Intra-individual reaction time variability in sustained attention

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A thesis submitted in partial fulfilment of the requirements of the regulations for the degree of Doctor of Philosophy

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September, 2017

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Acknowledgements

First and foremost, I would like to thank Professor Nicol Ferrier for funding my PhD and giving me the opportunity to pursue and expand my research interests.

I would also like to thank Dr Peter Gallagher, for his supervisory approach (calm, cool, and collected!), encouragement of ideas, and comments; Dr Hamish McAllister-Williams, and Professor Nicol Ferrier for their support and comments during the PhD process, as well as Professor Andrew Blamire for his support and discussions.

Thank you to supervisors and colleagues who have provided valuable feedback and discussions for separate thesis chapters: Dr Sue Lord and Dr Rachael Lawson for Chapter 3, as well as to Professor David Burn for approving the inclusion of ICICLE-PD data in Chapter 3 for this thesis; Dr Peter Gallagher, Dr Lucy Robinson, Dr Jill Thompson, Dr Andreas Finkelmeyer, and Professor Nicol Ferrier for Chapter 5, and Dr Stuart Watson for Chapter 6.

A special thank you goes to my interval reviewers, Dr Gabi Jordan and Dr David Cousins. Thank you for the valuable discussions about my project, and the PhD process itself, as well as your encouragement and enthusiasm. I very much appreciated the pastries and strong coffee. A heartfelt thank you to Gabi for taking on mentorship duties. I cannot thank you enough for your open door policy.

An extended thank you goes to the undergraduate and postgraduate students who have helped me with recruitment of participants during my PhD (undergraduates: Anna and Ben; postgraduates: Anna, Meghan, and Eileen), colleagues at the MRI centre who have supervised scans, and administrative staff at CAV and IoN who have helped with study administration and beyond, I am indebted to you. Thank you also to Dr Andreas Finkelmeyer for your help with MATLAB programming, as well as discussions as a whole.

Thank you to all participants from VoiceNorth. It has been a pleasure to get to know you throughout our testing sessions, as well as to discuss research and life generally. Thank you for giving up your time, and supporting my research.

Thank you also to colleagues at CAV and IoN for an enjoyable four years.

Finally, and on a personal note, I would like to thank my friends in Newcastle and beyond for their much needed support, and laughter. In particular, thank you Sophie, Jen (the ‘Council of Nerd Ladies’), and Alex for the much needed snacks on a regular basis, fun conversations in our little corner of IoN, as well as invaluable support from afar when I moved back down South. Thank you also to Yvonne for your unwavering belief in me.

I would also like to extend a heartfelt thank you to my family, both in the UK and the US, for their love, support, and encouragement over the years I have been a student. I consider myself lucky to have you all in my life.

I would like to dedicate this thesis to my Grandpa, Gordon Richard Hammett, who passed away in September 2016.

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General Abstract

BACKGROUND: Sustained attention, assessed using the Continuous Performance Test (CPT), is impaired in 'normal' ageing and, to a greater degree, in a number of clinical disorders. There are many variants of the CPT, each with different task parameters (e.g., target frequency), and theoretical cognitive demands (e.g., executive functioning). It is unclear how the associated cognitive load of CPTs contributes to measures of attentional impairment, such as intra-individual variability (IIV) in reaction time (RT). There is potential clinical utility in measures of IIV, due to its relationship with increasing age, and brain white matter. Variability can be modelled using the ex-Gaussian distribution, and consists of three parameters: mu (mean RT), and IIV, decomposed into variability across the entire RT distribution (sigma), and characterised by infrequent and long RTs (tau). This thesis aims to examine how the multiple cognitive demands of CPTs contributes to attentional RT/IIV, and how this relationship interacts with age, as well as pathology. The thesis aims are explored in healthy and clinical populations characterised by sustained attention impairment associated with increasing age ('normal' ageing and Parkinson's disease (PD)), or in theoretical 'accelerated ageing' (Bipolar disorder (BD) while depressed and in remission).

METHODS: Sustained attention was assessed in five cross-sectional studies, using variants of the CPT. Secondary neuropsychological measures of executive functioning, processing speed, and verbal memory were administered. Ex-Gaussian distributional parameters (mu, sigma, and tau) obtained from CPT RTs were analysed. A series of hierarchical regression analyses were examined.

RESULTS: (1) In 'normal' ageing, better performance on the secondary neuropsychological measures was associated with faster RT (mu) and more consistent responding (sigma, tau), but this varied across CPT. Similar results were obtained for the effect of age on RT and IIV. (2) In PD, better executive functioning was associated with consistent responding (tau), whilst age was associated with slower (mu) and inconsistent (tau) responding. (3) In BD (while depressed), better executive functioning was associated with slower responding (mu), and better processing speed with consistent responding (tau), whilst age did not explain variance in RT or IIV. (4) In BD (in remission), the secondary neuropsychological measures examined did not explain variance in RT or IIV, nor did age.

CONCLUSIONS: Attentional RT and IIV in 'normal' ageing and in clinical populations such as PD and BD, may be supported by secondary neuropsychological processes theorised to be involved in CPT variants. The neuropsychological profile underpinning attentional RT and IIV may reflect secondary cognitive scaffolding mechanisms, engaged depending on the age of participants, rather than the cognitive load of the task *per se*. The results have implications for our understanding of attentional RT and IIV in 'normal' ageing and pathology. Future research would further our understanding on the use of cognitive scaffolding in relation to the CPT, as well as the stability, reliability, and neurobiological origins of RT and IIV.

Acronym table

Acronym	Description
AA	Accelerated Ageing
AD	Alzheimer's Disease
ADHD	Attention Deficit Hyperactivity Disorder
BD	Bipolar Disorder
BDI	Beck Depression Inventory
BSQ	Berlin Sleep Questionnaire
CCPT-II	Connors Continuous Performance Test
CoV	Coefficient of Variation
CPT	Continuous Performance Test
CPT-IP	Continuous Performance Test, Identical Pairs
CRT	Choice Reaction Time
CRUNCH	Compensation-Related Utilization of Neural Circuits Hypothesis
DSM	Diagnostic Statistical Manual
DSST	Digit Symbol Substitution Test
DKI	Diffusion Kurtosis Imaging
DTI	Diffusion Tensor Imaging
DV	Digit Vigilance
ECT	Electroconvulsive Therapy
ESS	Epworth Sleepiness Scale
FA	Fractional Anisotropy
GDS	Geriatric Depression Scale
HAMD	Hamilton Depression Rating Scale
HC	Healthy Controls
IIV	Intra-Individual Variability
ISD	Intra-Individual Standard Deviation
ISI	Inter-Stimulus Interval
LLD	Late Life Depression

MCI	Mild Cognitive Impairment
MD	Mean Diffusivity
MDD	Major Depressive Disorder
MMSE	Mini Mental State Examination
ms	Milliseconds
MoCA	Montreal Cognitive Assessment
MPS-UPDRS-III	Movement Disorder Society Unified Parkinson's Disease Rating Scale, Motor Evaluation
NART	National Adult Reading Test
NPSLE	Neuropsychiatric Systemic Lupus Erythematosus
OTS	One Touch Stockings
PD	Parkinson's Disease
PDD	Parkinson's Disease with Dementia
RAVLT	Rey Auditory Verbal Learning Test
RT	Reaction Time
RVIP	Rapid Visual Information Processing
SCID-I	Structured Clinical Interview for DSM-IV-TR Axis I Disorders
SL	Systemic Lupus
SRT	Simple Reaction Time
STAC	Scaffolding Theory of Ageing and Cognition
TMT	Trail Making Test
WAIS	Wechsler Adult Intelligence Scale
YMRS	Young Mania Rating Scale

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Chapter 1. Sustained attention and IIV

1.1 Ageing

The numbers of the global population aged over 60 years are expected to triple by 2100 (WHO, 2016). The global ageing trend is also reflected in the UK. By 2039, the proportion of the UK population aged 65 and over is projected to increase to 24.3% of the total population (ONS, 2016).With an ageing global, as well as national population, come a variety of economic, as well as societal challenges. For instance, an ageing UK population is anticipated to place greater strain on health and social care, in particular, existing infrastructures such as the NHS. In addition, it is anticipated that there will be greater demand for treatment of long-term chronic conditions by 2030 for conditions such as diabetes (up 45% from 2010), and arthritis/heart disease/stroke (up 50% from 2010), as well as neurodegenerative disorders associated with cognitive changes, such as dementia (up 80% from 2010) (HoL, 2013).The general cognitive changes associated with age will be discussed in greater detail in the next section.

1.2 Cognitive Ageing

Changes in cognitive processing across the lifespan are considered a hallmark of the 'normal' (i.e. non-pathological) ageing process (Hedden and Gabrieli, 2004; Deary *et al.*, 2007), and typically follow developmental trajectories (explored in greater detail in sections 1.3.1-1.3.4). A reduction in cognitive processing, or cognitive impairment, is associated with a poorer quality of life for the individual (Saraçlı *et al.*, 2015), and a decline in one cognitive ability is associated with decline in another (Wilson *et al.*, 2002). However, individuals differ in the magnitude, as well as the rate of cognitive decline (Wilson *et al.*, 2002), and factors such as physical activity level, can be considered protective (Seeman and Chen, 2002). The prevalence of a number of clinical disorders affecting cognitive abilities increases with age (De Lau and Breteler, 2006), and such changes are also associated with impaired quality of life (Michalak *et al.*, 2005; Duncan *et al.*, 2014). Recently, accelerated cognitive ageing processes have been hypothesised in BD (e.g., Rizzo *et al.*, 2014) and epilepsy (e.g., Breuer *et al.*, 2016). The cognitive changes associated with age and pathology will be explored in the thesis. Of relevance to the thesis, a brief overview of the relationship between cognitive changes and age is discussed in the next sections.

1.3 Age-related cognitive change

1.3.1 Executive functioning

Executive functioning describes a collection of cognitive processes ('higher-order') that are associated with goal-directed ('lower-level') behaviours (Alvarez and Emory, 2006). Cognitive processes associated with executive functioning include inhibition, set-shifting, and working memory (Miyake *et al.*, 2000), with different age-related developmental trajectories proposed per process (Huizinga *et al.*, 2006).

In an analysis of working memory (remembering the colour, shape, and location of objects) in 55,753 individuals, with ages ranging between eight and 75, Brockmole and Logie (2013) reported that working memory peaked at age 20, and then declined throughout life. It is worth noting that age-related declines in working memory are purportedly larger for spatial-type tasks, compared to verbal. In addition, Hale *et al.* (2011) assessed the structure of working memory in 388 adults, aged between 20 – 89 years. Simple and complex tasks were employed in the verbal domain (Simple: Digit, letter, and word span; Complex: Reading, Counting and operation span), as well as spatial domain (Simple: Line, grid and dot span; Complex: Parallel, alignment and position span). The authors did not provide evidence for faster rates of decline across simple and complex tasks, noting that both decreased as a function of age. As such, the results highlighted that age-related deficits impacted all visuospatial processing, irrespective of whether the task was speeded or not. However, Hale *et al.* (2011) also noted that visuospatial working memory tasks (spatial domain tasks included in the study) may be more age-sensitive compared to verbal working memory tasks.

In another study, Logie and Maylor (2009) assessed prospective memory (performing a future action) and retrospective memory (recalling information) in 73,019 18 – 79 year olds in an internet based study. In addition to assessment of prospective memory, participants completed a battery of tasks designed to assess retrospective memory, which included feature binding, digit, visual pattern, as well as working memory span. All tasks demonstrated a linear decline across adulthood, however steeper age-related declines were noted in visual pattern span, followed by feature binding, prospective memory, working memory and digit span (which declined more steeply in older age).

In the thesis, only one component of executive functioning, working memory will be examined. Working memory will be assessed using the Digit Span (Backwards) task from the WAIS-III (Wechsler, 1998), with performance in this test reported to decline with age (Hester *et al.*, 2004).

For example, Orsini *et al.* (1987) assessed verbal and spatial immediate memory span (forward and backwards digit span from the WAIS and the Corsi block-tapping test to assess spatial span) in 1355 adults (20 – 99 years). Results indicated that digit and spatial span declined with age, with steeper decrements occurring after the late sixties. The Digit Span Backwards is thought to place high demands on the capacity to monitor and manipulate cognitive representations, thus, the ability to monitor the contents of working memory. In doing so, the task is thought to assess the central executive component of Baddeley and Hitch's (1974) influential model of working memory (Thompson *et al.*, 2006).

1.3.2 Processing speed

Processing speed concerns the speed at which cognitive processes are conducted (Salthouse, 2012). Cross-sectional data of 2,350 participants (18-60 years) from Salthouse (2009) indicates that speed of processing declines over the course of life, beginning in early adulthood. Brockmole and Logie (2013) highlighted that the developmental trajectory of processing speed suggests a peak in the third decade, followed by slowing of processing thereafter. In the thesis, processing speed will be assessed using the original DSST from the WAIS-III (Wechsler, 1998), a test that is sensitive to age-related decline (Salthouse, 1992b), and has become a standard assessment for information processing speed (Salthouse, 1992b).

1.3.3 Sustained attention

Sustained attention is defined as the ability to sustain attention over a period of time, or to detect an infrequent and unpredictably occurring stimulus (Davies and Parasuraman, 1982). Cross-sectional studies have indicated that indices of sustained attention follow a developmental pattern. For instance, McAvinue *et al.* (2012) utilised the Sustained Attention to Response Task (SART), a test in the visual domain that requires participants to withhold their responses to a rare numeric target and respond for all other digits presented. McAvinue *et al.* (2012) noted that commission (false alarms) and omission errors (misses), as well as CoV (a measure of IIV), declined from younger to older adulthood – with poorer performance (increases in errors and CoV) in childhood (age 12), followed by a plateau from young-middle adulthood, and a deterioration in older adults (increases in errors, as well as CoV). Further cross-sectional data from Fortenbaugh *et al.* (2015) utilised a different CPT, the gradual-onset CPT. Within the task, participants are presented with greyscale photographs of city and mountain scenes, with each scene gradually transitioning to the next over the course of the task. Participants were requested to respond when they viewed a city scene, and withhold their response for a mountain scene.

The results of Fortenbaugh *et al.* (2015) suggests that that there is a rapid improvement in *d'* (a measure of discrimination ability) and IIV as assessed by CoV from 10-16 years (*d'*: improved at 0.13 per year; CoV: decreased by – 0.018 ms per year), followed by a period of stability and peak at 43 years, and then a decrease in these indices of sustained attention from this age onwards (*d':* decline at rate of – 0.018 per year; CoV: decline at rate of – 0.0014 ms per year) (Fortenbaugh *et al.*, 2015). Moreover, Fortenbaugh *et al.* (2015) observed that the rate of decline in sustained attention ability was slower than the rapid improvement of ability during development.

Whilst both tasks were similar in terms of task length (SART = 5.4 minutes and gradual-onset CPT = 4 minutes), as well as task requirements (SART = 200 targets, 25 non-targets; gradual-onset CPT: 267 targets, 32 non-targets), differences in the developmental pattern of sustained attention outcome measures may be due to size of samples. For instance, McAvinue *et al.* (2012) included 113 participants, between the ages of 12 and 75, whilst Fortenbaugh *et al.* (2015) included 10,430 participants from 10 years to 70. Irrespective of sample size differences, cross-sectional data indicates that sustained attention outcome measures vary across age-ranges. Within the thesis, sustained attention will be assessed using variants of the CPT, as sustained attention is typically assessed using this methodology (described in section 1.6).

1.3.4 Verbal memory

Verbal memory refers to the memory for orally presented information, which is typically tested in the experimental domain via word lists, recall, and learning of sequences (Tatsumi and Watanabe, 2009). In a large cross-sectional study, Park *et al.* (2002) examined 345 participants, aged between 20 – 92 years, and separated participants into decade 'bins' (e.g., 20-29, up to 80-89 years). The authors tested visuospatial and verbal short term memory, processing speed, working memory, and verbal long term memory. Park *et al.* (2002) reported a decline in processing speed and working memory, but found little evidence for a decline in visuospatial, as well as verbal performance across the life span. Moreover, that knowledge-based verbal ability was improved in older participants, compared to younger. As the data presented by Park *et al.* (2002) is cross-sectional, it is possible that the results are linked with cohort effects. Some longitudinal studies have demonstrated age-related decline in verbal memory, as assessed by California Verbal Learning Test (Lamar *et al.*, 2003), the RAVLT (Savage and Gouvier, 1992), and in verbal memory/ability more generally by the ages of 67 and 81 (Schaie, 2005). In the thesis, the RAVLT (Rey, 1964) will be used to assess verbal learning and memory.

1.4 The hierarchical organisation of cognition

The cognitive processes described in the section 1.3 are of importance to a wider debate in normal ageing and clinical literature – whether cognitive impairments, as a result of age and/or pathology, are broad and represent independent processes, or whether the broad nature of impairments are secondary to 'core' or primary impairment(s) in a single cognitive domain (Robinson *et al.*, 2006). Thus, if the broad nature of impairments in ageing or pathology a secondary to a 'core' deficit, this could then be a targeted area for cognitive rehabilitation (Rodriguez-Sanchez *et al.*, 2007). This would be of clinical utility, given the reported relationship between cognitive impairment and quality of life in normal ageing and in a number of clinical disorders (Michalak *et al.*, 2005; Duncan *et al.*, 2014; Saraçlı *et al.*, 2015).

Within normal ageing and specific to adult individual differences, a processing-speed theory was proposed by Salthouse (1996) to account for age-related variations in cognitive ability. The theory assumes that a major contributing factor to age-related differences in cognitive domains is a reduction in speed at which processes can be completed. Two central tenets of the theory include: (1) Performance on cognitive tasks is limited by impairments in general processing efficiency, and (2) Speed of processing is a critical constraint that is associated with age. Evidence supports two mechanisms of operation: (1) A *limited time* mechanism, whereby cognitive operations are too slow to successfully support behavioural performance in the specified time, leading to slowed and less accurate responding, and (2) A *simulataneity* mechanism, whereby inefficient processing speed reduces the amount of information available at a later point for task-related processing, leading to an increased error rate. Salthouse (1996) reports that the available evidence suggests that up to 75% of the age-related variance in cognitive measures (e.g., memory, reasoning, spatial etc.) is shared with measures of processing speed (e.g., DSST). Moreover, in an earlier study, Salthouse (1994) provided evidence for processing speed attenuating age-related variance in working memory, stating that between 71% and 96% of age-related variance in measures of working memory is shared with processing speed.

Salthouse (1992a) suggests that the influence of speed on other cognitive domains may occur because older adults are slower than younger adults at encoding information or establishing adequate internal representations. The work of Salthouse has also been extended clinically, with studies investigating the hierarchical nature of cognition in disorders such as MDD, LLD, and BD, typically using ANCOVA or hierarchical regression analysis. The premise here is that if a particular impairment (e.g., executive functioning) is mediated by another (e.g., processing speed) (after establishing that between-subjects differences exist), then entry of group would not explain significant additional variance in the model.

Within MDD, Nilsson *et al.* (2016), investigated the hypothesis that a primary deficit in attention underpins other affected domains. After controlling for demographic variables and executive functioning (assessed via Digit Span Backwards, Stroop Interference, and TMT, part B (TMT-B)), group predicted attention (assessed via the TMT, part A (TMT-A), Stroop control measures, and the Forward Digit Span) in the models. However, group did not predict variance in executive functioning, after attention was controlled statistically, with the authors concluding that cognitive impairment in MDD may be secondary to a primary impairment in attention.

In LLD (onset aged 60 years and above) (Butters *et al.*, 2004), studies have principally investigated whether a general deficit in processing speed mediates/can explain the broad cognitive impairments observed in the disorder. There is some supporting evidence for processing speed representing a core deficit in LLD, underpinning broader impairments. For instance, Butters *et al.* (2004) reported that processing speed (a composite score consisting of the DSST, Grooved Pegboard, and TMT-A tests) predicted each of the neuropsychological domains examined (visuo-spatial, executive functioning, language and memory), concluding that cognitive impairment in LLD is largely accounted for by processing speed, and that this may represent a trait feature of the disorder. Other evidence suggests that processing speed may account for some, but not all, of the cognitive impairment noted in LLD.

For instance, Dybedal *et al.* (2013) observed that between-subject differences were removed in verbal memory, visuospatial memory and language domains when controlling for processing speed, but not in the executive functioning domain (assessed via the Tower Test, Colour Word Interference, and TMT-B). In addition, Sheline *et al.* (2006) noted that in patients, age-related variance still existed for episodic memory, after accounting for processing speed, but not for language function, working memory, or executive functioning. Moreover, Nebes *et al.* (2000) reported that when variance associated with processing speed (DSST) or working memory (N-back task) was removed first (and therefore 'controlled' in the models), the effects of depression were no longer significant on tests of episodic and visuo-spatial performance. Moreover, when processing speed was entered before working memory in the models, this attenuated the effect of working memory. Despite this, working memory still explained unique variance on three of the five tasks examined. The authors concluded that depression may be associated with cognitive impairment, but only in tasks that require substantial processing resources (e.g., processing speed and/or working memory) for efficient performance.

The notion that processing speed may underpin broader cognitive impairments has also been applied in BD. Kieseppa *et al.* (2005) noted that after adjusting for processing speed (measured via the DSST), group differences in working memory (assessed via the Digit Span Backwards) and immediate memory were no longer significant in the BD twins assessed. However, significant group differences still remained for delayed story recall and visual reproduction. Antila *et al.* (2011) reported that after adjustment for processing speed (measured via the DSST), no significant differences remained between patients and HC, as well as patients and their first-degree relatives (e.g., in visual attention and working memory, visual scanning and attention, executive functioning), apart from in short-delay cued recall and long-delay memory.

Other studies in BD have investigated the hierarchical organisation of cognition in cognitive domains aside from processing speed. For instance, Thompson *et al.* (2009) reported that an executive functioning deficit (represented using a composite of scores from attentional and executive functioning tasks) was not simply due to slowed processing speed, and represented an independent source of variance. Moreover, that the between-subjects differences in declarative memory (measured via the RAVLT) was accounted for by executive functioning.

In addition, Thompson *et al.* (2006) investigated whether an impairment on a visuospatial memory task (measured via the Corsi Block) in patients with BD represented impaired visuospatial memory, or compromised executive functioning (assessed via the Self-Ordered Pointing Task and Digit Span Backwards). Results indicated that patient impairment on the Corsi Block task was the result of impaired executive contribution to task performance, which would have otherwise scaffolded or supported spatial span performance.

In summary, evidence from normal ageing and clinical studies suggests that broad cognitive impairments (e.g., visuospatial, verbal memory) may be secondary to circumscribed impairments in a number of 'core' domains (e.g., processing speed, executive functioning etc.), but not all. Investigating the hierarchical organisation of cognition is applicable to any population (clinical or otherwise) which includes cognitive impairment as a core feature. As investigation is an underdeveloped area, the hierarchical organisation of cognition will be a theme of the thesis.

1.5 The importance of sustained attention

Whilst other age-sensitive cognitive abilities have been discussed, sustained attention will be the cognitive process of focus for the thesis. Sustained attention is argued to be important for more general cognitive functioning (Sarter *et al.*, 2001). For instance, attentional impairments have been linked to lowered quality of life, principally because of the impact deficits can have upon everyday activities such as driving or reading (Harada *et al.*, 2013; Langner and Eickhoff, 2013).

Moreover, attentional deficits are considered to be a core feature of a number of clinical disorders, such as MCI (e.g., Tales *et al.*, 2012), AD (e.g., Tse *et al.*, 2010), and PD (e.g., Burton *et al.*, 2006), as well as psychiatric disorders such as ADHD (e.g., Epstein *et al.*, 2003), MDD (e.g., Marazziti *et al.*, 2010), Schizophrenia (e.g., Rentrop *et al.*, 2010), and BD (e.g., Thompson *et al.*, 2005) - with sustained attention assessed using a variety of CPTs. The assessment of sustained attention is discussed in the next section.

1.6 Assessment of sustained attention

In an experimental context, sustained attention is typically assessed using the CPT (Rosvold *et al.*, 1956). The CPT has emerged as the most widely used task for assessing sustained attention (DuPaul *et al.*, 1992). Within the task, a number of stimuli (numbers and/or letters) are presented sequentially in the auditory or visual domain, in a specific order, and often over a lengthy time scale. The aim of the task is usually for the participant to detect an infrequent target (discriminating targets vs. non-targets), either by pressing a key, or by inhibiting a response (Cosmelli, 2009). Whilst auditory versions do exist (Corbett and Constantine, 2006), the most popular and widely used versions utilise numbers and letters in the visual domain. Three main task-types are commonly utilised in sustained attention research - ‘CPT-X’, ‘CPT-AX’, and a double version, in which participants respond to stimuli that has been repeated (Rapport *et al.*, 1993). Examples of all three tasks will be used in the thesis. Each will now be discussed in turn.

The original CPT was developed in 1956 by Rosvold *et al.* (1956), with the intention of assessing impairments in attention within a brain damaged (i.e. non-specific brain pathology) clinical population. In the 'CPT-X' version, participants were required to press a lever when they saw the target letter 'X', which appeared eight times in a presentation of 31 letters. In an alternative version, and described as more difficult due to the additional inhibitory component, participants were asked to press a lever when they saw target 'X', but only when it was preceded by an 'A' (CPT-AX). Stimuli were presented sequentially, at a fixed rate ISI of 920 ms, with a low target percentage (10%). The authors do not report the rates of distractor stimuli presentation. Rosvold *et al.* (1956) noted that the ability to correctly classify participants (into those with brain damage and those who were neurologically intact) improved with this increase in task difficulty, suggesting that the task could be clinically useful. Consequently, the CPT-AX is considered to be a general marker of brain dysfunction (Riccio *et al.*, 2002). Variations of the CPT-AX exist, such as the Vigil CPT (Cegalis and Bowlin, 1991), which has a total stimulus presentation of 985 ms, and 100 target 'AK' sequences (out of 480 stimuli in total) presented over eight minutes. Another variation of the CPT-AX, programmed by Robinson *et al.* (2013), changes the traditional task requirements of the CPT-AX, and presents 140 target 'AX' pairs (out of 200 stimuli in total), with a presentation time of 850ms over six minutes.

A variant of the 'CPT-X', the RVIP, is a popular alternative to the CPT variants developed by Rosvold *et al.* (1956) .The RVIP task was originally developed to examine the influence that cholinergic drugs (e.g., nicotine) had upon attention and information processing (Sahakian *et al.*, 1989). Previous results indicated that cholinergic drugs prevented the decline in detection rate (i.e. whether or not the participant thought the target was present or absent) over time, as well as improved accuracy and faster responding (Wesnes and Warburton, 1983a; Wesnes and Warburton, 1983b). Within the task, single digits (e.g., 2-9) are presented consecutively at a rate of either 100 or 200 digits per minute. The participant is asked to respond to three, three digit target sequences (2-4-6, 4-6-8, 3-5-7). The target digit strings remain displayed on the screen, purportedly serving to reduce the working memory demand of the task. Nine targets are presented every minute, for seven minutes (Clark *et al.*, 2002).

