974)
```




```
1.0
[[21  0]
 [ 0 56]]
             precision    recall  f1-score   support
```

```
      PD+ICD       1.00      1.00      1.00        21
      PD-ICD       1.00      1.00      1.00        56

avg / total       1.00      1.00      1.00        77
```

In [155]:

```
#Create predictive model with RTs of incorrect trials under 0.05 coher
#Input variables: age (when being assessed), onset age, LEDD, RTs of i
path = "/Users/yu-tinghuang/Documents/ML_Data/Difficulty_0.05_OFF.csv"
names = ['Age', 'Age of PD onset', 'LEDD', 'RT' ,'class']
dataset = pd.read_csv(path, names=names)

y = dataset.iloc[0:46, 4].values
y = np.where(y== 'PD+ICD', -1, 1)
X = dataset.iloc[0:118, [2, 3]].values
plt.scatter(X[:46,0], X[:46, 1], color='red', marker='o', label='PD+IC
plt.scatter(X[46:118,0], X[46:118, 1], color='blue', marker='x', label
plt.xlabel('LEDD')
plt.ylabel('RT')
plt.legend(loc='upper left')
plt.show()
y = dataset.iloc[0:46, 4].values
y = np.where(y== 'PD+ICD', -1, 1)
X = dataset.iloc[0:118, [1, 3]].values
plt.scatter(X[:46,0], X[:46, 1], color='red', marker='o', label='PD+IC
plt.scatter(X[46:118,0], X[46:118, 1], color='blue', marker='x', label
plt.xlabel('Age of PD onset')
plt.ylabel('RT')
plt.legend(loc='upper left')
plt.show()
y = dataset.iloc[0:46, 4].values
y = np.where(y== 'PD+ICD', -1, 1)
X = dataset.iloc[0:118, [1, 3]].values
plt.scatter(X[:46,0], X[:46, 1], color='red', marker='o', label='PD+IC
plt.scatter(X[46:118,0], X[46:118, 1], color='blue', marker='x', label
plt.xlabel('Age')
plt.ylabel('RT')
plt.legend(loc='upper left')
plt.show()

#box and whisker plots
dataset.plot(kind='box', subplots=True, layout=(2,2), sharex=False, sh
plt.show()

#scatter plot matrix
scatter_matrix(dataset)
plt.show()

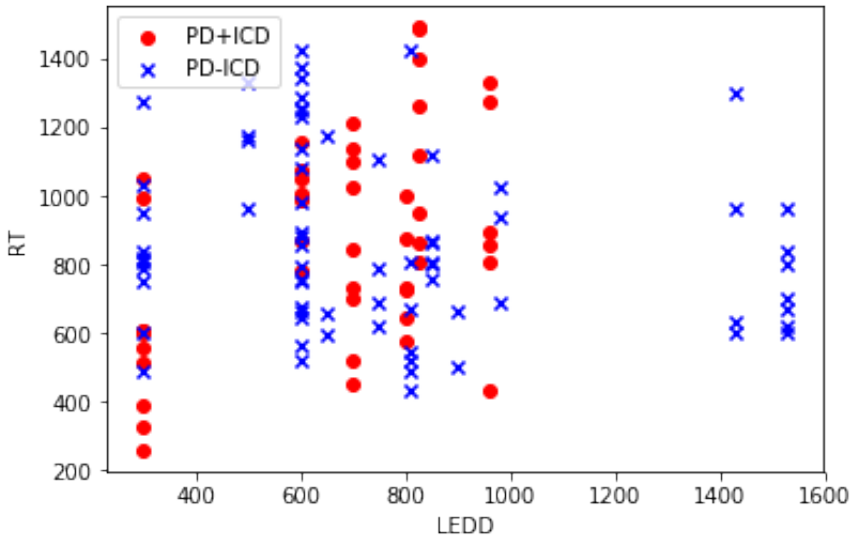
#Split-out validation dataset
array = dataset.values
X = array[:,0:4]
Y = array[:,4]
validation_size = 0.20
seed = 7
```

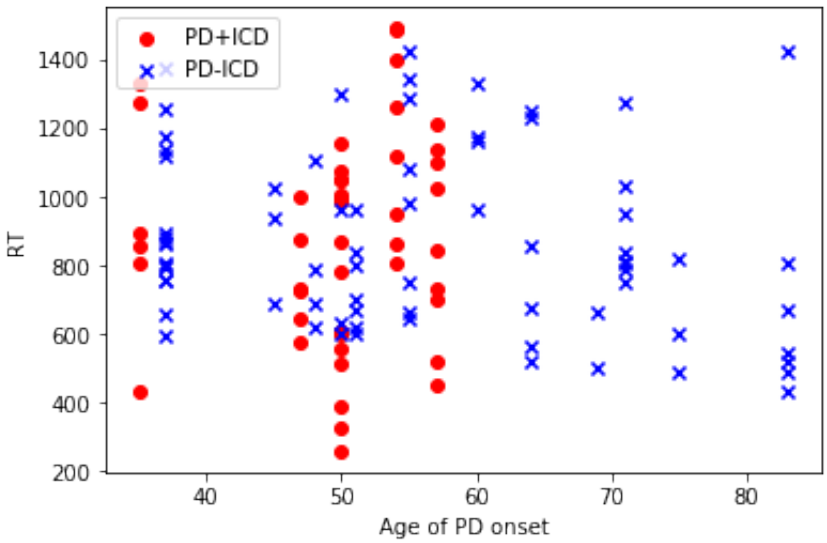
```
seed = 7
X_train, X_validation, Y_train, Y_validation = model_selection.train_t

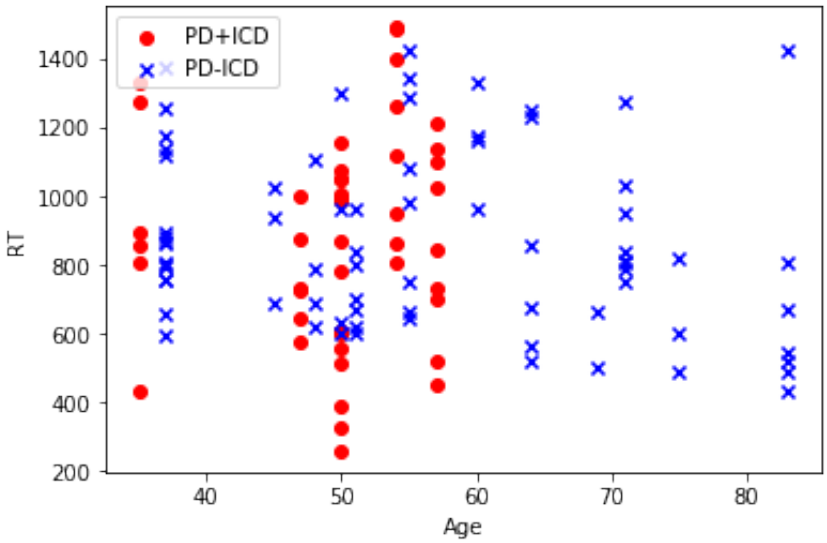
# Spot Check Algorithms
models = []
models.append(('LR', LogisticRegression()))
models.append(('LDA', LinearDiscriminantAnalysis()))
models.append(('KNN', KNeighborsClassifier()))
models.append(('CART', DecisionTreeClassifier()))
models.append(('NB', GaussianNB()))
models.append(('SVM', SVC()))
# evaluate each model in turn
results = []
names = []
for name, model in models:
    kfold = model_selection.KFold(n_splits=10, random_state=seed)
    cv_results = model_selection.cross_val_score(model, X_train, Y_tra
    results.append(cv_results)
    names.append(name)
    msg = "%s: %f (%f)" % (name, cv_results.mean(), cv_results.std())
    print(msg)

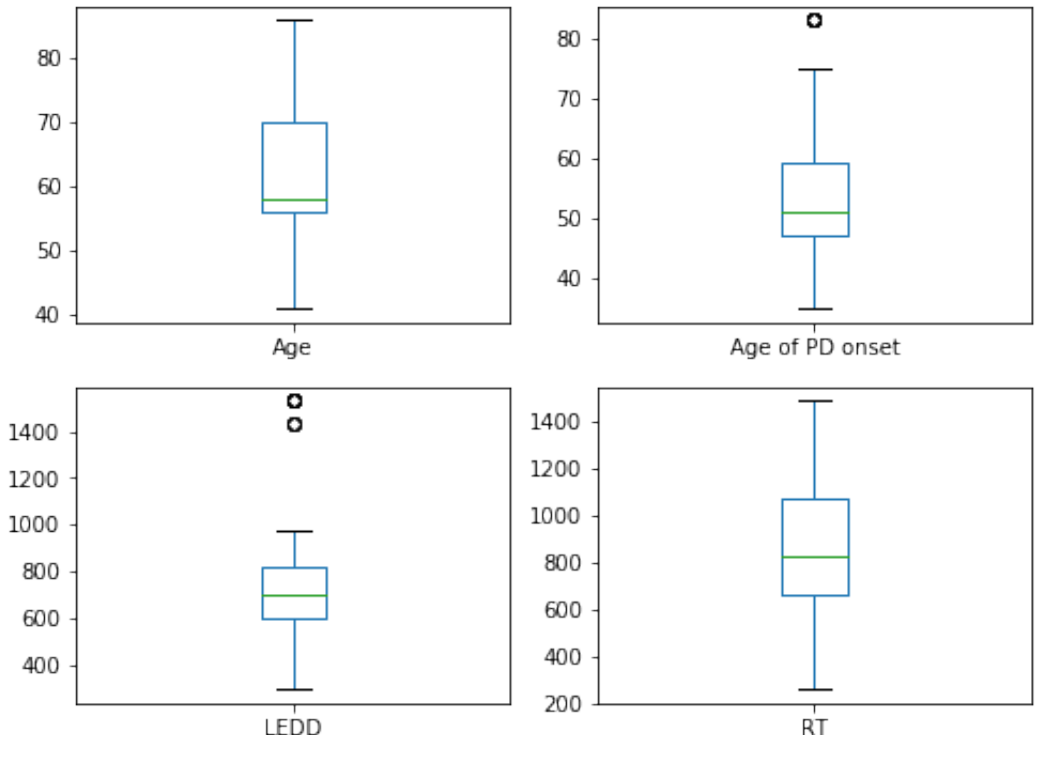
#Compare Algorithms
fig = plt.figure()
fig.suptitle('Algorithm Comparison')
ax = fig.add_subplot(111)
plt.boxplot(results)
ax.set_xticklabels(names)
plt.show()

# Make predictions on validation dataset
cart = DecisionTreeClassifier()
cart.fit(X_train, Y_train)
predictions = cart.predict(X_validation)
print(accuracy_score(Y_validation, predictions))
print(confusion_matrix(Y_validation, predictions))
print(classification_report(Y_validation, predictions))
```

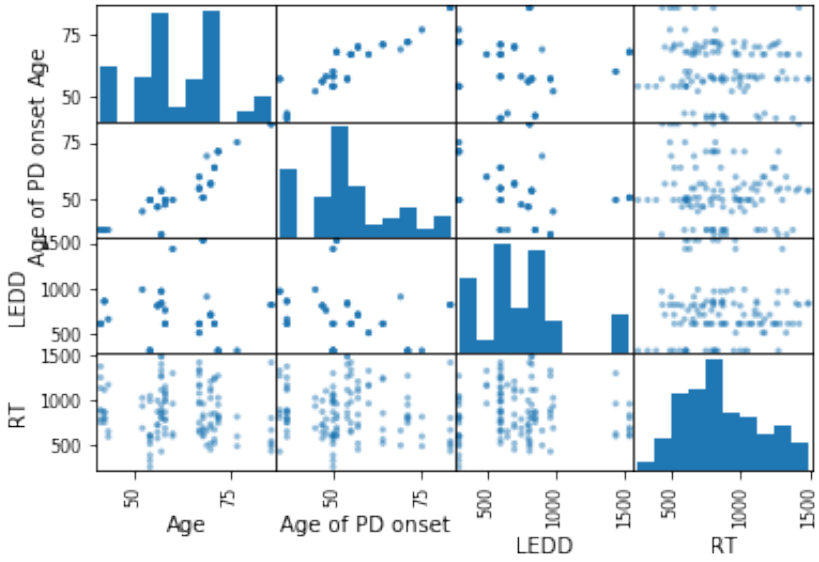



PD+ICD
PD-ICD
RT
Age of PD onset

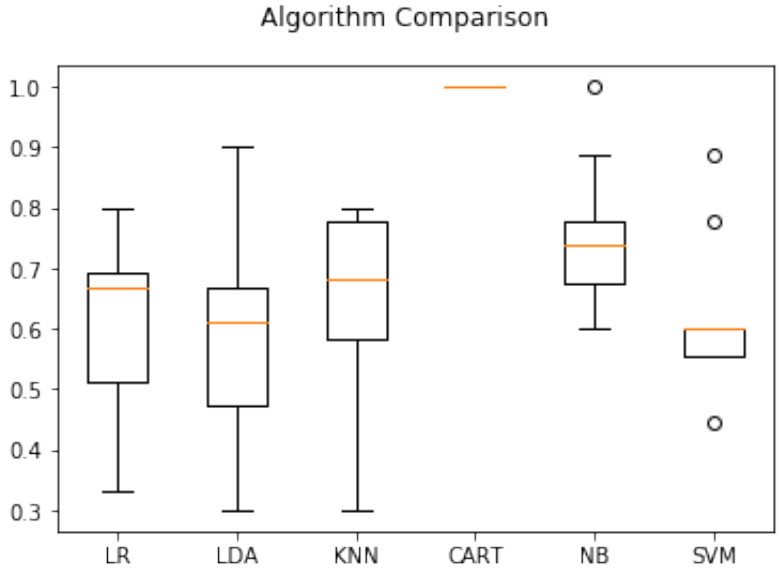

PD+ICD
PD-ICD
RT
Age


Age
Age of PD onset
LEDD
RT

```
/anaconda3/lib/python3.6/site-packages/ipykernel_launcher.py:40: Fut
ureWarning: 'pandas.tools.plotting.scatter_matrix' is deprecated, im
port 'pandas.plotting.scatter_matrix' instead.
```




```
LR: 0.606667 (0.147506)
LDA: 0.585556 (0.164133)
KNN: 0.642222 (0.163662)
CART: 1.000000 (0.000000)
NB: 0.755556 (0.111886)
SVM: 0.617778 (0.119174)
```




```
1.0
[[ 8  0]
 [ 0 16]]
             precision    recall  f1-score   support

     PD+ICD       1.00      1.00      1.00         8
     PD-ICD       1.00      1.00      1.00        16
```

```
avg / total       1.00      1.00      1.00        24
```

In [156]:

```
#Create predictive model with RTs of incorrect trials under 0.05 coher
#Input variables: age (when being assessed), onset age, LEDD, RTs of i
path = "/Users/yu-tinghuang/Documents/ML_Data/Difficulty_0.05_ON.csv"
names = ['Age', 'Age of PD onset', 'LEDD', 'RT' ,'class']
dataset = pd.read_csv(path, names=names)

y = dataset.iloc[0:76, 4].values
y = np.where(y== 'PD+ICD', -1, 1)
X = dataset.iloc[0:187, [2, 3]].values
plt.scatter(X[:76,0], X[:76, 1], color='red', marker='o', label='PD+IC
plt.scatter(X[76:187,0], X[76:187, 1], color='blue', marker='x', label
plt.xlabel('LEDD')
plt.ylabel('RT')
plt.legend(loc='upper left')
plt.show()
y = dataset.iloc[0:76, 4].values
y = np.where(y== 'PD+ICD', -1, 1)
X = dataset.iloc[0:187, [1, 3]].values
plt.scatter(X[:76,0], X[:76, 1], color='red', marker='o', label='PD+IC
plt.scatter(X[76:187,0], X[76:187, 1], color='blue', marker='x', label
plt.xlabel('Age of PD onset')
plt.ylabel('RT')
plt.legend(loc='upper left')
plt.show()
y = dataset.iloc[0:76, 4].values
y = np.where(y== 'PD+ICD', -1, 1)
X = dataset.iloc[0:187, [1, 3]].values
plt.scatter(X[:76,0], X[:76, 1], color='red', marker='o', label='PD+IC
plt.scatter(X[76:187,0], X[76:187, 1], color='blue', marker='x', label
plt.xlabel('Age')
plt.ylabel('RT')
plt.legend(loc='upper left')
plt.show()

#box and whisker plots
dataset.plot(kind='box', subplots=True, layout=(2,2), sharex=False, sh
plt.show()

#scatter plot matrix
scatter_matrix(dataset)
plt.show()

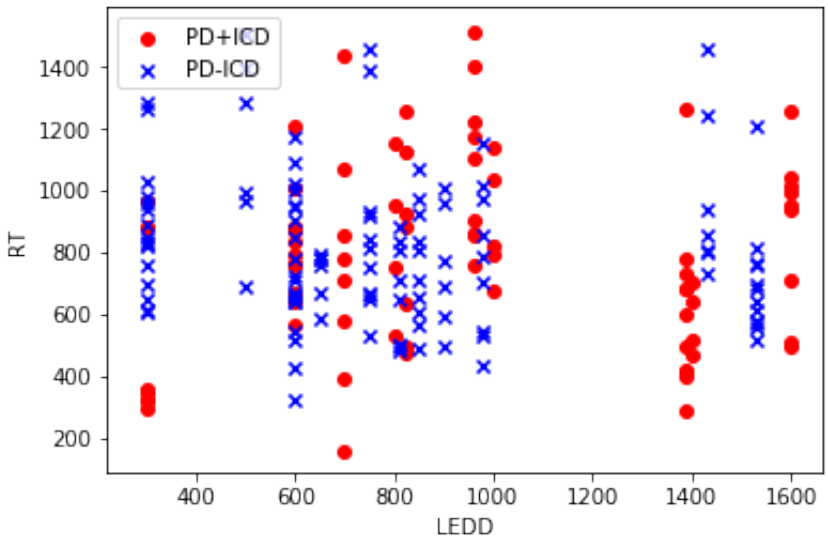
#Split-out validation dataset
array = dataset.values
X = array[:,0:4]
Y = array[:,4]
validation_size = 0.20
seed = 7
X_train, X_validation, Y_train, Y_validation = model_selection.train_t

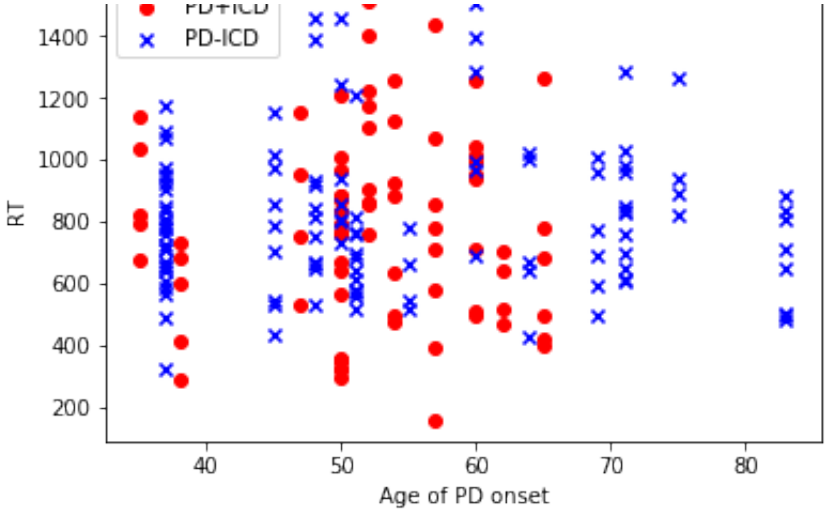
# Spot Check Algorithms
```

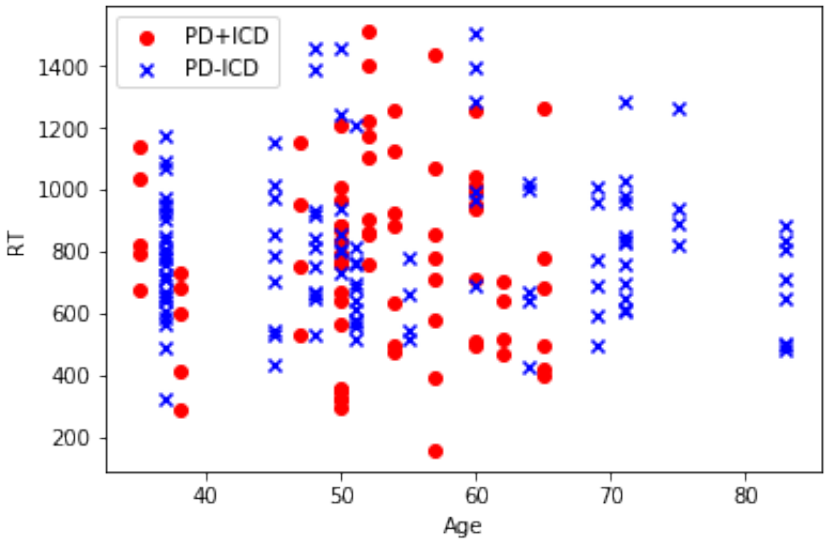
```
# Spot Check Algorithms
models = []
models.append(('LR', LogisticRegression()))
models.append(('LDA', LinearDiscriminantAnalysis()))
models.append(('KNN', KNeighborsClassifier()))
models.append(('CART', DecisionTreeClassifier()))
models.append(('NB', GaussianNB()))
models.append(('SVM', SVC()))
# evaluate each model in turn
results = []
names = []
for name, model in models:
    kfold = model_selection.KFold(n_splits=10, random_state=seed)
    cv_results = model_selection.cross_val_score(model, X_train, Y_tra
    results.append(cv_results)
    names.append(name)
    msg = "%s: %f (%f)" % (name, cv_results.mean(), cv_results.std())
    print(msg)

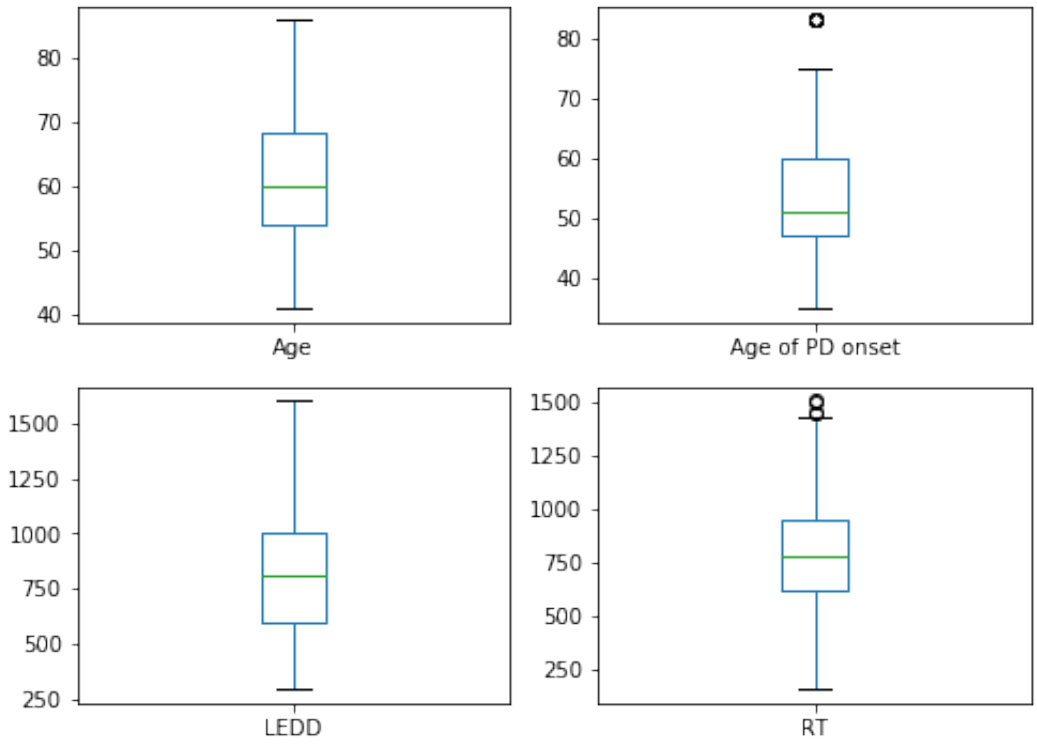
#Compare Algorithms
fig = plt.figure()
fig.suptitle('Algorithm Comparison')
ax = fig.add_subplot(111)
plt.boxplot(results)
ax.set_xticklabels(names)
plt.show()

# Make predictions on validation dataset
cart = DecisionTreeClassifier()
cart.fit(X_train, Y_train)
predictions = cart.predict(X_validation)
print(accuracy_score(Y_validation, predictions))
print(confusion_matrix(Y_validation, predictions))
print(classification_report(Y_validation, predictions))
```



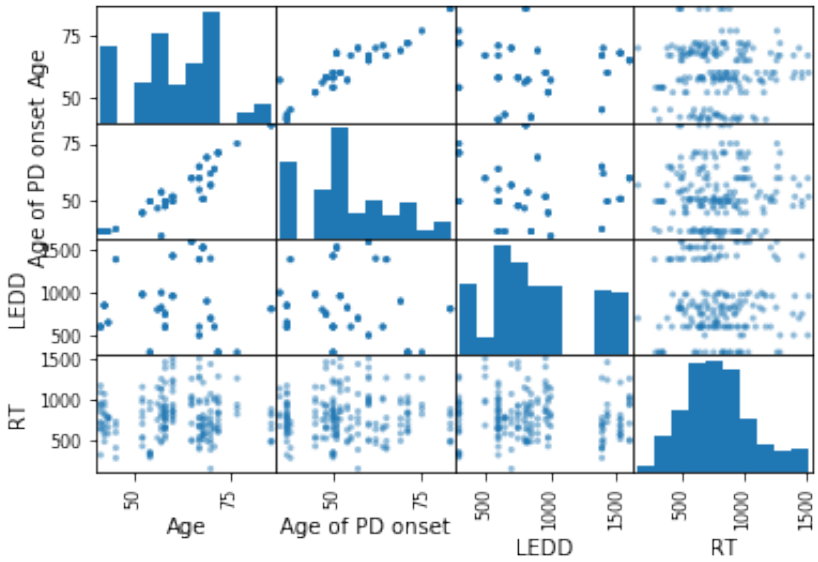




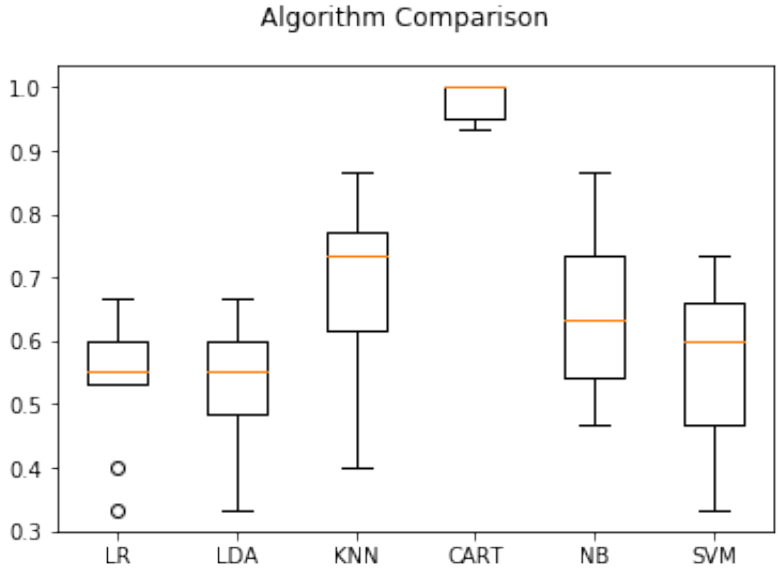



