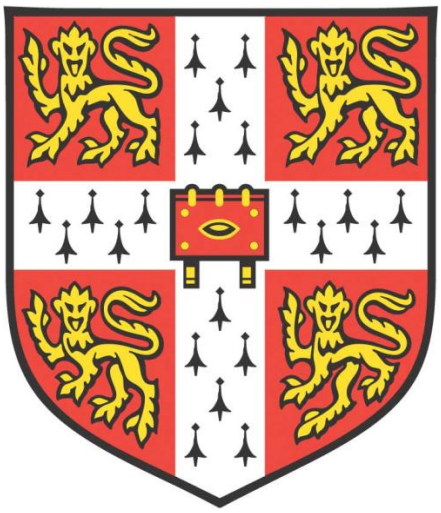
THE ROLE OF THE BASAL GANGLIA IN MEMORY AND MOTOR INHIBITION



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DECLARATION

The work in this thesis was carried out between October 2014 and September 2017 at the Medical Research Council Cognition and Brain Sciences Unit (MRC CBU), under the supervision of Professor Michael C. Anderson. This thesis is the result of my own work and the following collaborations:

- Chapter 3: Marieke Mur and Taylor Schmitz were involved in the descriptive analyses.
- Chapter 4: Chelan Weaver and Michael Anderson designed the original Combined Go/No-Go and Stop-signal task.
- Chapter 5: Taylor Schmitz and James Rowe provided guidance to the imaging analyses. Jonathan Fawcett contributed to the behavioural analyses.
- Chapter 6: Rafael Henriques contributed to the processing of diffusion data.

This thesis has contributed to the following publications:

Guo, Y., Schmitz, T. W., Catarina, F. & Anderson, M. C. (under review). Inhibition of both Memories and Actions in the Basal Ganglia: Meta-analytic Evidence.

Guo, Y., Henriques, R., Taylor, T. W., Correia, M. & Anderson, M. C. (in preparation). Involvement of the Basal Ganglia in Memory and Motor Inhibition evidenced by anatomical and effective connectivity.

Schmitz, T. W., Ferreira, C., **Guo, Y.**, & Anderson, M. C. (in preparation). Inhibitory Control of Thoughts and Actions: Common Control Processes, Dissociable Targets.

The work has been presented at the following conferences:

International Meeting of the Psychonomic Society (Granada, Spain, 2016)

International Conference on Memory (Budapest, Hungary, 2016)

British Neuroscience Association Biannual Festival (Birmingham, UK, 2017)

Organisation of Human Brain Mapping Annual Meeting (Vancouver, Canada, 2017)

Cambridge Memory Meeting (Cambridge, UK, 2017)

This thesis has not been previously submitted, in part or whole, to any university or institution for any degree, diploma, or other qualification. This thesis does not exceed 60,000 words, and contains less than 150 figures.

SUMMARY

This PhD thesis investigated the role of the basal ganglia in memory and motor inhibition. Recent neuroimaging evidence suggests a supramodal network of inhibition involving the lateral prefrontal cortex. Here we examined whether this supramodal network also includes subcortical structures, such as the basal ganglia. Despite their well-established role in motor control, the basal ganglia are repeatedly activated but never interpreted during memory inhibition.

We first used a series of meta-analysis to confirm the consistent involvement of the basal ganglia across studies using memory and motor inhibition tasks (including the Go/No-Go, Think/No-Think, and Stop-signal tasks), and discovered that there may be different subprocesses of inhibition. For instance, while the Go/No-Go task may require *preventing* a response from taking place, the Think/No-Think and Stop-signal tasks may require *cancelling* an emerging or ongoing response.

We then conducted an fMRI study to examine how the basal ganglia interact with other putative supramodal regions (e.g., DLPFC) to achieve memory and motor inhibition during prevention and cancellation. Through dynamic causal modelling (DCM), we found that both DLPFC and basal ganglia play effective roles to achieve inhibition in the task-specific regions (hippocampus for memory inhibition; primary motor cortex (M1) for motor inhibition). Specifically, memory inhibition requires a DLPFC-basal ganglia-hippocampus pathway, whereas motor inhibition requires a basal ganglia-DLPFC-M1 pathway. We correlated DCM coupling parameters with behavioural indices to examine the relationship between network dynamics during prevention and cancellation and the successfulness of inhibition. However, due to constraints with DCM parameter estimates, caution is necessary when interpreting these results.

Finally, we used diffusion weighted imaging to explore the anatomical connections supporting functions and behaviour. Unfortunately, we were unable to detect any white matter variability in relation to effective connectivity or behaviour during the prevention or cancellation processes of memory and motor inhibition at this stage.

This PhD thesis provides essential INITIAL evidence that not only are the basal ganglia consistently involved in memory and motor inhibition, but these structures are effectively engaged in these tasks, achieving inhibition through task-specific pathways. We will discuss our findings, interpretations, and future directions in the relevant chapters.

ACKNOWLEDGEMENTS

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List of Abbreviations and Acronyms

AAL	Anatomical Automatic Labelling
ACC	Anterior cingulate cortex
ADHD	Attention deficit hyperactivity disorder
ALE	Activation likelihood estimation
ANOVA	Analysis of variance
ATAG	Atlasing of the Basal Ganglia
BA	Brodmann Area
BDI	Beck's Depression Inventory
BOLD	Blood-oxygen level dependent
BMA	Bayesian model averaging
BMS	Bayesian model selection
CMA	Centre for Morphometric Analysis
CSF	Corticospinal fluid
DCM	Dynamic causal modelling
DLPFC	Dorsolateral prefrontal cortex
DTI	Diffusion tensor imaging
DWI	Diffusion-weighted imaging
EPI	Echo-planar imaging
ESD	Extreme studentised deviate
FA	Fractional anisotropy
FDR	False discovery rate
FEF	Frontal eye field
fMRI	Functional magnetic resonance imaging
fODF	Fibre orientation distribution function
FWHM	Full width at half maximum

GLM	General linear model
GPe	External globus pallidus
GPi	Internal globus pallidus
HARDI	High angular resolution diffusion imaging
HRF	Hemodynaic response function
Hz	Hertz
ICBM	International Consortium for Brain Mapping
ISI	Inter-stimulus interval
ITI	Inter-trial interval
IFG	Inferior frontal gyrus
LH	Left hemisphere
M1	Primary motor cortex
MD	Mean diffusivity
MiFG	Middle frontal gyrus
MNI	Montreal Neurological Institute
MPRAGE	magnetisation-prepared, rapid gradient echo
MRI	Magnetic resonance imaging
ms	Millisecond(s)
OFC	Orbitofrontal cortex
PFC	Prefrontal cortex
PMC	Premotor cortex
PTSD	Posttraumatic stress disorder
PVE	Partial volume effect
RH	Right hemisphere
ROI	Regions of interest
RT	Reaction time

s	Second(s)
SD	Standard deviation
SEF	Supplementary eye field
SIF	Suppression-induced forgetting
SMA	Supplementary motor area
SN	Substantia nigra
SNc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulata
SNR	Signal-to-noise ratio
SPM	Statistical parametric mapping
SSD	Stop-signal delay
SSRT	Stop-signal reaction time
STN	Subthalamic nucleus
TBSS	Tract-based skeletal statistics
TSE	Turbo spin echo
UKDI	United diffusion kurtosis imaging
VBM	Voxel-based morphometry
VLPFC	Ventrolateral prefrontal cortex
VMPFC	Ventromedial prefrontal cortex

APPENDIX

1 INTRODUCTION

Being able to stop actions and thoughts is fundamental to goal-directed behaviour. Much research has been conducted to understand how people stop prepotent responses when needed, a process known as inhibitory control. Although research on inhibitory control has often focused on stopping motor actions, there has also been significant interest in how people stop higher-level cognitive processes, such as memory retrieval. Recent evidence from neuroimaging studies suggests that inhibiting motor actions and memory retrieval may engage similar cortical mechanisms, and that a supramodal inhibition mechanism may be supported in part by the right dorsolateral and ventrolateral prefrontal cortices (DLPFC, VLPFC; Depue et al., 2015). However, whereas inhibiting memories and motor actions have been compared at the cortical level, no study has contrasted how these abilities engage subcortical structures. In the case of motor inhibition, subcortical mechanisms are known to contribute significantly, particularly the basal ganglia (Aron et al., 2014; Rae et al., 2015). Nonetheless, whether and how the basal ganglia are engaged in retrieval suppression remains unknown.

This PhD thesis aims to examine the parallel and integrative neural networks underlying retrieval suppression as opposed to motor stopping, with particular focus on the basal ganglia. In this introduction chapter, we will review both behavioural and neuroimaging findings of motor stopping and retrieval suppression, and identify the involvement of the basal ganglia in the latter. The second chapter will discuss the importance of the basal ganglia in cognitive functions in addition to motor control. Evidence includes the

functional and neuroanatomical organisations of the basal ganglia in the context of multiple cortical-basal ganglia and subcortical-basal ganglia loops. Chapters three to six will present the analyses and experiments investigating the role of the basal ganglia in retrieval suppression and motor stopping. Finally, chapter seven will conclude the PhD findings and discuss future directions.

1.1 Motor Stopping in the Go/No-Go and Stop-signal Paradigms

Motor stopping refers to the ability to refrain from making a response through motor action, and is often used to index an individual's capability of inhibitory control. For example, it is human nature to catch something that they dropped from their hands. However, as soon as people realise that it is a dangerous object that they have dropped (such as a kitchen knife), they would immediately refrain from catching that knife so as not to get hurt. Two experimental paradigms are often used to measure motor stopping: the Go/No-Go and the Stop-signal paradigms (Nigg, 2000; Zheng et al., 2008). In a typical Go/No-Go task (e.g., Garavan et al., 1999), participants are presented with visual stimuli, such as blue and green circles. When they see some stimuli (e.g., green circles), they need to respond with a motor action, such as pressing a button (hereinafter referred to as Go trials). In contrast, upon encountering other stimuli (e.g., blue circles), they need to refrain from making any motor responses at all (hereinafter, No-Go trials). The procedure ensures that go trials are much more frequent than are No-Go trials so that participants get into the habit of making the button press response, making it more challenging to stop the infrequent No-Go responses. A typical Stop-signal task (e.g., Logan & Cowan, 1984) is similar to the Go/No-Go task but with some differences. Participants also need to view visually presented stimuli and either carry out a motor response on a Go trial or stop a motor response on a Stop trial. However, in the Stop-signal task, all stimuli represent Go trials, except when an independent stop signal (e.g., an auditory tone) is presented sometime after stimulus onset, signalling the participant to stop. Taking the coloured circles example, participants need to respond to both the blue and green circles, except when a 'beep' tone is played shortly after either a blue or a green circle appears, indicating that they need to cancel the motor response.

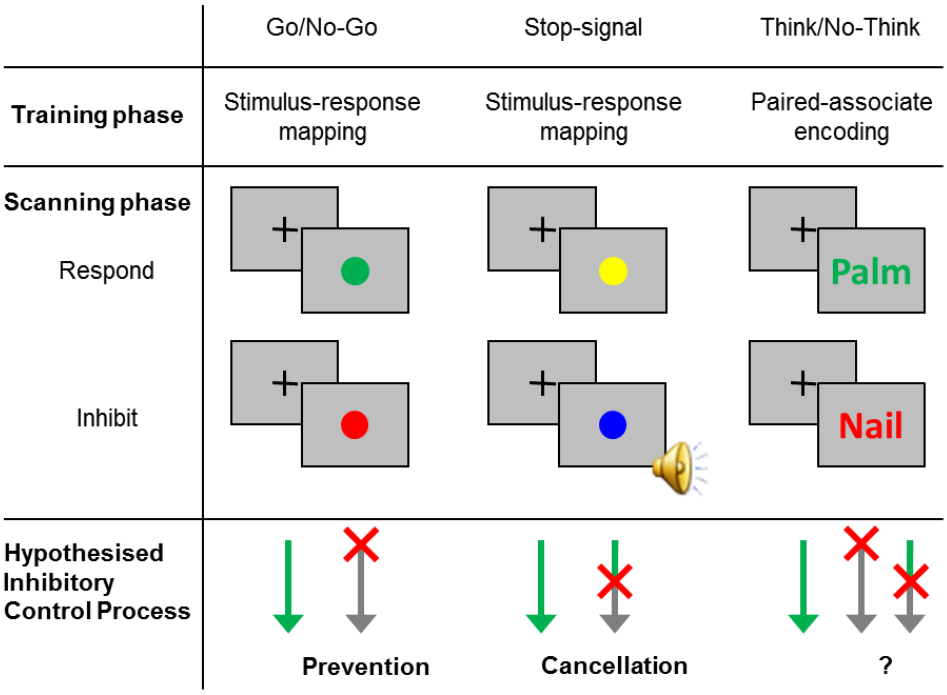

Figure 1.1: Typical Go/No-Go, Stop-signal, and Think/No-Think Paradigms and the Hypothesised Inhibitory Control Processes. In the hypothesised inhibitory control process panel, the arrows denote the time-flow within a single trial. In the bottom panel, the colour green represents the respond processes, the red "X" represents when inhibitory control is putatively engaged in the trial, and the grey represents the inhibited processes. On a Go or Think trial, participants would carry out the motor response or memory retrieval, respectively. On an inhibit trial, if prevention processes are engaged, inhibitory control should be effective from the very beginning of the trial, before the corresponding response is even started. If cancellation processes are engaged, inhibitory control would be recruited only to terminate an initiated response. In the lower right, the uncertain positioning of the "X" indicates that we do not know whether prevention or cancellation may be more important for the Think/No-Think task.

Although the Go/No-Go and Stop-signal tasks are often used for examining inhibitory control abilities, some have suggested that the two tasks may tap distinct stopping processes (Schachar et al., 2007; Figure 1.1). On one hand, the Go/No-Go task potentially allows participants to prevent a motor response before it is even initiated:

upon recognising a No-Go stimulus, participants could decide not to prepare for a movement, and hence prevent any motor response entirely. On the other hand, the Stop-signal task presents the stop-signal after the cue stimulus appears. Because of this delay in stop-signal onset, participants have likely initiated preparation or execution of the motor response, requiring them to cancel the action. It is unclear whether these different demands (hereinafter referred to as prevention and cancellation, respectively) engage distinct sub-processes that are implemented by different mechanisms within the basal ganglia. For example, whereas Eagle et al. (2008) suggested that the Go/No-Go and Stop-signal tasks have a similar anatomical basis but distinct neuropharmacological underpinnings, Dalley et al. (2011) argued that the tasks engage different brain regions due to the different subprocesses. Specifically, according to Dalley et al., stop-signal tasks primarily activate the right inferior frontal gyrus (IFG), whereas Go/No-Go tasks activate the left IFG. Within the basal ganglia, the specific regions involved in different tasks or subprocesses remain unresolved, although recent studies have emphasised the role of the STN in the stop-signal task (Aron et al., 2014).

1.2 Retrieval Suppression and the Think/No-Think Paradigm

It is suggested that retrieval suppression may be initiated by an individual's intrinsic will in order for the individual to remain emotionally and cognitively stable (Anderson & Huddleston, 2012). A typical way of studying retrieval suppression is by using the Think/No-Think paradigm (Anderson & Green, 2001; Figure 1.2). In the Think/No-Think paradigm, participants are first required to learn cue-target associations to a certain level of accuracy. In the subsequent Think/No-Think phase, each trial presents one cue from one of the pairs. Upon seeing the cues, participants need to either recall the corresponding target to the presented cue if it appears in green (Think trial) or to refrain from recalling the target if the cue appears in red (No-Think trial). Some pairs serve as the Baseline and so are omitted from this phase. Finally, a surprise cued-recall test is administered to measure how recall performance was influenced by retrieving the associated items (Think condition) or by suppressing their retrieval (No-Think condition). Two memory tests are typically used – the Same Probe test and the Independent Probe test. The Same Probe test simply uses the original cues from the pair associations that participants learned in the study phase. The Independent Probe test,

however, uses new cues that are related to the targets, such as category names or associates. The Independent Probe test is argued to be a more pure measure for cue-independent inhibition, uncontaminated by interference effects (Anderson & Spellman, 1995). The level of accuracy, the number of repetitions, and the use of Independent Probe test are determined by test materials and task design. Two measures of memory recall can be derived from the Think/No-Think paradigm. First, recall of the No-Think pairs is compared with that of the baseline pairs to examine whether repeated attempts to suppress unwanted memories can actually impair those memories. Second, recall of the Think pairs is compared with that of the baseline pairs to examine if repeatedly retrieving previously learned associations can strengthen the memories.

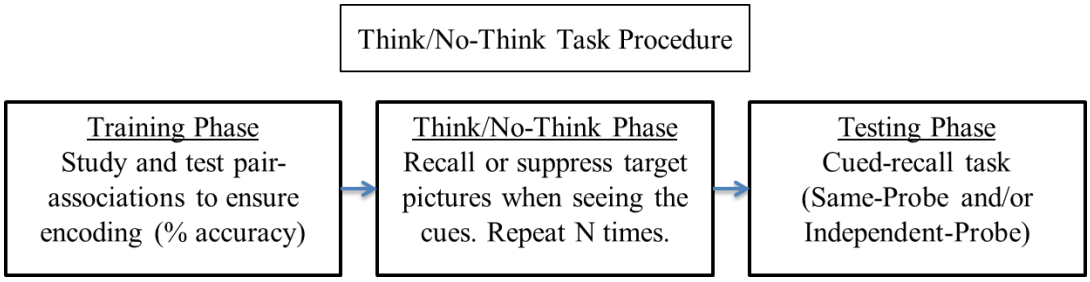

Figure 1.2: The Think/No-Think Paradigm.

Typical findings from the Think/No-Think paradigm include impaired memory for the No-Think items relative to Baseline, sometimes referred to as the suppression-induced forgetting (SIF) effect. The magnitude of SIF indicates the general cognitive control capacity to suppress or inhibit unwanted memories. Similar results have been replicated in studies using a variety of test materials, such as word-word pairs, face-word pairs, face-scene pairs, word-object pairs and object-scene pairs (Anderson & Huddleston, 2012; Gagnepain et al., 2014). People could perform equally well with emotional stimuli (as opposed to neutral stimuli; Depue et al., 2006), guilty knowledge (Bergström et al., 2013), episodic prospection (Benoit et al. 2016), and autobiographical memory (Noreen & MacLeod, 2013). The Think/No-Think paradigm has also been used to detect differences in ageing (Murray et al., 2015) and clinical populations, such as patients with ADHD (Depue et al., 2010) and PTSD (Catarino et al., 2015). It is important to note, though, the SIF effect may be attenuated if the items are not

suppressed for enough times in the Think/No-Think phase, or if the participants are fatigued (van Schie & Anderson, 2017).

On the other hand, Tomlinson et al. (2009) argued against the inhibition account and proposed that the reduced recall for the No-Think items may instead be due to interference between the memorable materials. Participants may generate new associations during the No-Think trials in order to suppress the targets, which may then interfere with the original targets and impair recall at test. In response to Tomlinson et al. (2009), Bäuml and Hanslmayr (2010) pointed out that if Tomlinson et al. were correct, increased memory-related brain activity should have been observed. To the contrary, typical neuroimaging and electrophysiology findings for the No-Think trials exhibit down-regulation of memory-related activity, providing strong evidence for the inhibition account instead of the interference account. Tomlinson and colleagues (Huber et al., 2010) followed up and suggested that inhibition and interference might co-exist depending on whether retrieval suppression took place through selectively inhibiting target memories or replacing target memories to avoid retrieval.

Indeed, Benoit and Anderson (2012) found that directly inhibiting retrieval processes or using alternative and potentially competitive thoughts to occupy awareness engage different neural mechanisms. They referred to the first as “direct suppression”, and the latter as “thought substitution”. In the experiment, Benoit and Anderson instructed participants to learn each cue word with two other words – one as the target, and the other as the substitute. During the Think/No-Think phase, participants were asked to directly suppress any associations they learned with the cue word if they were in the direct suppression group. In contrast, if they were in the thought substitution group, participants should retrieve the substitute so as to keep the target out of mind. While the direct suppression strategy down-regulates hippocampal activity through the right dorsolateral prefrontal cortex (DLPFC), the thought substitution strategy requires competition resolution through the interaction between left ventrolateral prefrontal cortex (VLPFC, including both anterior and middle) and the hippocampus. Critically, the hippocampal downregulation observed in direct suppression was not found in thought substitution. Later studies suggested that using direct suppression alone would be sufficient for suppressing both neutral and emotional unwanted memories (Küpper et al., 2014; Van Schie et al., 2013).

Subsequent studies replicated these phenomena and elucidated the relationship between prefrontal and hippocampal activations, as well as the possible stopping process that is recruited in retrieval suppression (Figure 1.3a). For example, Levy & Anderson (2012) introduced intrusion ratings into the Think/No-Think paradigm, where they asked participants to report whether the target had intruded into their minds after each No-Think trial. Although the Think/No-Think task is procedurally similar to the Go/No-Go task, where participants are instructed to respond or stop by the colour of the stimulus, the initial attempt to refrain from retrieving the target on a No-Think trial often fails. As a result, participants may experience intrusions from the unwanted target. Indeed, Levy and Anderson found that participants experienced frequent intrusions especially in the first half of the Think/No-Think phase. Although intrusions decrease in number over time, they never fully disappear during the course of the task. Through further analyses (Figure 1.3b; Figure 1.3c), Levy and Anderson found that overcoming intrusions induced larger hippocampal downregulation than did preventing a thought from coming into mind. Critically, the magnitude of the hippocampal downregulation when overcoming intrusions significantly predicted the magnitude of SIF. No such relationship was observed for thought prevention. In addition, Benoit et al. (2015) found that overcoming intrusions triggered greater inhibitory modulation of the hippocampus by the DLPFC, supporting the proposition that DLPFC exerts top-down regulation of the hippocampus in the context of retrieval suppression. Furthermore, the engagement of the DLPFC in overcoming intrusions is recently replicated by Gagnepain et al. (2017) in the context of suppressing emotional memories induced by emotional pictures. Using dynamic causal modelling, Gagnepain et al. found parallel DLPFC downregulation of the hippocampus, the parahippocampal gyrus, and the amygdala. These pieces of evidence suggest that the DLPFC plays a consistent role in suppressing different forms of memories, and that overcoming intrusions in the Think/No-Think task may be more similar to reacting to a stop tone in the Stop-signal task and primarily require a cancellation process that interrupts retrieval (Figure 1.1).

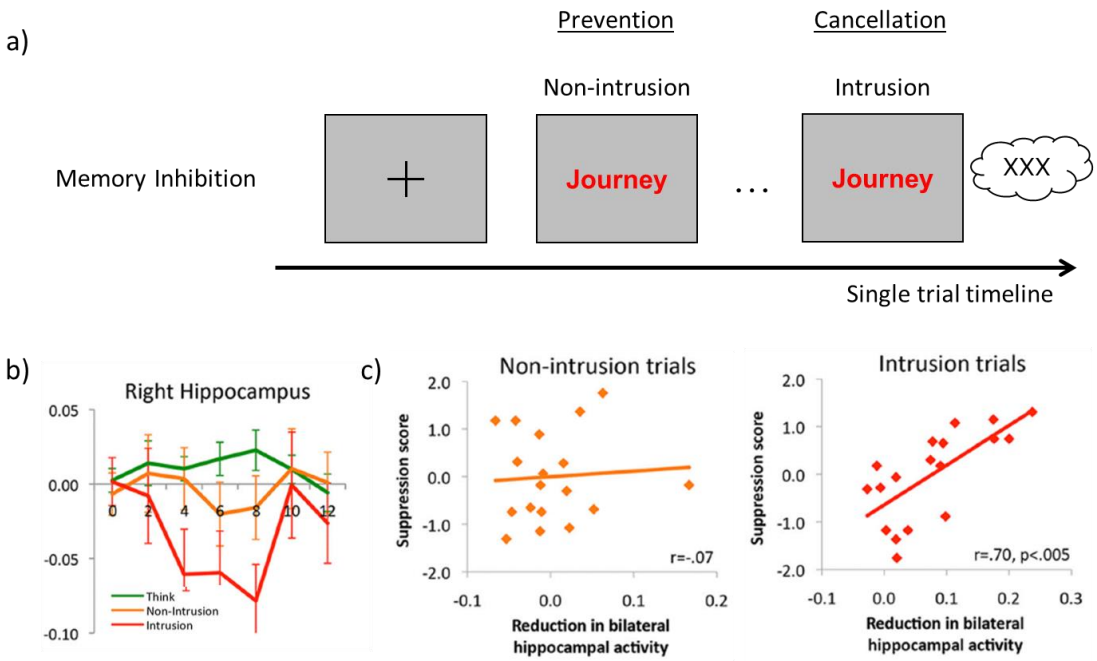

Figure 1.3. a) Possible inhibition subprocesses engaged by memory inhibition during intrusion and non-intrusion. During the course of a single trial, participants are presented with the fixation cross followed by the cue word. If the participant did not experience an intrusion, it is likely that they have successfully prevented the unwanted target from coming to mind and have kept mind clear. However, if at a later point in the trial, the target did intrude into their mind (represented by the thought bubble "XXX"), they will likely have to cancel the retrieval process and push the target out of mind. b) The magnitude of right hippocampal activity during Think, Non-intrusion, or Intrusion trials. c) The relationship between hippocampal activity and the magnitude of memory inhibition during intrusion or non-intrusion.

1.3 Parallel Functional Networks between Memory and Motor Inhibition

Memory and motor inhibition both require stopping of a prepotent response, be it a memory retrieval or a motor action (Anderson & Green, 2001; Anderson et al., 2004). Researchers have investigated whether similar functional networks underpin the inhibitory process supporting this stopping, and whether there exists a supramodal network of inhibition in the brain that encompasses memory and motor domains. Depue

et al. (2015) compared the brain mechanisms underlying memory, motor, and emotional inhibition through a within-subject study. In the experiment, participants performed the Think/No-Think task for memory inhibition, the Stop-signal task for motor inhibition, and an emotion stopping task for emotion inhibition. Through a conjunction analysis, Depue et al. found that the right DLPFC and the right angular gyrus were consistently activated in all three tasks. It is possible that the right DLPFC and angular gyrus are part of the supramodal inhibition network, responsible for inhibitory control across different task domains. In addition, researchers have also observed similar neurophysiological mechanisms in memory inhibition as in motor stopping. For example, Mecklinger et al. (2009) measured event-related potential (ERP) during retrieval and motor inhibition using the Think/No-Think and Stop signal task, respectively. They observed very similar centro-parietal N2 components during retrieval and motor stopping, and the two components were significantly correlated. This is evidence showing that memory and motor inhibition share common mechanisms not only in the network of brain structures involved but also in neurophysiological biomarkers.

In a more recent study, however, both the right DLPFC and VLPFC were found to be critical for memory and motor inhibition. Schmitz et al. (in preparation) conducted a within-subject fMRI experiment where participants completed the Think/No-Think task and the Stop-signal task in one single session. In their conjunction analysis, Schmitz et al. found that both the right DLPFC and VLPFC were activated by both memory and motor inhibition. In order to investigate how these putative supramodal regions interact with task-specific regions (hippocampus for memory inhibition, and the primary motor cortex or M1 for motor inhibition) to achieve inhibitory control, they conducted effective connectivity analyses using Dynamic Causal Modelling (DCM). They found that not only are the DLPFC and VLPFC involved in the network dynamics to achieve memory and motor inhibition, but the VLPFC functioned to modulate the coupling between DLPFC and the task-specific structures. This is the first evidence showing that the DLPFC and VLPFC are both involved in memory and motor inhibition, and possibly form an integral part of the supramodal network.

If the DLPFC and VLPFC are part of a supramodal network of inhibition, it leads to the question what other brain structures may be part of this network as well. One potential candidate is the basal ganglia. The basal ganglia have long been studied in the motor

domain. Through studying motor control, researchers have established neurobiological circuitries where the basal ganglia play important roles. A detailed review will be provided in the next chapter. On top of the motor functions, recent developments in the literature have suggested that the basal ganglia may be involved in various cognitive processes as well (e.g. Graybiel, 2005). Specific to retrieval suppression, a number of fMRI studies using the Think/No-Think task have reported basal ganglia activations (e.g., Anderson et al., 2004; Benoit & Anderson, 2012; Benoit et al., 2014; Levy & Anderson, 2012; Paz-Alonso et al., 2013; Schmitz et al., in preparation). However, these activations have been largely overlooked. To date, there has been no formal investigation of the role of the basal ganglia in memory inhibition and its possible parallelism to motor inhibition. This under-representation may be caused by the reliability of anatomical co-registrations due to the size and complexity of the basal ganglia structures, or the limited understanding of the basal ganglia cognitive functions.

This PhD thesis aims to examine the potential supramodality of the basal ganglia in memory and motor inhibition. The following chapter will review some basic anatomy and functioning of the basal ganglia, and propose hypotheses of the role of the basal ganglia in retrieval suppression and motor stopping.

2 BASAL GANGLIA FUNCTIONS AND ANATOMY

As introduced at the end of Chapter 1, the basal ganglia may be part of the supramodal network of inhibition due to its involvement in both cognitive and motor functions. It is important to first understand how the basal ganglia function through what sorts of brain networks and then develop specific hypotheses.

The basal ganglia are a group of subcortical nuclei linked by a circuit of excitatory and inhibitory connections, which coordinate to generate the appropriate amount of excitatory or inhibitory functional outputs according to task goals. The most studied function of the basal ganglia is motor control (Aron, 2007; Kandel et al., 2012; Graybiel, 2005), especially in Parkinson's disease (PD). However, an emerging body of research has suggested that the basal ganglia may contribute to cognitive control, and memory retrieval in particular, in a similar way. In this chapter, I will first review the intrinsic connections and the coordinating pathways between basal ganglia nuclei that allow for the selection and initiation of task-relevant responses, and hence the suppression of task-irrelevant responses. Second, I will illustrate the critical position of the basal ganglia in multiple cortical and subcortical networks, possibly implying the engagement of the basal ganglia in both high-level and low-level neural processing. Third, I will discuss the topographical and non-topographical inputs that the basal ganglia receive from the upstream structures, and how these may be related to the

possibility that the basal ganglia are involved in inhibitory processes across modalities. Finally, based on known anatomy, I will review existing theories and knowledge on basal ganglia functions and develop hypotheses regarding the specific role of the basal ganglia in memory and motor inhibition.

2.1 Intrinsic Connections within the Basal Ganglia

As summarised by Kandel et al. (2012), there are four principle structures in the basal ganglia - the striatum (consisting of the caudate, putamen, and nucleus accumbens), the internal and external global pallidus (GPi and GPe, respectively), the substantia nigra pars compacta (SNc) and pars reticulata (SNr), and the subthalamic nuclei (STN). These structures can be categorised as input, output, and intrinsic nuclei of the basal ganglia (Lanciego et al., 2012). While the input nuclei (mainly the striatum, and the STN) receives diffuse projections from all over the cortex and the thalamus, the output nuclei (GPi and SNr) send processed information to their efferent targets, such as the thalamus. As for the intrinsic nuclei, the GPe relays information between basal ganglia input and output nuclei; the SNc modulates the level of dopamine in the intrinsic connections to balance the amount of inhibitory and excitatory signals from the basal ganglia system. Almost all basal ganglia nuclei have inhibitory outputs, except the STN that sends excitatory signals to its downstream structures, and the SNc that modulate the level of dopamine.

Through studying motor control, researchers have used primate and rodent models to establish three coordinating pathways in the basal ganglia, constituted by the above structures that contribute to the different processes that the basal ganglia are involved in: the hyperdirect, direct, and indirect pathways (Alexander & Crutcher, 1990; Aron, 2007; Kandel et al., 2012; Graybiel, 2005; Nambu et al., 2002). In the context of movement control, the hyperdirect pathway has two primary roles (Takada et al., 2013): first, it globally inhibits all motor responses to prevent unnecessary movements from taking place prior to movement onset; and second, it engages an early selection process that implicitly determines the ideal goal-directed motor response. Following the hyperdirect pathway, the direct pathway initiates the selected motor response. Finally, the indirect pathway terminates the selected motor response either when it is achieved or when it needs to be cancelled (Freeze et al., 2013).

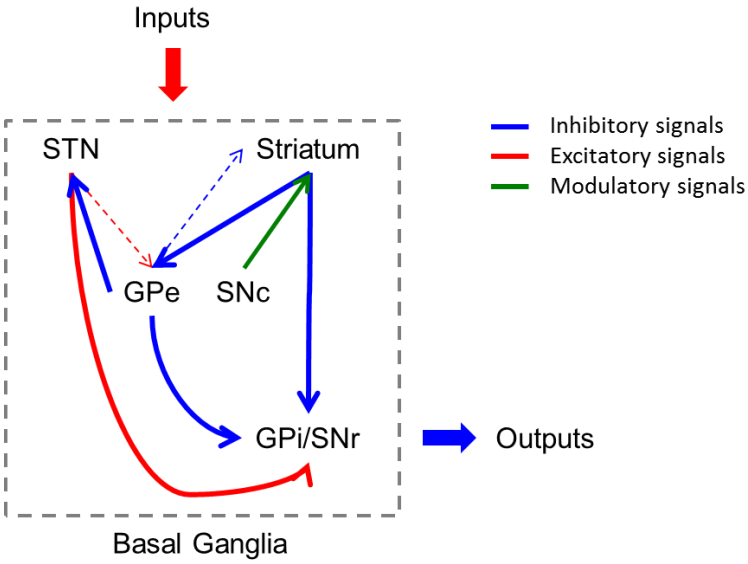

Figure 2.1. Intrinsic Basal Ganglia Pathways. The direct pathway involves the striatum and the GPi/SNr. The indirect pathway involves the striatum, GPe, STN, and GPi/SNr. The hyperdirect pathway involves the STN and GPi/SNr.

The specific intrinsic basal ganglia pathways are depicted in Figure 2.1. These pathways are particularly established in the primate and rodent literature, which are often cited in human studies. In the hyperdirect pathway, the STN receives direct cortical and thalamic inputs, and sends out excitatory signals to the GPi/SNr. Exciting the GPi/SNr enhances the inhibition of the downstream structures, and hence limits movement responses. In both the direct and indirect pathways, cortical and thalamic inputs are received through the striatum. The striatum then engages the direct pathway to initiate motor response, or the indirect pathway to inhibit responses. Specifically, the direct pathway encourages the response by the striatum inhibiting the GPi/SNr, which in turn disinhibit their efferent targets and lead to enhanced responses. On the other hand, the indirect pathway inhibits responses through the striatum inhibiting the GPe, which reduces the constraint on the GPi/SNr output either through direct projections or via the STN. This disinhibition of the GPi/SNR increases inhibition of the efferent targets and hence limits motor responses. As mentioned earlier, outputs from the striatum are modulated by the dopaminergic signals from the SNc. While the D1 receptor enhances the direct pathway, the D2 receptor inhibits the indirect pathway.

The aforementioned intrinsic connections are well integrated into classic theories on the basal ganglia functional networks in primates and rodents. In addition, there also exist feedback connections from the STN to the GPe, and from the GPe to the striatum. However, these feedback connections are not entirely reciprocal to the corresponding feedforward connections, and usually target a larger population of neurones than that where the feedforward projections originate (Voorn, 2010). However, whether the same pathways exist in humans is less clear. Using diffusion tractography that allows for estimating white matter connections *in vivo*, researchers have found evidence suggesting direct cortical inputs to the GPe (Leh et al., 2007), and reciprocal connections between the basal ganglia and the cerebellum (Bostan et al., 2013). Nevertheless, these connections still need to be confirmed with post-mortem histology.

2.2 Cortical and Subcortical Networks Involving the Basal Ganglia

The basal ganglia are proposed to be involved in different cortical and subcortical networks (Figure 2.2). In the cortical-basal ganglia loop, the striatum receives top-down excitatory inputs from all over the cortex, and then outputs the processed information to the thalamus through the output nuclei, which then sends feedback to the cortex to inform responses (Kandel et al., 2012). In the subcortical-basal ganglia loop, subcortical structures such as the midbrain and brainstem regions send inputs to the thalamus, which are then relayed to the basal ganglia. The basal ganglia process this information and then send feedback to the brainstem areas (For review, see Winn et al., 2010). According to Whishaw and Kolb (1984), there are fundamental differences in the functions performed by the cortico- and subcortico-basal ganglia loops. On one hand, the cortico-basal ganglia loop is responsible for high-level cognitive and motor functions such as executive functions and voluntary movement coordination. On the other hand, the subcortico-basal ganglia loop is primarily responsible for low-level associative learning and instinctive behaviour, such as foraging. Since this PhD thesis aims to investigate the role of the basal ganglia in memory and motor inhibition that require high-level inhibitory control mechanisms, the cortical-basal ganglia loop will be more relevant to the rest of this thesis. Specifically, if the basal gnalgia are part of the supramodal network of inhibition, they may interact with the prefrontal cortex (e.g.,

DLPFC and VLPFC) to process inhibitory commands. These commands may then be passed on to the task-specific structures, such as M1 for motor inhibition and the hippocampus for memory inhibition.

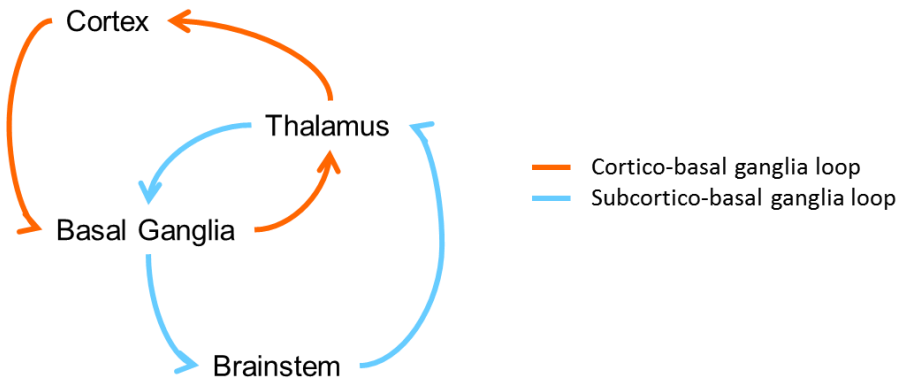

Figure 2.2. The Cortico- and Subcortico-Basal Ganglia Loops. The cortico-basal ganglia loop involves cortical projections into the basal ganglia, followed by the thalamus, and finally feedback to the cortex. The subcortical-basal ganglia loop involves the brainstem regions projecting to the thalamus, followed by the basal ganglia, and finally feedback to the brainstem.

2.3 Topographical and Non-Topographical Inputs to the Basal Ganglia

The basal ganglia receive both topographical and non-topographical inputs from the cortex. Through the topographical projections, distinct cortical regions innervate concentrated regions in the striatum, allowing parallel processing of multiple functions. For example, Seger (2013) summarised four functional loops in the cortico-basal ganglia system based on previous models: the visual, motor, executive, and motivational loops (Figure 2.3a). The executive functions loop (green) involves the fronto-parietal network and the caudate head and body. The motor loop involves the motor cortices and the putamen. The motivational loop involves the ventral prefrontal cortex, the basal forebrain, and ventral striatum. The visual loop involves the visual cortex and caudate tail. In a more recent meta-analysis using neuroimaging data, Pauli et al. (2016) was also able to delineate distinct but overlapping functional zones in the

striatum by classifying their meta-analytic connectivity profiles based on regions of co-activation in specific task contexts. As their first step, Pauli et al. used a large-scale fMRI database (Neurosynth; http://neurosynth.org) and identified 5,809 studies with basal ganglia activations. With these data, Pauli et al. constructed a meta-analytic connectivity profile of the basal ganglia by identifying regions of co-activation in the cortex. Using k-means clustering, Pauli et al. classified functional zones in the basal ganglia based on their connectivity profiles, and identified 5 distinct clusters that are large enough to be robustly detectable in human neuroimaging (Figure 2.3b). Their subsequent term-based analysis revealed the functional associations of these clusters to different task contexts. Specifically, the caudate is primarily associated with executive functions, the putamen for sensorimotor processes, and the ventral striatum for value processes. These clusters highly resemble the functional loops described in Seger (2013), providing meta-analytic evidence for the topographical organisation of the corticostriatal network. However, these results should not be taken for granted. First, Pauli et al. did identify stable solutions with up to 17 clusters in their k-means clustering analysis, suggesting that the functional topography in the striatum may be more like a continuum than clear-cut zones. Second, the term-based analysis may be biased by the amount of studies available for different tasks or psychological constructs, and may not reflect all of the functions that are associated with basal ganglia structures. For example, Pauli et al. found that the putamen is primarily part of the sensorimotor network. However, there has been evidence suggesting the involvement of the putamen in cognitive functions such as memory and probabilistic learning (Graybiel, 2005; Koster et al., 2015; Shohamy et al., 2008). Therefore, although these mapping efforts provide a useful rule-of-thumb for the basal ganglia functional divisions, care needs to be taken when making generalisation of the specific responsibilities of particular basal ganglia regions.

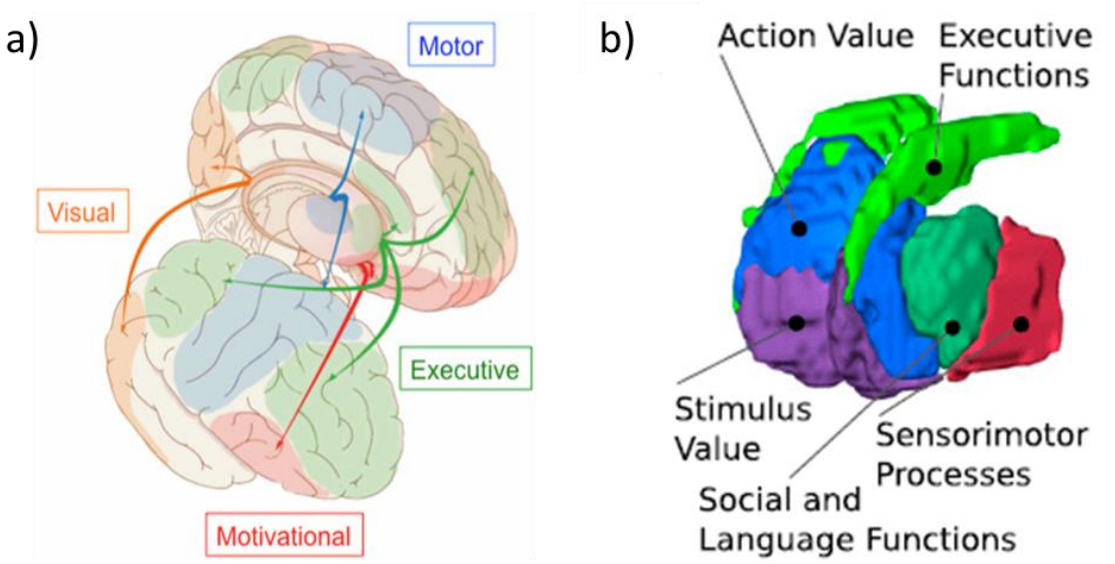

Figure 2.3: A) The Cortical-Gasal Ganglia Functional Loops in Seger (2013); B) The Five-Cluster Solution in Pauli et al. (2016).

The aforementioned functional divisions in the cortical-basal ganglia system are largely consistent with anatomical evidence from animal studies. Haber and Knutson (2010) reviewed the topographical corticostriatal projections based on tracing studies using macaque monkeys (Figure 2.4a). In general, ventromedial striatum receives input from the ventromedial prefrontal cortex (VMPFC), the orbitofrontal cortex (OFC), and the dorsal anterior cingulate cortex (dACC). Central striatum, such as caudate head/body and precommissural putamen, receives input from the DLPFC (areas 9 and 46). Finally, dorsolateral striatum receives input from the motor control areas. For example, the frontal eye field (FEF) projects to central and lateral caudate, as well as central putamen. The supplementary eye field (SEF) projections have more lateral striatal targets than the FEF. The rostral premotor cortex (rPMC) innervates both the caudate and the putamen. Hence the distribution of the topographical corticostriatal projections seems to follow a functional gradient – whereas the cognitive and limbic projections concentrate on the centromedial striatum, the motor projections concentrate on the lateral striatum. Notably, this functional topography also applies to the other connections relevant to the basal ganglia networks, including the intrinsic connections

between the basal ganglia nuclei, and the basal ganglia output to their efferent targets (Haber & Knutson, 2010).

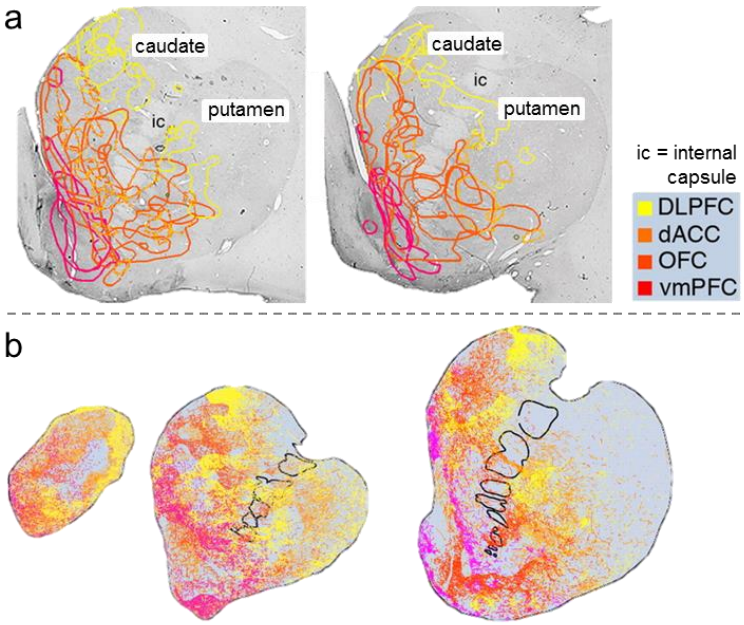

Figure 2.4: The (a) topographical and (b) non-topographical cortical projections into the striatum in macaque monkeys (Haber et al., 2006). The top panel presents the distinct target zones in the basal ganglia from different prefrontal regions. The bottom panel presents diffuse projections from the same prefrontal regions across different basal ganglia regions.

On top of the topographical projections, the cortex also sends non-topographical or diffuse projections to the striatum, allowing the different functional divisions to communicate between each other to achieve task goals. Haber et al. (2006) injected tracers from multiple motivation-related cortical regions and observed diffuse projections from these regions to the striatum (Figure 2.4b), on top of the concentrated topographical projections. It is also worth noting that even the focal termination fields from the topographical projections overlap with each other. Hence Haber and Knutson (2010) proposed that the topographical and non-topographical mappings in the corticostriatal system may serve to integrate domain-specific signals across functional domains to inform goal-directed behaviour.

However, one should be cautious when using animal evidence to make inference on human anatomy and functions. Choi et al. (2016) proposed that similar corticostriatal pathways may exist in both humans and monkeys. However, Neggers et al. (2015) used diffusion tractography and observed differential anatomical connectivity profile in the corticostriatal motor loop between humans and macaque monkeys (Figure 2.5). Specifically, target striatal areas from the FEF and the primary motor cortex (M1) appeared to shift posteriorly and concentrate more in the putamen in humans than in monkeys. The human FEF and M1 target fields also seem to largely overlap, whereas in macaque monkeys the two are more differentiated. Therefore, although the human and macaque corticostriatal system share similarities in the organisation, the specific pathways and connections may vastly differ. More research is needed to map the corticostriatal projections in the human brain.