Responses are classified as correct if they occur within 1800 ms of the target digit being presented (i.e. three stimulus presentations). Task difficulty can be manipulated by increasing or decreasing the number of digits presented per minute (e.g., 100 or 200 digits). In this instance, the amount of information processing required can be manipulated. In addition, the demand on information processing/working memory can be manipulated by increasing or decreasing the number of target sequences the participant responds to (Clark and Goodwin, 2004).

For example, the participant may be instructed to respond to four, three digit sequences, or three, three digit sequences. The RVIP also has a low working memory load variation, the DV task, which is used in the Cognitive Drug Research battery utilised in a number of clinical studies (Wesnes *et al.*, 2002). In the task, 450 single digits are presented to participants, at a rate of 150 digits per minute. Fifteen targets are presented every 150 stimuli, with the target digit differing per participant. Responses are classified as correct if they occur within 1500 ms of the target digit being presented (i.e. three stimulus presentations). The DV task lasts for three minutes, and participants are asked to press the 'YES' button as quickly as possible when the digit on the screen matches the target. Only one target has to be remembered during the task (without the target remaining on the screen, like the RVIP)

Since its inception, a number of alternative CPTs have proved popular. In some research fields, development of alternative paradigms has been a necessity to detect subtle impairments in clinical populations. For instance, the CCPT-II (Conners *et al.*, 2000) was originally designed as an objective method for the screening and/or diagnosis of clinical samples (e.g., ADHD and the neurologically impaired).

Within CCPT-II, participants are asked to respond to every sequentially presented letter (250 ms presentation), and refrain from responding to the infrequent, non-target (an 'X') for 14 minutes. The CCPT-II is an example of a 'not-X' paradigm due to the responding criteria. Participants complete the task over six blocks, each with three sub-blocks containing 20 trials. The ISI varies per sub-block between one, two, and four seconds (Hervey *et al.*, 2006). The high rate of targets (90%) compared to low non-targets (10%) produces a task environment in which a habitual rate of responding is formed. As presentation of non-targets is infrequent, the participant must continuously attend to the stimuli in order to inhibit this habitual response. As such, the CCPT-II differs from traditional measures (e.g., CPT-X/AX) of sustained attention due to its emphasis on inhibitory control, and variable ISI per block, rather than a fixed ISI (Hunter and Sparrow, 2012). As the 'core' deficit in ADHD is considered to be one of response inhibition (e.g., Barkley, 1997), use of the CCPT-II is frequent within this population, due to its emphasis on impulsivity (e.g., Advokat *et al.*, 2007).

Another version of CPT, the CPT-IP, is an example of a 'double' CPT paradigm and was developed as earlier paradigms lacked the sensitivity to detect subtle attentional deficits in unaffected first degree relatives of schizophrenic probands (Cornblatt *et al.*, 1988; Cornblatt *et al.*, 1989). Researchers expected that sustained attention deficits in the relatives were similar to, but more subtle that the impairments observed in patients (Cornblatt and Keilp, 1994), and could be explored with a task that was more difficult. In addition to sustaining attention, the CPT-IP places greater emphasis on working memory load via the length of digit sequences (two, three, and four digit set sizes are utilised), as well as information processing load with the fast presentation rate (Nuechterlein *et al.*, 1983).

Within the CPT-IP, participants respond when two identical stimuli (pairs) are consecutively presented (hence, the 'double' CPT description). Stimuli are presented quickly at a rate of 50 ms, with a one second ISI, over the course of 150 trials per stimuli type. Target frequency is low (20%), mimicking more traditional sustained attention paradigms (e.g., CPT-X/AX, rather than the CCPT-II).

The CPT-IP uses digit sequences, or nonsense shapes in set sizes of two (e.g., '22'), three (e.g., '222'), or four (e.g., '2222') (Cornblatt *et al.*, 1988; Cornblatt *et al.*, 1989). It should also be noted that many CPT variants are available, most utilising different task parameters (Greenberg and Waldmant, 1993).The three main types of CPT variants described – CPT-X, CPT-AX, and double CPT (e.g., CPT-IP), are used to assess sustained attention in normal and clinical populations.

There is debate as to whether all versions of the CPT measure the same construct (i.e. sustained attention) due to programming elements such as target frequency and ISI, with some paradigms emphasising impulsivity, such as the CCPT-II, and others, working memory, such as the CPT-IP. The idea that cognitive tasks may involve more than the primary cognitive domain of focus is not new *per se* (Cepeda *et al.*, 2013), but the application with the CPT is novel. In addition to the relevance of the cognitive domains discussed in section 1.3 to the hierarchical organisation of cognition, they also have implications in the assessment of sustained attention using variants of the CPT.

It is theorised that due to variations in the CPT and task parameters, the associated cognitive load differs (or task complexity), with varying demands on attentional, executive, and memory systems (Riccio *et al.*, 2003). Table 1-1 outlines variants of CPT and the hypothesised relationship between task parameters and multiple cognitive processes of interest in the thesis.

Table 1-1. Theoretical involvement of multiple cognitive processes in CPT variants.

Task	EF	PS	VM
CPT-X	+	+	+
CPT-AX[a]	++	+++	++
CPT-AX[b]	++	+++	++
Vigil CPT	++	+++	++
RVIP	+++	+++	+++
DV	+	+++	+
CCPT-II	+	+	+
CPT-IP	+++	+++	+++

Note. EF = Executive Functioning (working memory), PS = Processing Speed, VM = Verbal Memory, + = Low load, ++ Medium load, +++ High load.

[a] Variant from Rosvold *et al.* (1956).

[b] Variant from Robinson *et al.* (2013).

As highlighted in Table 1-1, all CPTs discussed in this section may involve cognitive processes other than sustained attention, such as executive functioning, processing speed, and verbal memory, due to task parameters (these cognitive domains are discussed in sections 1.3.1-1.3.4).

In terms of working memory, the load is anticipated to be low for the DV, CPT-X, and CCPT-II, as only one target needs to be remembered. As one target, in addition to a cue, needs to be maintained for the CPT-AX versions, and the Vigil CPT, a medium working memory load for these tasks is anticipated. The working memory load for the CPT-IP and RVIP is anticipated to be high, as the CPT-IP was developed to increase working memory load through conditions involving two, three, and four digit sequences. Moreover, the response requirements of the RVIP induce a task environment which places emphasis on working memory (manipulation of presentation speed, target sequences to respond to).

The tasks in Table 1-1 also rely on an individual's speed of processing, due to the total stimulus presentation rate (the duration the stimuli is on the screen, combined with the ISI), and the sequential nature of stimuli presentation, which will tax an individual's ability to process cognitive operations at speed.

Parasuraman's (1979) definition (a high event = more than 60 stimuli presented per minute) was used to determine whether the individual CPT requirements would have a high processing speed loading. In terms of task parameters, the digit stimuli in the DV/RVIP (< 1000 ms), and CPT-IP (1050 ms) are presented quickly, compared to the CPT-X, AX, or some conditions associated with the CCPT-II (2250 ms or 4250 ms), which resulted in their high compared to low anticipated loadings.

In addition, all CPT variants may involve an element of verbal memory, due to potential use of a verbal strategy to regulate task requirements, or as stimuli are presented in the visual domain, as letters or numbers. The verbal memory contribution to the RVIP and CPT-IP is anticipated to be high, as multiple target sequences need to be remembered for the RVIP and an increased target digit length for the CPT-IP. A medium verbal memory contribution is expected for the CPT-AX variants, as one target, in addition to a cue, needs to be remembered. A low verbal memory contribution is expected for the DV and CCPT-II, as only one target needs to be remembered in these tasks.

Considering the hierarchical organisation of cognition as outlined in section 1.4 and the hypothesised relationships in Table 1-1, it is unclear whether sustained attention performance on variants of the CPT outlined, in normal ageing or pathology, reflects a sustained attention impairment *per se*, or reflects deterioration in more general domains, such as processing speed and/or executive functioning (working memory). As highlighted earlier in section 1.6, many CPT variants exist, and it is possible that their required processing resources also vary. As such, task complexity could be a confounding factor to consider in determining whether a sustained attention impairment can be considered an independent process in normal ageing or pathology, or reflects a more general impairment in another cognitive domain.

In summary, as the relationship between variants of the CPT and different cognitive domains is inferred, rather than confirmed, this will be a theme addressed in the thesis. The next sections will examine the relationship between CPT parameters and sustained attention outcome measures, as variations in task complexity may impact behavioural measures of sustained attention performance.

1.6.1 Sustained attention performance outcome measures

Sustained attention performance, and whether a clinical population has an impairment in this domain, is typically indexed using behavioural outcome measures. Commonly used measures include hits (number of correct responses, typically expressed as a percentage), commission errors (responding to non-target, also known as a false alarm), omission errors (failing to respond to a target, known as a miss), and less frequently, RT(Conners *et al.*, 2003). In clinical studies, classification of impairments in sustained attention encompass alterations in these outcome measures, typically with a reduction (e.g., fewer hits), or with an increase (commission, omission errors, RT). For the purposes of the thesis, only hit RTs will be examined – this is further explored in sections 1.7 and 1.9.2.

As behavioural outcome measures are central to the definition of attentional impairment within a clinical population, it can be argued that an understanding of the task factors which may influence them is imperative. A short outline of common task parameters and their impact on sustained attention outcome measures will be discussed in the next section. The task parameters discussed are of relevance to the thesis, as variation in these parameters may be associated with the theorised involvement of multiple cognitive processes in different CPTs (see Table 1-1).

1.6.2 Impact of target frequency

The frequency of signal presentation, target frequency, is typically divided into low (infrequent), and high (frequent) events. A low target frequency task (e.g., 10% of total trials; Rosvold *et al.*, 1956; 20%; Cornblatt *et al.*, 1988) is associated with lower accuracy (or percentage of signals detected) (Colquhoun and Baddeley, 1964; Colquhoun and Baddeley, 1967), compared to high target frequency manipulations. Generally, a low target frequency task reflects the historical definition of sustained attention (i.e. responding to infrequent targets), and may therefore be a more appropriate index of sustained attention (Carter *et al.*, 2013).

In contrast, high target frequency manipulations (e.g., 90% of total trials; Conners *et al.*, 2003) are associated with higher levels of accuracy, compared to low target manipulations (Colquhoun and Baddeley, 1964; Colquhoun and Baddeley, 1967), as well as reduced discriminability of targets, and more errors generally, compared to low target frequency manipulations (Beale *et al.*, 1987). It is thought that this high target frequency manipulation induces a frequent response tendency (Conners *et al.*, 2003). Underlying this effect may be an altered demand on response inhibitory and motor control mechanisms, focussing on impulsivity, rather than sustained attention *per se* (Carter *et al.*, 2013).

1.6.3 Impact of ISI

The ISI is the time between presentations of each stimulus, and is typically manipulated to be short, long, or variable. Fast, or short ISIs (500 ms or less), are associated with faster mean RT, as well as an increase in omission errors, compared to tasks with a longer ISI (one second), or variable ISI (varies between one, two, and four seconds) (Ballard, 2001). If the ISI is variable and increases (e.g., from one – four seconds), omission errors decrease (Conners *et al.*, 2003), and commission errors (i.e. responses to non-targets) increase (Chee *et al.*, 1989). In addition, slower mean RT has been noted with an increase in ISI, as has a conservative response bias and increased RT IIV (Ballard, 2001; Conners *et al.*, 2003).

1.6.4 Impact of length of task

Duration of task is key to the 'sustaining' of attention, and is associated with the sustained attention decrement (Cohen, 2014), which is defined as a reduction in accuracy over the course of a task (Koelega, 1993). As task length increases, individuals with an attentional impairment are more likely to produce slower RTs and increased error rates (e.g., Duncan *et al.*, 1996). As no gold standard regarding the length of CPT is in use (Riccio and Reynolds, 2001), the length of CPTs range from three minutes (e.g., Bremer, 1989), to 30 minutes and above (e.g., Mansour *et al.*, 1996).

1.6.5 Impact of type of stimuli

Visual stimuli used by versions of CPT encompass letters, numbers, shapes, as well as manipulation of the quality of stimuli. Character similarity of the target can influence CPT outcome measures. If a target letter is selected from letters from the same character set (e.g., C, D, Q, O), it is more difficult to detect the target, than if the target was selected from between sets (e.g., target 'C', and distracting letters are I, N, R) (Smid *et al.*, 2006). Alternatively, the CPT-IP includes four digit number strings, as well as nonsense shapes (Cornblatt *et al.*, 1989).
Higher signal detectability (*d'*) and fewer commission errors have been reported for the nonsense shapes condition, compared to numbers strings, but this result seems contingent upon age (Cornblatt *et al.*, 1988). Finally, the 'quality' of the stimuli can be altered, through degradation of stimulus integrity over the course of an experiment. Typically, stimulus detection decreases with a degradation of the stimulus over time (Nuechterlein *et al.*, 1983).

1.6.6 Summary

In summary, existing research demonstrates that behavioural outcome measures such hit rate, errors (commission and omission), and RT, may vary according to manipulations of task parameters such as target frequency, ISI, length of task, as well as type of stimuli. The relationship between behavioural outcome measures and CPT parameters may provide further supporting evidence for the theorised involvement of multiple cognitive processes in the CPT outlined in Table 1-1. Of note, these task parameters may underlie differences in the hierarchical organisation of cognition associated with individual CPTs.

1.7 IIV

There is increasing interest in examining beyond the existing behavioural outcome measures of sustained attention performance identified in the previous sections of the current chapter (e.g., Gallagher *et al.*, 2015), and examining IIV in RT. Historically, variability in behavioural performance was treated as random noise, or measurement error (MacDonald and Stawski, 2015), which could explain its omission as a commonly utilised outcome measure when assessing sustained attention. Interest in these short-term fluctuations has re-emerged, as evidence suggests that variability is associated with developmental outcomes (i.e. lifespan development) and is of interest in the study of individual differences (Ram and Gerstorf, 2009; MacDonald and Stawski, 2005; Stawski *et al.*, 2015).

Recent evidence from Esterman *et al.* (2014) suggests that IIV could be utilised as a temporally sensitive index of sustained attention performance, similar to the sustained attention decrement. In the Esterman *et al.* (2014) study, participants completed a gradual onset CPT, whereby faces overlaid on a background scene transitioned from one to the next. Participants were instructed to respond to male faces. The authors noted that IIV, measured via CoV, increased as a function of time-on-task (split into two minute bins over a 10 minute task).

The results from Esterman *et al.* (2014) agrees with earlier research suggesting that RT (mean) increases as a function of time-on-task in sustained attention paradigms (Buck, 1966). The sections below will give an overview of the measurement and results obtained from the study of IIV in normal ageing and clinical populations.

1.8 The importance of IIV

Analysis of IIV has garnered attention due to its purported relationship with biology. In addition to its potential heritability (Andreou *et al.*, 2007), elevated IIV is associated with an increase in age (Deary and Der, 2005; Dykiert *et al.*, 2012), is related to cognitive decline over a six year period (MacDonald *et al.*, 2003; Bielak *et al.*, 2010), and could predict mortality (Shipley *et al.*, 2006; MacDonald *et al.*, 2008). Neurally/structurally, correlations between elevation of IIV and incidences of white matter hyperintensities (Bunce *et al.*, 2007; Bunce *et al.*, 2010), reduced white matter volume (Jackson *et al.*, 2012), as well as white matter integrity (Fjell *et al.*, 2011; Moy *et al.*, 2011) have all been observed. Clinically, elevated IIV compared to HC has been reported in MCI (Duchek *et al.*, 2009); Traumatic Brain Injury (Stuss *et al.*, 1989; Stuss *et al.*, 1994); PD (Crawford *et al.*, 1989; Camicioli *et al.*, 2003; Burton *et al.*, 2006; de Frias *et al.*, 2007; Camicioli *et al.*, 2008; de Frias *et al.*, 2012), ADHD (Leth-Steensen *et al.*, 2000; Buzy *et al.*, 2009; Vaurio *et al.*, 2009), BD (Brotman *et al.*, 2009), and Schizophrenia (Rentrop *et al.*, 2010).

Moreover, differences in IIV could predict time from normal ageing to MCI (Cherbuin *et al.*, 2010); be a marker of prodromal AD at the MCI stage (Tales *et al.*, 2012; Kälin *et al.*, 2014), as well conversion to PDD from PD (de Frias *et al.*, 2012). Taken to together, these results suggest that IIV could be a general marker of central nervous system integrity and health, or vulnerability (Hultsch and MacDonald, 2004; Dykiert *et al.*, 2012). Furthermore, that IIV may have clinical utility, particularly in the early detection of conversion from normal ageing to neurodegenerative disorders, or from neurodegenerative to more severe forms.

Due to the purported biological and clinical relevance of IIV, it will be the outcome measure of focus in the thesis, and will be examined in the context of sustained attention.

1.9 Measurement of IIV

Variability has been empirically studied and defined in three ways, namely *inconsistency*, *variability*, and *dispersion* across RT distributions (Diehl *et al.*, 2015). *Inconsistency* is defined as the within-person behavioural variation in performance within a single cognitive task (Burton *et al.*, 2006), whereas *variability* is specific to multiple testing sessions, on a single cognitive task (Hertzog *et al.*, 1992). Finally, *dispersion* refers to variation in behavioural performance across multiple tasks (Hilborn *et al.*, 2009). For the purposes of the thesis, *inconsistency* in RT will be the focus and the terms *inconsistency* and *variability* will be used interchangeably, consistent with existing research.

Studies typically utilise common measurements of IIV which include the ISD, CoV, and residual ISD, which index variability in RT distributions. Use of the ISD is frequent, given its ease of calculation. However, the ISD and mean RT correlate highly (e.g., $r = 0.90$) (Desman *et al.*, 2008). For instance, differences in ISD between younger and older adults may simply be due to higher mean RT in older adults (e.g., Burton *et al.,* 2006). As such, it is difficult to separate these two indices and interpret them independently (Tamm *et al.*, 2012; Bunce *et al.*, 2013).

To control for differences and to circumvent the limitations associated with use of the ISD, researchers have opted for an adjusted measure – the CoV (the measure is calculated as ((ISD/mean RT)*100) (Wagenmakers and Brown, 2007)). Consequently, IIV can be compared between participants, even if the mean RT differs significantly (Flehmig *et al.*, 2007). Similar to the limitation associated with ISD, use of this statistic still does not separate the relative contribution of mean and variance to IIV (Karalunas *et al.*, 2013).

Finally, an increasingly popular metric for analysing IIV concerns the residual ISD. This method controls for individual differences in IIV by utilising linear regression to partial out the influence on the mean RT on the ISD. The remaining residuals are used to calculate the residual ISD, which is argued to be independent from potential confounds such as time-on-task effects (e.g., trial number), fatigue, sex, group differences in mean RT (i.e. larger IIV in one group as a result of slower mean RT), and associated interactions (Hultsch *et al.*, 2002; Wagenmakers *et al.*, 2005; Bunce *et al.*, 2013). However, it is unlikely that calculation of residual ISD is independent of the effect of confounding variables, as adjustment does not eliminate their effect on the measure of interest (e.g., age and IIV) (Christenfeld *et al.*, 2004). Moreover, selected confounding variables may in fact be measures of interest in different research fields (e.g., time-on task and sustained attention decrement measured using IIV). In the next section, caveats to the application of the IIV, despite availability of adjusted indices such as CoV and ISD, will be considered.

1.9.1 Limitations of traditional measures of IIV

In general, IIV indices such as ISD, CoV, and residual ISD can only be described as coarse measures of IIV (Flehmig et al., 2007), as these metrics may obscure between-group differences in RT distributions sensitive to different experimental conditions (Ratcliff, 1979; Hervey *et al.*, 2006; Whelan, 2008; Gmehlin *et al.*, 2014). In addition to loss of detail when analysing RTs using traditional methods, there are statistical considerations as well. Measures such as ISD, CoV, and residual ISD assume that RTs follow a Gaussian (i.e. normal) distribution. However, RT distributions are typically positively skewed (Whelan, 2008). The distributional asymmetry of RT is the result of physiological limits to the speed of responding (i.e. genuine RTs have a minimum value of 100 ms and above) (Luce, 1986) but not to the slowing of responses (Ulrich and Miller, 1993). In skewed distributions, the mean is distorted in the direction of the skew and is not representative of typical responses (Whelan, 2008). Thus, traditional measures of IIV may not be robust, and may not be representing IIV of a particular group/condition as accurately as possible.

1.9.2 An alternative analysis of IIV

Reaction time data may also be fitted to mathematical functions, which may more accurately describe their shape compared to traditional methods of analysis which assume a Gaussian model is the best fit (e.g., mean, ISD etc.). Models tend to describe RT distributions using exponential tails (include an exponential distribution in the model), and includes models such as the Diffusion, ex-Gaussian, Gamma, Shifted-Wald, and Weibull (Van Zandt, 2000).

The ex-Gaussian distribution has garnered recent interest and will be explored in the thesis due to its potential usefulness in isolating the effect of experimental manipulations (e.g., CPT task parameters) to fast or slow RTs (Heathcote *et al.*, 1991), and for its clinical utility (see sections 1.10.1-1.10.4), which is of relevance to the thesis. The ex-Gaussian distribution is argued to be a good fit to empirical RT distributions (Heathcote *et al.,* 1991), and can be fitted to as few as 40 individual responses (correct responses) (McAuley *et al.,* 2006).
The ex-Gaussian distribution describes RT as the sum of two variables - a Gaussian (normal) and an exponential (Figure 1-1).

$$(x|\,\mu,\sigma,\tau) = \frac{1}{\tau}\exp\left(\frac{\mu}{\tau} + \frac{\sigma^2}{2\tau^2} - \frac{x}{\tau}\right)\Phi\left(\frac{x-\mu-\sigma^2\ /\tau}{\sigma}\right)\cdot$$

Figure 1-1. ex-Gaussian probability density function (PDF). The ex-Gaussian function is computed by the multiplication of the exponential function (exp) by the cumulative density value of the Gaussian function (Φ). The resulting ex-Gaussian distribution is comprised of three parameters – mu (μ), sigma (σ), and tau (τ). Equation re-created from Lacouture and Cousineau (2008).

Three parameters are defined when fitting the function: (i) *mu* (μ) and (ii) *sigma* (σ) represent the mean and ISD of the Gaussian component, whilst (iii) *tau* (τ) represents the mean and ISD of the exponential distribution (Figure 1-2).
As such, the ex-Gaussian distribution is determined by variability in these three parameter estimates. In addition, the mean of the ex-Gaussian distribution is the algebraic sum of mu and tau (mean of the RT distribution = μ + τ).

In contrast, its variance is equal to the sum of sigma squared and tau squared (variance of the RT distribution = $\sigma^2 + \tau^2$) (Ratcliff, 1979; Heathcote *et al.*, 1991). If a RT distribution is normally distributed, mu and sigma will equal the values for mean RT and SD respectively. The value for ex-Gaussian tau will equal zero (Kofler *et al.*, 2013).

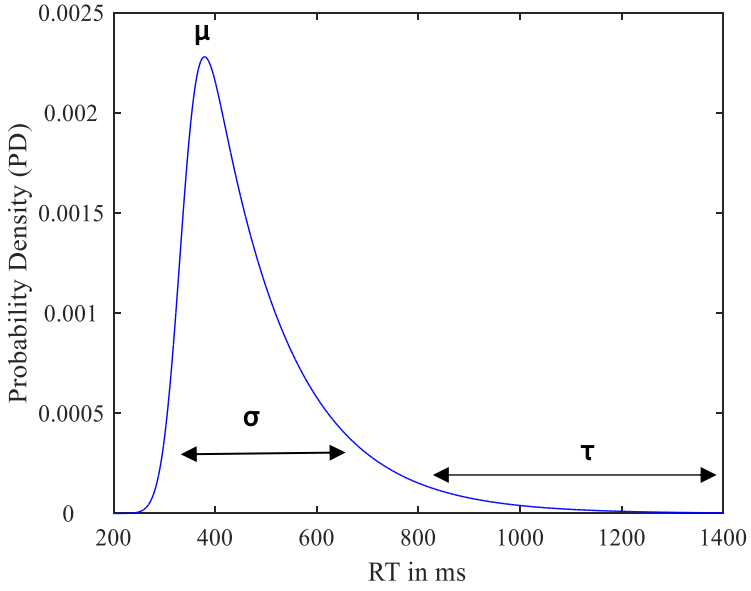

Figure 1-2. Example ex-Gaussian distribution, with parameters, mu (μ), sigma (σ), and tau (τ).

Conceptually, alterations in the mu parameter are thought to reflect a shift in the RT distribution as a whole, whereas changes in tau are typically reported as reflecting distributional skewness, with this skew composed of infrequent, and excessively slow responses (Ratcliff, 1979; Burbeck and Luce, 1982; Hervey *et al.*, 2006; Lacouture and Cousineau, 2008; Matzke and Wagenmakers, 2009). As such, the model is able to deconstruct a distribution and demonstrate whether RT, obtained from a variable (e.g., task condition, study group) is related to distributional shifting (μ), or IIV in the form of changes in the spread of RTs (σ) and/or changes in the tail of the distribution (τ) (Balota *et al.*, 2008).

The question of whether ex-Gaussian tau is an appropriate measure of distributional skew has also been addressed. Ex-Gaussian tau reflects the absolute length, or the positive leading tail of the distribution.

Statistically however, skew reflects the asymmetry of a distribution, i.e. the length of the positive tail (right-hand), relative to the negative (left-hand, or leading edge). It is possible that as a consequence of slowed responding, an increase in ex-Gaussian tau may be the result, but the distributional skew remains unchanged. To circumvent this potential issue, researchers have suggested use of the ratio between ex-Gaussian tau and sigma (Heathcote *et al.*, 2002; Myerson *et al.*, 2007). Nonetheless, ex-Gaussian tau is considered conceptually similar to the above description of distributional skewness. Moreover, ex-Gaussian tau has been cited more frequently as a measure of skewness than the ratio (Schmiedek *et al.*, 2007). Consequently, a skewness ratio will not be used in the thesis.