```
/anaconda3/lib/python3.6/site-packages/ipykernel_launcher.py:40: Fut
```

```
ureWarning: 'pandas.tools.plotting.scatter_matrix' is deprecated, im
port 'pandas.plotting.scatter_matrix' instead.
```




```
LR: 0.543810 (0.101280)
LDA: 0.530476 (0.097315)
KNN: 0.698571 (0.133164)
CART: 0.980000 (0.030551)
NB: 0.643810 (0.131429)
SVM: 0.564286 (0.118403)
```




```
1.0
[[11  0]
 [ 0 27]]
             precision    recall  f1-score   support

     PD+ICD       1.00      1.00      1.00        11
     PD-ICD       1.00      1.00      1.00        27

avg / total       1.00      1.00      1.00        38
```

Appendix - Programming codes for Chapter 4

In [1]:
```
#import the related toolboxes
import hddm
import pandas as pd
import matplotlib.pyplot as plt
```

```
/Users/Nicole/anaconda2/lib/python2.7/site-packages/IPython/parallel.py:13: Sh
imWarning: The `IPython.parallel` package has been deprecated. You should impo
rt from ipyparallel instead.
  "You should import from ipyparallel instead.", ShimWarning)
```

In [5]:
```
#load the data
data = hddm.load_csv('/Users/Nicole/Desktop/Latest drafts3/DBS_switching/DBS_swi
```

In [10]:
```
#Create the model with all available data
m1 = hddm.HDDMRegressor(data, ["a ~ C(DBS)","v ~ C(Block)*C(DBS)","t ~ C(DBS)"])
```

```
Adding these covariates:
['a_Intercept', 'a_C(DBS)[T.HC]', 'a_C(DBS)[T.STN DBS OFF]']
Adding these covariates:
['v_Intercept', 'v_C(Block)[T.B2]', 'v_C(Block)[T.B3]', 'v_C(DBS)[T.HC]', 'v_C
(DBS)[T.STN DBS OFF]', 'v_C(Block)[T.B2]:C(DBS)[T.HC]', 'v_C(Block)[T.B3]:C(DB
S)[T.HC]', 'v_C(Block)[T.B2]:C(DBS)[T.STN DBS OFF]', 'v_C(Block)[T.B3]:C(DBS)
[T.STN DBS OFF]']
Adding these covariates:
['t_Intercept', 't_C(DBS)[T.HC]', 't_C(DBS)[T.STN DBS OFF]']
```

In [11]:
```
#Start drawing 10000 samples and discarding 1000 as burn-in
m1.sample(10000, burn=1000)
```

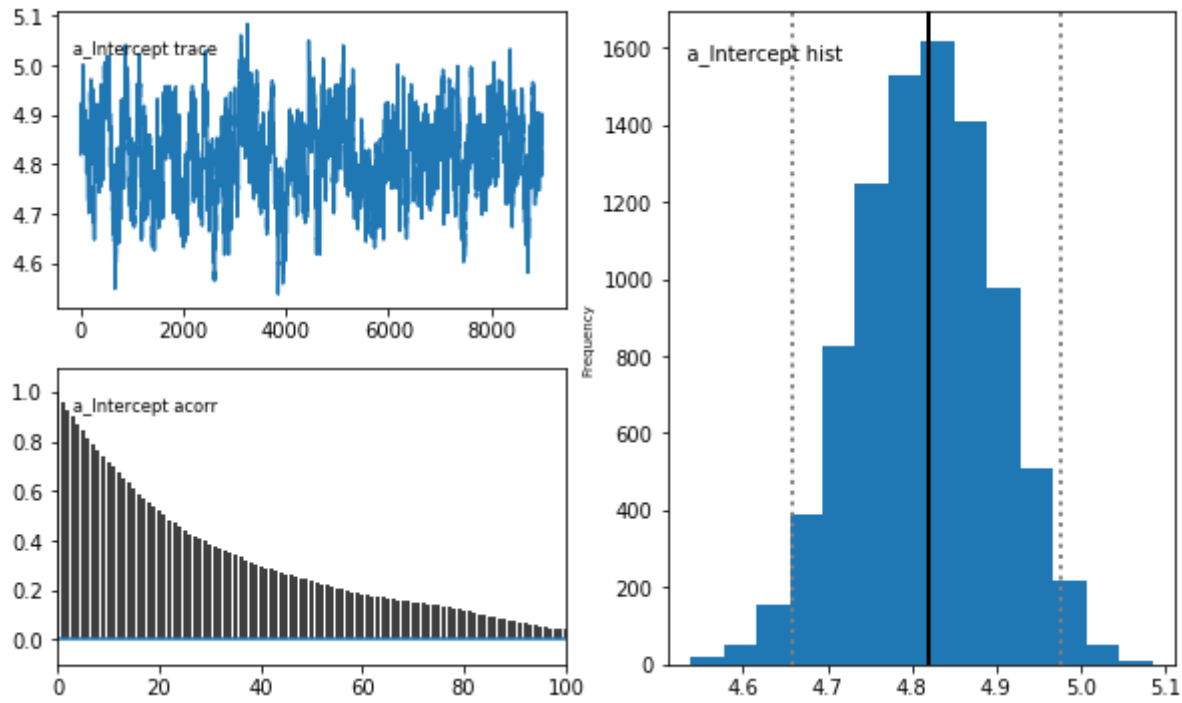
```
 [-----------------100%-----------------] 10001 of 10000 complete in 7494.0 se
c
```

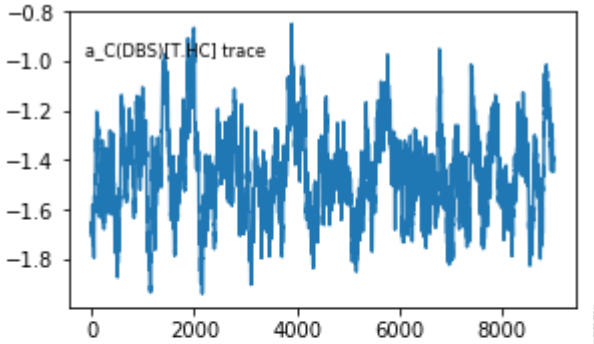
Out[11]:
```
<pymc.MCMC.MCMC at 0x1267d0c90>
```

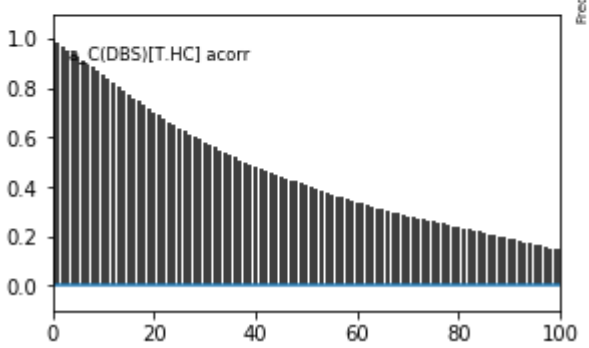
In [12]:
```
#Plot the figures to examine the convergence of the model
m1.plot_posteriors()
plt.show()

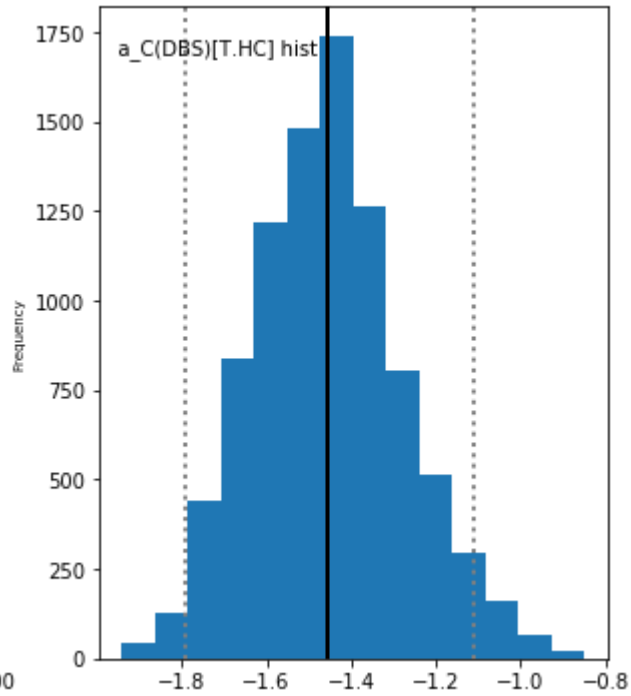
#A converged chain would have a stationary trace (upper left plots),
#low auto-correlation (lower left plots),
#and normally distributed subject and group mean posteriors,
#while group variability posteriors are Gamma distributed (right plots).
```

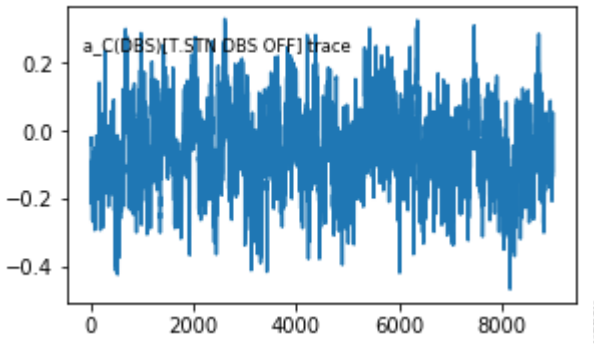
```
Plotting a_Intercept
Plotting a_C(DBS)[T.HC]
Plotting a_C(DBS)[T.STN DBS OFF]
Plotting v_Intercept
Plotting v_C(Block)[T.B2]
Plotting v_C(Block)[T.B3]
Plotting v_C(DBS)[T.HC]
Plotting v_C(DBS)[T.STN DBS OFF]
Plotting v_C(Block)[T.B2]:C(DBS)[T.HC]
Plotting v_C(Block)[T.B3]:C(DBS)[T.HC]
Plotting v_C(Block)[T.B2]:C(DBS)[T.STN DBS OFF]
Plotting v_C(Block)[T.B3]:C(DBS)[T.STN DBS OFF]
Plotting t_Intercept
Plotting t_C(DBS)[T.HC]
Plotting t_C(DBS)[T.STN DBS OFF]
```

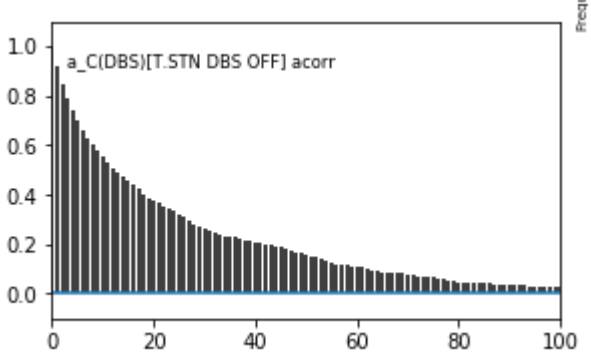


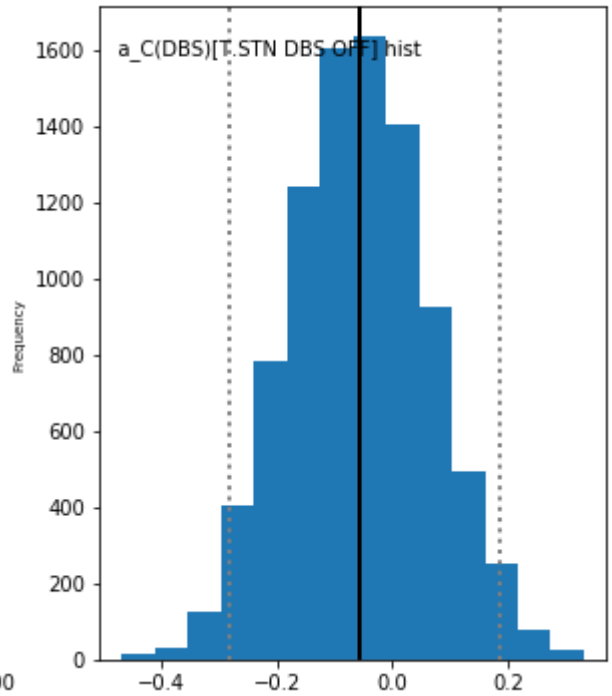

a_C(DBS)[T.HC] trace

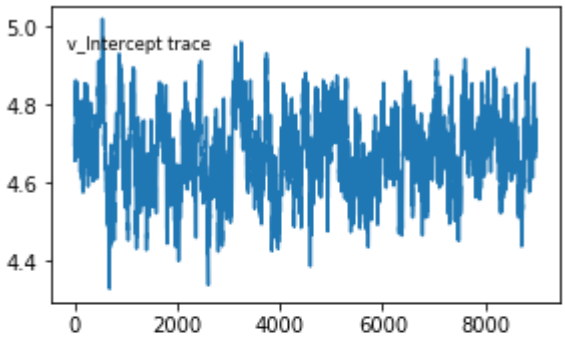

C(DBS)[T.HC] acorr

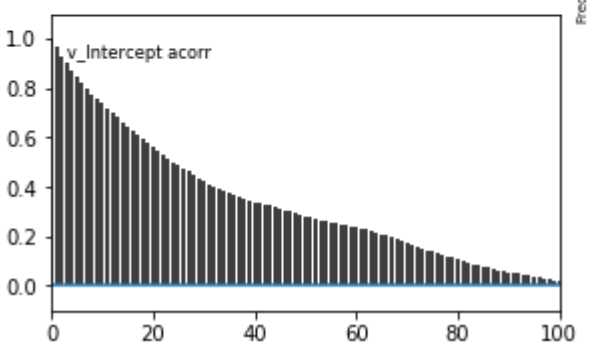

a_C(DBS)[T.HC] hist
Frequency

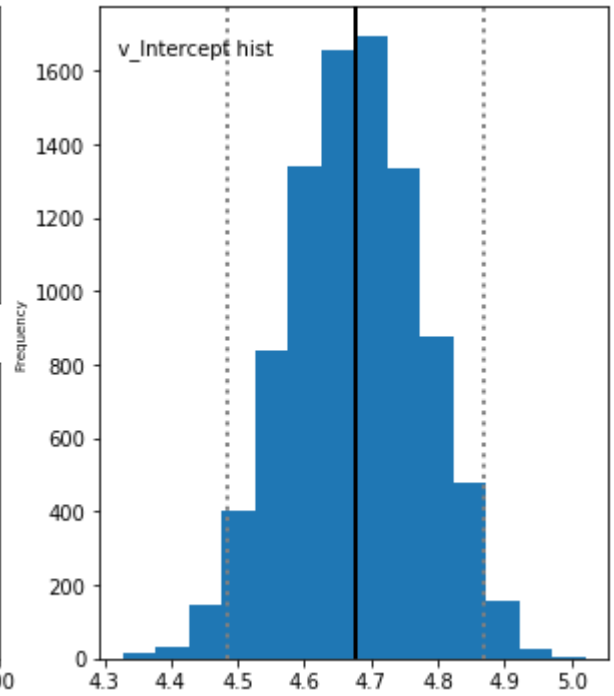

a_C(DBS)[T.STN DBS OFF] trace

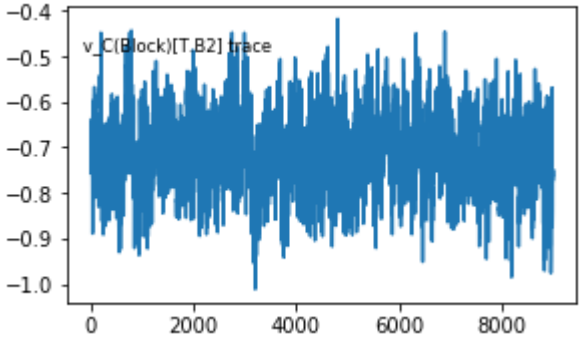

a_C(DBS)[T.STN DBS OFF] acorr

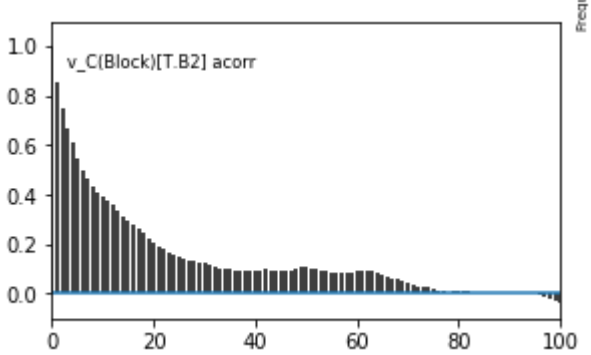

a_C(DBS)[T.STN DBS OFF] hist
Frequency

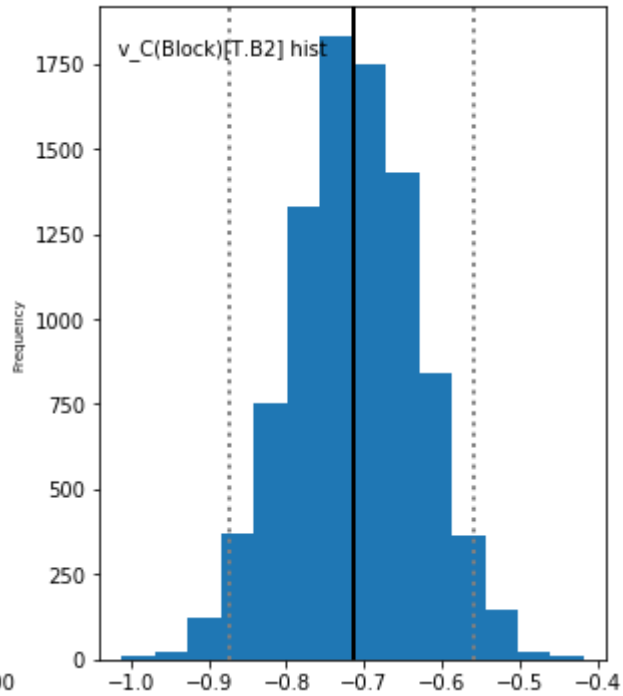

v_Intercept trace
5.0
4.8
4.6
4.4
0
2000
4000
6000
8000

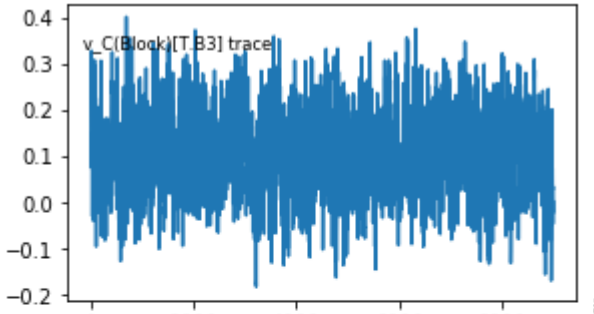

v_Intercept acorr
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100

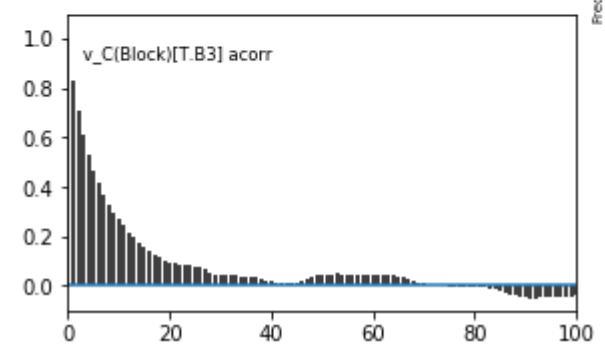

v_Intercept hist
Frequency
1600
1400
1200
1000
800
600
400
200
0
4.3
4.4
4.5
4.6
4.7
4.8
4.9
5.0

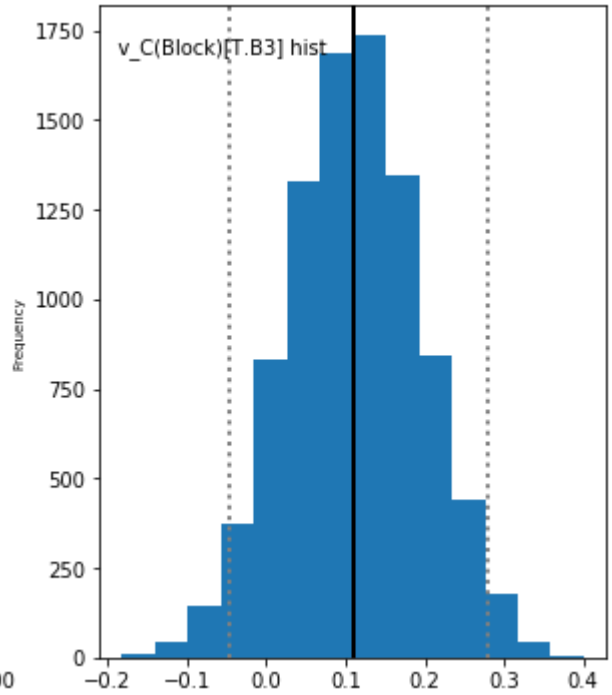

v_C(Block)[T.B2] trace
−0.4
−0.5
−0.6
−0.7
−0.8
−0.9
−1.0
0
2000
4000
6000
8000

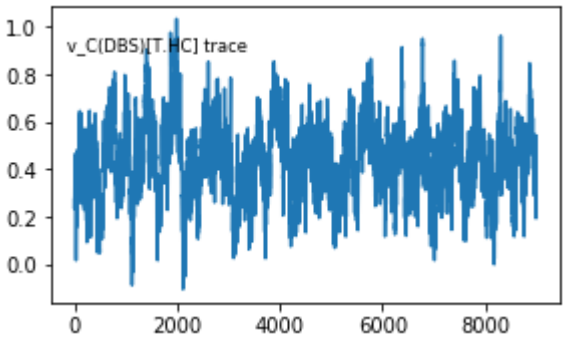

v_C(Block)[T.B2] acorr
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100

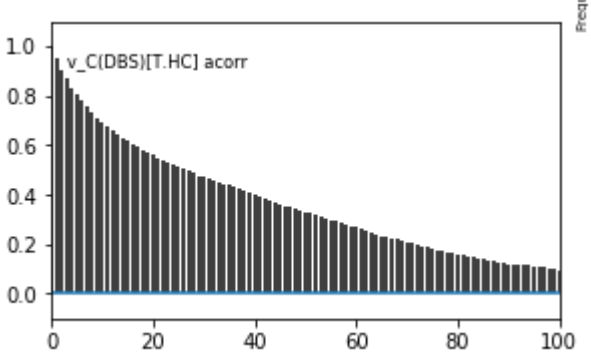

v_C(Block)[T.B2] hist
Frequency
1750
1500
1250
1000
750
500
250
0
−1.0
−0.9
−0.8
−0.7
−0.6
−0.5
−0.4

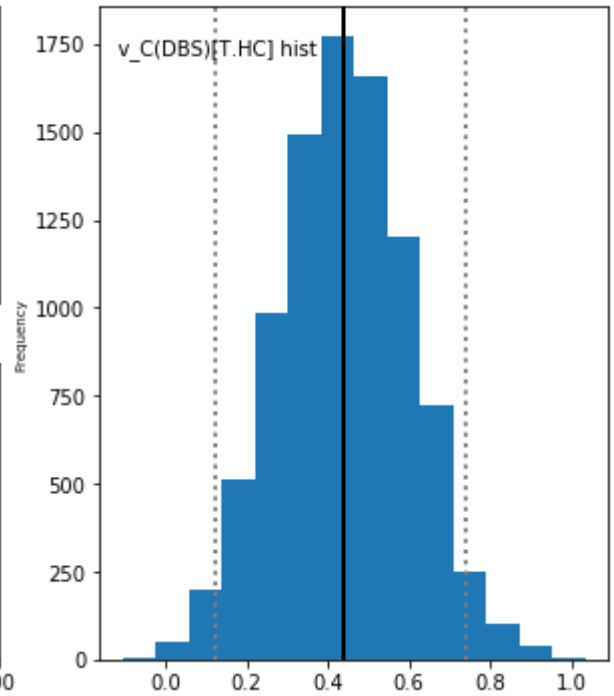

v_C(Block)[T.B3] trace

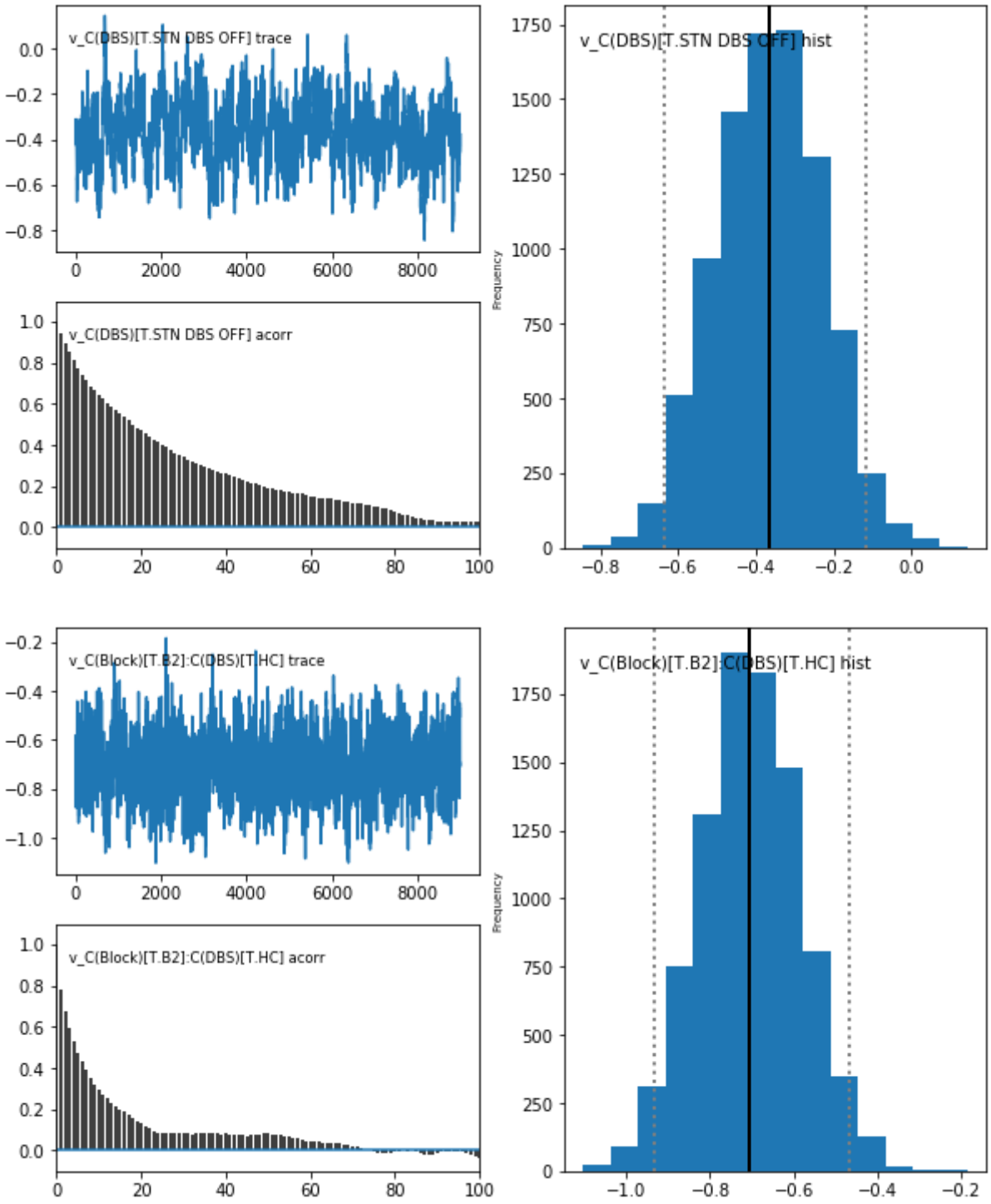

v_C(Block)[T.B3] acorr

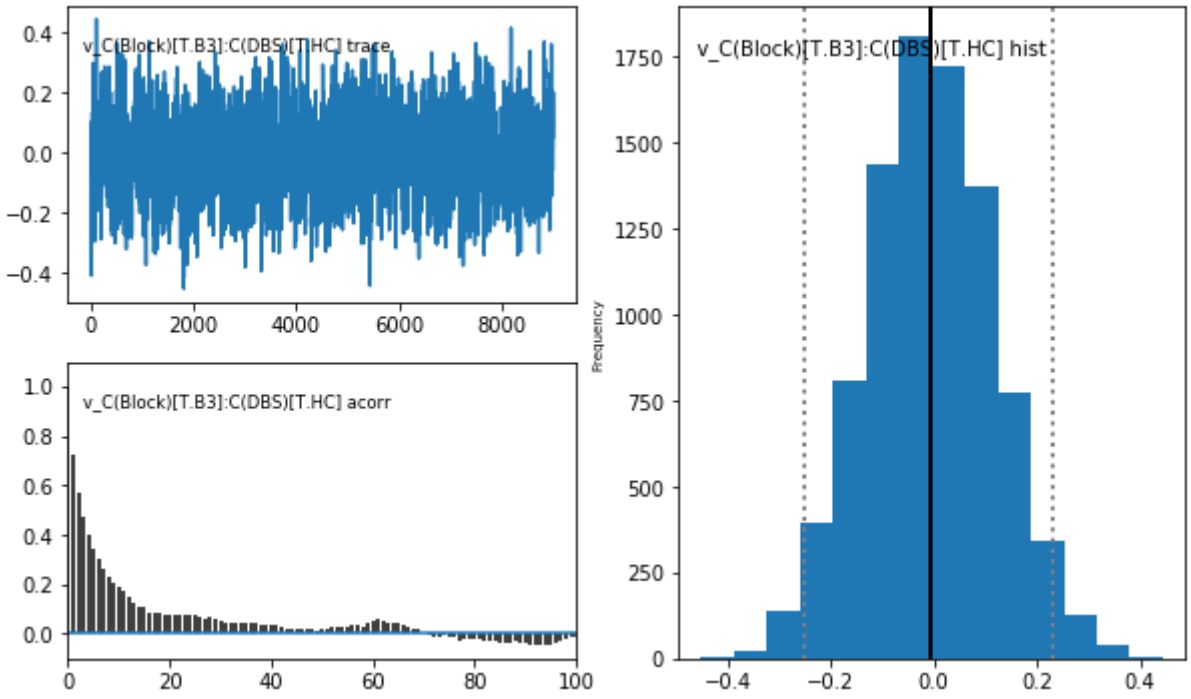

v_C(Block)[T.B3] hist
Frequency

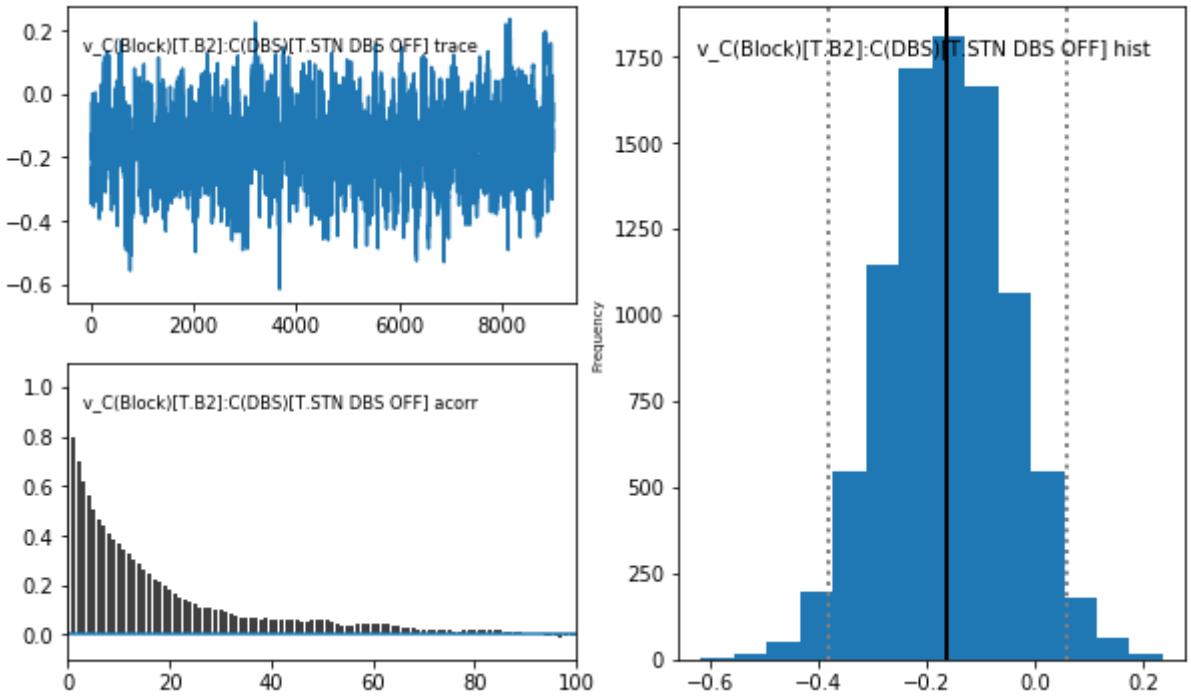

v_C(DBS)[T.HC] trace

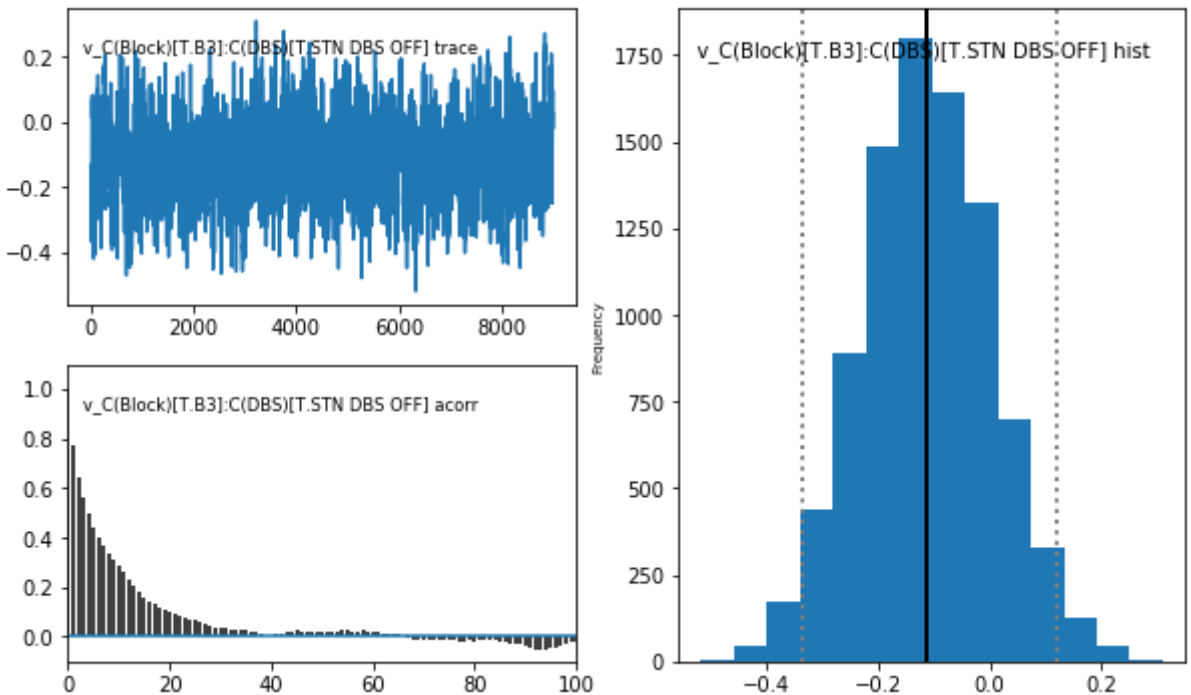

v_C(DBS)[T.HC] acorr

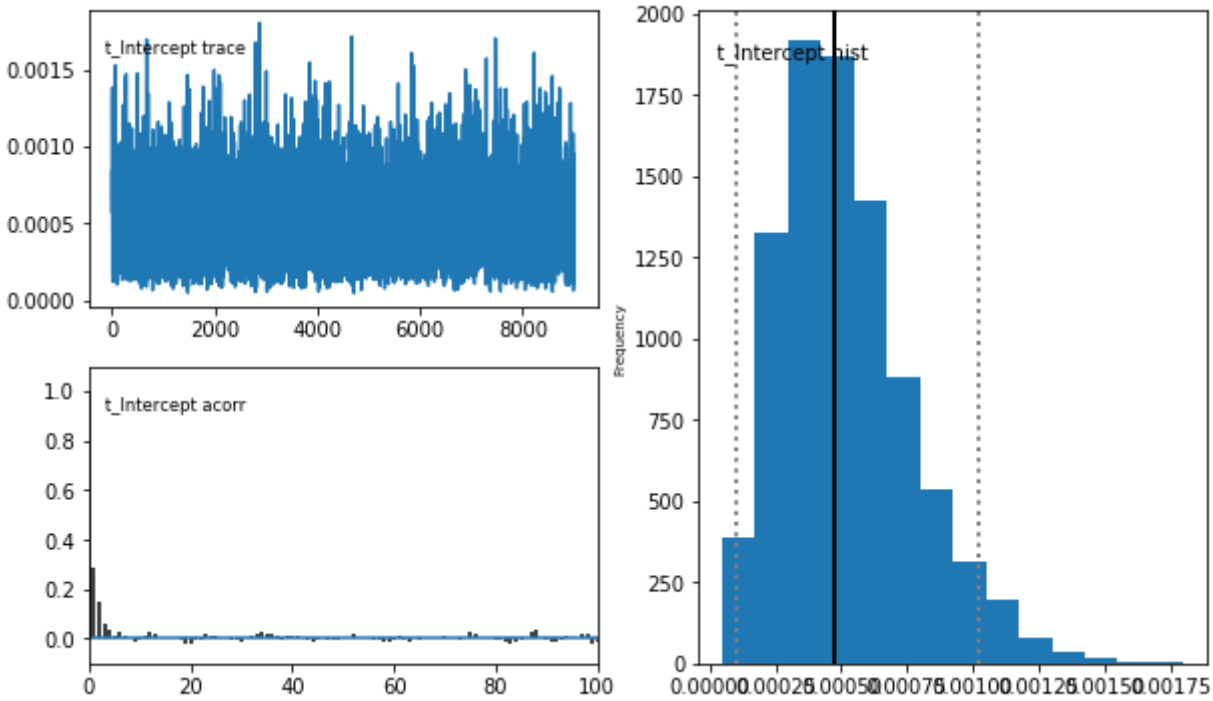

v_C(DBS)[T.HC] hist
Frequency

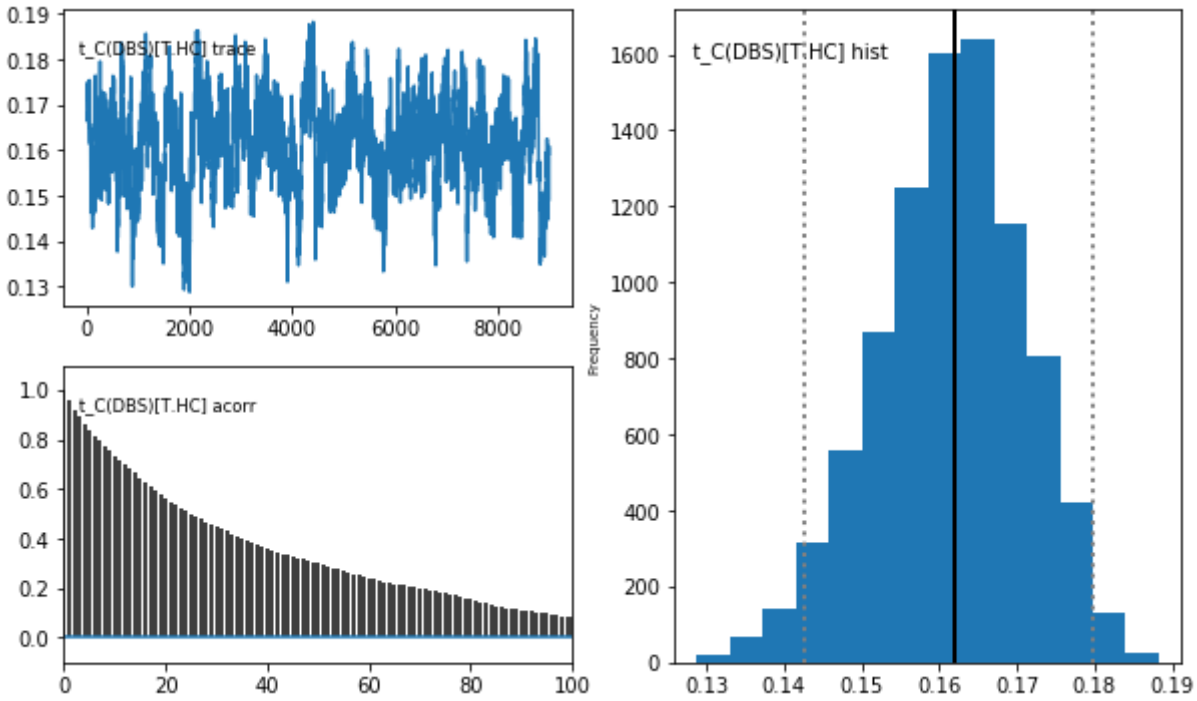

v_C(DBS)[T.STN DBS OFF] trace
v_C(DBS)[T.STN DBS OFF] acorr
v_C(DBS)[T.STN DBS OFF] hist
Frequency
v_C(Block)[T.B2]:C(DBS)[T.HC] trace
v_C(Block)[T.B2]:C(DBS)[T.HC] acorr
v_C(Block)[T.B2]:C(DBS)[T.HC] hist
Frequency

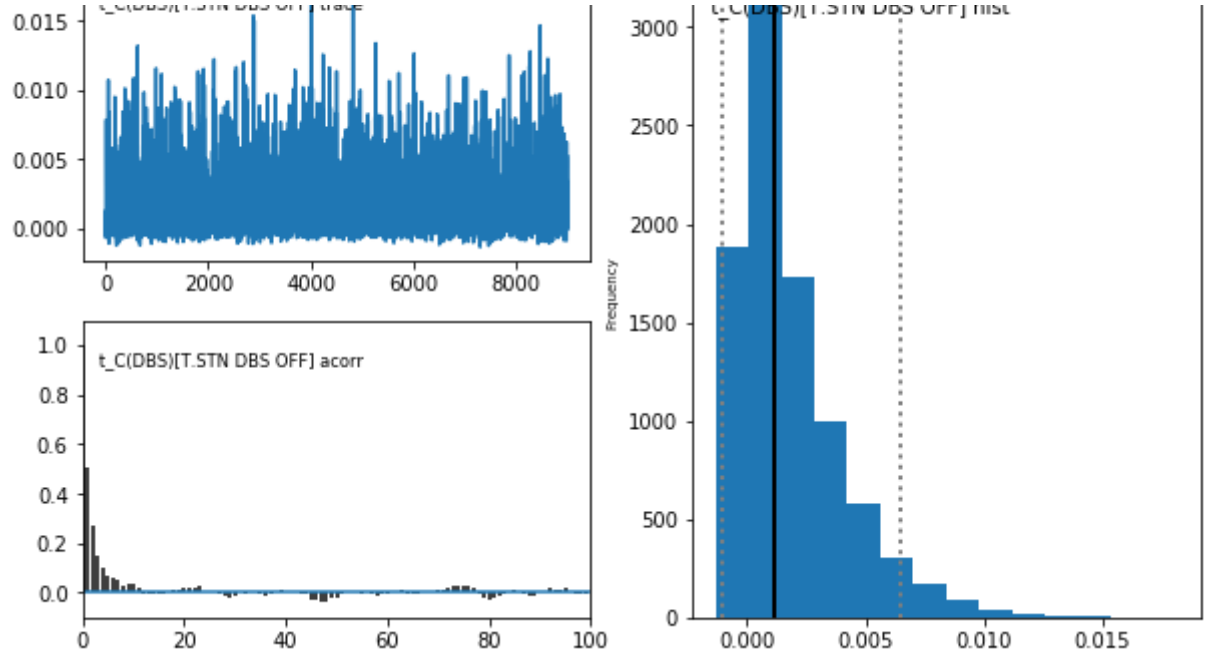

v_C(Block)[T.B3]:C(DBS)[T.HC] trace
v_C(Block)[T.B3]:C(DBS)[T.HC] acorr
v_C(Block)[T.B3]:C(DBS)[T.HC] hist
Frequency


v_C(Block)[T.B2]:C(DBS)[T.STN DBS OFF] trace
v_C(Block)[T.B2]:C(DBS)[T.STN DBS OFF] acorr
v_C(Block)[T.B2]:C(DBS)[T.STN DBS OFF] hist
Frequency


v_C(Block)[T.B3]:C(DBS)[T.STN DBS OFF] trace
v_C(Block)[T.B3]:C(DBS)[T.STN DBS OFF] acorr
v_C(Block)[T.B3]:C(DBS)[T.STN DBS OFF] hist
Frequency

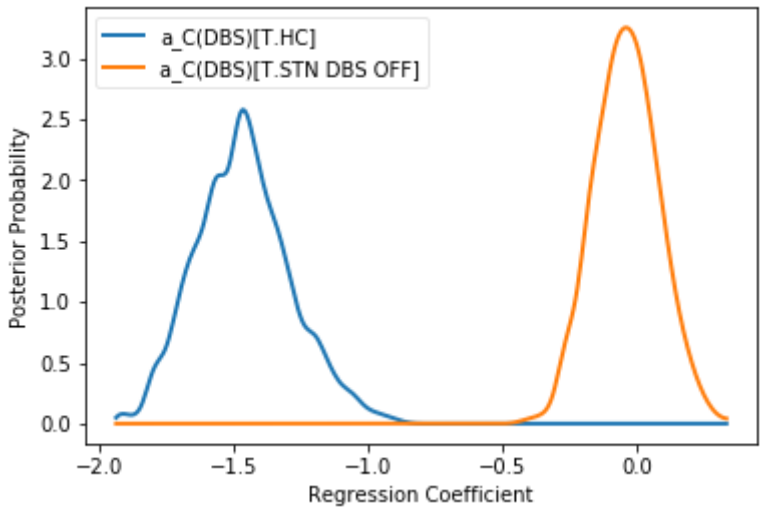

t_Intercept trace
t_Intercept hist
t_Intercept acorr
Frequency


t_C(DBS)[T.HC] trace
t_C(DBS)[T.HC] hist
t_C(DBS)[T.HC] acorr
Frequency



In [13]:
```
#Extract the estimated decision threshold (a) from the created model
a_Intercept, a_DBS_HC, a_DBS_OFF = m1.nodes_db.loc[['a_Intercept', 'a_C(DBS)[T.H