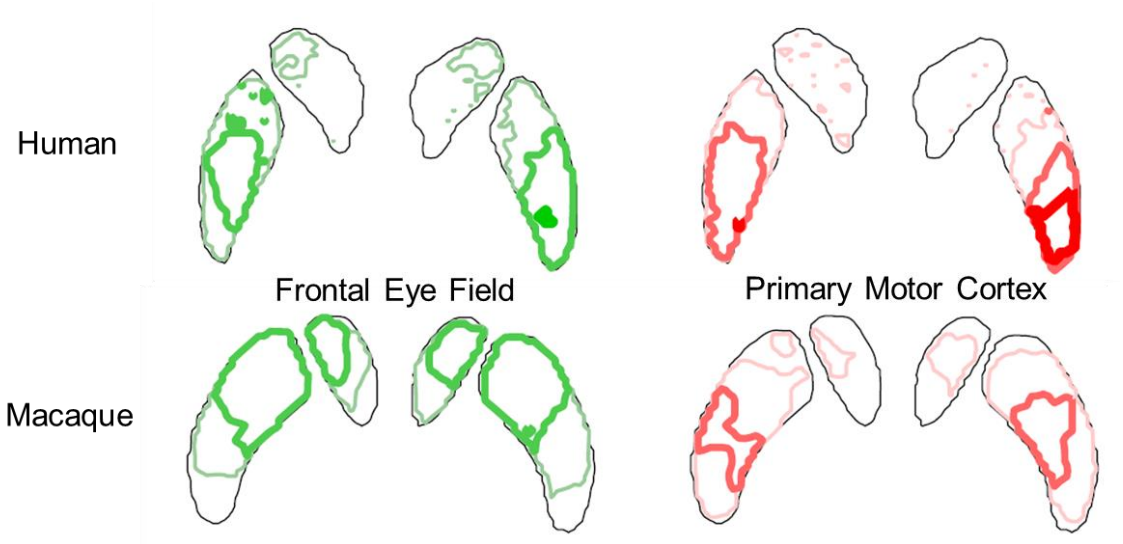

Figure 2.5: Projections from motor cortical regions to the striatum in humans and macaque monkeys presented on axial sections of the striatum (Neggers et al., 2015). The bounded areas represent the target regions from the projections. The thickness of the boundaries represent different thresholds they used (thicker lines represent more stringent threshold), showing the validity of the differences between human and macaque basal ganglia connectivity.

2.4 Theories of Basal Ganglia Functions

As discussed previously, the basal ganglia have an established role in motor control, and most of the basal ganglia functional pathways were discovered in the motor domain through primate and rodent studies. However, recent evidence suggest that the basal ganglia pathways may not be responsible for motor control *per se*, but may be involved in higher-order cognitive processes in general (Alexander et al., 1986; Schroll & Hamker, 2013).

Specific to the memory domain, it has long been perceived that the basal ganglia and the medial temporal lobe (MTL) support two distinct systems. While the basal ganglia are strongly associated with non-declarative memory, such as skill learning or classical conditioning (e.g., Cohen et al., 1997; Knowlton et al., 1994), the MTL system is necessary for declarative memory, including the formation, consolidation, and retrieval processes (Cohen et al., 1997; Squire, 1992). This distinction was extended to the context of spatial memory. For example, Döller et al. (2008) studied whether striatal and hippocampal systems interact during landmarks and boundaries processing in a spatial memory task. While the striatal system was more implicated in learning landmarks through associative reinforcement, the hippocampal system was more relevant to learning boundaries through more incidental processes. Using DCM, Döller et al. found more evidence for the two being independent than directly interacting, and hence concluded that the striatal and hippocampal systems are parallel in the context of spatial memory.

However, recent evidence from neuroimaging and neuropsychological studies suggest that the basal ganglia may also play a role in declarative memory, both at encoding and retrieval (e.g., Cohn et al., 2010; Shohamy and Adcock, 2010). For example, Shohamy (2011) reviewed that the basal ganglia and the hippocampus may jointly contribute to learning and memory due the following reasons. First, both the striatum and the hippocampus are anatomically connected with the PFC, a likely pathway for mediating interactions between the two systems (Alexander et al., 1986; Goldman-Rakic et al., 1984; Haber, 2003; Suzuki & Amaral, 2004). Second, functional interactions have been repeatedly observed between the basal ganglia and the hippocampus (e.g., Hartley &

Burgess, 2004; Voermans et al., 2004). These interactions may be competitive or collaborative in nature.

Some suggested the basal ganglia and the hippocampal systems are competitive due to the observation that increased activity in one is associated with decreased activity in the other (Dagher et al., 2001; Poldrack & Packard, 2003). Poldrack and Rodriguez (2004) reviewed evidence for the competition between the hippocampal and basal ganglia systems in classification learning, and proposed that the competition may be modulated by task demands and behavioural success. For example, Rodriguez and Poldrack (2003) re-analysed a classification learning dataset wherein participants performed a weather prediction task. In this task, participants performed on-line learning where they associated visual stimuli with weather categories. Using structural equation modelling, Rodriguez and Poldrack identified that the competitive interaction between the basal ganglia and the MTL is not direct, but is mediated by the prefrontal cortex (PFC). Specifically, they found mostly negative coupling between the PFC and the hippocampus, but mostly positive coupling between the striatum and either the PFC or the hippocampus. It is unclear from these results whether one structure is upstream to the others. Nevertheless, this work provided evidence that there are indirect interactions between the basal ganglia and the hippocampus, and that the two systems are not completely independent from each other.

Despite this evidence that the basal ganglia and the hippocampal systems are independent or interact through the prefrontal cortex, others have suggested that the basal ganglia and hippocampus may interact in other ways. For example, Sabatino and colleagues found evidence that basal ganglia activity influences hippocampal oscillations. Specifically, while caudate stimulation appeared to influence the hippocampal theta rhythm by inhibiting hippocampal spikes (La Grutta et al., 1985; Sabatino et al., 1985), pallidal stimulation triggered enhanced epileptiform activity, inducing generalised seizure activity (Sabatino et al., 1986). Berke et al. (2004) also found entrainment of ventral/medial striatal neurons to the hippocampal theta in rats. Moreover, using Granger Causal Modelling on fMRI data, Seger et al. (2011) found evidence for effective connectivity from the putamen to both the caudate and posterior hippocampus, as well as from posterior hippocampus to the caudate. These interactions were observed in two tasks. One was a weather prediction task, where participants

learned on-line whether a visual stimulus was meant to predict rain or sunshine. The other was a subjective judgement task, wherein the participants rated whether their weather categorisation was based on memories or guesses. These pieces of evidence point to the possibility that the basal ganglia and the hippocampal functions are closely associated.

In addition to the potential interactions between the basal ganglia and the hippocampus, Scimeca and Badre (2012) proposed a more specific role of the basal ganglia in the goal-directed gating of declarative memory retrieval. Specifically, retrieval may be an adaptive process of re-encoding modulated by the striatum, where the likelihood for memories to be retrieved in a particular context is determined by the expected context-specific utility of those memories. In addition, the striatum may selectively admit and maintain high utility information into working memory for successful future retrieval, while inhibiting irrelevant or misleading information that is of low utility. Finally, the striatum is involved in reinforcing and adjusting the utility level of each memory based on the outcome of retrieval.

This dynamic on-line modulation of memory retrieval by the basal ganglia highly resembles the forward model of action control computationally. The forward model (Frith & Wolpert, 2000) aims to optimise the course of action towards a desired state by minimising the discrepancies between the current body position and the desired position. Parallel to declarative memory gating, the action goal is achieved by selecting and initiating an ‘optimal’ course of action based on prior experience, and at the same time constantly refining the course of action according to the outcomes suggested by concurrent sensory feedbacks from the environment. Therefore, it may not be unreasonable to postulate that memory and action control may involve parallel computational mechanisms supported by a common anatomical substrate in the basal ganglia. Indeed, in a more recent review, Schroll and Hamker (2013) analysed a range of computational models depicting the cognitive and motor functions of the basal ganglia with possible contributions from the interacting pathways. Specifically, global blocking of activations, such as premature-response prevention and working memory updating, may be modulated by the hyperdirect and the indirect pathways; response inhibition/deferral and working memory gate closing may be modulated by the interaction between the direct and the short indirect pathways.

2.5 Hypotheses for the Basal Ganglia in Inhibitory Control

The goal of this PhD thesis is to answer the following questions.

1. Whether the basal ganglia are consistently involved in both memory and motor inhibition?
2. How are the basal ganglia involved in memory and motor inhibition, in relation to the prefrontal control regions and the task-specific regions?
3. What are the anatomical pathways underlying the functional interaction?

We plan to tackle the first question with a series of meta-analysis, the second question with an empirical fMRI study using univariate and effective connectivity analyses, and the final question with diffusion-weighted imaging.

2.5.1 The Basal Ganglia are Involved in Memory and Motor Inhibition, with either Spatially Distinct or Overlapping Activations from Different Task Domains or Inhibitory Processes

Based on previous literature, we would hypothesise that the basal ganglia do play a role in both memory and motor inhibition, as part of the supramodal network of inhibition including the DLPFC and VLPFC. On one hand, the basal ganglia seem to be involved in a range of cognitive functions, in addition to their well-established association with motor control. On the other hand, the basal ganglia have intrinsic pathways to modulate different inhibition processes, such as prevention and cancellation (e.g., Schroll & Hamker, 2014).

Regarding the specific regions in the basal ganglia that are involved in memory and motor inhibition, there are two possible alternatives. First, due to the functional divisions in the corticostriatal loop, it is possible that we may see spatially distinct activations in the basal ganglia from memory and motor inhibition. While the memory task may activate medial striatum, the motor task may activate lateral striatum (Voorn et al., 2004; Yin et al., 2004). However, if we believe that memory and motor inhibition engage domain-general processes of inhibitory control, there may be overlapping activity in the basal ganglia across the memory and motor tasks. Similarly, between the prevention and cancellation processes, it is possible that there are discrepant basal ganglia activations from the distinct functions. Alternatively, the prevention and

cancellation processes may activate similar regions in the striatum, but engage different basal ganglia pathways as reviewed by Schroll and Hamker (2014).

2.5.2 The Basal Ganglia are Part of the Supramodal Network that Supports Inhibition through Task-specific Pathways

To conceptualise how the basal ganglia help achieve inhibition across different task domains, we need to consider 1) how the supramodal regions interact between themselves, and 2) how the supramodal regions interact with the task-specific regions. Within the supramodal network, we hypothesise that inhibition may be supported by the corticostriatal connections. As reviewed in Section 2.3, there are topographical projections from the lateral PFC to the centromedial striatum (including the caudate and putamen) as part of the executive functions division of the corticostriatal loop. It is possible that this pathway is also involved in cognitive control processes such as inhibition. Moreover, this supramodal pathway should selectively engage task-specific pathways to achieve inhibition, such as the hippocampus for memory inhibition and M1 for motor inhibition.

In terms of how the supramodal regions in the basal ganglia and the PFC interact with the task-specific regions such as the hippocampus and M1, we have a few hypotheses. First, it is possible that the basal ganglia are an intermediate station between the PFC and the hippocampus. According to this "intermediary" hypothesis, when the prefrontal signals reach the basal ganglia, the basal ganglia system may engage the hyperdirect or the indirect pathways to inhibit responses, and hence reduce hippocampal and M1 activity. In the memory domain, although the specific pathway through which the basal ganglia communicates with the hippocampus remains unclear, there has been evidence showing influence from the caudate nucleus on hippocampal activity (La Grutta et al., 1985; Sabatino et al., 1985), as well as effective connectivity from the putamen to posterior hippocampus during probabilistic learning and subjective judgment (Seger et al., 2011).

Alternative to the intermediary hypothesis, it is also possible that the basal ganglia modulate the interaction between the PFC and the task-specific region. According to this "modulation" hypothesis, the basal ganglia may inform the inhibitory control processes from the PFC to the hippocampus or M1. Previous research has shown that

the basal ganglia are essential for goal-directed behavioural in both the memory and motor domains. In the memory domain, the basal ganglia may be involved in adaptive long-term memory retrieval, where memories with higher context-specific utility are gated into working memory so that they are more easily accessible, and memories with lower utility are gated out (Scimeca & Badre, 2012). Similarly, in the motor domain, the basal ganglia consist of the intrinsic pathways that modulate the initiation and termination of motor responses according to goal-context (see Section 2.1). These suggest that the basal ganglia may be critical for modulating commands of cognitive control from the PFC to the task-specific regions.

Finally, we have an "indirect" hypothesis, where the basal ganglia interact with the task-specific regions through other structures such as the PFC. Although there is electrophysiology and effective connectivity evidence suggesting the basal ganglia influence on hippocampal activity (Sabatino et al., 1985; Seger et al., 2011), the underlying anatomical pathways remain unclear. It is possible that this interaction is indirect. For example, using structural equation modelling, Rodriguez and Poldrack (2003) found that the interaction between the basal ganglia and the MTL is not direct, but through the PFC. Shohamy et al. (2011) also reviewed that the PFC may be a critical component through which the basal ganglia and the hippocampus interact.

2.5.3 Possible Anatomical Pathways from the Basal Ganglia to Task-specific Regions

As reviewed in Sections 2.1 and 2.2, most basal ganglia outputs go through the thalamus in the corticostriatal loop. How information is projected from there depends on how interaction is achieved between the basal ganglia and the downstream structures, according to the hypotheses presented in Section 2.5.2. If the intermediary hypothesis were true, the thalamus should project to M1 and the hippocampus as the next step. There has been extensive literature on the thalamic pathways involved in memory and motor control. For example, the anterior thalamic nuclei communicates with the hippocampus through the cingulum bundle for declarative memory (e.g., Aggleton, 2014), and the ventrolateral thalamic nuclei projects to M1 to deliver motor commands (e.g., Alexander et al., 1986).

Alternatively, if the modulation hypothesis were true, there may be projections from the thalamus to either the PFC or an intermediary between the PFC and the task-specific regions. According to the literature, there may be indirect pathways from the PFC to both M1 and the hippocampus. In the motor domain, Bracht et al. (2012) used diffusion tractography and identified that reduced motor activity in Huntington's patients are associated with altered structural connectivity in the preSMA-SMA, and the SMA-M1 pathways. In addition, pathological motor control is associated with altered involvement in the DLPFC-preSMA pathway. It is therefore possible that during motor inhibition, the DLPFC downregulates M1 activity through the preSMA and SMA. In the memory domain, Anderson et al. (2016) proposed two pathways from the PFC to the hippocampus that underlie retrieval suppression. First, memory inhibition may be achieved by the ACC modulating activity in the entorhinal cortex. Since the entorhinal cortex is a major input site to the hippocampus, suppressing these inputs may account for the reduced hippocampal activity during retrieval suppression, possibly leading to impaired memory retrieval. Second, the PFC modulation of hippocampal activity may be achieved through the ACC engaging the thalamic reuniens nucleus, which originates one of the major thalamic inputs to the MTL. It is possible that projections from the reuniens innervate inhibitory interneurons in the CA1 subregion of the hippocampus. This would result in local inhibition in the hippocampus and hence reduced memory retrieval.

We will discuss our findings in relation to the above hypotheses in the following chapters. Chapter 3 will focus on findings from the fMRI meta-analyses using memory and motor inhibition tasks. In Chapter 4, we will layout the behavioural paradigms that we have used to delineate the cancellation and prevention processes in memory and motor inhibition. Chapter 5 will present the empirical fMRI findings from the univariate and effective connectivity analyses. Chapter 6 will discuss our approaches using diffusion-weighted imaging to investigate the anatomical pathways underlying inhibitory control. Finally, we will conclude this PhD thesis in Chapter 7.

3 META-ANALYTIC EVIDENCE CONFIRMS BASAL GANGLIA INVOLVEMENT IN MEMORY AND MOTOR INHIBITION

The first two chapters discussed the possibility that there may be overlapping mechanisms between memory and motor inhibition especially in the basal ganglia. In the current chapter, we will test this idea by comparing meta-analytic activations both qualitatively by localising the clusters to specific basal ganglia structures, and quantitatively by computing conjunction and contrast maps between tasks. This coordinate-based meta-analysis approach is convenient for illustrating common activities across studies and task modalities. It is worth noting that this method does not address whether the activated regions are actually engaged by the task, or the anatomical connectivity underlying the functional roles. However, we will be able to compare meta-analytic activation patterns between the putative prevention and cancellation processes in the memory and motor domains. We will tackle the remaining questions in the later chapters where we present our imaging results.

The meta-analyses included data from the Go/No-Go, Stop-signal, and Think/No-Think tasks (Figure 1.1), as introduced in Chapter 1. All three tasks share the feature of having

to stop an active process in either the memory or the motor domain. These tasks thus provide the opportunity to evaluate support for a supramodal inhibitory control mechanism that contributes to stopping processes in general. If so, the basal ganglia activations induced by each task may co-localise. However, as reviewed in Chapter 1, each task may also engage different subprocesses through which stopping is achieved. The current meta-analysis would therefore be invaluable for examining both whether and how the basal ganglia contribute to different motor inhibition sub-processes. If domain- or subprocess-specific mechanisms are engaged during action prevention and cancellation, basal ganglia activations may be distinct. The meta-analysis will also be useful to examine basal ganglia activations during the Think/No-Think task, and to compare any findings to activations observed during the Go/No-Go and Stop-signal tasks and test if memory inhibition is more similar to action cancellation or action prevention.

To characterise the specific localisation of basal ganglia activations, we manually segmented the caudate head, body, tail, and putamen subregions of the striatum, as existing atlases either do not have these subregions available, or have imprecise segmentations. For the other fine nuclei in the basal ganglia, we used an existing ultra-high resolution basal ganglia atlas (Keuken et al., 2014). As suggested by previous findings, we hypothesised that if a supramodal inhibition mechanism existed in the basal ganglia, the task-induced clusters should overlap extensively with each other, possibly in the caudate head and anterior putamen that receive projections from the DLPFC (Haber, 2006). However, if inhibitory control is achieved in a domain-specific or process-specific fashion, the basal ganglia clusters may be distinct across tasks. Specifically, if basal ganglia involvement is domain-specific, there should be co-localised clusters between the motor inhibition tasks (i.e. Go/No-Go and Stop-signal), which also differ spatially from clusters observed in the memory inhibition task (i.e. Think/No-Think). However, if basal ganglia involvement is process-specific, there should be co-localised clusters in tasks tasks requiring cancellation of ongoing cognitive or motor operations (i.e. Think/No-Think and Stop-signal), which also differ spatially from clusters observed in the task that primarily engages prevention of motor responses (i.e. Go/No-Go). If this pattern is observed, it would raise the possibility of a supramodal basal ganglia contribution to the cancellation of both actions and thoughts.

Due to the emphasis of STN involvement in the human motor stopping literature (e.g. Aron et al., 2007), we will also explore whether the STN is engaged by the memory and motor inhibition tasks, or whether STN activation is specific to certain tasks or processes, in addition to the striatum.

3.1 Selection Criteria and the Meta-Analytic Approach

Studies using the Go/No-Go and Stop-signal tasks were selected for the motor inhibition meta-analyses, whereas studies using the Think/No-Think task were selected for the memory inhibition meta-analysis. Data from the relevant studies were selected according to the following criteria:

1. fMRI studies reporting results from whole brain analyses in a standardised coordinate space (MNI or Talairach);
2. Only data from healthy adults were included;
3. For the Stop-signal and Go/No-Go tasks, participants responded by hand;
4. Only contrasts concerning differences between inhibition and an active condition were included, i.e. No-Think>Think, Stop>Go, and No-Go>Go. We requested the relevant data from the author if they are not already reported in the original article.

According to these criteria, 16 Think/No-Think, 39 Stop-signal, and 30 Go/No-Go studies were identified (Appendix) and included in the meta-analyses.

The meta-analyses were conducted using Activation Likelihood Estimation with GingerALE v2.3.6 (Eickhoff et al., 2009; 2012; 2016; Turkeltaub et al., 2012). The following default settings were applied: less conservative mask size; non-additive ALE method (Turkeltaub et al., 2012); no additional FWHM; cluster analysis peaks at all extrema. Where applicable, coordinates reported in Talairach space in the original studies were transformed into MNI space using the icbm2tal transform in GingerALE (Laird et al., 2010; Lancaster et al., 2007) prior to the analyses.

The first step of the meta-analytic approach is to examine the spatial convergence across different studies within each task domain. To do this, three separate meta-analyses were conducted for the Think/No-Think, Stop-signal, and Go/No-Go tasks using cluster-level inference ($p<.05$, cluster-forming threshold uncorrected $p<.001$, threshold

permutations=1000). Secondly, to examine the spatial convergence and divergence between different task domains, contrast analyses (Eickhoff et al., 2011) were conducted between each pair of the Think/No-Think, Stop-signal and Go/No-Go Tasks (i.e., Think/No-Think & Stop-signal; Think/No-Think & Go/No-Go; Stop-signal & Go/No-Go). For analysing each pair of the tasks, the thresholded activation maps from the individual analyses, as well as the pooled results from both tasks were used as inputs. The outputs were conjunction and contrast maps between the conditions. The same GingerALE settings were applied to the contrast analyses (less conservative mask size; non-additive ALE method; no additional FWHM; cluster analysis peaks at all extrema.). The results were thresholded to voxel-wise uncorrected $p<.001$, with the p-value permutations of 10,000 iterations, and the minimum cluster volume of 200 mm^3.

3.2 ROI Definition and Analyses

Focused ROI analyses were performed to examine whether the memory and motor inhibition tasks consistently activated similar regions in the basal ganglia with similar likelihood. The basal ganglia ROIs were defined with both manual segmentation and an existing atlas (Atlasing of the Basal Ganglia; ATAG; Keuken et al., 2014). Although the ATAG atlas took averages of structural images from ultra-high resolution 7T MRI and thus provides very fine details of basal ganglia structures, it only treated the striatum as one single structure. No other existing atlases provided high-resolution parcellations of the relevant striatal subregions. We therefore performed manual segmentation of the striatal subregions, including bilateral caudate head, body, tail, and putamen, according to established anatomy and segmentation protocols (Eliez et al., 2002; Levitte et al., 2002; Nolte, 2013; segmentation guidelines provided by the Centre for Morphometric Analysis (CMA; http://www.cma.mgh.harvard.edu/manuals/segmentation/). The segmentations were performed using ITK-SNAP v3.2 (Yushkevich et al., 2005; www.itksnap.org) from the high-resolution ICBM 2009b template structural image (0.5mm isotropic; Fonov et al., 2009; 2011). Together, these segmentations of the human caudate and putamen improve upon the anatomical precision of several widely used atlases, such as Anatomical Automatic Labelling in SPM (AAL; Tzourio-Mazoyer et al., 2002) and Atlasing of the Basal Ganglia (ATAG; Figure 3.1 compares our segmentation with these atlases. The resulting subcortical activations are projected onto

the 3D rendering of the segmented structures using Mango v4.0 (Lancaster & Martinez; http://ric.uthscsa.edu/mango/).

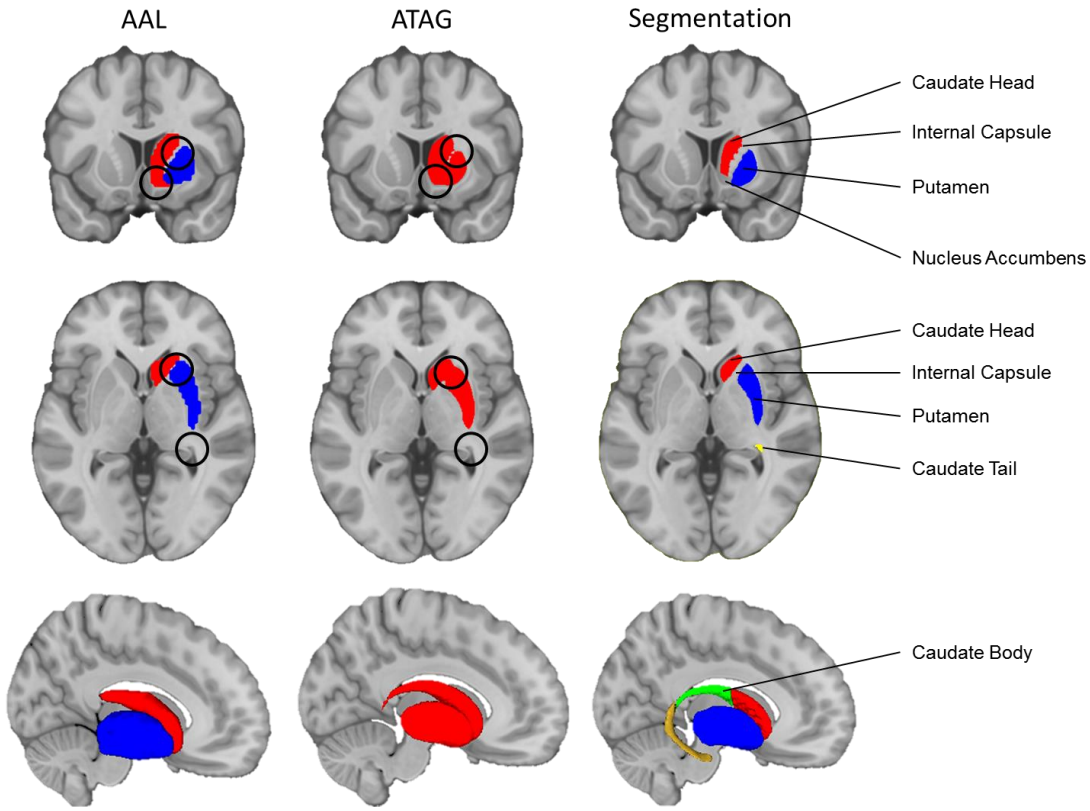

Figure 3.1: Segmentation of the Striatal Subregions. The three columns compare the AAL and ATAG atlases with our manual segmentation. The top row shows the coronal section, the middle row shows the axial section, and the bottom row shows the 3D rending of the structures in the sagittal plane. The relevant structures are labelled, and the differences are marked with black circles. Anatomical underlay and subcortical renders are displayed in MNI space.

3.2.1 Segmentation Protocols for the Striatal Subregions

3.2.1.1 Caudate head

The head of the caudate was segmented through the coronal plane, starting from the slice where it first appears in between the lateral boundaries of the lateral ventricle and the internal capsule, ending at the posterior edge of the anterior commissure, cutting in

the middle of the interventricular foramen of Monroe across the frontoparietal axis (Eliez et al., 2002; Levitt et al., 2002; Nolte, 2013). Care was taken not to include the sheet of meninges between the lateral ventricle and the caudate.

The nucleus accumbens was excluded from the caudate head following guidelines provided by the Centre for Morphometric Analysis (CMA) for creating the Harvard-Oxford Subcortical Atlas (http://www.cma.mgh.harvard.edu/manuals/segmentation/). See Figure 3.1 for an example of this parcellation error in the AAL.

3.2.1.2 Caudate body

The body of the caudate was segmented through the coronal plane, starting from the posterior edge of the anterior commissure until the slice where the cerebral aqueduct enlarges to form the opening of the fourth ventricle (Eliez et al., 2002; Nolte, 2013). The dorsal and ventral boundaries of the caudate body were refined in the sagittal plane, following the lateral ventricle and the internal capsule.

3.2.1.3 Caudate tail

The tail of the caudate started from the coronal slice containing the opening of the fourth ventricle, and was followed until it curved around the thalamus in the sagittal plane. The rest of the tail was traced cross-referencing the coronal, sagittal, and axial planes until it reaches the amygdala.

3.2.1.4 Putamen

The putamen was traced through the coronal plane, starting from the slice where it first shows up lateral to the internal capsule, surrounded by the other white matter tissues, and ending when it is no longer seen. Care was taken not to include blood vessels inferior to the putamen, the claustrum lateral to the putamen, or white matter tracts posterior to the putamen.

The nucleus accumbens was segmented out from the putamen when the internal capsule no longer separates the caudate nucleus and the putamen. Existing pipelines usually draw arbitrary lines to segment between the putamen and the accumbens, such as drawing a straight vertical line downwards from the lateral inferior tip of the internal capsule as suggested by the CMA guidelines. This is possibly due to the lower resolution of the structural image used in those segmentations. However, the anatomical

boundaries between the putamen and the nucleus accumbens in the ICBM 2009b structural template are more visible, and hence are directly used as references for segmentation.

3.2.2 Basal ganglia descriptive statistics

By using cluster-level inference with the ALE analysis, the results may predominantly represent activations that are highly clustered and may fail to detect activations that are more dispersed. To examine the dispersion of basal ganglia activations in each task, we adopted an ROI-based approach, focusing on the basal ganglia as a whole. To do this, we used our pre-defined basal ganglia ROIs to extract basal ganglia coordinates from the studies that we included in the meta-analyses. Subsequently, we counted the number of coordinates that located in these ROIs in the left and right hemispheres. Finally, we present the peak coordinates from each task on the 3D renders of the basal ganglia structures to illustrate the level of dispersion in these activations. It would be ideal to perform quantitative analyses of the spatial distribution of task-specific activations within these ROIs, preferably at the level of basal ganglia subregions, but the available data did not permit well-powered tests.

3.3 Results

On the whole, the ALE meta-analyses revealed both cortical and subcortical clusters in the Go/No-Go, Stop-signal, and Think/No-Think tasks. On the cortical level, preventing motor actions in the Go/No-Go task activated bilateral DLPFC and the right VLPFC, as well as regions in the right parietal lobes. Cancelling motor actions in the Stop-signal task, on the other hand, activated the right DLPFC, VLPFC, and precentral gyrus. Action cancellation also activated bilateral insula, temporal and parietal regions, and cingulate gyrus. The Think/No-Think task activated the right DLPFC, VLPFC, cingulate gyrus, precentral gyrus, and the parietal lobe, as well as the left insula and supramarginal gyrus. These results were generated using cluster-level inference ($p<.05$, uncorrected $p<.001$, threshold permutations=1000). Our observations provide strong evidence for the existence of domain-general regions that contribute to both memory and motor stopping. As illustrated in Figure 3.2, all of the Go/No-Go, Stop-signal, and Think/No-Think tasks activated the right DLPFC, VLPFC, and supramarginal/angular

gyrus primarily in the right hemisphere. In addition, the Stop-signal and Think/No-Think tasks also both activated the insula and posterior middle frontal gyrus (MiFG), possibly due to the potential engagement of cancellation processes in these tasks.

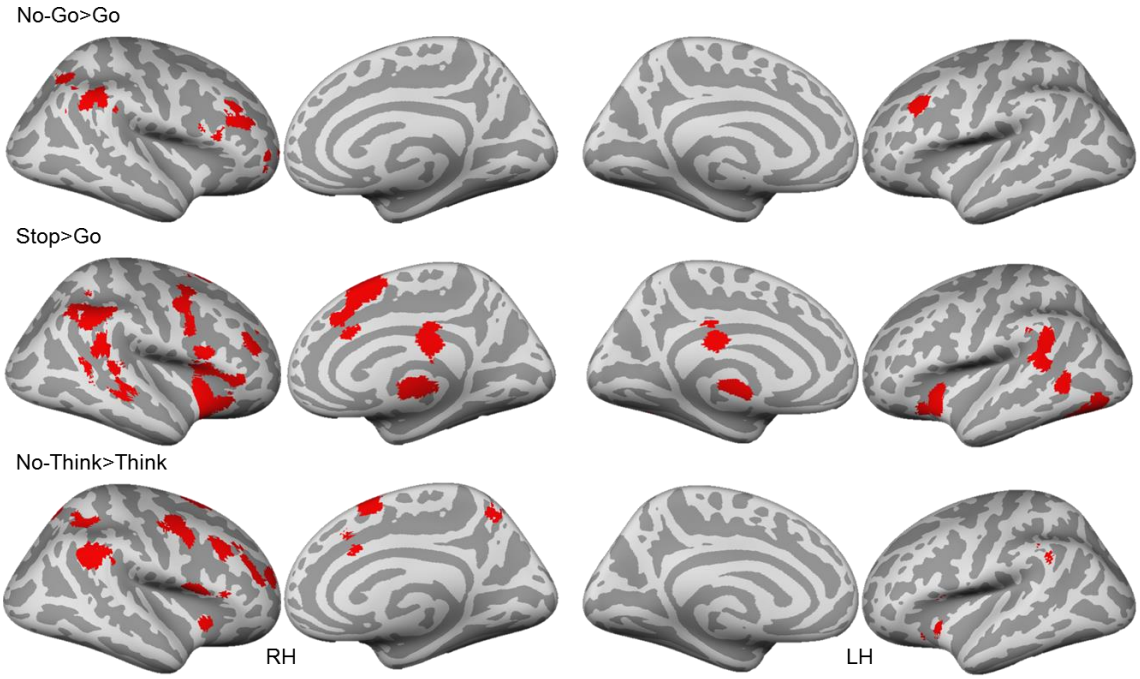

Figure 3.2: Cortical activations from the Go/No-Go, Stop-signal, and Think/No-Think Tasks. All clusters are thresholded at uncorrected *p*<.001, with the *p*-value permutations of 10,000 iterations, and the minimum cluster volume of 200 mm^3.

On the subcortical level, all three tasks produced reliable clusters in the basal ganglia, suggesting that the basal ganglia are involved in both memory and motor inhibition and may be part of a supramodal network of inhibitory control. By qualitatively comparing the ALE results, we found a task-specific hemispheric asymmetry in the location of basal ganglia clusters. Specifically, significant activation clustering was localised in the left hemisphere for the action prevention (Go/No-Go) task, whereas significant activation clustering was localised in the right hemisphere for the action cancellation (Stop-signal) and memory inhibition (Think/No-Think) tasks. However, our subsequent ROI based descriptive statistics, which take into account the dispersion of activation coordinates reported in each task, provided a slightly more nuanced picture. The following results sections will elaborate on findings in the basal ganglia.

3.3.1 Comparing the Cancellation and Prevention of Motor Actions

On the whole, our analyses indicated that both action cancellation and prevention yielded clusters of activation in the basal ganglia. However, action cancellation yielded more spatially extensive clusters, which scarcely overlapped with the clusters from action prevention. The largely distinct localisation of basal ganglia clusters suggests that action cancellation and action prevention may be two separate stopping processes that should not be assumed to be equivalent. This section illustrates these findings by detailing and comparing the clusters from the Go/No-Go and Stop-signal tasks.

3.3.1.1 Action Cancellation Engaged Right Basal Ganglia Structures

Across the 39 Stop-signal studies included in the analysis, cancelling a motor action yielded a consistent cluster in the right basal ganglia (Figure 3.3). First, cancelling a motor action is associated with a cluster in the right centromedial striatum, primarily in the caudate head, spanning into the caudate body and the right anteromedial putamen. This cluster also extended to the right anterior GPe. Visual inspection suggests that the localisation of this cluster may coincide with the putative homologue of the region that receives DLPFC projections identified in the monkey literature (Haber & Knutson, 2010). Second, significant clusters were also observed in bilateral STN and the left SN. The STN finding is compatible with the significant action cancellation role consistently attributed to this structure in previous literature (Aron & Poldrack, 2006). The SN activations are compatible with the dopaminergic modulation that is required by basal ganglia control mechanisms (Alexander & Crutcher, 1990). Finally, cancelling a motor action also yielded a cluster in the ventral thalamus. The ventral thalamus is downstream to the basal ganglia and is specifically implicated in motor processes (Alexander et al., 1986).

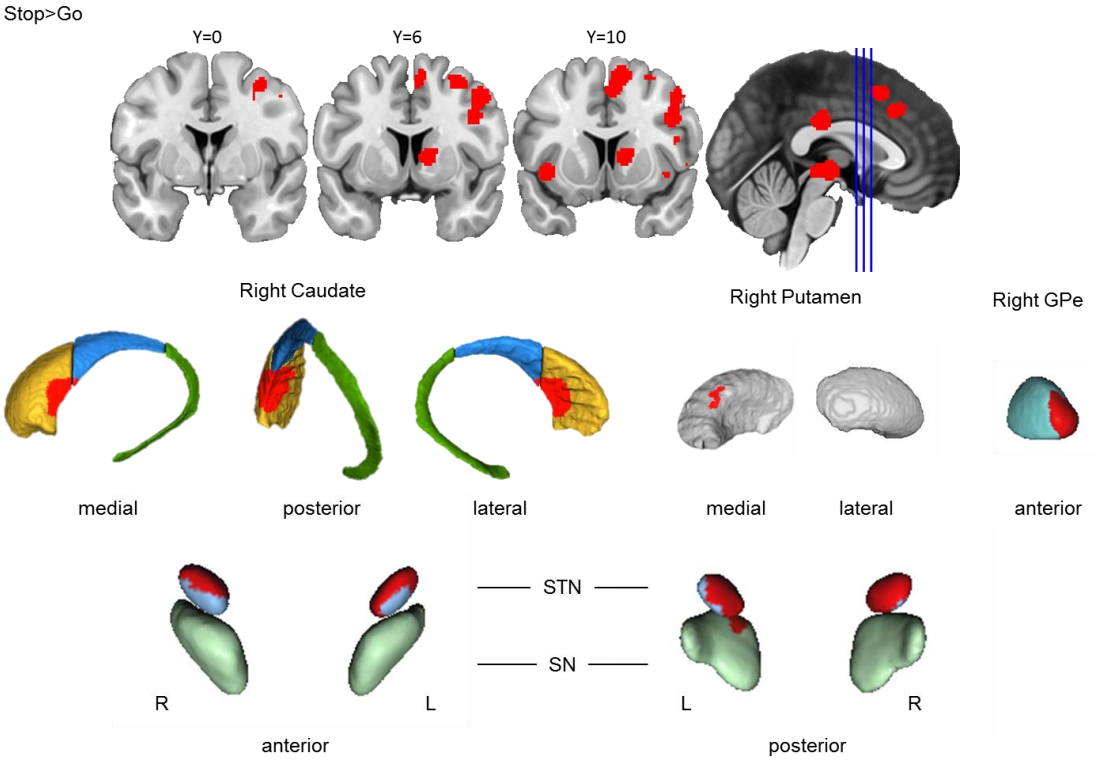

Figure 3.3: Basal Ganglia Activation for Action Cancellation. Top row: Clusters are presented on coronal slices of a high-resolution MNI atlas. Reference lines for the coronal slices are presented in the sagittal plane. Middle row: Clusters are displayed on high-resolution parcellations of the caudate, putamen, and external globus pallidus (GPe). Bottom row: Clusters are displayed on high-resolution parcellaions of the subthalamic nucleus (STN) and substantia nigra (SN). All clusters are thresholded using cluster-level inference (p<.05, uncorrected p<.001, threshold permutations=1000).

3.3.1.2 Action Prevention Reliably Activated Left Putamen and GPe, but not Caudate

Across the 30 Go/No-Go studies included in the analysis, preventing a motor action yielded a cluster in the left basal ganglia, including anterior putamen, spanning into anterior GPe, only touching on the medial wall of the caudate head (Figure 3.4). The putamen involvement aligns with classic models of the cortico-basal ganglia circuit for motor control (Alexander et al., 1986). However, the absence of a caudate cluster during action prevention, as compared to action cancellation, suggests that these motor inhibition tasks may place different demands on neural mechanisms in the basal ganglia.

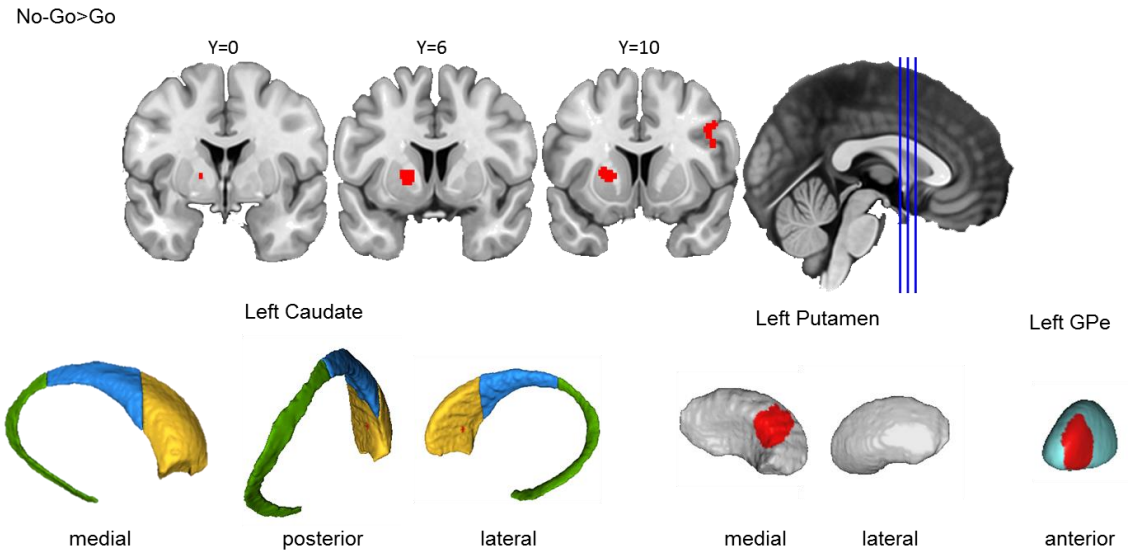

Figure 3.4 Basal Ganglia Activation for Action Prevention. Top row: Clusters are presented on coronal slices of a high-resolution MNI atlas. Reference lines for the coronal slices are presented in the sagittal plane. Bottom row: Clusters are displayed on high-resolution parcellations of the caudate, putamen, and external globus pallidus (GPe). All clusters are thresholded using cluster-level inference (p<.05, uncorrected p<.001, threshold permutations=1000).

3.3.1.3 Action Prevention and Cancellation Showed No Significant Co-Localisation in the Basal Ganglia

From the meta-analyses of individual task types, it is striking that action cancellation and prevention shared so few clusters, given that the Stop-signal and the Go/No-Go tasks are often used interchangeably to measure response inhibition. To formally test whether action cancellation and action prevention engaged similar basal ganglia structures, we computed a conjunction analysis between the Go/No-Go and Stop-signal tasks. No overlapping clusters were identified at the current threshold (Figure 3.5), although subthreshold clustering might exist in the Go/No-Go task (see contrast analysis in 3.3.1.4). It is unlikely that this surprising lack of similarity between these tasks is due to insufficient statistical power, given the large number of studies included in the analysis.

Some have suggested that putative differences between the two tasks may be due to the variations in the administration of the Go/No-Go task (Levy & Wagner, 2011). Typically, the prepotency of the to-be-stopped motor response in the Go/No-Go and Stop-signal tasks is created by having frequent Go trials and infrequent No-Go or Stop trials. However, some Go/No-Go studies have had equiprobable Go and No-Go trials, making the prepotency of the motor responses uncertain, and possibly undermining the necessity of inhibitory control. This is unlikely to be the case in our analysis, as only 9 out of 30 Go/No-Go studies used an equiprobable design, and another 2 with varying frequency of No-Go trials in different blocks of their task phase. The limited number of studies should not exert a strong influence on the results (Eickhoff et al., 2009; 2011). To confirm this, we conducted a control meta-analysis including only Go/No-Go studies with infrequent No-Go trials (N=19), which revealed an identical cluster of activation in the left basal ganglia as the one reported in the original Go/No-Go meta-analysis (see Figure 3.4). We then re-ran the conjunction between the Stop-signal and Go/No-Go tasks using the modified Go/No-Go sample (N=19). Again, we found no significant BG co-localisation of clusters between tasks. Hence, the null conjunction effect cannot be attributed to variation of prepotency in the Go/No-Go task.

3.3.1.4 Action Cancellation Engaged the STN and SN Significantly More than Action Prevention

Visual comparison of the clusters yielded by the Go/No-Go and Stop-signal tasks suggests that action cancellation engages both STN and SN, but that action prevention does not. To determine whether these differences are reliable, we computed a contrast analysis between the Stop-signal and Go/No-Go tasks. The results confirmed significantly greater clustered activation during action cancellation in bilateral STN and the left SN than during action prevention (Figure 3.5), indicating a robust difference between the two stopping processes. Although in the separate meta-analyses action cancellation yielded clusters in the right caudate and Go/No-Go did not, this apparent difference was not statistically significant in the direct contrast analysis. This finding suggests that conclusions about the lack of right caudate involvement in action prevention should be tempered until firmer evidence of differential engagement across cancellation and prevention is clearly established (see section 3.3.3 for data indicating that this apparent difference in caudate involvement is better described as a difference in

the spatial dispersion (clustering) of reported activation coordinates, as opposed to an absolute absence of reported coordinates *per se*). Nevertheless, our findings strongly suggest that the Go/No-Go and Stop-Signal tasks *should not* be assumed to be equivalent mechanistically, given that they place demands on distinct stopping processes in the STN and possibly in the caudate nucleus.

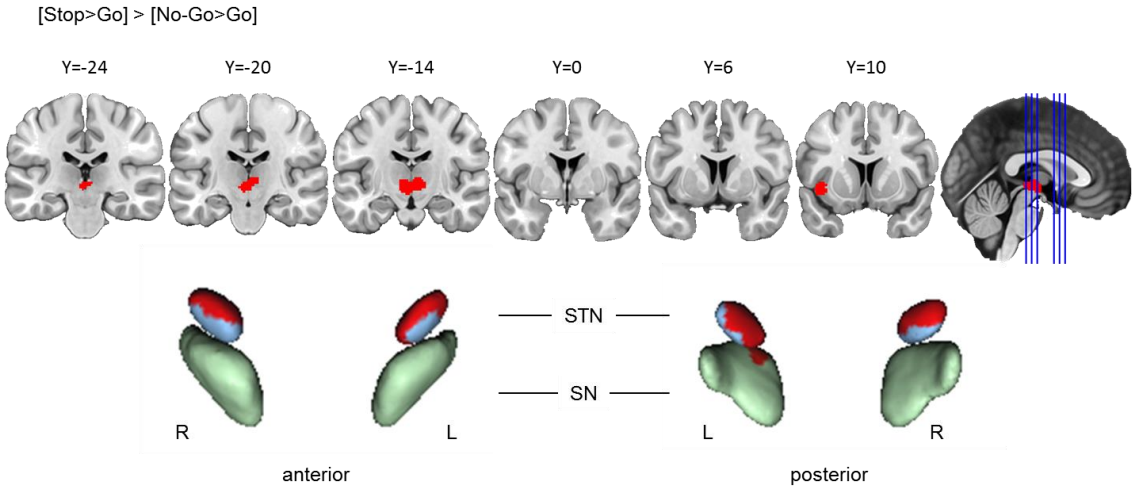

Figure 3.5 Action Cancellation Reliably Engaged STN and SN More than Action Prevention. Top row: Clusters are presented on coronal slices of a high-resolution MNI atlas. Reference lines for the coronal slices are presented in the sagittal plane. Bottom row: Clusters are displayed on high-resolution parcellaions of the subthalamic nucleus (STN) and substantia nigra (SN). The contrast analysis was computed using the thresholded ALE images from the individual analyses. All clusters are thresholded at uncorrected *p*<.001, with the *p*-value permutations of 10,000 iterations, and the minimum cluster volume of 200 mm^3.

3.3.1.5 Action Cancellation Engaged the Basal Ganglia More Extensively than Action Prevention

As mentioned previously, we observed significant clustering in the right striatum and GPe, bilateral STN, and left SN in the action cancellation task. By contrast, significant clustering was limited to the left striatum and GPe in the action prevention task. To quantify the extensiveness of basal ganglia clusters yielded by these tasks, we compared the total volumes of the clusters from the individual analyses. At our current threshold

(cluster-level inference p<.05, uncorrected p<.001, threshold permutations=1000), cancelling a motor action yielded more extensive basal ganglia activation clusters overall (1120 mm^3 in the right hemisphere and 216 mm^3 in the left hemisphere) than preventing a motor action (864 mm^3 in the left alone).

3.3.2 Comparing Memory and Motor Inhibition

Overall, our analysis revealed that memory inhibition yielded consistent activation clusters in the right basal ganglia, but not in the left. Importantly, when we compared the basal ganglia activation clusters observed for memory and motor inhibition, we found that memory inhibition yielded clusters that were highly similar to those involved in action cancellation, but not to those involved in action prevention. This section delineates the basal ganglia clusters observed for memory inhibition, and compares them with those yielded by action cancellation and action prevention.

3.3.2.1 Memory Inhibition Engaged Right Caudate, Putamen, and GPe

Across the 16 Think/No-Think studies included in the analysis, memory inhibition yielded a significant activation cluster in the right basal ganglia. This cluster was primarily located in the caudate head, spanning into caudate body, anterior putamen, and anterior GPe (Figure 3.6). This cluster is highly similar to the one yielded by action cancellation in the centromedial striatum, suggesting that a similar DLPFC-basal ganglia control mechanism may be engaged by both memory inhibition and action cancellation. Memory inhibition yielded a more extensive basal ganglia activation cluster in the right hemisphere (1648 mm^3) than did action cancellation (1120 mm^3).