In summary, analysis of the ex-Gaussian distribution can provide a useful description of the typical nature and shape of the RT distribution (Balota and Spieler, 1999). The level of detail obtained, and description of whether IIV is spread, or best represented in the positive tail of a distribution, is not possible through sole application of more traditional methods such as mean RT, CoV, ISD, or residual ISD. The ability to distinguish between different forms of IIV would provide further information to researchers about the response pattern of an individual or clinical group. As such, the thesis will focus on the application of the ex-Gaussian distribution to obtained RTs, due to the limitations of traditional methods of IIV analysis. The application of the ex-Gaussian distribution in normal and in clinical populations will be discussed in the next sections.

1.10 Application of the ex-Gaussian distribution

There are examples of application of the ex-Gaussian distribution in normal ageing, as well as a number of psychiatric and neurological disorders. An overview of research in these domains will now be discussed.

1.10.1 Normal ageing

McAuley *et al.* (2006) applied the ex-Gaussian distribution to RTs obtained from an inhibitory control task in 43 younger adults aged 17-22 (*M* = 19.6, *SD* = 1.3), and 33 older adults aged 61-82 (*M* = 72.9, *SD* = 5.6). The task involved participants responding to the brightness of circles situated to their left or right, and the authors noted higher values of mu, sigma, and tau in older, compared to younger adults. In another study, Tse *et al.* (2010) applied the ex-Gaussian distribution to RTs obtained from three attentional control tasks (Stroop, Simon, and a task-switching paradigm) in younger and older healthy adults (Younger: *M* = 20.3, *SD* = 1.1; Older: *M* = 71.7, *SD* = 7.7). The authors observed elevated mu, sigma, and tau in older, compared to younger adults across all three tasks. However, the study findings are limited in their generalisability, as analyses were conducted using uneven study groups (Younger *n* = 32, Older *n* = 246), which may have obscured the results. A further study completed by Jackson *et al.* (2012) utilised the same tasks as Tse *et al.* (2010) in a sample of 133 healthy older adults aged between 46-96 (*M* = 68.0, *SD* = 9.6). The authors noted that older age was associated with higher values of mu and tau, but not sigma. However, this study is limited by the analysis method. The ex-Gaussian parameter results were based on composite scores, calculated by averaging z-scores obtained from the Stroop, Simon, and Switching attentional control tasks. As such, it is not possible to determine the relationship between age and ex-Gaussian parameters on the individual tasks included in the study, as these values were not reported. It is not clear whether the results described above would be replicated using alternative attentional paradigms, with differing levels of task complexity, such as the CPT (see section 1.4).

1.10.2 ADHD

Analysis of RTs using the ex-Gaussian distribution is a popular method of examining IIV within ADHD, and commonly applied to RTs from the CCPT-II (Connors *et al.,* 2003). Generally, research has indicated that individuals with ADHD are better categorised as more variable (compared to use of the mean alone) compared to HC, with this variability attributed to increases in periodic and slow RTs indexed by ex-Gaussian tau (Epstein *et al.*, 2003; Hervey *et al.*, 2006; Buzy *et al.*, 2009; Karalunas *et al.*, 2013; Wolfers *et al.*, 2015). As such, elevated IIV is considered a core clinical feature of ADHD (Kofler *et al.,* 2013).

There has also been recent interest in examining the utility of increased IIV as a potential marker of disease state in ADHD (i.e. endophenotype). In the Lin *et al.* (2015) study, 411 probands with ADHD, 138 unaffected siblings, and 138 HC (8-16 years old) completed a sustained attention task (CCPT-II). Ex-Gaussian tau was higher in probands compared to relatives, and was higher in relatives compared to HC. Moreover, this pattern in ex-Gaussian tau was replicated in each ISI condition (one, two, and four seconds), but not in ex-Gaussian mu (no significant differences), or sigma (increases in every ISI condition, but only between ADHD and HC).

In another comparison study, Henríquez-Henríquez *et al.* (2014) administered a GO/NO-GO task to 20 discordant sibling-pairs (ADHD) and 15 unaffected HC (between 8 – 15 years old), and analysed RTs using the ex-Gaussian distribution. The task differed from the CCPT-II utilised in Lin *et al.* (2015), as the task was eight minutes long (versus 14 for the CCPT-II), with a stable ISI of one second, as opposed to the changing ISI per block (one, two, and four seconds) of the CCPT-II. The authors noted that a stair-like distribution of results (ADHD slower than unaffected siblings, who were slower than HC) was observed for ex-Gaussian mu, and sigma, although the latter relationship was non-significant when the results were adjusted for age and sex. No significant differences were observed for ex-Gaussian tau. Differences in the results obtained by Lin *et al.* (2015) and Henríquez-Henríquez *et al.* (2014) may be due to the type of task, and associated conditions (e.g., ISI) employed between the two studies.

It is possible that a longer task period, combined with a variable ISI, is needed to elicit the stair-case like distribution in ex-Gaussian tau between patients, their unaffected siblings and HC, as reported by Lin *et al.* (2015). The studies described did not examine the relationship between demographic (e.g., age), clinical characteristics and ex-Gaussian parameters.

1.10.3 Schizophrenia and BD

The ex-Gaussian analysis of RT distributions has been applied to psychiatric disorders such as schizophrenia and BD. Three studies thus far have examined ex-Gaussian parameters in schizophrenia.

Kieffaber *et al.* (2006) studied an attentional set switching and maintenance paradigm in 33 patients with schizophrenia and 30 HC. The task involved two different trials – 'shape' and 'size'. The participant was required to judge whether two shapes on a screen were a match or a mismatch in terms of shape or size, with the trial indicate orally. The authors reported higher overall values of mu and tau in patients, compared to HC, with no group effect observed in ex-Gaussian sigma. The authors did not examine the relationship between demographic (e.g., age), clinical characteristics and ex-Gaussian parameters.

In a further study, Rentrop *et al.* (2010) assessed attentional function using a GO/NO-GO task in 28 inpatients with either schizophrenia or schizoaffective disorder, as well as matched HC. In the task, participants responded to a visual target for over 80% of trials, withholding their responses for the remaining 20%. Ex-Gaussian tau was higher in patients, with medium-large effect sizes (d = 0.78), compared to HC, whilst values of mu and sigma did not significantly differ between the groups. The latter result is similar to Kieffaber *et al.* (2006). In terms of clinical utility, ex-Gaussian mu was positively correlated with illness duration, and a negative correlation between ex-Gaussian tau and work capability (utilising a capability profile assessment tool) was observed. The authors did not examine the relationship between demographic (e.g., age) and ex-Gaussian parameters.

Finally, Karantinos *et al.* (2014) studied volitional control in two RT tasks (finger lift reaction and voluntary saccadic task) in 23 male patients with schizophrenia and 23 HC. Karantinos *et al.* (2014) noted that patients had elevated IIV, as measured by ex-Gaussian sigma and tau, in the finger lift and voluntary saccadic tasks, compared to HC. However, ex-Gaussian mu did not significantly differ between the groups in either task. Clinically, and utilising a discriminant analysis, the authors stated that ex-Gaussian tau best discriminated patients from HC, in the tasks analysed. Furthermore, the authors reported that none of the ex-distributional parameters correlated with dose of antipsychotic medication, but did not examine the relationships with any demographic variables (e.g., age).

The ex-Gaussian distribution has also been applied in BD (Gallagher *et al.,* 2015). The authors analysed data obtained from a sample of patients with BD (while depressed and in remission), and MDD who completed the Vigil CPT, similar to the CPT-AX outlined in section 1.6. Elevated IIV (sigma and tau) was observed for patients with BD (while depressed), compared to HC, whilst tau was significantly increased in patients in remission, compared to HC. No significant group differences were observed for ex-Gaussian mu.

1.10.4 Neurodegenerative and inflammatory disorders

In AD research, elevation of ex-Gaussian tau has been reported in attentional control tasks (see section 1.10.1 for description of tasks) in mild dementia of Alzheimer's Type (Tse *et al.,* 2010), as well as in early-stage AD (Jackson *et al.,* 2012), compared to HC. The ex-Gaussian distribution has also been investigated in NPSLE, an inflammatory immune disease associated with cognitive deficits (Haynes *et al.*, 2015). In the Haynes *et al.* (2015) study, 14 patients with NPSLE, 22 with SL, but non-NPSLE, and 28 HC completed a computerised Stroop task. The NPSLE group were more variable than the non-NPSLE, as well as HC (ex-Gaussian sigma), but no significant differences were observed for ex-Gaussian mu or tau. The authors did not examine the relationship between demographic (e.g., age), clinical characteristics and ex-Gaussian parameters.

1.10.5 Summary

Studies in normal ageing, as well as a number of clinical disorders, such as ADHD, schizophrenia, BD, AD, and NPSLE, have reported elevated IIV, in the modal portion of the distribution (ex-Gaussian sigma), as well as in the positive tail (ex-Gaussian tau), utilising a variety of tasks from attentional/volitional control to task switching and maintenance. Few studies have examined the ex-Gaussian distribution utilising a wide range of CPTs, with studies in ADHD typically utilising the CCPT-II, and one study to date utilising the Vigil CPT in BD (e.g., Gallagher *et al.,* 2015). It is not clear how, or if RT distributions would change according to variants of CPT, in normal and clinical populations. Or indeed, whether elevated IIV, reflects an independent cognitive impairment in normal ageing and in a number of clinical disorders, or whether it is secondary to an impairment in another cognitive domain (see section 1.4).

A further point of consideration concerns the diagnostic specificity of IIV. At present, it is not clear what elevated IIV, and different ex-Gaussian parameters, represent clinically. Researchers have suggested that increased IIV, in particular ex-Gaussian tau, could simply be a general marker of psychopathology, or a *trans-diagnostic phenotype* (Gottesman and Gould, 2003; Nolen-Hoeksema and Watkins, 2011), i.e. a behavioural measure that may be related to symptoms/shared risk factors expressed in a number of disorders (e.g., cognitive impairment/attentional impairment). However, it is not clear how IIV as a proposed trans-diagnostic phenotype would lead to multiple clinical disorders (Nolen-Hoeksema and Watkins, 2011). Alternatively, the pattern of IIV, whilst similar between disorders, may be the result of different developmental, functional, neurological, as well as neuropsychological processes (i.e. the concept of *equifinality*) (Willcutt *et al.*, 2008; Kofler *et al.*, 2013). As such, IIV could be considered a biomarker per clinical disorder. However, further work is needed to clarify the clinical utility of the ex-Gaussian distribution and associated parameters. The next section will examine the theoretical implications of the ex-Gaussian distribution.

1.11 Theoretical interpretations of the ex-Gaussian distribution

Researchers have utilised the parameters obtained from the ex-Gaussian distribution in two ways - either as simple descriptive tools for better characterising RT distributions (Wagenmakers *et al.*, 2008), or by mapping alterations in these parameters onto specific cognitive processes. Each will now be discussed in turn.

The ex-Gaussian model is typically considered an atheoretical model of RT distributions (Luce, 1986; Heathcote *et al.*, 1991; Leth-Steensen *et al.*, 2000), as it was developed without a theoretical underpinning regarding cognitive interpretations of individual parameters (mu, sigma, and tau). For example, in an analysis of RT distributions obtained from the Stroop task, Heathcote *et al.* (1991) noted that their results did not fit with cognitive interpretation of parameters by Hohle in 1965. Hohle (1965) stated that mu and sigma reflected noise, whilst tau reflected decision-making processes. However, Heathcote *et al.* (1991) noted that mu and sigma were affected by presentation conditions, and tau by experimental manipulation. Therefore, the authors concluded that the ex-Gaussian distribution should be considered a descriptive account of RTs, rather than parameters representing models of cognitive processes. Furthermore, Matzke and Wagenmakers (2009) explored whether a cognitive interpretation could be given to ex-Gaussian parameters. The authors noted that whilst ex-Gaussian parameters seemed to be sensitive to experimental manipulation (e.g., ISI), the parameters did not map uniquely onto those obtained from the Drift Diffusion Model (Ratcliff and McKoon, 2008) – a RT distribution model with a strong theoretical basis. Consequently, the authors concluded that for forced two-choice RT tasks the parameters obtained from the ex-Gaussian should not be interpreted in the context of cognitive processing.

Despite the atheoretical origins of the ex-Gaussian distribution, researchers have mapped specific cognitive processes onto individual parameters, typically within clinical research domains. As RT distributions have typically been obtained from attentional tasks, researchers have interpreted elevations in ex-Gaussian parameters (commonly tau) in terms of a deterioration in attentional/executive control (i.e. being able to maintain a task-related goal, and ignore irrelevant information). The deterioration in attentional control account has been applied to early stage, mild dementia of Alzheimer's type (Tse *et al.*, 2010; Jackson *et al.*, 2012), in older, compared to younger adults (Jackson *et al.*, 2012), in ADHD (Sergeant, 2005), and in schizophrenia (Kieffaber *et al.*, 2006; Rentrop *et al.*, 2010; Karantinos *et al.*, 2014).

Alternative accounts of IIV in clinical disorders has also been discussed. In ADHD, elevation of ex-Gaussian tau is purported to reflect 'lapses' (i.e. longer RT because the individual is not paying attention to the task) in attention (Leth-Steensen *et al.*, 2000; Kofler *et al.*, 2013). However, researchers have argued that the lapse account is non-specific, which limits its explanatory power (Karalunas *et al.,* 2014). Further theories to account for elevated IIV (tau) in schizophrenia have also been proposed. For instance, Rentrop *et al.* (2010) noted the similarities between elevated IIV in ADHD and schizophrenia, suggesting that IIV may reflect a reduction in dopamine transmission, leading to an increase in prefrontal 'noise', and subsequent increase in IIV (Winterer and Weinberger, 2004).

An alternative account, highlighted by Karantinos *et al.* (2014) stems from dysfunction in adaptive gain (Aston-Jones and Cohen, 2005). The locus coeruleus norepinephrine system is proposed to have two modes of activity – *phasic*, which represents active engagement in the task, and facilitates task-related goals, and *tonic*, whereby an individual is disengaged from a task. In the theory, increased IIV in schizophrenia may be the result of noradrenergic neurons in the locus coeruleus in tonic mode, reflecting disengagement in the task. In BD, Gallagher *et al.* (2015) do not interpret their results in terms of cognitive processing.

1.11.1 Summary

Two common methods of interpreting the ex-Gaussian distribution exist within the literature- utilising ex-Gaussian parameters as simply a descriptive tool for RT distributions, and mapping purported cognitive phenomena onto individual parameters. Cognitive interpretations of ex-Gaussian parameters have focussed principally on tau, the right-hand tail of RT distributions, and interpretations vary according to research field, and are specific to type of task employed. However, these interpretations may not be theoretically valid, as the ex-Gaussian distribution is first and foremost, a descriptive tool (Heathcote *et al.,* 1991). For the purposes of the thesis, an a priori mapping of cognitive processes onto ex-Gaussian parameters will not be given. Instead, the ex-Gaussian distribution will be used as a descriptive tool, consistent with the atheoretical underpinning of the model.

1.12 Thesis aims and outline

The current chapter has highlighted literature examining age-related changes in cognitive processes (section 1.3-1.3.4), and the inter-relationship between cognitive processes (section 1.4), with a focus on sustained attention (section 1.3.4) and its measurement (section 1.6-1.6.5). The measurement of IIV (section 1.9-1.9.2), and application of the ex-Gaussian distribution (section 1.10-1.10.4), has also been explored.

As indicated in section 1.4, it is unclear whether sustained attention performance on variants of the CPT outlined, which are sensitive to the effects of normal ageing and pathology, reflects a sustained attention impairment *per se*, or reflects deterioration in more general domains, such as processing speed and/or executive functioning (working memory). Moreover, as numerous CPT variants exist, it is possible that variations in task complexity and associated cognitive load, which may be linked to programming parameters, could be a confounding factor in determining the above.

As the thesis will utilise IIV, measured by the ex-Gaussian distribution, it is important to determine what attentional RT and IIV represents, given the purported biological and clinical utility highlighted in sections 1.8, and 1.10.1-1.10.5.

Consequently, this thesis has identified two aims that will be examined in the studies included (hypotheses/predictions are addressed in individual studies):

1. To further our understanding of the relationship between the multiple cognitive processes purported to be involved in CPT variants and attentional RT and IIV. The multiple cognitive processes of executive functioning, processing speed, and verbal memory, will be examined, as well as the cognitive hierarchy.
2. Examine the relationship between RT/IIV, and age (as well as pathology), as assessed by the ex-Gaussian distribution.
    a. *Note.* Group differences will only be investigated in instances where the hypothesised mediator (e.g., neuropsychological measures) are associated with between-group differences and attentional RT or IIV, following the recommendations of Salthouse (1996).

As a general hypothesis for the thesis, if attentional RT and IIV represents an independent impairment (in normal ageing and/or pathology), the indices will not be secondary to impairments in other proposed 'core' domains such as processing speed (identified in section 1.4, and Table 1-1). The thesis is structured in the following manner: Chapter 2 explores the aims of the thesis in normal ageing, and Chapter 3 in PD. Next, a broad overview of sustained attention literature in BD is presented in Chapter 4, followed by two studies in patients with BD during remission (Chapter 5) and a depressed episode (Chapter 6). A short mediation analysis is presented in Chapter 7, and the thesis ends with a General Discussion in Chapter 8.

Chapter 2. Sustained attention and IIV in normal ageing

The current chapter presents research examining the relationship between CPT parameters and age (section 2.1), with a cross-sectional study in a normal ageing population following this overview.

2.1 Introduction

Studies have examined the impact of CPT parameters (e.g., target frequency, ISI etc.) on the age-related changes in sustained attention outcome measures. In a review of 23 sustained attention studies, Staub *et al.* (2013) noted that 11/23 studies observed age-related changes, with six studies reporting preservation (i.e. no differences between younger and older adults), and a further six reporting inconsistent results (some age-related changes, others preservation of ability). The studies which examined task manipulation in relation to age-related changes in sustained attention indices will now be discussed.

Within the 11 studies that indicated age-related changes, authors reported that alterations in sustained attention outcome measures were higher in older, compared to younger participants. The accentuation in age-related impairment was associated with the manipulation of task parameters such as stimulus discriminability and event rate, which are known to impact detrimentally on sustained attention performance (Sarter *et al.*, 2001). For instance, Parasuraman *et al.* (1989) examined age-related changes in a CPT similar to the Degraded Stimulus-CPT (i.e. with stimulus degraded over the course of the task), with three levels of stimulus discriminability (low, moderate, and high). In the study, the authors noted that older adults (aged 65-78 years) exhibited higher sustained attention impairments (lowered hit rate and increased false alarms), and lower overall attention (lower hit rate), than younger participants (aged 21-29 years), when the stimuli were highly degraded. The results of Parasuraman *et al.* (1989) are also supported by Bunce (2001), but with mean RT and stimulus discriminability (A') as indices of sustained attention impairment.

In a further study, Parasuraman and Giambra (1991) utilised a 30 minute detection task with two event rates: high (more than 40 per minute), and low (15 per minute). Three age-groups were included (n = 36): a young sample (19-27 years), middle-aged (40 – 55 years), and older (70-80 years). The authors noted that age-related differences in sustained attention impairment (reduced hit rate and increases in false alarms) were accentuated with an increase in age, when the event rate was high, compared to low. The results of Parasuraman and Giambra (2001) are also supported by Mouloua and Parasuraman (1995).

However, studies have also reported that no age-related changes exist when manipulating stimulus discriminability. In tasks similar to that employed by Parasuraman *et al.* (1989), Berardi (2001), as well as Bunce and Sisa (2002), reported similar sustained attention decrements in the age-groups utilised. However, the studies differ in the age-ranges of the samples, and their classification of age-groups, which may account for the discrepancies in results. For instance, Berardi *et al.* (2001) included a young (n = 21; 20-39 years), middle (n = 21; 40-59 years), and older sample (n = 20; 60-73 years). In contrast, Bunce and Sisa (2002) only assessed two groups: a younger (n = 26; 16-35 years), and older (n = 24; 45-65 years).

The results of Staub *et al.* (2013) suggest that if specific CPT parameters accentuate age-related differences in indices of sustained attention, such parameters may tax the multiple cognitive components associated with variants of the CPT that also decline with age (Park, 2000) (see also Table 1-1 in Chapter 1). As such, the question remains as to whether age-related deterioration of sustained attention outcome measures (e.g., RT), reflects an independent process, or is secondary to age-related deterioration in one (or more) of the theorised multiple cognitive processes that are involved in CPTs (e.g., processing speed, executive functioning, verbal memory). Moreover, this relationship may vary per CPT, as tasks tend to manipulate more than one parameter and thus, the task complexity differs. This will be a theme addressed in the current study.

The current study aims to provide evidence of whether an association between age and attentional RT and IIV represents an independent impairment, or reflects an impairment in secondary , more general cognitive domains (e.g., processing speed). The study aims are applied to RTs obtained from the CCPT-II, CPT-IP, and RVIP in a cross-sectional sample of normal adults. As cross-sectional studies have indicated that indices of attentional impairment deteriorate with age (Chapter 1, section 1.10.1), it is hypothesised that age will be associated with slower responding (mu), and increased inconsistency in responding across the whole distribution (sigma), as well as infrequent inconsistency in responding, or 'lapses' (tau), obtained from the CCPT-II, CPT-IP, and RVIP. If an association between age and attentional RT and IIV reflects an independent impairment, then entry of other neuropsychological processes (e.g., executive functioning, processing speed, verbal memory) will not account for any age-related associations.

Alternatively, if the studies outlined in section 1.4 are taken into account, then an association between age and attentional RT and IIV will be explained by variance in the other neuropsychological processes of interest. It is possible that the contribution of the other neuropsychological measures to attentional RT and IIV will vary, if the theorised cognitive loadings of the CPTs included in the current study is considered (Table 1-1). In which case, as the RVIP and CPT-IP involve greater processing resources, compared to the CCPT-II, processing speed and executive functioning may independently account for age-related variation in attentional RT and IIV across the tasks. In contrast, due to the anticipated cognitive load of the CCPT-II, processing speed may solely account for age-related variation in attentional RT and IIV. It is expected that the verbal memory contribution to attentional RT and IIV across tasks will be accounted for by processing speed and/or executive functioning, consistent with previous research (section 1.4).

2.2 Methods

2.2.1 Participants

Eighty-one individuals (42 female), between the ages 21 and 90 (*M* = 53.90, *SD* = 19.88), without a personal or first-degree family (e.g., siblings) history of mental health problems were tested (confirmed via self-report). Absence of personal mental illness was confirmed via the M.I.N.I (Sheehan *et al.*, 1998) which was administered by the doctoral candidate, or trained undergraduate and postgraduate placement students, and the BDI (Beck *et al.*, 1996), with a cut-off score of 10 (this removed eight participants, leaving a total sample size of 81). Participants were recruited from the North East of England, through the Institute of Neuroscience (IoN) volunteer database at Newcastle University (http://www.ncl.ac.uk/ion/involved/volunteer), VOICENorth (http://www.ncl.ac.uk/ageing/innovation/engagement/voicenorth/), advertisements in local facilities (e.g., libraries, leisure centres), and social networks. Participants were remunerated £5 for any travel costs incurred, whilst course credit was offered for undergraduates studying Psychology at Newcastle University. Participants were fluent in English in the opinion of the assessor; had a premorbid IQ of more than 70 (*M* = 123.09, *SD* = 4.29), as assessed via the NART (Nelson, 1982); were not dependent on alcohol and/or were abusing substances in the past 12 months (confirmed via M.I.N.I. and self-report); had corrected visual or auditory sensory deficits; had not experienced injury to the head (self-report), resulting in loss of consciousness of more than 10 minutes (self-report); had not previously participated in a study which could affect the results of the current (self-report). The study protocol was approved by a local ethics committee Newcastle University. Written informed consent was obtained prior to study participation.

2.2.2 Materials

The computerised sustained attention tasks described (CCPT-II, CPT-IP, and RVIP) in this section were selected to represent the breadth of CPTs available, as outlined in Chapter 1.

Within the **CCPT-II**, participants are asked to respond to every sequentially presented letter (250 ms presentation), and refrain from responding to the infrequent, non-target (an 'X') for 14 minutes (Figure 2-1). The task has a high target percentage (90%), compared to non-target (10%). Participants complete the task over six blocks, each with three sub-blocks containing 20 trials (two inhibition 'X' trials per 20 trials). The ISI varies per sub-block between one, two, and four seconds.

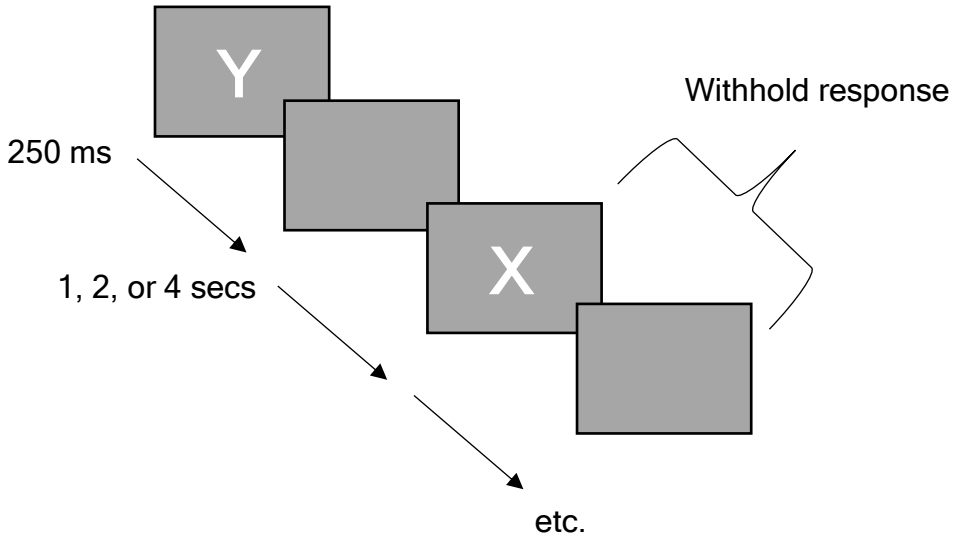

Figure 2-1. Example of target and non-target trial. In the CCPT-II, participants respond to all letters, but the non-target 'X'. Letters are presented for 250 ms, followed by a blank screen with the duration of the ISI (varies in the CCPT-II every 20 trials; 1, 2, or 4 seconds). Secs = seconds.

The version of the **CPT-IP** (Cornblatt *et al.,* 1988) used in the current study is based upon the task included to assess the 'Attention/Vigilance' cognitive domain in the Measurement and Treatment Research to Improve Cognition in Schizophrenia battery (Green *et al.*, 2004; Nuechterlein *et al.*, 2004). Within the CPT-IP, participants respond when two identical stimuli (pairs) are consecutively presented (Figure 2-2). Stimuli are presented quickly (two, three, and four digits appearing simultaneously) at a rate of 50 ms, with a one second ISI, over the course of 150 trials per stimuli type.