#Plot the posterior distribution of decision threshold (a) under the influence o
hddm.analyze.plot_posterior_nodes([a_DBS_HC, a_DBS_OFF])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(a_HC < 0)=", (a_DBS_HC.trace() < 0).mean()
print "P(a_DBSOFF < 0)=", (a_DBS_OFF.trace() < 0).mean()
```




```
P(a_HC < 0)= 1.0
P(a_DBSOFF < 0)= 0.681666666667
```

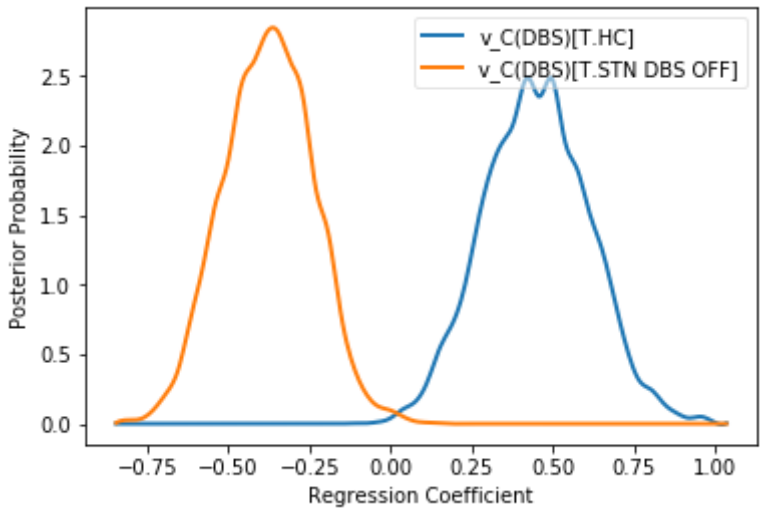
In [14]:
```
v_Intercept, v_DBS_HC, v_DBS_OFF = m1.nodes_db.loc[['v_Intercept', 'v_C(DBS)[T.H
v_Block2, v_Block3, v_Block2_HC, v_Block3_HC, v_Block2_DBSOFF, v_Block3_DBSOFF =


#Plot the posterior distribution of drift rate (v) under the influence of the DB
hddm.analyze.plot_posterior_nodes([v_DBS_HC, v_DBS_OFF])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(v_HC < 0)=", (v_DBS_HC.trace() < 0).mean()
print "P(v_DBSOFF < 0)=", (v_DBS_OFF.trace() < 0).mean()

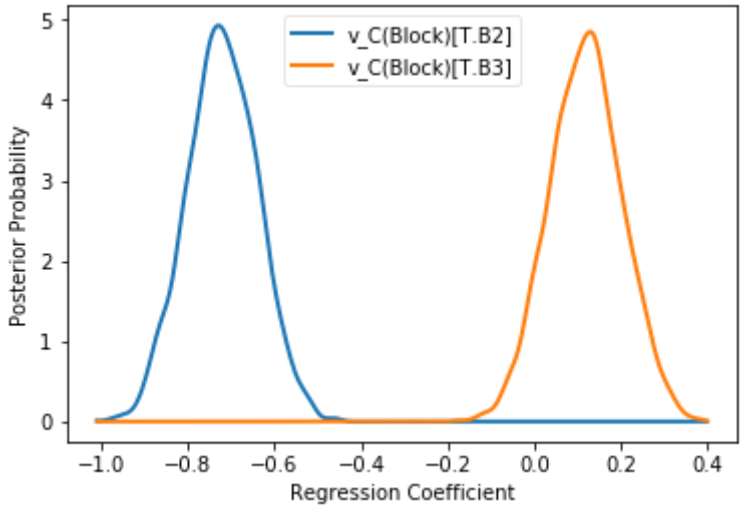
#Plot the posterior distribution of drift rate (v) under the influence of the Bl
hddm.analyze.plot_posterior_nodes([v_Block2, v_Block3])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(v_Block2 < 0)=", (v_Block2.trace() < 0).mean()
print "P(v_Block3 < 0)=", (v_Block3.trace() < 0).mean()

#Plot the posterior distribution of drift rate (v) under the influence of the tw
hddm.analyze.plot_posterior_nodes([v_Block2_HC, v_Block3_HC])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(v_Block2_HC < 0)=", (v_Block2_HC.trace() < 0).mean()
print "P(v_Block3_HC < 0)=", (v_Block3_HC.trace() < 0).mean()

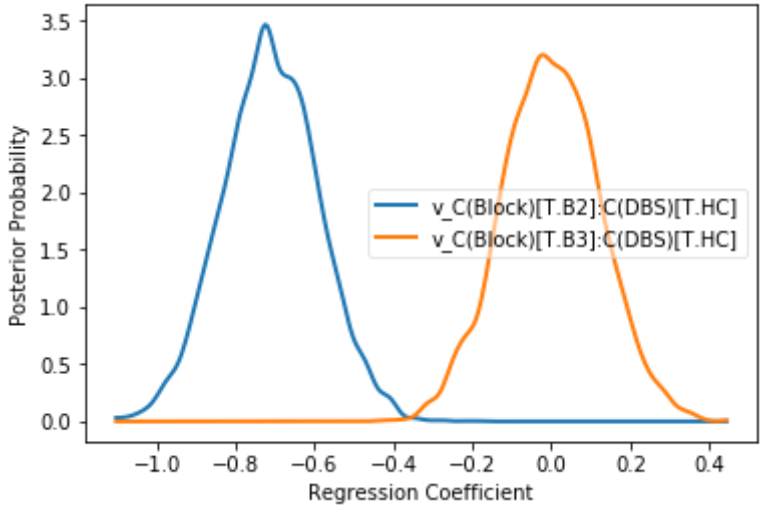
#Plot the posterior distribution of drift rate (v) under the influence of the tw
hddm.analyze.plot_posterior_nodes([v_Block2_DBSOFF, v_Block3_DBSOFF])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(v_Block2_DBSOFF < 0)=", (v_Block2_DBSOFF.trace() < 0).mean()
print "P(v_Block3_DBSOFF < 0)=", (v_Block3_DBSOFF.trace() < 0).mean()
```



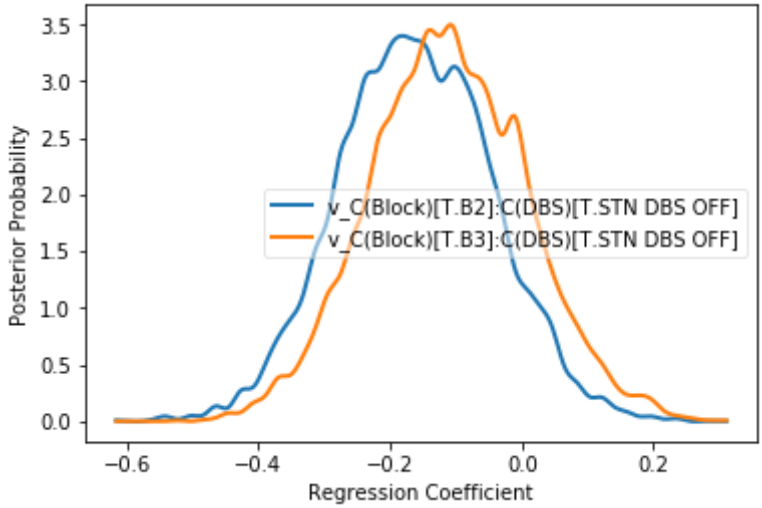