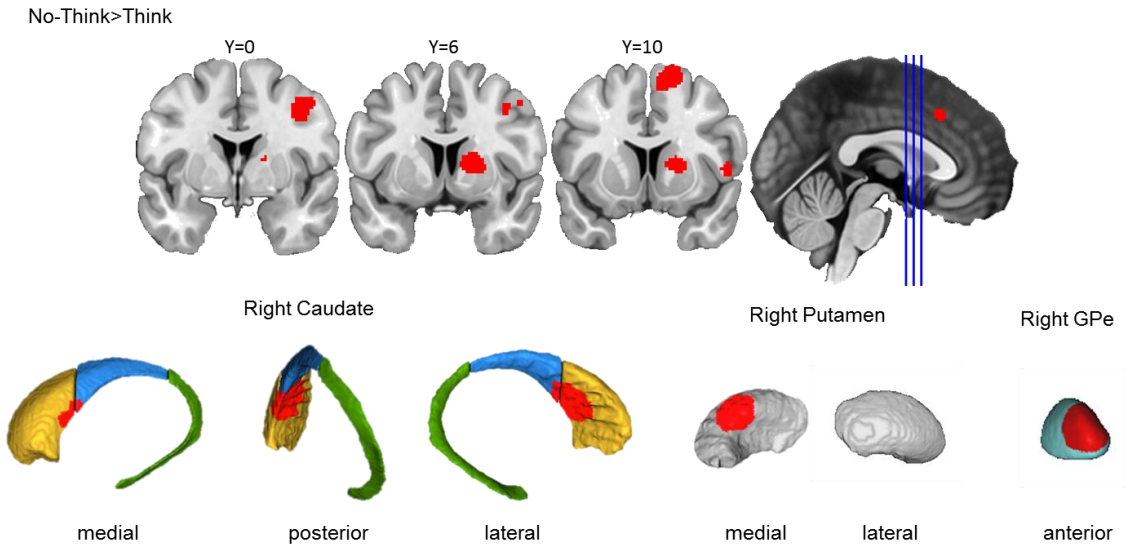

Figure 3.6 Memory Inhibition Engaged the Right Basal Ganglia. Top row: Clusters are presented on coronal slices of a high-resolution MNI atlas. Reference lines for the coronal slices are presented in the sagittal plane. Bottom row: Clusters are displayed on high-resolution parcellations of the caudate, putamen, and external globus pallidus (GPe). All clusters are thresholded using cluster-level inference (*p*<.05, uncorrected *p*<.001, threshold permutations=1000).

3.3.2.2 Memory Inhibition and Action Cancellation Engaged Right Caudate, Putamen, and GPe

To formally test whether the basal ganglia activation clusters generated by memory inhibition and action cancellation overlapped, we computed a conjunction analysis between the ALE maps for the Think/No-Think and Stop-signal meta-analyses. The results demonstrated that both memory inhibition and action cancellation activated the right caudate head/body, anterormedial putamen, and anterior GPe (Figure 3.7). Specifically, at the cluster-corrected threshold, the conjunction cluster resulted in an extensive overlap (552 mm^3) between the Think/No-Think and Stop-signal basal ganglia clusters, constituting 33% of the basal ganglia cluster volumes activated by memory inhibition, and 49% of those activated by action cancellation in the right hemisphere, or 41% overall. This indicates that the putative DLPFC-basal ganglia pathway may serve a supramodal inhibitory control function across memory and motor domains.

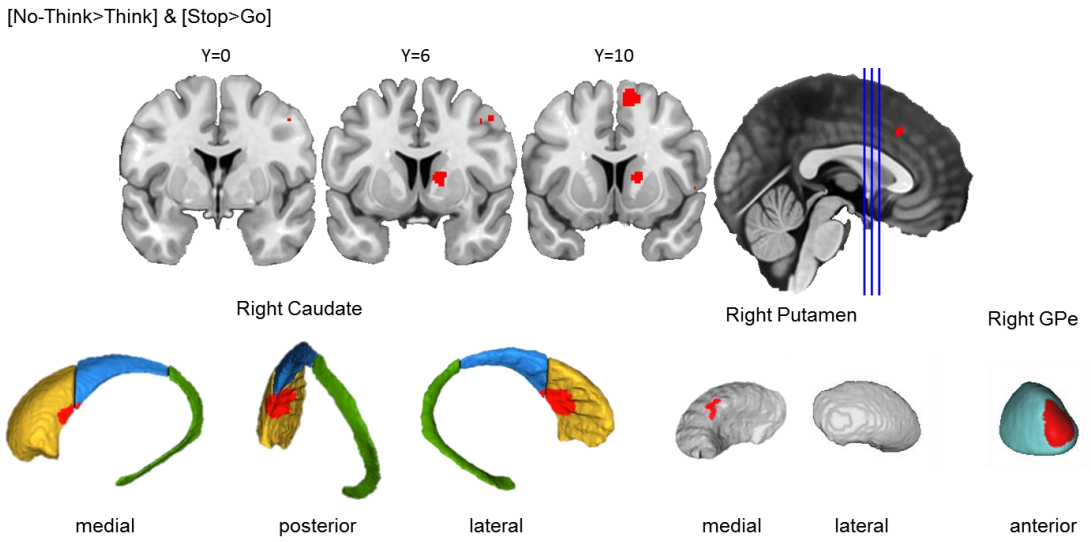

Figure 3.7 Spatial Co-localisation of Memory Inhibition and Action Cancellation in Basal Ganglia Subregions. Top row: Clusters are presented on coronal slices of a high-resolution MNI atlas. Reference lines for the coronal slices are presented in the sagittal plane. Bottom row: Clusters are displayed on high-resolution parcellations of the caudate, putamen, and external globus pallidus (GPe). All clusters are thresholded using cluster-level inference (*p*<.05, uncorrected *p*<.001, threshold permutations=1000).

3.3.2.3 Memory Inhibition and Action Prevention Did Not Reliably Co-localise in the Basal Ganglia

Intriguingly, memory inhibition and action prevention did not seem to share basal ganglia activation clusters from the individual maps, as the first yielded a cluster exclusively located in right basal ganglia, and the latter, a cluster exclusively in left basal ganglia. To quantitatively verify this finding, we computed a conjunction analysis between the Think/No-Think and Go/No-Go tasks. The results did not reveal any basal ganglia activation clusters at our current threshold. As with the stop-signal task, we also examined whether the failure to detect conjunction effects may be due to variation of prepotency in the Go/No-Go task. This was not the case: When we re-analysed the conjunction between the Think/No-Think and Go/No-Go tasks using the modified Go/No-Go sample (studies with offset ratios of Stop and Go trials; N=19), we were

unable to recover significant basal ganglia co-localised clusters between the Think/No-Think and Go/No-Go tasks.

3.3.2.4 Memory Inhibition Engaged Basal Ganglia Subregions More Reliably Than Motor Inhibition

To quantify the differences between memory inhibition, action cancellation, and action prevention, we computed contrast analyses between the Think/No-Think and Stop-signal tasks, and between the Think/No-Think and Go/No-Go tasks. Comparing the Think/No-Think and Stop-signal tasks, although both tasks yielded activation clusters in similar regions in the right basal ganglia, memory inhibition engaged the right anteromedial putamen and anterior GPe more than did action cancellation (Figure 3.8). This finding is intriguing as the putamen is usually construed as part of the motor circuit (Alexander et al., 1986). However, recent studies have shown putamen activations thought to reflect the interaction between memory, action and reward (Koster et al., 2015), indicating that the putamen is not functionally limited to involvement in motor control tasks. Indeed, Seger et al. (2011) reported evidence for effective connectivity between the putamen and the posterior hippocampus, providing at least one precedent for a potentially important role of the putamen in hippocampal interactions.

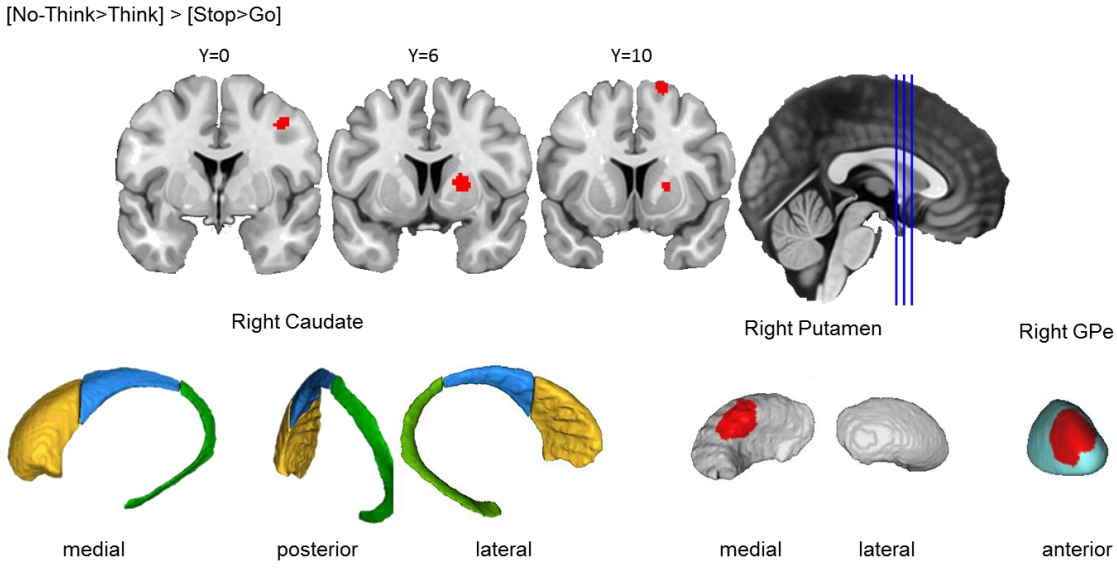

Figure 3.8 Memory Inhibition Engaged Putamen and GPe More Reliably Than Action Cancellation. Top row: Clusters are presented on coronal slices of a high-resolution MNI atlas. Reference lines for the coronal slices are presented in the sagittal plane. Bottom row: Clusters are displayed on high-resolution parcellations

of the caudate, putamen, and external globus pallidus (GPe). All clusters are thresholded using cluster-level inference (*p*<.05, uncorrected *p*<.001, threshold permutations=1000).

When we compared the Think/No-Think and Go/No-Go tasks (Figure 3.9), memory inhibition engaged more clustered activity in the right anteromedial putamen and anterior GPe than did action prevention. This echoes the contrast between memory inhibition and action cancellation. In addition, memory inhibition yielded stronger evidence of clustered activations in the right caudate head. The caudate is usually construed as part of the executive function circuit (Alexander, 1986; Seger, 2013). It is possible that inhibiting memory retrieval requires more active control processes especially when intrusions take place, whereas action prevention can be achieved by low-level associative learning.

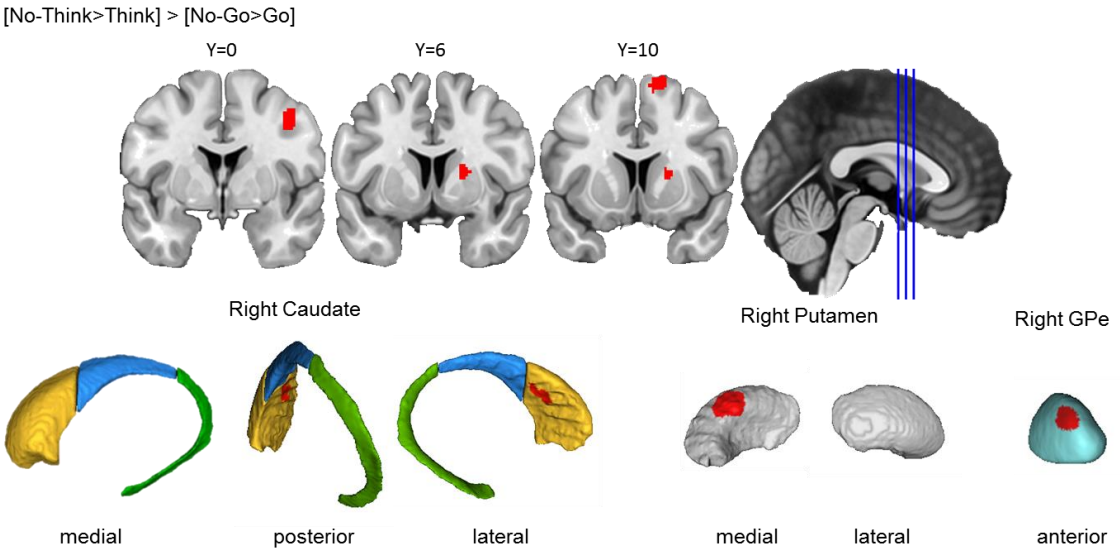

Figure 3.9 Memory Inhibition Engaged Caudate, Putamen, and GPe More Reliably Than Action Prevention. Top row: Clusters are presented on coronal slices of a high-resolution MNI atlas. Reference lines for the coronal slices are presented in the sagittal plane. Bottom row: Clusters are displayed on high-resolution parcellations of the caudate, putamen, and external globus pallidus (GPe). All clusters are thresholded using cluster-level inference (*p*<.05, uncorrected *p*<.001, threshold permutations=1000).

3.3.2.5 Action Cancellation Engaged STN More Reliably Than Memory Inhibition

We also examined which regions yielded greater activation clustering during action cancellation than by memory inhibition. Our individual analyses had revealed bilateral STN and left SN activation clusters in action cancellation but not in memory inhibition. To formally test these differences, we computed a contrast analysis between the Stop-signal and Think/No-Think tasks. Our results revealed that action cancellation yielded reliably greater activation clustering in bilateral STN than did memory inhibition, as well as the ventral thalamus (Figure 3.10). As action cancellation showed consistently more activation clustering in bilateral STN and ventral thalamus than memory inhibition or action prevention, it is possible that distinct processes relevant to these structures are required to achieve cancellation of a motor response.

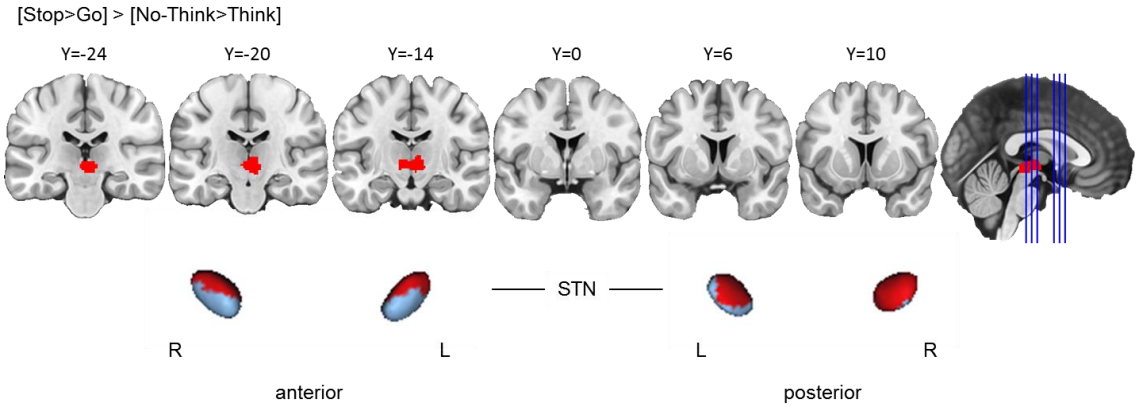

Figure 3.10 Action Cancellation Engaged STN More Reliably Than Action Prevention. Top row: Clusters are presented on coronal slices of a high-resolution MNI atlas. Reference lines for the coronal slices are presented in the sagittal plane. Bottom row: Clusters are displayed on high-resolution parcellaions of the subthalamic nucleus (STN). The contrast analysis was computed using the thresholded ALE images from the individual analyses. All clusters are thresholded at uncorrected *p*<.001, with the *p*-value permutations of 10,000 iterations, and the minimum cluster volume of 200 mm^3.

3.3.3 Summary of ALE results

The ALE results are summarised in Figure 3.11, including basal ganglia activations from the individual, conjunction, and contrast analyses. This summary gives the impression that while the Go/No-Go task primarily engages the left putamen and GPe, the Stop-signal and Think/No-Think tasks primarily engage the right caudate, putamen, and GPe. However, due to the cluster-based nature of the ALE analyses, we wondered if this lateralisation effect could be influenced by the dispersion of the basal ganglia activity from the original studies. Section 3.3.4 presents ROI-based descriptive statistics of the basal ganglia activations from the original studies to examine that possibility.

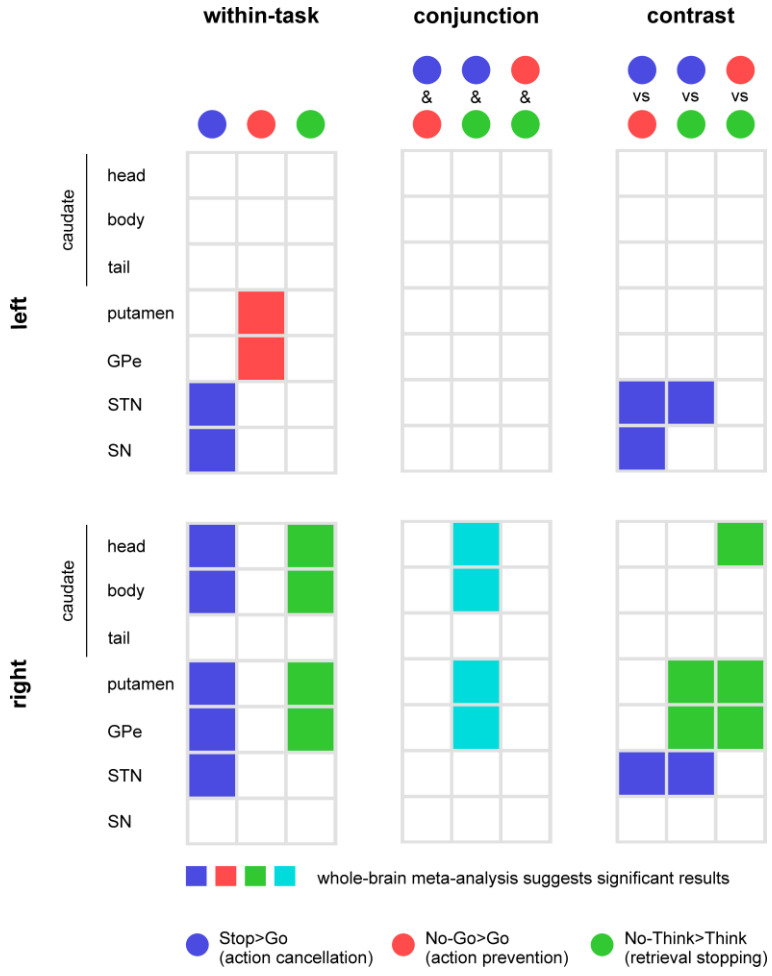

Figure 3.11. Basal Ganglia Activations in the Individual, Conjunction, and Contrast Analyses. The left column shows basal ganglia activations from the individual meta-analyses, colour-coded by task contrasts (Blue=Stop>Go, Red=No-Go>Go, and Green=No-Think>Think). The middle column shows the conjunction analyses. Activations shared by two tasks are presented in the mixed colour based

on the colours that we used to represent the individual tasks. The right column shows basal ganglia activations from the contrast analyses, with the colours denoting task-specific activity. For example, bilateral STN was activated more strongly in the Stop>Go contrast (blue) than the No-Go>Go and No-Think>Think contrasts. The top panel summarises activations in the left basal ganglia structures, while the bottom panel summaries those in the right.

3.3.4 Descriptive Statistics of Basal Ganglia Activations

The foregoing ALE analysis tests for spatial clusters of activation in our three main tasks. Absence of significant clusters in a region does not, however, necessarily mean that the region is not engaged by a task; in some cases, coordinates of activation may be too spatially diffuse within a region to be detected by the analysis we conducted. To examine this possibility, we considered the individual coordinates of studies yielding significant basal ganglia activation.

Table 3.1 summarises the basal ganglia coordinates extracted using the pre-defined basal ganglia ROIs as a whole from the studies included in the meta-analyses. Figure 3.12 shows the dispersion of these coordinates across the three tasks in both the left and right hemispheres. Several novel observations emerge from these summaries. First, although our ALE analysis only revealed significant clusters of activation in the left basal ganglia for the Go/No-Go task, there are, in fact, equally many coordinates that appear in both the left and right hemispheres. The key difference between the left and right basal ganglia activations seems to be the somewhat greater dispersion of coordinates in the right, reducing the apparent clustering. Second, although the ALE analysis only demonstrated significant clusters of activation in the right basal ganglia for the Stop-signal task, there are equally many coordinates in the left and right hemispheres. The coordinates seemed more dispersed in the left, again reducing the apparent clustering. Finally, memory inhibition qualitatively appears to be more right lateralised than the other tasks, consistent with the impression offered by ALE. A more precise characterisation of task differences in the spatial distribution of activations

across sub-regions is limited by the moderate number of coordinates available in this dataset.

	Left Hemisphere			Right Hemisphere		
	Studies	Coordinates	% of studies	Studies	Coordinates	% of studies
Go/No-Go	7	9	23%	7	10	23%
Stop-signal	10	15	26%	13	15	33%
Think/No-Think	3	3	19%	8	10	50%

Table 3.1 Number of Studies Reporting Basal Ganglia Coordinates in the Left and Right Hemispheres from the Go/No-Go, Stop-Signal, and Think/No-Think tasks.

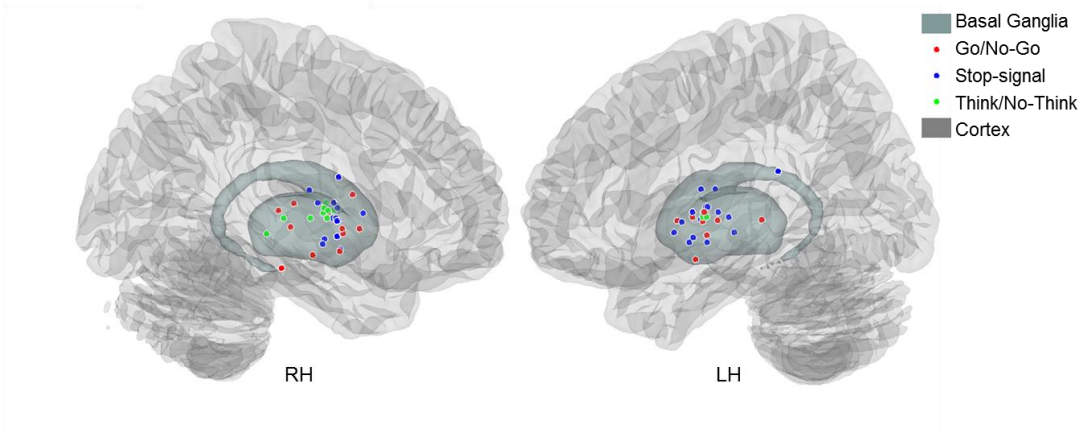

Figure 3.12 Peak Coordinates from the Basal Ganglia Activations in the Go/No-Go, Stop-signal, and Think/No-Think tasks.

3.4 Discussion

The current investigation examined the potential existence of common mechanisms in the basal ganglia that underlie the inhibition of actions and thoughts. Although the basal ganglia have an established role in motor inhibition, whether and how this structure is involved in memory inhibition remains unexplored. To address these issues, we conducted a set of meta-analyses using fMRI data from the Go/No-Go, Stop-signal, and Think/No-Think tasks. While the first two tasks require inhibiting motor actions, the

last task requires inhibition of episodic memory retrieval. After examining the ALE maps for each task, we computed conjunction and contrast analyses to formally examine the similarities and differences between the locations of significant basal ganglia clusters recovered in each task. Moreover, we also provided ROI based descriptive statistics to illustrate the prevalence and dispersion of basal ganglia activations yielded by each task. We precisely localised the observed basal ganglia clusters by manually segmenting the striatal sub-regions from a high-resolution template brain, including the caudate head, body, and tail, and the putamen. This is the first segmentation to our knowledge that has individual compartments of the striatum at this level of spatial resolution and precision. Our key observations and their implications are discussed below.

Although we observed basal ganglia clusters in all three tasks, the specific localisation of these clusters differed in informative ways. Strikingly, the Go/No-Go and Stop-Signal tasks – two of the most widely studied forms of motor stopping that are often assumed to engage similar functions – showed clusters in different basal ganglia regions. Whereas the Go/No-Go task consistently activated the left anterior putamen (spanning into anterior GPe), the Stop-signal task yielded more extensive right-lateralised spatial clusters of activation in the caudate head/body, anterodorsal putamen, anterior GPe, as well as bilateral STN and left SN. A formal conjunction analysis revealed that overlap between the activation clusters observed in these tasks was not statistically reliable. The differing localisations of these clusters may be very important for two reasons. First, distinct basal ganglia structures constitute different coordinating pathways supporting the prevention, initiation, and termination of motor or cognitive processes (Alexander & Crutcher, 1990; Graybiel, 2005; Scimeca & Badre, 2012). Second, cortical and subcortical structures project topographically to the basal ganglia (Haber, 2003; Winn et al., 2009). Therefore, differently localised activation clusters, such as those observed here, could indicate different computational functions (Alexander & Crutcher, 1990; Haber et al., 2006; Lanciego et al., 2012; Seger, 2013). These observations converge with recent findings suggesting that the Go/No-Go and Stop-signal tasks may differ in important respects, including the underlying cognitive processes engaged (Schachar et al., 2007; Verbruggen & Logan, 2008), cortical regions recruited (Dalley et al., 2011), their electrophysiological markers (Johnstone et al.,

2007) and neuropharmacological underpinnings (Eagle et al., 2008). These differences may arise because the Go/No-Go task primarily requires the prevention of a motor action from taking place, whereas the Stop-signal task requires cancelling an emerging or ongoing motor process. Thus, the current analysis of activation clusters support the view that despite their similarity as motor stopping procedures, these tasks may tap different control processes and should not be treated equivalently.

After comparing the Go/No-Go and Stop-signal tasks, we examined whether the basal ganglia were involved in stopping memory retrieval. Interestingly, we found that, like stopping actions, stopping thoughts also engages the basal ganglia. Memory inhibition in the Think/No-Think showed a consistent cluster of activation in the right caudate head/body, anterodorsal putamen, and anterior GPe. This cluster of activations was exclusively right lateralised, and was more spatially extensive than the analogous clusters from the motor stopping tasks. This clearly indicates that basal ganglia structures play an important role in stopping retrieval, perhaps akin to its role in stopping actions. This commonality raises the possibility that basal ganglia structures are involved in stopping in a more general way than is usually assumed in research on motor inhibition.

Although both memory and motor inhibition consistently activated the basal ganglia, the current data provide some evidence that memory inhibition in the Think/No-Think task may be more similar to action cancellation in the Stop-signal task than it is to action prevention in the Go/No-Go task. Indeed, a formal conjunction analysis revealed strong overlap between the activation clusters observed for memory inhibition and action cancellation, including the right caudate head/body, anterior putamen, and the anterior GPe. Critically, the conjunction cluster between memory inhibition and action cancellation constituted 33% of the voxels activated by memory inhibition, and 49% of those activated by action cancellation in the right hemisphere (or 41% when considering both hemispheres). These findings suggest that the particular basal ganglia regions observed here might play a computational role in cancelling a process, irrespective of whether that process involved motor action. Action cancellation, however, did engage bilateral STN and ventral thalamus more reliably than did memory inhibition. It is possible that these regions are uniquely required for cancelling a motor response, as the ventral thalamus is typically construed as the downstream target of the basal ganglia

during motor control (Alexander et al., 1986). The STN is also shown to be integral for cancelling a motor action (Aron & Poldrack, 2006), although which specific pathway the STN engages (either the hyperdirect or the indirect pathway) remains unresolved. However, given their small size and the lack of attention to these structures in the literature on memory inhibition, their activity during memory inhibition tasks might not have been consistently reported, even if it occurred. Future studies of memory inhibition should specifically examine the role of the STN in this process. More generally, connectivity analyses could be conducted to investigate the network dynamics between the basal ganglia structures to isolate the particular basal ganglia mechanisms underlying the inhibition of memory retrieval.

Despite the foregoing between-task differences in the STN activation clustering, the overall similarity between the clusters observed for memory inhibition and action cancellation in the striatum and GPe suggests that inhibiting thoughts may require active cancellation. This observation argues against the possibility that people prevent retrieval of an unwanted item by simply directing the retrieval process to distracting thoughts, or, instead, by passively failing to engage retrieval. Rather, the recruitment of cancellation-related striatal processes suggests that retrieval is being actively stopped. This interpretation converges with findings indicating that the engagement of inhibitory mechanisms during retrieval stopping is particularly robust when memories intrude into awareness and need to be purged (Levy & Anderson, 2012; Benoit et al. 2014). Using trial-by-trial intrusion reports, it has been found that intrusions elicit greater recruitment of right prefrontal cortex (Benoit et al., 2014) and greater down-regulation of hippocampal activity (Levy & Anderson, 2012), compared to trials without intrusions. The current findings suggest that retrieval cancellation may be key to overcoming intrusions. In contrast, we observed no overlap in activation clusters between memory inhibition and action prevention from the ALE analyses. These findings are consistent with the possibility that different basal ganglia regions contribute to distinct cancellation and prevention-related sub-processes, and that cancellation is not tied uniquely to motor action, but rather may be supramodal. To establish these conclusions more firmly, however, requires that we move beyond mere co-localisation of activations to study dynamic interactions of these basal ganglia structures with other elements of the putative control network, under conditions of cancellation and prevention.

Our findings raise questions about the connectivity underlying these dynamic interactions. Of particular interest is the connectivity of these basal ganglia regions with other putative supramodal areas associated with inhibitory control (e.g., DLPFC, VLPFC), and also with domain-specific regions involved in memory and action, such as the hippocampus and M1 respectively. For example, in our meta-analyses, by precisely localising clusters within the Basal Ganglia, we observed that all of the Go/No-Go, Stop-signal, and Think/No-Think tasks recovered clusters in the centromedial striatum, including the caudate head/body, spanning across the internal capsule into medial putamen. This cluster roughly coincides with the region identified by Haber et al. (2006) that receives projections from the DLPFC (areas 9/46). Although much care is needed when comparing anatomical landmarks across species, Neggers et al. (2015) presented evidence based on diffusion imaging that the frontostriatal projections from anterior prefrontal cortex are more similar between humans and macaque monkeys than those from posterior frontal regions such as the frontal eye field (FEF) and M1. Since the DLPFC is known to play important roles in stopping actions and thoughts (Anderson et al., 2004; Anderson & Hanslmayr, 2015; Depue et al., 2010; 2015), this putative DLPFC-striatal pathway could be a candidate through which memory and motor inhibition are achieved, a possibility that must await further confirmation.

Despite its similarity to action cancellation, the memory inhibition cluster extended to parts of the right putamen and GPe more than did motor stopping in general. It is unclear what functions these potentially memory-inhibition-specific activations of putamen and GPe may be performing, or whether these functions are unique to this process or simply a more robust and spatially extensive engagement of putamen processes observed during action cancellation. The possibility that parts of the putamen may serve functions specific to memory control should be considered. It is worth noting, for example, that although the putamen is often seen as a motor structure (Alexander et al., 1986), recent evidence suggests that it is involved in cognitive processes such as working memory (Voytek & Knight, 2010), episodic memory encoding (Sadeh et al., 2011), and cognitive control (Badre & Wagner, 2007), and both neuroimaging and computational modelling suggest that the basal ganglia play critical roles in memory processes (Gruber et al., 2006; O'Reilly and Frank, 2006; Scimeca & Badre, 2012). Indeed, Koster et al. (2015) also found that the putamen is significantly

activated in the interaction between memory, action, and reward. Specifically, participants learned four different categories of objects, each indicating whether the participants should respond to a following visual stimulus, and whether the correct action/inaction would lead to a reward or avoid a loss. They found that activity in the right dorsal putamen significantly predicted memory retrieval when the associated action/inaction led to the expected, than the unexpected, level of reward. Although these related findings don't speak to a role of the putamen in memory inhibition, they do indicate that this structure interacts with the medial temporal lobes during memory tasks, providing precedent for such a role. The circuitry underlying this potential contribution to memory inhibition remains to be identified.

On top of the established network of motor control involving the basal ganglia, several authors have discussed potential interactions between the basal ganglia and the hippocampus. While some found that the basal ganglia and the hippocampus may be largely independent from each other (Döller et al., 2008), others have suggested more complex relationships between the two systems during memory functions. On one hand, basal ganglia and hippocampal processes may be competitive in nature, such that increased activation in one structure is associated with decreased activation in the other (Dagher et al., 2001; Poldrack & Packard, 2003). Specifically, this competition may be mediated by the PFC (Rodriguez & Poldrack, 2003). On the other hand, the basal ganglia may be able to influence hippocampal activity in a causal way. For example, stimulation of the basal ganglia nuclei can modulate hippocampal spikes (La Grutta et al., 1985; Sabatino et al., 1985; Sabatino et al., 1986). Berke et al. (2004) also found entrainment of ventral/medial striatal neurons to the hippocampal theta in rats. The foregoing findings raise the possibility that the basal ganglia may exert a controlling influence on target structures in both memory and motor inhibition. In the case of memory inhibition, this controlling influence may arise through complex polysynaptic interactions with the hippocampus. Further research is needed to elucidate how these interactions might be achieved.

Although we sought to precisely localise basal ganglia clusters in memory and motor inhibition tasks, our approach is not without caveats. For example, Wager et al. (2007) discussed a few limitations in Activation Likelihood Estimation (ALE). Due to the coordinate-based nature of the ALE algorithm, the analysis only considers the peak

coordinates reported in each study, but not the extent of each cluster of activation where the peaks lie. In addition, the peak coordinates may be influenced by the specific methods used in each study (e.g., thresholding, smoothing). Furthermore, the ALE activation maps, rightfully, model the spatial uncertainty of the reported peak coordinates from each study, which introduces a certain level of spatial smoothness. These factors recommend caution when drawing conclusions about the precise localisation of our observed activations, given limitations on spatial resolution inherent to the meta-analytic method. Reporting bias is also a consideration, because some researchers may choose to omit activation peaks that do not fit prior expectations for a task, especially if the spatial extent of the activation is small, as would be true for some of the structures of key interest within the basal ganglia. These caveats have led some to argue that results from coordinate-based meta-analysis should be treated as an integration of existing knowledge instead of the absolute truth (Rottschy et al., 2012), as more accurate and complete information would require an image-based meta-analysis or 'mega-analysis' (Salimi-Khorshidi et al., 2009).

One final caveat, applicable to this and all other ALE meta-analyses, concerns how to interpret lack of significant clusters in a structure of interest. On one hand, failing to find a significant cluster for a particular task may indicate that the structure is genuinely not engaged in the task. On the other hand, because the ALE algorithm seeks to identify clusters of activation, lack of a significant cluster may also be consistent with the presence of more dispersed activation peaks that fail to constitute a significant cluster. Indeed, from our ROI-based descriptive statistics, there exist activations in basal ganglia structures in both hemispheres, especially for our two motor stopping tasks (see Table 3.1). Thus, whether one should interpret the differently lateralized clusters for action prevention and cancellation derived from ALE as indicating a meaningful task dissociation depends on the assumption that spatially clustered activations are more meaningful than those that are more dispersed. Regardless of the method of analysis, however, memory inhibition in the Think/No-Think task appeared to yield more spatially concentrated activations predominantly lateralised to the right basal ganglia. Due to the moderate number of coordinates available in current studies, however, quantitative examination of task-related differences in the spatial distribution of coordinates across sub-regions of the basal ganglia must await future studies.

Despite these limitations, our meta-analyses have provided the first evidence that memory and motor inhibition (action cancellation in particular) engage overlapping regions within the basal ganglia. These patterns suggest that similar frontostriatal pathways may be involved when people stop thoughts or actions. Moreover, by localising the observed clusters within our high-resolution manual segmentation of striatal subregions, we hope that our results can serve as a useful reference against which the results of future studies may be compared.

3.5 Conclusions

The current meta-analyses demonstrate that the basal ganglia are consistently activated in the inhibition of both actions and thoughts. This basic finding is broadly congruent with recent literature indicating that the basal ganglia are not merely involved in motor control, but also in higher-level cognitive processes, such as memory. Importantly, however, the surprising similarity of memory inhibition to action cancellation more than action prevention suggests that the nature of the stopping processes that are recruited may dictate the localisation of basal ganglia activity more so than does task domain, at least for the tasks we studied. Our data indicate that, during cancellation, similar regions in the basal ganglia are engaged, irrespective of the domain of the process that is controlled, consistent with the possibility of a supramodal cancellation process. Meanwhile, the differences in activation clusters between the Go/No-Go and Stop-signal tasks suggest that they may engage very different stopping processes that should not be treated equivalently. However, it bears emphasis that the current ALE meta-analysis is more sensitive to clustered activations than to dispersed ones. The inference that motor cancellation and motor prevention are distinctly localized in these data depends on the assumption that highly clustered activations (as detected by ALE) provide a more informative signature of functional specialization in the basal ganglia than more dispersed activations would, an assumption that deserves to be critically examined when more data is available. Importantly, future studies should characterise the specific basal ganglia engagement in memory and motor inhibition and how the frontal, basal ganglia, and domain specific target regions (e.g., motor cortex and hippocampus) interact to perform specific stopping processes in different task domains. Extending the study of the role of the basal ganglia in inhibitory control to measure the

stopping of both actions and thoughts will provide a valuable source of constraint on hypotheses about the computational functions that the basal ganglia perform.

4 BEHAVIOURAL PARADIGMS TO COMPARE INHIBITORY PROCESSES IN MEMORY AND MOTOR STOPPING

The meta-analyses revealed common cortical and basal ganglia involvement in both memory and motor stopping. Critically, there may be different subprocesses of inhibition that can be engaged across task domains, such as prevention and cancellation. The first refers to the process of preventing the thought or action from taking place at all, whereas the latter refers to cancelling the thought or action after it has emerged. The next step is to further investigate the specific role of the basal ganglia in these putative prevention and cancellation processes across the memory and motor domains. In this chapter, we will establish behavioural paradigms that can allow for parallel comparisons between prevention and cancellation across the memory and motor inhibition tasks.

In the Think/No-Think task, thought prevention and cancellation are assumed to manifest in whether participants experience intrusions for a given No-Think trial, i.e. whether the unwanted targets involuntarily came into mind. On one hand, if a participant did not experience an intrusion during a No-Think trial, it is likely that either the participant forgot the target already and no inhibition was needed, or the participant

was able to proactively prevent the unwanted target from coming into mind at all. On the other hand, if the participant did experience an intrusion, it is likely that the initial prevention processes failed. To follow the No-Think instructions, the participant would instead need to react to the intrusion and cancel the retrieval process that has emerged. However, this cancellation may be hampered by the willingness or ability to follow instructions. For example, some participants may be less willing to comply with the No-Think instructions either because they expect a final test on the learned items and want to maintain a good memory performance, or because they do not deem it necessary to supress retrieval, as they believe that the intrusion will dissipate on its own (Sahakyan et al., 2008). Other participants may be less able to cancel the unwanted retrieval process either because they are intrinsically less capable of controlling unwanted thoughts or they are affected by fatigue during the course of the task (van Schie & Anderson, 2017).

Considering existing evidence, it is likely that a cancellation process is often engaged during intrusions. For example, Levy and Anderson (2012) differentiated Intrusion and Non-intrusion trials by asking participants to rate to what extent the unwanted target came into mind after each trial in the Think/No-Think phase. Subsequently, they extracted BOLD signal from the hippocampus for the Think, Non-Intrusion, and Intrusion trials, and observed increased hippocampal activity during the Think trials, and robustly decreased hippocampal activity during the Intrusion trials. Hippocampal activity during Non-intrusion trials did not significantly differ from Think or Baseline activity (Figure 4.1). On one hand, the magnitude of hippocampal downregulation during Intrusion, rather than Non-intrusion, significantly correlated with SIF. These results indicate that there may be a larger contribution of the cancellation process to achieve memory inhibition than prevention in the hippocampus. In addition, this down-regulation of hippocampal activity may be achieved through prefrontal executive control regions such as the DLPFC (for review, see Anderson et al., 2016). Furthermore, this DLPFC control mechanism not only applies to suppressing word memory, but also emotional memory. Gagnepain et al. (2017) recently replicated the pattern of hippocampal activity when suppressing emotional memories. Using DCM, they found that the DLPFC down-regulates the hippocampus, amygdala, and parahippocampal gyrus in parallel. This observation points to the possibility that the DLPFC is involved in inhibitory control in a domain-general fashion.

On the other hand, the lack of hippocampal down-regulation in the Non-Intrusion condition may suggest that no retrieval process was suppressed during the Non-intrusion trials. However, in cases where the unwanted target is still retained, it is possible that the retrieval has been prevented before cue input engages the hippocampus. One possible prevention mechanism is the Entorhinal Gating Hypothesis (Anderson et al., 2016). This hypothesis suggests that the anterior cingulate cortex (ACC) may modulate the information flow by modulating activity in the entorhinal cortex, so as to suppress input to the hippocampus. Alternatively, this prevention may be achieved through prefrontal control regions such as the DLPFC, which appears, in some instances, to have elevated activity during Non-intrusion trials relative to baseline (Benoit et al., 2014).

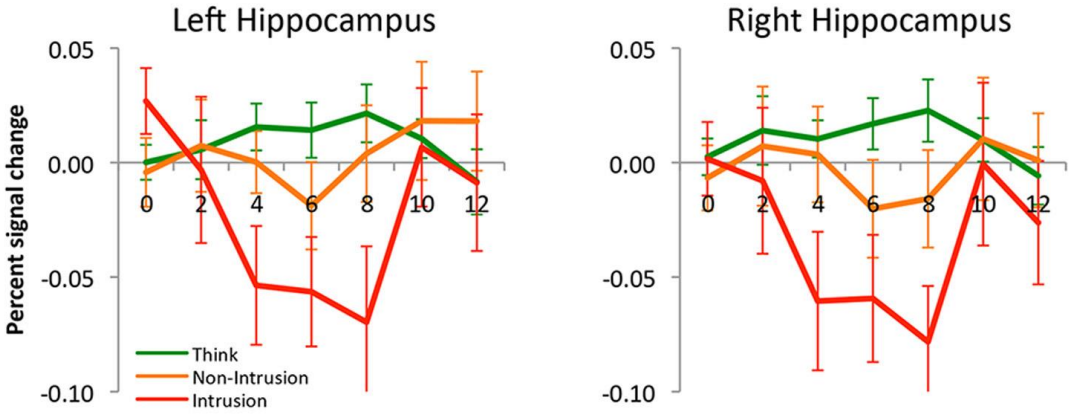

Figure 4.1. Hippocampal activity during Think, Non-intrusion, and Intrusion trials in Levy and Anderson (2012).

At the subcorticortical level, the basal ganglia are a prime candidate for engaging the prevention and cancellation processes through different pathways. As reviewed in Chapter 2.1, there are three intrinsic pathways in the basal ganglia system: the hyperdirect, direct, and indirect pathways. While the hyperdirect pathway is responsible for global inhibition and early selection of goal-directed responses (Takada et al., 2013), the direct pathway initiates the selected the response, and the indirect pathway terminates a response either because response has been achieved or the response needs to be cancelled (Freeze et al., 2013). Schroll and Hamker (2013) also reviewed

computational models describing the involvement of different basal ganglia pathways in cognitive and motor functions. They suggested that prevention may be modulated by the hyperdirect and the indirect pathways, whereas cancellation may be modulated by the interaction between the direct and indirect pathways. Overall, cancellation and prevention seem to engage distinct neural mechanisms on both the cortical and subcortical levels. In this PhD thesis, we want to compare these mechanisms in the memory and motor domains, and investigate whether and how the basal ganglia are involved.

In addition to incorporating intrusion ratings to segregate the distinct processes underlying preventing and cancelling memory retrievals, there are two other factors to consider for adapting the Think/No-Think paradigm – what strategies participants use to approach the Think/No-Think task, and how compliant participants are to inhibit unwanted targets instead of intentionally recalling them (Anderson & Huddleston, 2012). First, not all strategies adopted during the Think/No-Think task lead to SIF. In a typical Think/No-Think paradigm, participants are simply instructed to 'avoid thinking' of the target item when seeing the cue. This instruction is arguably ambiguous, as it does not specify how participants are expected to approach the task. For example, some participants may suppress the targets so that they can no longer retrieve them (memory inhibition), treating the instruction as an instruction to forget the association. Other participants may not assume that the associations are to be forgotten, but may merely seek to keep the targets out of awareness without breaking the original associations. This may enable them to remember the targets at a later point (awareness control). We were interested in comparing whether these strategies would influence the magnitude of SIF, and whether they would engage distinct neural mechanisms. We expected that while memory inhibition should induce significant SIF, awareness control may not lead to any SIF at all. At the neural level, it is possible that memory inhibition will engage the inhibition network more than awareness control, such as in the PFC and the basal ganglia. However, since both strategies involve keeping information out of mind, there may be overlapping activations from the memory inhibition and awareness control strategies, but memory inhibition may engage additional mechanisms to actually achieve memory suppression. For example, both memory inhibition and awareness control may engage the basal ganglia to keep the unwanted targets out of mind, since

these structures are associated with the adaptive gating of memory retrieval (Scimeca & Badre, 2012). However, memory inhibition may additionally engage neocortical regions to achieve suppression of the target that is associated with the cue.

Second, the level of compliance to following the inhibition instructions significantly correlate with SIF. Having a low level of compliance means that the participant are likely to intentionally retrieve the unwanted items, which may hamper the SIF effect. In a typical Think/No-Think study, participants often have varied levels of compliance because they are likely to expect a final test after the Think/No-Think phase for two reasons. First, their memories are not monitored during the task. Participants do not need to report how well they are accomplishing the No-Think instructions, nor are they tested in any way. Second, they are not provided with any reasons or motivations to properly suppress the target. This expectation of the final test may make the participants more likely to adopt the awareness control strategy or even covertly recall the unwanted target, possibly attenuating the SIF effect. For example, in a recent study, Yang et al. (in preparation) investigated the effect of compliance on memory inhibition using a large sample (N=146). In the study, Yang et al. administered a classic Think/No-Think paradigm and recorded participant's level of compliance using a 5-point Likert scale in a post-experimental questionnaire. They found that participants more compliant with the memory inhibition instructions showed larger magnitude of SIF. However, only 67% of their participants never (0 rating on the scale) intentionally recalled the unwanted targets. To obtain a more reliable SIF effect, it is therefore important to revise the Think/No-Think paradigm to maximise participant's compliance.

In the motor domain, as discussed in Section 1.1, the Go/No-Go and Stop-signal tasks may primarily require the prevention and cancellation process, respectively. In the Go/No-Go task, participants usually learn to associate specific stimulus with either the Go or the No-Go response. Therefore, as soon as a No-Go stimulus is presented, participants would know that they should not respond to the stimulus and hence *prevent* any motor actions from taking place. It is also possible that participants start to respond on a No-Go trial and catch themselves, since No-Go stimuli are only presented on a minority of the trials. However, this is unlikely because participants are usually trained with task instructions before performing the Go/No-Go task. On the other hand, for the Stop-signal task, participants only learn that they should not respond to a particular

stimulus after a delay (when the stop signal is presented). In that case, participants could have initiated a motor response already, and would need to *cancel* that motor response accordingly. To be able to compare prevention and cancellation processes in memory and motor stopping, it is hence important to combine the Go/No-Go and Stop-signal tasks into one paradigm. The following sections will introduce the behavioural paradigms for memory and motor inhibition for the fMRI study presented in Chapter 5. We will first describe the motor inhibition task that we adopted from Weaver and Anderson (unpublished), and then present two behaviour studies that we conducted to develop an adapted Think/No-Think paradigm for memory inhibition.

4.1 A Combined Go/No-Go and Stop-signal Task

We have discussed that one of the defining differences between the Go/No-Go and the Stop-signal procedure is when participants learn that they must stop on each trial. In the Go/No-Go procedure, participants know that they should stop as soon as they see the No-Go stimulus, and would be able to engage stopping processes concurrent to stimulus onset. Participants are likely to have engaged a *prevention* process to stop the motor response from taking place at all. The Stop-signal procedure, however, signals participants to stop well after stimulus onset, imposing a necessary delay in when participants may engage the stopping process. To successfully stop the motor response, participants will likely have to engage a *cancellation* process. As revealed by the meta-analysis, the concurrent and delayed stopping conditions in the Go/No-Go and Stop-signal tasks may engage distinct neural mechanisms both on the cortex and in the basal ganglia. Here we describe a Combined Go/No-Go and Stop-signal paradigm (Weaver & Anderson, unpublished) that incorporated both concurrent and delayed stop signals. We can use this paradigm to compare how preventing and cancelling motor actions differ in their underlying processes.