Trials consist of targets, catch, and random trials. Target frequency is low (20%; 30/150 trials), mimicking more traditional sustained attention paradigms. The remaining trials consisted of catch trial pairings (e.g., '23' followed by '22'; 60/150 trials), whereby the last digit of a pairing would alter. Responses to catch trials were defined as false alarms, or commission errors. In addition, 'random' trials were included (e.g., '22' followed by '68'; 60/150 trials). Responses to random trials were defined as random errors.

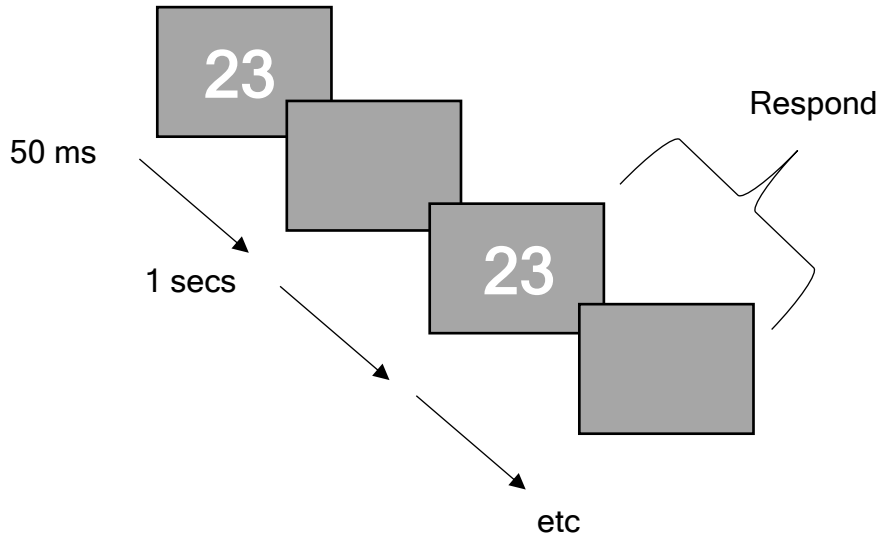

Figure 2-2. Example of a target trial for the CPT-IP. Participants respond when the two identical (pairs) digit sequences are presented. Stimuli are presented for 50 ms, followed by a blank screen lasting the duration of the ISI (one second). Secs = second.

Within the RVIP task (Wesnes and Warburton, 1983a), single digits (e.g., 2-9) are presented consecutively at a rate of 100 digits per minute. The participant is asked to respond to three targets, which consist of three-digit sequences (2-4-6, 4-6-8, 3-5-7; Figure 2-3). Nine targets are presented every minute, for seven minutes (Clark *et al.*, 2005). The target digit strings remain displayed on the screen, serving to reduce the working memory demands of the task. The task was programmed so that the beginning of each target stimuli (e.g., 2, 3, or 4) appeared at least three trials (1800 ms) from the end of a previous target sequence (e.g., 6, from the 2-4-6 target sequence).

Figure 2-3. Example of a target sequence during the RVIP. In the task, digits ranging from 2-9 are consecutively presented in the centre of the screen. Three target sequences (which the participant responds to) are presented next to the digit presented in the centre of the screen.

In addition to the tasks described, two sleep questionnaires were also administered, due to the reported relationship between sustained attention and sleep deprivation (Lim and Dinges, 2008). As such, two standardised sleep quality questionnaires were administered: the ESS (Johns, 1991) and the BSQ (Netzer *et al.*, 1999). General demographic information was also collected from participants, which included sex, age, education level/employment, and whether they smoked or not (due to its reported attention-enhancing effects;Foxe *et al.*, 2012). See Appendix A (section 9.1) for the general demographic questionnaire. For the neuropsychological assessment described, all tasks were administered according to standardised task instructions (Lezak *et al.*, 2004).

Storage capacity, as well as the working memory component of executive functioning was assessed using the **DIGIT SPAN SUBTEST** (Wechsler, 1998). In this task, the researcher reads a digit sequence at a rate of one second per digit (ranging from three to eight). The participant is given two trials per digit sequence. If both trails are incorrect, the test finishes. The backwards condition was included in the current study. In the backwards condition, the participant is asked to repeat the digit sequences in reverse order (e.g., 5-7-4; 4-7-5). For all conditions, no time limit is employed. The number of correct digit sequences was recorded.

The DSST is included in the wider intelligence battery from the WAIS-III (Wechsler, 1998) and is primarily used as an assessment of information processing speed (referred to as processing speed thereafter). The Original DSST was included in the current study. Participants are asked to copy the appropriate geometric symbol in the blank box beneath each digit (from 1-9), according to a key presented at the top of the test sheet. Participants complete the samples first (comprising of seven examples), which are then checked for accuracy by the researcher. Following this, the participant completes as many trials as they can (quickly and accurately) within 90 seconds, in order of presentation. The raw score per sub-test is comprised of the number of items completed in 90 seconds (or less).

The RAVLT (IMMEDIATE AND DELAYED conditions) (Rey, 1964) was administered as a test of verbal memory. During the task, the researcher reads a list of 15 unrelated words at a rate of one word per second (e.g., 'coffee') from list A (A1) to the participant. In the immediate condition ('recall trials'), the participant is asked to recall as many of the words as possible, in any order, with no time limit. The word list is repeated a further four times consecutively ('learning trials', coded A2-A5), and the participant continues to repeat as many words as remembered. Following this, 15 words from the distraction word list (B) (e.g., 'gun') are repeated by the researcher, and the participant is asked to immediately repeat. After list B, the participant repeats as many of the words from word list A (A6) that they can remember, without the researcher reading the list again. In the delayed condition (approximately 20 minutes following the immediate condition), free recall for word list A occurs once more (A7, no time limit). Finally, a series of words are repeated by the researcher. The participant is asked to state orally whether the word came from list A, B, or is a new word entirely ('recognition trial'). For parity with subsequent studies in the thesis, outcome measures used in the study presented in this chapter include the total score from A1-A5 (REY total), number of words recalled following the delay (A7), and number of correct words in the recognition trial (Recognition A).

2.2.3 General programming information

All stimuli for the sustained attention tasks were presented in the centre of the screen. For the CCPT-II and CPT-IP, stimuli were off-white (RGB values, [105 105 105]), and presented on a light grey background [192 192 192]. For the RVIP, stimuli were white [255 255 255], and presented on a black background [0 0 0], to closely resemble the CANTAB version. All stimuli per sustained attention task measured approximately 1.5cm in width and 2.2 cm in height, to resemble the CPT-IP stimuli presented in Cornblatt *et al.* (1988). For the CPT-IP, stimuli width for two digit presentation was approximately four cm, six cm for three digits, and eight cm for four digits.

All tasks were programmed at Newcastle University by the doctoral candidate and Dr Andreas Finkelmeyer using the Psychophysics Toolbox Version 3 extension (Brainard and Vision, 1997; Kleiner *et al.*, 2007) for MATLAB® R2013b version 8.2 64-bit (The MathWorks, Inc. (2013), Natick, Massachusetts, United States). A description of key task parameters associated with the tasks included in the current study is presented in Table 2-1.

Table 2-1. Description of key task parameters associated with the CCPT-II, CPT-IP, and RVIP tasks included in the current study.

Task	Trial type	Stim. Pres	ISI (secs)	Total trials	Target definition	Target % (trials)	Responses per condition/target	Task length (mins)
CCPT-II	Single Letters	250 ms	1, 2, or 4	360	Letter 'X'	90%(324)	324 per ISI	14
CPT-IP	2, 3, or 4 digits	50 ms	1	150 trials per condition	Digit repetition	20%(30)	30 responses per trial type	8
RVIP	Three-digit sequence	600 ms (100 digits/m)	0	700 (100 digits/m)	Presentation of sequence	9%(63)	21 per target sequence	7 (100 digits/m)

Note. Stim. Pres = Stimulus Presentation.

2.2.4 Procedure

Participants were tested in a quiet behavioural testing lab, within IoN, Newcastle University. Participants were tested individually and accompanied by the researcher, who was present throughout their participation. Following the informed consent procedure, demographic information was obtained, and questionnaires were completed (see section 2.2.2). Participants completed the questionnaires in their own time. Following this initial testing phase, participants completed the battery of paper-pencil based neuropsychological tasks (administered in the order presented in section 2.2.2). Administration of the paper-pencil based neuropsychological testing lasted for approximately one hour. Finally, participants completed three computerised sustained attention tasks (CCPT-II, CPT-IP, and RVIP), whose administration order was randomised (using the RAND function in Microsoft Excel). Practice trials were not given formally, but instructions for each test were explained to the participant prior to completion. Stimuli were presented on a PC with Windows 7, on a 51.05x 32.05 inch screen (ASUS PA248Q LED-backlit monitor, 1920 x 1200 screen resolution, 59 Hz refresh rate). Participants were given the option of a short (maximum of 10 minutes) rest between each task to avoid fatigue. Total study participation was one hour 30 minutes – two hours, and participants were debriefed following study completion.

2.2.5 Data pre-processing

Data available differed per task: 76 individuals completed the CCPT-II, all participants obtained over 50% accuracy. For the CPT-IP, 77 participants completed the test. Of these, two participants were removed as they did not obtain more than 50% accuracy, leaving a total sample size of 75. Seventy-one participants completed the RVIP. Of these, 19 participants were removed as they did not obtain more than 50% test accuracy, leaving a total sample size of 56.

The variations in accuracy scores across the CPT included in the current study may have been due to lack of formal practice trials. Raw RTs were trimmed - firstly, RTs below 100 ms were removed following established absolute cut-off principles (Luce, 1986; Ulrich and Miller, 1994), which was applied to all studies included in this thesis. In general, responses were considered valid if they occurred during stimulus presentation, or immediately after presentation of the stimulus (i.e. ISI) (see Table 2-2 for description of response windows per task).

Table 2-2. Description of valid response windows for classification of correct trials, or 'hits' across task.

Task	Stimulus presentation (ms)	ISI (sec)	Response window (ms)
CCPT-IP	250	1,2, or 4	1250; 2250;4250
CPT-IP	50	1	1050
RVIP	600	0	1800

Target sequences were classified as 'hits' if responses were made within the maximum response window corresponding to the ISI for that task. Only hits will be analysed in the studies included in this thesis. A total of 25,027 correct RTs were analysed in the CCPT-IP, 6,207 for the CPT-IP, and 3,101 for the RVIP.

Ex-Gaussian distributional analysis was applied to correct trials (hits), with this procedure applied in all studies included in the thesis. The DISTRIB toolbox (Lacouture and Cousineau, 2008) in MATLAB® R2013b (The MathWorks, Inc. (2013), Natick, Massachusetts, United States) was used to fit the ex-Gaussian probability density function to the distribution of correct response times from all computerised attention tasks. Three parameters of the ex-Gaussian distribution are estimated per individual using this function; *mu*, *sigma*, and *tau*. This approach will be adopted in all studies included in the thesis.

The algorithm failed to fit the distribution to RTs from eight participants. This resulted in the removal of two participant from analysis of the ex-Gaussian distribution in the CCPT-II (total $n = 74$), four removed from the CPT-IP (total $n = 71$), and two removed from the RVIP (total $n = 54$). The CCPT-II and CPT-IP contain individual conditions (described in Chapter 1, section 1.6). The RT IIV variables were calculated per task, rather than per condition, and these averaged values were used in subsequent analyses.

2.2.6 Statistical analysis

Data in this study and the thesis were analysed using the SPSS version 21 (SPSS, Inc., Boston, Mass., 2012). Data were checked for normal distribution using the Shapiro-Wilk test, as well as skewness and kurtosis. Data were not transformed if the assumptions of normality were violated, the appropriate non-parametric test was used. To check for linearity, Pearson's (r) or Spearman's correlations (r_s) were examined before regressions were conducted, and all analyses were two-tailed. Hierarchical multiple regression assumptions for independence of data, variable/predictor type (continuous), no multicollinearity (Tolerance > 0.2; Menard, 1995 and VIF < 10; Myers, 1990), or homoscedasticity as indicated on a regression plot, were met.

To understand the relationship between age and ex-Gaussian parameters (mu, sigma, and tau), taking into account other neuropsychological processes such as executive functioning, processing speed, and verbal memory, a series of hierarchical multiple regressions (using the Enter method) were performed. The dependent variables consisted of the ex-Gaussian distributional measures (mu, sigma, and tau) from the CCPT-II, CPT-IP, and RVIP. Age, a verbal memory composite (an average score of RAVLT Total, A7, and Recognition A), executive functioning (working memory as assessed by the Digit Span Backwards) and processing speed (DSST, original) were selected as predictors.

These measures were selected as representative of multiple cognitive domains theorised to be involved in CPTs, and to enable comparison between the results of the current study to following, subsequent studies included in the thesis. The current methodology will be applied to subsequent studies.

Age was entered into the last step of the models. For all analyses and throughout the thesis (unless otherwise indicated), the contributions of age (Model 1), executive functioning and age (Model 1a), processing speed and age (Model 1b), as well as verbal memory and age (Model 1c) were examined. Further models examined order of entry, given the reported hierarchy of cognitive processes (see Chapter 1, section 1.4). Model 2a examined the contributions of age, executive functioning, and processing speed. Model 2b examined the contributions of age, executive functioning and verbal memory, whilst Model 2c examined the contributions of age, processing speed, and verbal memory. Executive functioning, processing speed, or verbal memory were entered into either in the first or second steps of Models 2a, b, or c. These steps were completed separately for the CCPT-II, CPT-IP, and RVIP. For the hierarchical regression analyses, outliers (+3 SD from mean) were removed from analyses until no further outliers remained. Individuals were removed from analyses on a case-by-case basis, and exclusion from one analysis did not preclude exclusion from subsequent analyses. The data presented in this study is with outliers removed. The total *n* varied per hierarchical regression model, and per ex-Gaussian parameter. For total *n* see Tables 9-1 to 9-3 in the Appendix A.

Demographic characteristics such as BDI, and education/employment level were not included as covariates in subsequent analyses as these measures were intended to describe the sample at a coarse level.

2.3 Results

2.3.1 Sample characteristics

Twenty participants were in full time work (> 35 hours per week), 12 were in part-time work, one unemployed, 38 were retired and 10 were students. Eleven participants obtained a highest level of education of O-Level/GCSE, 11 A-Levels, 33 undergraduate, and 26 postgraduate. Participants in the current study had a low risk for sleep aponea (BSQ: $M = 0.08$, $SD = 0.28$; ESS: $M = 4.65$, $SD = 3.81$). The majority of the sample (80/81 participants) did not smoke. Ex-Gaussian parameters did not differ between the sexes in any task (all $p > 0.050$). As such, sex was not included as a covariate in subsequent analyses. Whilst NART was negatively associated with ex-Gaussian sigma obtained from the RVIP ($r_{s\,(48)} = -0.323$, $p < 0.050$), no other significant association was noted (all $p > 0.050$). However, as this reduced the sample size from 56 to 48 in the RVIP, NART score was not included as a covariate in subsequent analyses.

2.3.2 Relationship between age and ex-Gaussian parameters

Age was significantly positively correlated with mu obtained from all paradigms, with sigma obtained from the CCPT-II and CPT-IP, and with tau obtained from the CCPT-II and RVIP (Table 2-3).

Table 2-3. Spearman correlations between age, and ex-Gaussian parameters obtained from the CCPT-II, CPT-IP, and RVIP.

		CCPT-II[a]	CPT-IP[b]	RVIP[c]
Age	Mu	**0.630****	**0.460*****	**0.552****
	Sigma	**0.567****	**0.415****	0.050
	Tau	**0.297***	0.001	**0.306***

* $p < 0.050$, ** $p < 0.010$, *** $p < 0.001$. Significance highlighted in bold.

[a] $n = 74$

[b] $n = 71$

[c] $n = 54$

Age was significantly negatively correlated with the cognitive domains of interest – processing speed and verbal memory (processing speed: $r_{s\,(79)} = -0.685$, $p < 0.001$; verbal memory: $r_{s\,(44)} = -0.598$, $p < 0.001$), but not executive functioning ($r_{s\,(74)} = -0.192$, $p = 0.101$).

The relationship between ex-Gaussian parameters and the other neuropsychological processes of interest (executive functioning, processing speed, and verbal memory) was also examined. Executive functioning significantly negatively correlated with sigma obtained from the CCPT-II, and mu and tau from the RVIP. Processing speed significantly negatively correlated with mu obtained from all tasks, as well as sigma obtained from the CCPT-II and CPT-IP, whilst verbal memory significantly negatively correlated with mu and sigma obtained from the CCPT-II and tau from the RVIP (Table 2-4).

Table 2-4. Spearman correlations between ex-Gaussian parameters obtained from the CCPT–II, CPT-IP, and RVIP, and other neuropsychological processes.

		EF	PS	VM
CCPT-II[a]	Mu	- 0.177	**- 0.384****	**- 0.345***
	Sigma	**- 0.265***	**- 0.398****	**- 0.408****
	Tau	- 0.200	**- 0.243***	- 0.030
CPT-IP[b]	Mu	- 0.140	**- 0.344****	- 0.160
	Sigma	- 0.212	**- 0.424****	- 0.171
	Tau	- 0.091	- 0.058	0.043
RVIP[c]	Mu	**- 0.361****	**- 0.437****	- 0.188
	Sigma	- 0.129	- 0.074	0.074
	Tau	**- 0.298***	- 0.243	**- 0.353***

Note. EF = Executive Functioning, PS = Processing Speed, VM = Verbal Memory.

$p < 0.050$, ** $p < 0.010$. Significance highlighted in bold.

[a] Executive Function $n = 73$; Processing Speed $n = 69$; Verbal Memory $n = 43$.

[b] Executive Function $n = 65$; Processing Speed $n = 69$; Verbal Memory $n = 41$.

[c] Executive Function $n = 52$; Processing Speed $n = 54$; Verbal Memory $n = 43$.

In order to examine the relationship between age and ex-Gaussian parameters (mu, sigma, and tau), whilst taking into account the hypothesised multiple cognitive demands of the CCPT-II, CPT-IP, and RVIP, a series of hierarchical regressions were performed.

EX-GAUSSIAN MU: Single predictor models (1a, 1b, and 1c) were examined. Entry of processing speed significantly predicted variance in mu in all CPTs examined (all $\Delta R^2 > 11.1\%$), whereas entry of executive functioning predicted variance in mu obtained from the RVIP ($\Delta R^2 = 16.2\%$), and entry of the verbal memory composite for the CCPT-II ($\Delta R^2 = 11.5\%$). The final entry of age significantly predicted variance in mu in all models (Table 2-5).

Next, the order of entry models (2a, 2b, and 2c) were examined per CPT. In the CCPT-II, entry of processing speed significantly predicted variance in mu (all $\Delta R^2 > 5.9\%$), but not when entered into the second step of Model 2c ($\Delta R^2 = 7\%$), after verbal memory. Entry of verbal memory significantly predicted variance in mu, when entered into the first steps of Models 2b ($\Delta R^2 = 12.9\%$), and 2c ($\Delta R^2 = 11.5\%$), before executive functioning. In the CPT-IP, processing speed was a significant predictor of mu (all $\Delta R^2 > 11\%$), irrespective of order of entry. In the RVIP, and similar to the CPT-IP, processing speed was a significant predictor of mu in all models (all $\Delta R^2 > 8.4\%$). Entry of executive functioning significantly predicted variance in mu, irrespective of order of entry in Model 2b (all $\Delta R^2 > 10.6\%$), but only before entry of processing speed in Model 2a ($\Delta R^2 = 12.9\%$). The final entry of age significantly predicted variance in mu in all models (Table 2-5).

Table 2-5. Hierarchical regressions for ex-Gaussian mu obtained from the CCPT-II, CPT-IP, and RVIP.

ex-Gaussian mu		CCPT-II				CPT-IP				RVIP			
Model		R^2	ΔR^2	**Sig. F Change**	**β**	R^2	ΔR^2	**Sig. F Change**	**β**	R^2	ΔR^2	**Sig. F Change**	**β**
	Age	0.404	0.404	**< 0.001**	0.635	0.243	0.243	**< 0.001**	0.493	0.362	0.362	**< 0.001**	0.602
1a	EF	0.050	0.050	0.067	- 0.223	0.018	0.018	0.289	- 0.135	0.116	0.116	**< 0.050**	- 0.341
	Age	0.374	0.324	**< 0.001**	0.588	0.291	0.273	**< 0.001**	0.537	0.367	0.251	**< 0.001**	0.536
1b	PS	0.111	0.111	**< 0.010**	- 0.333	0.135	0.135	**< 0.010**	- 0.367	0.162	0.162	**< 0.010**	- 0.403
	Age	0.423	0.313	**< 0.001**	0.749	0.245	0.110	**< 0.010**	0.469	0.363	0.201	**< 0.001**	0.573
1c	VM	0.115	0.115	**< 0.050**	- 0.339	0.009	0.009	0.557	- 0.094	0.083	0.083	0.061	- 0.288
	Age	0.452	0.337	**< 0.001**	0.776	0.336	0.327	**< 0.001**	0.727	0.484	0.401	**< 0.001**	0.796
2a	EF	0.049	0.049	0.072	- 0.222	0.018	0.018	0.304	- 0.133	0.116	0.116	**< 0.050**	- 0.341
	PS	0.108	0.059	**< 0.050**	- 0.256	0.128	0.110	**< 0.010**	- 0.358	0.201	0.084	**< 0.050**	- 0.309
	Age	0.415	0.306	**< 0.001**	0.733	0.295	0.168	**< 0.001**	0.562	0.268	0.167	**< 0.010**	0.527
	PS	0.090	0.090	**< 0.050**	- 0.300	0.128	0.128	**< 0.010**	- 0.357	0.151	0.151	**< 0.010**	- 0.389
	EF	0.108	0.018	0.258	- 0.142	0.128	0.000	0.987	0.002	0.201	0.050	0.087	- 0.237
	Age	0.415	0.306	**< 0.001**	0.733	0.295	0.168	**< 0.001**	0.562	0.368	0.167	**< 0.010**	0.527
2b	EF	0.076	0.076	0.082	- 0.275	0.096	0.096	0.055	- 0.309	0.144	0.144	**< 0.050**	- 0.379
	VM	0.164	0.089	0.052	- 0.308	0.110	0.015	0.445	- 0.126	0.165	0.021	0.336	- 0.150
	Age	0.481	0.317	**< 0.001**	0.729	0.445	0.335	**< 0.001**	0.713	0.528	0.364	**< 0.001**	0.734
	VM	0.129	0.129	**< 0.050**	- 0.359	0.041	0.041	0.218	- 0.202	0.059	0.059	0.127	- 0.243
	EF	0.164	0.036	0.210	- 0.196	0.110	0.070	0.101	- 0.275	0.165	0.106	**< 0.050**	- 0.338
	Age	0.481	0.317	**< 0.001**	0.729	0.445	0.335	**< 0.001**	0.713	0.528	0.364	**< 0.001**	0.734
2c	PS	0.174	0.174	**< 0.010**	- 0.417	0.163	0.163	**< 0.010**	- 0.403	0.217	0.217	**< 0.010**	- 0.466
	VM	0.185	0.011	0.465	- 0.133	0.189	0.027	0.271	0.198	0.219	0.002	0.772	- 0.049
	Age	0.457	0.272	**< 0.001**	0.742	0.377	0.187	**< 0.010**	0.607	0.499	0.280	**< 0.001**	0.728
	VM	0.115	0.115	**< 0.050**	- 0.339	0.009	0.009	0.557	- 0.094	0.083	0.083	0.061	- 0.288
	PS	0.185	0.070	0.072	- 0.335	0.189	0.180	**< 0.010**	- 0.516	0.219	0.135	**< 0.050**	- 0.439
	Age	0.457	0.272	**< 0.001**	0.742	0.377	0.187	**< 0.010**	0.607	0.499	0.280	**< 0.001**	0.728

Note. β = Standardised coefficients; EF = Executive Functioning; PS = Processing Speed; VM = Verbal Memory. Significance highlighted in bold and light blue.

EX-GAUSSIAN SIGMA: Single predictor models (Models 1a, 1b, and 1c) were examined. Entry of processing speed predicted sigma obtained from the CCPT-II ($\Delta R^2 > 17.3\%$), and CPT-IP ($\Delta R^2 > 18.2\%$), whereas entry of executive functioning ($\Delta R^2 > 8.5\%$) and the verbal memory composite ($\Delta R^2 > 18\%$) were only significant for sigma obtained from the CCPT-II. The final entry of age significantly predicted variance in sigma obtained from the CCPT-II (all $\Delta R^2 > 9.7\%$), but only in Models 1a and 1c for the CPT-IP (Table 2-6).

Next, the order of entry models (Models 2a, 2b, and 2c) were examined per CPT. For the CCPT-II, entry of executive functioning was significant, but only when entered before processing speed in Model 2a ($\Delta R^2 = 8.6\%$), or the verbal memory composite in Model 2b ($\Delta R^2 = 11.4\%$). Entry of processing speed was significant, irrespective of order of entry in Model 2a ($\Delta R^2 > 10.3\%$), but only when entered into the first step of Model 2c ($\Delta R^2 = 19.5\%$). Entry of verbal memory was significant, irrespective of order of entry in Model 2b ($\Delta R^2 > 14.1\%$), but only when entered into the first step of Model 2c, before processing speed ($\Delta R^2 = 18\%$). The final entry of age significantly predicted sigma in Models 2a ($\Delta R^2 = 16.3\%$) and b ($\Delta R^2 = 8.5\%$), but not c ($\Delta R^2 = 6.2\%$). For the CPT-IP, entry of processing speed predicted sigma, irrespective of order of entry (all $\Delta R^2 < 20.5\%$). Entry of executive functioning significantly predicted sigma, but only when entered into the first step of Model 2a ($\Delta R^2 = 11\%$), before the verbal memory composite. The final entry of age was only significant for Model 2a, after entry of executive functioning, or the verbal memory composite ($\Delta R^2 = 13.3\%$) (Table 2-6).