```
P(v_HC < 0)= 0.001
P(v_DBSOFF < 0)= 0.995444444444
```



P(v_Block2 < 0)= 1.0
P(v_Block3 < 0)= 0.092



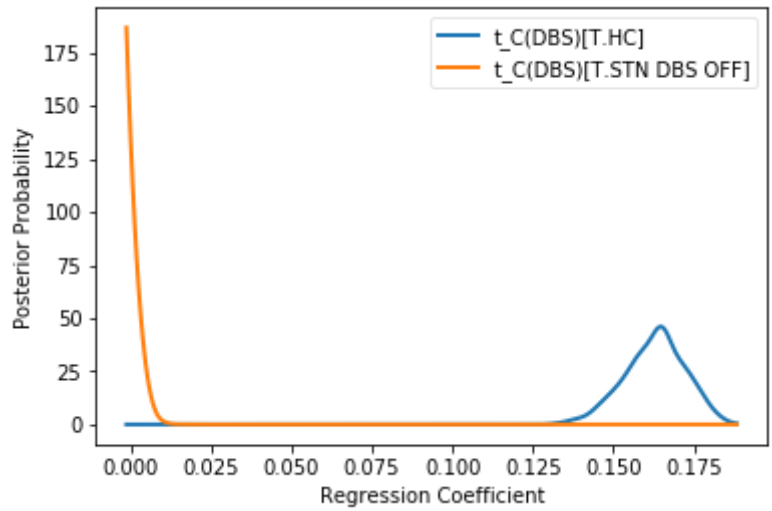
P(v_Block2_HC < 0)= 1.0
P(v_Block3_HC < 0)= 0.524888888889



P(v_Block2_DBSOFF < 0)= 0.920444444444
P(v_Block3_DBSOFF < 0)= 0.836444444444

In [15]:
```
#Extract the estimated non-decision time (t) from the created model
t_Intercept, t_DBS_HC, t_DBS_OFF = m1.nodes_db.loc[['t_Intercept', 't_C(DBS)[T.H

#Plot the posterior distribution of non-decision time under the influence of the
hddm.analyze.plot_posterior_nodes([t_DBS_HC, t_DBS_OFF])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(t_HC < 0)=", (t_DBS_HC.trace() < 0).mean()
print "P(t_DBSOFF < 0)=", (t_DBS_OFF.trace() < 0).mean()
```




```
P(t_HC < 0)= 0.0
P(t_DBSOFF < 0)= 0.195888888889
```

In [ ]:

Appendix - Programming coeds for Chapter 4

In [1]:
```
#import the related toolboxes
import hddm
import pandas as pd
import matplotlib.pyplot as plt
```

```
/Users/Nicole/anaconda2/lib/python2.7/site-packages/IPython/parallel.py:13: Sh
imWarning: The `IPython.parallel` package has been deprecated. You should impo
rt from ipyparallel instead.
  "You should import from ipyparallel instead.", ShimWarning)
```

In [4]:
```
#load the data
data = hddm.load_csv('/Users/Nicole/Desktop/Latest drafts3/DBS_switching/DBS.csv
```

In [5]:
```
#Create the model with all available data
m = hddm.HDDMRegressor(data, ["a ~ C(Type)*C(Coherence)*C(DBS)","v ~ C(Coherence
```

```
Adding these covariates:
['a_Intercept', 'a_C(Type)[T.SP]', 'a_C(Coherence)[T.High]', 'a_C(Coherence)
[T.Low]', 'a_C(DBS)[T.HC]', 'a_C(DBS)[T.STN DBS OFF]', 'a_C(Type)[T.SP]:C(Cohe
rence)[T.High]', 'a_C(Type)[T.SP]:C(Coherence)[T.Low]', 'a_C(Type)[T.SP]:C(DB
S)[T.HC]', 'a_C(Type)[T.SP]:C(DBS)[T.STN DBS OFF]', 'a_C(Coherence)[T.High]:C
(DBS)[T.HC]', 'a_C(Coherence)[T.Low]:C(DBS)[T.HC]', 'a_C(Coherence)[T.High]:C
(DBS)[T.STN DBS OFF]', 'a_C(Coherence)[T.Low]:C(DBS)[T.STN DBS OFF]', 'a_C(Typ
e)[T.SP]:C(Coherence)[T.High]:C(DBS)[T.HC]', 'a_C(Type)[T.SP]:C(Coherence)[T.L
ow]:C(DBS)[T.HC]', 'a_C(Type)[T.SP]:C(Coherence)[T.High]:C(DBS)[T.STN DBS OF
F]', 'a_C(Type)[T.SP]:C(Coherence)[T.Low]:C(DBS)[T.STN DBS OFF]']
Adding these covariates:
['v_Intercept', 'v_C(Coherence)[T.High]', 'v_C(Coherence)[T.Low]', 'v_C(DBS)
[T.HC]', 'v_C(DBS)[T.STN DBS OFF]', 'v_C(Coherence)[T.High]:C(DBS)[T.HC]', 'v_
C(Coherence)[T.Low]:C(DBS)[T.HC]', 'v_C(Coherence)[T.High]:C(DBS)[T.STN DBS OF
F]', 'v_C(Coherence)[T.Low]:C(DBS)[T.STN DBS OFF]']
```

In [6]:
```
#Start drawing 10000 samples and discarding 1000 as burn-in
m.sample(10000, burn=1000)
```

```
 [-----------------100%-----------------] 10001 of 10000 complete in 13535.5 s
ec
```

Out[6]:
```
<pymc.MCMC.MCMC at 0x1194e03d0>
```

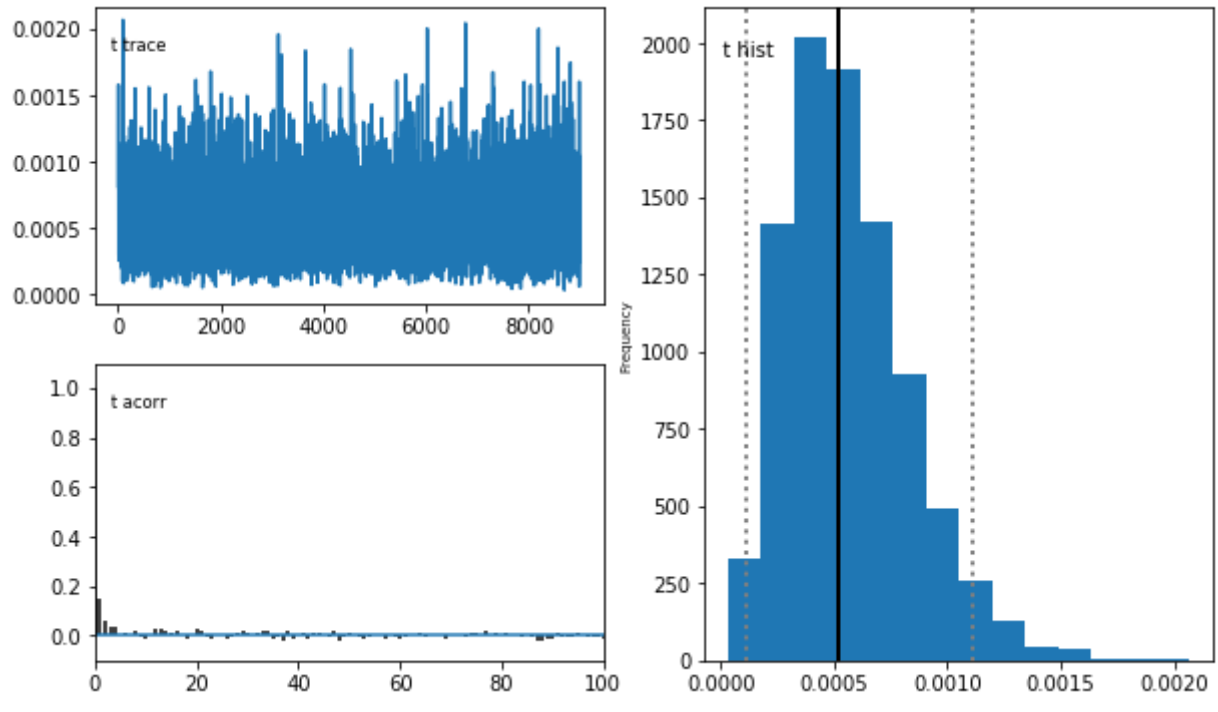
In [7]:
```
#Plot the figures to examine the convergence of the model
m.plot_posteriors()
plt.show()