4.1.1 Materials and Procedure

This Combined Go/No-Go and Stop-signal task is a computer based procedure, wherein participants responded using a customised button box (Figure 4.2a). The Go stimuli are four visually discriminable coloured circles of 2.5 cm in diameter presented in a grey background (Figure 4.2b). The four coloured circles are randomly assigned to two

response buttons for each participant, each button associated with two colours. The stop signal is a 100 ms 1000 Hz beep tone that is presented at a comfortably audible volume. Responses are made by pressing the button associated with the colour of the circle. Participants always respond with the thumb of their dominant hand. Between trials, participants always rest their thumb in the centre of the button box, equidistant from both buttons.

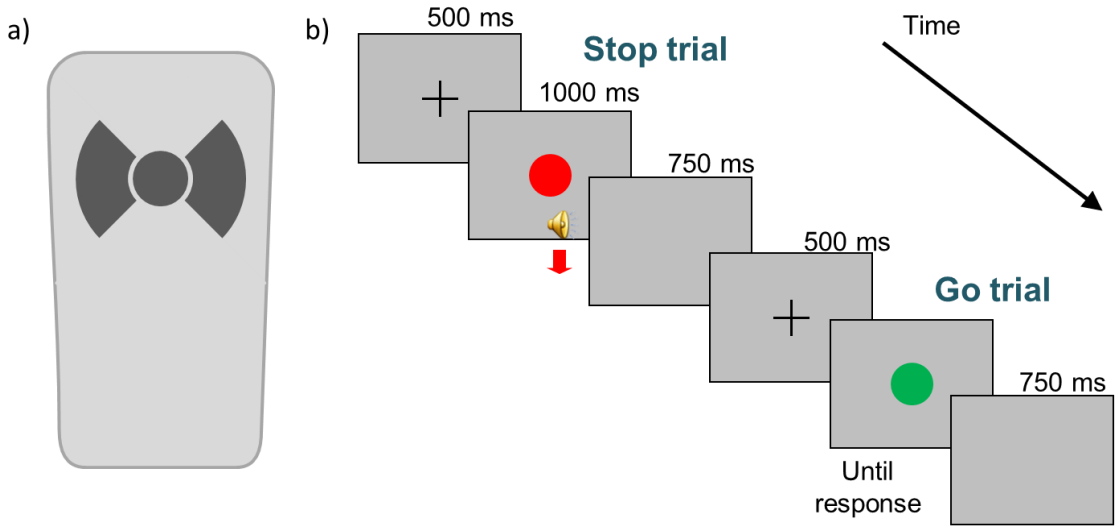

Figure 4.2: The button box (a) and procedure (b) for the Combined Go/No-Go and Stop-signal paradigm.

The Combined Go/No-Go and Stop-signal procedure is divided into a training phase and a main experimental phase. In the training phase, participants first learn the colour-button mappings in two blocks. In each block, they learn to associate two colours, with the first colour associated to one button, and the second colour associated to the other button. They practice the colour-button mappings extensively to make sure that they can press the correct button as soon as they see a coloured circle. Upon completion of these two blocks, each button is associated to two distinct coloured circles, yielding a total of 4 colour-button mappings. After that, participants practice the mappings with all four colours presented in random order, and again until they respond correctly for each colour on 10 consecutive trials. In the final practice, stop tones are added. There are 176 trials in this final practice, 25% of which are stop trials. Of the 25% of trials, 1/3 is Concurrent Stop trials, and 2/3 are Delayed Stop trials. Each trial starts with a fixation

cross (500 ms), followed by presentation of the coloured circle. For a Go trial, the coloured circle either remains on the screen for 3000 ms when no response is detected, or disappears immediately when a response is made. For a No-Go or Concurrent Stop trial, the stop signal is presented simultaneously with a coloured circle. On a Stop or Delayed Stop trial, the stop signal is presented after a 250 ms, 500 ms, or 750 ms delay. While the Concurrent Stop trial is similar to the No-Go trial in the Go/No-Go task that primarily engages the prevention process, the Delayed Stop trial is identical to the Stop trial in a Stop-signal task that primarily requires the cancellation process. For the Delayed Stop trials, the three delay latencies (250 ms, 500 ms, 750 ms) are varied according to an adaptive algorithm on a trial-by-trial basis, the staircase tracking algorithm (Logan, 1997), and correspond to three levels of inhibitory success (approximately 70%, 50% and 30%). The stop signal and the stop signal latencies occur with equal probability after each colour. Participants are instructed to respond as quickly and accurately as possible when they see a coloured circle, but they should be attentive to the beep tones and try to stop when they hear them. They are also told that they may not be able to stop in time since the beep tone is sometimes delayed. However, instead of slowing down and "waiting" for the beep tone to be better at stopping, participants are instructed to treat this failure to stop as normal and keep responding quickly and accurately for the rest of the trials. Feedback is provided if the participants responded too slowly for a Go trial (reaction time greater than 1000 ms; "TOO SLOW"), pressed the wrong button ("ERROR"), or responded to a Stop trial ("OOPS").

After the training phase, participants moved on to the experimental phase, which comprises of six blocks that are identical to the final practice. The adaptive algorithm varying the delay latencies for each trial is similarly implemented for all six blocks.

4.2 A Modified Think/No-Think Task

As mentioned earlier, the modified Think/No-Think paradigm should 1) isolate memory inhibition processes from awareness control, 2) better maximise participants' compliance in following the No-Think instructions, and 3) incorporate intrusion ratings in the design. In this section, we report data from two behavioural studies that achieve

these modifications. The first study addressed the first two issues, and the second study subsequently added intrusion ratings.

4.2.1 Think/No-Think Behavioural Study 1

In the first behavioural study, we devised two new versions of the Think/No-Think paradigm to compare whether adopting the memory inhibition or awareness control approaches would have differential effects on suppressing the retrieval of unwanted thoughts, the Forget and the Suspend conditions (Figure 4.3). Both conditions manipulated participants' metacognitive beliefs – the subjective understanding of the task that they were performing – in order to successfully separate the different approaches to retrieval suppression. The metacognitive belief for a typical Think/No-Think paradigm would be Unspecified, since participants are only instructed to avoid thinking of the unwanted targets. We conducted a between-subjects experiment with three separate groups, each following the Forget, Suspend, or Unspecified instruction.

The Forget condition was designed to encourage memory inhibition by providing a reason to suppress. Participants in this condition believed that they had to suppress targets for the No-Think trials so that they could be prepared for learning new associations. Specifically, participants were told to discard the previously-learned original pair-associations for the No-Think items so that they could better re-associate the cue to a different target that would be presented when the No-Think cue (wherein the cue word was presented in red) changed to a Think cue (wherein the cue word was presented in green) for the first time. The impression of having these trial switches was achieved through an additional set of filler items that we will introduce in detail in later paragraphs. Critically, however, the main Think and No-Think items for which we ultimately measured recall remained unchanged throughout the Think/No-Think phase, i.e., they were always Think or always No-Think items. Participants were told that because they only had one chance to learn the new target, they had to make sure that the original target was successfully inhibited so that it would not intrude into awareness and interfere with the new target.

In contrast to the Forget condition, the Suspend condition was designed to test the effect of awareness control on later retention. Participants in this condition believed that they were only temporarily suspending the No-Think items but would need to eventually

recall the target when the No-Think cue (in red) became a Think cue (turned green). Therefore, for the Suspend group, on No-Think trials, participants could simply block everything out of mind without necessarily actively suppressing the target. In fact, participants in the Suspend condition may choose to prevent memory suppression from happening due to the potential future relevance of the No-Think items. In a third and final group of participants, the meta-cognitive belief about the task was simply left Unspecified, as in the standard Think/No-Think task, allowing participants to interpret the instructions either way.

The meta-cognitive beliefs were manipulated through the introduction of a group of additional "filler" items (i.e. items that we didn't ultimately score – hereinafter referred to as "context fillers"), which served different purposes in different conditions as discussed previously. In all conditions, these additional context filler pairs were learned along with all of the other critical pairs in the learning phase. In the Forget and Suspend conditions, however, these pairs would differ from critical Think and No-Think pairs in one critical respect during the Think/No-Think phase. Whereas the critical Think and No-Think pairs would be consistently presented as Think or No-think items, the context filler pairs would, at a certain point, switch status. The context fillers would always first show up as No-Think items, and then eventually switch to become Think items (the exact repetition on which this switch happened was varied over items, to make it hard to predict). The addition of these context fillers made it plausible that all pairs could change at any point, encouraging participants to properly follow the No-Think instructions. In the Forget condition, this would be to properly suppress the No-Think targets in preparation for learning new associations. In the Suspend condition, this would be to keep the No-Think targets out of awareness, until when the switch takes place and they would need to retrieve the targets instead. In the Unspecified condition, the context fillers did NOT switch between trial types in the Think/No-Think phase. We simply used them to match the distribution of the Think and No-Think trials as in the Forget and Suspend conditions. Finally, participants were not aware of any distinction between the context fillers and the critical Think, No-Think, and Baseline items at any point throughout the experiment.

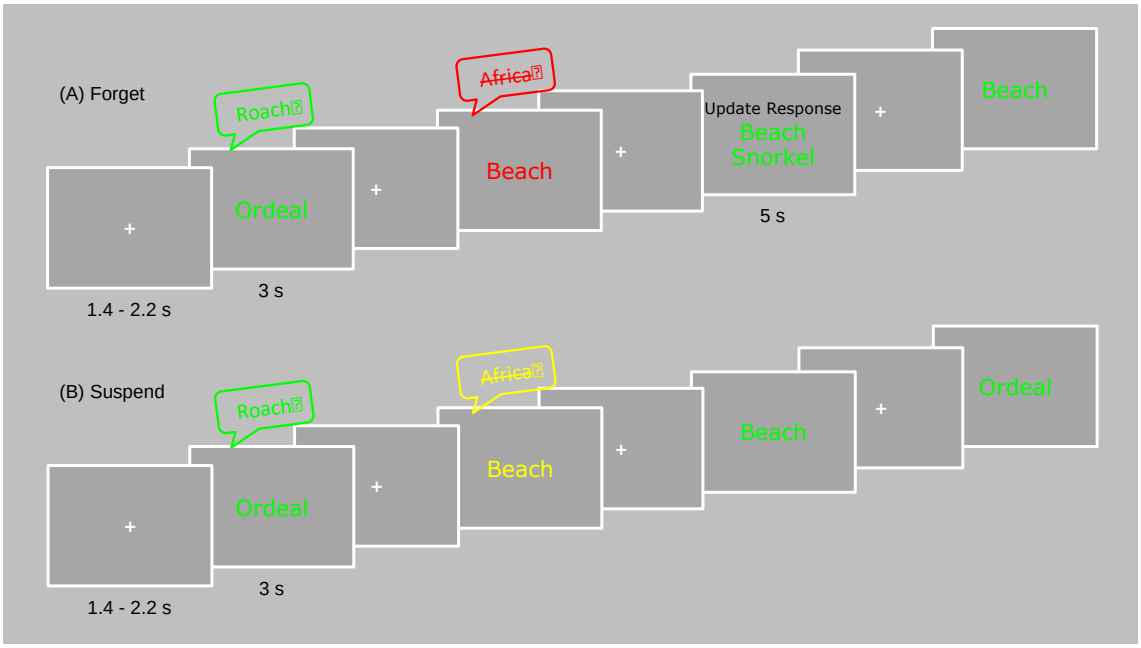

Figure 4.3: Example procedure of the Forget (A) and Suspend (B) conditions. Each cue word is presented for 3 s, with the inter-trial interval (ITI) jittering between 1.4 – 2.2 s. The update trial in the Forget condition lasts for 5 s.

Based on previous research, we hypothesised that the Metacognitive Belief manipulations should influence the extent of retrieval suppression. Two Specific predictions were made. First, we expected to replicate the typical SIF effect. That is, recall for the No-Think items should be impaired compared to Baseline. Second, the Metacognitive Belief conditions should modulate the probability of the participant invoking the inhibitory control mechanism to suppress unwanted memories. While the probability is unclear in the Unspecified condition, as participants may adopt different strategies given their belief on whether they will need to later recall the targets, this probability is much greater in the Forget condition, since participants believe that they need to truly suppress the unwanted targets to better learn the new associations. Finally, this probability is reduced in the Suspend condition due to the certainty that unwanted targets will need to be recalled later. Facilitation effects and participants' experience during the task will be examined for exploratory reasons.

4.2.1.1 Methods

4.2.1.1.1 Participants

We recruited 88 healthy young adults. 16 participants were excluded because 7 did not pass the learning criteria in the study phase, 4 showed medium to high depression as assessed by Beck Depression Inventory II (BDI-II; Beck et al., 1996), and 1 reported history of ADHD and dyslexia. As a result, data were available from 24 participants for each of the Unspecified (Male=6; *Mean Age* = 23.42 years; *SD Age* = 6.82 years), Forget (Male=7; *Mean Age* = 24.17 years; *SD Age* = 5.09 years), and Suspend (Male=15; *Mean Age* = 23.71 years; *SD Age* = 4.64 years) conditions.

All participants were native English speakers with normal or normal-corrected vision. All self-identified to have normal colour perception, to be exempt from ADHD and other learning, language or attentional deficits, and to be free from other psychological or neurological impairments.

4.2.1.1.2 Design

The experiment used a mixed-subjects design. There was one between-subjects variable, Metacognitive Belief (Unspecified vs. Forget vs. Suspend); and two within-subjects variables, Memory Control (Think vs. No-Think vs. Baseline) and Test Type (Same Probe vs. Independent Probe). Participants were randomly assigned to one of the Meta-cognitive Belief conditions. The word lists assigned to the Memory Control conditions were counterbalanced.

4.2.1.1.3 Materials and Procedure

We used 84 weakly relatable word pairs for this experiment constructed from the University of South Florida Free Association Norms (Nelson et al., 1998). For each pair, we generated a separate "independent probe" that is semantically related to the target but not the cue word. We used 16 pairs for each group of the critical items (Think, No-Think, and Baseline) and context fillers. Word lists for the critical items were counterbalanced. The remaining 20 were fillers to control for recency and primacy effects and block randomisation in list learning. In addition, we chose substitute words for new learning during the Forget condition. Of the substitute words, 16 were for the context fillers during the Think/No-Think phase, and 4 were for the fillers used in the Think/No-Think practice.

We used PsychToolbox (Brainard, 1997; Pelli, 1997) in MATLAB to execute the Think/No-Think task and to collect responses. In the study phase, participants learned the word pairs (each presented for 5 s) to at least 60% accuracy through 2 study and test-feedback blocks. Each study and feedback block trained them with half of the word pairs. In the study blocks, participants were presented with one pair of words on each trial for 5 s, with an inter-stimulus interval of 1 s. The word pairs were presented as white text on a grey background, centred on the screen, with the cue words on the top and the target at the bottom. In the test-feedback blocks, participants were presented with a cue words from the learned associations on each trial for 5 s and were asked to recall the corresponding target. Regardless of whether they recalled correctly, they were presented the associated target as feedback immediately after the cue word disappeared. The feedback was presented for 2.5 s and the inter-stimulus interval was .5 s.

Following learning, a criterion test was subsequently administered to examine the outcome of learning. The purpose of the criterion test is to identify which word pairs the participants truly learned. Items that they did not successfully encode by the criterion test were excluded from the final analyses, a procedure that we call conditionalization. If the participants could not recall certain words during the final test, it could either be that they successfully inhibited those targets due to repeated attempts of memory suppression, or that the words were never learned and they simply did not have an answer. Conditionalising the data therefore allows us to more reliably detect the effect of suppression-induced forgetting.

After the criterion test, participants had two chances to practice the main Think/No-Think task on filler items. After each practice, we administered a diagnostic questionnaire to ensure that the participants have fully understood and followed the instructions. Specifically, in the questionnaire, we asked them whether they have focused their attention on the screen the entire time without shifting their eyes. For the Think trials, we made sure that they recalled the targets as soon as possible and kept them in mind the entire time when the cue word was on the screen. For the No-Think trials, we ensured that they never intentionally retrieved the associated target for the cue word on the screen. If the target involuntarily intruded into their minds, we instructed them to push those targets out of mind and keep their minds clear. For participants in the Forget group, we additionally ensured that they paid attention to the switch trials, as

they were only allowed one chance to learn the new association, and hence giving them more incentive to dissociate the original target. For participants in the Suspend group, we made sure that they only started recalling the targets after the switch took place.

After a short break, participants briefly reviewed the 84 word pairs again before proceeding to the main Think/No-Think phase. The word pairs were presented for 2.5 s each, with an inter-stimulus interval of .8 s. In the Think/No-Think phase, participants performed corresponding tasks depending on the Meta-cognitive Belief conditions, as specified in the previous section. Only cues for the Think, No-Think (or Suspend), and context fillers were presented in this phase. Each cue word was presented for 3 s on each trial. The inter-stimulus interval was jittered between 1.4 – 2.6 s. The Think trials had the cue words presented in green font, indicating that the participants should recall the corresponding target as quickly as possible and keep it in mind as long as the trial lasts. The No-Think trials had the cue words presented in red font, indicating that the participants should keep the corresponding target out of mind without replacing the target with anything else. For the Forget and Suspend conditions, the context fillers always began as No-Think items, but switched to become a Think item at a later trial. We systematically ensured that the switch was distributed over delays of 1 to 9 trials, and the switches were evenly distributed across blocks. Each word was presented for 10 repetitions throughout the Think/No-Think phase, which is separated into 5 blocks (2 repetitions in each block). Due to the switch, the amount of Think and No-Think trials varied as the Think/No-Think phase progressed. We matched the distribution of Think and No-Think trials across the three Meta-cognitive Belief groups. Participants had around 40 s short breaks in between the blocks. Another diagnostic questionnaire was administered during the 3rd break to further ensure that participants were closely following instructions.

In the testing phase, participants first practiced cued-recall with filler items. Critically, since participants only saw part of the word pairs they learned (Think, No-Think, and context fillers) during the Think/No-Think phase, it is important to get them back in the context of the criterion test phase so that they could recall all items equally. Following the context reinstatement, participants completed the final recall, where we tested their memories with both the Same Probe and the Independent Probe tests. The order of the Same Probe and Independent Probe tests was counterbalanced across participants.

Before the Independent Probe test, we also administered an Independent Probe practice to help participants get familiar with what they need to do (as they have never experienced this test form in the previous stages of the Think/No-Think task). In both the Same Probe and the Independent Probe tests, each trial lasted for 3 s, with an inter-stimulus interval of .5 s.

Finally, participants completed a demographics questionnaire and a post-experimental questionnaire. The post-experimental questionnaire captured experiences and strategies used in the main Think/No-Think task, as well as noncompliance. Specifically, to understand participants' experiences during the Think/No-Think task, we asked how often they experienced intrusions overall during the Think/No-Think phase and how much effort they had to spend keeping the unwanted targets out of mind. In addition, we asked to what extent they anticipated a final test. Finally, we measured how closely the participants followed the No-Think instructions by asking if they intentionally recalled any unwanted targets during different stages of the Think/No-Think phase as an index for compliance. We asked participants to rate how often then intentionally recalled unwanted target during the fixation cross, when the cue word was presented, and after the cue word disappeared on three separate 0-4 scales. We then used the sum of the three ratings to index the level of compliance.

4.2.1.2 Results

According to the criterion test, participants in all three conditions reached on average 84% of accuracy in recalling the word pairs. Recall performance on the final tests were conditionalised by excluding items that were not initially learned, to ensure that variations in recall across conditions reflect the effects of our manipulations on demonstrably learned items.

4.2.1.2.1 The Forget Condition Yielded Stronger SIF than the Suspend and Unspecified Conditions

In order to examine the SIF effect, we compared the percentage of correct recall between the No-Think and Baseline items across conditions for both the Same Probe and Independent Probe tests (Figure 4.4). We conducted a 3 (Meta-cognitive Belief: Unspecified vs. Forget vs. Suspend) by 2 (Memory Control: Baseline vs. No-Think) by 2 (Test Type: Same Probe vs. Independent Probe) mixed-model ANOVA, taking into

account the counterbalancing for word lists and orders of test. Our results showed a main effect of Memory Control, $F(1,66)=13.19$, $p<.001$, $\eta_p^2=.17$, and Test Type, $F(1,66)=880.94$, $p<.001$, $\eta_p^2=.93$, but not for Meta-cognitive Belief, $F<1$, or the interaction, $p>.05$. To compare the magnitude of SIF across the Metacognitive Belief conditions, we computed suppression scores (by subtracting the No-Think recall from the Baseline recall) in each. We predicted that the Forget condition should generate the largest SIF, followed by the Unspecified and then the Suspend condition. We found that the Forget condition yielded significantly larger suppression-induced forgetting than the Unspecified condition, $t(69)=-2.40$, $p=.02$. The difference in suppression scores between the Unspecified and Suspend conditions, and between the Suspend and Forget conditions were not significant, $p>.05$.

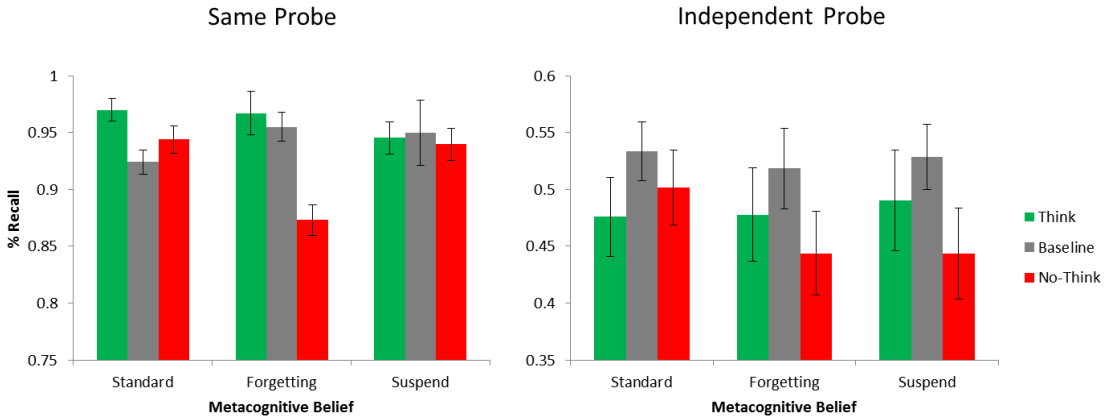

Figure 4.4: Percentage Recall for the Think, No-Think and Baseline Items in Same Probe and Independent Probe Tests across Meta-cognitive Belief Conditions.

4.2.1.2.2 Retrieval Practice Facilitated Recall than Baseline for the Same Probe Test, but Reduced Recall for the Independent Probe Test

For the facilitation effect, we conducted a 3 (Meta-cognitive Belief: Unspecified vs. Forget vs. Suspend) by 2 (Memory Control: Baseline vs. Think) by 2 (Test Type: Same Probe vs. Independent Probe) mixed-model ANOVA, again taking into account the counterbalancing for word lists and test orders. We observed a significant main effect of Test Type, $F(1,66)=1165.31$, $p<.001$, $\eta_p^2=.95$, and a significant interaction between Memory Control and Test Type, $F(1,66)=6.73$, $p=.01$, $\eta_p^2=.09$. As we can see from

Figure 4.4, a facilitation effect was present on the Same Probe test, but a reverse facilitation effect was present on the Independent Probe test. This difference was significant according to a paired-sample *t*-test, $t(71)=2.519$, $p=.014$.

The reverse facilitation effect is often observed in the Independent Probe test, where recall for the Think items is lower than that for the Baseline items (e.g., Paz-Alonso et al., 2009). In the current study, this reverse facilitation effect is present in all three manipulations. Although seemingly counterintuitive, this effect may be caused by encoding specificity, where the initial encoding and the repeated retrieval practice during the Think/No-Think phase biased the meaning of the target to the cue word, and made it less accessible by a different cue, especially when the association between the original cue and target is strong (e.g. Murphy & Wallace, 1974; Thomson & Tulving, 1970).

4.2.1.2.3 The Suspend Condition Induced Numerically Higher Intrusions and Noncompliance

Figure 4.5 exhibits responses from the post-experimental questionnaire, where we asked participants about their experiences during the task and whether they intentionally retrieved the unwanted targets during the No-Think trials. We found that participants in the Suspend condition showed a trend to experience more intrusions during the Think/No-Think phase, although a one-way ANOVA did not reveal significant group effect on intrusions ($p>.10$). They also showed a marginally significant tendency to cheat more often, $F(2, 70)=2.96$, $p=.059$, meaning that they were more likely to intentionally bring the unwanted target into awareness on a No-Think trial. It is possible that the increase in intrusions in the Suspend condition is due to the instructions – participants were told to supress the target from coming into mind during a No-Think trial, but retrieve it later when the No-Think items switched to become Think items. This may encourage the participants to keep the unwanted targets active at the back of the mind so that they are ready to recall them when needed, making the target more likely to intrude. The amount of perceived effort to successfully limit awareness of unwanted targets did not differ across groups. Participants from the Unspecified group showed slightly higher likelihood to anticipate a final test but this tendency was not significant.

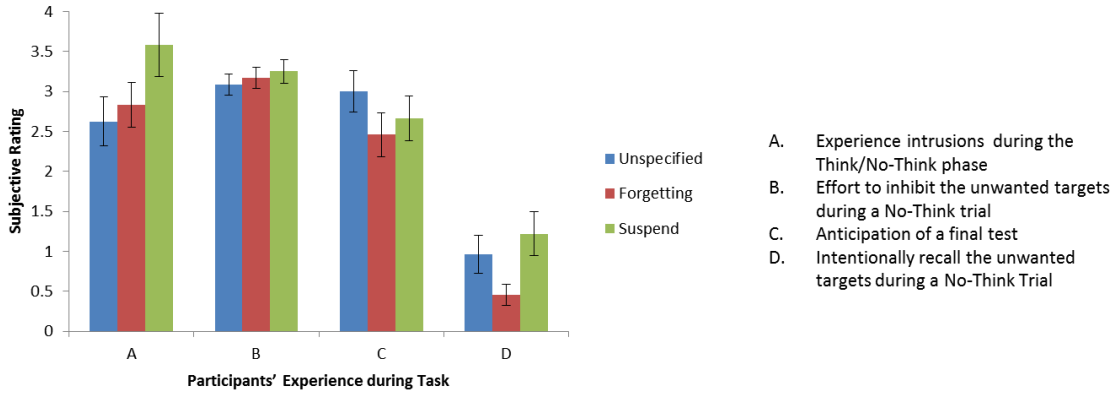

Figure 4.5. Post-Experimental Questionnaire.

4.2.1.3 Discussion

In this first behavioural study of the new Think/No-Think task, we aimed to 1) compare whether memory inhibition and awareness control yield different SIF effect, and 2) improve participants' compliance with the No-Think instructions. Our results showed that participants in Forget group had the most reliable SIF effect and were the best at using a dissociation strategy to supress the unwanted memories. This could be due to the fact that they were provided a reason to suppress the No-Think targets, that they should clear their mind to get ready for re-associating the original cue word with a different target. This is evidence that having a meta-cognitive belief of "forgetting" is essential for participants to perform retrieval suppression. If participants merely believe that they need to avoid thinking of the unwanted target and "suspend" thinking of it, this is not going to be sufficient for successfully dissociating the unwanted target from the cue.

Unfortunately, we did not replicate the SIF effect in the Unspecified condition, possibly due to a number of reasons. First, the ambiguity of task instructions may have undermined participant's voluntary effort to suppress memory. Specifically, as discussed earlier, the ambiguous instructions may lead some participants to dissociate and inhibit the target (like those in the Forget group in this experiment), but the others to simply keep the unwanted target out of awareness while making sure the target is retrievable at a later point (like those in the Suspend group). This diminished suppression-induced forgetting effect in the Unspecified group highlights the necessity

of developing instructions that can encourage participants to dissociate, so as to more validly test people's ability to suppress unwanted memories. Second, as the Think/No-Think phase lasted for around 60 minutes, participants may have been fatigued from the task. This can cause them to be less effective at inhibiting unwanted thoughts and lead to intrusions (Anderson & Huddleston, 2012). For example, van Schie and Anderson (2017) tested the effect of sustained inhibition efforts (possibly inducing fatigue), and used intrusion ratings to measure the success of inhibition. Specifically, they had Think/No-Think trials with short and long durations in the experimental phase. For each item, they examined whether (a) an intrusion on one trial was followed by successful intrusion prevention at the next trial (new successes), or (b) whether successfully preventing an intrusion on a trial was followed by a relapse at a later trial (relapses). They found that the number of successes increased in the initial repetitions but decreased in the final repetitions for both short and long Think/No-Think trials, showing that the ability to overcome intrusions may have been impaired by fatigue as the task progressed. In addition, the number of relapses decreased over the initial set of trials, but increased in the final repetitions for the long Think/No-Think trials. These results suggest that having to sustain efforts to inhibit unwanted memories may cause a decline in control after a certain period of time, possibly due to fatigue.

Intriguingly, the Suspend condition did not yield significantly different SIF effects from either the Unspecified or the Forget conditions. As can be seen in Figure 4.4, the Suspend condition did not yield any inhibition effect on the Same Probe test, but the recall for No-Think items was lower than baseline for the Independent Probe test. Although this reduced recall in Independent Probe appears like the SIF effect, it could also be similar to the reverse facilitation effect. As discussed in Section 4.2.1.2.2, the reverse facilitation effect is usually attributed to encoding specificity, whereby retrieval practice strengthened the learned associations for the Think items, and hence impaired the flexibility of retrieving the same targets from different associations. In the Suspend condition, participants are instructed to keep the target out of awareness during the task, although they may be tested again at a later point. This may have caused them to implicitly retain or even strengthen the learned associations for the No-Think items, and reducing the accessibility of the target with an independent probe.

Overall, this behavioural study suggests that merely keeping the unwanted target out of mind is not sufficient for achieving memory inhibition, but the participants have to have the intention to forget and actively suppress memory retrieval. Considering the Meta-cognitive Belief groups, both the Forget and Suspend instructions may require the basal ganglia to selectively "gate in" information that need to be retrieved for the Think condition, and to "gate out" information that need to be suppressed for the No-Think condition. As proposed by Scimeca and Badre (2012), the basal ganglia may be critical for the adaptive retrieval of declarative memory given the utility of the memories in certain goal contexts. In a Think/No-Think paradigm, associations from the Think items would have a higher utility as they are supposed to be retrieved. Associations from the No-Think items would have a lower utility as it is undesirable for them to be retrieved.

To identify basal ganglia mechanisms specific to intentional forgetting, we would have had to conduct a between-group fMRI experiment and compare between the brain activity yielded by the Forget and Suspend instructions. However, we will not pursue this direction, since the focus of this PhD thesis is to investigate the role of the basal ganglia in memory and motor inhibition. Through the first behavioural study, we identified that the Forget instructions generated a more robust SIF effect. We will adopt the Forget instructions in our next step, and incorporate intrusion ratings into the paradigm.

4.2.2 Think/No-Think Behavioural Study 2

According to Study 1, the Forget instructions yielded the most reliable SIF effect. In this study, we incorporated the following changes and improvements. First, in order to examine the possible prevention and cancellation processes in memory inhibition, we added intrusion ratings in the design, i.e. participants would rate how often the target came into mind after each trial in the Think/No-Think phase. Second, we jittered inter-trial-intervals (ITI) in anticipation of using this paradigm in the fMRI experiment. Having jittered ITIs allows for more sensitive detection of differences between trials that are close in time (e.g., less than 20 second), since the fMRI BOLD signal is sluggish in nature (http://imaging.mrc-cbu.cam.ac.uk/imaging/DesignEfficiency). Third, since adding intrusions would further prolong the experiment, we reduced the number of stimuli to keep the task within a reasonable time frame (around 50 minutes), as

fatigue can severely impact an individual's ability to inhibit unwanted thoughts (van Schie & Anderson, 2017). Finally, we edited the instructions so that they further emphasised the importance of dissociating the unwanted target from the original cue. The specific methods are outlined below.

For this second behaviour study, we expected to replicate the SIF effect, and observe significant reductions of intrusion frequency during the task (e.g., Gagnepain et al., 2017; Levy & Anderson, 2012). We will use the post-experimental questionnaire to compare whether participants' experience significant differed between experiments due to the changes we have introduced.

4.2.2.1 Methods

4.2.2.1.1 Participants

We recruited 26 healthy young adults for this behavioural study. Two participants were excluded because they did not reach learning criteria. Data from the resulting 24 participants were included in the analysis (Male=10; *Mean Age* = 23.67 years; *SD Age* = 6.21 years). All participants were native English speakers with normal or normal-corrected vision. All self-identified to have normal colour perception, to be exempt from ADHD and other learning, language or attentional deficits, and to be free from other psychological or neurological impairments.

4.2.2.1.2 Design

This experiment used a within-subject design, testing the level of recall for each of the Memory Control conditions (Think vs. No-Think vs. Baseline). The word lists assigned to the Memory Control conditions were counterbalanced. Memory Control was measured with both the Same Probe and the Independent Probe tests.

4.2.2.1.3 Materials and Procedure

This experiment used 64 weakly relatable word pairs constructed from the University of South Florida Free Association Norms (Nelson et al., 1998). For each pair, we selected an "independent probe" that was semantically associated with the target but not the cue word. 12 pairs were used for each group of the critical items (Think, No-Think, and Baseline) and context filler. Word lists for the critical items were counterbalanced. The remaining 16 were fillers to control for recency and primacy effects and block

randomisation in list learning. In addition, we also chose 16 substitute words for new learning during the Think/No-Think phase. 12 of these were for the context fillers, and 4 were for the fillers during Think/No-Think practice.

The procedure was exactly the same as in Study 1 with a few exceptions. First, the Think/No-Think practice is now comprised of 3 parts. In the first part, participants practiced a standard Think/No-Think phase with the Forget instructions to get the gist of the task. In the second part, they practiced pressing buttons for the intrusion rating using their right index, middle, and ring fingers. The button presses were collected from a customised three-button button box. In the final practice, participants integrated intrusion ratings into the Think/No-Think trials and rated how often the target came into mind immediately after each trial. The rating was collected for both Think and No-Think trials, and participants were allowed 1.5 seconds to respond. Participants pressed "1" if the target never came to mind, "2" if the target came to mind briefly, and "3" if the target came to mind throughout the trial. They were instructed to respond quickly and intuitively without thinking about the response word, and that they should press the buttons as accurately and honestly as possible. The Think/No-Think phase was in the same format as the last Think/No-Think practice. There were 5 blocks in the Think/No-Think phase, lasting in total about an hour.

4.2.2.2 Results

Participants reached an average of 82% accuracy learning the initial pair-associations according to the criterion test. Recall performance on the final tests were conditionalised by excluding items that were not initially learned, to ensure that variations in recall across conditions reflect the effects of our manipulations on demonstrably learned items.

4.2.2.2.1 The Modified Paradigm Yielded a Significant Effect of SIF and Difference between Test Types, but not the Interaction between the Two

In order to examine the SIF effect, we compared the percentage of correct recall between the No-Think and Baseline items across conditions for both the Same Probe and Independent Probe tests (Figure 4.6). We conducted a 2 (Memory Control: No-Think vs. Baseline) by 2 (Test Type: Same Probe vs. Independent Probe) repeated-measure ANOVA, taking into account the counterbalancing for word lists and test

orders. We observed a significant main effect of Memory Control, $F(1,23)=8.16$, $p=.009$, replicating the SIF effect. We also found a significant main effect of Test Type, $F(1,23)=79.83$, $p<.001$. We often observe a lowered overall recall from the Independent Probe than the Same Probe test. The Same Probe test may be easier since the participants were trained with the associations. The interaction between Memory Control and Test Type was not significant, $F(1,23)=.398$, $p=.54$.

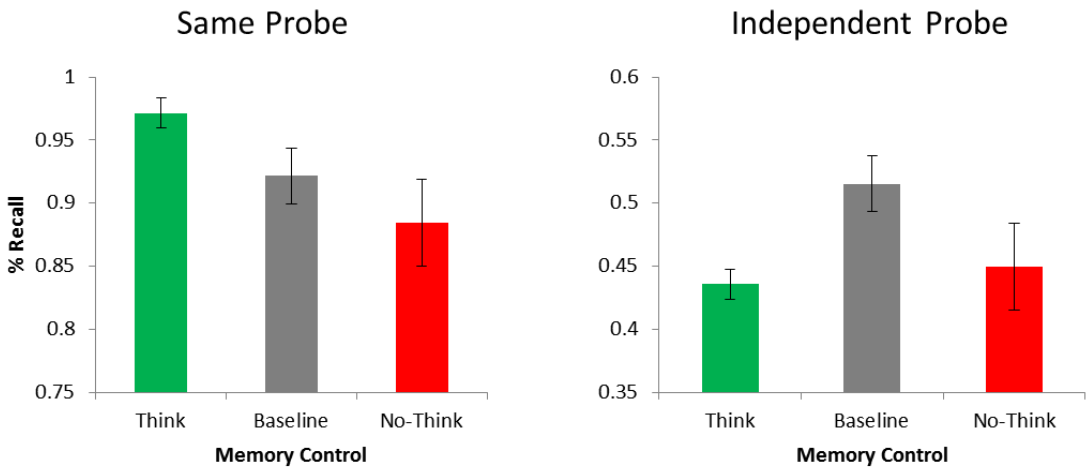

Figure 4.6: Percentage Recall for the Think, No-Think and Baseline Items in Same Probe and Independent Probe.

4.2.2.2.2 Frequency of Intrusions Significantly Reduced Over Repetitions

In addition to SIF, we examined the change in intrusion frequency throughout the Think/No-Think phase by calculating the percentage of items that participants rated as "having come into mind" either briefly or often during the No-Think trials. To calculate intrusion frequency, we binarised the intrusion ratings. We identified "intrusion" trials if participants reported to have thought of the unwanted target briefly (originally rated as 2 points) or often (rated as 3 points). We identified "non-intrusion" trials if participants did not think of the unwanted target at all (rated as 1 point). We calculated the proportion of intrusion trials for each repetition as the intrusion frequency, and fitted a linear function that describes the reduction of intrusions over the repeated suppression attempts in the Think/No-Think phase (Figure 4.7a). We observed a significant reduction of intrusions over repeated attempts to suppress the unwanted targets,

comparing the amount of intrusions from the first and the last repetition, $t(23)=5.14$, $p<.001$. Next, we quantified the proportionalised rate of intrusion reduction by calculating the slope of the linear fitting function for each individual, divided by the initial amount of intrusions they experienced in the first repetition in the Think/No-Think phase. This proportionalised slope takes into account individual differences in the initial amount of intrusions that need to be suppressed (on the first trial), which varies widely from participant to participant. This correction should better reflect participants' abilities to suppress memories that still intrude into their minds. For example, if a participant had 100% intrusions to begin with, the proportion of intrusions they managed to suppress should be on a scale of 0-100%. However, if they had 80% intrusions to begin with, this scale should be 0-80%. Taking the initial amount of intrusions into account standardises individual differences in the rate of intrusion reduction into a common scale.

4.2.2.2.3 Slope of Intrusion Reduction and SIF Marginally Correlated

To examine the relationship between the ability to overcome intrusions and the ability to suppress unwanted targets, we correlated the rate of intrusion reduction with the magnitude of suppression-induced forgetting (SIF; the reduced recall for the No-Think items relative to Baseline) using the Robust Correlation Toolbox (Pernet et al., 2013). Although we found that the better people were at overcoming intrusions during the Think/No-Think phase, the more unwanted targets they were able to suppress, this relationship did not reach significance ($r = -.30$, $p = .15$; Figure 4.7b). Previous studies have found significant correlations between intrusion slope and the magnitude of SIF (e.g. Hellerstedt et al., 2017; Gagnepain et al., 2017; Levy & Anderson, 2012). The weaker trend in the current experiment may be due to the complexity of the task, as participants had to beware of the trial switches and learn new associations in addition to performing retrieval suppression. This added task-set switching may have required more cognitive resources that made participants less effective at suppressing unwanted targets while keeping intrusions out of awareness. It is also possible that there is too much variance due to individual differences in their ability to suppress unwanted thoughts. In the actual fMRI experiment, we increased the sample size to 30 to address this issue.

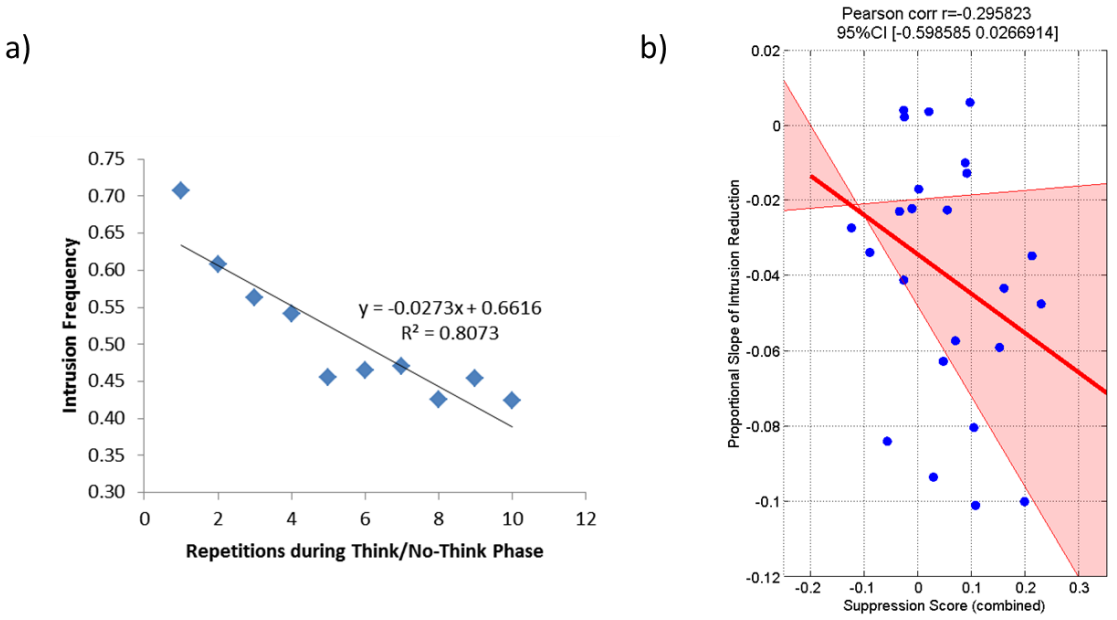

Figure 4.7: A) Reduction of Intrusions over the Think/No-Think Phase; B) Robust Pearson Correlation between Slope of Intrusion Reduction and SIF. The suppression score is calculated by subtracting No-Think recall from Baseline recall, combining results from the Same Probe and Independent Probe tests.

4.2.2.2.4 Participants in Study 2 Experienced Less Intrusions, but Were More Likely to Intentionally Recall Unwanted Targets

In addition, we wanted to examine whether the improved instructions and the addition of intrusion ratings in Study 2 made any difference to participants' experience compared to in Study 1 (Figure 4.8). Therefore, we compared participants' reports from the post-experimental questionnaire, in which they rated their overall experience in the following aspects:

A. Experience of intrusions during the Think/No-Think phase
B. Effort to inhibit the unwanted targets during a No-Think trial
C. Anticipation of a final test
D. Intentionally recalled the unwanted targets during a No-Think Trial

Out of these measurements, we found that participants in Study 2 reported to have experienced less intrusions overall, $t(46)=-4.30$, $p<.001$, suggesting that they may have been more successful at keeping unwanted targets out of mind. It is possible that our

improved instructions further motivated participants to suppress intrusions. However, we found that participants in Study 2 were more likely to report intentionally recalling the unwanted targets during a No-Think trial, although this difference was only marginally significant, $t(46)=-1.98$, $p=.054$. It is possible that the intrusion ratings prompted the participants to implicitly check if they still remembered the targets, even though they also reported that they always tried to keep the unwanted targets out of mind in the diagnostic questionnaires during the task.

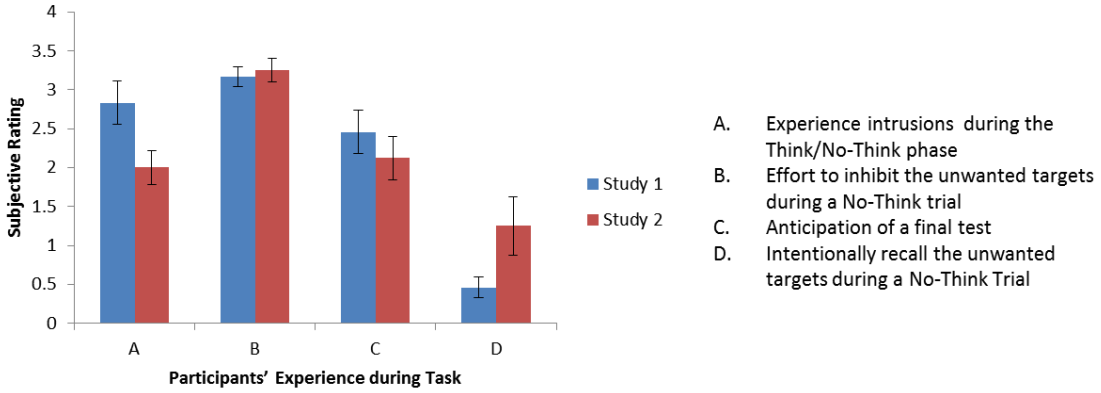

Figure 4.8: Comparing participants' subjective experience during Study 1 and 2. The Top panel presents their overall experience and the extent of compliance. The bottom panel presents the strategies they used to achieve memory inhibition.

4.3 Discussion and General Discussion

In the chapter, we established the behavioural paradigm that we will use in the subsequent fMRI study to compare memory and motor inhibition processes. Specifically, we described a Combined Go/No-Go and Stop-signal task to study action prevention and action cancellation; we incorporated intrusion ratings into an adapted Think/No-Think task to examine retrieval prevention and retrieval cancellation. For the adapted Think/No-Think paradigm, we used two behavioural experiments to show that 1) the intention to forget, rather than merely keeping unwanted memories out of mind, is essential for SIF; and 2) Adding intrusion ratings did not affect the SIF effect, and reduced intrusions overall.

Figure 4.9 further illustrates the parallel between the memory and motor inhibition tasks in the frame of a single trial. Both memory and motor inhibition tasks have trials starting with a fixation cross. In the case of memory inhibition, participants will see a cue word presented on the screen during the Think/No-Think phase. If the participant does not experience an intrusion of the unwanted target on a No-Think trial, it is possible that the participant has successfully engaged a proactive inhibitory control process that *prevents* the target from coming into mind, especially when considering pairs that are demonstrably learned. However, if the unwanted target does intrude into awareness at any time after stimulus onset, the participant will then need to react to the intrusion and *cancel* the ongoing retrieval process to keep the target out of mind. Similarly, in the case of motor inhibition, if the stop signal takes place simultaneously with stimulus onset as in the Go/No-Go task, participants immediately know that they should not respond on this trial and *prevent* pressing the button associated with the presented stimulus. However, if the stop signal takes place after stimulus onset, participants will have started the process of pressing the corresponding button, and hence will need to *cancel* this process to stop their motor response.

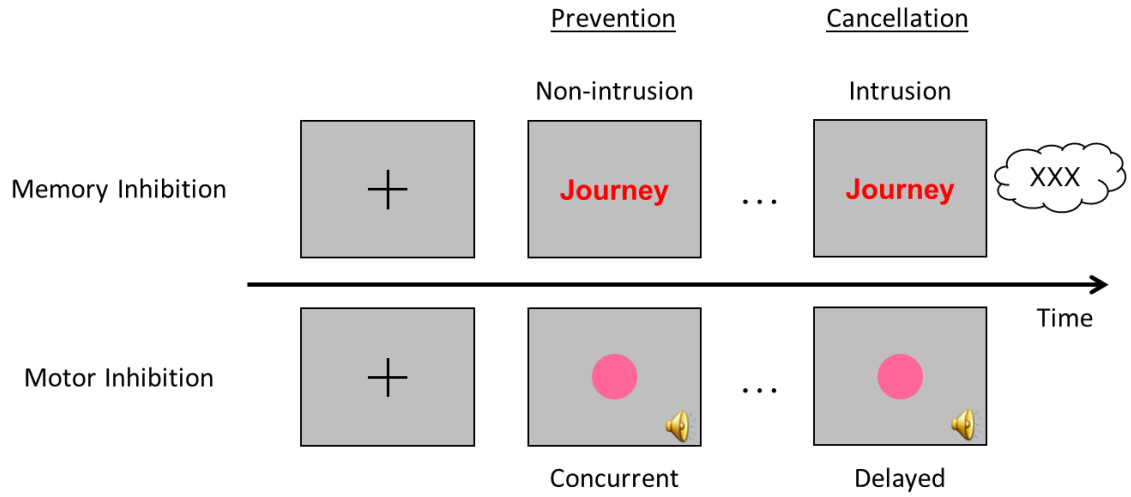

Figure 4.9: Comparing the Prevention and Cancellation Processes in Memory and Motor Inhibition in the Current Design within the Time Frame of a Single Trial. All trials start with a fixation cross, followed by a cue word in the memory task, and a coloured circle in the motor task. Prevention mechanisms may be engaged during a Non-intrusion trial (when the participant successfully prevented an unwanted target from coming into mind) or a Concurrent stop trial. On the other

hand, cancellation mechanisms may be engaged if they later experienced intrusions or if the stop signal is delayed.