Table 2-6. Hierarchical regressions for ex-Gaussian sigma obtained from the CCPT-II, CPT-IP, and RVIP.

ex-Gaussian sigma		CCPT-II				CPT-IP				RVIP			
Model		R^2	ΔR^2	**Sig. F Change**	**β**	R^2	ΔR^2	**Sig. F Change**	**β**	R^2	ΔR^2	**Sig. F Change**	**β**
	Age	0.339	0.339	**< 0.001**	0.582	0.145	0.145	**< 0.010**	0.380	0.007	0.007	0.542	0.085
1a	EF	0.085	0.085	**< 0.050**	- 0.292	0.036	0.036	0.129	- 0.190	0.000	0.000	0.875	- 0.022
	Age	0.353	0.268	**< 0.001**	0.536	0.203	0.167	**< 0.010**	0.419	0.008	0.008	0.539	0.094
1b	PS	0.173	0.173	**< 0.001**	- 0.416	0.182	0.182	**< 0.001**	- 0.426	0.001	0.001	0.815	- 0.033
	Age	0.339	0.166	**< 0.001**	0.553	0.196	0.014	0.290	0.166	0.008	0.007	0.558	0.105
1c	VM	0.180	0.180	**< 0.010**	- 0.424	0.026	0.026	0.313	- 0.161	0.006	0.006	0.635	0.074
	Age	0.277	0.097	**< 0.050**	0.417	0.140	0.114	**< 0.050**	0.430	0.007	0.002	0.806	- 0.049
2a	EF	0.086	0.086	**< 0.050**	- 0.294	0.034	0.034	0.150	- 0.183	0.000	0.000	0.875	- 0.022
	PS	0.190	0.103	**< 0.010**	- 0.339	0.205	0.172	**< 0.010**	- 0.447	0.002	0.001	0.818	- 0.035
	Age	0.352	0.163	**< 0.001**	0.543	0.242	0.036	0.098	0.261	0.009	0.007	0.563	0.108
	PS	0.158	0.158	**< 0.010**	- 0.398	0.205	0.205	**< 0.001**	- 0.453	0.001	0.001	0.785	- 0.039
	EF	0.190	0.032	0.116	- 0.187	0.205	0.000	0.900	- 0.016	0.002	0.000	0.945	- 0.010
	Age	0.352	0.163	**< 0.001**	0.543	0.242	0.036	0.098	0.261	0.009	0.007	0.563	0.108
2b	EF	0.114	0.114	**< 0.050**	- 0.337	0.110	0.110	**< 0.050**	- 0.331	0.005	0.005	0.646	0.074
	VM	0.255	0.141	**< 0.050**	- 0.389	0.160	0.050	0.152	- 0.233	0.011	0.005	0.661	0.074
	Age	0.340	0.085	**< 0.050**	0.378	0.293	0.133	**< 0.050**	0.450	0.011	0.001	0.887	- 0.029
	VM	0.202	0.202	**< 0.010**	- 0.449	0.094	0.094	0.058	- 0.306	0.008	0.008	0.581	0.089
	EF	0.255	0.053	0.109	- 0.238	0.160	0.066	0.101	- 0.268	0.011	0.003	0.750	0.054
	Age	0.340	0.085	**< 0.050**	0.378	0.293	0.133	**< 0.050**	0.450	0.011	0.001	0.887	- 0.029
2c	PS	0.195	0.195	**< 0.010**	- 0.442	0.197	0.197	**< 0.010**	- 0.444	0.002	0.002	0.759	0.048
	VM	0.233	0.038	0.169	- 0.246	0.210	0.012	0.449	0.134	0.006	0.003	0.718	0.068
	Age	0.295	0.062	0.072	0.354	0.240	0.030	0.234	0.243	0.007	0.001	0.810	- 0.053
	VM	0.180	0.180	**< 0.010**	- 0.424	0.026	0.026	0.313	- 0.161	0.006	0.006	0.635	0.074
	PS	0.233	0.052	0.106	- 0.290	0.210	0.184	**< 0.010**	- 0.520	0.006	0.000	0.954	0.011
	Age	0.295	0.062	0.072	0.354	0.240	0.030	0.234	0.243	0.007	0.001	0.810	- 0.053

Note. β = Standardised coefficients; EF = Executive Functioning; PS =Processing Speed; VM = Verbal Memory. Significance highlighted in bold and light blue.

EX-GAUSSIAN TAU: Single predictor models (1a, 1b, and 1c) were examined. In the RVIP, executive functioning, processing speed, and verbal memory predicted variance in tau (all $\Delta R^2 > 8.2\%$).The final entry of age did not significantly predict variance in tau in any model or CPT. Next, the order of entry models (2a, 2b, and 2c) were examined per CPT. In the RVIP, entry of executive functioning predicted variance in tau in Model 2a, irrespective of order of entry (all $\Delta R^2 > 7.4\%$). Entry of processing speed predicted variance in tau, but only when entered into the first step of Models 2a ($\Delta R^2 = 9.5\%$) and c ($\Delta R^2 = 12.5\%$), before executive functioning and the verbal memory composite. Entry of the verbal memory composite significantly predicted variance in tau, irrespective of order of entry in Model 2b (all $\Delta R^2 > 14.2\%$), but only when entered into the first step of Model 2c ($\Delta R^2 = 12.2\%$). The final entry of age did not significantly predict variance in tau in any model (Table 2-7).

Table 2-7. Hierarchical regressions for ex-Gaussian tau obtained from the CCPT-II, CPT-IP, and RVIP.

ex-Gaussian tau		CCPT-II				CPT-IP				RVIP			
Model		R^2	ΔR^2	**Sig. F Change**	**β**	R^2	ΔR^2	**Sig. F Change**	**β**	R^2	ΔR^2	**Sig. F Change**	**β**
	Age	0.045	0.045	0.074	0.212	0.001	0.001	0.751	0.039	0.094	0.094	**< 0.050**	0.306
1a	EF	0.005	0.005	0.580	- 0.069	0.016	0.016	0.313	- 0.127	0.130	0.130	**< 0.010**	- 0.361
	Age	0.052	0.048	0.077	0.224	0.016	0.000	0.924	0.012	0.183	0.053	0.081	0.246
1b	PS	0.016	0.016	0.297	- 0.125	0.003	0.003	0.659	- 0.054	0.082	0.082	**< 0.050**	- 0.287
	Age	0.038	0.022	0.215	0.204	0.003	0.000	0.959	0.009	0.109	0.027	0.221	0.209
1c	VM	0.000	0.000	0.944	- 0.011	0.003	0.003	0.756	- 0.050	0.122	0.122	**< 0.050**	- 0.349
	Age	0.027	0.026	0.304	0.218	0.003	0.001	0.859	0.037	0.126	0.004	0.666	0.081
2a	EF	0.006	0.006	0.531	- 0.079	0.019	0.019	0.283	-0.137	0.130	0.130	**< 0.010**	- 0.361
	PS	0.018	0.011	0.396	- 0.111	0.023	0.004	0.608	- 0.071	0.169	0.039	0.134	- 0.211
	Age	0.045	0.028	0.186	0.225	0.026	0.002	0.703	- 0.067	0.190	0.021	0.274	0.185
	PS	0.016	0.016	0.319	- 0.125	0.013	0.013	0.380	- 0.113	0.095	0.095	**< 0.050**	- 0.308
	EF	0.018	0.002	0.720	- 0.047	0.023	0.011	0.424	- 0.111	0.169	0.074	**< 0.050**	- 0.289
	Age	0.045	0.028	0.186	0.225	0.026	0.002	0.703	- 0.067	0.190	0.021	0.274	0.185
2b	EF	0.008	0.008	0.585	- 0.088	0.017	0.017	0.435	- 0.129	0.071	0.071	0.092	- 0.267
	VM	0.008	0.000	0.963	- 0.008	0.028	0.012	0.515	0.112	0.213	0.142	**< 0.050**	- 0.391
	Age	0.035	0.027	0.314	0.214	0.028	0.000	0.997	- 0.001	0.217	0.004	0.651	0.081
	VM	0.001	0.001	0.853	- 0.030	0.005	0.005	0.678	0.069	0.189	0.189	**< 0.010**	- 0.435
	EF	0.008	0.007	0.610	- 0.086	0.028	0.024	0.357	- 0.159	0.213	0.024	0.292	- 0.160
	Age	0.035	0.027	0.314	0.214	0.028	0.000	0.997	- 0.001	0.217	0.004	0.651	0.081
2c	PS	0.003	0.003	0.725	0.055	0.014	0.014	0.456	- 0.120	0.125	0.125	**< 0.050**	- 0.353
	VM	0.006	0.003	0.719	- 0.072	0.015	0.000	0.894	0.026	0.159	0.035	0.205	- 0.223
	Age	0.047	0.040	0.206	0.286	0.015	0.000	0.904	- 0.028	0.160	0.000	0.916	- 0.021
	VM	0.000	0.000	0.944	- 0.011	0.003	0.003	0.756	- 0.050	0.122	0.122	**< 0.050**	- 0.349
	PS	0.006	0.006	0.620	0.100	0.015	0.012	0.495	- 0.135	0.159	0.038	0.189	- 0.231
	Age	0.047	0.040	0.206	0.286	0.015	0.000	0.904	- 0.028	0.160	0.000	0.916	- 0.021

Note. β = Standardised coefficients; EF = Executive Functioning; PS =Processing Speed; VM = Verbal Memory. Significance highlighted in bold and light blue.

2.4 Discussion

The current study aimed to examine the relationship between the other neuropsychological processes (executive functioning, processing speed, and verbal memory) theorised to be involved in CPT variants and attentional RT and IIV. In addition to determine whether age-related variance in attentional RT and IIV was an independent process, or secondary to deterioration in another cognitive domain. The results indicated that better performance on multiple neuropsychological processes was associated with faster RT (mu) and/or more consistent responding (sigma, tau), but this varied across CPT. Similar results were obtained for the effect of age on RT and IIV, with age predicting slower responding and increased inconsistency, but the latter varied across CPT. Moreover, the association between age and mu is not independent of, or secondary to the multiple neuropsychological processes examined per se. These processes share variance with mu, and age accounts for additional unique variance. However, age may not account for additional unique variance in IIV (sigma or tau), depending on the task examined.

2.4.1 Relationship between other neuropsychological processes and attentional RT and IIV

The involvement of processing speed in RT (mu) may reflect the high event rate (more than 40 events per minute; Parasuraman and Giambra, 1991) inherent in all tasks included in the current study, with stimuli presented quickly across each task. However, it is difficult to state that mu is simply associated with information processing capacity, as the DSST, the measure used to assess processing speed in the current study, measures a collection of cognitive processes such as sustained attention, visual scanning, motor speed, and coordination (Lezak *et al.*, 2012), all of which echo the requirements of CPT variants generally.
Better executive functioning predicted faster responding in the RVIP.

As executive functioning in the current study was measured using the Digit Span Backwards (Wechsler, 1998), the results indicate that larger working memory capacity is associated with faster mu. Theoretically, the Digit Span backwards relies on an executive-phonological loop interface, as outlined by the Baddeley and Hitch (1974) model of working memory. The task involves the short term maintenance of items on the digit list, which is managed by two 'slave' systems involved in the temporary storage and rehearsal of information (phonological loop), as well as the integration of information (visuospatial sketchpad). Additionally, an individual is required to mentally manipulate the digit list to achieve the correct order. As such, the task requires the resources of the Central Executive, which is a system that maintains attentional control of working memory (Baddeley, 1996; Monaco *et al.*, 2013).

Consequently, to respond quickly in the RVIP, an efficient central executive system may be necessary. Of note, the involvement of working memory in the RVIP does not reflect the assertion that the working memory load of the task is reduced by the presence of target sequences on the screen (Clark *et al.*, 2002). Despite the involvement of other neuropsychological processes in attentional RT across all CPT variants examined in the current study, age still accounted for additional unique variance.

The association between other neuropsychological processes and attentional IIV as indexed by ex-Gaussian sigma, differed per paradigm. Better processing speed was associated with reduced inconsistency in the CCPT-II and CPT-IP, executive functioning in the CCPT-II, and verbal memory in the CPT-IP. The results specific to IIV (sigma) suggests that this index of IIV not be related to performance on cognitive tests (e.g., Tse *et al.,* 2010). For IIV as indexed by the positive tail of the RT distribution (ex-Gaussian tau), processing speed, executive functioning, and verbal memory were all predictors of tau obtained from the RVIP task, but not for the CCPT-II, or CPT-IP. These results emphasise the cognitively-demanding nature of the RVIP, and involvement of 'higher-order' processes in supporting IIV, compared to similar CPT variants.

Tau obtained from the CCPT-II or CPT-IP may reflect white matter health, which may also be a clinically relevant marker of disease state (e.g., de Frais *et al.,* 2012). Thus far, the ISD has been utilised as a marker of IIV in neuroimaging studies (Hultsch and MacDonald, 2004; Dykiert *et al.*, 2012), rather than ex-Gaussian indices.

The relationship between the other neuropsychological processes of focus and ex-Gaussian parameters observed in the current study may suggest a role of compensatory cognitive scaffolding (Park and Reuter-Lorenz, 2009). Alternatively, this could reflect the intrinsic properties of the task itself. This will be discussion in greater depth in the General Discussion, section 8.2.1.

2.4.2 Relationship between age and attentional RT and IIV

Age was associated with slowed responding (mu) across all models, irrespective of CPT variant. The result is consistent with research indicating age is associated with a decline in a individuals speed of processing (Brockmole and Logie, 2013), and could be linked to the high event rate across all CPTs examined (more than 40 events per minute, as defined by Parasuraman and Giambra (1991)).
For attentional IIV characterised by inconsistency across the entire distribution (sigma), age was only associated with inconsistency obtained from the CCPT-II and CPT-IP. In the CCPT-II, the association between age and sigma was not secondary to, nor independent from, the neuropsychological processes examined and age accounted for additional unique variance. Variability in RT obtained from the CCPT-II also shared variance with executive functioning, processing speed, and verbal memory. However, for the CPT-IP, the association between age and sigma could be accounted for by processing resources such as processing speed and executive functioning, as the effect of age on sigma was no longer significant when these variables were entered into the models.

These results provide support for the processing-speed theory of cognition, as highlighted by Salthouse (1996). Moreover, the results also indicated that processing speed could be the key cognitive domain, as the effect of executive functioning on age was accounted for when processing speed was included in the first step of the model, providing support for Salthouse (1994). As indicated in Table 1-1, the CPT-IP was anticipated to be associated with a high level of executive functioning, processing speed, and verbal memory load, due to its task parameters. Therefore, the current results could reflect the task complexity of the CPT-IP.

In addition, the CPT-IP and CCPT-II are the only tasks in the thesis which include three individual conditions – two, three, and four digit presentations for the CPT-IP, and one, two, and four second ISI presentations for the CCPT-II. These conditions were collapsed, and an average score used to represent mu, sigma, and tau for these particular tasks. The alteration in task demands and/or cumulative task demands may lead to inconsistency in responding across the entire distribution with an increase in age, rather than infrequent inconsistency in responding, indexed by ex-Gaussian tau.

For attentional IIV characterised by infrequent instances of long RTs (tau), only tau obtained from the RVIP was associated with age, as a single predictor. Inclusion of the other neuropsychological processes of interest accounted for the association between age and ex-Gaussian tau in the RVIP, suggesting that the association may be secondary to age-related changes in cognitive processes such as executive functioning, processing speed, and verbal memory. This result may reflect the effortful nature of the task, and reliance on processing resources for efficient performance.

The current results are also in contrast to the results of McAuley *et al.* (2006), Tse *et al.* (2010), and Jackson *et al.* (2012). However, differences in these studies and the current may account for the discrepancy in results. As detailed in Chapter 1, the results of Tse *et al.* (2010) and Jackson *et al.* (2012) are limited by uneven group sizes and use of composite scores. McAuley *et al.* (2006) included two groups, a younger (M = 19.6) and older (M = 72.9), with the latter group older than the sample included in the current study (M = 53.90).
The lack of association between ex-Gaussian indices of variability (sigma and tau) across tasks and age may highlight that IIV may not be exclusively accounted for by general brain changes indexed by the ageing process. Ageing, or chronological age, may be used a proxy marker for general brain changes, but use of this metric alone lacks specificity (Rabbitt *et al.*, 2007). Generally, elevated IIV has been correlated with incidences of white matter health. In addition, elevated IIV (ex-Gaussian sigma, but more commonly tau), is associated with a wide range of clinical disorders (sections 1.10.1-1.10.4). Thus, these parameters may instead represent clinical markers of disease state, rather than age *per se*.

2.4.3 Study limitations and future research

Methodological issues of the current study also need to be considered. The total sample sizes differed per hierarchical regression model, due to incomplete data sets. However, the regression models analysed were valid, with an adequate number of participants included per model, in addition to parametric assumptions of the hierarchical linear regressions met (section 2.2.6).

In addition, 19 participants were removed from the RVIP was removed from further analyses, due to participants performing below 50% accuracy. It is possible that this was an overly conservative method of data pre-processing, as the data removed may well have still been valid and reflected the increased task-difficulty of the RVIP, compared to the CCPT-II and CPT-IP. However, it is also possible that participants were more likely to respond randomly in the RVIP, which may be linked to motivation and/or perceived task difficulty.

Moreover, out of 71 participants who completed the RVIP in the current study, ex-Gaussian distributions were fitted successfully to RT data from 64 participants. The removal of those who scored below 50% accuracy only resulted in the removal of 10 participants (final $n = 54$). The conservative method of data-analysis employed here provides greater reassurance that the participants included in further analyses were more able to respond to the task.

A further limitation concerns the neuropsychological battery included in the current study, which involved a measure of processing speed, working memory, and verbal memory, with interpretation limited to these domains. As CPT variants are hypothesised to place emphasis on a number of neuropsychological domains (Riccio and Reynolds, 2001; Riccio *et al.*, 2002), greater detail and specificity is required in relation to their contribution to measures of sustained attention, such as IIV. For example, working memory was analysed in the current study, but other indexes of executive control not included such as set-shifting and inhibition (see Miyake, 2000), could be investigated, the analyses of which would also be relevant (e.g., inhibitory control and the CCPT-II task demands).

2.4.4 Conclusions

The results of the current study suggests: (1) The involvement of other neuropsychological processes in attentional RT and IIV may represent cognitive scaffolding, or the intrinsic properties of the CPT examined, and (2) The association between age and attentional RT and IIV may not be independent of, nor secondary to other neuropsychological processes, but may instead suggest that attentional RT and IIV shares variance with multiple neuropsychological processes, depending on the CPT examined. The sharing of variance could account for task-related differences in the relationship between age and attentional RT and IIV. With regard to (1), it was not possible to demonstrate this in the current study, as groups (e.g., younger versus older) were not included for comparison. This will be a theme addressed in the following studies, but with comparison between patients and HC.

With regard to (2), if attentional RT and IIV shares variance with other cognitive domains, but cannot be accounted for by deterioration within them (i.e. age or group-related differences in attentional RT or IIV are not secondary to deterioration in other cognitive processes), this would have implications for clinical studies. Elevated IIV is reported to have biological and clinical utility. Its relevance as a clinical tool may rest on demonstrating that it is not an artefact of impairment in another cognitive domain. As such, the following experimental studies will assess the thesis aims in two clinical populations – PD and BD (with patients in remission and while depressed).

Chapter 3. An ex-Gaussian distributional analysis of RT in PD

The current chapter will present a broad overview of the clinical, and cognitive characteristics of PD, with a focus on sustained attention and RT and IIV. A study in PD will follow this overview (section 3.1.7 onwards).

3.1 Introduction

3.1.1 Clinical symptoms and diagnosis

Parkinsonism is defined clinically by slowness of movement (bradykinesia), and at least one of the following: resting tremor, muscular rigidity, and postural instability (Hughes *et al.*, 1992).Parkinsonian disorders are classified as idiopathic, secondary (e.g., head trauma), heredodegenerative (e.g., Dementia with Lewy Bodies), and those involving multiple system degeneration (e.g., progressive supranuclear palsy) (Jankovic, 2008). Idiopathic PD is the most commonly encountered classification, with much research focussed on this domain (Fahn, 2003). As such, the study included in this chapter will focus on idiopathic PD.

The diagnosis of PD is based on clinical examination and history, as diagnostic tests are not currently able to definitively confirm PD during a lifetime (Massano and Bhatia, 2012). Between 75%- 95% of patients with PD have their diagnoses confirmed at autopsy (Litvan *et al.*, 2003). To diagnose PD, recognised clinical criteria are utilised, with the most common criteria presented by the Queen's Square Brain Bank (Hughes *et al.*, 1992). Motor severity is typically assessed using the Hoehn and Yahr scale (Hoehn and Yahr, 1967), and the modified version of the MDS-UPDRS-III (Goetz *et al.*, 2008). The Brain Bank criteria, Hoehn and Yahr scale, as well as the MDS-UPDRS-III were all utilised in the current study.

3.1.2 Neuropathology of PD

Neuropathologically, PD is characterised by the loss of dopaminergic neurons in the nigrostrial pathway, concentrated within the ventrolateral and caudal portions of the substantia nigra pars compacta (SNpc) (Dauer and Przedborski, 2003).

Onset of typical motor symptoms has been associated with a 48% loss of dopaminergic neurons within the SNpc, resulting in a depletion of striatal dopamine by up to 80% (Fearnley and Lees, 1991). Intracytoplasmic eosinophilic inclusions, known as *Lewy bodies*, in the surviving neurons, are typically present in PD, and are confirmed at autopsy (Braak *et al.*, 2006). However, not all patients with PD have Lewy bodies (e.g., PARK2 gene mutation; Halliday *et al.*, 2008). The progressive loss of dopamine results in increasing severity of motor symptoms (Fahn, 2003). Such motor symptoms, termed dopamine-responsive signs, are alleviated when levodopa (L-3,4-dihydroxyphenylalanine), a dopamine precursor, is administered (Dauer and Przedborski, 2003).

Beyond basal ganglia disruption, and the characteristic loss of dopamine, widespread white matter tract deterioration has been reported. In a large sample of patients with PD (n = 63), higher MD and lower FA values have been reported in the corpus callosum (Melzer *et al.*, 2013), compared toHC. Smaller samples have reported increased MD and lowered FA in the corpus callosum (genu), and superior longitudinal fasciculus in early-stage PD patients (Gattellaro *et al.*, 2009). Reduced FA has also been reported in the supplementary motor area, the pre-supplementary motor areas, the cingulum (all bilateral) (Kendi *et al.*, 2008), as well as the anterior cingulate tract (Kamagata *et al.*, 2012). Altered white matter integrity has also been linked to cognitive impairment in PD. For instance, Duncan *et al.* (2016) reported that greater MD in the cingulum, superior longitudinal fasciculus, inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus in early-stage PD patients (compared to HC), was associated with reduced behavioural performance on a semantic fluency task, and an executive planning task.

These studies suggest that axonal damage is apparent in the early stages of the disorder, is widespread, and could be used as markers of disease progression.

3.1.3 Age of onset and incidence

Parkinson's disease is a common neurodegenerative disorder, second most after AD (De Lau and Breteler, 2006). The incidence of PD rises with age (De Lau and Breteler, 2006; Hirsch *et al.*, 2016), with a median age of onset of 60 years (Aarsland *et al.*, 2010). In a literature review of the prevalence and incidence rates of PD in European countries, von Campenhausen *et al.* (2005) identified crude prevalence rates of 65.6 and12,500/100,000, and incidence rates (yearly) between 5 and 346/100,000. The heterogeneity amongst studies may have been a consequence of age-ranges studied, methodologies, and use of diagnostic criteria (von Campenhausan *et al.*, 2005). Men may be more susceptible to the development of PD (Gillies *et al.*, 2014), with male/female ratios reported to ranging from 1.1:1 to 3:1 (Schrag *et al.*, 2000).

3.1.4 Aetiology

The majority of PD cases are termed as 'sporadic', with no known cause, and the remaining the result of familial genetic mutations (Dauer and Przedborski, 2003), such as alpha synuclein (Klein and Schlossmacher, 2007). Heritability estimates amongst first-degree relatives may differ depending upon whether their related proband was diagnosed with early, or late-onset PD. In siblings of early-onset PD patients, a seven-fold increase in risk of developing PD has been reported (Marder *et al.*, 2003). In contrast, higher risk-ratios for first-degree relatives of older-onset patients with PD have also been reported (Sveinbjornsdottir *et al.*, 2000). Low heritability estimates for PD have been reported in twin studies. Tanner *et al.* (1999) observed similar pairwise concordance heritability estimates between monozygotic (0.155) and dizygotic (0.111) twin pairs. Heritability estimates close to zero have also have been reported (Wirdefeldt *et al.*, 2004).

The variable and low heritability estimates for PD have led researchers to suggest that unknown susceptibility genes may be involved and/or environmental factors (e.g., exposure to pesticides), which could underlie the aetiology of PD (Wirdefeldt *et al.*, 2004).

3.1.5 Clinical course of PD

The clinical course of PD is typically slow and progressive (Fahn, 2003). Although treatment with dopaminergic medication (e.g., Levodopa) improves motor symptoms, treatment does not alter the neurodegenerative progression of the disease (Poewe, 2006). Indeed, as the disease progressives, the benefit of dopaminergic medication reduces, with complications such as dyskinesia (difficulties with voluntary movements) (Shulman, 2007). However, it is not possible to examine the true progression of motor symptoms in PD in untreated patients due to ethical considerations (Poewe, 2006). From diagnosis of PD to death, the mean disease duration is estimated between 10-15 years (Hughes *et al.*, 2000; Katzenschlager *et al.*, 2008). The socioeconomic cost of PD is substantial, with estimates of £3.3 billion in the UK, as a result of the cost of care in the more severe stages (Findley, 2007).

In addition to the typical neurodegenerative course, the risk of developing PDD is three to six higher in patients with PD compared to HC of the same age (Aarsland *et al.*, 2001). Estimates for development range from 25-50% (Emre, 2003; Evans *et al.*, 2011), up to 80% (Aarsland *et al.*, 2003). Whilst age and duration of illness are known risk factors for development of PDD (Buter *et al.*, 2008), the exact mechanisms leading to PDD are unknown (Aarsland *et al.,* 2010). As such, identification of PDD symptoms are of clinical importance, to reduce healthcare costs, and lengthen quality of life (Bosboom *et al.*, 2004).

In summary, PD is a severe neurodegenerative disorder typically comprised of motor symptoms. In the next section, additional symptoms of PD will be discussed.

3.1.6 Cognitive symptoms of PD

Parkinson's disease was traditionally viewed as a motor disorder (Poliakoff *et al.*, 2003). However, in addition to clinical symptoms, non-motor symptoms are also evident and can include neuropsychiatric disturbances (e.g., depression), autonomic changes (e.g., constipation), sensory (e.g., pain), as well as cognitive changes (Fahn, 2003). Such non-motor symptoms are likely due to pathology outside of the basal ganglia (Chaudhuri and Schapira, 2009). At present, the cause (s) of non-motor symptoms in PD in general are poorly understood (Dexter and Jenner, 2013), and there are a paucity of treatments available (DeGutis *et al.*, 2016). There is growing interest in examining non-motor symptoms in PD such as cognitive impairment, and for the purposes of the current study, will be the non-motor symptom of focus. Cognitive changes are believed to be a core feature of PD (Chaudhuri *et al.*, 2011). At the time of diagnosis, cognitive impairment in PD is heterogeneous – with presentation ranging from the negligible, the subtle, through to MCI and dementia (Aarsland *et al.*, 2009).