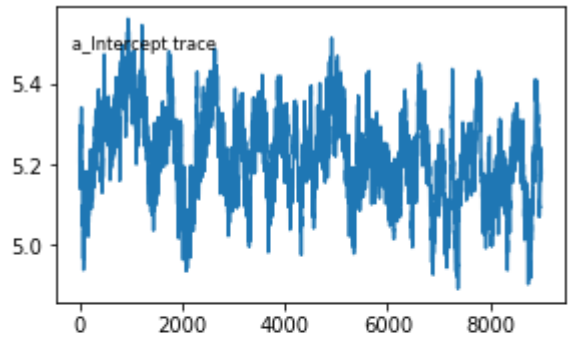
#As the figures shown, the model doesn't seem to be we
```

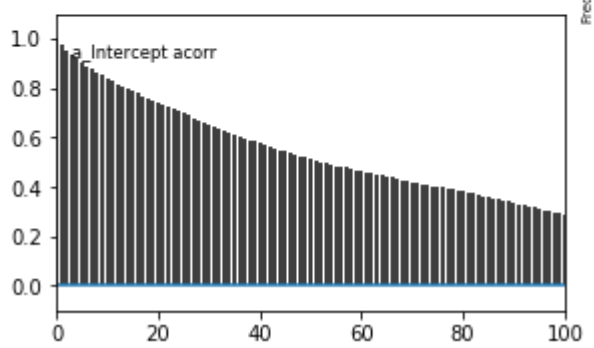
```
Plotting t
Plotting a_Intercept
Plotting a_C(Type)[T.SP]
Plotting a_C(Coherence)[T.High]
Plotting a_C(Coherence)[T.Low]
Plotting a_C(DBS)[T.HC]
Plotting a_C(DBS)[T.STN DBS OFF]
Plotting a_C(Type)[T.SP]:C(Coherence)[T.High]
Plotting a_C(Type)[T.SP]:C(Coherence)[T.Low]
Plotting a_C(Type)[T.SP]:C(DBS)[T.HC]
Plotting a_C(Type)[T.SP]:C(DBS)[T.STN DBS OFF]
Plotting a_C(Coherence)[T.High]:C(DBS)[T.HC]
Plotting a_C(Coherence)[T.Low]:C(DBS)[T.HC]
Plotting a_C(Coherence)[T.High]:C(DBS)[T.STN DBS OFF]
Plotting a_C(Coherence)[T.Low]:C(DBS)[T.STN DBS OFF]
Plotting a_C(Type)[T.SP]:C(Coherence)[T.High]:C(DBS)[T.HC]
Plotting a_C(Type)[T.SP]:C(Coherence)[T.Low]:C(DBS)[T.HC]
Plotting a_C(Type)[T.SP]:C(Coherence)[T.High]:C(DBS)[T.STN DBS OFF]
Plotting a_C(Type)[T.SP]:C(Coherence)[T.Low]:C(DBS)[T.STN DBS OFF]
Plotting v_Intercept
Plotting v_C(Coherence)[T.High]
```

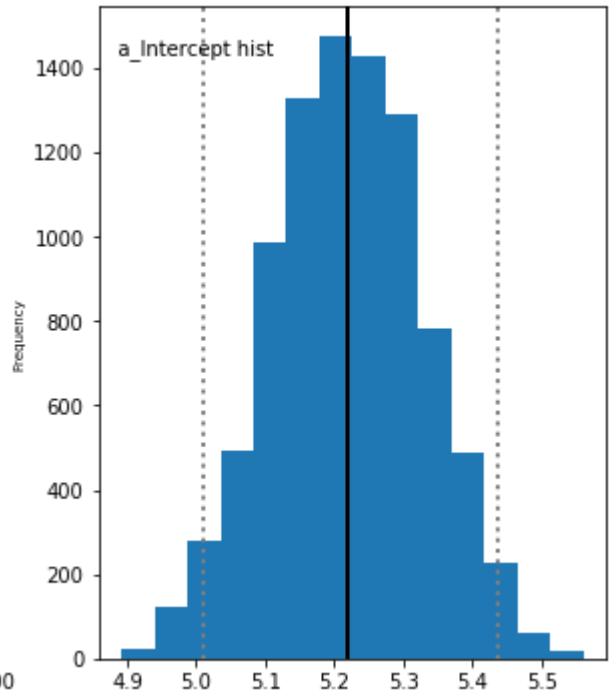
```
/Users/Nicole/anaconda2/lib/python2.7/site-packages/matplotlib/pyplot.py:524:
RuntimeWarning: More than 20 figures have been opened. Figures created through
the pyplot interface (`matplotlib.pyplot.figure`) are retained until explicitl
y closed and may consume too much memory. (To control this warning, see the rc
Param `figure.max_open_warning`).
  max_open_warning, RuntimeWarning)
```

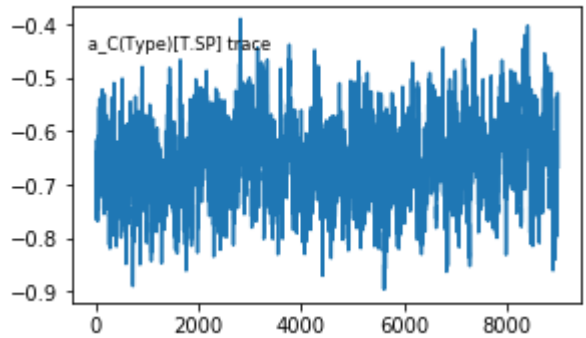
```
Plotting v_C(Coherence)[T.Low]
Plotting v_C(DBS)[T.HC]
Plotting v_C(DBS)[T.STN DBS OFF]
Plotting v_C(Coherence)[T.High]:C(DBS)[T.HC]
Plotting v_C(Coherence)[T.Low]:C(DBS)[T.HC]
Plotting v_C(Coherence)[T.High]:C(DBS)[T.STN DBS OFF]
Plotting v_C(Coherence)[T.Low]:C(DBS)[T.STN DBS OFF]
```

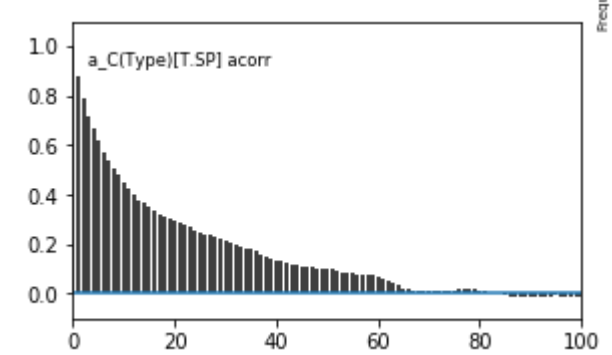


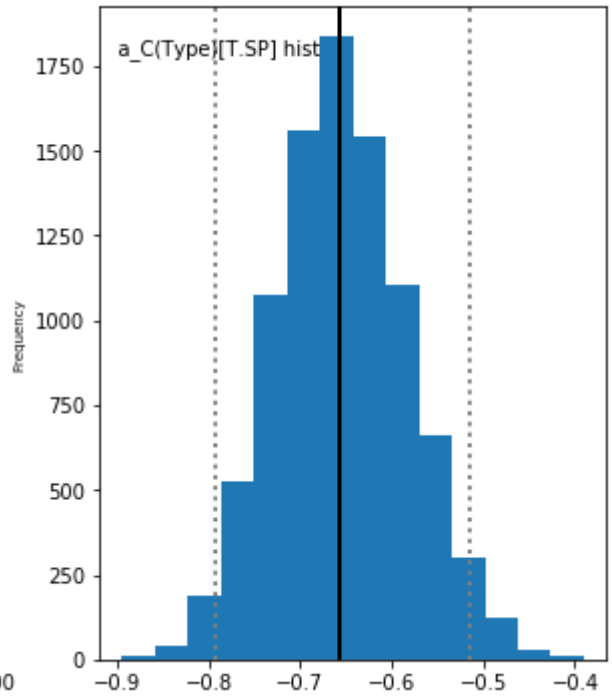

a_Intercept trace
5.4
5.2
5.0
0
2000
4000
6000
8000

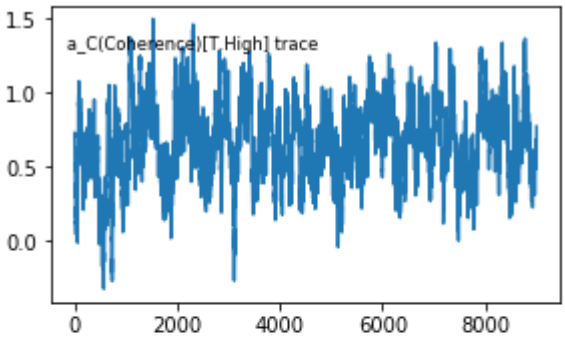

a_Intercept acorr
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100

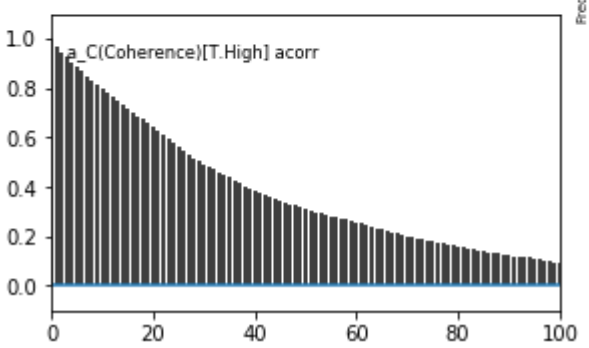

a_Intercept hist
Frequency
1400
1200
1000
800
600
400
200
0
4.9
5.0
5.1
5.2
5.3
5.4
5.5

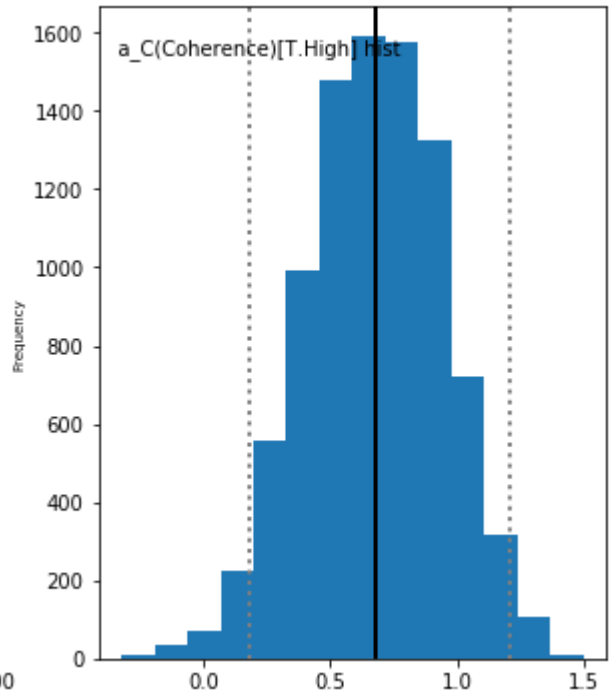

a_C(Type)[T.SP] trace
−0.4
−0.5
−0.6
−0.7
−0.8
−0.9
0
2000
4000
6000
8000

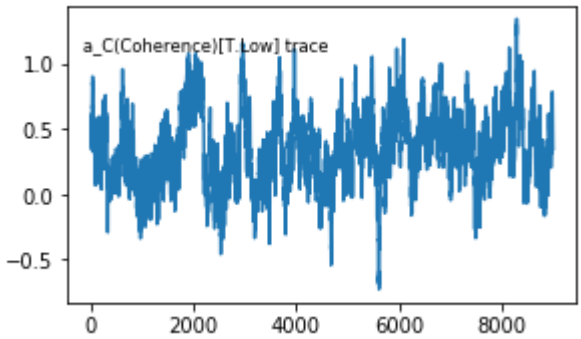

a_C(Type)[T.SP] acorr
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100

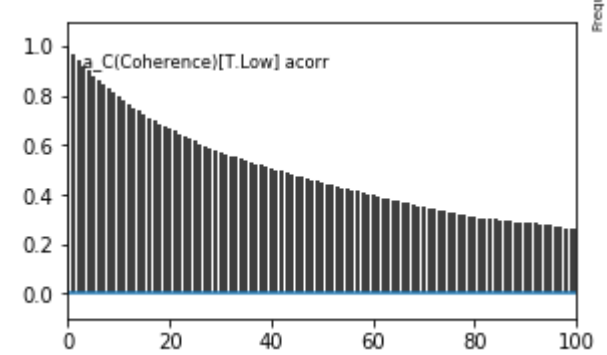

a_C(Type)[T.SP] hist
Frequency
1750
1500
1250
1000
750
500
250
0
−0.9
−0.8
−0.7
−0.6
−0.5
−0.4

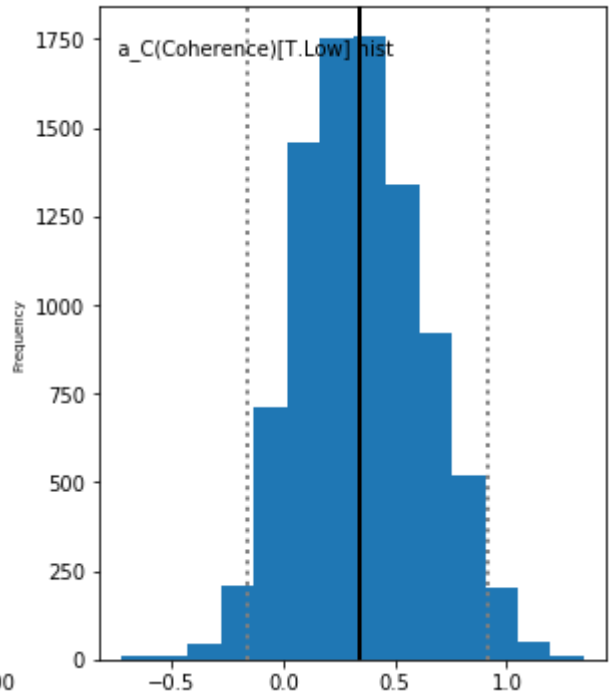

a_C(Coherence)[T.High] trace

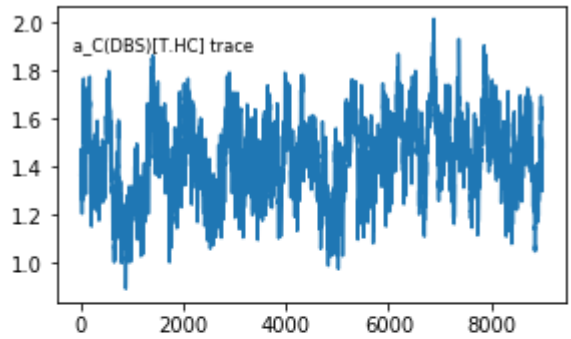

a_C(Coherence)[T.High] acorr

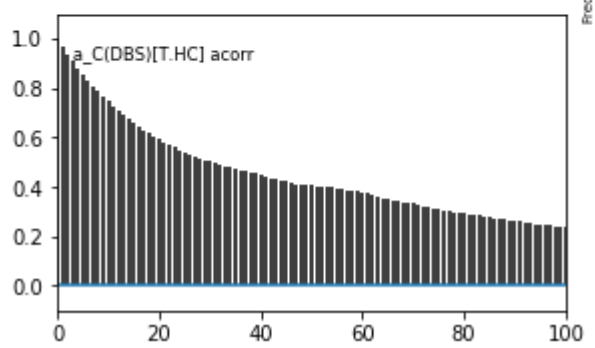

a_C(Coherence)[T.High] hist
Frequency

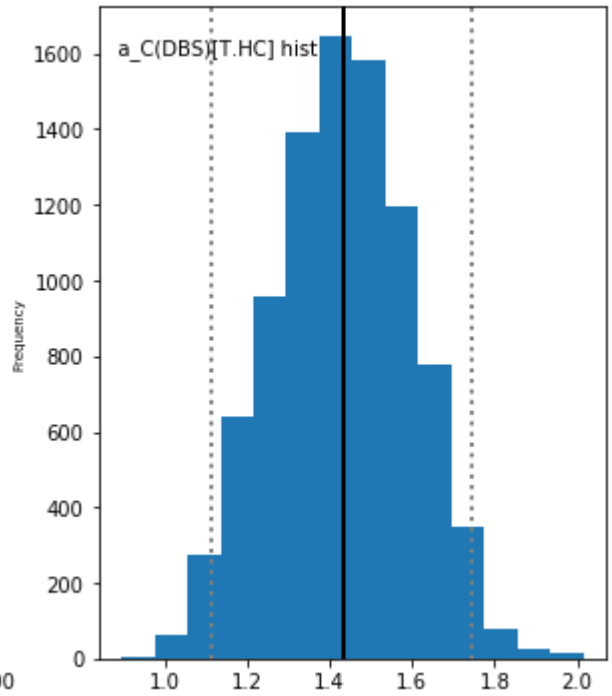

a_C(Coherence)[T.Low] trace

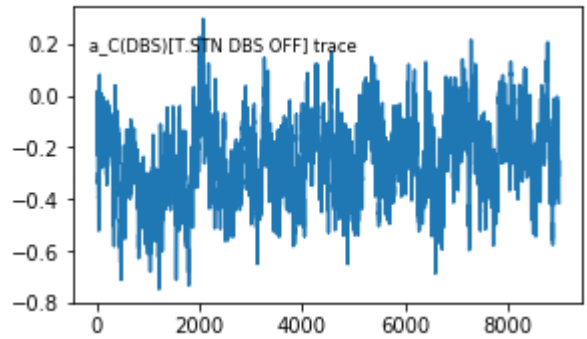

a_C(Coherence)[T.Low] acorr

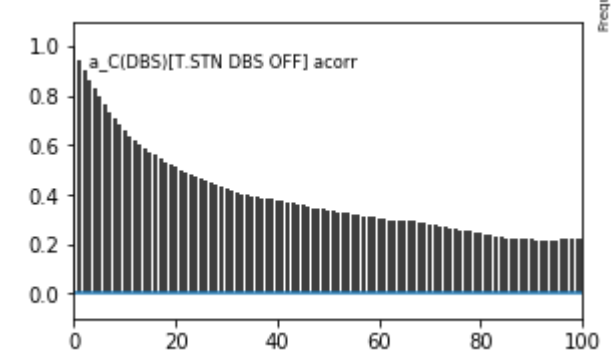

a_C(Coherence)[T.Low] hist
Frequency

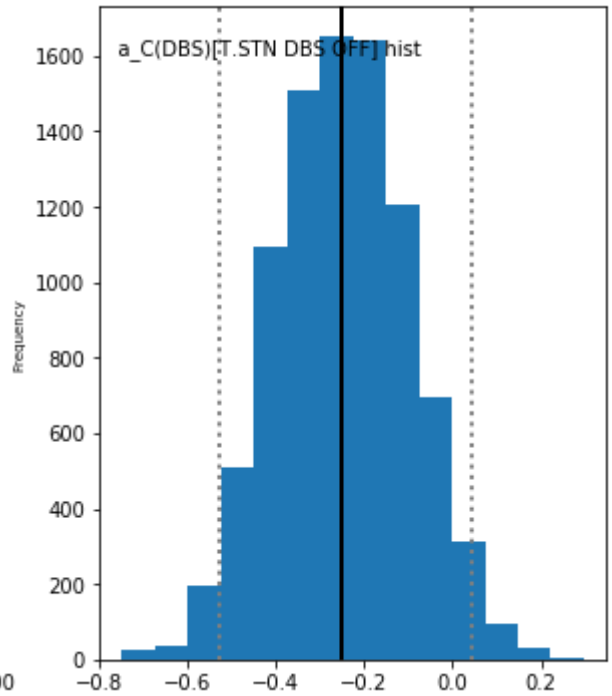

a_C(DBS)[T.HC] trace

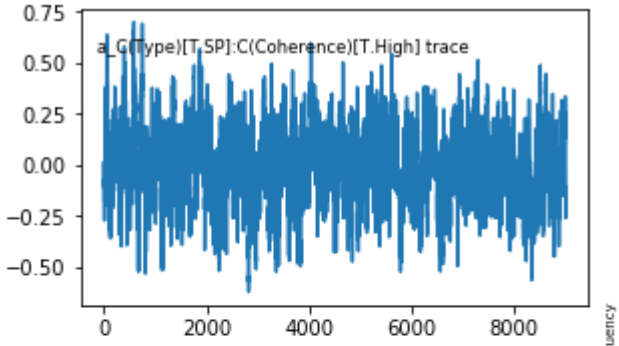

a_C(DBS)[T.HC] acorr

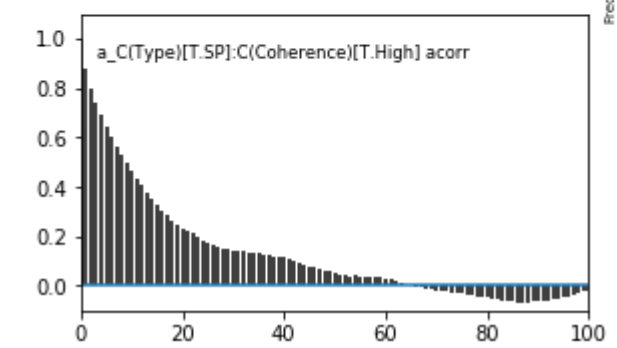

a_C(DBS)[T.HC] hist
Frequency

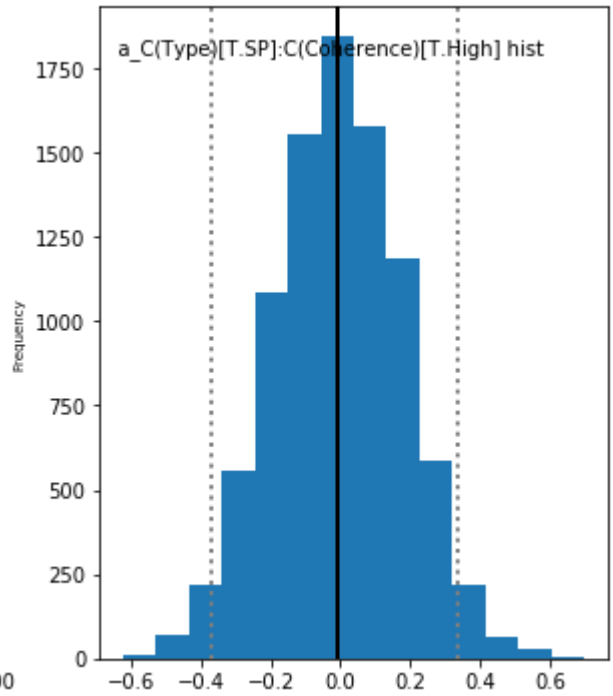

a_C(DBS)[T.STN DBS OFF] trace

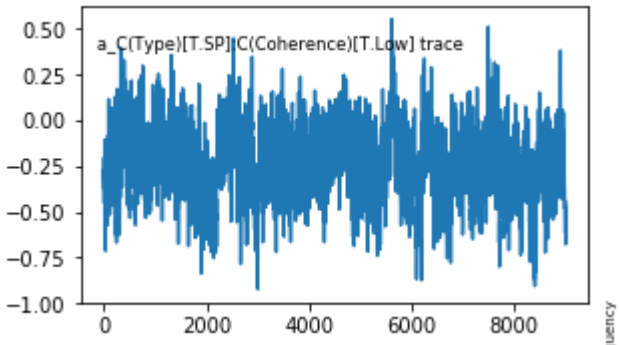

a_C(DBS)[T.STN DBS OFF] acorr

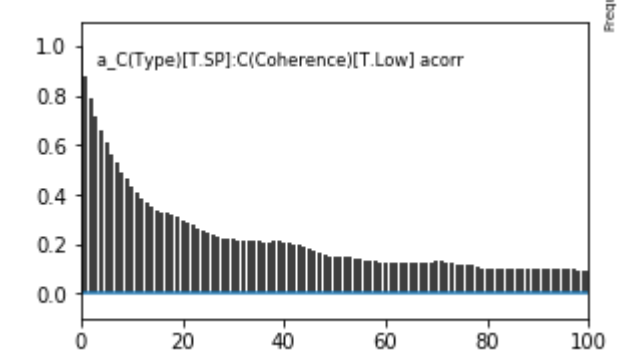

a_C(DBS)[T.STN DBS OFF] hist
Frequency

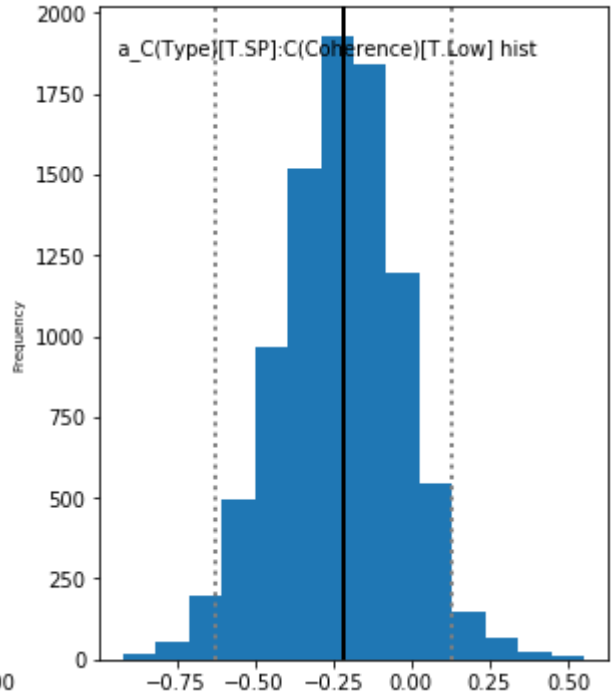

a_C(Type)[T.SP]:C(Coherence)[T.High] trace

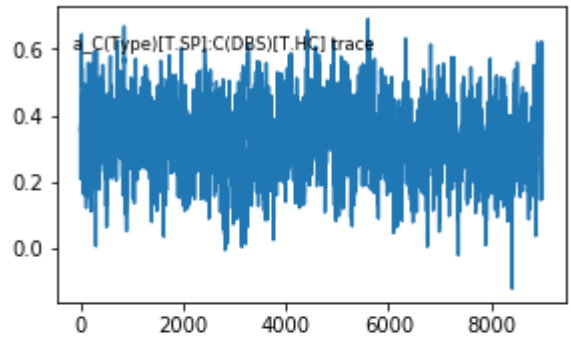

a_C(Type)[T.SP]:C(Coherence)[T.High] acorr

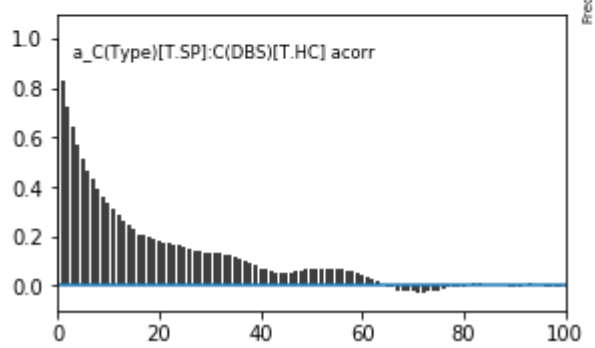

a_C(Type)[T.SP]:C(Coherence)[T.High] hist
Frequency


a_C(Type)[T.SP]:C(Coherence)[T.Low] trace


a_C(Type)[T.SP]:C(Coherence)[T.Low] acorr


a_C(Type)[T.SP]:C(Coherence)[T.Low] hist
Frequency


a_C(Type)[T.SP]:C(DBS)[T.HC] trace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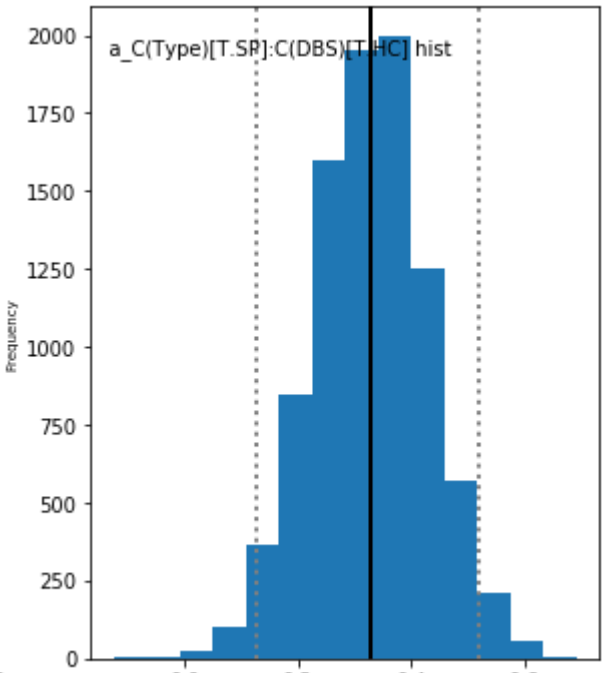
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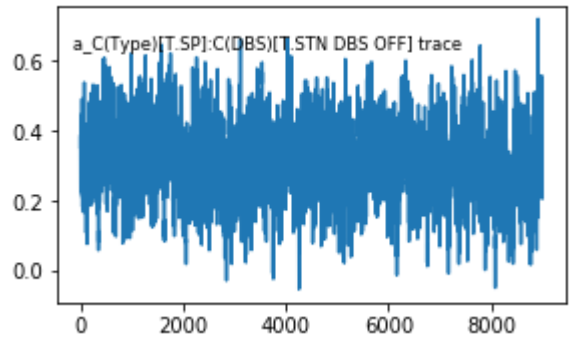
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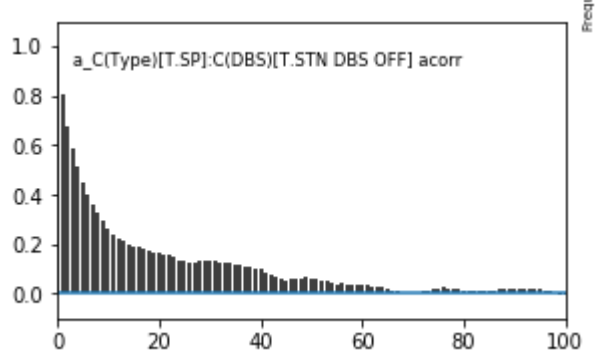
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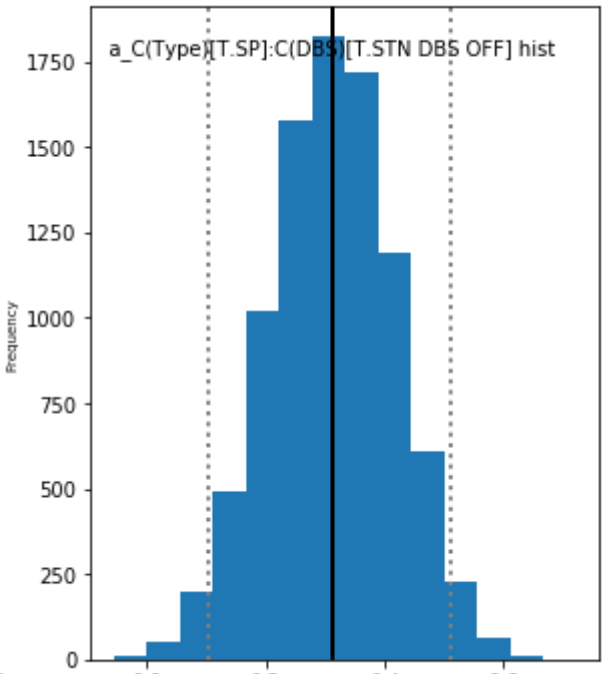
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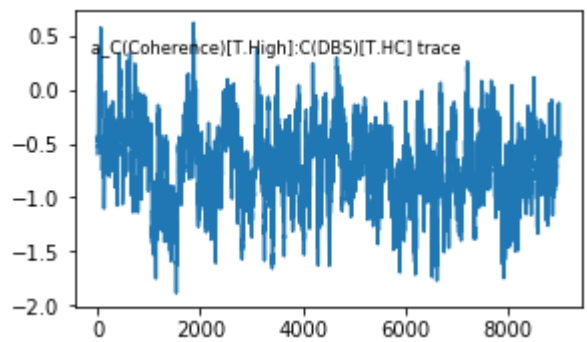
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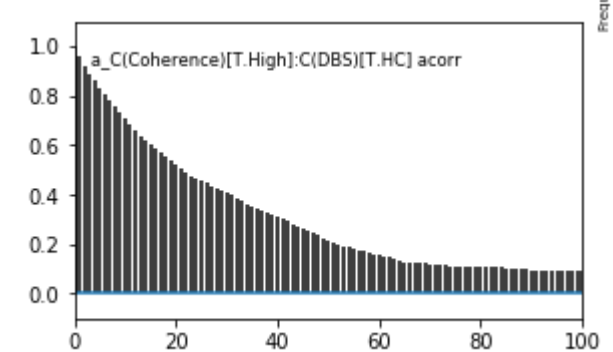
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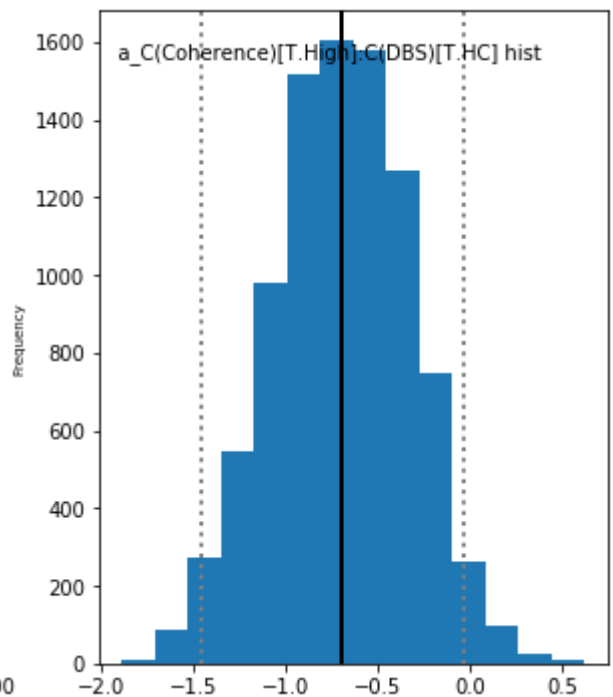
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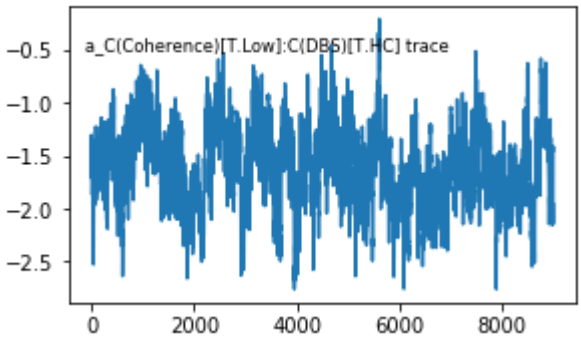