After establishing the behavioural paradigms, we then used these paradigms in an MRI experiment to compare the brain mechanisms underlying memory and motor inhibition, and between prevention and cancellation processes. Especially of interest was whether the basal ganglia play similar roles across different domains and processes of inhibition, and how the basal ganglia interact with other relevant structures to achieve the prevention and/or cancellation of unwanted memory retrievals and motor actions. We also wanted to explore the anatomical pathways underlying these functional interactions.

We used the following approaches to tackle those questions. First, to examine if similar regions in the basal ganglia were activated for different domains and processes of inhibition, we compared functional activations between the memory and motor inhibition tasks, and between the prevention and cancellation conditions. We expected overlapping activations between memory and motor inhibition, but possibly distinct patterns of activation between prevention and cancellation. From the meta-analysis shown in Chapter 3, although memory and motor inhibition both activated the basal ganglia, the prevention process in the Go/No-Go task primarily activated the left basal ganglia, while the cancellation process in the Stop-signal and Think/No-Think tasks primarily activated the right basal ganglia.

Second, we used DCM to investigate how the basal ganglia interact with other regions involved in memory and motor inhibition. Specifically, we were interested in whether the basal ganglia are effectively involve in inhibitory processes as other putative supramodal regions, such as the DLPFC. If so, how the putative supramodal regions work with each other, and whether inhibition is achieved through down-regulating task-specific regions, such as the hippocampus for memory, and M1 for motor. Furthermore, we would like to relate effective connectivity to behaviour, and find out which task modulated pathways are best associated with higher abilities to inhibit unwanted thoughts and actions.

Finally, we acquired diffusion-weighted imaging (DWI) to explore the possible anatomical connections underlying memory and motor inhibition. As we discussed in Chapter 2, although there is much evidence for the basal ganglia pathways involved in motor control, whether similar mechanisms are required in memory control remains unclear. We proposed some hypotheses in Sections 2.5.2 and 2.5.3. First, according to the intermediary hypothesis, the basal ganglia system may process control signals from the PFC, and then communicate with the task-specific regions via its own output through the thalamus. While the ventrolateral thalamic nuclei may directly connect with M1 for motor control, the anterior thalamic nuclei may connect with the hippocampus through the cingulum bundle. Second, according to the indirect hypothesis, the basal ganglia may interact with the task-specific regions through the PFC. For motor control, the DLPFC may connect with M1 through the preSMA and SMA. For memory control, the DLPFC may connect with the hippocampus through the ACC, either by suppressing input to the hippocampus from the entorhinal cortex, or by engaging the thalamic reuniens nucleus to achieve local inhibition in the hippocampus. Finally, according to the modulation hypothesis, the basal ganglia may connect with either the DLPFC or an intermediary between the DLPFC and the task-specific regions to achieve inhibition. Using DWI, we hope to identify anatomical pathways that relate to the effective connectivity or behavioural performances of memory and motor inhibition.

We will present our fMRI findings in Chapter 5, and discuss our DWI approach in Chapter 6.

5 The Role of the Basal Ganglia in Memory and Motor Inhibition: An FMRI Study

As summarised in Section 2.5, this PhD thesis aims to tackle three main questions. First, whether the basal ganglia are consistently involved in both memory and motor inhibition? Second, how are the basal ganglia involved in memory and motor inhibition, in relation to the prefrontal control regions and the task-specific regions? Third, what are the anatomical pathways underlying the functional interactions? Using a meta-analytic approach (Chapter 3), we answered the first question that the basal ganglia are indeed consistently involved in both memory and motor inhibition, across the Go/No-Go, Stop-signal, and Think/No-Think tasks. Specifically, all three tasks activated the centromedial striatum, except that the Go/No-Go task activated the left basal ganglia, while the Stop-signal and Think/No-Think tasks activated the right basal ganglia. On one hand, this lateralisation effect may be due to the ALE algorithm being more sensitive to clustering activity. After all, when we examined the original input to the meta-analyses, there was basal ganglia activity in both hemispheres in all three tasks. On the other hand, the differences may imply that the three tasks may engage distinct

subprocesses of inhibition. While the Go/No-Go task may primarily require a prevention process, the Stop-signal and Think/No-Think tasks may primarily require a cancellation process.

In this chapter, we attempt to tackle the second question, using the behavioural paradigms that we presented in Chapter 4. With the adapted Think/No-Think paradigm and the Combined Go/No-Go and Stop-signal task, we will be able to separate the prevention and cancellation processes in both memory and motor inhibition. In the Think/No-Think task, prevention and cancellation is separated by experience of intrusions. If the participant did not experience any intrusions on a given trial, it is likely that they have successfully prevented the unwanted target from coming to mind. If the participant did experience intrusions, it is likely that they would need to cancel the retrieval process to push the unwanted target out of mind. In the Combined Go/No-Go and Stop-signal task, prevention and cancellation are distinguished by concurrent and delayed stop signals. If participants successfully stopped on a trial where the stop signal is simultaneously presented as the stimulus, it is likely that they knew to stop early on in the process and were able to prevent the motor response from taking place. If participants successfully stopped on a trial with a delayed stop signal, it is likely that they were able to cancel an emerging motor response.

The question of how the basal ganglia interact with other brain regions to achieve inhibition is two-fold. First, we would like to compare if the basal ganglia play similar roles in the prevention and cancellation subprocesses of inhibition, across the memory and motor domains. According to the meta-analysis, although the memory and motor inhibition tasks activated similar regions in the basal ganglia, there was a lateralisation effect possibly due to the distinct subprocesses. The Go/No-Go task is thought to engage prevention processes and primarily activated the left basal ganglia, while the Stop-signal and Think/No-Think tasks are thought to engage cancellation processes and primarily activated the right basal ganglia. In this study, we would like to use univariate analyses to examine the basal ganglia activations yielded by the prevention and cancellation processes across memory and motor domains. It is possible that the inhibitory subprocesses indeed activate distinct regions of the basal ganglia in the left and right hemispheres. Alternatively, as hypothesised in Section 2.5.1, the prevention

and cancellation processes may activate similar regions in the striatum, but engage distinct basal ganglia pathways to achieve inhibition (Schroll & Hamker, 2013).

Second, we would like to use DCM to investigate how the basal ganglia interact with other putative supramodal regions (e.g., DLPFC) and the task-specific regions (hippocampus and M1) to achieve inhibition. We planned two sets of DCMs to tackle this question. The first set of DCM analyses will examine whether the basal ganglia is part of the supramodal pathway, and contribute to inhibition in similar ways as the DLPFC. We hypothesised that the basal ganglia should be effectively involved in memory and motor inhibition as the DLPFC. Specifically, they both exert top-down regulation of the task-specific regions to achieve inhibition. The second set of DCM analyses will focus on the interaction between the DLPFC and the basal ganglia during the inhibitory control processes across tasks. We came up with three hypotheses in Section 2.5.2. First, according to the intermediary hypothesis, the basal ganglia process prefrontal control signals and pass them on to the task-specific regions. The second is the indirect hypothesis, where the basal ganglia interact with the task-specific regions through the DLPFC. Finally, the modulation hypothesis postulated that the basal ganglia may modulate the connectivity between the DLPFC and the task-specific regions, since the basal ganglia system has intrinsic pathways that are responsible for initiating and inhibiting responses.

In addition to investigating the neural pathways through which inhibition is achieved, it is also important to examine whether effective connectivity actually contribute to behaviour. To do this, we will extract DCM parameter estimates with Bayesian Model Averaging (BMA), and correlate these estimates with behavioural indices of memory and motor inhibition, such as SIF and slope of intrusion reduction for memory inhibition, and SSRT for motor inhibition. We would expect that the effective connectivity between the putative supramodal regions (DLPFC and basal ganglia) is associated with both memory and motor inhibition, while the effective connectivity with the task-specific regions is associated with the corresponding task. For example, parameter estimates on the pathway to the hippocampus should be associated with memory inhibition, and those on the pathway to M1 should be associated with motor inhibition. Furthermore, we would like to explore whether the prevention and cancellation processes contribute equally to inhibition. If they do, we may see similar

correlations between behaviour and the modulation parameters during prevention and cancellation. Otherwise we may see stronger correlation between behaviour and the modulation parameters during prevention than cancellation, or vice versa.

5.1 Methods

5.1.1 Participants

We recruited 33 healthy young adults for the experiment. Data from three participants were excluded from the analyses due to mismatched task and scanner onsets (two) and drop-out (one). As a result, data from 30 participants were considered for analyses (Male=13; *Mean Age* = 22.77 years; *SD Age* = 3.49 years). All participants were native English speakers, right-handed with normal or normal-corrected vision. All self-identified to have normal colour perception, to be exempt from ADHD and other learning, language or attentional deficits, and to be free from other psychological or neurological impairments.

5.1.2 Behaviour Paradigms and Procedure

The behavioural paradigms were exactly the same as described in Chapter 4.1 and 4.2.2 for motor and memory inhibition respectively. We also collected RTs for the intrusion ratings during the Think/No-Think phase. Participants were invited to complete the tasks in two sessions. Participants completed the Combined Go/No-Go and Stop-signal task in the first session, and the Think/No-Think task in the second session. Since the motor task did not require a final test, we hoped that this would reduce the likelihood of the participants expecting a final test in the Think/No-Think task.

In the first session, participants were trained with the Combined Go/No-Go and Stop-signal task in a behavioural lab. They were then directed to the scanner facility for the main task. Finally, they completed a post-experimental questionnaire that asked about their experiences and strategies during the task, the Beck's Depression Inventory II (BDI II) to make sure they were not experiencing stress or depression as that could influence their ability to inhibit, and a demographics questionnaire. In the second session, participants went through a similar procedure, except that they were taken back to the behavioural lab after the Think/No-Think phase for the final test.

We collected the following data from each participant from the MRI scanner. In the first session, we collected a structural volume of their brain, event-related fMRI data when they were performing the Combined Go/No-Go and Stop-signal task in the scanner, a functional localiser for the primary motor cortex, and diffusion-weighted imaging. The functional localiser consisted of 8 short blocks, with alternating blocks requiring passive viewing of coloured circles, and button pressing when seeing a circle. If it was the first time that a participant was ever scanned at our facility, we would also acquire a T2-weighted image to make sure that the participant had a healthy brain. In the second session, we simply acquired a structural volume and the event-related data for the Think/No-Think task. The acquisition protocol is outlined below.

5.1.3 MRI Acquisition Protocol

Scanning was performed on a 3T Siemens Magnetom Prisma MRI system using a 32-channel whole-head coil. Participants were positioned supine. We used foam pads to fixate the subject's head within the radiofreqeuncy coil housing, as well as under their arms and legs to make them comfortable. We monitored their pulses throughout the scanning phase and provided headsets, emergency buzzer, and when necessary MRI compatible spectacles. We acquired magnetisation-prepared, rapid gradient echo (MPRAGE) structural images (256×256×192; 1 mm^3 isotropic voxels; repetition time = 2250 ms; echo time = 3.02 ms; flip angle 9°; interleaved slice acquisition). Functional data were acquired using a multi-band gradient-echo, echo-planar pulse sequence (EPI; 192×192×120; 2 mm^3 isotropic voxels; repetition time = 1120 ms; echo time = 30 ms; 60 horizontal slices; interleaved slice acquisition; multi-band acceleration factor = 4). The first nine volumes of each session were discarded to allow for magnetic field stabilisation. When the participant was scanned at our facility for the first time, a turbo spin echo (TSE) T2-weighted structural image was also acquired (220×220×150; 4 mm^3 isotropic voxels; repetition time = 5060 ms; echo time = 102 ms; interleaved slice acquisition).

5.1.4 Behavioural Analyses

For the Think/No-Think task, we first conditionalised the data, i.e. we excluded items that they did not successfully encode at the learning phase, as indicated by the criterion

test. Second, we computed their suppression scores by subtracting their level of recall for the No-Think items from that for the Baseline items. We also computed their facilitation scores by subtracting the Baseline recall from the Think recall. We did this separately for the Same Probe and Independent Probe tests.

For the Combined Go/No-Go and Stop-signal task, we estimated the stop-signal reaction time (SSRT) for each participant using the integration method based on the independent-race model (Logan & Cowan, 1984; Verbruggen & Logan, 2009). The independent race model describes stop-signal performance as a race between a go process triggered by a go stimulus, and a stop process triggered by the stop signal. Whether response inhibition is successful depends on the relative finishing time of the go and stop processes.

Since the stop signal occurs after a variable interval, the stop-signal delay (SSD), the point at which the stop process finishes is estimated by integrating the response time (RT) distribution and finding the point at which the integral equals the probability of responding, *p*(respond|signal), for a particular SSD. SSRT is then calculated by subtracting SSD from the finishing time. To account for the dynamically adjusting SSD in our design, the integration method assumes that the finishing time of the stop process corresponds to the *n*th RT, with *n* equal to the number of RTs in the RT distribution multiplied by the overall *p*(respond|signal); SSRT can then be estimated by subtracting the mean SSD from the *n*th RT. We followed these calculations for each block, resulting in an SSRT value for each subject for each block. We then averaged the SSRT values across blocks to get a mean SSRT for each participant (Verbruggen, Chambers & Logan, 2013).

To make sure that our data was not affected by anomalies, we conducted the generalised extreme studentised deviate (ESD) test (Rosner, 1983) to formally detect if there were outliers, and if so, how many. The ESD test was run on the suppression scores, facilitations scores, and the SSRT separately. For the suppression and facilitation scores, we tested for outliers in the Same Probe and the Independent Probe tests, and with the two tests combined. Finally, we identified and removed the corresponding participants from further relevant analyses.

The Think/No-Think task was a 3 (Condition: Baseline, Think, No-Think) by 2 (Test Type: Same Probe, Independent Probe) design. To test for the general suppression-induced forgetting effect, we compared the level of recall between the Baseline and No-Think items, aggregating across the Same Probe and Independent Probe tests. We also took into account nuisance variables that may be induced by variances amongst the stimuli, the participants, and the assignment of items to the Baseline/Think/No-Think conditions. To do this, we fitted a multi-level logistic regression model, where we specified recall as the dependent variable. We defined the model as binomial since recall is a binary variable (either the participants remembered the correct target or not). We further specified Condition as the independent variable, and subject variability and stimulus variability as random intercepts. We then fitted a similar model to test the facilitation effect by comparing recall between the Baseline and Think items.

In addition to the suppression and facilitation effect, we also examined the frequency of intrusions throughout the Think/No-Think phase. Specifically, we calculated the slope of reduction in the frequency of intrusions, and divided that by the intrusion frequency in the first run. This is to take into account individual differences in the initial amount of intrusions participants had to suppress, so as to standardise the scale of intrusion reduction across participants (Levy & Anderson, 2008). Next, we used the Robust Correlation Toolbox (Pernet et al., 2013) to calculate whether reduction of intrusions is correlated with the magnitude of SIF. Finally, we correlated the SSRT with SIF to examine if better performance in stopping motor actions is associated with higher ability to suppress unwanted memories.

5.1.5 MRI Analyses

5.1.5.1 Preprocessing

We used Statistical Parametric Mapping to determine the functional activation from the BOLD signal (SPM12, University College London, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Following image reconstruction, we applied motion correction to the time series data for each participant, including re-alignment and co-registration. Structural and time series data from the second session (where participants performed the Think/No-Think task) were co-registered with those

from the first session (where participants performed the Combined Go/No-Go and Stop-signal task).

5.1.5.2 Univariate Analysis

We submitted single subject time series data to a first-level general linear statistical model (GLM). Using the SPM design specification, we convolved the task-specific boxcar stimulus functions with the canonical hemodynamic response function (HRF). Each model included within-session global scaling (default), high-pass filtering using a cutoff frequency set at 1/128 Hz, and the AR1 method of estimating temporal autocorrelation. We created regressors by convolving box-car functions with a canonical hemodynamic response function (HRF) with trial durations set to 1000 ms for the Combined Go/No-Go and Stop-signal task, and 3000 ms for the Think/No-Think task. For the Think/No-Think task, we modelled Non-Intrusion, Intrusion and Think trials as separate regressors, as well as context fillers and unlearned items. For the Combined Go/No-Go and Stop-signal trials, we modelled correct and incorrect trials for the Go, Concurrent Stop, and Delayed Stop conditions as separate regressors. The six motion parameters produced at realignment were included in the model to account for linear residual motion artefacts.

The above analyses were performed on native space images. We then transformed the contrast-images produced from the first-level analyses to MNI space for subsequent group-level analyses. The transformation was achieved using the parameters derived from the nonlinear normalisation of individual gray-matter T1 images to the T1 template of the Montreal Neurological Institute (MNI, Montreal). The normalised contrast images were spatially smoothed using a 6-mm FWHM Gaussian kernel.

5.1.5.3 Dynamic Causal Modelling (DCM)

To test how the putative supramodal regions (DLPFC and basal ganglia) effectively interact with task specific regions (M1 for motor inhibition and hippocampus for memory inhibition), we modelled the effective connectivity between these four regions using DCM12. DCM allows for the estimation of the causal relationship between the pre-specified regions of interest given the specific task context and the underlying anatomical connections (Friston et al., 2003). It is worth noting that modelling interactions between regions does not necessarily suggest that the connectivity is

underpinned by monosynaptic connections. Rather, the resulting coupling parameters represent the effective connectivity between these regions, which may well be substantiated by a relay of connections.

We constructed separate but identical DCM model structures for the memory and motor tasks, with the No-Think and Stop conditions as modulatory inputs respectively. For each subject, we extracted signal from the putative supramodal regions (DLPFC and basal ganglia) and the task specific regions (M1 and hippocampus). Details for defining these ROIs will be provided in the next section.

First, we investigated whether the basal ganglia, the DLPFC or both are involved in memory and motor inhibition, modulating the task-preferred pathways (Figure 5.1). We used bilinear DCM analysis that requires three types of input for each model: (1) Intrinsic connections (based on hypothesized mono- and poly-synaptic connections between the nodes), (2) bilinear modulation of connections by experimental conditions, and (3) driving inputs into nodes from experimental conditions. For both the memory and motor DCMs, we specified bidirectional Task independent connectivity between each pair of the ROIs except between the hippocampus and M1. For the memory inhibition DCM, we specified that the Non-intrusion and Intrusion conditions could be modulating the connectivity between the putative supramodal regions (DLPFC, basal ganglia, or both) and the task-specific regions (M1, hippocampus, or both) in a top-down fashion. For the motor inhibition DCM, we specified similar modulations but with the Concurrent Stop and Delayed Stop conditions. We only tested models with top-down modulations based on previous DCM results. For example, Benoit et al. (2014) compared models containing bottom-up, top-down, and bidirection task modulations between the DLPFC and the hippocampus during memory inhibition. While the bottom-up models won little evidence, BMS was unable to differentiate between the top-down and bidirectional models, suggesting that it may be the top-down modulations that are primarily influencing the network dynamic for achieving inhibitory control. Finally, the driving inputs were going into both the DLPFC and the basal ganglia for all models. Overall, we had a model space of nine models for the memory and motor inhibition DCMs separately.

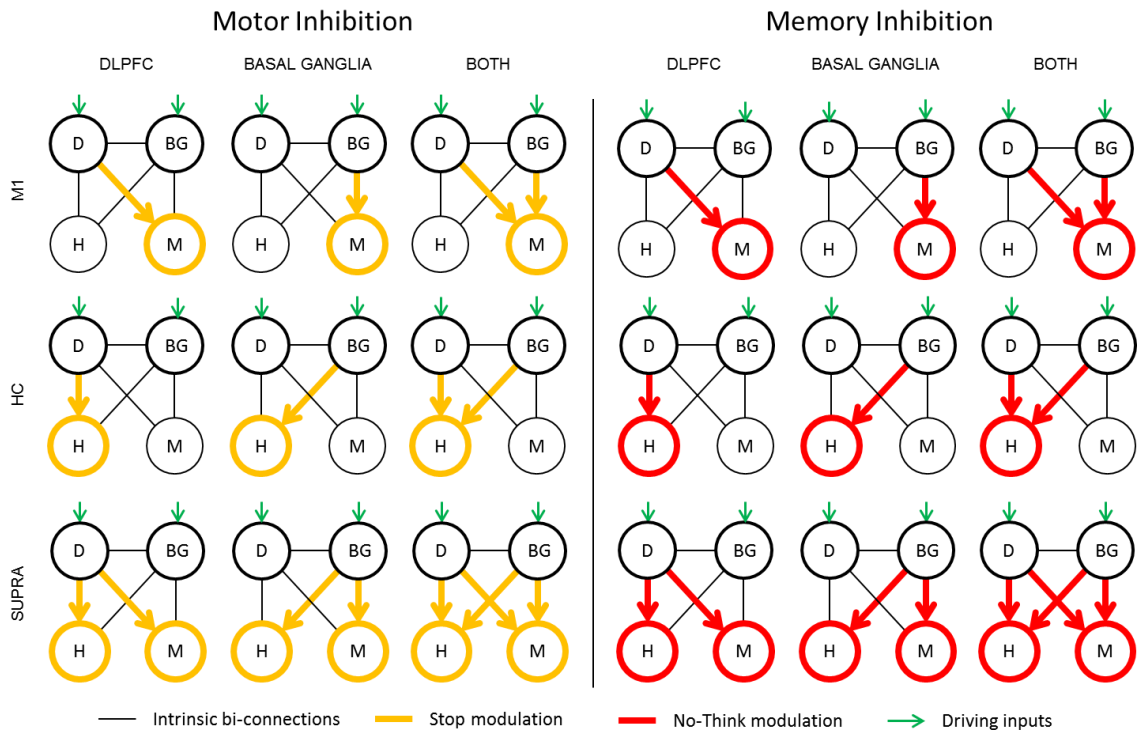

Figure 5.1. Step 1 DCM Model Space for Memory and Motor Inhibition. D=DLPFC; BG=basal ganglia; H=hippocampus; M=M1.

Second, we examined how the supramodal regions (DLPFC and basal ganglia) interact to achieve inhibition in the task-specific regions (Figure 5.2). On one hand, it could be that one supramodal region is influencing the other, which then modulates activity in the task specific regions. For example, according to our intermediary hypothesis, the basal ganglia may process commands from the PFC and pass them on to the hippocampus or M1. Alternatively, according to our indirect hypothesis, the basal ganglia may interact with the hippocampus and M1 through the PFC. On the other hand, it could be that one supramodal regions is influencing the pathway through which the other communicates with the task-specific regions. According to our modulation hypothesis, the basal ganglia may modulate the connectivity between the PFC and the task-specific regions to achieve inhibition. We used nonlinear DCM analysis to test the modulation hypothesis, for which we had to specify nonlinear modulation of connections in addition to those required by the bilinear DCM.

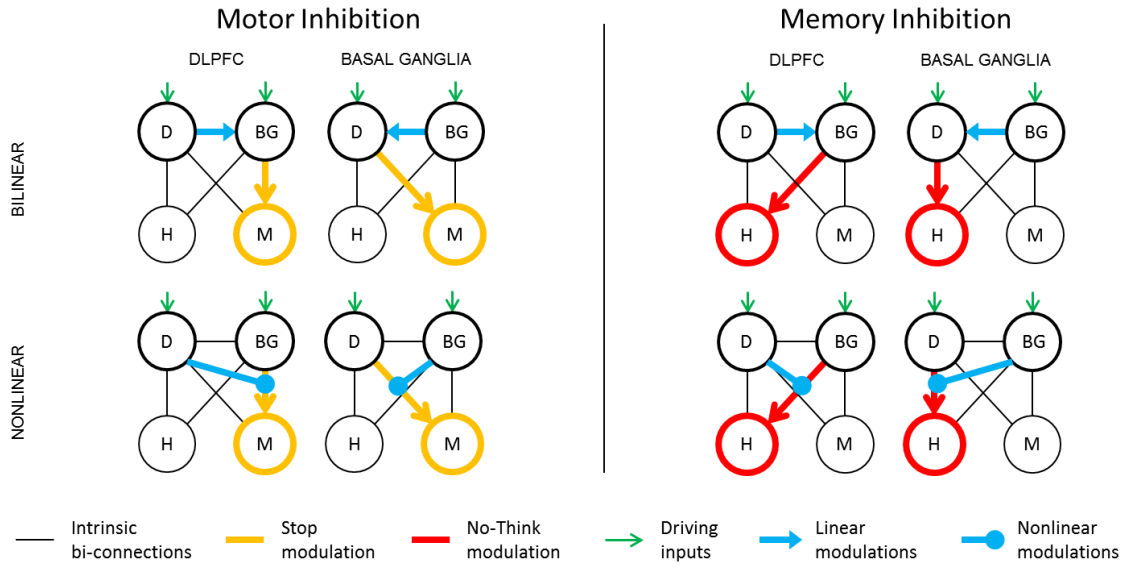

Figure 5.2. Step 2 DCM Model Space for Memory and Motor Inhibition. D=DLPFC; BG=basal ganglia; H=hippocampus; M=M1.

Model fitting was achieved by adjusting the model parameters to maximise the free-energy estimate of the model evidence. Neural activity from each node was extracted and Bayesian model selection (BMS) was then used to identify the family that could account the best for the data (Penny, 2010). A random-effects approach was taken, since it does not assume that the optimal model will be the best for each individual (Stephan, 2010). Model evidence in the BMS is represented by exceedance probability, i.e., the probability to which a given model is more likely than any other included model to have generated the data from a randomly selected participant.

Furthermore, to examine the contribution of prevention and cancellation processes in memory and motor inhibition, we extracted DCM coupling parameters on the task independent and task-modulated pathways from the relevant conditions (Non-intrusion and Concurrent Stop for prevention; Intrusion and Delayed Stop for cancellation). We first used one-sample *t*-tests to examine if the coupling parameters are significantly different from zero. We then used ANOVAs to test whether there were significant differences in the coupling parameters due to pathway (top-down control from the DLPFC or the basal ganglia) or inhibitory subprocess (prevention or cancellation) in the memory and motor domains.

5.1.5.4 Defining Regions of interest

We defined four distinct *a priori* regions of interest (ROI), the right DLPFC, right basal ganglia, left hippocampus, and the left M1. For the DLPFC ROI, we first derived a binarised map of the (No-Think & Stop) > (Think & Go) contrast in Schmitz et al. (in preparation). We then isolated from this map the DLPFC cluster, which centred on the following MNI coordinates: x=33, y=41, z=21. For each participant, the DLPFC ROI was transformed into native space using the deformation field produced at the non-linear warping step of their fMRI data pre-processing. For the basal ganglia ROI, we combined the manual segmentation of the caudate head, caudate body, and putamen regions from the meta-analysis with the GPe ROI from the ATAG atlas (Chapter 3.2). We transformed the combined ROI into native space using similar methods. For both the DLPFC and the basal ganglia, we extracted the 40% signal of activity from the No-Think>Think contrast for the memory DCM, and from the Stop>Go contrast for the motor DCM. For the Hippocampus ROI, we used the AAL template from SPM (Yushkevich et al. 2006). Finally for the M1 ROI, we derived a binarised map of the ButtonPress>View contrast from the group analyses of our independent functional localiser task, isolated the left M1 cluster (centring at x=-42, y=-25, z=49), and transformed the cluster into native pace. For both the hippocampus and M1, we extracted the 40% signal of activity from the Think>No-Think contrast for the memory DCM, and from the Go>Stop contrast for the motor DCM.

5.2 Results

5.2.1 Behavioural Results

5.2.1.1 Logistic Regression Revealed Significant Effect of SIF

For the Think/No-Think task, according to the criterion test, participants reached on average 84% of accuracy in recalling the word pairs. Recall performance on the final tests were conditionalised by excluding items that were not initially learned, to ensure that variations in recall across conditions reflect the effects of our manipulations on demonstrably learned items. The descriptive statistics for the suppression and facilitations cores and the SSRTs are summarised in Table 5.1.

The ESD test suggested there was one outlier participant who had extraordinary facilitation and suppression scores in the Same Probe test (Table 5.1). Since our analyses used combined suppression scores where no outliers were identified, we included all 30 participants in our analyses (Male=13; *Mean Age* = 22.83 years; *SD Age* = 3.54 years).

	Suppression			Facilitation			SSRT
	SP	IP	Combined	SP	IP	Combined	
Mean	1.6%	10.7%	6.1%	0.3%	-9.2%	-4.4%	464.87
SD	12%	23%	13.4%	15.3%	23.3%	13.2%	41.98
No. of Outliers	1	0	0	1	0	0	0

Table 5.1 Descriptive Statistics of the Suppression and Facilitation Scores from the Think/No-Think Task, and the Stop-signal Reaction Time (SSRT) from the Combined Go/No-Go and Stop-Signal Tasks (N=30).

According to our logistic regression analysis combining the Same Probe and Independent Probe tests (N=30), we found a significant effect of memory inhibition between the No-Think and Baseline items (Log Likelihood=- 708.3, p=.04), as well as a significant effect of memory facilitation between the Think and the Baseline items (Log Likelihood=- 688.6, p=.01). These results replicated the SIF and facilitation effects from the literature (e.g. Anderson & Green, 2001; Anderson et al., 2004).

5.2.1.2 Rate of Intrusion Reduction Significantly Correlated with SIF

In addition to the suppression and facilitation effects, we examined the change in intrusion frequency throughout the Think/No-Think phase by calculating the percentage of items that participants rated as "having come into mind" during the No-Think trials. We found a significant reduction of intrusions from the first to the tenth repetition $t(29)=6.49$, $p<.001$, and fitted a linear function that describes the reduction of intrusions over the Think/No-Think phase (Figure 5.3a). Next, we quantified the rate of intrusion reduction by calculating the slope of the linear fitting function from each individual, taking into account the initial amount of intrusions they experienced in the first

repetition in the Think/No-Think phase (Levy & Anderson, 2012). On average, participants experienced 5% reduction of intrusion over each repetition in the Think/No-Think phase (*SD*=5%).

Critically, a Pearson correlation revealed that the slope of intrusion reduction significantly correlated with SIF (as measured by the combined suppression score between the Same Probe and Independent Probe tests), *r*=-0.36, *p*=.05 (Figure 5.3b). This significant correlation indicates that higher ability to suppress unwanted thoughts is associated with greater reduction of intrusions (a negative value of the slope indicates reduction of intrusion, while a positive value indicates increment of intrusion). These results suggest that individuals with higher ability at thought suppression are better at reducing intrusions, possibly engaging the cancellation processes in the brain.

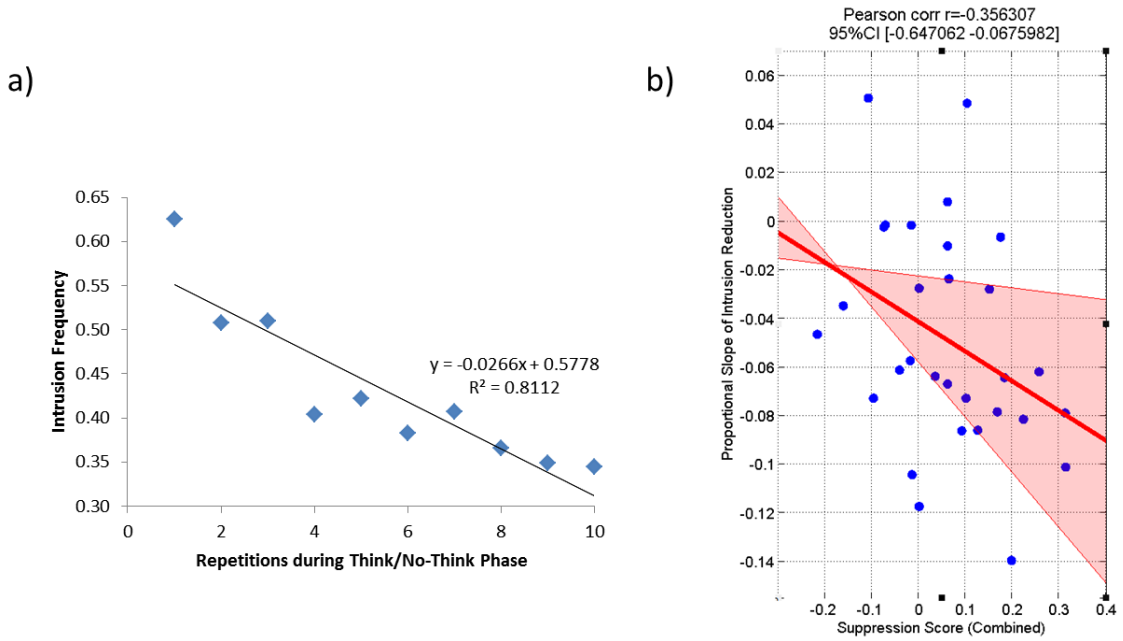

Figure 5.3. A) Reduction of Intrusions over the Think/No-Think Phase; B) Pearson Correlation between Slope of Intrusion Reduction and SIF.

5.2.1.3 RT for Intrusion Rating is Shortest for Think, Followed by Intrusion and Non-intrusion

In addition to testing the SIF effect and how that is associated with intrusion reduction, we examined whether there were differences in RT for the intrusion ratings that participants were required to give after each trial in the Think/No-Think phase (Figure

5.4). This may provide insight into how different thought control processes during the Think, Non-intrusion, and Intrusion conditions may influence subsequent motor responses. Overall, we observed a significant reduction of RT when comparing between the first and the tenth repetitions in all conditions (Think: $t(29)=19.63$, $p<.001$; Intrusion: $t(29)=18.45$, $p<.001$; Non-intrusion: $t(29)=24.32$, $p<.001$). This reduction of RT possibly indicates that participants are getting better at both the button pressing and the metacognition of their experiences during the past trial. Critically, using a repeated-measure ANOVA, we found a significant main effect of RT across conditions, $F(2,18)=32.42$, $p<.001$. Specifically, the Think condition generated a significantly faster RT than the Intrusion condition, $t(9)=3.98$, $p=.003$, which in turn generated a significantly faster RT than the Non-intrusion condition, $t(9)=5.08$, $p=.001$.

There may be two interpretations for the differences in RT across conditions. First, the difference in RT may simply be a by-product from when participants decided on their intrusion ratings for a given trial. For instance, during a Think trial, participants may be able to decide whether a target had come into might very early on in the trial, and would be ready to press a button as soon as the intrusion rating showed up. For most Think trials, they would know whether they still remembered the target straight away. Meanwhile, during an Intrusion trial, if the intrusion popped into their mind as soon as they saw the cue, it would be similar to a Think trial and they would be able to respond to the intrusion rating very quickly. However, if the intrusion only took place later in the trial, they may only be able to press a button at a delay, since they possibly needed a similar amount of time to prepare for the button press. Finally, for a Non-intrusion trial, participants would have had to wait until the end of the trial to be sure that the target did not come into mind, and then start the motor response. Hence the RT for Non-intrusion trials may appear longer.

An alternative interpretation is that the different thought processes required during the Think, Intrusion, and Non-intrusion trials may create different impacts on the subsequent motor responses. The impacts may be related to the congruency between the control process required during the trial and that required for the intrusion rating. For example, during a Think condition, participants were instructed to respond to the cue and recall the associated target. This is congruent with the intrusion ratings, where participants also had to respond by pressing a button. In contrast, during a No-Think

trial, participants were instructed to inhibit the associated target until trial offset. This is incongruent with the subsequent response. If we believe that memory and motor control may require similar neural mechanisms, inhibiting those mechanisms in memory may make it harder to subsequently initiate a motor response. A similar idea has been tested within the memory domain. Hulbert et al. (2016) adapted the Think/No-Think paradigm and occasionally inserted unrelated stimuli in between the Think and No-Think trials. They later tested participants on their memories of the unrelated stimuli, and found that they had reduced memories for the unrelated stimuli surrounded by No-Think trials than those surrounded by Think trials. This is evidence showing that engaging suppression mechanisms for specific items may create a more general effect on the memory system, which can impair new learning. In the current study, we observed a possibility that engaging suppression mechanisms in one modality may create a more general effect on other tasks that require similar mechanisms. Future studies could test this hypothesis in a supramodal context, and investigate whether inhibition in one domain can influence performance in a different domain.

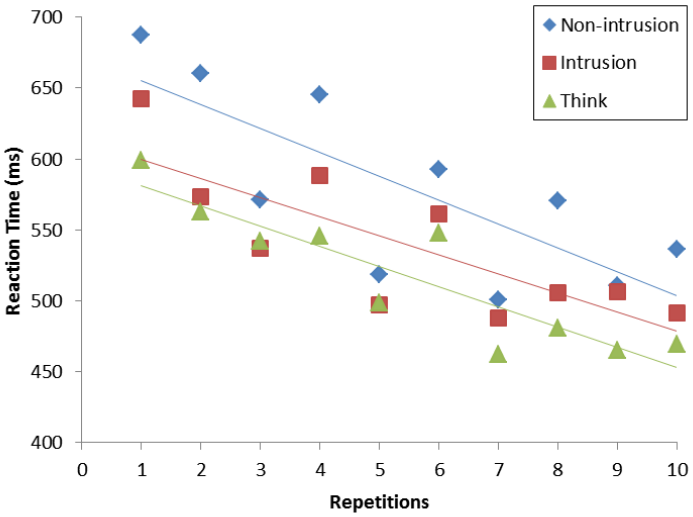

Figure 5.4. RT for Intrusion Ratings during the Think, Non-intrusion, and Intrusion Conditions.

5.2.1.4 Blocked Integration Produced Average SSRT for Each Participant

Using the blocked integration method based on the independent race model, we estimated the mean SSRT for each individual (*Mean* = 464.87 ms; *SD* = 41.98 ms). Our SSRT seems to be much longer than previously established SSRTs in other studies, such as 266 ms in Aron et al. (2007), and 223 ms in Zheng et al. (2008). This longer SSRT may be caused by three main factors. First, our Combined Go/No-Go and Stop signal task has a more complicated design than most standard Stop-signal tasks. Most Stop-signal paradigms have simple stimulus-response mappings, where participants only need to interact with one button (Zheng et al., 2008) or the left/right arrow keys when seeing left/right arrows on the screen (Aron et al., 2007). However, our current design involves mapping four coloured circles on two buttons. Although participants were trained with the colour mapping extensively before performing the task in the scanner, when they saw a coloured circle on the screen, they may still need to recall which button the colour circle was associated with, prolonging the RT and hence the SSRT. In the current study, average Go RT is 737.67 ms (SD=56.62 ms). In Aron et al. (2007) and Zheng et al. (2008), the Go RT is 465 ms (SD=85 ms) and 369.8 ms (DF=75.4 ms), respectively. Second, in order to measure the effect of stopping compared to baseline, we jittered the duration of the inter-stimulus interval (ISI). Introducing a jittering ISI increased the uncertainty of stimulus onset and may make the participants less prepared for the upcoming trial. In consequence, participants may found it harder to respond to the Go trials, prolonging RT and hence the SSRT. Finally, it is possible that participants purposefully slowed their responses during Stop trials to increase their chances of correctly withholding a button press. However, this is unlikely as our tracking algorithm for the Stop trials successfully differentiated stopping accuracy for different SSDs (88% for the 250 ms SSD, 56% for the 500 ms SSD, and 39% for the long SSD).

In order to examine whether the ability to stop memory retrieval is associated with the ability to stop motor actions, we used Pearson correlation to relate the average SSRT from each individual to their magnitude of SIF (combined between the Same Probe and Independent Probe tests). Unfortunately, this correlation was not significant (r=-0.09). This lack of relationship between memory and motor inhibition may be due to the

individual variability in the behavioural performance, as previous studies have found significant correlations between SIF and SSRT (e.g., Schmitz et al., in preparation).

5.2.2 FMRI Univariate Results

5.2.2.1 Memory and Motor Inhibition Yielded Similar Activation Patterns as the Meta-analyses

Overall, our univariate fMRI findings resemble the activation patterns from the meta-analyses from Chapter 3, both on the cortex and in the basal ganglia. Similar to previous studies, we also observed reduced activity in task-specific regions, such as the hippocampus for memory inhibition, and M1 for motor inhibition. We will present these findings in the following sections. All results were corrected to False Discovery Rate (FDR) $p<.05$.

5.2.2.1.1 Retrieval Suppression Engaged Lateral Prefrontal Cortex and the Basal Ganglia, and Reduced Hippocampal Activity

According to the meta-analysis, memory inhibition in the Think/No-Think yielded cortical activations in the right DLPFC, VLPFC, cingulate gyrus, precentral gyrus, and the supramarginal/angular gyrus. Our univariate analysis revealed similar results. We observed that inhibiting unwanted memories in the No-Think condition, relative to the Think condition, activated cortical regions including bilateral DLPFC (BA9/10/46), VLPFC (BA44/45/47/insula), preSMA (BA6/8), ACC (BA32), and supramarginal/angular gyrus in the inferior parietal lobe (Figure 5.5). These activations appeared to be more extensive in the right hemisphere than in the left. In addition, replicating previous findings from Levy and Anderson (2012) and Gagnepain et al., (2017), we observed reduced hippocampal activity during No-Think relative to baseline. According to previous DCM efforts (Benoit et al., 2014; Gagnepain et al., 2017), it is likely that this hippocampal downregulation originates from prefrontal control regions such as the DLPFC.

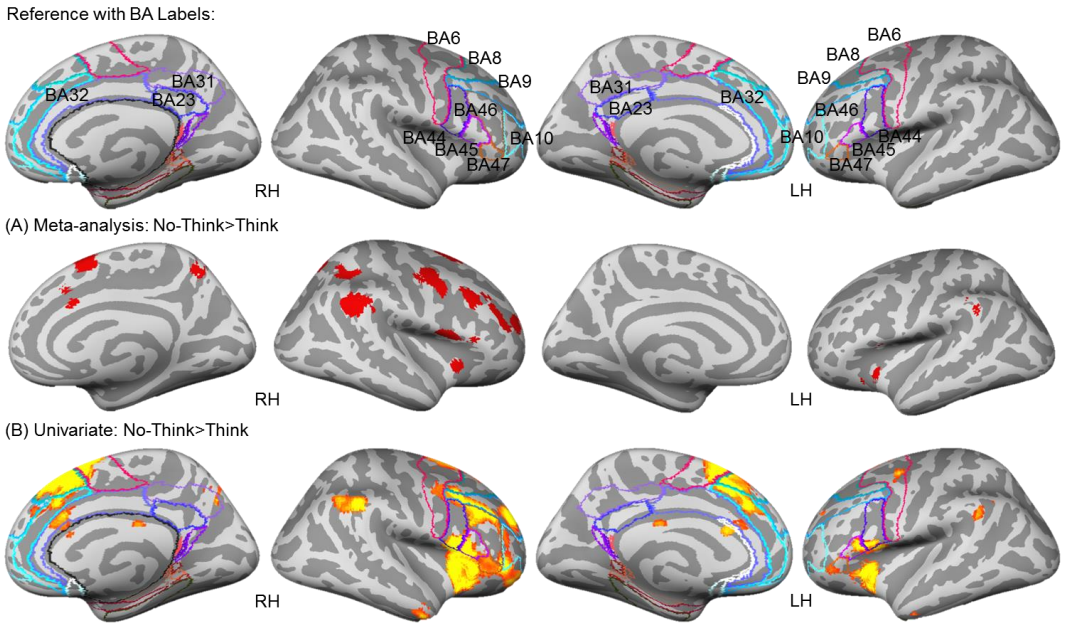

Figure 5.5. Cortical Activations from Memory Inhibition. The top row illustrates reference cortices overlaid with selected Brodmann areas. The bottom rows illustrate activation maps from A) the meta-analysis, B) our univariate analysis. All activations were thresholded to FDR *p*<.05.

On the subcortical level, the meta-analysis showed that memory inhibition activated the right basal ganglia, including caudate head, anterior putamen, and anterior GPe. We again replicated these findings, except that we observed these activations in both hemispheres (Figure 5.6). As we discussed in Chapter 3.4, although the original input to the meta-analysis had basal ganglia coordinates from both hemispheres, the output was only significant in the right hemisphere. It is possible that the ALE algorithm is more sensitive to clustering activities and may not best represent the authentic patterns of activation in the basal ganglia.

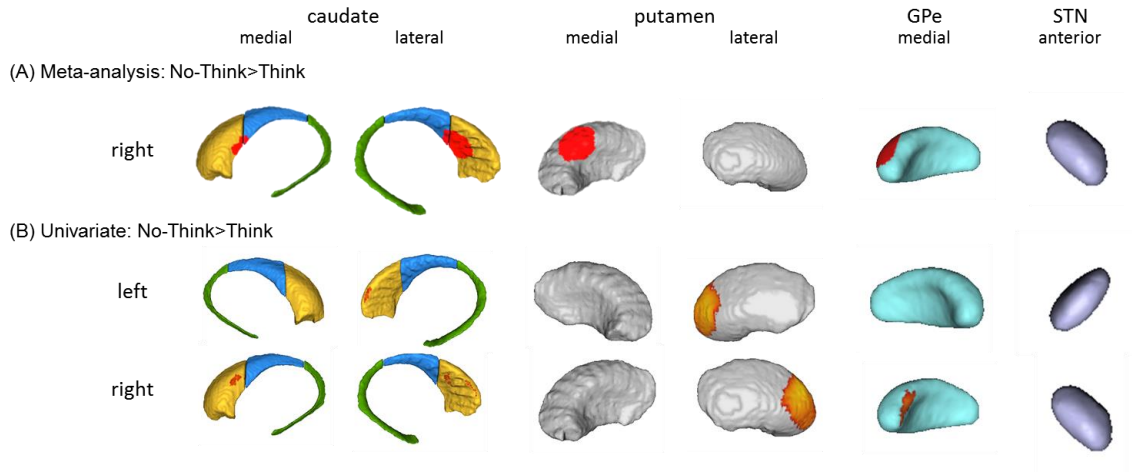

Figure 5.6. Basal Ganglia Activations from Memory Inhibition. The top row illustrates basal ganglia activations from the meta-analysis. The bottom row illustrates basal ganglia activations from the current univariate analysis. For the caudate structure, yellow is caudate head, blue is caudate body, and green is caudate tail. All activations were thresholded to FDR *p*<.05.

5.2.2.1.2 Motor Inhibition Engaged the Lateral Prefrontal Cortex and the Basal Ganglia, and Reduced M1 Activity

On the cortical level, our meta-analysis showed that stopping motor responses activated the DLPFC, VLPFC, and the supramarginal/angular gyrus primarily in the right hemisphere. Our univariate analysis replicated this pattern, and observed that the Stop condition, relative to the Go condition, yielded activations in the DLPFC(BA9/10/46), VLPFC (BA44/45/47/insula), preSMA (BA6/8), ACC (BA32), and supramarginal/angular gyrus (Figure 5.7). Consistent with Schmitz et al. (in preparation), we also observed reduced M1 activity during motor stopping relative to baseline. It is possible that the prefrontal cortex is exerting similar downregulation to M1 during motor inhibition as to the hippocampus during retrieval suppression.