Moreover, such symptoms may present early or later over the clinical course of the disease (Aarsland *et al.*, 2003), and are not simply due to a disrupted dopaminergic system (Thanvi *et al.*, 2003). Cognitive impairment in PD may be due to the cumulative load of PD-related brain pathology (Braak *et al.*, 2006). Of importance to the early identification of the disease, cognitive impairment may precede the presentation of the common motor symptoms associated with PD (Bhidayasiri and Truong, 2012). Cognitive impairment is considered to be one of the highest reported non-motor symptom associated with PD (Lee *et al.*, 2015), and is present in early-stage, drug naïve patients (Pont-Sunyer *et al.*, 2015). Moreover, cognitive impairment follows a neurodegenerative course (Braak *et al.*, 2006; Muslimović *et al.*, 2007), may be associated with motor symptoms, such as functional mobility (Varalta *et al.*, 2015), reduced quality of life (Lawson *et al.*, 2016), as well as risk of falling in PD, which can lead to injury, loss of independence, and further infringe on an individual's quality of life (Allcock *et al.*, 2009).

The MMSE and the MoCA are widely used tools to assess cognition in PD (Tang *et al.*, 2016). However, researchers have questioned the sensitivity of both tools to assess cognitive impairment in PD (Tang *et al.*, 2016). Cognitive impairment is underestimated in PD, due to a reliance on the MMSE and its low-specificity for detecting changes in cognitive domains (Meyers and Wefel, 2003). Moreover, Burdick *et al.* (2014) reported that use of the MMSE alone as a screening tool for cognitive impairment would have missed 55% of PDD cases within their study. The authors recommended that the MMSE be used with caution for screening for cognitive impairment, and suggested that a full neuropsychological evaluation would be more suitable. As a result of a reliance on the MMSE and MoCA for examining cognitive impairment in PD, only a narrow range of individual cognitive outcome measures have been examined (Varalta *et al.*, 2015), with few reviews and/or meta-analyses available. Individual cognitive domains in PD will be discussed below.

Cognition is impaired in a number of domains in PD. The prototypical pattern in PD is that cognitive impairment presents as difficulties in executive functioning (dysexecutive syndrome), with additional visuo-spatial, processing speed, and attentional impairments (Emre *et al.*, 2007; Litvan *et al.*, 2011). However, it is unclear what the inter-relationships between these cognitive impairments is in PD. As such, the current study will focus on executive functioning, processing speed, as well as attention. Executive functioning is typically impaired in PD (Muslimović *et al.*, 2005; Yu *et al.*, 2012; Dirnberger and Jahanshahi, 2013), and is one of the earliest impairments reported (Dubois and Pillon, 1997; Elgh *et al.*, 2009; Yu *et al.*, 2012). Difficulties in working memory are frequently reported (Owen *et al.*, 1993; Lewis *et al.*, 2005), as well as in the manipulation of information, the latter of which improves with dopaminergic medication (Lewis *et al.*, 2005). Verbal fluency is also a measure of executive functioning assessed in PD, with semantic, rather than phonemic fluency, impaired (Henry and Crawford, 2004; Koerts *et al.*, 2013). However, preserved executive functioning has been reported (Bohlhalter *et al.*, 2009).

Additional cognitive impairments in PD have been reported in visuo-spatial functioning (Hovestadt *et al.*, 1987; Hindle *et al.*, 2016), processing speed (Burdick *et al.*, 2014; Koerts *et al.*, 2013; Muslimovic *et al.*, 2005), verbal memory (Bohlhalter *et al.*, 2009; Muslimovic *et al.*, 2005), as well as implicit and explicit memory (Watson and Leverenz, 2010).

Although few studies have examined the longitudinal course of impairments in PD, Gamaldo *et al.* (2012) reported that impairments and greater performance variability in domains such as attention, executive functioning, semantic memory, and language, may be present at least five years before clinical cognitive impairment. In addition, Muslimović *et al.* (2009) noted that over the course of three years, patients with PD had a faster rate of cognitive decline than HC (beyond normal age-related decline), particularly in the domains of attention (assessed via the TMT-B), and processing speed (as assessed via the DSST).

Whilst cognitive impairment has been noted in a number of domains, there is increasing interest in examining attention specifically. General attentional impairments may be present early in the PD disease course (Barone *et al.*, 2009), and worsen with disease progression (Muslimović *et al.*, 2009; Antonini *et al.*, 2012). As with cognitive impairment generally, poorer attentional abilities are associated with a poorer quality of life in PD (Klepac *et al.*, 2008; Barone *et al.*, 2009), with a decline in attention holding the greatest predictive power when demonstrating cognitive impairment contributions to longitudinal quality of life change (Lawson *et al.*, 2016). Moreover, Bronnick *et al.* (2006) argue that in PDD, attentional dysfunction may be the primary cognitive factor influencing functional impairment. Attentional impairments may also moderate some of the motor symptoms observed in PD (Cagigas *et al.*, 2007). For instance, fall frequency in PD is associated with the ability to focus attention, as well as fluctuating attentional abilities, after adjusting for disease severity (Allcock *et al.*, 2009). As dopaminergic treatment is reported to be ineffective in alleviating attentional impairments (Barone *et al.*, 2009; Lewis *et al.*, 2005), utilising cognitive strategies to improve attentional abilities holds promise.

Attentional cues have been shown to improve performance on motor tasks such as gait stability (Rochester *et al.*, 2004), and alleviate visuo-spatial deficits in PD (DeGutis *et al.*, 2016).

Investigation of attentional dysfunction in PD has reported impairments in specific attentional domains. Studies have reported impairments in patients with PD, compared to HC, in measures of sustained attention (Ballard *et al.*, 2002), shifting attention (Owen *et al.*, 1993; Valrata *et al.*, 2015), simple attention (e.g., digit span forward, TMT-A) (Watson *et al.*, 2010), complex attention (Watson *et al.*, 2010), inhibition (Dujardin *et al.*, 1999), as well as selective attention (Filoteo and Maddox, 1999). Although, no differences in selective attention have also been reported (Cagigas *et al.*, 2007). Impairments in divided attention have also been reported (Brown and Marsden, 1991; Dujardin *et al.*, 2013), with poorer divided attention ability linked to worsening gait performance (Tseng *et al.*, 2012). 'Fluctuating attention', defined as ISD and CoV on a CRT task (rather than a specific attentional task, such as the CPT), may also distinguish between PD with and without dementia, as well as dementia with Lewy Bodies (Ballard *et al.*, 2002).

The measures of 'fluctuating attention' utilised by Ballard *et al.* (2002), ISD and CoV, may be of interest to researchers searching for biomarkers that can predict cognitive decline and conversion from PD to PDD (Martínez-Horta and Kulisevsky, 2011; Svenningsson *et al.*, 2012). Increased IIV in PD is predicted by the catecholamine hypothesis (Li and Lindenberger, 1999). In this theory, catecholamines, (such as dopamine) are proposed to modulate age-related reductions in information processing/efficiency. The reduction of dopamine in the basal ganglia and striatum may lead to compromised information processing at a neural and behavioural level, consistent with an increase in age. As PD is associated with decreased dopamine in the nigrostriatal system, the model hypothesises that the reduction in dopamine reported in PD would be related to a reduction in neural transmission.

This reduced transmission could lead to increased variability in neural processing, as well as in behaviour (Burton *et al.*, 2006). Consistent with the catecholamine hypothesis, increased IIV has been reported in PD. Early studies of IIV and PD noted elevated IIV (ISD) in idiopathic PD in a coincidental timing and simple RT task (Crawford *et al.*, 1989), as well as a horizontal arm extension and flexion task (Reed, 1998). In the Reed (1998) study, less severe patients (Hoehn and Yahr scale I-II) were more consistent in their responding (although the IIV measure was not indicated), compared to more severe patients (Hoehn and Yahr scale III-IV), suggesting that IIV in pre-programming tasks may be due to inconsistent functioning of the basal ganglia.

Later studies have focussed on investigating IIV in measures of psychomotor speed, such as SRT and CRT tasks, with the CRT tasks of varying complexity (two-choice, four-choice, and eight-choice). These studies have exclusively analysed IIV using residual ISD (see Chapter 1, section 1.9) to account for group differences in speed or accuracy, as well as practice effects over the course of trials, which are argued to confound the investigation of IIV (Hultsch *et al.*, 2002; Wagenmakers *et al.*, 2005; Bunce *et al.*, 2013).

Slower and more variable responses, irrespective of task complexity, have been reported in drug naïve PD patients (Camicioli *et al.*, 2008). Within this patient population, Camicioli *et al.* (2008) also noted that there was no association between RT and IIV measures and motor or cognitive impairment. This is consistent with the suggestion that elevated RT and IIV may not be responsive to dopaminergic medication, and may represent a distinct biomarker of PD (Molloy *et al.*, 2006; Michely *et al.*, 2012). In early-stage PD, although responses of PD patients were slower in all complex tasks (as well as in a more severe disease stage), compared to HC, greater IIV was observed solely in the eight-choice CRT task (de Frias *et al.*, 2007). Moreover, IIV in this task predicted group membership.

However, slower RT and IIV was attenuated when covarying for motor severity, indicating that dopamine response (associated with motor severity) may account for IIV differences in more complex tasks (de Frais *et al.,* 2007).

Elevated IIV may also be able to identify specific types of neurological dysfunction. Burton *et al.* (2006) noted that after adjusting for cognitive decline (IQ discrepancy score) and severity of cognitive impairment (MMSE), patients with AD were more variable than PD, who in turn, were more variable than HC. Burton *et al.* (2006) concluded that IIV is associated with specific types of neurological dysfunction, rather than indexing a general nervous system compromise. Elevated IIV may also distinguish between PD and PDD. In a longitudinal study, de Frias *et al.* (2012) noted that over an 18-month period, the PD and PDD groups became slower from baseline to follow-up, while only the PDD group became more inconsistent over time. However, these interactions were attenuated when adjusting for motor impairment at baseline, with the authors suggesting that task performance was related to the overall progression of PD. Changes in mean RT and IIV were significant predictors of group membership, indicating that speed and inconsistency may be clinical markers of PDD.

Studies that have investigated IIV in PD thus far have exclusively examined ISD, or residual ISD. Moreover, these have been restricted to psychomotor speed tasks, not traditional measures of sustained attention, such as the CPT. However, there are caveats to the application of traditional measures of IIV which should be considered. The ex-Gaussian distribution may more accurately describe RT data. A detailed discussion of the ex-Gaussian distribution, as well as its application to observed RTs from attention tasks in clinical disorders is given in Chapter 1.

As outlined previously, examining IIV may be a useful and sensitive measure of underlying neurological disturbance (e.g., Burton *et al.*, 2006). Given that early and accurate detection of onset of PDD would facilitate clinical management of the disorder (de Frias *et al.*, 2012), examining potential biomarkers such as IIV may have clinical implications for PD. In addition, it is not clear whether elevated IIV in PD is independent of deterioration in other cognitive processes, or is associated with them. Furthermore, whether elevated IIV is secondary to an impairment in another cognitive domains (section 1.4). Determining this relationship would have implications for the clinical utility of IIV in PD.

However, only a narrow range of IIV measures have been utilised in the study of IIV in PD (e.g., ISD and residual ISD) thus far, and to the knowledge of the doctoral candidate, ex-Gaussian distributional modelling has not been applied in PD. At present, it is unclear whether IIV in PD is simply indexing severity of motor impairment (thus, a confound) and exclusive to motor tasks such as simple and choice RT, or whether inconsistency would be obtained from other neuropsychological domains, such as sustained attention. Moreover, whether IIV in PD would represent distinct impairment, or is secondary to impairment in another cognitive domain. As such, to examine the specificity of IIV in PD, it would be useful to examine whether inconsistency is specific to type of task, or of neuropsychological domain. Given that attention is impaired in PD (e.g., Barone *et al.*, 2009), is linked with functional outcomes such as quality of life (e.g., Lawson *et al.*, 2016), frequency of falling (e.g., Allcock *et al.*, 2009), and gait stability (e.g., Rochester *et al.*, 2004), examining IIV within an attentional domain would have clinical, as well as functional relevance in PD.

The current study applied the ex-Gaussian distribution to RTs obtained from a sustained attention task (the DV) in patients with idiopathic PD and HC. Consistent with the catecholamine hypothesis and based on the findings of previous research, it was hypothesised that the RT distributions between patients and HC would differ. In addition, it was predicted that patients with PD would have a generalised performance deficit (mu), as well as greater variability across the entire RT distribution (sigma), and in the positive tail (tau), compared to HC.

The current study also aims to provide evidence of whether an association between age (as well as group-related differences) and attentional RT and IIV represents an independent impairment, or reflects an impairment in other cognitive domains (e.g., processing speed). This study aim is applied in a different task to the normal ageing study, the DV, which is anticipated to have a high processing speed loading, but low executive functioning loading (Table 1-1).

As cross-sectional studies have indicated that indices of attentional impairment deteriorate with age (Chapter 1, section 1.10.1), and taking into account the results of the normal ageing study, it is hypothesised that age will be associated slower responding (mu), and an increase in inconsistent responding (tau) in patients and HC. Age-related associations are anticipated for mu and tau, due to the programming similarities between the RVIP and the DV task utilised in the current study.

If an association between age (as well as group) and attentional RT and IIV reflects an independent impairment, then entry of the other neuropsychological processes of interest (e.g., executive functioning, processing speed) will not account for any age-related, or group-related associations. However, given the results of Chapter 1, it must also be considered that attentional RT and IIV, as well as the other neuropsychological processes of interest, are not independent *per se*, but share variance.

Alternatively, if the studies outlined in section 1.4 are taken into account, then an association between age (as well as group) and attentional RT and IIV, the latter a marker of sustained attention, will be explained by variance in other neuropsychological processes of interest. Processing speed is a candidate here, given the studies outlined in section 1.4, the RVIP results in the normal ageing study, as well as the high anticipated processing speed loading of the DV task utilised (Table 1-1). It is not anticipated that executive functioning would account for any age-related, or group-related variance in attentional RT or IIV, due to low anticipated loading of the domain in the DV task.

3.2 Methods

Participants completed a neuropsychological battery and computerised tests as part of the Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation-PD (ICICLE-PD) study (Yarnall *et al.*, 2014). Participants were tested at baseline (first study visit), and were followed up at 18 and 36 months. A sub-set of this data is presented in the current study (baseline). The doctoral candidate was involved in the analysis and dissemination of data obtained from the ICICLE-PD study, but was not involved in the design of the study, or participant recruitment.

3.2.1 Participants

Baseline data was obtained from 147 patients who were newly diagnosed with idiopathic PD (Months since diagnosis $M = 6.20$, $SD = 4.56$), between the ages of 41 and 87 ($M = 66.38$, $SD = 10.10$). Diagnosis was confirmed by a movement disorder specialist using the Queen's Square Brain Bank criteria (Hughes *et al.*, 2000). Patients were recruited from community and outpatient clinics in Newcastle upon Tyne, and Gateshead from 1st June 2009 – 31st December 2011. Clinical ratings of motor severity were obtained from the Hoehn and Yahr scale (Hoehn and Yahr, 1967), and the MDS-UPDRS-III (Goetz *et al.*, 2008). The majority of patients ($n = 88$) were in stage II (bilateral involvement) in terms of motor severity according to the Hohn and Yahr scale, and the predominant motor phenotype was postural instability with gait difficulty ($n = 66$) (Table 3-1). Additional clinical ratings were obtained from the GDS-15 (Yesavage *et al.*, 1982), whilst global cognitive functioning was assessed using the MMSE (Folstein *et al.*, 1975), and the MoCA (Nasreddine *et al.*, 2005). One hundred and 31 patients (89%) were prescribed Levodopa, and 16 patients (11%) were medication free. The current study reports levodopa equivalent dose (LED), which was derived using the methods described by Tomlinson *et al.* (2010).

Patients did not have significant memory impairment or dementia, defined as a score of ≤ 24 on the MMSE or confirmation of DSM-IV assessment of dementia (APA, 2000); had a good command of English, in the opinion of the assessor; Parkinsonism was diagnosed before the onset of the study, and patients did not have any vascular co-morbidities (e.g., vascular parkinsonism), or atypical parkinsonism disorders (progressive supranuclear palsy, corticobasal degeneration). Exclusion criteria were assessed according to recognised criteria (Litvan *et al.,* 2003).

One hundred and ninety HC, between the ages of 48 and 89 (M = 69.97, SD = 7.65), participated in the current study. Controls were recruited from the community of Newcastle upon Tyne, and Gateshead, as part of the ICICLE-PD study and a sub-study, ICICLE-gait. Study groups were not matched and differed significantly in terms of age, MoCA, MMSE, and GDS-15 score (Table 3-1). The study protocol was approved by the Newcastle and North Tyneside research ethics committee and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants prior to participation.

Table 3-1. Demographic, cognitive and clinical characteristics of patients with PD and HC.

	PD (n = 147) Mean ± SD	HC (n = 190) Mean ± SD	$t_{(df)}/U/\chi^2_{(df)}$	p, direction
Demographics				
Sex (F:M)	52:95	111:79	17.62 (1)	**< 0.001**
Age	66.38 ± 10.10	69.97 ± 7.65	3.58 (264.17)	**< 0.001,HC >PD**
NART	114.78 ±10.77	116.83 ± 7.96	13083.00	**0.326**
Cognitive				
MoCA[a]	25.21 ± 3.63	26.95 ± 2.50	4572.50	**< 0.001,HC >PD**
MMSE	28.63 ± 1.33	29.24 ± 1.04	10036.00	**< 0.001,HC >PD**
Clinical				
GDS	2.90 ± 2.59	1.17 ± 1.85	7412.50	**< 0.001,PD >HC**
MPS-UPDRS-III	27.06 ± 12.23	-	-	-
Duration (months)	6.20 ± 4.56	-	-	-
Levodopa[b]	180.94 ± 147.77	-	-	-
Hoehn & Yahr[c]	33:88:25:1	-	-	-
Motor Phenotype[d]	66:23:58	-	-	-

[a] Data only available for n = 95 HC.

[b] LED 100 mg.

[c] Data are presented as number of - only unilateral involvement (Stage 1): Bilateral involvement (Stage 2): Bilateral disease with some postural instability (Stage 3): Severely disabling disease (Stage 4).

[d] Data are presented as number of - postural instability gait difficulty: Indeterminant: Tremor Dominant.

3.2.2 Neuropsychological measures

Participants completed cognitive tasks from the Cognitive Drug Research (CDR) computerised assessment battery (Wesnes *et al.*, 2002), and CANTAB (Cambridge Cognition Limited, Cambridge, United Kingdom). Tasks were selected to measure sustained attention (the DV from the CDR battery), processing speed (the SRT task from the CDR battery), and executive functioning (Verbal Fluency and OTS from CANTAB), which were matched as closely as possible with the neuropsychological tasks included in Chapter 2. Similarities and differences between the tasks included in the current study, and previous studies of this thesis are discussed below.

In the **DV TASK**, 450 single digits are presented to participants, at a rate of 150 digits per minute. Fifteen targets are presented every 150 stimuli, with the target digit differing per participant. Responses are classified as correct if they occur within 1500 ms of the target digit being presented (i.e. three stimulus presentations). The DV task lasts for three minutes, and participants are asked to press the 'YES' button as quickly as possible when the digit on the screen matches the target. Correct RT is recorded in ms. The DV task is a lower working memory load variant of the RVIP included in Chapter 2, as only one target must be remembered. In addition, the target digit does not remain on screen. The DV task also has a lowered number of target sequences to detect, has a shorter task duration, and stimuli are presented more quickly.

In the **SRT**, 50 stimuli are presented to participants. The ISI varies between 1 and 3.5 seconds. Participants are instructed to press the 'YES' key when the word 'YES' appears on the screen. Correct RT is recorded in ms. The SRT task differs from the processing speed task included in the normal ageing study (Chapter 2, DSST original), as only basic motor responses are measured in this task.

In the Controlled Oral Association Test, PHOENEMIC VERBAL FLUENCY (FAS) (Benton and Hamsher, 1976), participants are asked to generate unique words beginning with letters F, A, and S. The total number of unique words generated within a minute were recorded.

The OTS from CANTAB (Cambridge Cognition Limited, Cambridge, United Kingdom) is a measure of executive functioning (planning, decision-making, working memory), based on the Tower of Hanoi test. Participants are required to plan a sequence of moves using three coloured balls, in order to achieve a goal arrangement specified at the top of the screen. Outcome measures included in the current study consisted of accuracy measures – problems solved on first attempt, and mean choices to the correct solution.

Both of the executive functioning tasks (FAS and OTS) included in the current study differ from the measure included in the normal ageing study (Chapter 2, Digit Span Backwards). However, working memory is necessary to complete both tasks. A verbal memory task was not included in the longitudinal neuropsychological battery.

3.2.3 Data pre-processing

Data pre-processing followed the methods outlined in the normal ageing study (Chapter 2). In addition, responses ± 3 SD from a participant's individual mean RT were removed, due to a recording error. This error did not occur in the normal ageing study, and as such, was not a method utilised for cleaning the data in that study. In the SRT, 17,293 correct RTs were analysed, and in the DV task, 14,664. The ex-Gaussian probability density function failed to fit the distribution to a number of participants (patients $n = 1$; HC $n = 2$), who were subsequently excluded from further analysis. A further three patients were removed from the analysis of ex-Gaussian distribution for the DV as their overall accuracy was below 50%.

The final sample size for the DV task was 143 patients and 188 HC. Vincentile plots were also calculated to demonstrate an overall graphical representation of the data, without prior assumptions regarding shape (Balota *et al.*, 2008).Vincentiles rank order mean RTs from the fastest 12.5% to the slowest, in eight equal bins.

3.2.4 Statistical analysis

Statistical procedures followed the method outlined in the normal ageing study (Chapter 2). Behavioural outcome measures (ex-Gaussian distribution) were analysed using a number of univariate ANCOVA, with age included as a covariate as the study groups were not matched on this demographic characteristic. Vincentiles were also analysed in this manner. Covariate interactions were included in the models initially. If non-significant, these were later removed from the model. If significant, the interaction remained in the model. In all analyses, the RT parameters obtained from the DV task (mu, sigma, or tau) were the dependent variables and group (patients vs. HC), was the fixed factor. Significant main effects were analysed using Bonferroni *post-hoc* tests.

Hierarchical regressions were conducted using the methods outlined in the normal ageing study (Chapter 2), with Models 1a, 1b, and 2a included in the current chapter. In addition, hierarchical regressions were conducted to examine the effect of group on predicting variance in attentional RT and IIV, after accounting for other neuropsychological processes such as executive functioning and processing speed, theorised to be involved in CPTs. The assumptions of hierarchical regression analyses were met. The total *n* varied per model and between patients and HC due to inconsistencies in the data obtained per group, and removal of outliers (please see Tables 9-4 to 9-6 in Appendix B). Outliers were removed from the hierarchical regression analysis until no outliers remained. Age, measures of executive functioning and processing speed (mean RT from the SRT) were selected as predictors. Executive functioning was represented as a composite of accuracy scores from the FAS (total correct), and OTS (problems solved on first attempt and mean choices to correct solution).

The OTS accuracy score of mean choices was expressed as a standardised z-score (with an average value calculated per person for the composite). The OTS accuracy scores, as well as total correct from the FAS were averaged, and used as the executive functioning composite. The mean RT measure representing processing speed was also expressed as a standardized z-score.

Standardised z-scores were utilised so that a higher score on the executive functioning composite, and processing speed measure, indicated better overall performance, rather poorer. Sex and NART characteristics were not included as covariates as significant differences/associations between groups was not observed (all $p > 0.050$).

3.3 Results

3.3.1 Group differences

The covariate, age, was a significant predictor for ex-Gaussian mu and tau (all $p < 0.001$), but not sigma ($p = 0.107$). Bonferroni-adjusted post-hoc comparisons indicated that patients completed the DV task significantly more slowly than HC, as indicated by ex-Gaussian mu (PD: $M = 416.81$, $SE = 3.74$; HC: $M = 396.06$, $SE = 3.25$). Patients were also more variable than HC, across the entire distribution (PD (sigma): $M = 34.82$, $SE = 1.32$; HC: $M = 28.83$, $SE = 1.15$), and in instances of infrequent, and long RTs (PD (tau): $M = 67.33$, $SE = 2.19$; HC: $M = 54.52$, $SE = 1.90$; Table 3-2 , Figure 3-1).Examination of the Vincentile plots (Figure 3-1) indicated that patients with PD performed the DV task more slowly across the whole distribution (at each comparison from V_1 - V_8) compared to HC (all $p < 0.010$)

Table 3-2. Univariate ANCOVA for RT and IIV indices in PD patients and HC for the DV task.

Parameter	$F_{(df)}$	Partial η^2
ex-Gaussian mu	$17.16_{(1, 328)}$	**0.05*** **
ex-Gaussian sigma	$11.63_{(1, 329)}$	**0.03** **
ex-Gaussian tau	$19.01_{(1, 328)}$	**0.05*** **

Note. η^2 = eta-squared.

** $p < 0.010$, *** $p < 0.001$

With regard to the multiple cognitive processes assessed in the study, patients were slower than HC in the SRT (mean RT) ($U = 10499.50$, $p < 0.001$; PD mean rank = 190.59, HC mean rank = 150.55), whilst patients performed better than HC in the executive functioning composite ($U = 7970.00$, $p < 0.001$; PD mean rank = 186.19, HC mean rank= 135.29).