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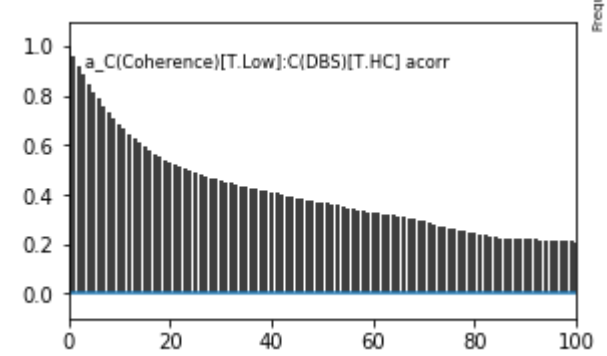
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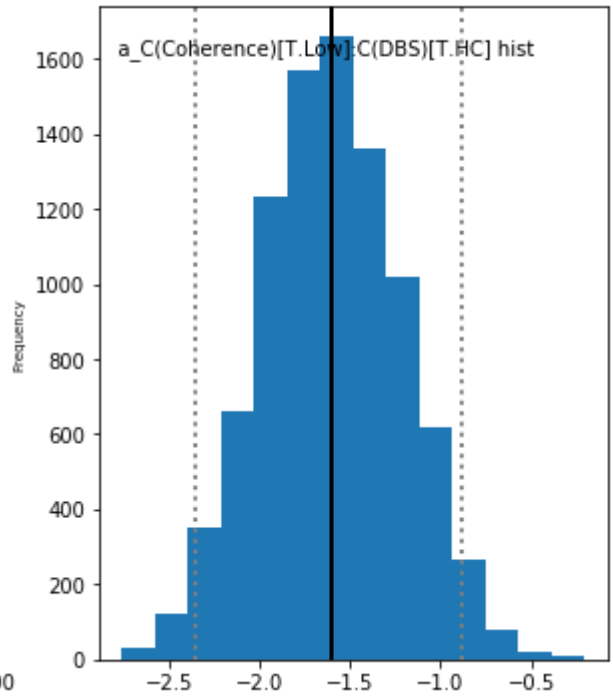
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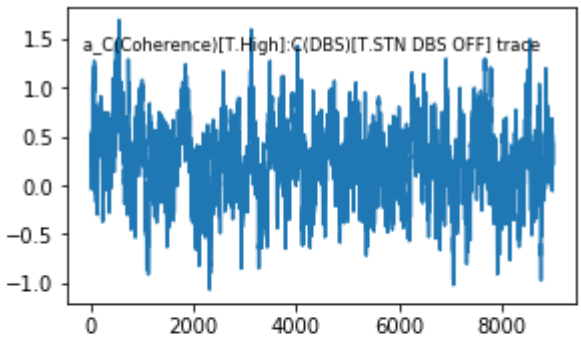
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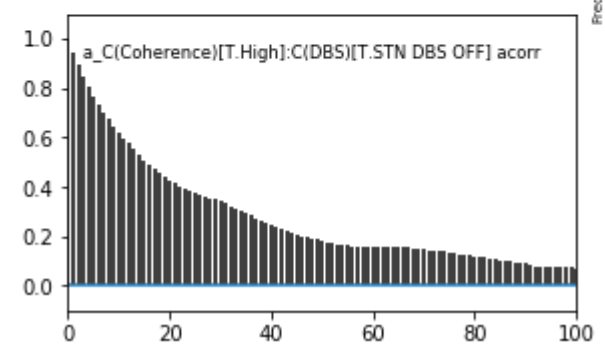
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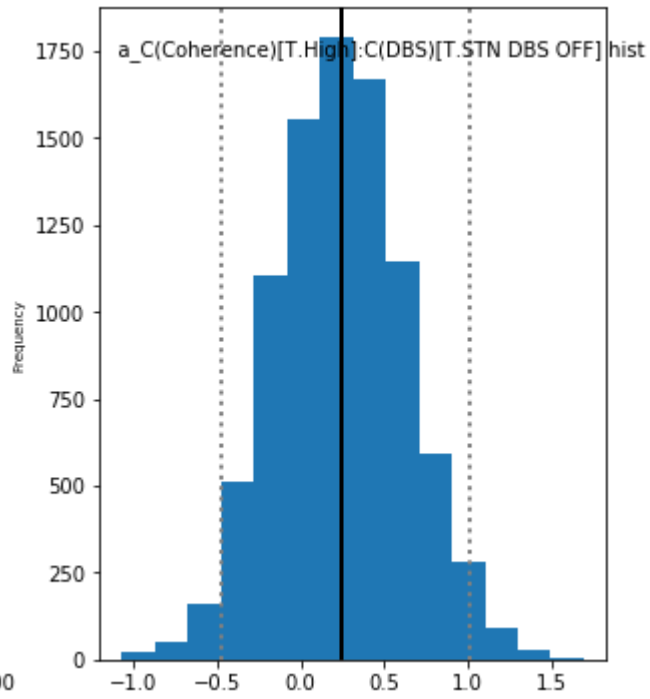
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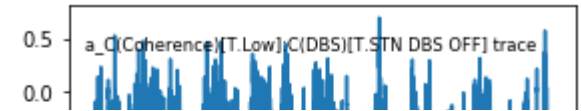
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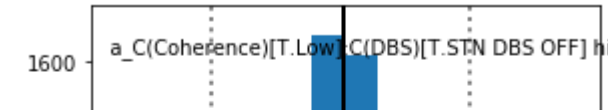
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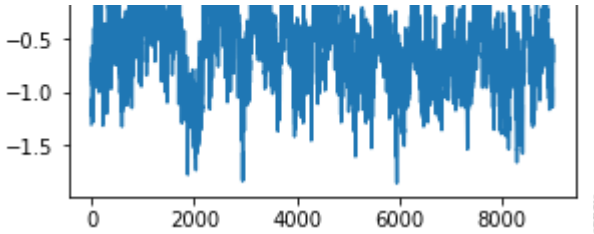

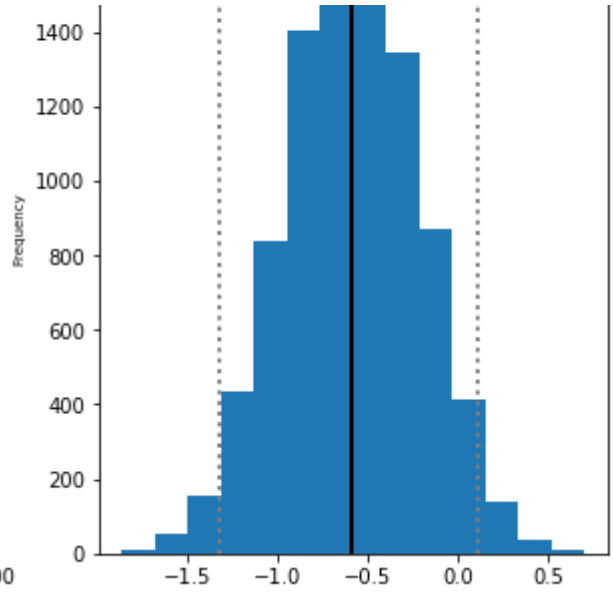
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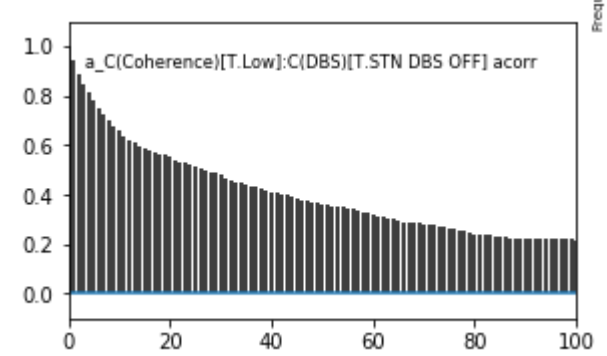
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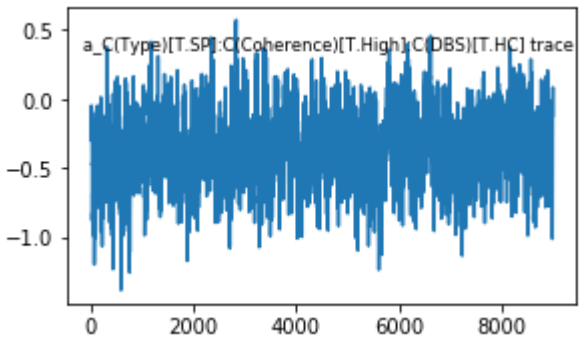
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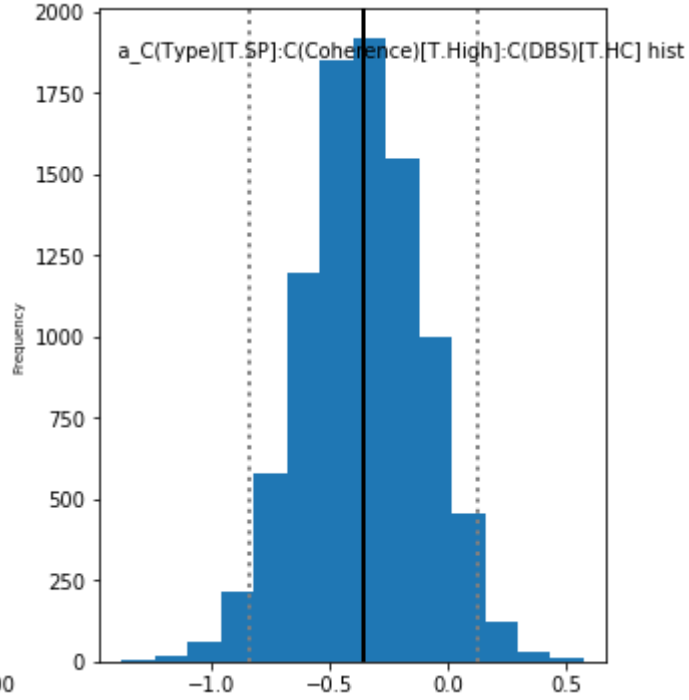
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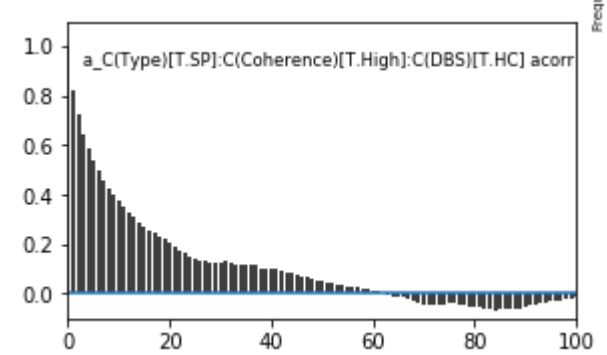
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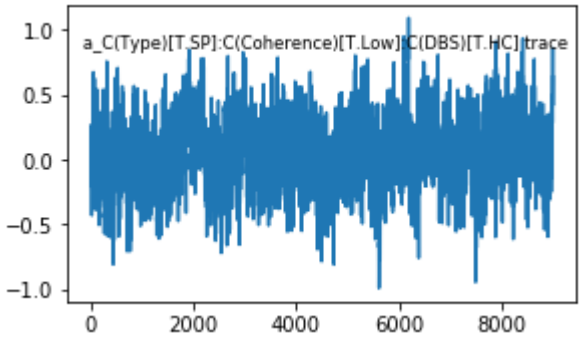
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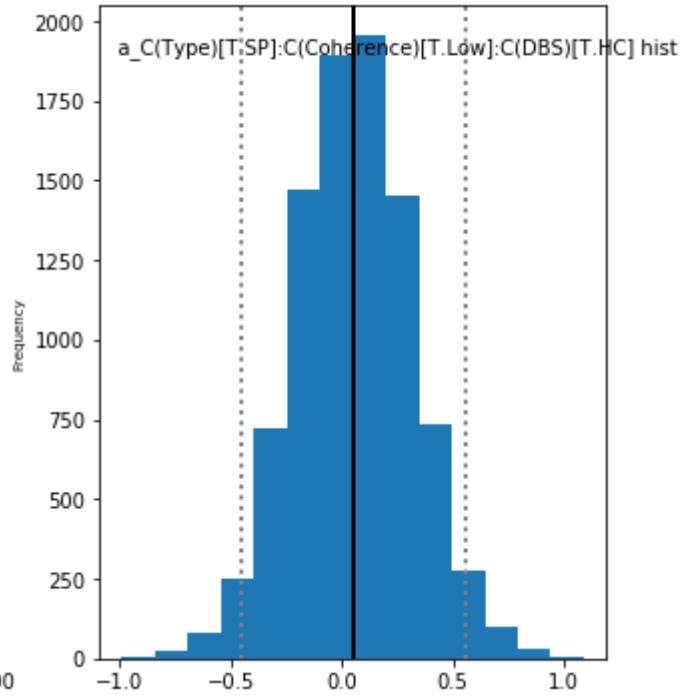
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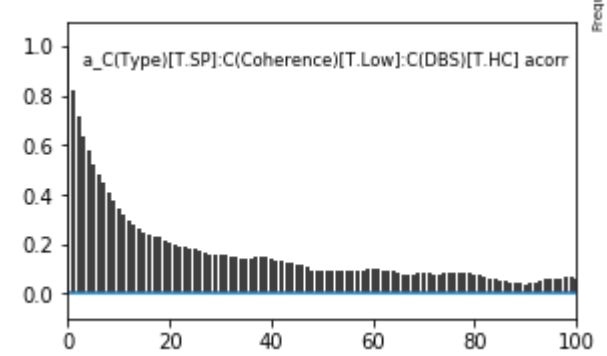
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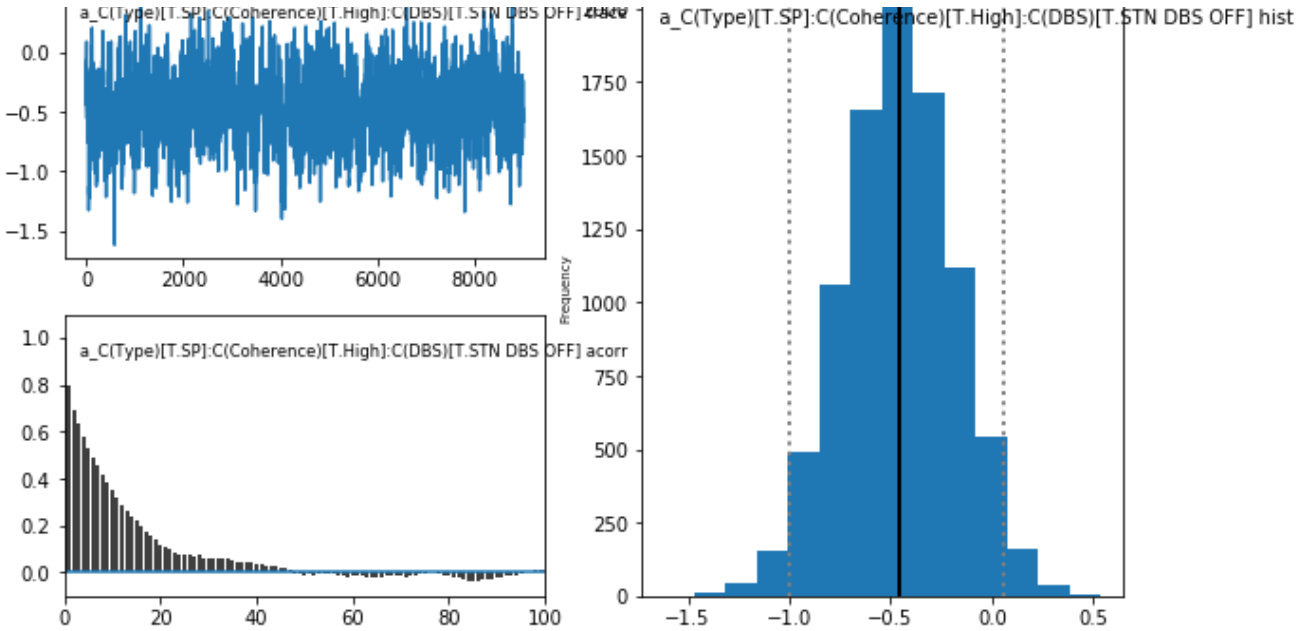
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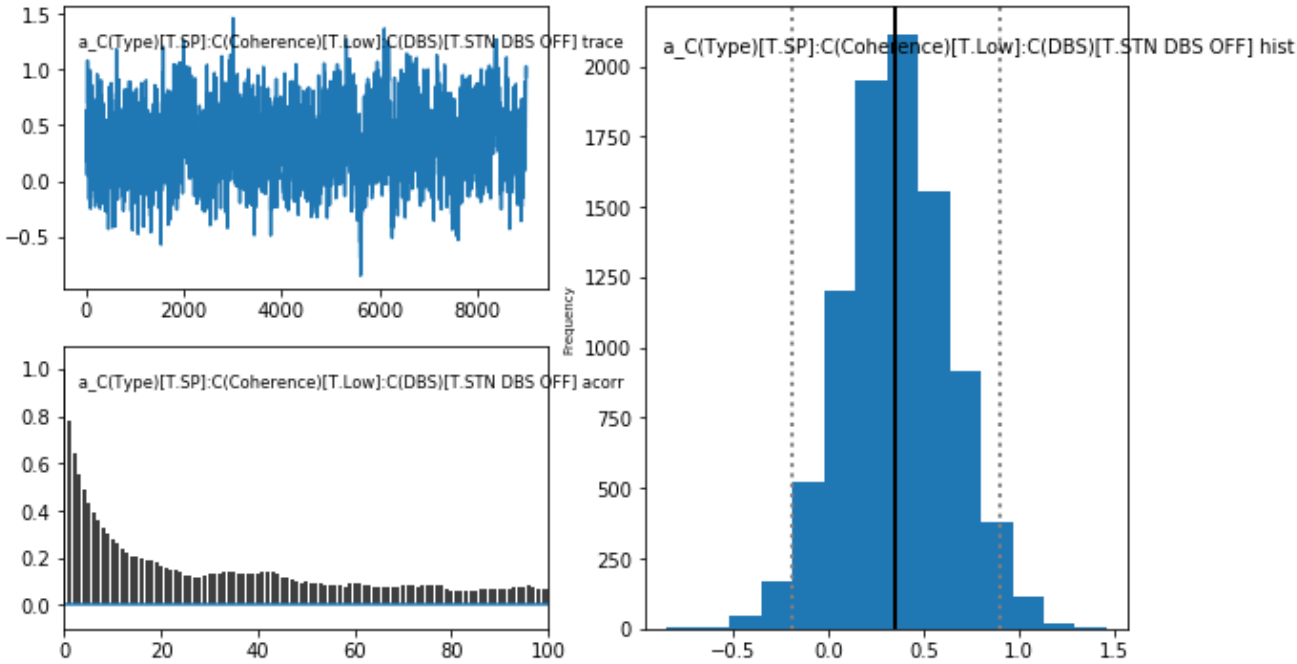
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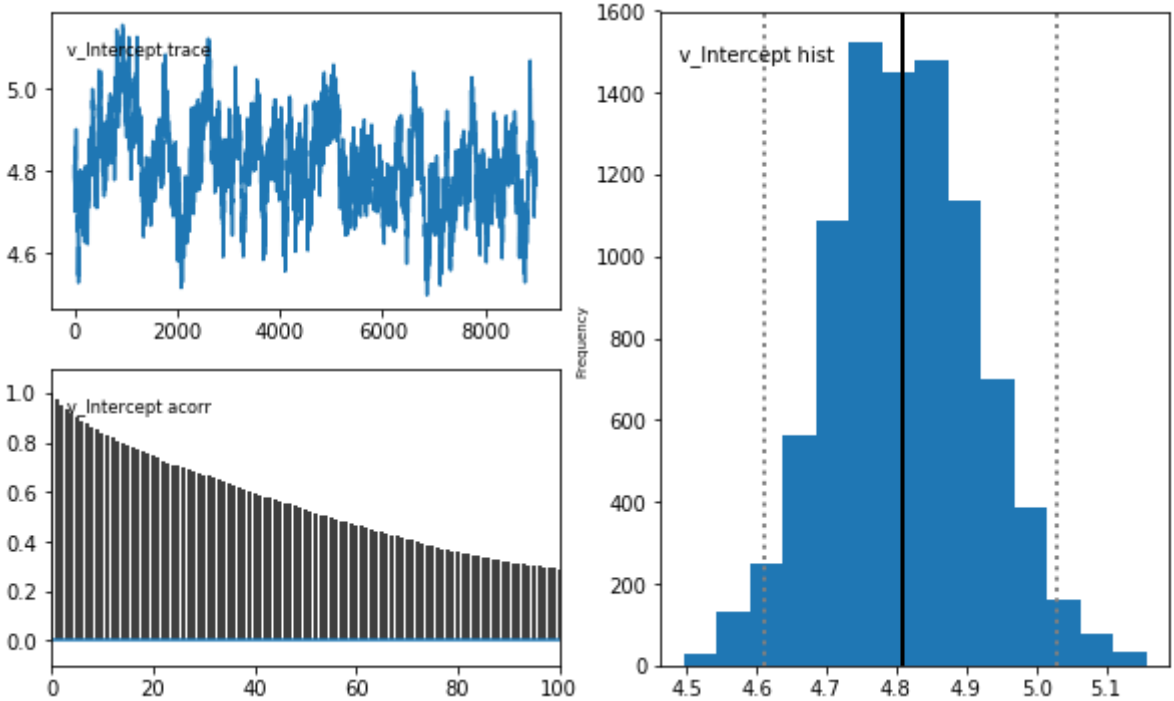
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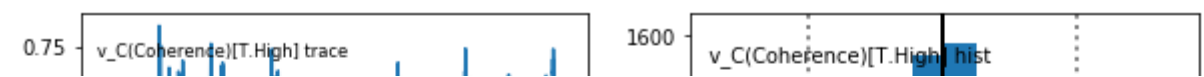
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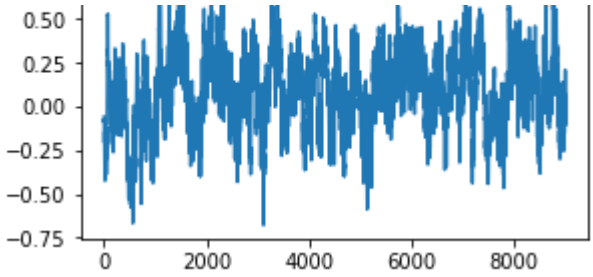

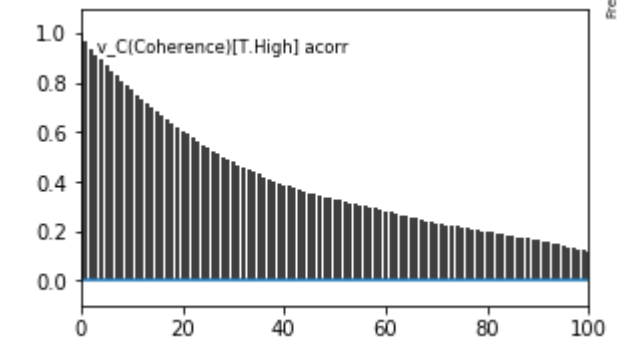
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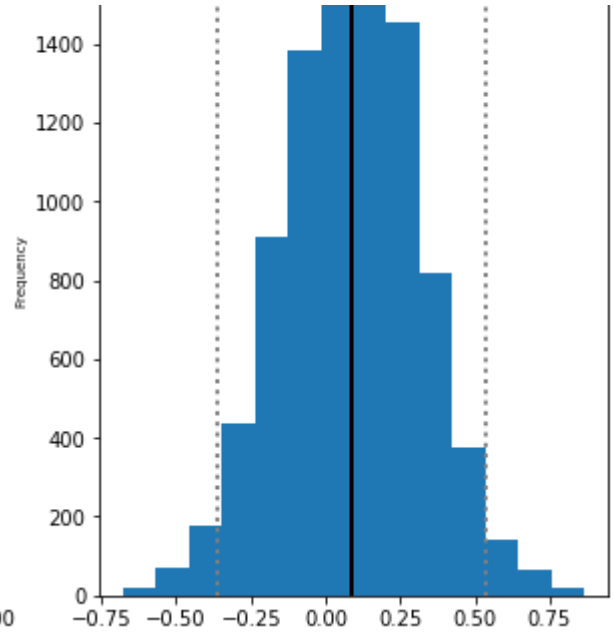
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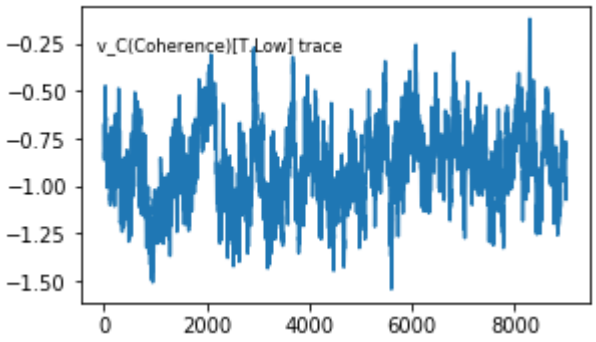
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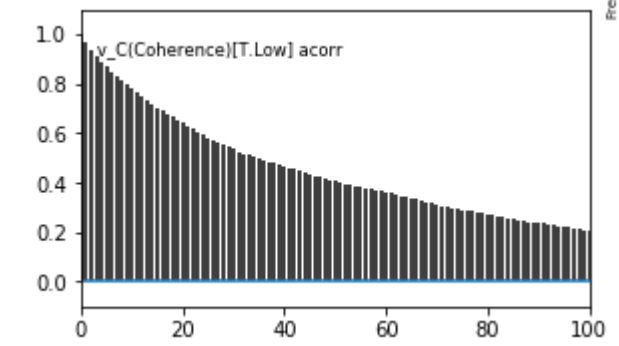
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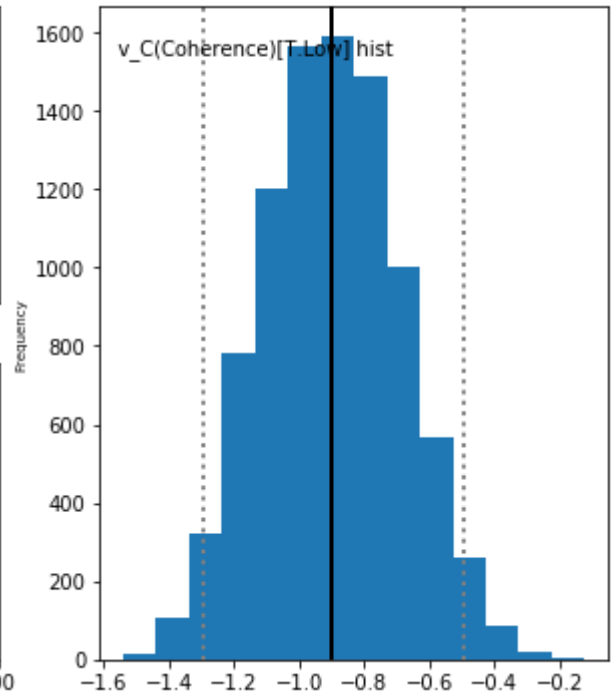
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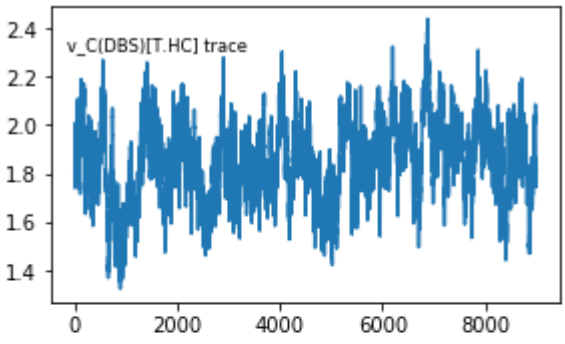
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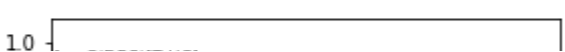

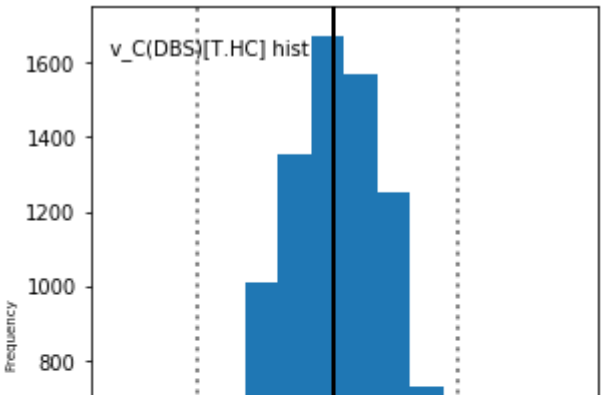
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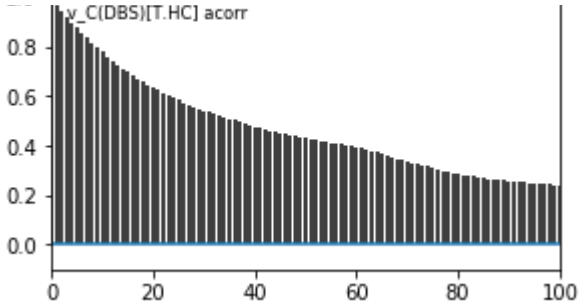
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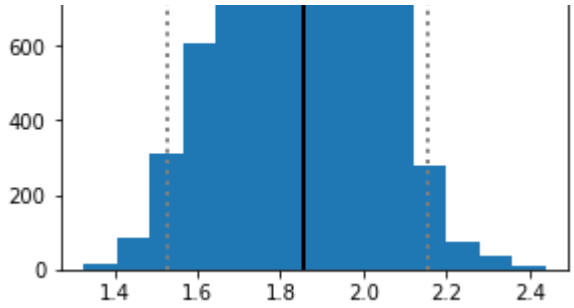

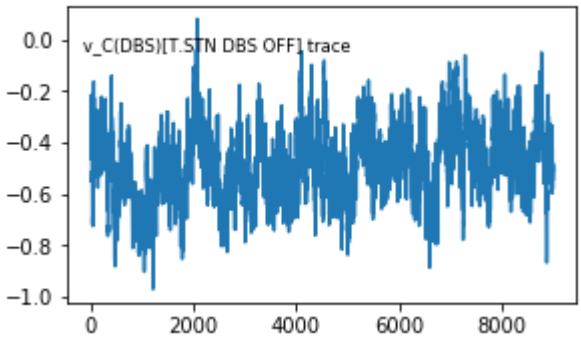
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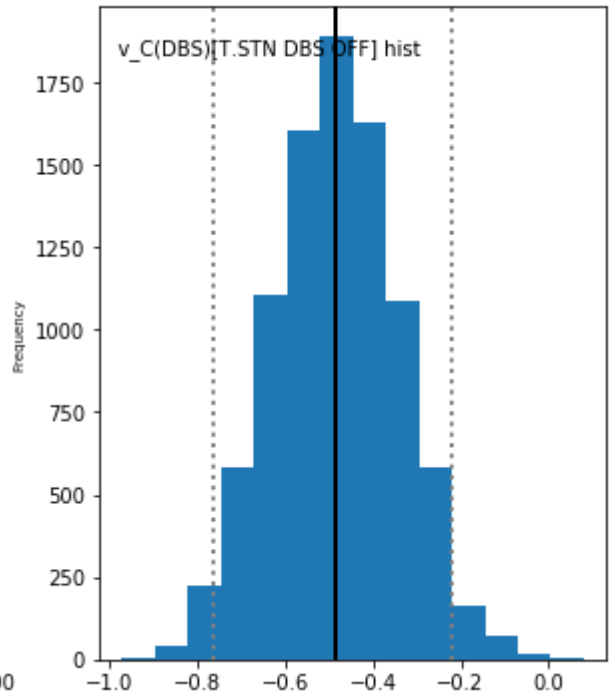
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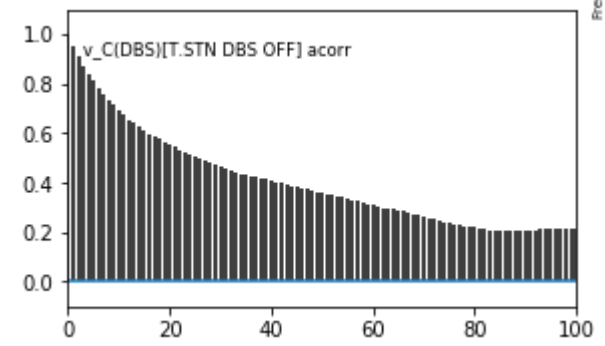
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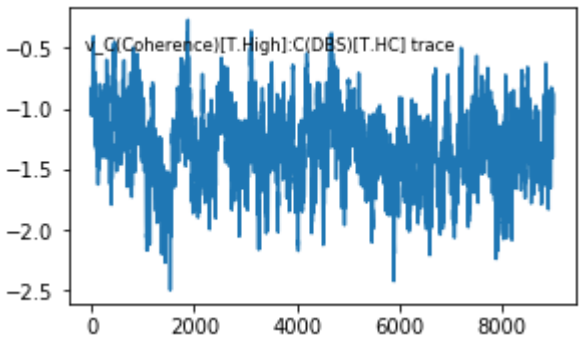
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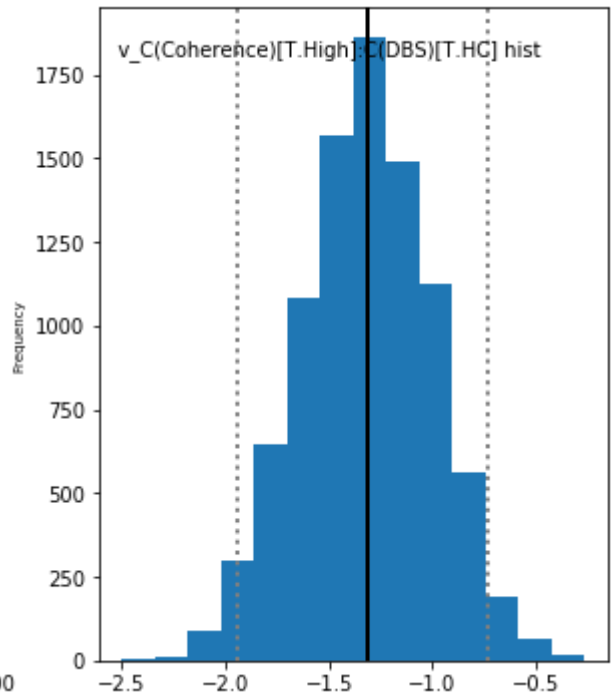
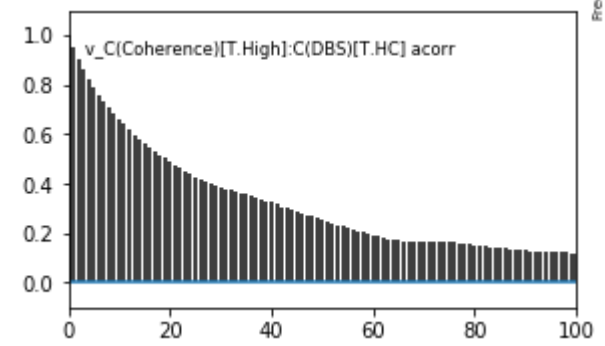
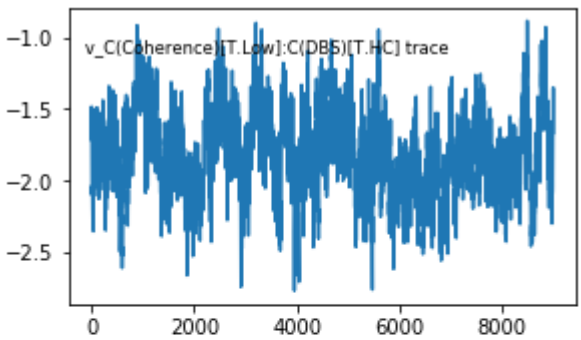
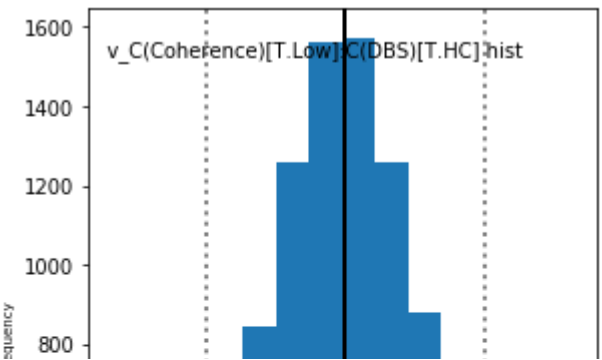
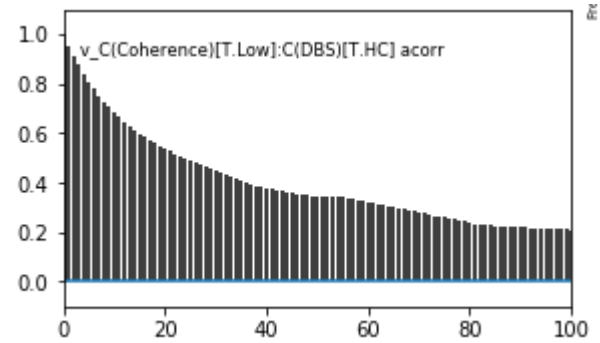
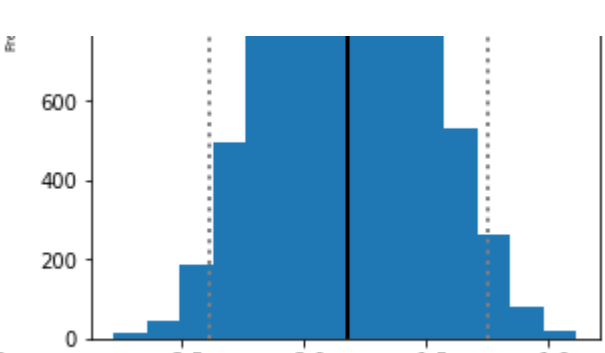

v_C(Coherence)[T.High]:C(DBS)[T.HC] hist
Frequency

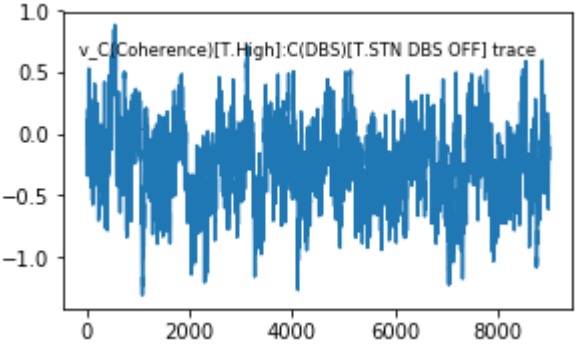

v_C(Coherence)[T.High]:C(DBS)[T.HC] acorr

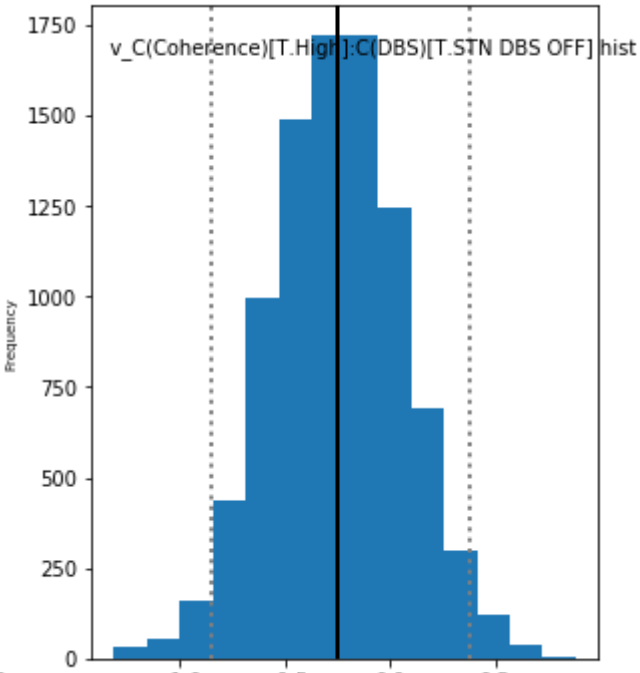

v_C(Coherence)[T.Low]:C(DBS)[T.HC] trace

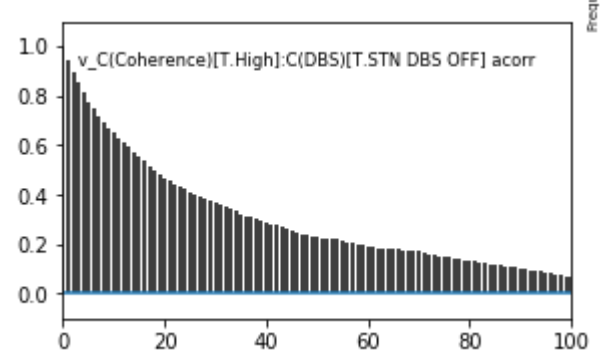

v_C(Coherence)[T.Low]:C(DBS)[T.HC] hist
Frequency

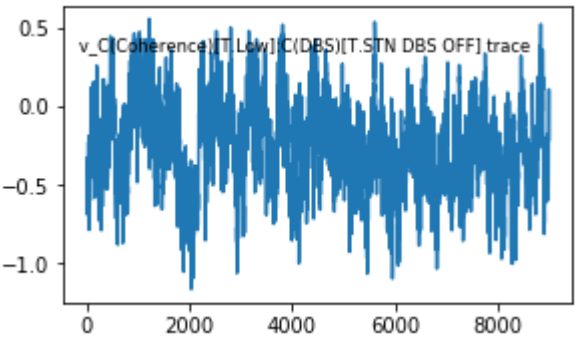

v_C(Coherence)[T.Low]:C(DBS)[T.HC] acorr

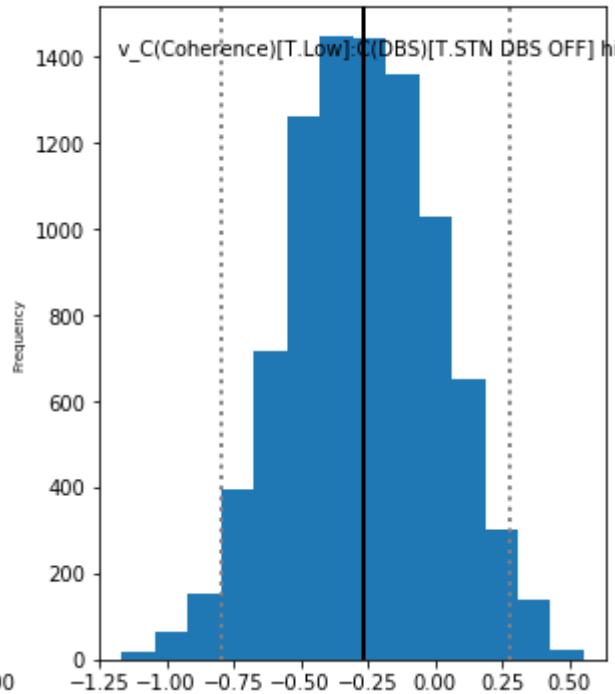


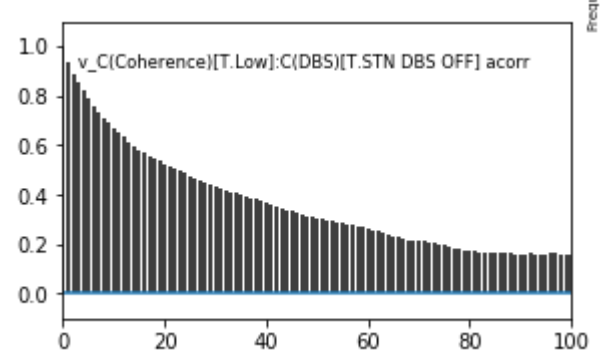

v_C(Coherence)[T.High]:C(DBS)[T.STN DBS OFF] trace


v_C(Coherence)[T.High]:C(DBS)[T.STN DBS OFF] hist
Frequency


v_C(Coherence)[T.High]:C(DBS)[T.STN DBS OFF] acorr


v_C(Coherence)[T.Low]:C(DBS)[T.STN DBS OFF] trace


v_C(Coherence)[T.Low]:C(DBS)[T.STN DBS OFF] hist
Frequency


v_C(Coherence)[T.Low]:C(DBS)[T.STN DBS OFF] acorr

In [9]:
```
ract the estimated decision threshold (a) from the created model
tercept, a_Type, a_High, a_Low, a_HC, a_DBSOFF = m.nodes_db.loc[['a_Intercept', '
pe_High, a_Type_Low, a_Type_HC, a_Type_DBSOFF = m.nodes_db.loc[['a_C(Type)[T.SP]:
gh_HC, a_Low_HC, a_High_DBSOFF, a_Low_DBSOFF = m.nodes_db.loc[['a_C(Coherence)[T.
pe_High_HC, a_Type_Low_HC, a_Type_High_DBSOFF, a_Type_Low_DBSOFF = m.nodes_db.loc