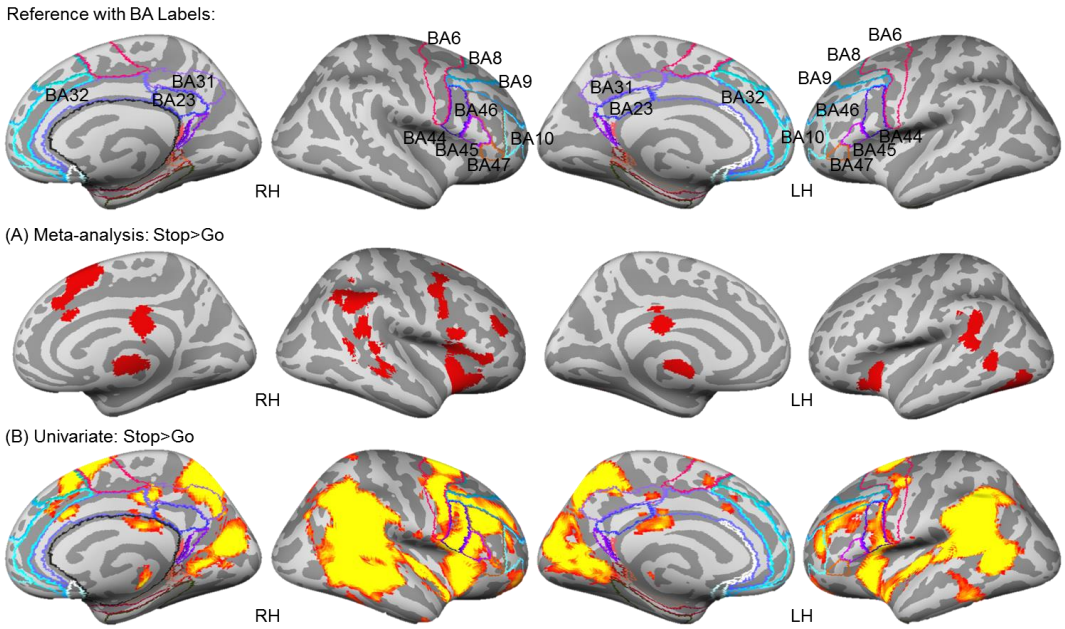

Figure 5.7. Cortical Activations from Motor Inhibition. The top row illustrates reference cortices overlaid with selected Brodmann areas. The bottom rows illustrate activation maps from A) the meta-analysis, B) our univariate analysis. All activations were thresholded to FDR *p*<.05.

In the basal ganglia, our meta-analysis showed that motor inhibition activated small regions of caudate head, anteromedial putamen, and anterior GPe. However, action cancellation activated the right basal ganglia, while action prevention activated the left basal ganglia, although the input coordinates were from both hemispheres. In our univariate analysis, we found similar activation pattern in both hemispheres, except that the putamen activity was from the lateral surface (Figure 5.8). This may be due to functional specialisation of different striatal subregions, as lateral putamen is typically associated with sensorimotor processes (Voorn et al., 2004; Yin et al., 2004).

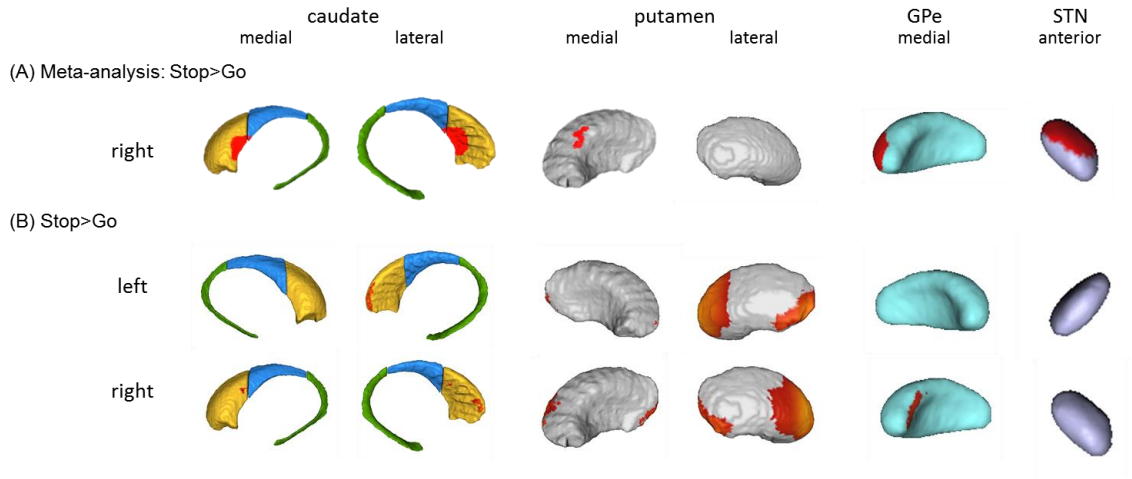

Figure 5.8. Basal Ganglia Activations from Motor Inhibition. The top row illustrates basal ganglia activations from the meta-analysis. The bottom row illustrates basal ganglia activations from the current univariate analysis. For the caudate structure, yellow is caudate head, blue is caudate body, and green is caudate tail. All activations were thresholded to FDR *p*<.05.

5.2.2.1.3 Memory and Motor Inhibition Share Prefrontal and Basal Ganglia Activations

We performed a conjunction analysis and revealed regions that were activated by both inhibiting thoughts and actions, including the right DLPFC (BA9/10/46), bilateral VLPFC (BA44/45/47/insula), SMA (BA6) and supramarginal/angular gyrus (Figure 5.9). These activations seemed to be more extensive in the right hemisphere. In the basal ganglia, we observed activations in bilateral caudate head, bilateral anterior putamen, and right anterior GPe (Figure 5.10).

This pattern of activation is largely consistent with our findings from the meta-analysis, again showing that memory and motor inhibition share neural mechanisms on both the cortical and basal ganglia levels. In particular, inhibiting retrieval and motor responses seem to engage right lateralised prefrontal activity. This agrees with previous emphasis on the role of the right DLPFC and VLPFC in memory and motor inhibition (e.g., Aron et al., 2007; 2014; Benoit et al., 2012; Schmitz et al., accepted). We also observed similar basal ganglia activation as in the meta-analysis. Although these activations seem to be slightly anterior to the meta-analysis cluster, is is still consistent with the executive functions region found by Haber et al. (2006).

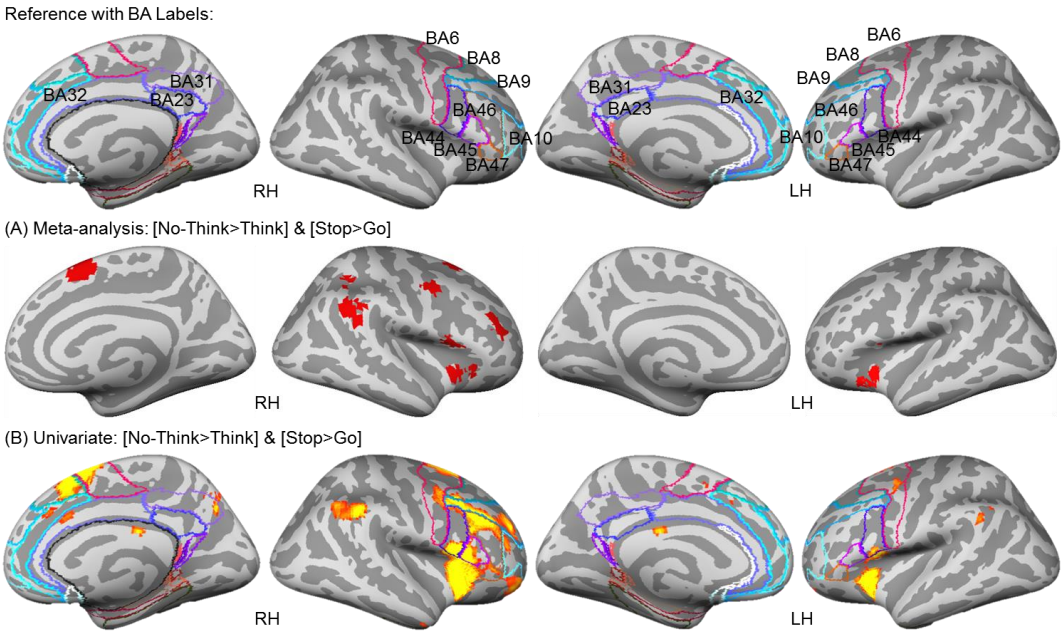

Figure 5.9. Cortical Activations from the Conjunction between Memory and Motor Inhibition. The top row illustrates reference cortices overlaid with selected Brodmann areas. The bottom rows illustrate activation maps from A) the meta-analysis, B) our univariate analysis. All activations were thresholded to FDR *p*<.05.

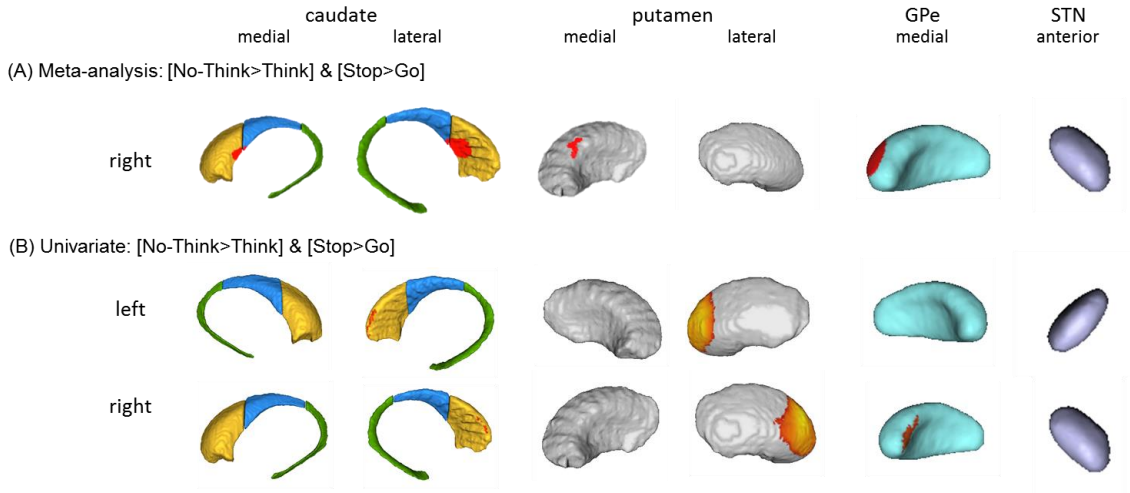

Figure 5.10. Basal Ganglia Activations from the Conjunction between Memory and Motor Inhibition. The top row illustrates basal ganglia activations from the meta-analysis. The bottom row illustrates basal ganglia activations from the current univariate analysis. For the caudate structure, yellow is caudate head, blue

is caudate body, and green is caudate tail. All activations were thresholded to FDR *p*<.05.

5.2.2.2 Preventing Memory Retrieval and Motor Actions Engaged Prefrontal and Basal Ganglia Activity Similar to the Meta-analysis

One of the objectives of the current project is to differentiate the neural mechanisms underlying specific inhibitory processes such as prevention and cancellation. As reviewed earlier, in memory inhibition, this distinction was drawn by whether participants experienced an intrusion of the unwanted memory during a No-Think trial. If they did not experience an intrusion, it is likely that the participants engaged proactive *prevention* processes so that memory retrieval would not take place at all. If they did experience intrusion, it is likely that they engaged reactive *cancellation* processes to push the emerging target out of mind. Similarly in the motor task, if participants succeeded at stopping on a Concurrent Stop trial, it is likely that they engaged *prevention* processes so that the motor response would not take place at all. If they succeeded at stopping on a Delayed Stop trial, it is like that they engaged *cancellation* processes to terminate a motor response that was already initiated when they saw the coloured circle. To examine the effect of prevention in memory and motor stopping, we first examined activations related to prevention in general using the prevention>response contrast. Following that, we isolated activations specific to prevention using the prevention>cancellation contrast. We will first present the results in the memory and motor domains separately, and then examine the conjunction for supramodal activations.

5.2.2.2.1 Preventing Memory Retrieval Generally Activated Bilateral Prefrontal Regions and the Basal Ganglia

During prevention of memory retrieval (Non-intrusion>Think), we observed activations in in a number of cortical regions (Figure 5.11a), including the DLPFC along the middle frontal gyrus (MiFG; BA9/10/46), VLPFC (BA44/45/47/insula), preSMA (BA6/8), and ACC (BA32) in both hemispheres. Preventing memory retrieval also activated bilateral supramarginal/angular gyrus and the left cerebellum. In the basal ganglia, retrieval prevention activated bilateral caudate head and body, anterior putamen and GPe (Figure

5.12a). This is the first time basal ganglia activity has been characterised for preventing unwanted memory retrievals.

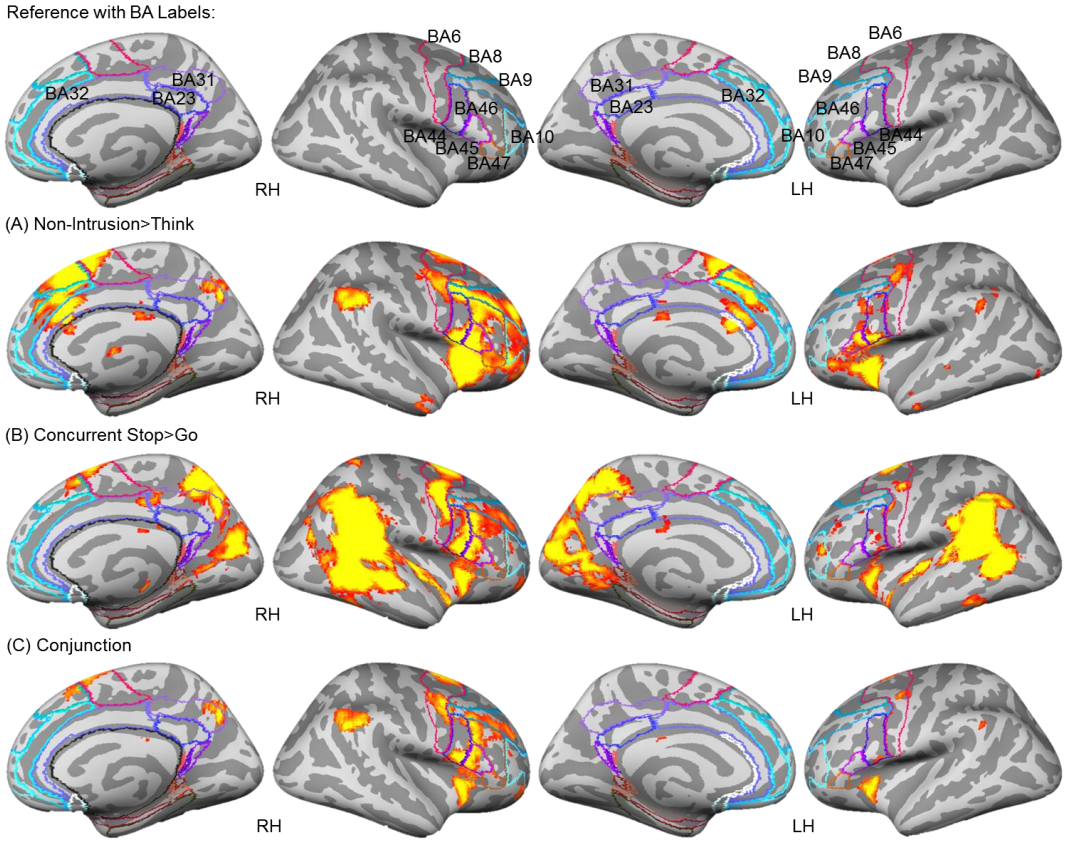

Figure 5.11. Cortical Activations from Prevention. The top row figures are reference cortices overlaid with selected Brodmann areas. The bottom rows illustrate regions activated by A) preventing memory retrieval, B) preventing motor responses, and C) both. All activations were thresholded to FDR *p*<.05.

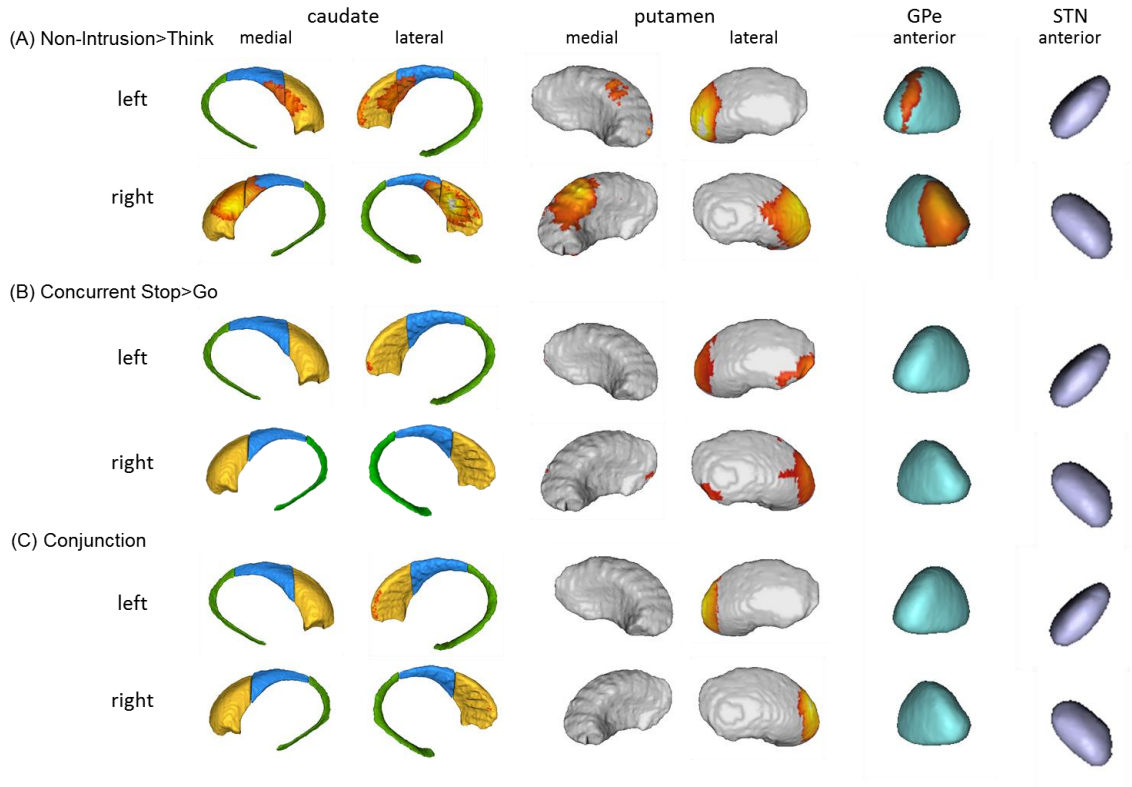

Figure 5.12. Basal ganglia activations during A) preventing memory retrieval, B) preventing motor responses, and C) both. For the caudate structure, yellow is caudate head, blue is caudate body, and green is caudate tail. All activations were thresholded to FDR *p*<.05.

5.2.2.2.2 Retrieval Prevention Activated Right DLPFC, Bilateral VLPFC, and Bilateral Basal Ganglia more than Retrieval Cancellation

To isolate neural mechanisms specific to retrieval prevention, we examined activations from the retrieval prevention>retrieval cancellation contrast. We observed increased activity in the right DLPFC, bilateral VLPFC (BA44/45/insula), precentral gyrus (BA6/8) and cingulate gyrus. Retrieval prevention also activated the precuneus, thalamus, the visual cortex, lateral temporal cortex, fusiform gyrus, and the cerebellum (Figure 5.13a).

In the basal ganglia, retrieval prevention activated bilateral caudate head and body, anterior putamen, and anterior GPe more than cancellation (Figure 5.14a). These activations coincide with the basal ganglia clusters from the meta-analysis. Since the

meta-analysis was investigating the basal ganglia involvement in memory inhibition in general, our results suggest two possibilities. First, retrieval prevention is essential for achieving SIF. Second, the basal ganglia involvement in memory suppression is predominantly preventing unwanted retrievals. We will use effective connectivity to tackle these questions. Critically, according to primate anatomy,, these basal ganglia regions receive extensive inputs from the DLPFC (Haber et al., 2006) as part of the executive functions division in the cortico-basal ganglia loop. Therefore, the DLPFC and the basal ganglia may work together to achieve memory inhibition through prevention.

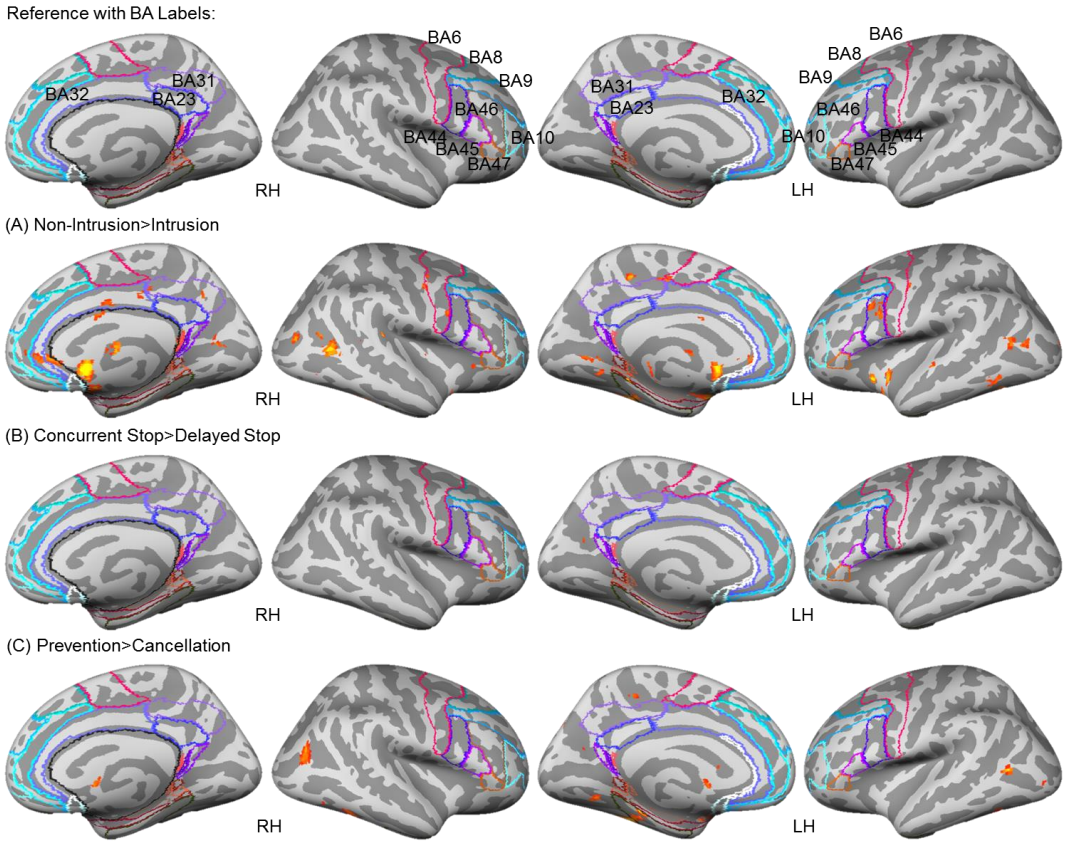

Figure 5.13. Cortical Activations Specific to Prevention. The top row figures are reference cortices overlaid with selected Brodmann areas. The bottom rows illustrate regions activated by A) preventing>cancelling memory retrieval, B) preventing>cancelling motor responses, and C) preventing retrieval and motor responses>cancelling retrieval and motor responses. All activations were thresholded to FDR *p*<.05.

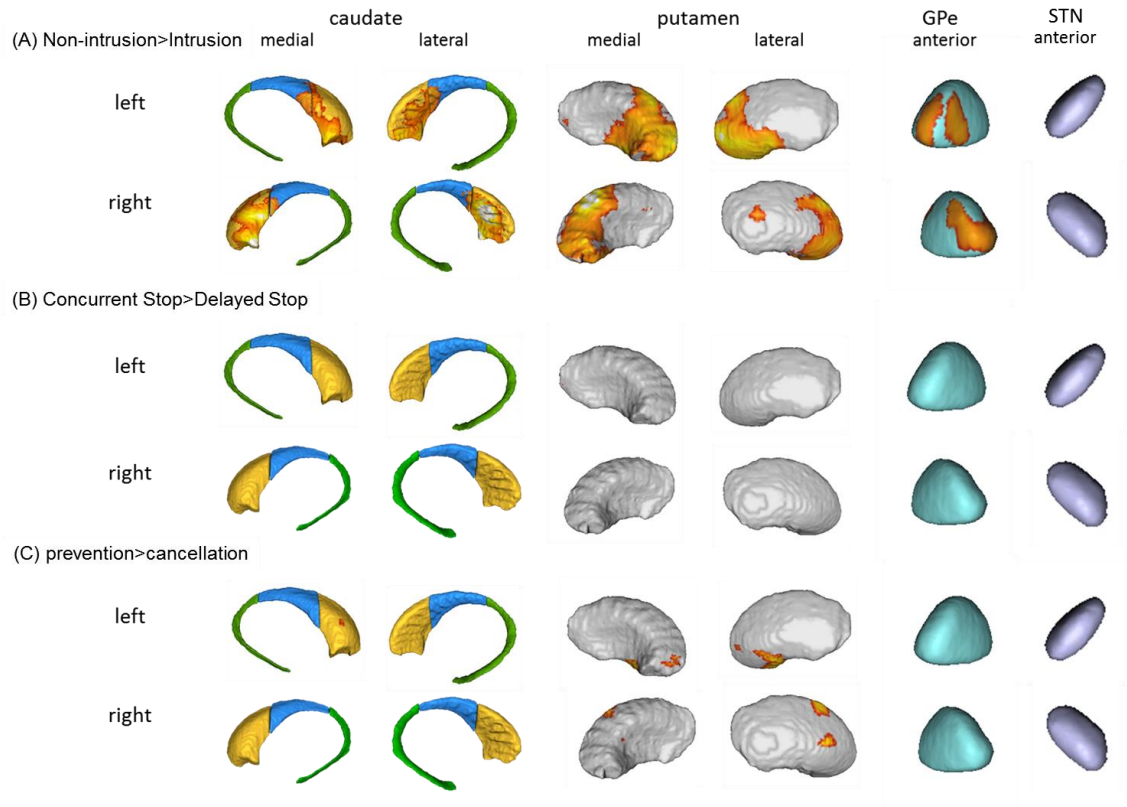

Figure 5.14. Basal ganglia activations specific to A) preventing memory retrieval, B) preventing motor responses, and C) preventing retrieval and motor responses>cancelling retrieval and motor responses. For the caudate structure, yellow is caudate head, blue is caudate body, and green is caudate tail. All activations were thresholded to FDR *p*<.05.

5.2.2.2.3 Preventing Motor Responses Generally Activated Similar Frontoparietal Regions as in the Meta-analysis, with some Presence of the Basal Ganglia

During prevention of motor responses (Concurrent Stop>Go), we observed similar increased activity in the frontoparietal regions (including the DLPFC, VLPFC, and supramarginal/angular gyrus), as well as the right lateral putamen, visual cortices, and the cerebellum (Figure 5.11b; Figure 5.12b). Although the cortical activations are similar to those from the meta-analysis, the basal ganglia activation is more lateral and bilateral, as opposed to the centromedial striatum in the left hemisphere. As discussed earlier, the meta-analysis may not be the most representative of basal ganglia activations due to limitations in the method. By activating lateral putamen, motor prevention may

be engaging the sensorimotor loop in the basal ganglia system. Alternatively, it is possible that the basal ganglia are particularly involved in preventing motor actions, in a similar way as to preventing memory retrievals.

5.2.2.2.4 Motor Prevention did not Activate Prefrontal or Basal Ganglia Regions more than Motor Cancellation

On the cortical level, action prevention activated these regions more than action cancellation, including the right medial temporal lobe and postcentral gyrus, as well as the left parahippocampal gyrus and visual cortex (Figure 5.13b). We did not observe prefrontal or basal ganglia activation for this contrast (Figure 5.14b). According to the simple contrasts that we reported previously, motor cancellation and motor prevention seemed to have activated very similar regions in the DLPFC, VLPFC, and basal ganglia. This is the case even when we lowered the significance threshold to uncorrected $p<.001$. It is possible that cancellation and prevention processes are more alike in the motor domain, making it hard to differentiate the control processes. Another possibility is that prevention and cancellation processes may not be as distinctive as we assumed in the Concurrent and Delayed Stop conditions. For example, on a Concurrent Stop trial, participants might have been preparing for a motor response prior to trial onset, but instead had to cancel that response when hearing the stop signal. On a Delayed Stop trial, due to the relatively long RT in the current experiment, participants might still be deciding which button they should press when hearing the stop signal instead of actually making the button press. In that case, no cancellation would be needed.

Specific to the basal ganglia, it is possible that the basal ganglia play similar roles in motor cancellation and motor prevention, since no differences were detected on a univariate level. However, it may be that cancellation and prevention engage different basal ganglia pathways, even though the overall activations seem identical. While cancellation is primarily associated with interactions between the direct and indirect pathways, prevention is more associated with the hyperdirect and indirect pathways (Schroll & Hamker, 2013). Finally, the similarity between motor prevention and motor cancellation may be due to individual differences in their ability and strategy to inhibit prepotent responses. Future studies could look into characterising differences between

"preventers" and "cancellers", and examine how that affects their inhibitory control overall.

5.2.2.2.5 Retrieval and Motor Prevention Activated Predominantly Right Frontoparietal and Basal Ganglia Regions

A conjunction between memory and motor prevention revealed activations primarily in the right frontoparietal regions, including the DLPFC, VLPFC, preSMA, the supramarginal/angular gyrus, caudate head and anterior putamen. There were fewer activations in the left hemisphere, including only small clusters in posterior MFG (BA6), VLPFC (BA44/insula), and the supramarginal gyrus (Figure 5.11c; Figure 5.12c). These results suggest that there may be supramodal mechanisms underlying retrieval and motor prevention. This supramodal network overlaps with the meta-analysis, involving both cortical regions in the DLPFC, VLPFC, preSMA and the supramarginal gyrus, and basal ganglia regions including the caudate head and anterior putamen. This is evidence that prevention processes may be an integral part of inhibitory control.

5.2.2.2.6 Prevention did not activate the Frontoparietal and Basal Ganglia Regions more than Cancellation

Finally, we tested the main effect of prevention>cancellation across the memory and motor domains. We used the contrast [Non-intrusion & Concurrent Stop]>[Intrusion & Delayed Stop], and found that action/thought prevention activated bilateral putamen, parahippocampal gyrus, and visual cortices, along with regions in the temporal cortex and the fusiform gyrus (Figure 5.13c; Figure 5.14c). It is worth noting that the putamen activation was primarily from retrieval prevention rather than motor prevention. This lack of overlap may be due to our findings in the motor task, where prevention and cancellation processes seemed to recruit similar control regions. These results indicate that while the basal ganglia are clearly involved in both prevention and cancellation processes across the memory and motor domains, they may be more involved in retrieval prevention than motor prevention in a specific way. Alternatively, it is possible that motor prevention and cancellation recruit different basal ganglia pathways, which may not be detectable by univariate analyses. Future studies could look into differentiating how different basal ganglia pathways are involved in prevention and

cancellation processes during memory and motor inhibition, either through animal electrophysiology, or possibly high-field fMRI.

5.2.2.3 Cancelling Memory Retrieval and Motor Actions Activated Frontoparietal Regions and the Basal Ganglia

To examine the effect of Cancellation in memory and motor stopping, we first examined activations related to cancellation in general using the cancellation>response contrast. Following that, we isolated activations specific to cancellation using the cancellation>prevention contrast. We will first present the results in the memory and motor domains separately, and then examine the conjunction for supramodal activations.

5.2.2.3.1 Retrieval Cancellation Activated Bilateral Frontoparietal Regions and Anterior Putamen

During cancellation of memory retrieval (Intrusion>Think), we observed increased activity in DLPFC (right BA9/46; left BA9), VLPFC (BA44/45/insula), supramaginal gyrus, (Figure 5.15.a). These activations were found in both hemispheres. In terms of the basal ganglia, we only observed activations in the anterior putamen bilaterally (Figure 5.16a). These activations are similar to those found in retrieval prevention but slightly restricted spatially. Compared to the meta-analysis findings, the putamen activations are more lateral, which are usually conceptualised as part of the motor functional loop (e.g., Haber & Knutson, 2010). On one hand, the lateral putamen activity may be induced by the motor components in both the memory and motor inhibition tasks, as they both involve button-press responses. On the other hand, this lateral putamen activity may also contribute to cognitive control functions (Koster et al., 2016), which may be less investigated in the literature.

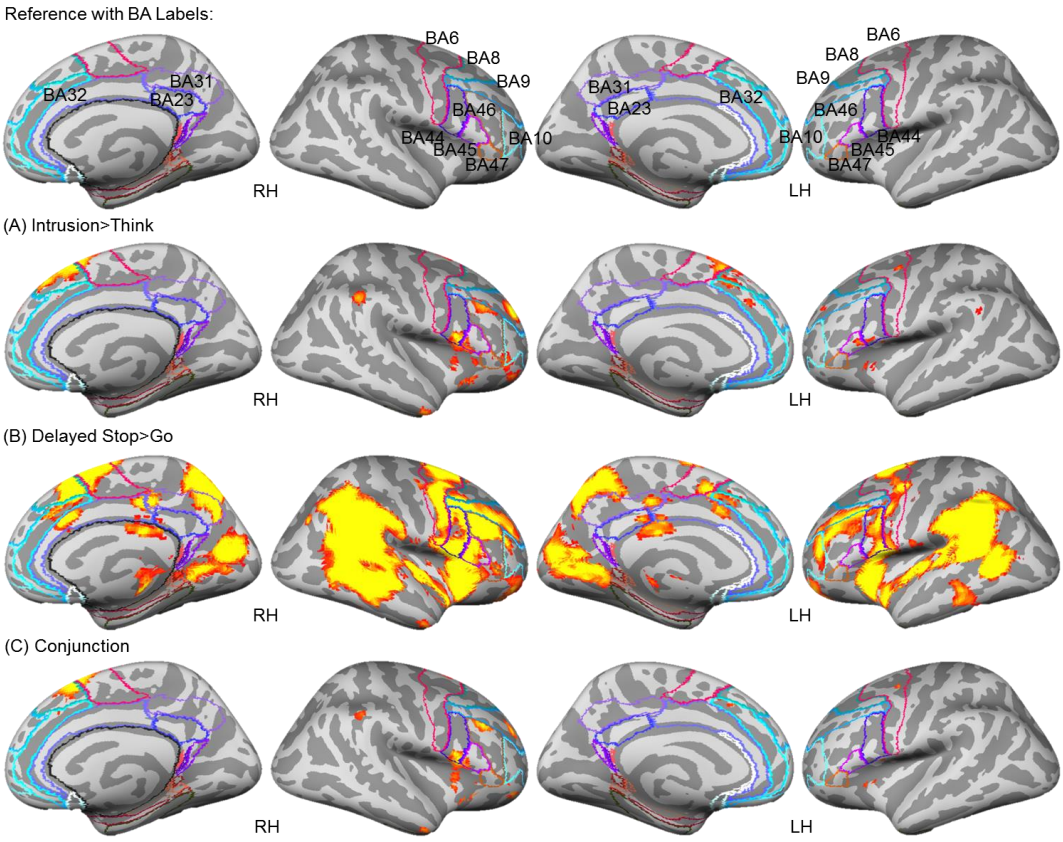

Figure 5.15. Cortical Activations from Cancellation. The top row figures are reference cortices overlaid with selected Brodmann areas. The bottom rows illustrate regions activated by A) cancelling memory retrieval, B) cancelling motor responses, and C) both. All activations were thresholded to FDR *p*<.05.

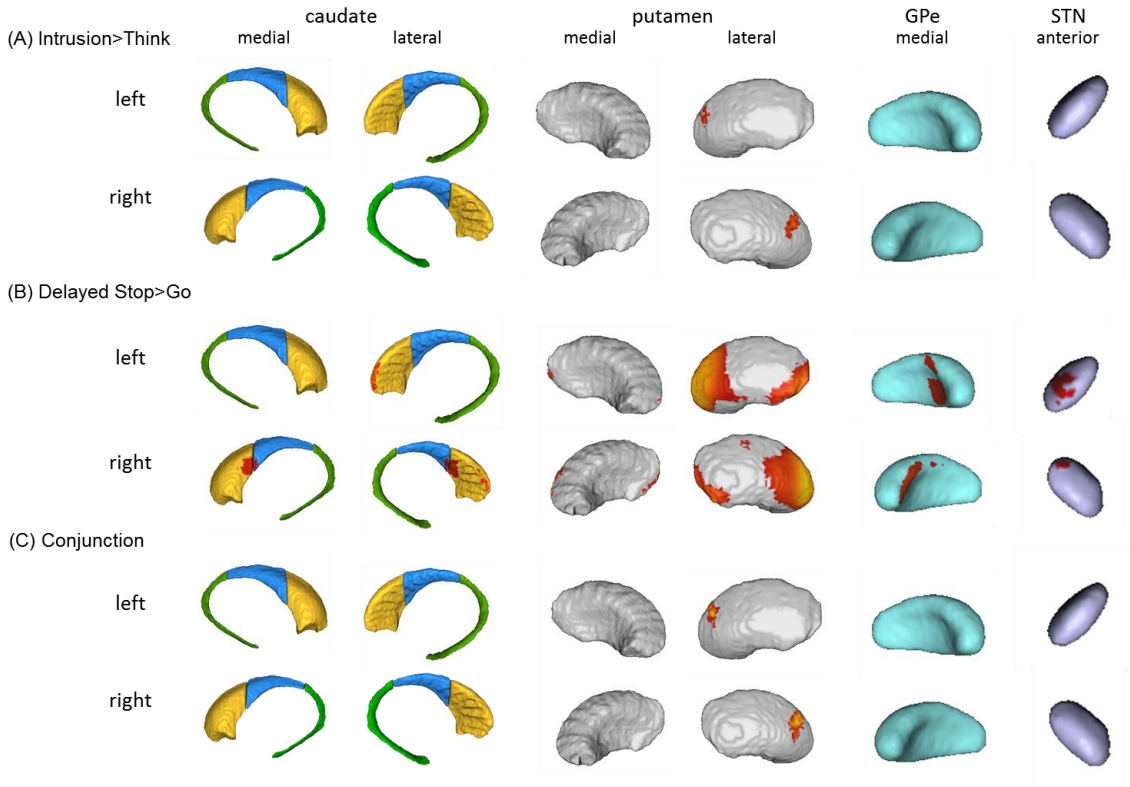

Figure 5.16. Basal ganglia activations during A) cancelling memory retrieval, B) cancelling motor responses, and C) both. For the caudate structure, yellow is caudate head, blue is caudate body, and green is caudate tail. All activations were thresholded to FDR *p*<.05.

5.2.2.3.2 Retrieval Cancellation Did not Yield more Activations than Retrieval Prevention

When we tried to isolate activations specific to retrieval cancellation through the retrieval cancellation>retrieval prevention contrast, we did not find any significant clusters (Figure 5.17a; Figure 5.18a). There could be a few explanations for this observation. First, it could be that retrieval prevention and cancellation engage similar neural mechanisms. This is unlikely as we have presented prevention-specific activity relative cancellation in section 5.2.2.2.2. Second, it may be that the Intrusion and Non-intrusion trials did not distinctively reflect the cancellation and prevention processes, respectively. For example, although participants should ideally cancel an intrusion when an unwanted target came into mind, they might not always engage the cancellation process. During a Non-intrusion trial, apart from successfully preventing an unwanted

target from coming to mind, it is also possible that the participant has forgot the association and did not have to inhibit anything anymore. Finally, retrieval prevention and cancellation may engage specific basal ganglia pathways, which may be hard to detect with fMRI.

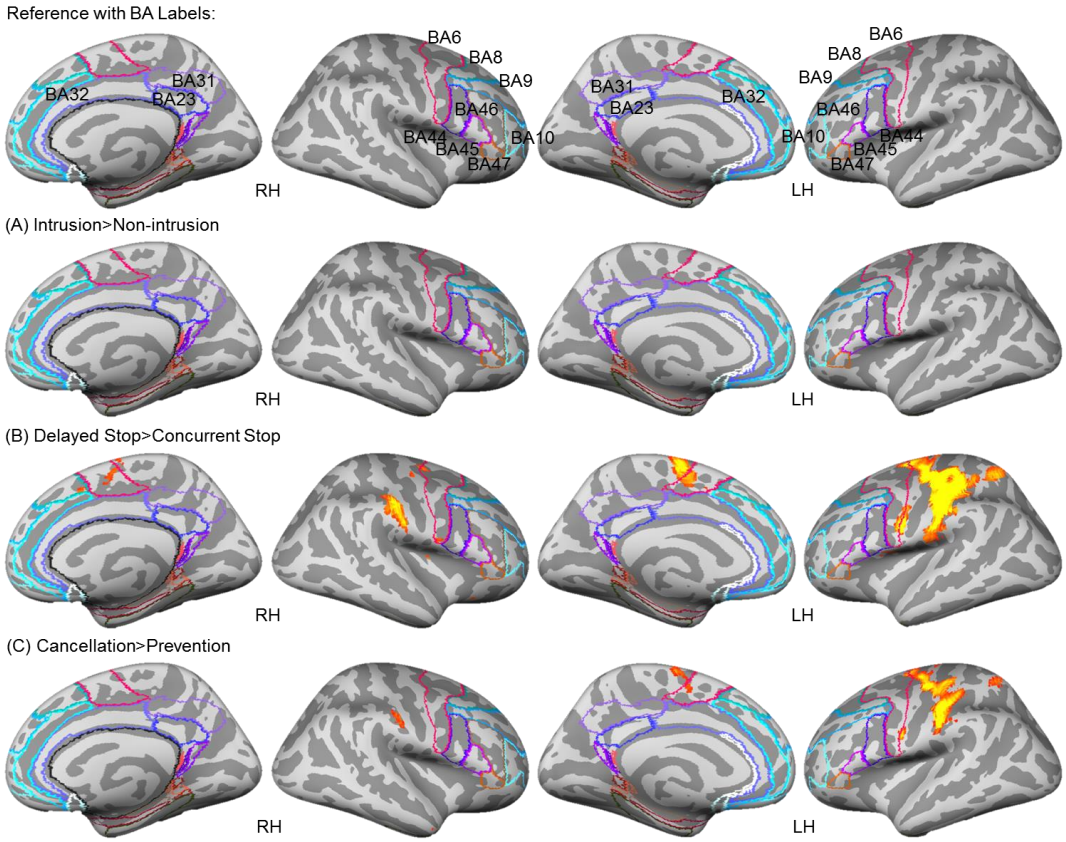

Figure 5.17. Cortical Activations Specific to Cancellation. The top row figures are reference cortices overlaid with selected Brodmann areas. The bottom rows illustrate regions activated by A) cancelling>preventing memory retrieval, B) cancelling>preventing motor responses, and C) cancelling retrieval and motor responses>preventing retrieval and motor responses. All activations were thresholded to FDR *p*<.05.

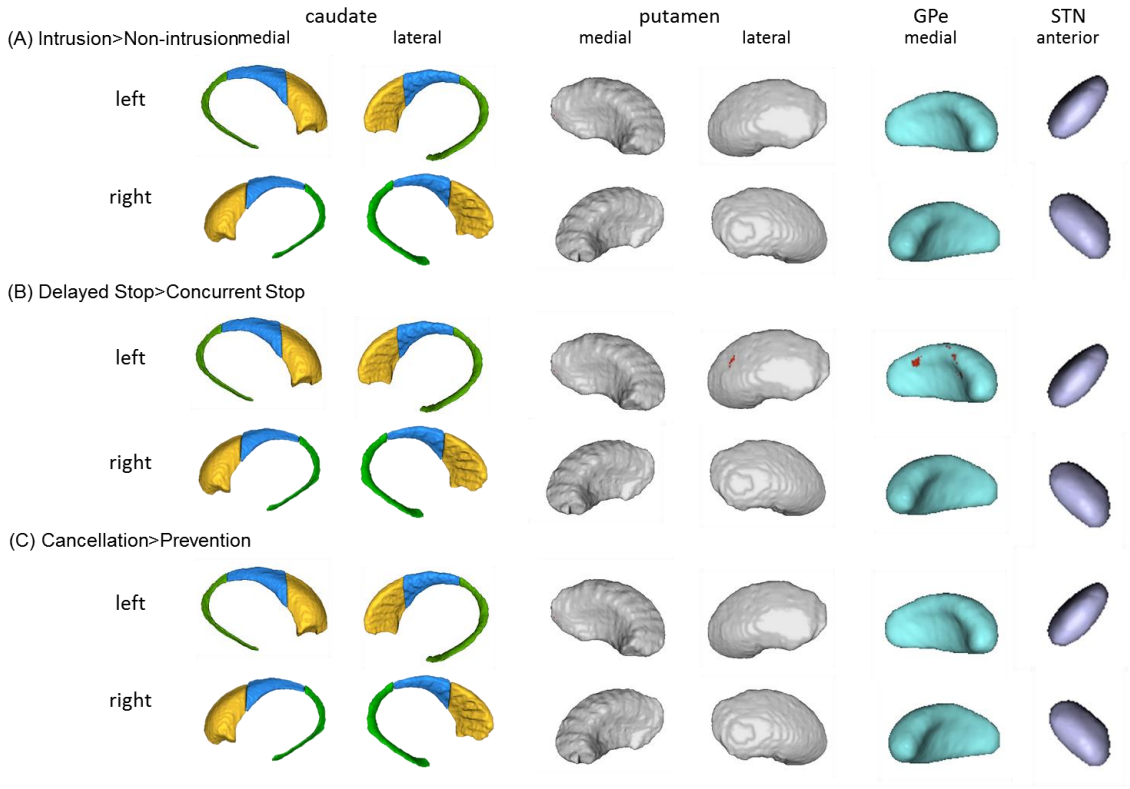

Figure 5.18. Basal ganglia activations specific to A) cancelling memory retrieval, B) cancelling motor responses, and C) cancelling retrieval and motor responses>preventing retrieval and motor responses. For the caudate structure, yellow is caudate head, blue is caudate body, and green is caudate tail. All activations were thresholded to FDR *p*<.05.

5.2.2.3.3 Cancelling Motor Responses Activated Frontoparietal and Basal Ganglia Regions Similar to the Meta-analysis

Our meta-analysis showed that cancelling motor actions activated cortical regions including the right DLPFC, VLPFC, precentral gyrus, supramarginal/angular gyrus, and the cingulate. Our univariate analysis found a similar pattern of activations in the Delayed Stop>Go contrast (Figure 5.15b). These findings again suggest the importance of the frontoparietal network in motor inhibition. In particular, both the DLPFC and the VLPFC are involved, rather than just the VLPFC as usually emphasised in previous studies (Schmitz et al., in preparation).

In the basal ganglia, the meta-analysis found activations in the right caudate head/body, putamen, GPe, and bilateral STN. Here we observed largely identical activations in the caudate head, putamen, GPe, and STN, except these activations are all bilateral and the striatal activity seem to be more lateral (Figure 5.16b). As discussed earlier, although the meta-analysis only found significant activations in the right hemisphere, the input coordinates were from both hemispheres. The results may have been due to the ALE algorithm being more sensitive to clustering activity. In addition, there is a medial-lateral gradient in the striatum, where the medial striatum is more often associated with learning and cognition, and the lateral striatum more often associated with sensorimotor functions (Haber & Knutson, 2010). We are observing lateral striatum activity in the univariate analysis possible due to motor cancellation engaging the sensorimotor loop of the basal ganglia system.

5.2.2.3.4 Motor Cancellation Activated Little Basal Ganglia and no Prefrontal Cortex more than Motor Prevention

Relative to motor prevention, motor cancellation yielded more activation in bilateral postcentral gyrus and some regions in the left parietal lobe (Figure 5.17.b). Activation of these sensorimotor regions may have arisen from the early motor processes, when participants were preparing for motor responses before hearing the stop signal. In the basal ganglia, there were limited activations in the left putamen and GPe (Figure 5.18.b), suggesting that the indirect pathway may have been engaged for cancelling motor processes (Alexander et al., 1986; Kandel et al., 2012).

5.2.2.3.5 Retrieval and Motor Cancellation Activated Frontoparietal Regions and the Putamen

A conjunction analyses revealed increased activity primarily in the right DLPFC (BA9/46), VLPFC (BA44/45), preSMA (BA6/8), ACC (BA32) and the supramarginal gyrus (Figure 5.15.c). There were also small clusters of activation in the right insula and lateral putamen (Figure 5.16.c). These suggest that cancelling memory retrieval or motor responses largely engages the same network as preventing memory retrieval or motor responses. However, we have also shown that there are unique activations specific to the prevention processes (Section 5.2.2.2.6), indicating that there may be process-specific mechanisms in addition to the supramodal network of inhibition.