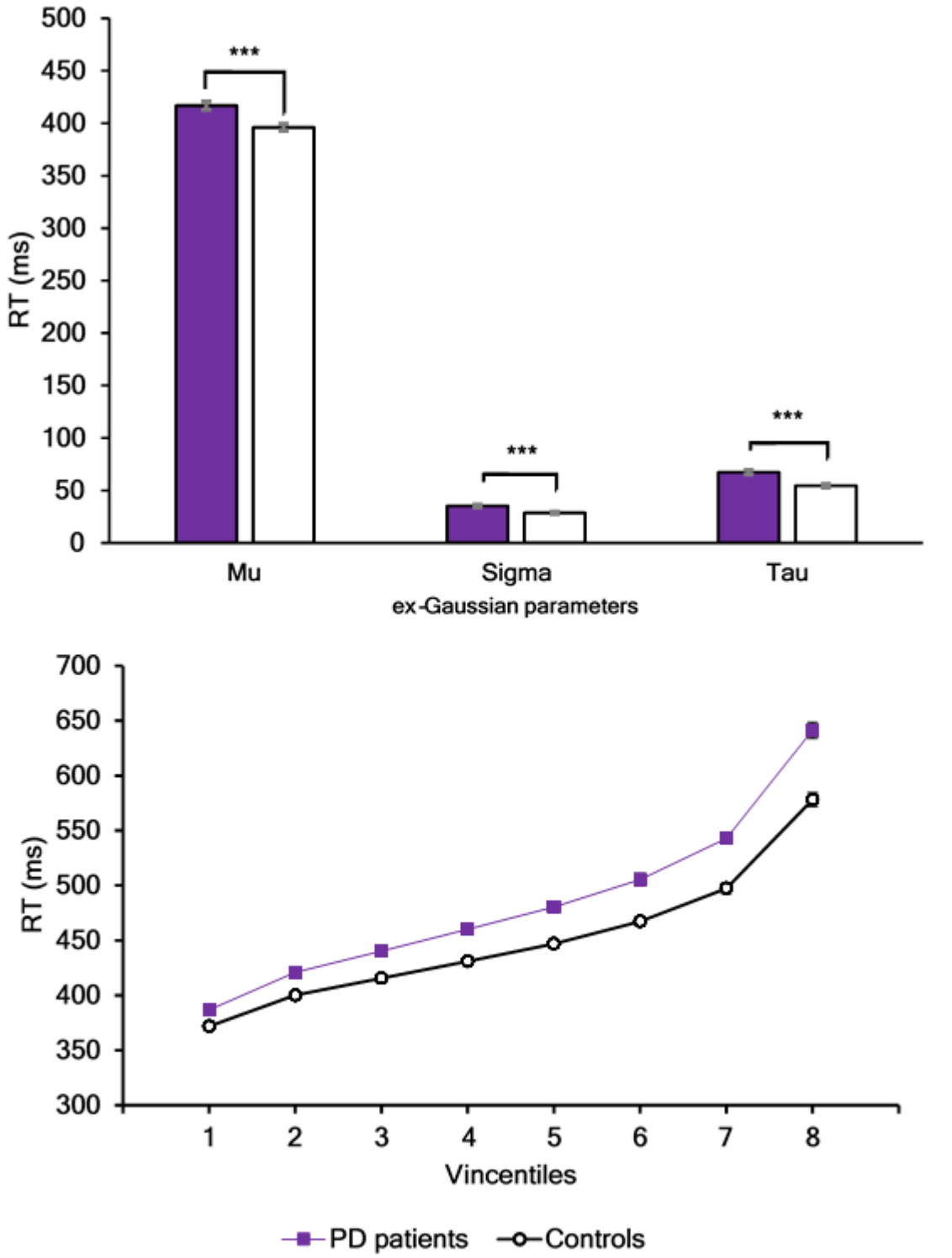

Figure 3-1. Ex-Gaussian distributions (top panel) and Vincentiles (bottom panel) between patients with PD and Controls, adjusted for age. Error bars represent standard error of the mean (SEM), adjusted for age. *** $p < 0.001$

3.3.2 Relationship between age and ex-Gaussian parameters

In patients and controls, age significantly positively correlated with ex-Gaussian mu and tau (all $p < 0.050$; Table 3-3).In patients, age significantly positively correlated with processing speed, and negatively correlated with executive functioning (processing speed: $r_{s\,(146)} = 0.210$, $p < 0.050$; executive functioning: $r_{s\,(130)} = -0.206$, $p < 0.050$). The same pattern was observed in HC (processing speed: $r_{s\,(189)} = 0.315$, $p < 0.001$; executive functioning: $r_{s\,(182)} = -0.242$, $p < 0.010$).

The relationship between ex-Gaussian parameters and the other neuropsychological processes of interest was also examined. In patients, ex-Gaussian tau was significantly negatively correlated with the executive functioning composite, whereas for both groups, mu and tau were significantly positively correlated with processing speed, with the addition a positive association between ex-Gaussian sigma and processing speed in HC(Table 3-3).

Due to the motor symptoms experienced in PD, the relationship between an index of severity (MDS-UPDRS-III), and the relationship between ex-Gaussian parameters was explored. None of the ex-Gaussian parameters obtained from the DV were significantly correlated with the MDS-UPDRS-III (Mu: $r_{s\,(143)} = 0.018$, $p = 0.833$; Sigma: $r_{s\,(143)} = 0.042$, $p = 0.620$; Tau: $r_{s\,(143)} = 0.129$, $p = 0.126$). The measure of processing speed utilised in the current study (SRT mean RT) significantly positively correlated with score on the MDS-UPDRS-III ($r_{s\,(147)} = 0.219$, $p < 0.010$), but executive functioning did not ($r_{s\,(130)} = -0.099$, $p = 0.264$).

Table 3-3. Spearman correlations between ex-Gaussian parameters, age, and other neuropsychological processes for patients with PD and HC.

Parameter	PD			HC		
	Age[a]	EF[b]	PS[c]	Age[d]	EF[e]	PS[f]
ex-Gaussian mu	**0.343****	0.005	**0.418****	**0.251****	-0.122	**0.439****
ex-Gaussian sigma	0.084	0.027	0.086	-0.010	-0.074	0.167*
ex-Gaussian tau	**0.300****	**- 0.330****	**0.360****	**0.148***	0.090	**0.161***

Note. EF = Executive Functioning, PS = Processing Speed.

*$p < 0.050$, **$p < 0.010$

[a] $n = 143$; [b] $n = 127$; [c] $n = 143$; [d] $n = 188$; [e] $n = 180$; [f] $n = 188$

In order to examine the relationship between age and ex-Gaussian parameters (mu, sigma, and tau), whilst taking into account the varied cognitive demands of the DV task, a series of hierarchical regressions were performed.

EX-GAUSSIAN MU: In all models, entry of processing speed, but not the executive functioning composite, significantly predicted variance in mu in patients (all $\Delta R^2 > 7.4\%$) and HC (all $\Delta R^2 > 16.4\%$). The final entry of age significantly predicted variance in mu in patients in all models (all $\Delta R^2 > 11\%$), whereas in HC, age did not predict variance in mu when order of entry was examined in Model 2 ($\Delta R^2 < 1\%$) (Table 3-4).

Table 3-4. Hierarchical regression analysis with ex-Gaussian mu in patients with PD and HC.

ex-Gaussian mu		PD				HC			
Model		R^2	ΔR^2	Sig. F Change	β	R^2	ΔR^2	Sig. F change	β
	Age	0.116	0.116	**< 0.001**	0.341	0.053	0.053	**< 0.010**	0.230
1a	EF	0.000	0.000	0.885	0.013	0.016	0.016	0.089	- 0.127
	Age	0.140	0.140	**< 0.001**	0.382	0.057	0.041	**< 0.010**	0.209
1b	PS	0.102	0.102	**< 0.001**	0.320	0.179	0.179	**< 0.001**	0.423
	Age	0.214	0.112	**< 0.001**	0.335	0.197	0.018	**< 0.050**	0.137
2a	EF	0.000	0.000	0.885	0.013	0.016	0.016	0.089	- 0.127
	PS	0.079	0.079	**< 0.010**	0.288	0.180	0.164	**< 0.001**	0.413
	Age	0.210	0.131	**< 0.001**	0.370	0.193	0.013	0.091	0.122
	PS	0.074	0.074	**< 0.010**	0.272	0.178	0.178	**< 0.001**	0.422
	EF	0.079	0.005	0.408	0.073	0.180	0.002	0.523	- 0.044
	Age	0.210	0.131	**< 0.001**	0.370	0.193	0.013	0.091	0.122

Note. β = Standardised coefficients; EF = Executive Functioning; PS = Processing Speed. Significance highlighted in bold and light blue

EX-GAUSSIAN SIGMA: For both study groups, entry of processing speed and the executive functioning composite, independently, or into the same model, did not significantly explain variance in sigma (all $\Delta R^2 < 1\%$). In all models, the final entry of age was non-significant in patients (all $\Delta R^2 < 1\%$) and HC (all $\Delta R^2 < 1\%$) (Table 9-7, Appendix B).

EX-GAUSSIAN TAU: In patients and in all models, entry of the executive functioning composite and/or processing speed significantly predicted variance in tau, whereas in HC (all models), only processing speed significantly predicted variance (all $\Delta R^2 > 6\%$). In patients, and in all models, the final entry of age significantly predicted variance in tau (all $\Delta R^2 > 4\%$), but only in Models 1a ($\Delta R^2 = 4.4\%$) and 2a ($\Delta R^2 = 2.4\%$) for HC (Table 3-5).

Table 3-5. Hierarchical regression analysis with ex-Gaussian tau in patients with PD and HC.

ex-Gaussian tau		PD				HC			
Model		R^2	ΔR^2	Sig. F Change	β	R^2	ΔR^2	Sig. F change	β
	Age	0.078	0.078	**< 0.010**	0.280	0.021	0.021	**< 0.050**	0.146
1a	EF	0.132	0.132	**< 0.001**	-0.364	0.007	0.007	0.259	0.085
	Age	0.175	0.042	**< 0.050**	0.210	0.051	0.044	**< 0.010**	0.218
1b	PS	0.129	0.129	**< 0.001**	0.359	0.027	0.027	**< 0.050**	0.163
	Age	0.209	0.080	**< 0.001**	0.283	0.038	0.012	0.135	0.112
2a	EF	0.135	0.135	**< 0.001**	-0.368	0.007	0.007	0.259	0.085
	PS	0.230	0.095	**< 0.001**	0.315	0.076	0.069	**< 0.001**	0.268
	Age	0.274	0.044	**< 0.010**	0.213	0.100	0.024	**< 0.050**	0.165
	PS	0.144	0.144	**< 0.001**	0.380	0.058	0.058	**< 0.010**	0.240
	EF	0.230	0.086	**< 0.001**	-0.300	0.076	0.019	0.062	0.139
	Age	0.274	0.044	**< 0.010**	0.213	0.100	0.024	**< 0.050**	0.165

Note. β = Standardised coefficients; EF = Executive Functioning; PS = Processing Speed. Significance highlighted in bold and light blue.

3.3.3 Relationship between group differences in ex-Gaussian parameters and cognitive impairment in other neuropsychological processes

Additional hierarchical regression models were examined, to determine whether the between-subjects differences in executive functioning and/or processing speed accounted for the group-related differences observed for ex-Gaussian mu and tau.

EX-GAUSSIAN MU: Whilst age and processing speed were significant predictors of variance in mu, group explained additional variance, after age and processing speed were accounted for in the model (ΔR^2 = 2%) (Table 3-6).

Table 3-6. Ex-Gaussian mu hierarchical regression with group (PD vs. HC).

ex-Gaussian mu (n = 329)[a]		PD			
Model		R^2	ΔR^2	Sig. F Change	β
1	Age	0.059	0.059	**< 0.001**	0.244
	PS	0.188	0.128	**< 0.001**	0.360
	Group: PD vs. HC	0.210	0.022	**< 0.010**	0.155

Note. β = Standardised coefficients; EF = Executive Functioning; PS = Processing Speed. Significance highlighted in bold and light blue.

[a] Removal of two outliers (original n = 331

EX-GAUSSIAN TAU: In all models, entry of group (patient or HC) explained additional variance in ex-Gaussian tau, after age, executive functioning and /or processing speed had been accounted for in the models (all > ΔR^2 = 1%) (Table 3-7).

Table 3-7. Ex-Gaussian tau hierarchical regression with group (PD vs. HC).

ex-Gaussian tau					
Model		R^2	ΔR^2	**Sig. F Change**	**β**
1a[a]	Age	0.039	0.039	**< 0.010**	0.198
	EF	0.041	0.002	0.432	0.046
	Group: PD vs. HC	0.067	0.026	**< 0.010**	0.171
1b[b]	Age	0.031	0.031	**< 0.010**	0.176
	PS	0.111	0.080	**< 0.001**	0.283
	Group: PD vs. HC	0.149	0.039	**< 0.001**	0.205
2a[c]	Age	0.039	0.039	**< 0.010**	0.198
	EF	0.042	0.002	0.379	0.052
	PS	0.136	0.094	**< 0.001**	0.312
	Group: PS vs. HC	0.152	0.016	**< 0.050**	0.136
	Age	0.039	0.039	**< 0.010**	0.198
	PS	0.129	0.090	**< 0.001**	0.302
	EF	0.136	0.007	0.123	0.087
	Group: PS vs. HC	0.152	0.016	**< 0.050**	0.136

Note. β = Standardised coefficients; EF = Executive Functioning; PS = Processing Speed. Significance highlighted in bold and light blue.

[a] n = 304 (Three outliers removed from n = 307)

[b] n = 328 (Three outliers removed from n = 331)

[c] n = 304 (Three outliers removed from n = 307)

3.3.4 Exploratory analysis between clinical characteristics and ex-Gaussian parameters (patients only)

In patients, ex-Gaussian tau significantly negatively correlated with MMSE score (Table 3-8). In HC, MMSE score did not significantly correlate with ex-Gaussian parameters (all p > 0.050).

Table 3-8. Spearman correlations ex-Gaussian parameters and clinical characteristics in patients with PD.

Parameter[a]	PD Months	MMSE	LED	GDS-15
ex-Gaussian mu	0.045	-0.081	0.134	0.132
ex-Gaussian sigma	0.032	0.025	0.024	0.093
ex-Gaussian tau	0.056	**-0.267****	0.070	0.103

**p <0.010

[a] ex-Gaussian n = 143

3.3.5 Exploratory analysis between the RVIP and DV tasks (HC only)

Due to the similarity in programming between the RVIP and DV, an additional post-hoc analysis was completed to determine whether the tasks differed in their effects on RT distributions. The RT distributions obtained from participants completing the RVIP (n = 54) in the normal ageing study (Chapter 2), and HC who completed the DV task (n = 188) in the current study, were compared using a Mann-Whitney U test. The two samples significantly differed in terms of overall speed of responding (U =1850.00, p < 0.001), with HC from the PD cohort completing the DV more slowly, compared to RVIP (DV mean rank=138.66; RVIP mean rank =61.79). The two samples also differed in the tail of the distribution, as indexed by ex-Gaussian tau (U = 668.00, p < 0.001), with elevated tau in the RVIP, compared to DV (RVIP mean rank =203.13; DV = 98.05)). The samples did not differ in sigma (U =5020.00, p = 0.0.901). These results did not differ when the age-range of the RVIP was restricted to 48-89 years, to reflect the ages of the HC who completed the DV in the current study (Mu: U =1607.00, p < 0.010; Sigma: U =2268.00, p = 0.560; Tau: U = 84.00, p < 0.001). The Spearman correlations (two-tailed) between age and mu and tau in the RVIP were no longer significant when the age-range was restricted (Mu: $r_{s\,(26)}$ = 0.266, p = 0.188; Sigma: $r_{s\,(26)}$ = 0.165, p = 0.422; Tau: $r_{s\,(26)}$ = 0.082, p = 0.692).

3.4 Discussion

The current study sought to model RT data obtained from a sustained attention task (the DV), using the ex-Gaussian distribution, in patients with idiopathic PD and HC. In addition, the study sought to examine the relationship between other neuropsychological processes (e.g., executive functioning) and attentional RT and IIV, as well as between age and RT and IIV, consistent with the themes of the thesis. Patients completed the DV task significantly more slowly (mu) than HC, as well as demonstrating increased variability across the entire RT distribution (sigma), and in the positive tail, characterised by infrequent, and long RTs (tau), which was not due to an impairment in executive functioning or processing speed. Similar to the normal ageing study, better executive functioning was associated with reduced inconsistency in responding (tau, and in patients only). Moreover, age was associated with slower responding (mu) and increased inconsistency (tau) in patients and HC, similar to the RVIP in the normal ageing study, and was not accounted for by an impairment in another domain (e.g., executive functioning).

3.4.1 Group differences

The results are consistent with previous research reporting elevated IIV in PD (Crawford *et al.*, 1989; Reed, 1998; Burton *et al.*, 2006; de Frias *et al.*, 2007; Camicioli *et al.*, 2008; de Frias *et al.*, 2012). In addition, the study extends previous research as it is the first, to knowledge of the doctoral candidate, to apply ex-Gaussian distributional analysis in PD. Patients exhibited elevated ex-Gaussian tau, indicating that a proportion of their responses on the DV task consisted of infrequent, and slow RTs, which were not due to motor symptoms, nor were they secondary to an impairment in another cognitive domain (e.g., processing speed or executive functioning). Consistent with previous research, IIV obtained from PD patients was not associated with Levodopa dose, indicating that IIV may not respond to dopaminergic medication, and may represent a distinct biomarker of PD (Molloy *et al.*, 2006; Camicioli *et al.*, 2008; Michely *et al.*, 2012).

Clinically, ex-Gaussian tau was also associated with performance on the MMSE in the current study, which is a measure of generalised cognitive impairment (Tang *et al.*, 2016). Given the purported insensitivity of the MMSE in detecting cognitive impairment in PD (Burdick *et al.*, 2014; Meyers and Wefel, 2003), future research should examine the sensitivity of IIV in detecting cognitive change in PD, perhaps utilising ROC curve analyses. This would determine whether IIV (tau) could be a useful and sensitive measure of neurological disturbance (e.g., Burton *et al.*, 2006).

Elevated tau has been observed in a number of clinical disorders, such as mild dementia of Alzheimer's Type (Tse *et al.*, 2010), and is purported to be an index of attentional 'lapses', or fluctuating attentional capacity (Leth-Steensen *et al.*, 2000; Kofler *et al.*, 2013). Given reports of elevated IIV in a wide range of clinical disorders, researchers have suggested that IIV may be a general marker of psychopathology, or trans-diagnostic phenotype (Gottesman and Gould, 2003). Alternatively, the pattern of IIV may be diagnosis-specific (i.e. *equifinality*), and related to different neurological, neuropsychological, or indeed functional processes (Kofler *et al.*, 2013). Further research should clarify the diagnostic role of IIV in PD, which could be explored via logistic regression.

3.4.2 Relationship between other neuropsychological processes and attentional RT and IIV

Results will be discussed in terms of executive functioning (please see section 3.4.4 for processing speed limitations).The current study highlighted that better executive functioning in patients with PD was associated with reduced inconsistency in responding, in the positive tail of the RT distribution (tau).
The relationship between executive functioning and ex-Gaussian tau reported in the current study is consistent with interpretations of the index as reflecting deterioration in attentional/executive control (i.e. being able to maintain a task-related goal, and ignore irrelevant information).

This interpretation has been applied to early stage, mild dementia of Alzheimer's type (Jackson *et al.*, 2012; Tse *et al.*, 2010), in older, compared to younger adults (Jackson *et al.*, 2012), in ADHD (Sergeant, 2005), and in schizophrenia (Kieffaber *et al.*, 2006; Rentrop *et al.*, 2010; Karantinos *et al.*, 2014).Executive functioning is typically impaired in PD (Muslimović *et al.*, 2005; Yu *et al.*, 2012; Dirnberger and Jahanshahi, 2013), and is reported to be one of the earliest cognitive impairments in the disorder (Dubois and Pillon, 1997; Elgh *et al.*, 2009; Yu *et al.*, 2012).However, in the current sample, patients with PD outperformed HC in the composite of executive functioning measures examined. It should be noted that preservation of executive functioning has also been reported in PD (Bohlhalter *et al.*, 2009).

It is possible that preserved neuropsychological processes, such as executive functioning, may have been recruited by patients to support deteriorating attentional IIV, indexed by tau. Similar to the results obtained in the normal ageing study, this may represent secondary compensatory scaffolding typically associated with ageing (Park and Reuter-Lorenz, 2009). Recruitment may be specific to pathology in this instance however, as the result was not replicated in HC – with recruitment expected if scaffolding was in response to age-related deterioration of attentional IIV.

Alternatively, the current results may be associated with task demands, as it is possible that the significant loading of executive functioning in the hierarchical regression models may reflect the intrinsic properties of the task itself. As highlighted in Table 1-1 in Chapter 1, it was anticipated that the DV task would have a low level of executive functioning (working memory) load, due to the task demands (e.g., only one target to be remembered). In the current study, executive functioning was associated with reduced inconsistency in responding (tau), but only in patients. It is possible that for HC, the task was of such a low level of difficulty that engagement of other neuropsychological processes such as executive functioning may not have provided additional benefit.

In contrast, participants in the normal ageing study may have engaged additional neuropsychological processes (executive functioning, processing speed, and verbal memory) to support attentional IIV (tau) when completing the RVIP, due to the greater difficulty of the task, with its higher working memory load compared to the DV.

Taken together, the results suggest that engagement of executive functioning for patients was beneficial, as this was associated with reduced inconsistency in responding. It is possible that this neuropsychological process in patients with PD is engaged at lower levels of task demand, compared to HC, reflecting cognitive disturbance/impairment associated with PD. This would be predicted by the CRUNCH model (Reuter-Lorenz and Cappell, 2008). Although the CRUNCH model has been applied in the study of normal ageing, it could be applied to PD. Under this interpretation, patients with PD would have to 'work harder' to maintain task related goals and to perform effectively, compared to their non-pathological counterparts. Inefficient processing may lead to the recruitment of more resources, with compensatory activation effective when task demands are low.

3.4.3 Relationship between age and attentional RT and IIV

In the current study, and in patients with PD and HC, age was associated with slower responding (mu), due to increased infrequent variability in responding (tau). Variability across the entire distribution (sigma) was not associated with age. The effects of age on mu and tau have also been reported in normal ageing, in three attentional control tasks (Jackson *et al.*, 2012), although this is the first study to the doctoral candidate's knowledge to demonstrate this pattern in PD. The relationship between mu, tau and age may reflect the general decline of information processing ability with increasing age (Brockmole and Logie, 2013).

As an extension, the catecholamine hypothesis (Li and Lindenberger, 1999) posits that age-related reductions in dopamine reduces neural transmission, resulting in increased variability in information processing at a neural and behavioural level. As such, the current results may reflect the prefrontal 'noise' associated with increased age. Interestingly, similar age-effects between the DV in the current study, and the RVIP in the normal ageing study were observed, despite different study populations, and task requirements of the DV and RVIP. The DV is a lower working memory load version of the RVIP, which requires participants to remember a single digit target, compared to the three, three digit targets of the RVIP. Whilst the DV task is presented at a faster rate (150 digit/per min), compared to the RVIP (100 digits/min), the RVIP includes more targets over the course of the task (63/700), compared to DV (45/450). The RT distributions in HC were compared between the RVIP and DV tasks in an exploratory analysis. The samples did not differ in terms of ex-Gaussian sigma, but only in mu and tau, with the DV completed more slowly (mu) compared to RVIP, but longer RT distributions obtained from the RVIP compared to DV (tau). The latter result highlights that increases in the working memory demands of a task may increase the likelihood of infrequent, and slow RTs.

It must also be noted that age was a poor predictor (< 10% of variance) of mu and tau in patients and HC. Age may be used a proxy marker for general brain changes, but use of this metric alone lacks specificity (Rabbitt *et al.*, 2007). Elevated IIV has been linked with a number of white matter microstructural alterations, as well as clinical disease. As such, rather than age, IIV could be better characterised as a marker of neuronal integrity, and/or clinical marker of disease state, although this would need to be confirmed in future studies.

3.4.4 Study limitations

Methodological limitations should also be discussed. Investigation of the current study aims was limited by the sparse neuropsychological battery included in the longitudinal study. Whilst dissimilar to the normal ageing study in Chapter 2, the tasks included in the current study consisted of a measure of processing speed (mean RT from the SRT), and tasks which formed an executive functioning composite (OTS and FAS). These tasks were selected for consistency with the other neuropsychological measures of focus within the thesis, given a restrictive cognitive battery.

A potential limitation concerns the selection of mean RT from the SRT to represent processing speed in the current study. Within the literature, the results from the SRT have been interpreted as reflecting deficiencies in the execution of pre-programmed motor responses (Sheridan *et al.*, 1987). Due to the emphasis on motor pre-programming, it is possible that the behavioural outcome measures obtained from the SRT are confounded with the general motor symptoms associated with PD, such as bradykinesia. Indeed, the RT outcome measures obtained from the SRT in the current study were positively associated with a measure of motor symptom severity, the MDS-UPDSR-III.

The associations between ex-Gaussian mu, tau, and processing speed suggest that overall speed of responding, and infrequent long RTs are partly the result of the speed at which individuals can respond to a simple RT task, which is confounded with the motor symptoms of PD. Inclusion of mean RT from the SRT as measure of processing speed, may be obscuring the true contribution of processing speed to IIV obtained from the DV task, with interpretation of its contribution to the hierarchical regression models correspondingly limited. To circumvent this issue in the future, the contribution of processing speed should be clarified by utilising an appropriate, and well-reported measure, such as the DSST from the WAIS-III (Wechsler, 1998).

In contrast, the ex-Gaussian parameters (mu, sigma, and tau) obtained from the DV task were not associated with the MDS-UPDRS-III, possibly representing a non-motor symptom associated with early-stage PD. Moreover, in further analyses, ex-Gaussian parameters were not associated with Levodopa dose, indicating that IIV obtained from the DV task may not be related to dopaminergic dysfunction characteristic of PD. However, caution is warranted, as RT and IIV still involves a motor response. Future work could include a basic motor speed task (e.g., finger-tapping) within the neuropsychological test battery (Yokoe *et al.*, 2009), and include the results as a covariate in analyses of RT and IIV. The current result would need to be replicated in the same cohort of PD patients, particularly as the disease progresses and motor symptoms worsen, for IIV obtained from the DV to represent a non-motor, and enduring symptom of PD.

3.4.5 Future research

Future studies exploring cognitive impairment in PD should utilise full, and complete, neuropsychological batteries, given the paucity of individual cognitive outcomes measured widely (Varalta *et al.*, 2015). The use of global measures of cognitive impairment, such as the MMSE, or the MoCA is sufficient for some studies. However, should the focus be on cognitive impairment, and the contribution of multiple neuropsychological measures to IIV (investigation of the cognitive hierarchy), inclusion of a full neuropsychological battery would enable researchers to gain a greater understanding of the specific cognitive domains limited in the disease. Future research may also benefit from examining the specificity of IIV in detecting cognitive impairment, given the insensitivity of measures such as the MMSE and MoCA (Meyers and Wefel, 2003; Burdick *et al.*, 2014).

Future studies should also aim to understand the neurological origins of IIV in PD. Intra-individual variability in RT is considered biologically and clinically meaningful, with elevated IIV purportedly indexing the deterioration of the central nervous system (Dykiert *et al.*, 2012). In the same early-diagnosed PD cohort utilised in the current study, Duncan *et al.* (2016) observed that patients had greater MD than HC, in frontal, as well as parietal subcortical tracts. Moreover, this increase in MD was associated with poorer behavioural performance on a semantic fluency task, and an executive planning task. It would be interesting to note whether these early white matter tract changes were also associated with the IIV reported in PD in the current study.