.analyze.plot_posterior_nodes([a_Type])
xlabel('Regression Coefficient')
ylabel('Posterior Probability')
show()
t "P(a_Type < 0)=", (a_Type.trace() < 0).mean()

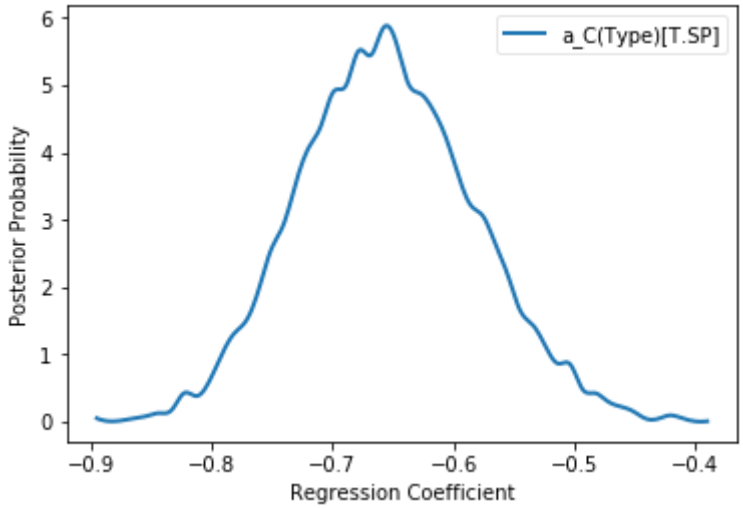
.analyze.plot_posterior_nodes([a_High, a_Low])
xlabel('Regression Coefficient')
ylabel('Posterior Probability')
show()
t "P(a_High < 0)=", (a_High.trace() < 0).mean()
t "P(a_Low < 0)=", (a_Low.trace() < 0).mean()

.analyze.plot_posterior_nodes([a_HC, a_DBSOFF])
xlabel('Regression Coefficient')
ylabel('Posterior Probability')
show()
t "P(a_HC < 0)=", (a_HC.trace() < 0).mean()
t "P(a_DBSOFF < 0)=", (a_DBSOFF.trace() < 0).mean()

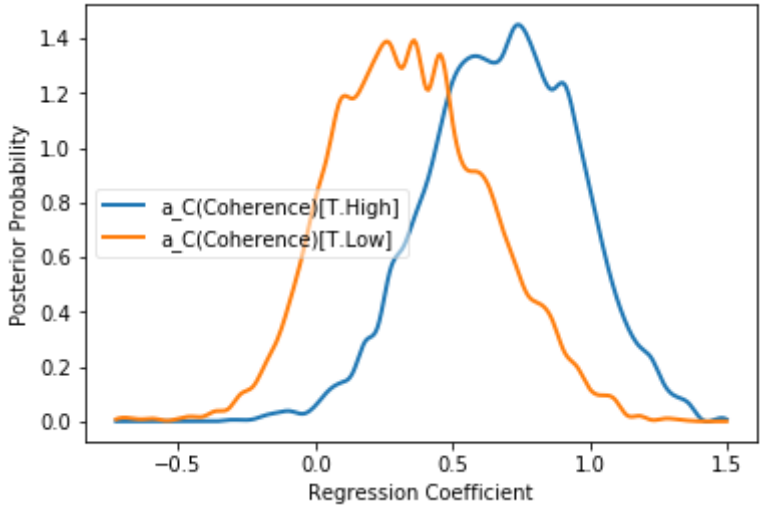
.analyze.plot_posterior_nodes([a_Type_HC, a_Type_DBSOFF])
xlabel('Regression Coefficient')
ylabel('Posterior Probability')
show()
t "P(a_HC < 0)=", (a_HC.trace() < 0).mean()
t "P(a_DBSOFF < 0)=", (a_DBSOFF.trace() < 0).mean()

.analyze.plot_posterior_nodes([a_Low_HC, a_High_HC, a_Low_DBSOFF, a_High_DBSOFF])
xlabel('Regression Coefficient')
ylabel('Posterior Probability')
show()
t "P(a_Low_HC < 0)=", (a_Low_HC.trace() < 0).mean()
t "P(a_High_HC < 0)=", (a_High_HC.trace() < 0).mean()
t "P(a_Low_DBSOFF < 0)=", (a_Low_DBSOFF.trace() < 0).mean()
t "P(a_High_DBSOFF < 0)=", (a_High_DBSOFF.trace() < 0).mean()

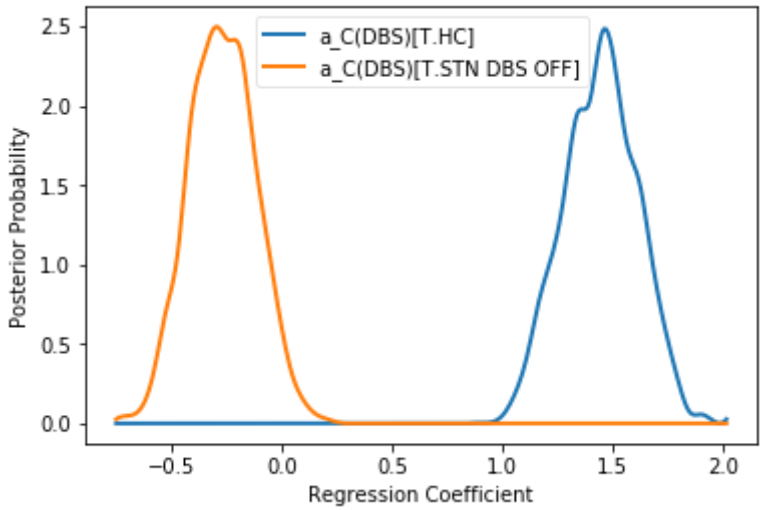
.analyze.plot_posterior_nodes([a_Type_Low_HC, a_Type_High_HC, a_Type_Low_DBSOFF,
xlabel('Regression Coefficient')
ylabel('Posterior Probability')
show()
t "P(a_Type_Low_HC < 0)=", (a_Type_Low_HC.trace() < 0).mean()
t "P(a_Type_High_HC < 0)=", (a_Type_High_HC.trace() < 0).mean()
t "P(a_Type_Low_DBSOFF < 0)=", (a_Type_Low_DBSOFF.trace() < 0).mean()
t "P(a_Type_High_DBSOFF < 0)=", (a_Type_High_DBSOFF.trace() < 0).mean()
```



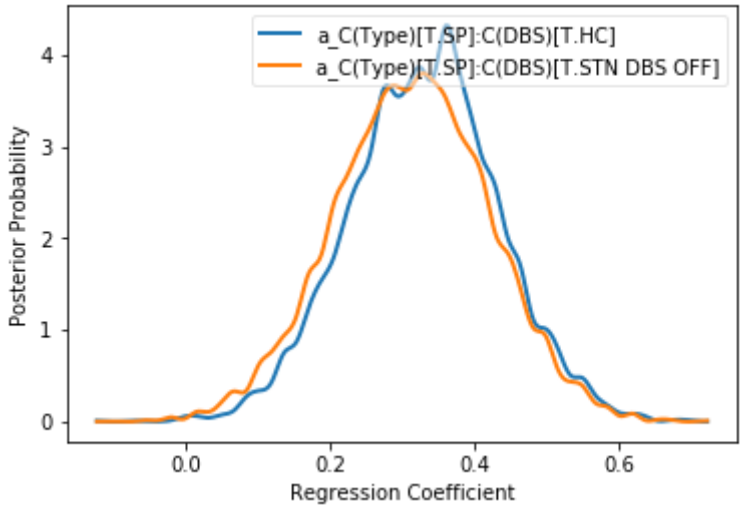
P(a_Type < 0)= 1.0



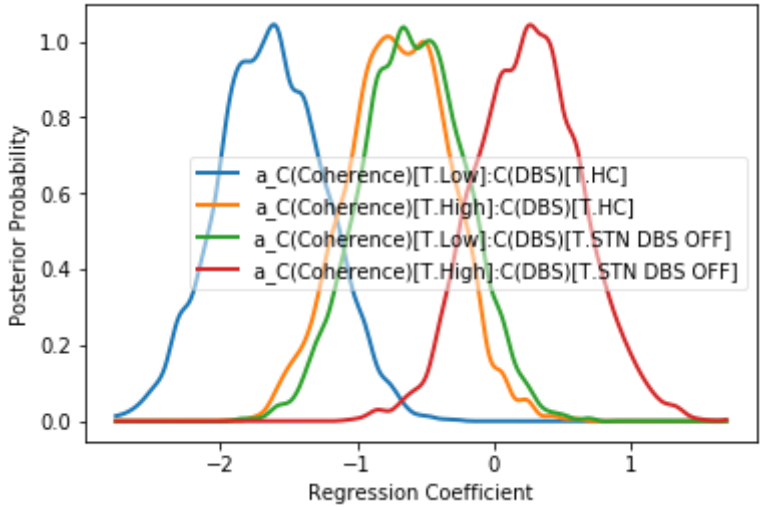
P(a_High < 0)= 0.007
P(a_Low < 0)= 0.0991111111111



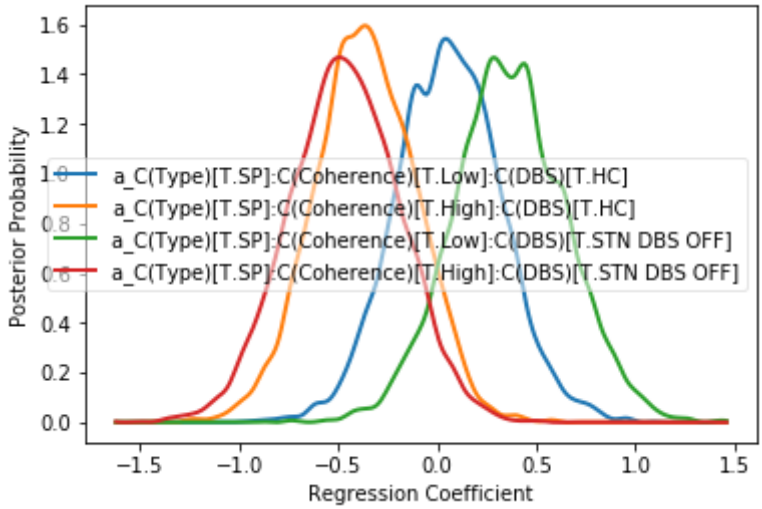
P(a_HC < 0)= 0.0
P(a_DBSOFF < 0)= 0.951333333333



P(a_HC < 0)= 0.0
P(a_DBSOFF < 0)= 0.951333333333



P(a_Low_HC < 0)= 1.0
P(a_High_HC < 0)= 0.973888888889
P(a_Low_DBSOFF < 0)= 0.944111111111
P(a_High_DBSOFF < 0)= 0.272777777778



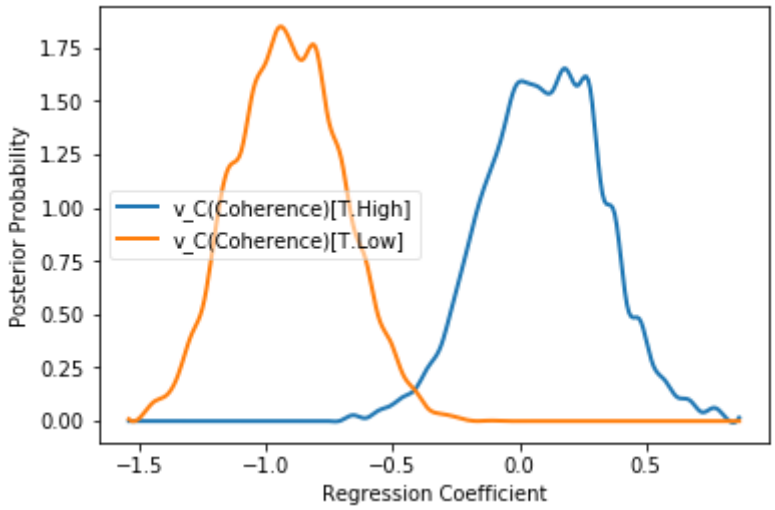
P(a_Type_Low_HC < 0)= 0.418888888889
P(a_Type_High_HC < 0)= 0.922555555556
P(a_Type_Low_DBSOFF < 0)= 0.099
P(a_Type_High_DBSOFF < 0)= 0.954777777778

In [11]:
```
v_Intercept, v_High, v_Low, v_HC, v_DBSOFF = m.nodes_db.loc[['v_Intercept', 'v_C
v_High_HC, v_Low_HC, v_High_DBSOFF, v_Low_DBSOFF= m.nodes_db.loc[['v_C(Coherence

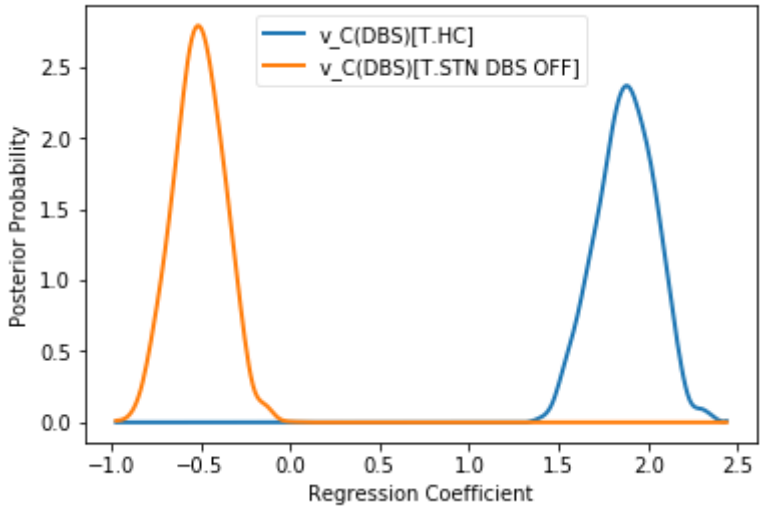
hddm.analyze.plot_posterior_nodes([v_High, v_Low])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(v_High < 0)=", (v_High.trace() < 0).mean()
print "P(v_Low < 0)=", (v_Low.trace() < 0).mean()

hddm.analyze.plot_posterior_nodes([v_HC, v_DBSOFF])
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(v_HC < 0)=", (v_HC.trace() < 0).mean()
print "P(v_DBSOFF < 0)=", (v_DBSOFF.trace() < 0).mean()

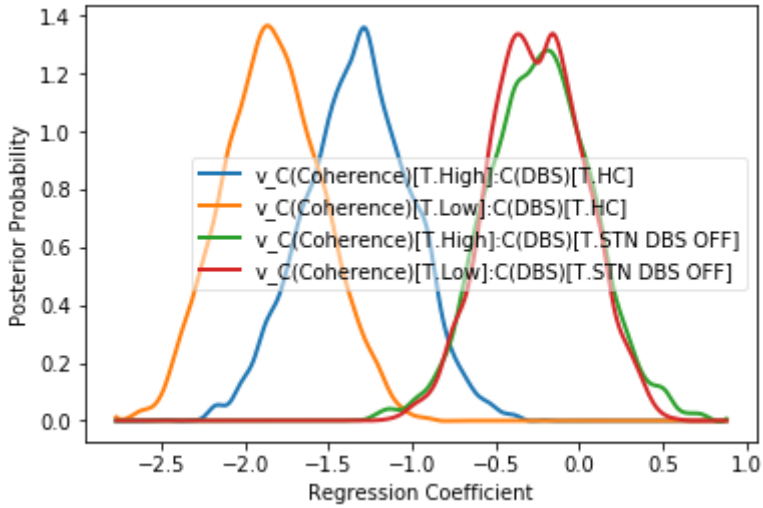
hddm.analyze.plot_posterior_nodes([v_High_HC, v_Low_HC, v_High_DBSOFF, v_Low_DBS
plt.xlabel('Regression Coefficient')
plt.ylabel('Posterior Probability')
plt.show()
print "P(v_High_HC < 0)=", (v_High_HC.trace() < 0).mean()
print "P(v_Low_HC < 0)=", (v_Low_HC.trace() < 0).mean()
print "P(v_High_DBSOFF < 0)=", (v_High_DBSOFF.trace() < 0).mean()
print "P(v_Low_DBSOFF < 0)=", (v_Low_DBSOFF.trace() < 0).mean()
```