5.2.2.3.6 Cancellation Activated Frontal Regions more than Prevention, but not the Basal Ganglia

To isolate neural mechanisms specific to cancellation, we tested the main effect of cancellation>prevention across the memory and motor domains through the contrast [Intrusion & Delayed Stop]>[Non-intrusion & Concurrent Stop]. We found that action/thought cancellation selectively activated bilateral precentral gyrus (BA6), left postcentral gyrus and medial frontal gyrus, but not in the basal ganglia (Figure 5.17.c; Figure 5.18.c). On one hand, these results suggest that cancellation may not engage the basal ganglia or the DLPFC, but rather involves more posterior frontal regions. On the other hand, as previously discussed, our cancellation and prevention conditions may not have solely invoked the corresponding cancellation and prevention processes, or they may engage different basal ganglia pathways that are hard to detect with fMRI. Finally, we did have fewer trials for cancellation than prevention in both memory and motor inhibition tasks. This may have caused the cancellation activities to be less robust and hence appear to be less extensive.

5.2.3 DCM Results

To investigate whether the basal ganglia regions are effectively involved in memory and motor inhibition, and whether cancellation and prevention processes excited different network dynamics, we conducted separate but parallel DCM analyses on the Combined Go/No-Go and Stop-signal task and the Think/No-Think task. Overall, we observed that both the DLPFC and the basal ganglia are effectively involved in memory and motor inhibition, achieving inhibition through task-specific pathways (hippocampus for memory inhibition, and M1 for motor inhibition). Specifically, motor inhibition is achieved through a basal ganglia-DLPFC-M1 pathway, while memory inhibition is achieved through a DLPFC-basal ganglia-hippocampus pathway. We also conducted BMA analyses to identify significant task modulations on particular pathways.

5.2.3.1 BMS and BMA Results from the Step 1 DCMs

Our Step 1 DCMs aimed to investigate whether the basal ganglia and the DLPFC are both required for memory and motor inhibition, and whether inhibition is achieved through task-specific pathways, such as to the hippocampus for memory inhibition and M1 for motor inhibition. Using BMA analyses, we explored the network dynamics in

the relevant pathways during the prevention and cancellation processes of memory and motor inhibition.

5.2.3.1.1 Motor Inhibition Modulated DLPFC-M1 and Basal Ganglia-M1 Connectivity

We used Bayesian Model Selection (BMS) to identify the winning model, i.e. model with the most evidence, from the model space illustrated in Figure 5.1. In BMS, the winning model is selected by the value of exceedance probability. The higher the exceedance probability a model has, the more likely that model is going to fit the data from a randomly selected subject. In the process of identifying the winning model, we first tested which of the putative supramodal regions (DLPFC, basal ganglia, or both) were effectively involved in stopping motor actions (Figure 5.19). BMS provided overwhelming evidence for the "both" family, with an exceedance probability of .9958. We then tested the pathway through which motor inhibition is achieved amongst the models that had DLPFC and basal ganglia involvement specified. We expected that the model involving M1 but not the hippocampus should win the most evidence. Indeed, BMS provided overwhelming evidence for the task modulation over the DLPFC- and basal ganglia-M1 pathways (exceedance probability=.9164). These results suggest that the DLPFC and the basal ganglia are both critical for suppressing motor responses in M1. Critically, the DLPFC and the basal ganglia do not modulate hippocampal activity during motor stopping.

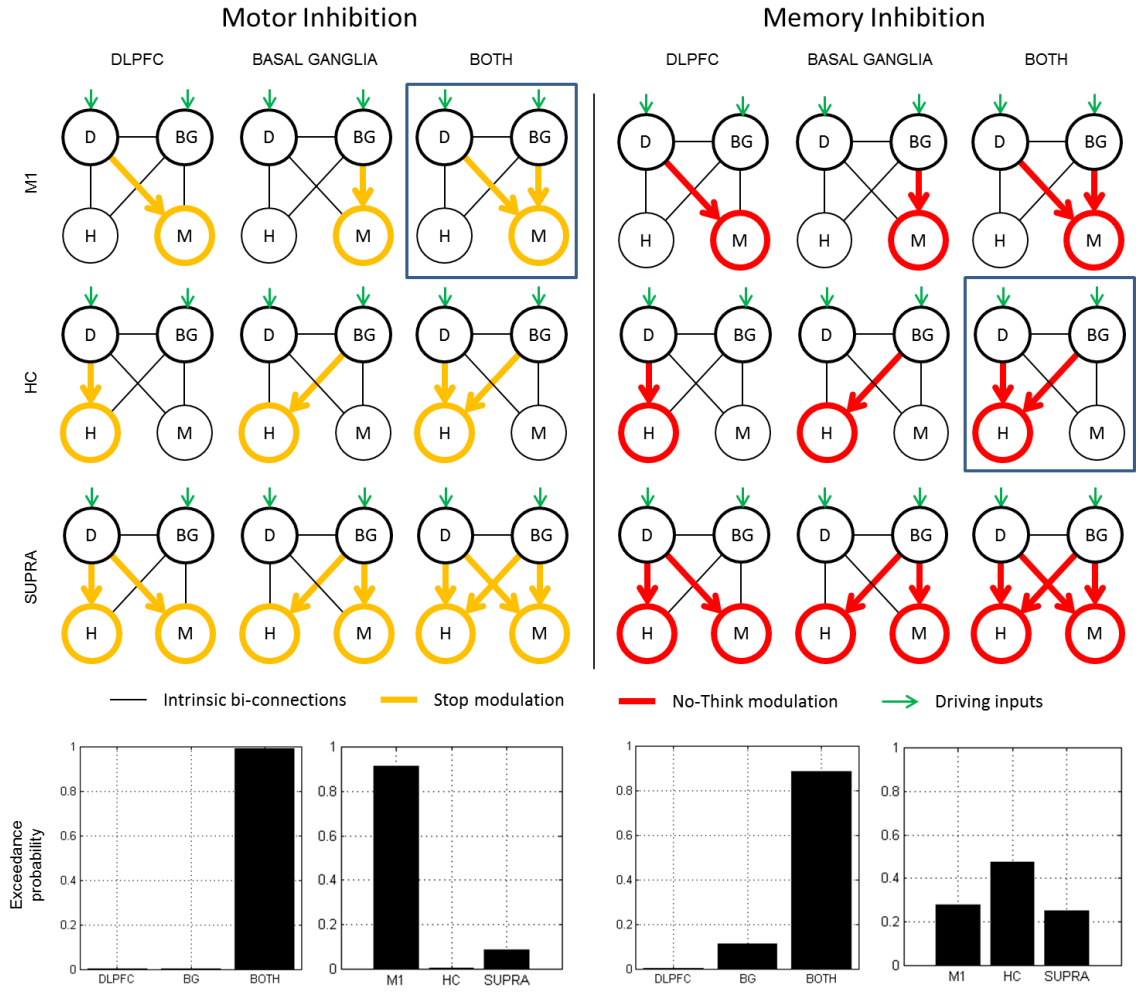

Figure 5.19. Inhibitory Pathways of Effective Connectivity. The top panel shows the model spaces for the memory and motor inhibition DCMs. The bottom panel shows the exceedance probability from the hierarchical BMS analyses. D=DLPFC; BG=basal ganglia; H=hippocampus; M=M1.

5.2.3.1.2 Motor Cancellation and Prevention were both Associated with Negatively Coupling from the DLPFC to M1, despite Significant Task-independent Connectivity between the Basal Ganglia and M1

Furthermore, in order to examine the effect of prevention and cancellation processes in motor inhibition, we extracted DCM coupling parameters from the task independent (DCM.A) and modulatory (DCM.B) connections in the DLPFC-M1 and basal ganglia-M1 pathways. We applied Bayesian model averaging (BMA) on the preferred "both" family, where the DLPFC and basal ganglia are both involved in inhibiting M1 during

motor control. From this model family, we extracted six parameters for each participant from the DLPFC-M1 and the basal ganglia-M1 pathways. These parameters include 1) the task-independent connectivity between the DLPFC and M1, and between the basal ganglia and M1, and 2) task modulation from the cancellation (Delayed Stop) and prevention (Concurrent Stop) conditions on the DLPFC-M1 and basal ganglia-M1 pathways. The task-independent connectivity refers to how strongly two regions are associated at baseline level, when no task is being performed. The task modulation parameters represent how engaging in a certain task influences the connectivity between two regions. After extracting these parameters, we first tested whether the parameters differed significantly from zero using one-sample *t*-tests (Table 5.2). We found a significant task-independent connectivity between the basal ganglia and M1, $t(29)=2.21$, $p=0.035$, but not between the DLPFC and M1. In terms of task modulations, we found a marginally significant negative coupling from the DLPFC to M1 for motor cancellation, $t(29)=-1.92$, $p=0.065$), and a significant negative DLPFC to M1 coupling for motor prevention, $t(29)=-3.23$, $p=0.003$. Coupling parameters from the basal ganglia to M1 were not significantly different from zero. Using a 2 (Pathway: DLPFC-M1 vs. basal ganglia-M1) by 2 (Inhibitory process: cancellation vs. prevention) repeated-measure ANOVA, we further tested if the top-down coupling parameters differed between pathways and inhibitory processes. We found a marginally significant main effect of Pathway, $F(1,29)=3.13$, $p=0.087$. The main effect of Inhibitory process or the interaction was also not significant. These results suggest that even though we observed significant task-independent connectivity between the basal ganglia and M1, there was a trend of greater negative coupling from the DLPFC to M1 than from the basal ganglia to M1 across the cancellation and prevention subprocesses of inhibitory control.

	DCM.A	DCM.B	
	Task independent	Cancellation	Prevention
DLPFC	-0.0939	-0.388^	-0.7116**
->M1	(0.8093)	(1.1056)	(1.2083)
Basal Ganglia	0.2742*	-0.0091	-0.0645
->M1	(0.6803)	(1.3818)	(1.3675)

Table 5.2 Step 1 DCM Task independent and Modulatory Parameters for Motor Cancellation and Prevention. The values represent the mean with the standard deviation in parentheses. ^ denotes marginal significance; ** denotes *p*<.01.

5.2.3.1.3 Memory Inhibition Modulated DLPFC-Hippocampus and Basal Ganglia-Hippocampus Connectivity

We followed the same steps to identify the winning model for the memory inhibition DCM using the hierarchical BMS analysis (Figure 5.19). We observed overwhelming evidence for models with both the DLPFC and basal ganglia involved (exceedance probability=.8870). We further tested the pathways to achieve memory inhibition, and found the model with DLPFC- and basal ganglia-hippocampus pathways to win the most evidence than models with M1. These findings suggest that the DLPFC and the basal ganglia are both critically involved in memory inhibition, and they modulate hippocampal rather than M1 activity during retrieval suppression. One concern with the current results is that the advantage of the "hippocampus" model (exceedance probability=.4725) was slim over the "M1" and "both" models. The M1 involvement may be due to the button pressing that is required after each Think/No-Think trial for the intrusion ratings. Participants may have prepared for the motor action during the trial, invoking M1 activity.

5.2.3.1.4 Retrieval Prevention was Associated with Positive Coupling from the Basal Ganglia to the Hippocampus, while Cancellation and Prevention were both Associated with Negative Coupling from the DLPFC to the Hippocampus

Using similar methods to Section 5.2.3.1.2, we extracted DCM parameters from task-independent connectivity (DCM.A) and task modulation (DCM.B) from the basal ganglia-to-hippocampus and the DLPFC-to-hippocampus pathways. We examined the effect of prevention and cancellation processes in memory inhibition by applying BMA to the "both" family, which reflects top-down modulation from both the DLPFC and the basal ganglia. The one-sample *t*-tests (Table 5.3) revealed significant task independent connectivity between the DLPFC and the hippocampus, $t(29)=2.51$, $p=0.018$, significant negative coupling from the DLPFC to the hippocampus during cancellation, $t(29)=-2.58$, $p=0.015$, and during prevention, $t(29)=-2.30$, $p=0.029$. In addition, preventing memory retrieval also induced significant positive coupling between the basal ganglia and the hippocampus, $t(29)=2.20$, $p=0.036$. Using a 2 (Pathway: DLPFC-hippocampus vs. basal ganglia-hippocampus) by 2 (Inhibitory process: cancellation vs. prevention) repeated-measure ANOVA, we further tested if the top-down coupling parameters differed between pathways and inhibitory processes. We found a significant main effect of Pathway, $F(1,29)=6.75$, $p=0.015$, and marginally significant main effect of Inhibitory process, $F(1,29)=3.74$, $p=0.063$. However, the interaction was not significant. Taken together, these results suggest that memory inhibition is generally associated with negative coupling from the DLPFC to the hippocampus, but positive coupling from the basal ganglia to the hippocampus (particularly during a prevention condition). The opposite signs of the coupling parameters indicate that there may be a hierarchical relationship between the DLPFC and the basal ganglia to achieve retrieval prevention. We are going to probe this possibility with the second step DCM analyses.

	DCM.A	DCM.B	
	Task independent	Cancellation	Prevention
DLPFC ->Hippocampus	0.0731* (0.1593)	-0.3605* (0.7649)	-0.3609* (0.8583)
Basal Ganglia ->Hippocampus	0.0286 (0.1524)	0.0205 (0.7245)	0.3534* (0.8816)

Table 5.3 Step 1 DCM Task independent and Modulatory Parameters for Memory Cancellation and Prevention. The values represent the mean with the standard deviation in parentheses. * denotes *p*<.05; ^ denotes marginal significance.

5.2.3.2 BMS and BMA Results from the Step 2 DCMs

The foregoing DCM analyses provided evidence that both the DLPFC and basal ganglia are critical for memory and motor inhibition, and inhibition was achieved through task-specific pathways (hippocampus for memory inhibition, and M1 for motor inhibition). In the following DCM analyses, we constructed a new model space that allowed us to examine how the DLPFC and basal ganglia interact to achieve inhibition in the task-specific regions in a bilinear or nonlinear fashion. The bilinear models specified that either the DLPFC influences Basal Ganglia activity, or vice versa, before reaching the task-specific regions. The nonlinear models specified that either the DLPFC influences basal ganglia-hippocampal connectivity, or the basal ganglia influences the DLPFC-hippocampal connectivity to achieve inhibition (Figure 5.2).

5.2.3.2.1 DLPFC Serves as an Intermediary between Basal Ganglia and M1 in Motor Inhibition

We first tested how the DLPFC and basal ganglia interact to achieve motor inhibition (Figure 5.20). Using BMS we found greater evidence for the bilinear than the nonlinear models (exceedance probability=.7588). We then tested whether the DLPFC was influencing the basal ganglia or vice versa. BMS showed greater evidence for the basal ganglia modulating DLPFC activity, which then inhibits M1 activity through top-down

modulations (exceedance probability=.7873). These findings support the indirect hypothesis, where motor inhibition engages a basal ganglia-DLPFC-M1 pathway in a stepwise fashion, suggesting a critical role of the basal ganglia in the cognitive control of motor actions.

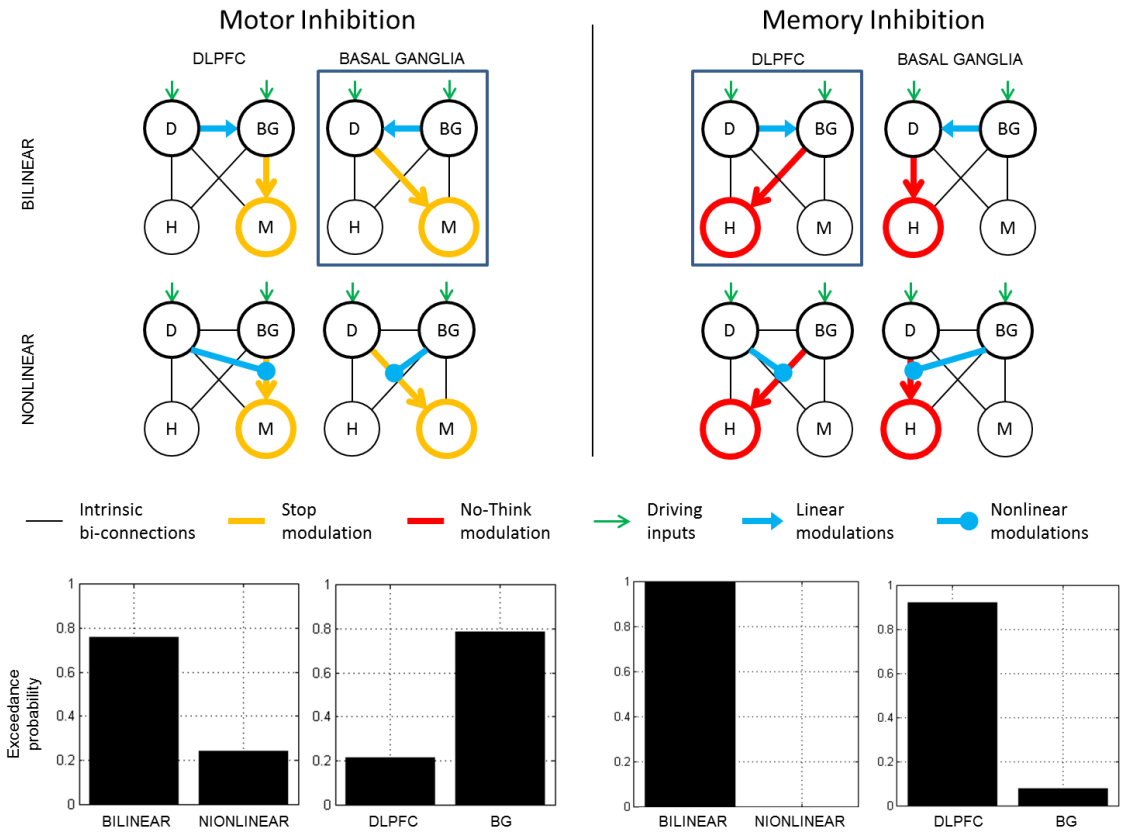

Figure 5.20. Bilinear vs Nonlinear Modulation of Inhibitory Control. The top panel shows the model spaces for the memory and motor inhibition DCMs. The bottom panel shows the exceedance probability from the hierarchical BMS analyses. D=DLPFC; BG=basal ganglia; H=hippocampus; M=M1.

5.2.3.2.2 Motor Cancellation and Prevention were Associated with Significant Negatively Coupling from the DLPFC to M1, and Marginally Significant Negative Coupling from the Basal Ganglia to DLPFC

Similar to the methods described in 5.2.3.1.2, we extracted DCM parameters from task-independent connectivity (DCM.A) and task modulation (DCM.B) from the basal ganglia-to-DLPFC and the DLPFC-to-M1 pathways. We applied BMA on the "bilinear family", where we specified bilinear modulation from the DLPFC to the basal ganglia

and vice versa. We found that for the modulatory parameters, motor stopping was associated with marginally significant negative coupling from the basal ganglia to DLPFC for cancellation, $t(29)=-1.92$, $p=0.065$, and significant DLPFC to M1 negative coupling for both cancellation, $t(29)=-2.58$, $p=0.015$, and prevention, $t(29)=-2.35$, $p=0.026$ (Table 5.4). These results again suggest that motor inhibition is achieved through DLPFC downregulation of M1 activity, during both cancellation and prevention conditions. However, as previously discussed, the cancellation and prevention processes may not have been as distinct as we assumed in our Concurrent and Delayed Stop conditions. Hence we need to take caution when interpreting these results.

	DCM.A	**DCM.B**	
	Task independent	Cancellation	Prevention
Basal Ganglia ->DLPFC	0.0256 (0.2477)	-0.2581^ (0.7356)	0.1191 (1.1365)
DLPFC ->M1	-0.0755 (0.6941)	-0.5363* (1.1365)	-0.5963* (1.3923)

Table 5.4 Step 2 DCM Task independent and Modulatory Parameters for Motor Cancellation and Prevention. The values represent the mean with the standard deviation in parentheses. ^ denotes marginal significance; * denotes $p<.05$.

5.2.3.2.3 Basal Ganglia Served as an Intermediary between the DLPFC and the Hippocampal in Memory Inhibition

Here we tested how the DLPFC and basal ganglia interact to achieve memory inhibition (Figure 5.20). Using BMS, we found overwhelming evidence for models with bilinear modulation between the DLPFC and the basal ganglia during memory inhibition (exceedance probability=1). Furthermore, there was overwhelming evidence that the DLPFC influences basal ganglia activity (exceedance probability=.9236) which then inhibits hippocampal activity during memory inhibition. These findings support the intermediary hypothesis, and suggest that memory inhibition engages a DLPFC-basal ganglia-hippocampus pathway in a stepwise fashion, suggesting a critical role of the basal ganglia in retrieval suppression. However, the DCM does not provide information

regarding the anatomical connections through which the functional interactions are achieved. We hoped to use diffusion weighted imaging to explore that question, as we will discuss in Chapter 6.

5.2.3.2.4 Memory Inhibition was Associated with Marginally Significant Negative Coupling from the Basal Ganglia to the Hippocampus

Using similar methods to 5.2.3.1.2, we extracted DCM parameters from task-independent connectivity (DCM.A) and task modulation (DCM.B) from the basal ganglia-to-hippocampus and the DLPFC-to-hippocampus pathways. According to the BMA results (Table 5.5), retrieval suppression is associated with marginally significant negative coupling from the basal ganglia to the hippocampus for both cancellation, $t(29)=-2.00$, $p=0.055$, and prevention, $t(29)=-1.92$, $p=0.065$. The task independent and other coupling parameters were not significantly different from zero. These results suggest that the basal ganglia-to-hippocampus coupling may be more relevant for retrieval suppression than the DLPFC-to-basal ganglia coupling, although this difference is not significant. It is worth noting that these BMA results suggest negative coupling from the basal ganglia to the hippocampus, while the BMA presented in 5.2.3.1.4 showed positive coupling. The opposite signs in the coupling parameter may be due to different DCM model specification. In the Step 1 DCM analysis, we compared models with task modulations to both the hippocampus and M1, and did not find an overwhelming winner. We discussed that the button pressing component for the intrusion rating may have contributed to the M1 involvement. Hence, in the Step 2 DCM, we assumed that memory inhibition should only concern the hippocampus, and did not specify any task modulations to M1. The differences in model structures may have influence the BMA outcome. According to Rowe et al. (2010), DCM parameter estimates have lower test-retest reliability than BMS, even when the same model space is being tested. Here we have vastly different model structures, and hence need to be extra cautious when interpreting the BMA results

	DCM.A	DCM.B	
	Task independent	Cancellation	Prevention
DLPFC->Basal Ganglia	-0.0035 (0.1898)	-0.3038 (1.0531)	0.01559 (0.8815)
Basal Ganglia ->Hippocampus	0.0081 (0.1862)	-0.2614^ (0.7148)	-0.2717^ (0.7763)

Table 5.5. Step 2 DCM Task independent and Modulatory Parameters for Memory Cancellation and Prevention. The values represent the mean with the standard deviation in parentheses. ^ denotes marginal significance.

5.2.4 Relating Behavioural Performance to Effective Connectivity

In order to relate behavioural performance to effective connectivity, we correlated DCM coupling parameters with behavioural measures. For motor inhibition, we correlated DCM coupling parameters with SSRT. For memory inhibition, we used SIF as an indicator of the overall ability to suppress unwanted memories, possibly reflecting the combined effort of cancellation and prevention processes. We also used the slope of intrusion reduction as an indicator for the ability to overcome intrusions during suppression practice, possibly reflecting cancellation-specific processes. Our correlation analyses were conducted using the Robust Correlation Toolbox (Pernet et al., 2013). Bivariate outliers were removed from the analyses.

5.2.4.1 Relating Step 1 DCM Parameters to Behaviour

In the first DCM analysis, we found that both the DLPFC and the basal ganglia are involved in inhibition, and they down-regulate the task-specific pathways to achieve inhibition in the memory and motor domains. Results from our correlation analyses are shown in Table 5.6.

Task	Pathway	Behavioural Correlates	Cancellation	Prevention
Motor Inhibition	Basal Ganglia -> M1	SSRT	0.08	0.16
	DLPFC -> M1	SSRT	-0.11	0.30^
Memory Inhibition	Basal Ganglia -> Hippocampus	Slope	0.02	-0.17
		SIF	0.02	0.42*
	DLPFC -> Hippocampus	Slope	-0.41*	-0.14
		SIF	0.09	-0.07

Table 5.6. Correlation coefficients between the coupling parameters from the Step 1 DCM and behavioural indices from the memory and motor inhibition tasks. SIF=suppression-induced forgetting; Slope=slope of intrusion reduction; SSRT=stop signal reaction time; * denotes significant correlations; ^ denotes marginal significance.

5.2.4.1.1 Basal Ganglia-to-hippocampus Coupling during Retrieval Prevention Positively Correlated with SIF

First, we found a significant positive correlation between SIF and the positive coupling from the basal ganglia to the hippocampus during retrieval prevention (r=.42, p=.033). This shows that a stronger up-regulation from the basal ganglia to the hippocampus during retrieval prevention is associated with greater suppression-induced forgetting. These results suggest that the basal ganglia may play an active role in proactive memory inhibition. The positive correlation may be that if engaging the basal ganglia successfully prevents retrieval of unwanted targets, inhibiting hippocampal activity will no longer be necessary. However, the fact that we found negative coupling between the basal ganglia and the hippocampus during prevention in our Step 2 DCM analysis made the role of the basal ganglia puzzling. As discussed before, DCM parameter estimates have lower test-retest reliability and may be influenced by other factors such as the DCM model structure (Rowe et al., 2010).

5.2.4.1.2 DLPFC-to-hippocampus coupling during Retrieval Cancellation Negatively Correlated with Slope of Intrusion Reduction

Second, we found a significant negative correlation between the negative coupling from the DLPFC to the hippocampus during retrieval cancellation and the slope of intrusion reduction (r=-.41, p=.038). This means that a steeper slope of intrusion reduction is associated with less negative DLPFC-to-hippocampus coupling during cancellation. This may seem counter-intuitive, as one may predict that there should be stronger top-down negative coupling as participants become more successful at retrieval suppression, reflected by reduced amounts of intrusions (Gagnepain et al., 2017). However, it is possible that as participants get better at suppressing unwanted thoughts, they require less downregulation from the DLPFC to achieve inhibition. Therefore, the better participants can overcome intrusions, the less DLPFC downregulation they may need. For example, Roland et al. (2014) observed decreased negative coupling between the DLPFC and the hippocampus as the Think/No-Think phase progressed. The slope of this decrement also predicted intrusion regulation. These findings suggest that as unwanted targets become less intrusive due to repeated practice of retrieval suppression, they become to require less control.

5.2.4.1.3 DLPFC-to-M1 Coupling during Motor Prevention Shows a Marginally Positive Correlation with SSRT

Finally, we observed a weak trend for positive correlation between the negative coupling from the DLPFC to M1 during motor prevention and SSRT (r=.30, p=.11). This indicates that the more negative the coupling from the DLPFC to the M1, the faster SSRT would be, showing that the DLPFC down-regulation of M1 may be an important contribution to preventing unwanted motor actions. The weak correlation may be due to the indirect connections between the DLPFC and M1, some of which may not be specific to motor inhibition. Future studies could focus more on which specific pathways between the DLPFC and M1 are recruited to achieve motor stopping.

It is worth noting that we did not find any significant correlation between the coupling parameters during motor cancellation and SSRT. It could mean that motor inhibition may predominantly require prevention processes than cancellation. For example, when participants successfully stopped on a Delayed Stop trial, it is possible that they have waited to hear the stop tone instead of immediately engaging motor processes. Although

we have explicitly instructed participants not to adopt this waiting strategy, and they should always respond as quickly as possible when seeing a stimulus, we are not able to differentiate this objectively in the current experiment. Future studies could use classification techniques (such as multivariate pattern analysis) to detect when participants are preventing or cancelling motor responses and provide more insights to which is more important for achieving motor inhibition.

5.2.4.2 Relating Step 2 DCM Parameters to Behaviour

In the second DCM, we tested the interaction between the DLPFC and the basal ganglia, and found that memory inhibition is achieved through a DLPFC-basal ganglia-hippocampus pathway, while motor inhibition is achieved through a Basal ganglia-DLPFC-M1 pathway. Results from our correlation analyses are shown in Table 5.7.

Task	Pathway	Behavioural Correlates	Cancellation	Prevention
Motor Inhibition	Basal Ganglia -> DLPFC	SSRT	-0.08	0.32
	DLPFC -> M1	SSRT	0.27	0.48*
Memory Inhibition	Basal Ganglia -> Hippocampus	Slope	0.18	0.12
		SIF	-0.15	0.23
	DLPFC -> Basal Ganglia	Slope	0.10	0.31^
		SIF	0.31^	-0.02

Table 5.7. Correlation coefficients between the coupling parameters from the Step 2 DCM and behavioural indices from the memory and motor inhibition tasks. SIF=suppression-induced forgetting; Slope=slope of intrusion reduction; SSRT=stop signal reaction time; * denotes significant correlations; ^ denotes marginal significance.

5.2.4.2.1 Marginally Significant Positive Correlation between the DLPFC-to-basal ganglia Coupling during Prevention and Slope of Intrusion Reduction, and during Cancellation and SIF

During retrieval prevention, we observed a marginally significant positive correlation between the DLPFC-to-basal ganglia coupling and the slope of intrusion reduction (r=.31, p=.099). This means that a steeper slope of intrusion reduction is associated with more positive coupling from the DLPFC to the basal ganglia, suggesting that suppressing intrusions may be achieved through the DLPFC engaging the basal ganglia system to prevent intrusions from taking place. Specifically, the basal ganglia indirect and hyperdirect pathways may have been recruited to downregulate hippocampal activity, through the negative basal ganglia-hippocampal coupling shown from the Step 2 BMA results. However, as we have discussed previously, we need to take caution when interpreting these results due to the limited reliability of DCM parameter estimates. In addition, this DLPFC-to-basal ganglia coupling was also marginally correlated with SIF during retrieval cancellation (*r*=.31, p=.096), suggesting that memory inhibition is associated with less negative DLPFC regulation of basal ganglia activity. This may again allow the basal ganglia to engage the indirect or hyperdirect pathways to inhibit hippocampal activity to achieve memory inhibition. As presented in Section 5.2.3.2.4, there exists marginally significant negative coupling from the basal ganglia to the hippocampus during retrieval cancellation. These pieces of evidence suggest that the DLPFC-basal ganglia pathway may be critical for both retrieval cancellation and retrieval prevention, supporting the possibility that these supramodal regions are responsible for inhibition across processes in the memory domain.

5.2.4.2.2 During Prevention, SSRT Significantly Correlated with DLPFC-to-M1 Coupling, and Marginally Correlated with Basal Ganglia-to-DLPFC Coupling

In terms of motor inhibition, we found a significant positive correlation between SSRT and the negative DLPFC-to-M1 coupling during prevention (*r*=.48, *p*=.007), showing that better motor stopping (as indicated by faster SSRT) is associated with more negative DLPFC-to-M1 downregulation. We also observed a similar relationship between SSRT and the positive basal ganglia-to-DLPFC coupling, although this correlation did not reach significance (*r*=.32, *p*=.082). This means that faster SSRT is associated with less positive coupling from the basal ganglia to the DLPFC during prevention. This finding seems counterintuitive as one may expect basal ganglia

upregulation of the DLPFC, which then downregulates M1 activity to achieve motor inhibition. It may also be the case that as participants become perfected at preventing motor responses, the basal ganglia become disengaged from the process as stopping becomes more automatic. Future studies could look into how the network dynamic between the DLPFC and the basal ganglia changes at different stages in the motor inhibition tasks.

Our findings provide evidence for the importance of the DLPFC in motor inhibition, in addition to the VLPFC as usually emphasised in the literature (e.g., Schmitz et al., accepted). It is unclear from these results the exact role of the basal ganglia in motor inhibition, as we did not observe significant correlations between coupling parameters in the basal ganglia pathways with the behavioural index of motor stopping (SSRT). As discussed previously, this could be that our Concurrent and Delayed Stop conditions did not exclusively reflect the prevention and cancellation processes, and hence adding confounds to our analyses. Alternatively, it could also be due to the lack of reliability in DCM parameter estimates. Finally, the current basal ganglia ROI only included the striatum and GPe, while the prevention process may also engage the hyperdirect pathway through the STN. It is possible that we need to improve our DCM model structure to better encapsulate all pathways and processes in the basal ganglia system.

5.3 Discussion

The current fMRI study investigated the role of the basal ganglia in memory and motor inhibition, and whether there are distinct neural mechanisms underlying different subprocesses of inhibition, such as prevention and cancellation. To answer these questions, we conducted a two-session fMRI experiment. Participants performed the Combined Go/No-Go and Stop-signal task in the first session, and the adapted Think/No-Think task with intrusion rating in the second session. We first examined if we successfully replicated typical findings from memory and motor inhibition paradigms through behavioural and univariate fMRI analyses. We then conducted a series of conjunction and contrast analyses to reveal distinct patterns of activations from prevention and cancellation inhibitory processes. Finally, we used effective connectivity analyses to investigate the specific network dynamics underlying the inhibition of memory retrieval or motor actions during prevention and cancellation processes, and

related effective connectivity to behaviour. Our key observations and their implications are discussed below.

5.3.1 Our Behavioural Findings Largely Conform with Previous Literature

Behaviourally, we replicated previous findings from the Think/No-Think paradigm by observing a significant effect of suppression-induced forgetting (SIF) and retrieval-induced facilitation. These results indicate that participants were able to initiate or inhibit memory retrieval using cognitive control. In addition, we found a significant correlation between the magnitude of SIF and the rate of intrusion reduction, showing that the better people can eliminate intrusions during the Think/No-Think phase, the more they can suppress unwanted targets overall. Finally, we found significant differences between the RTs of responding to intrusion rating across the Think, Intrusion, and Non-intrusion conditions. This could be a by-product from when people decide on their rating responses and start to prepare for the button press. Alternatively, it is possible that since memory and motor control may require similar mechanisms, inhibiting one may impair the response in the other.

In the motor inhibition task, we observed a relatively prolonged SSRT as compared to previous studies. As discussed previously, this slowed SSRT may be due to prolonged Go RT from the complexity of the button-mapping paradigm, or the uncertainty of timing from the jittered ISI. Although memory and motor inhibition performance was shown to be related (Schmitz et al., in preparation), this relationship was absent in the current study. It is possible that the jittered ISI added variance to participants' performances, and hence made the relationship less clear.

5.3.2 Univariate Analyses Revealed Similar Activations during Memory and Motor Inhibition as the Meta-analysis

Our univariate analyses successfully replicated previous findings. On one hand, we observed overlapping activations from memory and motor inhibition in the DLPFC, VLPFC, preSMA, ACC, the supramarginal/angular gyrus, and the basal ganglia more extensively in the right hemisphere. These activations are identical to findings from the meta-analysis, again providing evidence for the supramodal network of inhibition. On the other hand, we observed domain-specific deactivation in the task-relevant structures.

For example, we observed reduced activity in the hippocampus during retrieval suppression and in M1 during motor stopping. These results are consistent with Schmitz et al. (in preparation), and suggest that inhibition may be achieved locally at the task-specific regions, which receive control signals from the putative supramodal regions such as the DLPFC and basal ganglia..

5.3.3 Prevention and Cancellation Share Largely Overlapping Activations with some Discrepancies

One of the major goals of this fMRI study is to compare if prevention and cancellation processes engage distinct neural mechanisms, especially in the basal ganglia. According to the meta-analysis, we hypothesised two possible alternatives. First, prevention and cancellation may activate different parts of the brain to achieve inhibition, since the meta-analysis revealed left basal ganglia activity during prevention, and right basal ganglia activity during cancellation. However, this lateralisation effect may be accounted for by constraints of the ALE algorithm. Therefore, it is also possible that the cancellation and prevention processes may activate similar regions in the brain. If this is the case, these distinct subprocesses of inhibitory control may require similar commands from the supramodal regions, but different downstream mechanisms. For example, prevention may primarily require the hyperdirect pathway, while cancellation may primarily require the indirect pathway (e.g., Schroll & Hamker, 2013).

Our findings largely agree with the second possibility that cancellation and prevention processes share overall control mechanisms from the putative supramodal regions, but may require distinct process-specific mechanisms to achieve inhibition. On one hand, prevention and cancellation both activated regions similar to those found in the meta-analysis, including the DLPFC, VLPFC, preSMA, and the supramarginal/angular gyrus, and the basal ganglia. This is evidence that prevention and cancellation share neural mechanisms, and that the putative supramodal network is not only engaged across tasks but also across inhibitory processes. On the other hand, in addition to the supramodal regions, prevention and cancellation also activated distinct regions in the brain, possibly suggesting that the two processes are achieved through different pathways or mechanisms. We will discuss the cortical and basal ganglia findings separately in the following paragraphs.

On the cortical level, prevention activated the parahippocampal gyrus, visual cortices and inferior temporal regions more than cancellation. These activations are primarily from the difference between memory prevention and cancellation rather than from the motor task (Figure 5.13). The parahippocampal gyrus includes the entorhinal cortex, which provides major inputs into the hippocampus. According to the entorhinal gating hypothesis (Anderson et al., 2016), memory inhibition may be achieved by the ACC modulating entorhinal activity through inhibitory neurons. Inhibiting inputs from the entorhinal cortex to the hippocampus may contribute to the successful prevention of memory retrieval. Meanwhile, cancellation activated bilateral precentral gyrus, left postcentral gyrus and medial frontal gyrus more than prevention. As shown in Figure 5.17, these activations are primarily from the difference between motor cancellation and motor prevention rather than from the memory task. It is possible that neural mechanisms specific to cancellation are more pronounced in motor inhibition than memory inhibition on the cortical level. Alternatively, activity in the sensorimotor cortices during cancellation may have arisen due to the emerging motor responses before the stop signal was presented. Overall, our cortical findings revealed stronger activity from the prevention process during memory inhibition, but from the cancellation process during motor inhibition. These results suggest that memory and motor inhibition may require different subprocesses. However, this preference of activity may have been due to an unbalanced amount of trials for the prevention and cancellation conditions in each task. In the adapted Think/No-Think task, due to the significant reduction of intrusions during the Think/No-Think phase, prevention may have become predominant as the amount of Non-intrusion trials increases. In the Combined Go/No-Go and Stop-signal task, there are twice as many Delayed Stop trials than Concurrent Stop trials, possibly resulting in more robust activations for cancellation.

In the basal ganglia, we observed little activity that is unique to the cancellation or prevention processes. Prevention activated small regions in the left caudate and bilateral anterior putamen, but these activations were primarily from retrieval prevention rather than motor prevention. Cancellation, on the other hand, did not activate the basal ganglia more than prevention. On one hand, this preference of activity may be due to an unbalanced amount of trials in each task. On the other hand, the lack of difference

between cancellation and prevention may be accounted for by the design of the current experiment. As briefly discussed in Section 5.2.4, although we have tried to distinguish the cancellation and prevention processes through our experimental manipulations, this may not have been perfectly achieved. If so, it would be hard to detect differences between these processes. In addition, it is also possible that our current technique is not sensitive enough to the activity of different basal ganglia pathways, since they involve intricate connections between small subcortical nuclei. For example, of the 16 Think/No-Think, 30 Go/No-Go, and 39 Stop-signal studies that we included in the meta-analysis, only less than 1/3 of them reported basal ganglia activity. Future studies should adopt methods with higher spatial resolution to capture the involvement of these fine basal ganglia structures in memory and motor inhibition tasks.

5.3.4 DLPFC and the Basal Ganglia Interact in Different Ways to Achieve Inhibition at the Task-specific Regions

To investigate whether the basal ganglia regions are effectively involved in inhibitory control and the different network dynamics required by prevention and cancellation, we conducted DCM analyses and examined the coupling parameters from task modulations. Findings from the Step 1 DCMs were consistent with our hypothesis. We observed overwhelming evidence that both the DLPFC and the basal ganglia are effectively involved in stopping unwanted thoughts or actions. In the motor DCM, there was strong evidence for task modulation on the domain-specific pathways to M1. In the memory DCM, this evidence on the domain-specific pathways to the hippocampus was slim. This is slightly different from the findings from Schmitz et al. (accepted), who found overwhelming evidence for task modulation on the domain-specific pathways in both memory and motor inhibition. This inconsistency may be due to the additional intrusion ratings in our design. It is possible that the model evidence accumulated for the pathways to M1 since participants had to press buttons for the intrusion ratings after each trial in the Think/No-Think phase.

In the Step 2 DCMs, we tested how the DLPFC and basal ganglia interact to achieve inhibition at the task-specific regions. We had three alternative hypotheses for the interaction:

1. The intermediary hypothesis – the basal ganglia are an intermediary between the DLPFC and the task-specific regions;
2. The modulation hypothesis – the basal ganglia modulate the connectivity between the DLPFC and the task-specific regions;
3. The indirect hypothesis – the basal ganglia interact with the task-specific regions indirectly through the DLPFC.

Our results showed that the indirect hypothesis fit with motor inhibition, as there was overwhelming evidence for the task modulation through a basal ganglia-DLPFC-M1 pathway. It is possible that output from the basal ganglia system projects to the DLPFC via the thalamus. The DLPFC may then down-regulate M1 activity through the preSMA and the SMA to achieve motor inhibition (Bracht et al., 2012; Rowe et al., 2010). On the other hand, the intermediary hypothesis fit with memory inhibition, as we found overwhelming evidence for the task modulation through a DLPFC-basal ganglia-hippocampus pathway. After receiving control signals from the DLPFC through direct projections, the basal ganglia may commute with the hippocampus via the thalamus through the cingulum bundle (e.g., Aggleton, 2014).

In addition to alluding to the possible anatomical pathways underlying memory and motor inhibition, these DCM results also provided strong evidence that the basal ganglia and the hippocampus are not independent, unlike what was suggested by Döller et al. (2008). Rather, the basal ganglia effectively interact with the hippocampus to keep the unwanted target out of mind in the context of retrieval suppression. There has been some evidence on how the basal ganglia may regulate hippocampal activity. As reviewed in Section 2.4, Sabatino and colleagues found that, in cats, stimulation of the caudate nucleus inhibits hippocampal spikes (La Grutta et al., 1985; Sabatino et al., 1985), while stimulation of the pallidum induced generalised seizure activity (Sabatino et al., 1986). Berke et al. (2004) also found that neurons from the ventral and medial striatum entertain hippocampal theta in rats.

5.3.5 Motor Inhibition is Associated with the DLPFC-to-M1 Pathway

After identifying the most likely models in memory and motor inhibition, we examined how effective connectivity was related to behaviour performance. To do so, we extracted DCM coupling parameters from the relevant pathways, and correlated them

with behavioural indices. In the context of motor inhibition, from the Step 1 DCM, we found that although there is significant positive task-independent connectivity between the basal ganglia and M1, it is the DLPFC-to-M1 pathway that is significantly negatively modulated by motor inhibition. It is possible that the basal ganglia are critical for motor control in general, but inhibiting unwanted actions requires the DLPFC more than the basal ganglia. Indeed, when correlating DCM coupling parameters with motor inhibition, we found a marginally significant positive correlation between the negative DLPFC-to-M1 coupling during prevention and SSRT. The correlation between the basal ganglia-to-M1 coupling and SSRT was not significant. These results suggest that the DLPFC down-regulation of M1 plays a causal role in preventing motor responses. Although the basal ganglia are critical for motor control, they may not directly interact with M1 to prevent motor actions.

We found similar results in the Step 2 DCM, where we further probed the interactions between the DLPFC and the basal ganglia in their relations to M1. We found that while the task modulation was significantly negative for the DLPFC-to-M1 pathway during both cancellation and prevention, this negative modulation was only marginally significant for the basal ganglia-to-DLPFC pathway during cancellation. In addition, the negative DLPFC-to-M1 coupling significantly correlated with SSRT during prevention. These findings again suggest that the DLPFC may be more involved in motor inhibition than the basal ganglia. However, the lack of involvement of the basal ganglia may have resulted from relatively liberal basal ganglia ROIs. For the DCM analyses, we extracted the top 40% most active voxels from the anatomically defined basal ganglia ROI for each participant. We expected that our ROIs from the memory and motor inhibition tasks should represent the corresponding functional zones in the basal ganglia. Unfortunately, the resulting ROIs appeared to have encompassed the entire structure (Figure 5.21). This liberal ROIs may have introduced basal ganglia functions that are not specific to memory and motor inhibition, adding confounds to the DCM results. In the future, we can revise the basal ganglia ROIs to be more stringent (e.g., extracting only the top 10% most active voxels), and see if the extracted ROIs from memory and motor inhibition will be more specific to the corresponding functional zones. If so, using these new ROIs for the DCM analyses may improve the interpretability of the results.

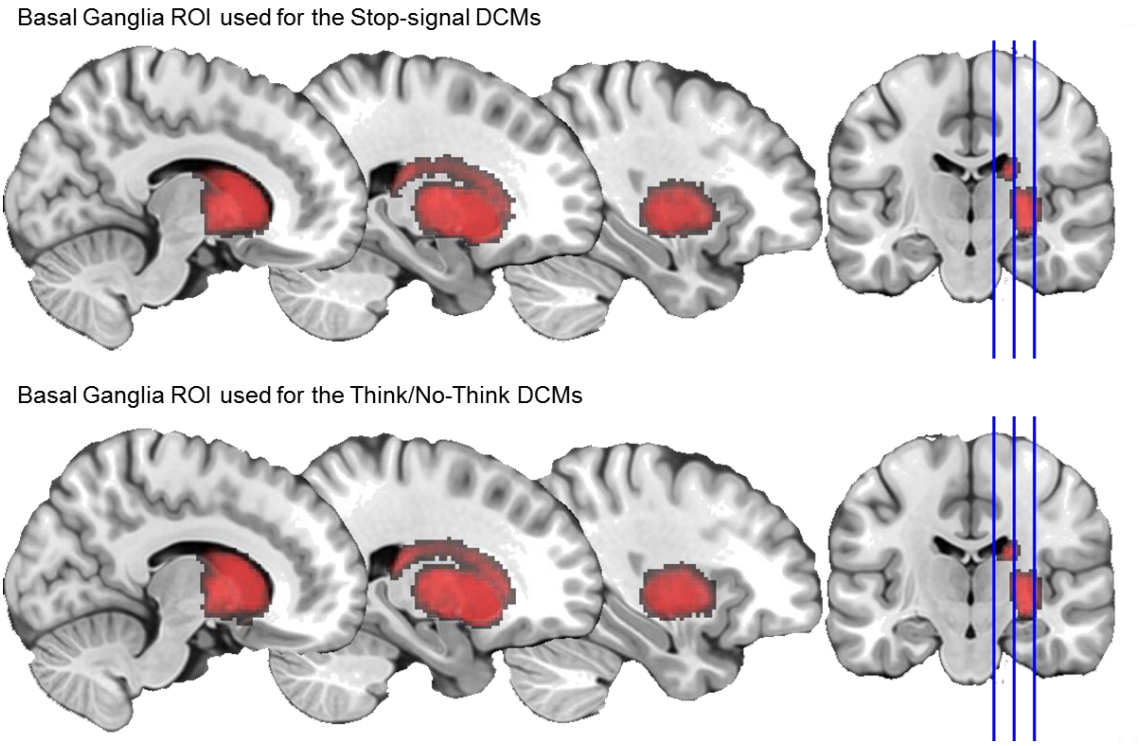

Figure 5.21. Aggregated Basal Ganglia ROIs used in the Stop-signal and Think/No-Think DCMs. For each participant, we extracted the top 40% most activated voxels in the combined basal ganglia ROI (including caudate head and body, putamen, and GPe) from the Stop>Go contrast for motor inhibition, and the No-Think>Think contrast for memory inhibition. We aggregated the individual basal ganglia ROIs for display in this figure

5.3.6 Memory Inhibition is associated with both DLPFC-hippocampus and Basal Ganglia-hippocampus Pathways

As for memory inhibition, from the Step 1 DCM, we found significant positive task-independent and negative task-modulated connectivity for the DLPFC-to-hippocampus pathway, indicating a causal role of the DLPFC in down-regulating hippocampal activity to achieve memory inhibition. In addition, this negative coupling from the DLPFC to the hippocampus significantly negatively correlated with the slope of intrusion reduction during cancellation. This provides further evidence that the DLPFC is actively involved in suppressing unwanted intrusions by inhibiting hippocampal activity. For the basal ganglia-to-hippocampus pathway, there was only a significant positive modulation during prevention, and this positive coupling is positively

correlated with SIF. These findings may be counterintuitive as they suggest that retrieval suppression is associated with the basal ganglia up-regulating hippocampal activity. However, according to previous research, hippocampal activity is not different from baseline during Non-intrusion trials (e.g. Levy & Anderson, 2012), and that preventing retrievals may be achieved by inhibiting inputs to the hippocampus (Anderson et al., 2016). Therefore, although it may appear that the basal ganglia causes increased hippocampal activity during retrieval prevention, it is possible that engaging the basal ganglia is already sufficient for preventing unwanted retrievals, sparing the need to suppress hippocampal activity to achieve inhibition. Alternatively, these results may be similarly influenced by the relatively liberal basal ganglia ROIs (Figure 5.21). Constraining the ROIs may clarify the DCM results.