```
P(v_High < 0)= 0.357444444444
P(v_Low < 0)= 1.0
```




```
P(v_HC < 0)= 0.0
P(v_DBSOFF < 0)= 0.999555555556
```




```
P(v_High_HC < 0)= 1.0
P(v_Low_HC < 0)= 1.0
P(v_High_DBSOFF < 0)= 0.789333333333
P(v_Low_DBSOFF < 0)= 0.822555555556
```

In [ ]:

Appendix - Information sheets, Consent forms and questionnaires

University College London Hospitals NHS
NHS Foundation Trust

National Hospital for Neurology and Neurosurgery
Queen Square,
London. WC1N 3BG

Telephone: 020 3448 8733

Control information sheet:

UCLH Project ID number: 07/Q0512/27
Version number: 28/10/15

Study title **Perceptual Decision-Making on patients with Parkinson's disease**

You are invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
The aim of this study is to provide information about the ability to change movement speed to achieve either fast or accurate movements and how this may be changed in people with Parkinson's disease.

Why have I been chosen?
You have been invited to take part because you are a similar age to many people with Parkinson's disease and do not have significant mobility or cognitive problems or depression.

Do I have to take part?
It is up to you to decide whether or not to take part. If you decide to take part, you will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your medical care or your future relationship with the Institute of Neurology or the National Hospital for Neurology and Neurosurgery. Your medical records may be inspected by competent researchers, but if any information is released, this will be done in a coded form so that confidentiality is strictly maintained. Participation in this study will in no way affect your legal rights.

What will happen to me if I take part?
You will be asked to participate in a behavioural study. The behavioural study will take place at the Sobell Department, Institute of Neurology, UCL at 33 Queen Square, London. Testing will take about 30 minutes to complete.

Are there any risks or side effects?
We don't anticipate any risks or side-effects from participation in the study.

What do I have to do?
On arriving at the Sobell Department you will complete some pre-experiment pen-and-paper questionnaires. Then you will complete a computerized task. On each trial you will see a series of dots and your task is to decide whether the majority of the dots are moving to the left or to the right by pressing buttons with your left or right index fingers. This task will be performed under speed (make your decision as quickly as possible) or accuracy (make your decision so that it is accurate) with different levels of task difficulty.

What is being tested?
By measuring your speed of reactions or reaction times, we can compare your performance under speed and accuracy instructions and determine if so-called speed-accuracy trade-offs in people with Parkinson's disease are similar or different to healthy people of the same age.

What are the possible benefits of taking part?
Participation in this study may not give you any direct benefit. But the information we obtain from this study may help us understand Parkinson's disease better and particularly contribute to improving mobility in Parkinson's disease. We will reimburse you for your travel costs to and from Queen Square.

Will my taking part in this study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

What information about me will be held?
We will keep a record of your name, age, address, contact details, physical and mental examinations. The results will be stored on computer for analysis. All information which is collected about you during the course of the study will stay strictly confidential and remain within the Institute of Neurology / UCL. Any information about you which leaves the Institute of Neurology will have your name, address, birth date and identifiable information removed so that you cannot be recognised from it. The principal investigator, Prof. Marjan Jahanshahi, will be in charge of ensuring that the security and confidentiality of your information is maintained.

What will happen to the results of the research study?
The data will be analysed and published in scientific journals and presented at scientific conferences. It should be emphasised that your name or any information that could identify you (e.g. your date of birth) will not be published. We will be happy to provide you with a copy of the completed article for you to keep.

What can I do if I am harmed during this study or wish to make a complaint?
We will welcome your feedback on your experience of this experiment and at the end of each session you will have a chance to record any comments on the experiment in writing. These comments will be shown (without identifying the person it came from) to the clinician involved in the study to ensure that the experiments do not produce too much discomfort. Please remember that you are free to withdraw at any point without giving a reason.

If you are harmed by taking part in this research project, there are no special compensation arrangements. NHS Indemnity does not offer no-fault compensation i.e. for non-negligent harm, and NHS bodies are unable to agree in advance to pay compensation for non-negligent

harm. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it.

Regardless of this, if you wish to complain, or have any concerns with this study, the normal National Health Service complaints mechanisms should be available to you.

Who is organising and funding the research?
This research is being conducted by members of the Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, Queen's Square, London. This study has been reviewed by the Programme Panel of the Sobell Department of Motor Neuroscience and Movement Disorders and approved by the National Hospital for Neurology and Neurosurgery/Institute of Neurology Joint Research Ethics Committee. The study is sponsored by University College London Hospitals Trust.

Contact for further information
Please do not hesitate to contact the principal investigator Prof Jahanshahi (contact details given below) should you have any questions at any stage of the research study:

Miss Yu-Ting Huang
Sobell Department of Motor Neuroscience and Movement Disorders
UCL Institute of Neurology,
33 Queen Square, London, WC1N 3BG
Mobile: 07940452298 , email: yth1975@gmail.com

Prof. Marjan Jahanshahi
Sobell Department of Motor Neuroscience and Movement Disorders
UCL Institute of Neurology
33 Queen Square, London, WC1N 3BG.
Tel:0203 4488733, email: m.jaahnshahi@ucl.ac.uk

Prof. Patricia Limousin
Sobell Department of Motor Neuroscience and Movement Disorders
UCL Institute of Neurology
33 Queen Square, London, WC1N 3BG

University College London Hospitals NHS
NHS Foundation Trust

National Hospital for Neurology and Neurosurgery
Queen Square,
London. WC1N 3BG

Telephone: 020 3448 8733

Information sheet – PD participants

UCLH Project ID number: 07/Q0512/27
Version number: 05/10/12, version 6b

Study title **Behavioural studies of paradoxical kinesis in Parkinson's disease**

You are invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
The aim of this study is to provide information about the ability to change movement speed to achieve either fast or accurate movements and how this may be changed in people with Parkinson's disease. This study is part of a larger project in which we are seeking to (i) understand the mobility problems in Parkinson's disease and (ii) develop techniques and aids for improving them.

Why have I been chosen?
You have been invited to take part because you are under STN DBS treatment for Parkinson's disease.

Do I have to take part?
It is up to you to decide whether or not to take part. If you decide to take part, you will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your medical care or your future relationship with the Institute of Neurology or the National Hospital for Neurology and Neurosurgery. Your medical records may be inspected by competent researchers, but if any information is released, this will be done in a coded form so that confidentiality is strictly maintained. Participation in this study will in no way affect your legal rights.

What will happen to me if I take part?
You will be asked to participate in a behavioural study. We will be happy to reimburse you for your travel costs to and from Queen Square.

The behavioural study will take place at the Sobell Department, Institute of Neurology, UCL at 33 Queen Square, London. Testing will take about 3½ hours to complete.

Are there any risks or side effects?
We don't anticipate any risks or side-effects from participation in the study.

What do I have to do?
On arriving at the Sobell Department you will complete some pre-experiment pen-and-paper questionnaires. Then you will complete a computerized task. On each trial you will see a series of dots and your task is to decide whether the majority of the dots are moving to the left or to the right and then to press a right hand or left hand response button. This task will be performed under speed (make your decision as quickly as possible) or accuracy (make your decision so that it is accurate) and with different levels of task difficulty.

What is being tested?
By measuring your speed of reactions or reaction times, we can compare your performance under speed and accuracy instructions and determine if so-called speed-accuracy trade-offs in people with Parkinson's disease are similar or different to healthy people of the same age.

What are the possible benefits of taking part?
Participation in this study may not give you any direct benefit. But the information we obtain from this study may help us understand Parkinson's disease better and particularly contribute to improving mobility in Parkinson's disease. We will reimburse you for your travel costs to and from Queen Square.

Will my taking part in this study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

What information about me will be held?
We will keep a record of your name, age, address, contact details, physical and mental examinations. The results will be stored on computer for analysis. All information which is collected about you during the course of the study will stay strictly confidential and remain within the Institute of Neurology / UCL. Any information about you which leaves the Institute of Neurology will have your name, address, birth date and identifiable information removed so that you cannot be recognised from it. The principal investigator, Prof. Marjan Jahanshahi, will be in charge of ensuring that the security and confidentiality of your information is maintained.

What will happen to the results of the research study?
The data will be analysed and published in scientific journals and presented at scientific conferences. It should be emphasised that your name or any information that could identify you (e.g. your date of birth) will not be published. We will be happy to provide you with a copy of the completed article for you to keep.

What can I do if I am harmed during this study or wish to make a complaint?
We will welcome your feedback on your experience of this experiment and at the end of each session you will have a chance to record any comments on the experiment in writing. These comments will be shown (without identifying the person it came from) to the clinician

involved in the study to ensure that the experiments do not produce too much discomfort. Please remember that you are free to withdraw at any point without giving a reason.

If you are harmed by taking part in this research project, there are no special compensation arrangements. NHS Indemnity does not offer no-fault compensation i.e. for non-negligent harm, and NHS bodies are unable to agree in advance to pay compensation for non-negligent harm. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it.

Regardless of this, if you wish to complain, or have any concerns with this study, the normal National Health Service complaints mechanisms should be available to you.

Who is organising and funding the research?
This research is being conducted by members of the Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, Queen's Square, London. This study has been reviewed by the Programme Panel of the Sobell Department of Motor Neuroscience and Movement Disorders and approved by the National Hospital for Neurology and Neurosurgery/Institute of Neurology Joint Research Ethics Committee. The study is sponsored by University College London Hospitals Trust.

Contact for further information
Please do not hesitate to contact the principal investigator Prof Jahanshahi (contact details given below) should you have any questions at any stage of the research study:

Ms Yu Ting Huang
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University College London Hospitals NHS
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National Hospital for Neurology and Neurosurgery
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Sobell Department of Motor Neuroscience and Movement Disorders

Information sheet – HC participants

UCLH project number: 07/Q0512/27
Version Number: Version 2, 27/10/2015

Study title **Action Reprogramming on PD patients treated with STN DBS**

You are invited to take part in a research study. Before you decide whether you want to do this, it is important for you to understand why the research is being done and what you will have to do.

Please take time to read the following information carefully and talk to others about it if you wish. Ask us if you have any questions. Take time to decide whether or not you wish to take part.

What is the purpose of this study?
The aim of the study that you are asked to participate in is to see how deep brain stimulation (DBS) on subthalamic nucleus (STN) affects the action reprogramming as surprise events takes place. You will take part in two studies. The aim of the first study is to examine your action responses to simple visual stimuli on a computer screen. The aim of the second study is to examine your action responses to simple visual stimuli on a computer screen after learning. We will compare the responses to visual stimuli in Parkinson's disease patients ON and OFF DBS and to healthy individuals. These studies advance our knowledge about the integration of mental and motor systems affected by Parkinson's disease and how we can improve it. All information is anonymous and confidential.

Why have I been chosen?
You have been invited to take part because you are of similar age to many people with Parkinson's disease and do not have significant mobility or cognitive problems or depression.

Do I have to take part?
You can decide whether or not you want to take part. If you decide to take part, we will ask you to sign a consent form. You are still free to withdraw at any time without giving a reason.

Your medical care won't be affected if you decide not to take part in the study, or if you take part and then withdraw from the study later on. Also, this will not affect future relationship with the Institute of Neurology or the National Hospital for Neurology and Neurosurgery.

Compete researchers may look at your medical records. If any information is released, your name will be left out, so that everything stays strictly confidential. Participation in this study does not affect your legal rights.

What will happen to me if I take part?
You will be interviewed by a researcher who will ask you for some information about your physical and mental health. You will then complete a computer-based reaction time task by pressing buttons on a response box with your fingers. During the task, there will be four different kinds of visual stimuli image presented on a computer screen. Each visual stimuli image will be associated with pressing a specific button. You will perform the reaction-time task twice.

Are there any risks or side effects?
There are no major risk or side effects in this study. The manipulation has been used previously and no negative effects have been documented.

What do I have to do?
We would like you to complete the tests described below. The purpose of each test will be explained to you, followed by a demonstration of what you have to do. On some tests such as the questionnaire measures of mood, there are no right or wrong answers and we are simply interested in how you are feeling a the time you are completing the form. The assessment will take about 2.5 hours with short breaks in between tests.

1. *Computer-based reaction time test*: You will be asked to complete a reaction time task by pressing buttons on a response box. When you see specific image on the computer screen, simply respond by pressing a specific button. The task would require you to be fully focused due to the presenting time of the images may be fast.
2. *Questionnaires*: An experimenter will do small examinations on your cognitive functions such as memory, mood...etc.

What is being tested?
The aim is to determine the execution of action reprogramming, namely how fast can one re-initiate an action when surprising events occur. The reaction time and accuracy would be recorded.

What are the possible benefits of taking part?
Participation in this study means that you will be making an important contribution to scientific research, helping us understand how Parkinson's disease and its treatment affecting the integration of cognitive functions and motor movement.

Will my taking part in this study be kept confidential?
All information collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will remove your name and address so that you cannot be recognised from it.

What information about me will be held?
We will keep a record of your name, age, address, contact details, physical and mental examinations and data collected during the study.

The results will be stored on computer for analysis. All information collected about you during the study will stay strictly confidential and remain within the Institute of Neurology/UCL. Any information about you that leaves the Institute of Neurology will have your name, date of birth, address, contact details, and identifiable information removed so that you cannot be recognised from it. The principal investigator, Prof. Marjan Jahanshahi, will be in charge of ensuring that the security and confidentiality of your information is maintained.

What will happen to the results of the research study?
The data will be analysed and published in scientific journals and presented at scientific conferences. We will NOT publish your name or any information that could identify you (e.g. your date of birth). We will be happy to give you a copy of the completed article for you to keep.

What can I do of I am harmed during this study or I wish to make a complaint?
We will welcome your feedback on your experience of this experiment and at the end of each session you will have a chance to record any comments on the experiment in writing. These comments will be shown (without identifying the person it came from) to the clinician involved in the study to ensure that the experiments do not produce too much discomfort. Please remember that you are free to withdraw at any point without giving a reason.

If you are harmed by taking part in this research project, there are no special compensation arrangements. NHS Indemnity does not offer no-fault compensation i.e. for non-negligent harm, and NHS bodies are unable to agree in advance to pay compensation for non-negligent harm. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it.

Regardless of this, if you wish to complain, or have any concerns with this study, the normal National Health Service complaints mechanisms should be available to you.

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This research is being conducted by members of the Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, Queen's Square, London. This study has been reviewed by the Programme Panel of the Sobell Department of Motor Neuroscience and Movement Disorders and approved by the National Hospital for Neurology and Neurosurgery/Institute of Neurology Joint Research Ethics Committee. The study is sponsored by University College London Hospitals Trust.

Contact for further information

Please do not hesitate to contact the principal experimenter Miss Yu-Ting Huang (contact details given below) should you have any questions at any stage of the research study.

Miss Yu-Ting Huang

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Prof. Marjan Jahanshahi

Sobell Department of Motor Neuroscience and Movement Disorders

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Sobell Department of Motor Neuroscience and Movement Disorders

Information sheet – PD participants

UCLH project number: 07/Q0512/27
Version Number: Version 2, 27/10/2015

Study title **Action Reprogramming on PD patients treated with STN DBS**

You are invited to take part in a research study. Before you decide whether you want to do this, it is important for you to understand why the research is being done and what you will have to do.

Please take time to read the following information carefully and talk to others about it if you wish. Ask us if you have any questions. Take time to decide whether or not you wish to take part.

What is the purpose of this study?
The aim of the study that you are invited to participate in is to see how deep brain stimulation (DBS) on subthalamic nucleus (STN) affects the action reprogramming as surprise events takes place. You will take part in two studies. The aim of the first study is to examine your action responses to simple visual stimuli on a computer screen when being ON DBS. The aim of the second study is to examine your action responses to simple visual stimuli on a computer screen when being OFF DBS. We will compare the responses to visual stimuli in Parkinson's disease patients ON and OFF DBS and to healthy individuals. These studies advance our knowledge about the integration of mental and motor systems affected by Parkinson's disease and how we can improve it. All information is anonymous and confidential.

Why have I been chosen?
You have been invited to take part because you are under STN DBS treatment for Parkinson's disease.

Do I have to take part?
You can decide whether or not you want to take part. If you decide to take part, we will ask you to sign a consent form. You are still free to withdraw at any time without giving a reason.

Your medical care won't be affected if you decide not to take part in the study, or if you take part and then withdraw from the study later on. Also, this will not affect future relationship with the Institute of Neurology or the National Hospital for Neurology and Neurosurgery.

Compete researchers may look at your medical records. If any information is released, your name will be left out, so that everything stays strictly confidential. Participation in this study does not affect your legal rights.

What will happen to me if I take part?
You will be interviewed by a researcher who will ask you for some information about your physical and mental health. You will then complete a computer-based reaction time task by pressing buttons on a response box with your fingers. During the task, there will be four different kinds of visual stimuli image presented on a computer screen. Each visual stimuli image will be associated with pressing a specific button. You will perform the task twice, one ON stimulation and one OFF stimulation.

Are there any risks or side effects?
There are no major risk or side effects in this study. The manipulation has been used previously and no negative effects have been documented.

What do I have to do?
We would like you to complete the tests described below. The purpose of each test will be explained to you, followed by a demonstration of what you have to do. On some tests such as the questionnaire measures of mood, there are no right or wrong answers and we are simply interested in how you are feeling a the time you are completing the form. The assessment will take about 2.5 hours with short breaks in between tests.

1. *Computer-based reaction time test*: You will be asked to complete a reaction time task by pressing buttons on a response box. When you see specific image on the computer screen, simply respond by pressing a specific button. The task would require you to be fully focused due to the presentation of the images may be fast.
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The data will be analysed and published in scientific journals and presented at scientific conferences. We will NOT publish your name or any information that could identify you (e.g. your date of birth). We will be happy to give you a copy of the completed article for you to keep.

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We will welcome your feedback on your experience of this experiment and at the end of each session you will have a chance to record any comments on the experiment in writing. These comments will be shown (without identifying the person it came from) to the clinician involved in the study to ensure that the experiments do not produce too much discomfort. Please remember that you are free to withdraw at any point without giving a reason.

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Neuroscience and Movement Disorders and approved by the National Hospital for Neurology and Neurosurgery/Institute of Neurology Joint Research Ethics Committee. The study is sponsored by University College London Hospitals Trust.

Contact for further information

Please do not hesitate to contact the principal experimenter Miss Yu-Ting Huang (contact details given below) should you have any questions at any stage of the research study:

Miss Yu-Ting Huang

Sobell Department of Motor Neuroscience and Movement Disorders

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E-mail: yu.huang.13@ucl.ac.uk

Prof. Marjan Jahanshahi

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Tel:0203 4488733, email: m.jaahnshahi@ucl.ac.uk

Prof. Patricia Limousin

Sobell Department of Motor Neuroscience and Movement Disorders

UCL Institute of Neurology

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UCL INSTITUTE OF NEUROLOGY
THE NATIONAL HOSPITAL FOR NEUROLOGY AND NEUROSURGERY
QUEEN SQUARE
LONDON WC1N 3BG

Sobell Department of Motor Neuroscience and Movement Disorders

Professor Marjan Jahanshahi BSc, MPhil (Clinical Psychol), PhD
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UCLH Project ID number: 07/Q0512/27
Version number: 05/09/2012, version 6b

CONSENT FORM

Study title: Study title **Behavioural studies of paradoxical kinesis in Parkinson's disease**

Name of Principal Investigator: Prof. Marjan Jahanshahi

		Please **initial** box
1	I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions	☐
2	I confirm that I have had enough time to consider whether or not I want to be included in the study.	☐
3	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐

Please **initial** box

4. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Institute of Neurology, where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

5. I agree to take part in the above study. ☐

_____	_____	_____
Name of participant	Date	Signature

_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature

Name of the researcher to be contacted if there are any problems:

Ms Yu Ting Huang
email: yth1975@gmail.com
Mobile: 07940452298

Professor Jahanshahi; (contact details as above)

Comments or concerns during the study

If you have any comments or concerns you may discuss these with the investigator. If you wish to go further and complain about any aspect of the way you have been approached or treated during the course of the study, you should write or get in touch with the Complaints Manager, University College Hospitals. Please quote the **UCLH** project number at the top of this consent form.

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP-Anytime During PD-Short)

Reported by: _____ Patient _____ Informant* _____ Patient and Informant

Patient name: _____

Date: _____

*If information reported by an informant, answer questions based on your understanding of the patient.

Answer ALL QUESTIONS based on BEHAVIORS ANYTIME DURING PD LASTING AT LEAST 4 WEEKS

A. GAMBLING

1. Do [Did] you or others think you have [had] an issue with too much gambling behaviors (such as casinos, internet gambling, lotteries, scratch tickets, betting, or slot or poker machines)? **__Yes __No**

2. Do [Did] you have difficulty controlling your gambling behaviors (such as increasing them over time, or having trouble cutting down or stopping them)? **__Yes __No**

B. SEX

1. Do [Did] you or others think you have [had] an issue with too much sex behaviors (such as making sexual demands on others, promiscuity, prostitution, change in sexual orientation, masturbation, internet or telephone sexual activities, or pornography)? **__Yes __No**

2. Do [Did] you think too much about sex behaviors (such as having trouble keeping thoughts out of your mind or feeling guilty)? **__Yes __No**

C. BUYING

1. Do [Did] you or others think you have [had] an issue with too much buying behaviors (such as too much of the same thing or things that you don't need or use)? **__Yes __No**

2. Do [Did] you engage in activities specifically to continue the buying behaviors (such as hiding what you are [were] doing, lying, hoarding things, borrowing from others, accumulating debt, stealing, or being involved in illegal acts)? **__Yes __No**

D. EATING

1. Do [Did] you or others think you have [had] an issue with too much eating behaviors (such as eating larger amounts or different types of food than in the past, more rapidly than normal, until feeling uncomfortably full, or when not hungry)? **__Yes __No**

2. Do [Did] you have urges or desires for eating behaviors that you feel are [felt were] excessive or cause [caused] you distress (including becoming restless or irritable when unable to participate in the behavior)? **__Yes __No**

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP-Anytime During PD-Short)

E. OTHER BEHAVIORS

Do [Did] you or others think that you spend [spent] too much time….

1. On specific tasks, hobbies or other organized activities (such as writing, painting, gardening, repairing or dismantling things, collecting, computer use, working on projects, etc.)? **__Yes __No**

2. Repeating certain simple motor activities (such as cleaning, tidying, handling, examining, sorting, ordering, or arranging objects, etc.)? **__Yes __No**

3. Walking or driving with no intended goal or specific purpose? **__Yes __No**

F. MEDICATION USE

1. Do [Did] you or others (including your physicians) think that you consistently take [took] too much of your Parkinson's medications? **__Yes __No**

2. Do [Did] you have difficulty controlling your use of Parkinson's medications (such as experiencing a strong desire for more medication, or having worse mood or feeling unmotivated at a lower dosage)? **__Yes __No**

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP-Current-Short)

Reported by: _____ Patient _____ Informant* _____ Patient and Informant

Patient name: _____

Date: _____

*If information reported by an informant, answer questions based on your understanding of the patient.

Answer ALL QUESTIONS based on CURRENT BEHAVIORS LASTING AT LEAST 4 WEEKS

A. GAMBLING

1. Do you or others think you have an issue with too much gambling behaviors (such as casinos, internet gambling, lotteries, scratch tickets, betting, or slot or poker machines)? **__Yes __No**

2. Do you have difficulty controlling your gambling behaviors (such as increasing them over time, or having trouble cutting down or stopping them)? **__Yes __No**

B. SEX

1. Do you or others think you have an issue with too much sex behaviors (such as making sexual demands on others, promiscuity, prostitution, change in sexual orientation, masturbation, internet or telephone sexual activities, or pornography)? **__Yes __No**

2. Do you think too much about sex behaviors (such as having trouble keeping thoughts out of your mind or feeling guilty)? **__Yes __No**

C. BUYING

1. Do you or others think you have an issue with too much buying behaviors (such as too much of the same thing or things that you don't need or use)? **__Yes __No**

2. Do you engage in activities specifically to continue the buying behaviors (such as hiding what you're doing, lying, hoarding things, borrowing from others, accumulating debt, stealing, or being involved in illegal acts)? **__Yes __No**

D. EATING

1. Do you or others think you have an issue with too much eating behaviors (such as eating larger amounts or different types of food than in the past, more rapidly than normal, until feeling uncomfortably full, or when not hungry)? **__Yes __No**

2. Do you have urges or desires for eating behaviors that you feel are excessive or cause you distress (including becoming restless or irritable when unable to participate in the behavior)? **__Yes __No**

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP-Current-Short)

E. OTHER BEHAVIORS

Do you or others think that you spend too much time….

1. On specific tasks, hobbies or other organized activities (such as writing, painting, gardening, repairing or dismantling things, collecting, computer use, working on projects, etc.)? **__Yes __No**

2. Repeating certain simple motor activities (such as cleaning, tidying, handling, examining, sorting, ordering, or arranging objects, etc.)? **__Yes __No**

3. Walking or driving with no intended goal or specific purpose? **__Yes __No**

F. MEDICATION USE

1. Do you or others (including your physicians) think that you consistently take too much of your Parkinson's medications? **__Yes __No**

2. Do you have difficulty controlling your use of Parkinson's medications (such as experiencing a strong desire for more medication, or having worse mood or feeling unmotivated at a lower dosage)? **__Yes __No**

Name: **Date:**

DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly.

1 I plan tasks carefully.	Rarely/never	Ocasionally	Often	Almost always/ Always
2 I do things without thinking.	Rarely/never	Ocasionally	Often	Almost always/ Always
3 I make-up my mind quickly.	Rarely/never	Ocasionally	Often	Almost always/ Always
4 I am happy-go-lucky.	Rarely/never	Ocasionally	Often	Almost always/ Always
5 I don't "pay attention."	Rarely/never	Ocasionally	Often	Almost always/ Always
6 I have "racing" thoughts.	Rarely/never	Ocasionally	Often	Almost always/ Always
7 I plan trips well ahead of time.	Rarely/never	Ocasionally	Often	Almost always/ Always
8 I am self controlled.	Rarely/never	Ocasionally	Often	Almost always/ Always
9 I concentrate easily.	Rarely/never	Ocasionally	Often	Almost always/ Always
10 I save regularly.	Rarely/never	Ocasionally	Often	Almost always/ Always
11 I "squirm" at plays or lectures.	Rarely/never	Ocasionally	Often	Almost always/ Always
12 I am a careful thinker.	Rarely/never	Ocasionally	Often	Almost always/ Always
13 I plan for job security.	Rarely/never	Ocasionally	Often	Almost always/ Always
14 I say things without thinking.	Rarely/never	Ocasionally	Often	Almost always/ Always
15 I like to think about complex problems.	Rarely/never	Ocasionally	Often	Almost always/ Always
16 I change jobs.	Rarely/never	Ocasionally	Often	Almost always/ Always

17 I act "on impulse."	Rarely/never	Ocasionally	Often	Almost always/ Always
18 I get easily bored when solving thought problems.	Rarely/never	Ocasionally	Often	Almost always/ Always
19 I act on the spur of the moment.	Rarely/never	Ocasionally	Often	Almost always/ Always
20 I am a steady thinker.	Rarely/never	Ocasionally	Often	Almost always/ Always
21 I change residences.	Rarely/never	Ocasionally	Often	Almost always/ Always
22 I buy things on impulse.	Rarely/never	Ocasionally	Often	Almost always/ Always
23 I can only think about one thing at a time.	Rarely/never	Ocasionally	Often	Almost always/ Always
24 I change hobbies.	Rarely/never	Ocasionally	Often	Almost always/ Always
25 I spend or charge more than I earn.	Rarely/never	Ocasionally	Often	Almost always/ Always
26 I often have extraneous thoughts when thinking.	Rarely/never	Ocasionally	Often	Almost always/ Always
27 I am more interested in the present than the future.	Rarely/never	Ocasionally	Often	Almost always/ Always
28 I am restless at the theater or lectures.	Rarely/never	Ocasionally	Often	Almost always/ Always
29 I like puzzles.	Rarely/never	Ocasionally	Often	Almost always/ Always
30 I am future oriented.	Rarely/never	Ocasionally	Often	Almost always/ Always

Beck Depression Inventory

BDI®-II

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

_____ Subtotal Page 1

Continued on Back

Beck Depression Inventory

11. Agitation

0 I am no more restless or wound up than usual.

1 I feel more restless or wound up than usual.

2 I am so restless or agitated that it's hard to stay still.

3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.

1 I am less interested in other people or things than before.

2 I have lost most of my interest in other people or things.

3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.

1 I find it more difficult to make decisions than usual.

2 I have much greater difficulty in making decisions than I used to.

3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.

1 I don't consider myself as worthwhile and useful as I used to.

2 I feel more worthless as compared to other people.

3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.

1 I have less energy than I used to have.

2 I don't have enough energy to do very much.

3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.

1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.

2b I sleep a lot less than usual.

3a I sleep most of the day.

3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.

1 I am more irritable than usual.

2 I am much more irritable than usual.

3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.

1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.

2b My appetite is much greater than usual.

3a I have no appetite at all.

3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.

1 I can't concentrate as well as usual.

2 It's hard to keep my mind on anything for very long.

3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.

1 I get more tired or fatigued more easily than usual.

2 I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

Subtotal Page 2

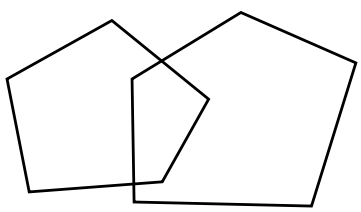
Subtotal Page 1

Total Score

MINI MENTAL STATE EXAMINATION (MMSE)

Patient's name:

Hospital number:

ONE POINT FOR EACH ANSWER	DATE			
ORIENTATION				
Year Month Day Date Time	____/5	____/5	____/5	____/5
Country Town District Hospital Ward	____/5	____/5	____/5	____/5
REGISTRATION				
Examiner names 3 objects (eg apple, table, penny) Patient asked to repeat (1 point for each correct). THEN patient to learn the 3 names repeating until correct.	____/3	____/3	____/3	____/3
ATTENTION AND CALCULATION				
Subtract 7 from 100, then repeat from result. Continue 5 times: 100 93 86 79 65 Alternative: spell "WORLD" backwards - dlrow.	____/5	____/5	____/5	____/5
RECALL				
Ask for names of 3 objects learned earlier.	____/3	____/3	____/3	____/3
LANGUAGE				
Name a pencil and watch.	____/2	____/2	____/2	____/2
Repeat "No ifs, ands, or buts".	____/1	____/1	____/1	____/1
Give a 3 stage command. Score 1 for each stage. Eg. "Place index finger of right hand on your nose and then on your left ear".	____/3	____/3	____/3	____/3
Ask patient to read and obey a written command on a piece of paper stating "Close your eyes".	____/1	____/1	____/1	____/1
Ask the patient to write a sentence. Score if it is sensible and has a subject and a verb.	____/1	____/1	____/1	____/1
COPYING				
Ask the patient to copy a pair of intersecting pentagons: 	____/1	____/1	____/1	____/1
TOTAL	____/30	____/30	____/30	____/30

8. Digit Span

DISCONTINUE RULE
Digits Forward & Backward
Score of 0 on both trials of any item
For both Digits Forward & Backward, administer both trials of each item even if Trial 1 is passed. Administer Digits Backward even if examinee scores 0 on Digits Forward

SCORING RULE
Each Trial [illegible]
Item Score = Trial 1 + Trial 2

Digits Forward Trial Item Response	Trial Score	Item Score (0 1 or 2)
2 1-7		
2-6-3		
3 5-8-2		
6-9-4		
4 6-4-3-9		
7-2-8-6		
5 4-2-7-3-1		
7-5-8-3-6		
6 6-1-9-4-7-3		
3-9-2-4-8-7		
7 5-9-1-7-4-2-8		
4-1-7-9-3-8-6		
8 5-8-1-9-2-6-4-7		
3-8-2-9-5-1-7-4		
9 2-7-5-8-6-2-5-8-4		
4-1-3-9-4-2-5-6-8		

Digits Forward Total Score
(Maximum = 16)

Digits Backward Trial Item Response	Trial Score	Item Score (0 1 or 2)
1 2-4		
5-7		
2 6-2-9		
4-1-5		
3 3-2-7-9		
4-9-6-8		
4 1-5-2-8-6		
6-1-8-4-3		
5 5-3-9-4-1-8		
7-2-4-8-5-6		
6 8-1-2-9-3-6-5		
4-7-3-9-1-2-8		
7 9-4-3-7-6-2-5-8		
7-2-8-1-9-6-5-3		

Digits Backward Total Score
(Maximum = 14)

Forward	+	Backward	=	Maximum = 30

9. Information

REVERSE RULE
Score of 0 on Item 5 or 6, administer Items 1–4 in reverse sequence until two consecutive perfect scores are obtained

DISCONTINUE RULE
5 consecutive scores of 0

SCORING RULE
All Items 0 or 1 pt
for each response

Item	Response	Score (0 or 1)	Item	Response	Score (0 or 1)
1.	[illegible]		7	Hamlet	
2.	Age		8	Brazil	
3.	Bird		9	Milk	
4.	[illegible]		10	[illegible]	
5	[illegible]		11	[illegible]	
	[illegible]		12	[illegible]	
	[illegible]		13	Pain	
	[illegible]		14	[illegible]	