In the Step 2 DCM, we only observed marginally significant positive correlations between the negative DLPFC-to-basal ganglia coupling during cancellation and SIF, and the slightly positive DLPFC-to-basal ganglia coupling during prevention and the slope of intrusion reduction. These show that the negativity of DLPFC-to-basal ganglia coupling is associated with greater retrieval suppression in general. It may be that reduced DLPFC down-regulation of basal ganglia activity led to increased activity in the indirect pathway, which in turn inhibits memory retrieval in the hippocampus (Scimeca & Badre, 2012).

Overall, there was a trend that the DLPFC-basal ganglia effective connectivity is associated with both memory and motor inhibition, pointing to the possibility that the interactions between the DLPFC and the basal ganglia are critical for achieving supramodal inhibitory control. The association between task-specific connectivity and behaviour was less clear. In Step 2 DCMs, while we observed significant positive correlation between the DLPFC-to-M1 coupling during prevention and SSRT, the correlations between the basal ganglia-to-hippocampus coupling and behaviour were not significant. As pointed out earlier, we need to take caution when interpreting DCM parameter estimates, as they are not as reliable as BMS. The current results may have been influenced by our experimental design, the DCM model structure, or the ROI definition. Refinement in these respects may help clarify the BMA results.

5.3.7 Limitations and Future Directions

We have briefly mentioned that there is a few things we could improve in this fMRI study. First of all, we could further optimise our experimental design. Although we aimed to investigate the role of the basal ganglia in memory and motor stopping, the memory and motor tasks may not perfectly isolate memory and motor stopping processes in our current design. On one hand, there may be a motor component in the memory task, since the participants have to provide intrusion ratings through a button press after each trial in the Think/No-Think phase. Although the button press only takes place after the Think/No-Think trials, it is possible that participants have already started preparing for the motor responses during the trials. For example, in the Step 1 memory DCM, although there was strong evidence for both the DLPFC and the basal ganglia being involved in memory inhibition, whether they are interacting with M1, hippocampus, or both was unclear. The DLPFC-M1 and the basal ganglia-M1 connectivity may have arisen due to the preparation of motor responses. On the other hand, there may be a memory component in the motor task, as participants had to learn colour-button mapping between four colours and two buttons. .

Future studies should try to make the memory and motor tasks as pure as possible. For example, to remove the motor component from the memory task, we could try to find a more objective method to distinguish Intrusion and Non-intrusion trials instead of asking for subjective ratings from the participants. For example, with fMRI, we could use a classification approach to identify the neural activity associated with each stimulus (e.g. Wimber et al., 2015), and detect whether unwanted targets have intruded into mind by monitoring the item-specific activity. To remove the memory component from the motor task, we could simplify the Combined Go/No-Go and Stop-signal task to involve only one button. Participants would always press the button when seeing the stimuli, unless when a stop signal is presented. To match it better with the Think/No-Think task, where all stimuli are visually presented, we could change the auditory stop signal in the motor task to a different visual stimulus. Using visual stop signals can also help rule out auditory neural responses from motor inhibition. For example, we could have blue and yellow coloured circles. Participants could be trained to respond to blue circles for the Go trials. However, they need to stop pressing buttons whenever they see a yellow circle. For the No-Go trial, the yellow circle will be presented straight away. For the

Stop trial, the yellow circle will replace the blue circle after a delay. Using these "purer" paradigms, we would hope to further clarify the DCM results in identifying task-specific pathways. On the univariate level, we may also be at a better position to identify distinct basal ganglia activations between the memory and motor tasks.

In addition, there may be alternative ways for defining the basal ganglia ROI. For example, we based our ROI definition on the meta-analysis, which revealed activations in the caudate head and body, putamen, and GPe. We therefore defined our basal ganglia region by combining the caudate head and body, putamen, and GPe. However, others may disagree with this decision: 1) although there are feedforward and feedbackward projections between the striatum and the GPe, the classic basal ganglia model posits the GPe to be downstream from the striatum. Therefore, some may prefer to exclude the GPe from our ROI and model it separately. And 2) the meta-analysis may not have revealed all activity that is related to memory and motor inhibition, due to the constraints of coordinate-based meta-analytic approaches that we discussed in Chapter 3. For example, many have confirmed the importance of the STN, part of the basal ganglia hyperdirect pathway, in motor inhibition. However, STN activity is not always reported, possibly due to the small size of the structure. Therefore, our basal ganglia ROI may not have represented all basal ganglia mechanisms that are engaged in memory and motor inhibition. Moreover, as discussed earlier, our basal ganglia ROIs may be overly liberal by size. Constraining the ROIs may help clarify our results.

Finally, there may be ways to improve our DCM model structure. We specified the current model structure, so that we could 1) test the hypothesis that the basal ganglia are part of the supramodal network of inhibition in that they are involved in both memory and motor stopping, and that they contribute to inhibition through task-specific pathways instead of task-irrelevant pathways; and 2) investigate how the basal ganglia interact with other putative supramodal regions (e.g., DLPFC) before reaching the downstream task-specific regions. Since we ran separate DCMs on the memory and motor inhibition tasks, we kept the model structures consistent (including the DLPFC, basal ganglia, hippocampus, and M1 nodes), but only switching the modulatory and driving inputs to the corresponding task. However, this may be problematic as we have included presumably task-irrelevant information in the model structure, which could skew model evidence and influence our results. For example, in the motor task, we

would not hypothesise hippocampal involvement; in a pure memory task, we would not expect M1 involvement. In addition, for some model or family comparisons, we would be comparing between a plausible and a theoretically unlikely model, which may not provide useful information for our inferences. Therefore, in addition to refining experimental design and ROI definition, we may also need to reconsider the most appropriate DCM model structure for our purposes. One option would be to reduce the number of nodes, and include only the DLPFC, basal ganglia, and the task-specific region.

Despite the above limitations, we believe that our DCM modelling presents some important initial evidence that the basal ganglia play effective roles in both memory and motor inhibition. Future studies could explore alternative model structures to further investigate how specific basal ganglia nuclei interact to achieve inhibition in humans. One challenge for these alternative model structures is complexity. As a model space gets more complicated, it can take extensive computing resources to run the analyses, and the results may become harder to interpret as well. Finally, we need to be aware of the robustness of the DCM coupling parameters. We extracted DCM coupling parameters from the relevant task modulation pathways to correlate with the corresponding behavioural indices. However, previous studies have found that coupling parameters are not as stable as BMS. For example, Rowe et al. (2010) examined the reproducibility of DCM model selection and parameter estimates across two scanning sessions in both healthy controls and patients with Parkinson's disease in the context of action selection. They repeated the same 48-model DCM analysis for both sessions and compared if the results are consistent in the patient group and in the healthy control group. They found that DCM model selection is relatively stable, and that the same model was identified as most likely across sessions in both healthy controls and medicated patients. However, the parameters for task-independent connectivity and task modulation were poorly correlated across sessions. Rowe et al. therefore concluded that BMS may be sufficient for critical inferences, but caution is required when interpreting the connectivity parameter estimates.

5.3.8 Conclusion

This fMRI study aimed to investigate 1) how the basal ganglia interact with the prefrontal control regions and the task-specific regions to achieve memory and motor inhibition, and 2) whether the prevention and cancellation processes require distinct neural mechanisms. Through our univariate analysis, we replicated the meta-analysis, and observed overlapping activity between memory and motor inhibition in the DLPFC, VLPFC, supramarginal/angular gyrus and the basal ganglia. The prevention and cancellation processes also activated the same network, although the activity during prevention is mainly from memory inhibition, while the activity during cancellation is mainly from motor inhibition. This could be due to the prevention and cancellation conditions having unequal amounts of trials in the current experiment.

Through the DCM analyses, we confirmed our hypothesis that both the DLPFC and the basal ganglia are effectively involved in memory and motor inhibition, and the inhibition is achieved through targeting task-specific regions. This provides crucial first evidence that not only are the basal ganglia important for motor control, but they are part of a larger network responsible for inhibition across the memory and motor domains. In terms of how the basal ganglia interact with the DLPFC and the task-specific regions, we found that the indirect hypothesis fit the motor inhibition task, where the basal ganglia communicate with M1 through the DLPFC. Meanwhile, the intermediary hypothesis fit the memory inhibition, where the DLPFC communicates with the hippocampus through the basal ganglia. These provide strong evidence that the basal ganglia play causal roles in both memory and motor inhibition through interactions with the prefrontal control regions and the task-specific regions.

In addition, we identified mechanisms specific to the cancellation and prevention subprocesses of inhibitory control. In the motor domain, while the basal ganglia are critical for motor control in general, the DLPFC seems to be more actively involved in stopping, especially during prevention. In the memory domain, both the DLPFC and the basal ganglia causally interact with the hippocampus to achieve inhibition. However, due to the current constraints, we still need to work towards a better understanding of the anatomical connections between the basal ganglia and the relevant regions of interest, a purer design to compare inhibitory control in different domains, and more

robust modelling approaches that we can reliably use to better understand the relationship between effective connectivity and behaviour.

After investigating the functional interactions between the basal ganglia and the relevant regions to achieve inhibition across domains and processes, our next step is to explore the underlying anatomical connections. As an initial attempt, we acquired diffusion-weighted imaging (DWI) that allows us to study white matter connections and microstructure *in vivo*. The next chapter will present a brief overview of DWI, the methods we used, and our findings and concerns.

6 DIFFUSION-WEIGHTED IMAGING TO EXPLORE INHIBITION PATHWAYS

Previous chapters established the functional role of the basal ganglia in memory and motor inhibition, and specifically in the prevention and cancellation inhibitory processes. In this chapter, we discuss our approach with diffusion-weighted imaging (DWI) to investigate the relationship between anatomical connections and functional and behavioural indices. We planned to 1) explore which portions of the white matter connections throughout the whole brain are significantly associated with DCM coupling parameters and behavioural performance across the prevention and cancellation conditions in the memory and motor tasks, and 2) use diffusion tractography to defined the task- or process-specific tracts, from which we would extract diffusion parameters for individual differences analyses. Unfortunately, our attempts did not turn out as we expected. First, we were unable to identify any white matter differences in association with effective connectivity or behaviour. Second, we had to hold off the tractography because our ROIs were across the left and right hemispheres. We are not aware of any studies tracing inter-hemispheric white matter connections using diffusion tractography, and the tracing may require more anatomical knowledge than we currently have. We discuss our concerns and future directions in this chapter.

6.1 A Brief Overview of Diffusion-weighted Imaging

Diffusion-weighted imaging (DWI) is a relatively recent technique that allows researchers to measure microstructures in the brain *in vivo*, and examine the white matter tracts that connect different brain regions anatomically and non-intrusively. DWI estimates neural bundles by measuring the diffusivity of water molecules in different body tissues. For example, in the corticospinal fluid (CSF), the movement of water is almost completely free (isotropic) as compared to in the grey matter and then in the white matter. Compared to grey matter and CSF, water diffusion is much faster in the white matter as it is constrained to only follow the direction of the neural bundles (anisotropic; Figure 6.1). Therefore, by applying diffusion-weighted gradients at different orientations, the diffusivity of the water molecules can be used to estimate tissue type and reconstruct white matter tracts.

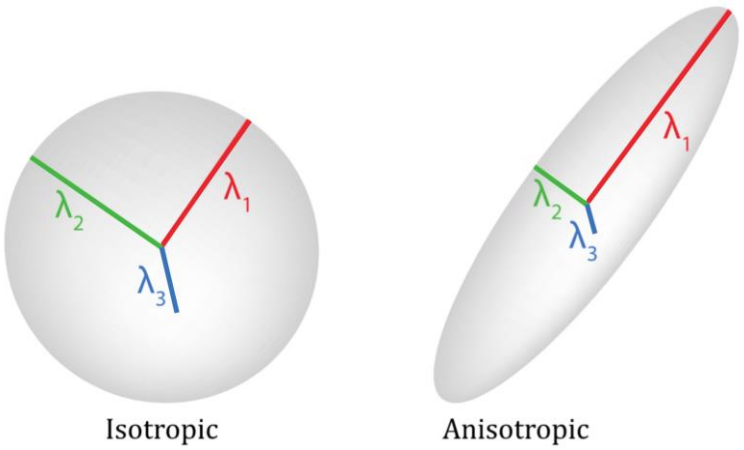

Figure 6.1. Isotropic and Anisotropic Water Diffusion in the Diffusion Tensor Model. λ_1, λ_2, and λ_3 denote the degree of diffusion along the three principles.

A simple model of the diffusion process is Diffusion Tensor Imaging (DTI), which assumes a single ellipsoid in each voxel, estimating the extent of axial and radial diffusivity, as if the axons travelling through a voxel travel in the same direction. However, in reality, depending on the size and location of the voxel, there can be crossing fibres following different directions in one single voxel. One voxel may also contain multiple tissue types, inducing the Partial Volume Effect (PVE). Hence more advanced diffusion models are developed to address these issues.

One of the more advanced diffusion models is spherical deconvolution (Tournier et al., 2004). To improve resolving crossing fibres, spherical deconvolution requires data from High Angular Resolution Diffusion Imaging (HARDI), where stronger diffusion weightings (b-value) are applied for higher angular resolution and hence sensitivity to fibre orientation (Tuch et al., 2002). Spherical deconvolution then estimates the fibre orientation density function (fODF) to find the most plausible white matter tracts from the data, regardless of the number of underlying fibre orientations. To resolve the PVE, spherical deconvolution assumes that all white matter fibre bundles share identical diffusion characteristics. Therefore, any tissue that has different diffusion characteristics will be implicitly assigned to PVE. Indeed, Farquharson et al. (2013) compared deterministic and probabilistic DTI tract reconstruction with probabilistic constrained spherical deconvolution, and observed more realistic results from the latter.

The problem with having a stronger diffusion weighting is its trade-off with the signal-to-noise ratio (SNR). To compensate for this trade-off, multi-shell diffusion imaging has been developed, where data are acquired with multiple b-values. While data from the higher b-value acquisition are more optimal for fibre reconstruction, data from the lower b-value acquisition could be used to recover the SNR.

DWI is advantageous for two reasons. First, it allows for the estimation of multiple diffusion properties that indicates the microstructure underlying a specified region, such as diffusivity and anisotropy. Regarding measures of diffusivity, in DTI, the extent of diffusion is usually denoted with mean diffusivity (MD), which is calculated by averaging the eigenvalues that represent the length, width, and depth of the ellipsoid in a voxel. More advanced techniques, such as spherical deconvolution, use the fODF. The fODF does not assume the number of fibres going through a voxel or the diffusivity, but simply fits the diffusion signal to expected fibre responses with appropriate constraints to construct a distribution of fibre orientations. In terms of measures of the degree of anisotropy in a voxel, a popular one is fractional anisotropy (FA). FA is calculated by square rooting the sum of squares of the diffusivity differences, divided by the sum of squares of the diffusivities.

Second, the processed DWI data can be used for tract re-construction to illustrate the neural bundles connecting specified structures in the brain. This technique is often

referred to as diffusion tractography. Diffusion tractography is advantageous in that it is a non-intrusive technique to illustrate the neural bundles connecting brain regions based on the estimated diffusion parameters. However, the reliability of diffusion tractography is limited by a number of factors. First, the currently available algorithms may not be able to accurately resolve crossing fibres. In the final illustration, there may be single neural bundles that consist of multiple smaller ones heading different directions, or there may be seemingly independent fibres that should have crossed over. Second, the resolution of diffusion-weighted imaging is typically 2 mm isotropic. At this resolution, diffusion tractography can easily detect major well-known fibres in the brain, but is much less sensitive to smaller fibres. Finally, although diffusion tractography can illustrate the general shape of the neural bundles, it does not infer directionality, i.e., it is unclear whether a neural bundle between two brain structures contains projections from A to B, or B to A, or both.

In summary, DWI provides a useful tool to examine white matter connections in the brain *in vivo*. However, due to the constraints in the current technology, one needs to take caution in both processing the data and interpreting the results. In this study, we acquired multi-shell diffusion-weighted imaging data to best account for concerns over crossing fibres, PVE, and the trade-off between the strength of diffusion gradient and the SNR.

6.2 Diffusion Tractography and the Basal Ganglia

Despite the extensive effort illustrating basal ganglia anatomy and connectivity in the animal literature, there remains limited evidence on whether those findings also apply to humans. Kotz et al. (2013) used diffusion imaging to identify anatomical connectivity between the caudate nucleus and cortical structures. According to their results, caudate body mainly connects with the motor cortices, caudate head with the PFC, and ventral striatum with the frontopolar regions. Caudate tail was not included in the analyses. These findings are mostly consistent with the basal ganglia functional loops summarised in Seger (2013). In addition, Draganski et al. (2008) were able to create voxel-based connectivity profile and identify basal ganglia connectivity patterns that are similar to the topographical and integrative networks described in Haber and Knutson (2010) and Choi et al. (2016).

In addition to using DWI measures to study anatomical connections in a brain, some studies also explored using similar techniques to identify possible neurological mechanisms underlying different diseases. For example, Marrakchi-Kacem et al. (2014) compared the proportion of functional subregions in the basal ganglia that are identified through their connectivity profiles between healthy individuals and patients with Huntington's disease. They observed that Huntington's patients exhibit a change of distribution in the functional subregions in the striatum when compared with healthy subjects, suggesting selective neurodegeneration in particular regions. For example, they observed reduced proportion of the associative territories (central striatum), which may account for the cognitive dysfunctions in Huntington's patients (e.g., executive functions, motor and psychomotor speed) and the altered microstructure as described in preclinical Huntington disease. In addition, Sweet et al. (2014) identified that the subthalamopontocerebellar tract and the dentatothalamic tract may be related to symptoms expression in Parkinson's disease and that using diffusion imaging to localise these tracts may assist targeting for deep brain stimulation. Last but not the least, Jung et al. (2015) also found significant correlations between the integrity of several white matter tracts and a range of verbal and non-verbal cognitive functions in patients with basal ganglia stroke, including the superior longitudinal fasciculus, the right inferior longitudinal fasciculus, and the frontostriatal fibres.

Specific to our purpose, we aimed to investigate which white matter connections involving the basal ganglia may contribute to the prevention and cancellation stopping processes in memory and motor inhibition. According to the DCM results from Section 5.2.3, memory inhibition is achieved through a DLPFC-basal ganglia-hippocampus pathway, while motor inhibition is achieved through a basal ganglia-DLPFC-M1 pathway. Not all of these pathways are well illustrated, especially in relation to stopping memory retrieval and motor actions. In the following paragraphs, we are going to develop hypotheses for the connections that are less understood based on current knowledge of the anatomical connections along these routes.

For the DLPFC-basal ganglia-hippocampus pathway for memory inhibition, we have reviewed in Section 2.3 that there are projections from the DLPFC to the centromedial striatum (e.g. Haber et al., 2006). However, how the basal ganglia connect to the hippocampus is less clear. On one hand, it is possible that the basal ganglia process the

DLPFC projection through the intrinsic pathways to the output nuclei (i.e., GPi and SNr), which pass on the processed information to the thalamus. It has been shown that the anterior thalamic projects to the hippocampus through the cingulum bundle, a pathway critical for episodic memory (see Aggleton (2014) for review). As summarised by Kita (2010), the topographical organisation of the corticostriatal projections is maintained in the basal ganglia nuclei and the thalamus. It is therefore likely that the DLPFC-basal ganglia connections will follow through to the associative regions of the thalamus, such as the anterior thalamic nuclei, and then communicate with the hippocampus.

Regarding the basal ganglia-DLPFC-M1 pathway for motor inhibition, although there is an extensive literature on the corticostriatal projections, evidence is sparse for the reverse. It is likely that this connection is indirect, such as through the basal ganglia output nuclei and the thalamus. In terms of the DLPFC-to-M1 projection, this may also be indirect through the preSMA. For example, Bracht et al. (2012) used diffusion tractography to investigate the relationship between motor pathways and psychomotor retardation in major depressive disorder. Psychomotor retardation involves speech, facial expression, posture, as well as pace and extent of movements. Bracht et al. identified the association between reduced motor activity and altered structural connectivity in the preSMA-SMA proper, and SMA proper-M1 pathways. Specific to motor control, they found altered involvement in the DLPFC-preSMA and the ACC-preSMA pathways. These findings point to the role of the DLPFC in motor control, possibly through a DLPFC-preSMA-SMA-M1 pathway.

6.3 Our Approach and Concerns

To identify the white matter connections underlying the functional interactions between the putative supramodal regions (DLPFC and basal ganglia) and the task specific regions (hippocampus and M1), we took a two-step approach. First, we used an exploratory analysis to isolate portions of the white matter tracts that are associated with the cancellation and prevention processes in memory and motor inhibition. Second, we planned to reconstruct the relevant tracts so that we can extract diffusion parameters for individual differences analyses.

For the first step exploratory analysis, we used tract-based skeletal statistics (TBSS). TBSS is part of the FSL distribution (Smith et al., 2006) and is a recently developed automated method for detecting voxel-wise changes in the whole brain. One of the challenges for conducting group analyses with DWI is registering individual subject's images to a common space, due to its highly directional and topographical nature. TBSS aims to solve these issues by 1) carefully tuned nonlinear registration, and then 2) projection onto an alignment-invariant tract representation, in the hope to improve the sensitivity, objectivity, and interpretability of analysis of multi-subject diffusion imaging studies.

For the second step tractography analysis, we used spherical deconvolution for tract reconstruction. However, we did not proceed with tract tracing mainly for two reasons. First, our TBSS analysis did not reveal any significant individual differences in white matter connections that are associated with the prevention and cancellation processes in the memory and motor inhibition tasks. This did not help us isolate potential pathways that we could focus on for the tractography. Second, and more importantly, our regions of interest located across the left and right hemispheres. Specifically, our DLPFC and basal ganglia ROIs were in the right hemisphere, and our M1 and hippocampus ROIs were in the left hemisphere. Understanding how the anatomical pathways support functional interactions would require tracing white matter connections across hemispheres. This is challenging because the specific pathways through which our ROIs communicate across hemispheres remains unclear. Due to the time constraints of this PhD, we had to leave the tractography analysis for later. We will outline the methods that we have used for both TBSS and tractography, and discuss our null finding at the end.

6.4 Methods

6.4.1 DWI Acquisition

As mentioned in Chapter 5, diffusion-weighted imaging was acquired at the end of the first session, in which participants performed the Combined Go/No-Go and Stop-signal task. The MRI setup was identical to those described in Section 5.1.3. Diffusion-weighted imaging was acquired using a multi-band diffusion-weighted sequence

(192×192×136; 2 mm^3 isotropic voxels; repetition time = 2320 ms; echo time = 89 ms; interleaved slice acquisition; multi-band acceleration factor = 4) with the following b-values and diffusion gradient directions: b-value = 0 s/mm (0 directions), b-value = 300 s/mm (8 directions), b-value = 1000 s/mm (30 directions) and b-value = 2000 s/mm (60 directions). We acquired two repetitions for the diffusion data, one with anterior to posterior phase encoding direction, and the other with posterior to anterior phase encoding direction. This is to better account for eddy current correction.

6.4.2 DWI Pre-processing and Analyses

6.4.2.1 Preprocessing

We used the following steps to preprocess our diffusion data. First, we denoised the diffusion images using the random matrix field theory (Veraart et al., 2016). This method allows for the estimation of noise level in a local neighborhood based on the singular value decomposition of a matrix combining neighborhood voxels and diffusion directions. Second, we used Fourier's transform sub-voxel shifts to remove Gibbs-Ringing artifacts, which are spurious oscillations in the vicinity of sharp image transients such as at tissue boundaries (Kellner et al., 2015). Finally, we corrected motion and susceptibility-induced distortions using FSL's topup function, where we combined the images acquired with opposite phase-encoding directions to achieve maximal geometric fidelity in the resulting diffusion images (Andersson et al., 2003).

6.4.2.2 TBSS

We conducted TBSS following the procedures detailed in the FSL user manual. First we aligned all subjects' FA maps into a common space using the nonlinear registration tool FNIRT (Andersson, 2007a; 2007b), which uses a b-spline representation of the registration warp field (Rueckert, 1999). Next, we created a mean FA image, and thinned the mean FA image to create a mean FA skeleton that represents the centres of all tracts common to the group. We then projected each subject's aligned FA data onto this skeleton and fed the resulting data into computing the voxel-wise cross-subject statistics. We computed separate TBSS analyses for each of the effective connectivity or behavioural parameters that we wanted to investigate, including the coupling parameters from the DCM winning models, SSRT, SIF, and the slope of intrusion induction. Since

we only collected one DWI measure for each participant, we conducted 1-sample *t*-tests and examined the effect of each covariate on white matter changes.

6.4.2.3 Tractography

In anticipation to performing diffusion tractography, we reconstructed white matter tracts following these two steps. First, we estimated fibre orientation distribution using the damped Richardson-Lucy algorithm (Dell'Acqua et al., 2010). This is a variant of the spherical deconvolution algorithm based on an adaptive regularisation that is better at reducing isotropic partial volume effects. Second, we performed tractography following the methods described in Henriques et al. (2015a), where they used an adapted version of a DTI streamline brute force algorithm. This algorithm allows the reconstruction of tracts from multiple fibre directions estimated per voxel. DTI was processed using the united diffusion kurtosis imaging (UDKI) toolbox (Henriques et al., 2015b).

6.5 Results and Discussion

We aimed to use DWI to 1) identify portions of white matter tracts that are associated with either effective connectivity or behavioural indices of the prevention or cancellation processes during memory and motor inhibition, and 2) extract diffusion parameters from the relevant tracts for individual differences analyses. Unfortunately, using TBSS, we were unable to detect any inter-individual differences in white matter that is related to memory or motor inhibition. This was the case both when we used the recommended threshold ($p<.05$) or with relaxed thresholds.

This lack of findings may have resulted from multiple factors. First, it is possible that TBSS is not optimised for our type of analyses. Most of the studies using TBSS compared white matter differences between groups, such as between patients and healthy controls (e.g. Rae et al., 2016; Ye et al., 2015) or between genders (e.g. Kanaan et al., 2014). In our analysis, we are only examining the effect of covariates in one single group. Second, we may lack statistical power. It may be that our sample size (N=30) is still too small to be sensitive to individual differences in white matter in relation to effective connectivity or behavioural performances, or there is too much variance in the functional or behavioural measures to easily detect meaningful

individual variability in the associated white matter tracts. Finally, it is also possible that functional or behavioural changes are not related to white matter variability, but rather grey matter changes local to the region of interest. If this is true, individual differences in functional performance and connectivity may be manifested in grey matter volume or integrity in the regions of interest, instead of white matter tracts through which different regions communicate. However, this is unlikely, as there have been previous studies relating white matter microstructure with effective connectivity during motor inhibition. For example, Rae et al. (2015) conducted a DCM analysis to investigate the network dynamics between the IFG, preSMA, STN, and M1 during motor inhibition. After identifying the winning model, they extracted mean diffusivity from the tracts connecting preSMA and STN, and IFG and STN. They found that mean diffusivity in these tracts predicted individual differences in stopping efficiency, and correlated with effective connectivity in the same pathway during successful motor inhibition. To improve our TBSS results, we will need to 1) increase our sample size, and 2) optimise our experimental design so that we can better differentiate between the prevention and cancellation processes, and between the memory and motor tasks (see Section 5.3 for a more detailed discussion).

Based on current findings and concerns, there is a number of directions for future research First, to improve our confidence in tractography, we need to first understand the anatomical pathway between our regions of interest, especially how they communicate across hemispheres. For example, how the right DLPFC controls left M1 activity, and how the right basal ganglia influences left hippocampal activity. To do this, we will need to either collaborate with animal researchers to trace these connections in the primate brain, or to work with histology to find out how these connections are formed in the human brain. Second, we could examine whether grey matter indices in the regions of interest are related to effective connectivity or behaviour. For example, we could use voxel-based morphometry (VBM) to investigate whether grey matter volume is correlated with the ability to inhibit unwanted memories or actions. We could also extract diffusion parameters from grey matter structures to see if they are significantly associated with effective connectivity or behaviour.

Once we have a better understanding of the anatomical pathways between our ROIs, we can use tractography to define those connections, extract diffusion parameters, and

investigate their relationship with functional interactions (as indexed by effective connectivity) and behaviour. Since we have already processed whole-brain tract reconstruction, we will be able to isolate the relevant tracts by defining regions of inclusion and regions of exclusion. We will be specifically interested in the following pathways. For memory inhibition, we will first illustrate the connection between the DLPFC and the striatum. For the basal ganglia-hippocampal pathway, if we assume it goes through the basal ganglia intrinsic nuclei to output to the thalamus, we can try to illustrate the thalamic connection with the hippocampus through the cingulum bundle. Although this cingulum pathway is only part of the basal ganglia-hippocampus connection, it should reflect the basal ganglia influence to regulating hippocampal activity as it is efferent to the basal ganglia system. For motor inhibition, we will first try to illustrate the basal ganglia-DLPFC connection, possibly by isolating connections between the thalamus and the DLPFC. We will then isolate pathways between the DLPFC and M1 by defining the intermediaries (i.e. preSMA and SMA).

After we have extracted diffusion parameters, such as mean diffusivity and fractional anisotropy, from these pathways, we can correlate them with effective connectivity and behavioural indices. It would be specifically of interest to see whether the white matter structure between the putative supramodal regions will be associated with both prevention and cancellation during memory and motor inhibition. In addition, we would like to investigate if the white matter structure in the task-specific tracts is only associated with the corresponding task context. We would expect that the basal ganglia-hippocampus pathway is only associated with memory inhibition but not motor inhibition, while the DLPFC-M1 pathway is only associated with motor inhibition but not memory inhibition.

7 CONCLUSIONS AND FUTURE DIRECTIONS

This PhD thesis aimed to investigate the role of the basal ganglia in memory and motor inhibition. The basal ganglia have had an established role in motor control, including motor initiation and motor inhibition. However, recent evidence suggests that these structures may also be involved in cognitive control, such as the voluntary suppression of unwanted memories. It has been proposed that there may be a supramodal network of inhibition involving cortical regions such as the DLPFC and the VLPFC. Here we investigated whether the supramodal network also includes subcortical structures such as the basal ganglia. If so, how are the basal ganglia interacting with the other supramodal regions and the task-specific regions to achieve inhibition. Finally, what are the anatomical pathways underlying the inhibition of prepotent responses.

7.1 Summary of Findings and Implications

To tackle these questions, we first used a series of meta-analyses to confirm that the basal ganglia are consistently activated across studies using memory and motor inhibition tasks (Chapter 3). Specifically, we observed left centromedial striatum activity in the Go/No-Go task, but right centromedial striatum activity in the Stop-signal and Think/No-Think tasks. On one hand, this striatal cluster is consistent with the associative functional zone that receives direct projections from the DLPFC (Haber,

2003; Haber et al., 2006), suggesting that a DLPFC-basal ganglia interaction may be critical for inhibitory control. On the other hand, the lateralisation effect indicates that there may be distinct subprocesses of inhibition that are supported by different neural mechanisms (Dalley et al., 2011; Schachar et al., 2007; Verbruggen & Logan, 2008). While the Go/No-Go task may primarily engage a prevention process, the Stop-signal and the Think/No-Think tasks may primarily engage a cancellation process.

In Chapter 4, we presented behavioural paradigms to differentiate prevention and cancellation processes in memory and motor inhibition tasks. For memory inhibition, we developed an adapted Think/No-Think paradigm, where we 1) adjusted the experimental design and instructions so that participants are more motivated to suppress the unwanted associations, and 2) asked participants whether the unwanted targets came to mind after each trial as an indicator of whether they successfully *prevented* the retrieval of unwanted memories, or whether they had to *cancel* a retrieval process due to intrusions. For motor inhibition, we adopted a Combined Go/No-Go and Stop-signal paradigm designed by Weaver and Anderson (unpublished). There were two types of stop signals in this paradigm. One is a Concurrent Stop signal that is presented simultaneously with the stimulus. This is similar to the Go/No-Go task and may require a prevention process. The other is a delayed stop signal that is presented after stimulus onset. This is the typical Stop-signal task and may require a cancellation process.

We then conducted an empirical fMRI study (Chapter 5) using these behavioural paradigms, and found that both the basal ganglia and the DLPFC play causal roles to achieve inhibition through task-specific pathways. This is largely consistent with findings from Schmitz et al. (in preparation), as they also observed top-down regulation from the supramodal regions (DLPFC and VLPFC in their case) through the task-specific pathways to the hippocampus for memory inhibition, and to M1 for motor inhibition. Furthermore, we found that the DLPFC and the basal ganglia interact in different ways to achieve inhibition in different task domains. On one hand, memory inhibition requires a DLPFC-basal ganglia-hippocampus pathway, consistent with the intermediary hypothesis. It is possible that the basal ganglia process control signals from the DLPFC, and then communicate with the hippocampus via the thalamus through the cingulum bundle (Aggleton, 2014). On the other hand, motor inhibition requires a basal ganglia-DLPFC-M1 pathway. This is consistent with the indirect

hypothesis, where the basal ganglia communicate with M1 via the prefrontal cortex, possibly through the preSMA and SMA (Bracht et al., 2012; Rowe et al., 2010). However, since effective connectivity from DCM does not imply the underlying anatomical pathways, it is possible that there are other intermediaries between the nodes that we have specified in the model. For example, in memory inhibition, the basal ganglia outputs may instead engage the limbic cortex, such as the ACC, which then regulate hippocampal activity either through the entorhinal cortex, or through the thalamic reuniens nuclei (Anderson et al., 2016). In motor inhibition, the DLPFC may regulate M1 activity through the basal ganglia again, instead of through the preSMA and SMA, given the critical role of the basal ganglia in motor control (Alexander et al., 1986; Kandel et al., 2012).

When comparing cancellation and prevention, although these inhibitory subprocesses activated common regions in the frontoparietal and basal ganglia, they also yielded unique activations. The univariate analysis showed that prevention activated bilateral putamen, parahippocampal gyrus, and other temporal and occipital regions more than cancellation. Cancellation, on the other hand, activated bilateral preSMA, left postcentral gyrus, and medial frontal gyrus. These suggest that the cancellation and prevention processes may require distinct neural processes and should not be treated equivalently. We then correlated DCM coupling parameters from prevention and cancellation modulations with behavioural indices. For motor inhibition, we found significant correlations between the DLPFC-to-M1 coupling during prevention and SSRT for Step 1 and Step 2 DCMs. For memory inhibition, in Step 1 DCM, we found significant correlations between the basal ganglia-hippocampus coupling during prevention and SIF, and between the DLPFC-to-hippocampus coupling during cancellation and the slope of intrusion reduction. In Step 2 DCM, we found marginally significant correlations between the DLPFC-basal ganglia coupling during prevention and the slope of intrusion reduction, and during cancellation and SIF. It seems that the DLPFC-basal ganglia effective connectivity is associated with both memory and motor inhibition, during prevention and cancellation processes. Connectivity in the task-specific pathways appears to be associated with the corresponding task performance. However, we do need to take caution interpreting these results, both for the constraints in the current design, and the reliability of DCM parameter estimates in general.

Finally, we tried to identify anatomical pathways that are associated with these functional interactions during memory and motor inhibition (Chapter 6), but unfortunately did not find any significant result. As discussed in Section 6.5, this lack of finding may be due to the TBSS analysis not being optimal for detecting individual differences in a single group, or a lack of statistic power in our sample size.

7.2 Future Directions

This PhD thesis resolved two questions. First, we confirmed that the basal ganglia are consistently involved in memory and motor inhibition. Second, we found that the basal ganglia causally interact with the DLPFC to achieve memory and motor inhibition. However, the anatomical connections underlying the functional and effective interactions still remain unclear.

To understand how the basal ganglia interact with task-specific regions during memory and motor inhibition, we need to find out the efferent pathways from the basal ganglia to the hippocampus and M1. To do this, we can collaborate with anatomists and trace projections from specific brain structures to their target regions. For example, Haber et al. (2006) used macaque monkeys and injected tracers in a number of prefrontal regions. They observed that the DLPFC project to the centromedial striatum, a functional division associated with cognitive control. If we believe that this is also the region involved in inhibition, we could use the same method to trace its downstream targets. Since the topography in the corticostriatal projections is maintained throughout the basal ganglia system (Haber & Knutson, 2010), the tracers may lead up to the associative or control region of the thalamus. Using similar logic, we could follow through projections from the thalamus to the hippocampus and M1. We may be able to identify multiple candidate pathways using this method.

Once we have identified possible anatomical pathways between the basal ganglia and the task-specific regions, we can use neuroimaging methods to test whether those pathways are engaged during memory and motor inhibition. There could be a number of possible directions. First, with animal studies, we could use single-neuron recording to measure neural activity in the brain structures along the pathways, and analyse whether the activity changes with task. We could also use electrical stimulation to modulate activity in particular structures and examine whether the stimulation influences task

performance. Second, with human fMRI, we could use effective connectivity analyses to test whether the memory or inhibition tasks effectively modulate certain pathways. However, this may create an overly complicated model structure, which will be computationally consuming, and make the results hard to interpret (Stephan et al., 2010). Finally, with diffusion imaging, we can define the candidate pathways through tractography, and extract diffusion parameters from the pathways. We can then correlate the diffusion parameters with behavioural indices to test whether these pathways are associated with inhibiting retrieval or motor actions.

In addition to understanding the anatomical pathways, another question of interest is the scope of influence of the putative supramodal network. Here we have observed common activation in the PFC and the basal ganglia between memory and motor inhibition. However, the basal ganglia are also involved in other functions, such as reward processing, probabilistic learning, social and language functions, and visual processes, etc. (e.g. Pauli et al., 2016; Seger, 2013; Shohamy, 2011; Shohamy et al., 2009). As reviewed in the introduction, Depue et al. (2015) observed common mechanisms of inhibition in the PFC across cognitive, emotional, and motor processes. It would be curious to investigate whether these common mechanisms also involve the basal ganglia.

On the other hand, it would be important to differentiate whether the common mechanisms are truly due to inhibitory control processes, rather than other features that the tasks may have in common, such as difficulty between conditions, attention to different types of stimulus, or task-set shifting, as response and inhibition present opposite task goals, etc. For example, although the Stop-signal task is typically used to measure inhibitory control, some have argued that it may instead be attention to infrequent stimuli. Erika-Florence et al. (2014) used four different versions of the Stop-signal task and found that the inferior frontal cortex, usually associated with inhibition, is more active when processing infrequent and novel stimuli, regardless of behavioural inhibitory demands. Similarly, in the Think/No-Think task, although the DLPFC is repeated activated during retrieval suppression, and is hence associated with memory inhibition, it is also involved in other functions such as salience detection in the dorsal attention system. For instance, Shulman et al. (2001) presented participants with brief intervals of coherent motion embedded in dynamic noise, and asked them to determine

the direction of the motion. They found that although there were overlaps in brain activity between detecting stimulus onset and searching for motion, some regions, including the DLPFC, were unique to stimulus detection. It is possible that the DLPFC activations in the Think/No-Think task is a consequence of participants having the recognise the Think and No-Think stimuli rather than inhibition per se. Overall, future studies should consider including control tasks that tap into other functions that may be common to memory and motor inhibition tasks, so that we can more confidently isolate neural mechanisms that are unique to inhibition

Finally, the current research may gain insight into the relationships between the cognitive and motor deficits from patients with basal ganglia impairments, including neurological diseases such as Parkinson's disease (PD) and psychiatric disorders such as attention deficit hyperactivity disorder (ADHD). As reviewed in Davie (2008), the hallmark of PD is cell loss in the substantia nigra. The substantia nigra sends dopaminergic modulation to the striatum, which then engages the direct and indirect pathways to initiate or terminate responses, respectively. Impairment in the substantia nigra can hence lead to imbalanced control of the basal ganglia on motor functions. PD patients are often treated with dopamine to help restore the control mechanism. However, some have observed that dopamine treatment can induce intrusive behaviour, such as impulsivity and compulsion, since the treatment is of rewarding nature (Evans et al., 2009; Robbins & Cools, 2014). For our purpose, it would be of interest to see if the same intrusiveness applies in memory control. For example, in PD patients, will they struggle with retrieving memories in similar ways as initiating actions when they are off-medication? In contrast, will they have trouble inhibiting memories as controlling impulsive or inappropriate behaviour when they are medicated? Future studies could compare patients' behaviour when they are on- or off-medication, so as to establish the relationship between dopaminergic modulation in the basal ganglia and memory and motor control.

Similarly, ADHD is characterised by persistent and developmentally-inappropriate levels of overactivity, inattention and impulsivity (American Psychiatric Association, 1994). Thapar et al. (2013) reviewed that the causes to ADHD are manifold, including genetics and the environment. However, there is evidence that symptoms in ADHD may be associated with impaired reinforcement learning, particularly the involvement of

dopamine in the frontostriatal system (Tripp & Wickens, 2009). For example, Booth et al. (2005) showed that compared to healthy children, ADHD performed less well on motor responses inhibition, as they made more errors and had slower reaction time. ADHD children also showed less activity in the frontostriatal network compared to control. Durston et al. (2003) also showed that ADHD children are more susceptible to interference than healthy children during motor response inhibition, which may be associated delayed maturation of the frontostriatal system in ADHD. It would be of our interest to investigate whether ADHD children or adults would be similarly impaired at memory inhibition compared to healthy control, and whether they would also show hypoactivity in the frontostriatal network during the task. If so, this would be additional evidence that the frontostriatal network is associated with both memory and motor inhibition, and may be supramodal in nature.

Despite the exciting possibilities of using patient studies to further our understanding of how the basal ganglia are involved in memory and behavioural inhibition, challenges do apply. First, neurological and psychiatric disorders are often associated with complex causes, mechanisms, and symptoms. For example, PD is not only affected by dopamine, but also other neurotransmitters such as serotonin, noradrenaline, and acetylcholine (Robbins & Cools, 20124). The frontostriatal network is not unique to inhibition, but other higher level functions such as attention and planning. Therefore, we need to be cautious when developing future studies in a way that isolate the basal ganglia contribution to memory and motor inhibition. Second, the current experimental procedure may not be the most practical for patients, as the tasks typically last more than two and a half hours, which could be mentally and physically consuming. Future studies should adapt the current procedures to be more appropriate for patient studies, either by simplifying the tasks, or possibly by allowing more breaks during the experiment. We believe that patient studies can 1) help establish causal roles of the basal ganglia in supramodal inhibition, and 2) facilitate a better understanding of the basal ganglia functions across modalities, and hence improve the intervention on symptoms and impairments that are associated with basal ganglia malfunctions.

7.3 Concluding Remarks

Overall, this PhD thesis provides a crucial initial examination of the role of the basal ganglia in stopping memory retrievals, in addition to stopping motor action. We observed encouraging evidence of the causal involvement of the basal ganglia in memory and motor inhibition. To further investigate how the basal ganglia interact with the relevant regions to achieve inhibition, we need to have a better understanding over the underlying anatomical connections, improve our experimental design, and develop more robust modelling approaches so that we can more reliably relate function, anatomy and behaviour. Future research could also look into whether the basal ganglia control mechanisms are generalizable to domains other than memory and motion, and establish causal relationships through patient studies.

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9 Appendix

LIST OF STUDIES INCLUDED IN THE META-ANALYSES

Think/No-Think Task

First Author	Year	N	Journal
Anderson	2004	24	Science
Benoit	2012	18a	Neuron
Benoit	2012	18b	Neuron
Benoit	2015	16	Journal of Cognitive Neuroscience
Butler	2010	14	Cognitive, Affective, & Behavioral Neuroscience
Depue	2007	16	Science
Depue	2015	21	Cerebral Cortex
Gagnepain	2014	24	Proceedings of the National Academy of Sciences
Levy	2012	18	Journal of Neuroscience
Paz-Alonso	2013	33	Journal of Neuroscience
Gagnepain	2017	24	Journal of Neuroscience
Schmitz	2017	24	Nature Communications
Fawcett	In prep	30	
Levy	In prep	18	
Sacchet	2016	16	Cognitive, Affective, & Behavioral Neuroscience
Liu	2016	18	Nature Communications

Stop-Signal Task

First Author	Year	N	Journal
Aron	2006	13	Journal of Neuroscience
Aron	2007	10	Journal of Neuroscience
Berkman	2014	60	Journal of Neuroscience
Boecker	2011	15	Human Brain Mapping

Boehler	2010	15	NeuroImage
Cai	2009	12	Brain Research
Cai	2011	23	PLos One
Cai	2014	19	Human Brain Mapping
Chamberlain	2009	20	Biological Psychiatry
Chevrier	2007	14	Human Brain Mapping
Chikazoe	2009	22	Journal of Neuroscience
Cohen	2010	9	Frontiers in Human Neuroscience
Congdon	2014	62	Psychiatry Research: Neuroimaging
Cumins	2011	50	Molecular Psychiatry
De Wit	2012	37	American Journal of Psychiatry
Depue	2015	21	Cerebral Cortex
Ghahremani	2012	18	Journal of Neuroscience
Hendrick	2010	60	PLos One
Mendrick	2012	18	Behaviour and Psychology
Hughes	2013	15	Behavioural Brain Research
Jahfari	2011	20	Journal of Neuroscience
Lenartowicz	2011	23	Journal of Cognitive Neuroscience
Leung	2007	12	Journal of Neuroscience
Marco-Pallares	2008	10	Journal of Cognitive Neuroscience
McNab	2008	11	Neuropsychologia
Montojo	2013	30	Cerebral Cortex
Passarotti	2010	15	Neuropsychologia
Ramautar	2006	16	Brain Research
Rubia	2001	15	NeuroImage
Sagaspe	2011	14	NeuroImage

Schel	2014	14	Frontiers in Human Neuroscience
Sebastian	2012	24	Psychiatry Research: Neuroimaging
Sebastian	2013	49	Neurobiology of Ageing
Sebastian	2013	24	NeuroImage
Sharp	2010	26	Proceedings of the National Academy of Sciences
Tabu	2012	13	NeuroImage
Van der Meer	2011	19	NeuroImage
Xue	2008	15	Cerebral Cortex
Zheng	2008	20	Journal of Cognitive Neuroscience

Go/No-Go Task

First Author	Year	N	Journal
Altshuler	2005	13	Biological Psychiatry
Asahi	2004	17	European Archives of Psychiatry and Clinical Neuroscience
Braver	2001	14	Cerebral Cortex
Falconer	2008	23	Journal of Psychiatry & Neuroscience
Fassbener	2004	18	Cognitive Brain Research
Garavan	1999	14	Proceedings of the National Academy of Sciences
Garavan	2002	14	NeuroImage
Garavan	2003	16	NeuroImage
Hester	2004	15	Journal of Cognitive Neuroscience
Horn	2003	19	Neuropsychologia
Kaladjian	2007	21	Schizophrenia Research
Kaladjian	2009	10	Bipolar Disorder
Kaladjian	2009	20	Psychiatry Research: NeuroImage
Kelly	2004	15	European Journal of Neuroscience

Kiehl	2000	14	Psychophysiology
Konishi	1998	5	European Journal of Neuroscience
Langenecker	2007	22	Biological Psychiatry
Liddle	2001	16	Human Brain Mapping
Maltby	2005	14	NeuroImage
Mazzola-Pomietto	2009	16	Journal of Psychiatric Research
McNab	2008	11	Neuropsychologia
Mostofsky	2003	48	Cognitive Brain Research
Mostofsky	2003	28	Cognitive Brain Research
Roth	2007	14	Biological Psychiatry
Rubia	2001	15	NeuroImage
Rubia	2006	23	Human Brain Mapping
Sebastian	2012	24	Psychiatry Research: NeuroImage
Simoes-Franklin	2010	16	Human Brain Mapping
Watanabe	2012	11	NeuroImage
Zheng	2008	20	Journal of Cognitive Neuroscience