As an extension of the research reported in the current study, its application to PDD could also be explored. In PDD, IIV holds promise as a potential marker for development of PDD (de Frias *et al.*, 2012). In addition, widespread white matter tract deterioration has been reported in PDD (Melzer *et al.*, 2013). To clarify its potential clinical implications, IIV should be examined in the longitudinal follow-ups (at 18 and 36 months) associated with the ICICLE-PD study (Yarnell et al., 2014), in conjunction with exploration of the relationship with white matter tracts, to determine whether IIV could be a prodromal marker of PDD development. Moreover, to confirm that the current pattern of results are enduring as the disease progresses.

3.4.6 Conclusions

To conclude, the current study demonstrated that IIV in PD occurs across the entire RT distribution, as well as instances of infrequent and long RTs, possibly indicative of response 'lapses'. The current study has also demonstrated that (1) The contribution of executive functioning to attentional IIV in patients, but not HC, may represent engagement of secondary cognitive scaffolding. Alternatively, this could reflect the properties of the DV (Chapter 1, Table 1-1); (2) Group differences in attentional IIV are not accounted for by impairments in other cognitive domains (e.g., processing speed and executive functioning), despite sharing variance with these domains and (3) Age-related decline is observed in mu and tau when obtained from tasks involving quick, sequential presentation of single digits.

The work presented in the current study will be extended to BD in the chapters to follow, as BD is associated with both severity of cognitive impairment, and elevated IIV (discussed in greater detail in Chapter 4). As highlighted in section 2.4.4 of Chapter 2, the relevance of IIV as a clinical tool may rest on demonstrating that it is not an artefact of impairment in another cognitive domain. The next Chapter (4) discusses the clinical and cognitive symptoms of BD generally, with the thesis aims later explored in patients with BD during remission (Chapter 5) and in a depressive episode (Chapter 6).

Chapter 4. Sustained attention in BD

The current chapter will present a broad overview of the clinical and cognitive characteristics of BD, as well as a narrative review of CPT variants utilised in BD (section 4.5).

4.1 Diagnosis of BD

In the thesis, BD is defined using criteria described by the DSM-IV-TR (APA, 2000). The DSM-IV-TR makes the distinction between BD I (primarily manic presentation) and II (hypomanic). Manic episodes are characterised by symptoms lasting one week or more (any duration if the individual was hospitalised), and include three or more symptoms which can include increased grandiosity, reduction in the need for sleep, and increased talkativeness. Hypomanic episodes are considered milder forms of the manic episodes previously described, and are not sufficiently severe to cause marked functional impairment or hospitalisation. At least one hypomanic episode is necessary for a definition of BD II under the DSM-IV-TR criteria. Symptoms for a depressive episode must be present for at least two weeks or more, and cause clinically significant impairments in daily functioning (e.g., social, work). At least five (or more) symptoms must be present and can include depressed mood all day, sleeping too often, or too little, fatigue, and feelings of excessive guilt or worthlessness amongst others.

4.2 Epidemiology

4.2.1 Prevalence

In World Mental Health surveys, the cross-national lifetime prevalence of bipolar spectrum disorders was 0.6% - 2.4% for BD I and 0.4% for BD II (Merikangas *et al.*, 2011). Significant sex differences are not reported in prevalence rates (Bauer and Gitlin, 2016).

4.2.2 Age of onset

Presentation of symptoms tends to occur between late adolescence and early twenties (Goodwin *et al.*, 2008), with a mean age of 20.8 years (any sub-type) (Merikangas *et al.*, 2007). Age of onset does not differ between BD I and II (Bauer and Gitlin, 2016) and symptom presentation is similar between females and males (Kawa *et al.*, 2005). Cross-national studies have reported three peaks of symptom presentation; early (17 years), intermediate (26 years), and late onset (40 years) (Bellivier *et al.*, 2001; Leboyer *et al.*, 2005), with instances of BD occurring after 60 years typically attributed to alternative causes (e.g., neurological, infectious, or inflammatory; Bauer and Gitlin, 2016).

4.2.3 Course of illness and initial presentation

Bipolar disorder is typically defined as a recurrent clinical disorder (Bauer and Gitlin, 2016), with studies reporting that 85-95% of individuals have recurrence of mood symptoms (e.g., Goodwin and Jamieson, 2007). The most common type of first episode is depressive (Bauer and Gitlin, 2016). Over the course of the illness, individuals are more likely to spend time in depressive episodes, rather than manic or hypomanic (Baldessarini *et al.*, 2010). Depressive mood polarity and chronic symptom course has been reported for BD I and II. In a longitudinal weekly follow-up of patients with BD I, around half (47.3%) of patients experienced mood symptoms over the 12.8 year follow-up period. Of those 47.3%, 31.9% experienced depressive episodes, 8.9% manic/hypomanic, and 5.9% cycling/mixed (Judd *et al.*, 2002). Similarly, in BD II, 53.9% of patients experienced mood symptoms over the 13.4 year follow-up. Of those 53.9%, the majority experienced depressive episodes (50.3%), followed by 1.3% hypomanic, and 2.3% cycling/mixed (Judd *et al.*, 2003).

4.2.4 Comorbidity

Bipolar disorder is highly comorbid with other psychiatric and medical conditions. According to the National Comorbidity Survey Replication, around 90% of those with lifetime BD, also meet the criteria for another disorder (Merikangas *et al.,* 2007). Comorbidity with anxiety disorders is common, with more than 80% of patients with BD also having a lifetime history of DSM-IV anxiety disorders (e.g., panic attacks; Merikangas *et al.* 2007) Cross-nationally, World Mental Health surveys indicate rates of lifetime mental disorder comorbidity of 88.2% for BD I, 83.1% for BD II (Merikangas *et al.*, 2011). In addition to psychiatric disorders, BD is also comorbid with substance use disorders, such as alcohol abuse (Bauer and Gitlin, 2016).

4.2.5 Health consequences

The global and local health burden of BD is substantial. Worldwide, BD was responsible for 4.4-10.3 millions years lost due to the burden of the disorder (7% of total disability-adjusted life years) (Whiteford *et al.*, 2010). When disability in working age adults between 15 and 44 years is considered, the WHO places BD as the sixth leading cause of disability in the world (Murray and Lopez, 1997). Additional health consequences include decreased life expectancy (Chang *et al.*, 2011), partly due to death by ‘unnatural causes’ such as suicide, but also ‘natural’ causes such as a higher general rates of comorbid cardiovascular disease (Goldstein *et al.*, 2009). The functional impairment (Judd *et al.,* 2008) experienced by patients with BD reduces their quality of life (Michalak *et al.*, 2005), and contributes to reduced socioeconomic status and higher rates of unemployment (Schoeyen *et al.*, 2011).

4.2.6 Economic consequences

As well as the notable personal impact, with reduced functioning and quality of life, BD has socio-economic consequences. The annual cost of BD to the NHS between 2009 and 2010 was £342 million – 60% accounted for by hospitalisations and 26.7% for community mental health (Young *et al.*, 2011).

4.3 Genetic influence

4.3.1 Family studies

Bipolar disorder is highly heritable. Family studies indicate that first-degree relatives ('at risk' population) of bipolar probands have a 5-10% risk of developing the disorder (Craddock and Jones, 1999; Smoller and Finn, 2003). As relatedness decreases, so does genetic risk for the disorder (Craddock and Sklar, 2013). Despite an elevated risk of developing BD (approximately a 10-fold increase, compared to HC), relatives have a higher risk of developing other psychiatric disorders, such as recurrent MDD, compared to the general population (Tsuang and Faraone, 1990).

4.3.2 Twin studies

Twin studies enable genetic influences to be teased apart from environmental, and are useful in determining familial transmission, more so than adoption studies (Barnett and Smoller, 2009). Studies have reported concordance rates (presence of BD) of up to 43% for monozygotic (identical), and 6% for dizygotic twins (who share half their genes) (McGuffin *et al.*, 2003; Kieseppa *et al.*, 2004). Heritability (risk of the disorder attributable to genetic factors) of BD is as a high as 79%-93% according to these studies (Barnett and Smoller, 2009).

4.3.3 Molecular studies

Both family and twin studies indicate that genes are involved in transmission of BD. However, as concordance estimates are not 100% (e.g., in monozygotic twins), genes alone are not sufficient for the development of BD (Barrett and Smoller, 2009). No single mutation of a gene is known to cause the disorder. It is likely that genes increase risk (Barrett and Smoller, 2009), with alleles inferring genetic risk passed from parent to child (Gottesman and Bertelsen, 1989). Nevertheless, transmission from one generation to the next is not entirely understood (Antila *et al.*, 2007). Approaches to understanding the genetic basis of BD comes from a variety of sources, including linkage, candidate gene, genome-wide, as well as structural variant studies. However, due to the complex and heterogeneous nature of the disorder, researchers have argued that additional strategies are required to examine the genetic influence of BD. One such strategy is examining the role of intermediate (endo) phenotypes (Barrett and Smoller, 2009).

4.3.4 Endophenotypes in BD

Endophenotypes are the subclinical characteristics or markers between the BD genotype and the related, phenotype (observable characteristics, or traits) (Gottesman and Gould, 2003). Criteria for identifying endophenotypes include: (1) Association with an illness in the population; (2) Heritability; (3) State independence (occurs in a symptomatic state, and in remission); (4) Co-segregation (inheritance) of endophenotype and illness within families; (5) Endophenotype occurs at a higher rate within unaffected relatives of illness probands, compared to the general population (Hasler *et al.*, 2006). Identifying endotypic markers may assist with the diagnosis (i.e. of the disorder itself, but also of ‘at risk’ populations), and classification of disorders (i.e. sub-types), as well as to inform clinical research and treatment (Frantom *et al.*, 2008).

4.4 Cognitive impairment in BD

A potential endophenotype for BD is cognition (Glahn *et al.*, 2004), which may reflect genetic risk. Cognitive impairments (i.e. patients performing more poorly than HC in behavioural outcome measures) within a number of tests are well described in BD. Cognitive impairment is considered a core feature of the disorder (Lim *et al.*, 2013), is related to poor functioning (Zarate *et al.*, 2000), may be predictive of long term functional outcome (Bonnín *et al.*, 2010) and linked with reduced psychosocial functioning (Martínez-Arán *et al.*, 2004). For the purposes of the thesis, discussion of cognitive impairment in BD is restricted to published meta-analyses, systematic and/or narrative reviews, and longitudinal studies.

4.4.1 Course of cognitive impairment

Cognitive impairment is evident in BD, as early as the first episode. In a meta-analysis conducted by Lee *et al.* (2014), medium – large (d = 0.5 – 0.8) effect sizes were noted for processing speed, attention/working memory, and cognitive flexibility, and small effect sizes (d = 0.2 - 0.5) noted for verbal learning and memory, as well as attentional switching. Whilst the Lee *et al.* (2014) meta-analysis was the first to characterise cognitive functioning in first-episode BD, the meta-analysis is limited in its generalisability. The authors were unable to examine cognitive functioning between different mood states, due to aggregation of patients across clinical states in the small selection of primary studies (n = 12). Moreover, pooled effect sizes were not completed per task, but per cognitive domain, due to the heterogeneity of tests included in the primary studies. As such, it is not clear whether the pattern of cognitive impairment during the first episode (separated per sub-type) would be replicated.

Longitudinally, few studies have examined the course of cognitive impairments in BD. In a recent meta-analytic study of 12 longitudinal studies, Samamé *et al.* (2014) examined the differences between baseline and follow-up performance in 14 cognitive variables (e.g., processing speed, attention) in patients with BD. The studies included in the analyses had follow-up periods between 1 and 8.9 years.

For the purposes of the analysis, Samamé *et al.* (2014) restricted the follow-up range to 2.18-4.62 years. The authors concluded that there was insufficient evidence to suggest that cognitive deficits are progressive in BD, with the authors highlighting that the limitations of the primary studies included in the analysis (small sample sizes, lack of a control group, inconsistent mood rating measurement, wide range of neuropsychological assessments utilised, short follow-up ranges) may be obscuring the longitudinal course of cognitive impairments.

Whilst evidence suggests cognitive impairment is present early in the course of BD, evidence associated with the progression of impairment is inconclusive. Further, more detailed studies are needed, with longer follow-up periods (e.g., 10 years +) to examine the stability of cognitive impairment, with studies taking into account the limitations of previously published work.

4.4.2 Cognitive impairment in acute mood states

In acute mood states (hypomania, mania, and depression), patients exhibit cognitive impairments, compared to HC. Impairments in attention, verbal memory, and executive functioning have been reported (Quarishi and Frangou, 2002). In a meta-analysis by Kurtz and Gerraty (2009), large effect size impairments have been noted for verbal learning/ memory (d = 1.43 and 1.05), and moderate-large effect sizes noted for attention (sustained (d = 0.79), and speeded visual scanning (d = 0.90)), verbal fluency (letter (d = 1.05) and semantic (d = 0.59)), and executive functioning (perseveration (d = 0.72) and set-shifting (d = 0.64)), for patients in a manic/mixed mood state (study n = 13). Compared to patients in remission, manic patients had greater effect-size impairments for verbal learning, but were similar for all other cognitive measures (Kurtz and Gerraty, 2009). In depressive mood states (study n = 5), large effect sizes have been noted for verbal learning (d = 1.20) and phonemic fluency (d = 0.93), with moderate-large effect sizes for attention (d = 0.80), and executive functioning (d = 0.64) (Kurtz and Gerraty, 2009).

The authors noted that compared to patients in remission, depressed patients had a greater effect-size impairment for phonemic fluency. These results indicate that the magnitude of cognitive impairment in acute clinical states, compared to remission, may depend on the cognitive domain. Further studies are required to confirm the presence of specific cognitive impairment and magnitude, across acute mood states, and compared to remission.

4.4.3 Cognitive impairment in remission

In remission, patients experience cognitive impairments, compared to HC. Large ($d \geq 0.8$) effect sizes have been observed in working memory, executive control, verbal memory/fluency, mental speed (Arts *et al.*, 2008), sustained attention (Bora *et al.*, 2009), verbal learning, and executive functioning (category fluency and mental manipulation) (Robinson *et al.*, 2006; Arts *et al.*, 2008; Bora *et al.*, 2009). Moderate to large effect sizes ($d = 0.5 - 0.8$) have been noted in attention (including sustained), working memory, verbal memory, executive functioning (problem-solving, verbal interference, set-shifting), verbal fluency (phonemic and semantic), processing speed, episodic memory, and response inhibition (Robinson *et al.*, 2006; Torres *et al.*, 2007; Arts *et al.*, 2008; Bora *et al.*, 2009; Kurtz and Gerraty, 2009). Small effect sizes ($d = 0.2 - 0.5$) have been observed for auditory attention, visuo-spatial functioning (Kurtz and Gerraty, 2009), visuo-perception, working memory, verbal fluency (letter), immediate memory, and sustained attention (Robinson *et al.,* 2006; Arts *et al.,* 2007; Bora *et al.,* 2009; Kurtz and Gerraty, 2009).

Meta-analyses suggest that cognitive impairment may be a stable, trait marker of BD, persistent in remission, as well as acute mood states. However, there is debate regarding the impact of medication on cognitive impairment in BD, with researchers emphasising that whilst medication status is unlikely to wholly account for cognitive impairment in BD, further studies are required to clarify this position (Torres *et al.,* 2007; Arts *et al.,* 2008; Bora *et al.,* 2009; Kurtz and Gerraty, 2009).

The cognitive impairments observed during remission have raised the question of whether they could represent potential endophenotypes of the disorder. Whilst other potential cognitive endophenotypes have been identified such as verbal memory and executive functioning (Glahn *et al.*, 2004), for the purposes of the thesis, only sustained attention will be discussed in detail.

4.5 Narrative review of sustained attention in BD

Sustained attention is considered a potential cognitive endophenotype for BD, as the impairment is noted in remission, acute mood states, and may be present in first-degree relatives (Clark *et al.*, 2002; Hasler *et al.*, 2006; Bora *et al.*, 2009; Ancín *et al.*, 2010).Within the BD literature, sustained attention is commonly measured using variants of the CPT.

The aim of the following narrative literature review is to examine whether the sustained attention impairment in BD varies according to type of CPT and/or behavioural outcome measure which a sustained attention 'impairment' is defined by. If behavioural outcome measures vary per task type, this may indicate that the sustained attention impairment in BD may depend upon the method of assessment and/or the definition of impairment (via use of hit rate, omission errors etc.). In turn, this could be linked to the multiple neuropsychological processes involved in CPTs (Chapter 1, section 1.4).

The review below has selected CPTs included in the Camelo *et al.* (2013) systematic review of studies investigating attention in BD, the majority of which included patients in remission. Thirteen studies were selected from the review, as these included bipolar probands in an acute mood state or in remission, and utilised CPTs which this thesis is examining. Therefore, 13 studies from the Camelo *et al.* (2013) systematic review were examined.

In addition, a further four studies (Thompson *et al.,* 2005; Robinson *et al.,* 2013; Gallagher *et al.,* 2014; 2015) not included in the Camelo *et al.* (2013) review were selected which used CPT-X/AX type tasks. A further five studies (Clark *et al.*, 2002; Clark *et al.*, 2005; Maalouf *et al.*, 2010; Walshe *et al.*, 2012; Braw *et al.*, 2013) were included as examples of research utilising the RVIP. Results are separated per task type below (CCPT-II, CPT X/AX, RVIP, and CPT-IP). Tasks are described in detail in Chapter 1 (section 1.6) and will not be repeated here.

4.5.1 CCPT-II

One study in the Camelo *et al.* (2013) review assessed sustained attention in an acute mood phase using the CCPT-II. In Bora *et al.* (2006) manic patients were reported to make more commission and omission errors, have more variable RT (variability of standard error), have a higher hit RT standard error, and were slower per block (mean RT), compared to patients with BD in remission, and HC. These results suggest that the magnitude of sustained attention impairment in BD may be state-dependent. No study included within the Camelo *et al.* (2013) review used the CCPT-II to examine sustained attention in patients during a depressive episode.

Several studies used the CCPT-II to assess sustained attention during remission (Bora *et al.*, 2006; Mur *et al.*, 2008; Brooks *et al.*, 2010; Kung *et al.*, 2010; Mora *et al.*, 2013; Okasha *et al.*, 2014), although inconsistent results have been reported. Three studies reported that patients were slower (mean RT) than HC in completing the CCPT-II (Mur *et al.*, 2008; Kung *et al.*, 2010; Mora *et al.*, 2013), whilst two reported no differences (Trivedi *et al.*, 2008; Okasha *et al.*, 2014).

All studies that investigated signal detection indices in the Camelo *et al.* (2013) review reported detectability (*d'*) only. One study reported lowered *d'* (Kung *et al.*, 2010), whilst three reported no difference (Mur *et al.*, 2008; Brooks *et al.*, 2010; Mora *et al.*, 2013) in BD (remission), compared to HC.
It is possible that the discrepancy in signal detection indices is due to a combination of sample size and clinical characteristics.

In the Kung *et al.* (2010) study, 51 patients and 20 HC were tested, but patients were in remission for a minimum of one week and were considered to be between-episodes, as well as mildly symptomatic. Stricter criteria was used in Mur *et al.* (2008), Brooks *et al.* (2010) and Mora *et al.* (2013), with the duration of remission varying between one and three months in these studies. In terms of sample size, Mur *et al.* (2008) tested 15 patients and 15 HC, Brooks *et al.* (2010) tested 16 patients and 11 HC, whilst Mora *et al.* (2013) tested 28 patients and 26 HC.

Patients made more commission errors (false alarms) than HC (Kung *et al.,* 2010; Okasha *et al.,* 2014), although some studies have reported no difference (Bora *et al,* 2006; Brooks *et al.,* 2010). In addition, patients made more omission errors (misses) than HC (Bora *et al;* 2006; Brooks *et al.,* 2010; Okasha *et al.,* 2014), although no differences have also been reported (Kung *et al.,* 2010).

4.5.2 CPT-X/AX type tasks

One more recent study has examined sustained attention using a CPT-X/AX type task in patients with BD (while depressed). Gallagher *et al.* (2015) examined measures of RT measures of central tendency (mean RT, ISD, and CoV) and the ex-Gaussian distribution (mu, sigma, and tau). Patients in a depressive episode were more variable (ISD, CoV, ex-Gaussian sigma, and tau), which occurred without a slowed speed of responding, compared to HC. No studies included in the Camelo *et al.* (2013) review examined sustained attention using CPT-X/AX type tasks in patients experiencing a manic episode.

Four studies which were not included in the Camelo *et al.* (2013) review assessed sustained attention impairment in patients in remission using CPT-X/AX. Thompson *et al.* (2005), and Gallagher *et al.* (2014; 2015) used the Vigil CPT (low target frequency AX-type task (< 25%)), whilst Robinson *et al.* (2013) used a high target frequency variant of the CPT-AX (70%).

Patients in remission made more commission and omission errors (Gallagher *et al.*, 2014), respond more slowly compared to HC (Thompson *et al.,* 2005), and were more variable (ISD and ex-Gaussian tau) (Gallagher *et al.,* 2015), suggesting that the sustained attention impairment in patients with BD during remission is characterised by inattention, impulsivity, as well as fluctuating attentional task engagement. Gallagher *et al.* (2014) and Robinson *et al.* (2013) did not observe significant differences in the RT between patients and HC (mean RT).

In Robinson *et al.* (2013), patients with BD (in remission) completed a high target frequency (70%) version of the CPT-AX, similar to the CCPT-II (Conners, 2000). Overall, patients had a lower hit percentage, as well as reduced *d'* and *d'* context ('BX' errors). The authors also examined behavioural performance per block – although no differences were observed between patients and HC in blocks one and three, in blocks 2 and 4, patients made more 'BX' errors (*d'* context) and had reduced *d'*, compared to HC. In addition, by block four, patients had reduced target percentage, and made more commission and omission errors generally, compared to HC, suggesting that sustained attention deficits emerge over time.

4.5.3 RVIP

Two studies from the Camelo *et al.* (2013) review examined sustained attention using the RVIP in patients with BD experiencing a depressive episode. Roiser *et al.* (2009) did not find significant differences between patients and HC in sensitivity (*d'*), or response bias (β), whilst Holmes *et al.* (2008) reported similar results using commission errors and RT. No studies included in the Camelo *et al.* (2013) review examined sustained attention using the RVIP in patients experiencing a manic or hypomanic episode.

Five studies (Clark *et al.*, 2002; Clark *et al.*, 2005; Maalouf *et al.*, 2010; Walshe *et al.*, 2012; Braw *et al.*, 2013) which were not included in the Camelo *et al.* (2013) review assessed sustained attention impairment in patients in remission using the RVIP, with inconsistent results reported.

Three studies reported lowered sensitivity (*A*') in patients, compared to HC (Clark *et al.*, 2002; Clark *et al.*, 2005; Walshe *et al.*, 2012; Braw *et al.*, 2013). One study reported lowered target detection (% correct) in patients, compared to HC (Clark *et al.,* 2002), although another did not report a difference using an accuracy percentage (Clark *et al.,* 2005). Two studies did not report a significant difference between patients and HC in response bias (Clark *et al.,* 2005; Walshe *et al.,* 2012). No studies reported rate of omission errors, and one study reported no significant difference between patients and HC in commission errors (Walshe *et al.,* 2012). Two studies reported a slowed response latency (mean RT) in patients (Clark *et al.,* 2002; Clark *et al.,* 2005), although one study did not report any differences in response speed (Walshe *et al.,* 2012).

4.5.4 CPT-IP

One study in the Camelo *et al.* (2013) review assessed sustained attention using the CPT-IP in patients with BD during a manic episode. Whilst patients and HC did not differ in RT (mean), or response bias (β), steeper sustained attention decrements (reduced accuracy over the course of the task) have been reported (Fleck *et al.*, 2012). No studies included in the Camelo *et al.* (2013) review examined sustained attention using the CPT-IP in patients experiencing a depressive episode.

Five studies in the Camelo *et al.* (2013) review examined used the CPT-IP to assess sustained attention in remission, with consistent results reported. Higher rates of commission errors (Chaves *et al.*, 2011; Harmell *et al.*, 2014), lower signal detection (e.g., *A*') (Najt *et al.*, 2005; Chaves *et al.*, 2011; Harmell *et al.*, 2014), lowered hit rate (Najt *et al.*, 2005; Kolur *et al.*, 2006; Chaves *et al.*, 2011; Harmell *et al.*, 2014), more omission errors (Kolur *et al.,* 2006), and longer RTs (mean RT) (Najt *et al.,* 2005; Kolur *et al.,* 2006), have been reported in patients, compared to HC.

Of note, studies that utilised the CPT-IP in remission consistently reported sustained attention impairment across a number of behavioural outcome measures. These results indicate that compared to alternative CPTs, the task may have been sufficiently challenging, perhaps due to the increased working memory component, to elicit a task impairment in patients in remission. However, due to the heterogeneity in CPT variants (whether the two, three, or four digit version was utilised/reported, or results averaged across sub-tests), it is unclear whether the results are specific to the sub-tests utilised.

4.6 Summary of Chapter 4

The aim of the present narrative literature review was to examine whether the sustained attention impairment in BD varies according to type of CPT and/or behavioural outcome measure which a sustained attention impairment is defined by. If so, this could be linked to the multiple neuropsychological processes involved in CPTs (Chapter 1, section 1.4).

Despite using different CPTs, studies reported patients with BD made more commission and omission errors, had reduced signal detection, sensitivity, and/or response bias, responded more slowly, and were more variable in RT, compared with HC. These results suggest that the attentional impairment in BD encompasses inattention, impulsivity, as well as fluctuations in attention, which may be trait (i.e. associated with the disorder itself, irrespective of mood state) related, rather than state (i.e. specific to mood state).

Despite some commonalities between tests, discrepant results have been reported, with these results more apparent in studies utilising patients in remission, than in acute mood states. There was also heterogeneity in the behavioural outcome measures used/reported across studies. Discrepant results may reflect the inconsistency of behavioural outcome measures in detecting subtle attentional impairment in heterogeneous populations such as BD.
In addition, the results may highlight type II error, given the variations in sample size and subsequent power in the studies examined in this review.

Of note, there is a paucity of studies investigating and/or reporting RT and IIV when examining sustained attention in BD. Fifteen studies out of 22 studies included in this review reported RT measures (mean RT), and two with IIV (Bora *et al.,* 2006; Gallagher *et al.,* 2015), with one investigating the ex-Gaussian distribution in one version of CPT (Gallagher *et al.,* 2015). It is not clear at present whether elevated IIV in BD is a consistent impairment (across tasks), and therefore a potential cognitive endophenotype, or represents a state marker. Moreover, whether elevated IIV in BD is independent of impairment in other cognitive domains (perhaps sharing variance), or is secondary to them (Chapter 1, section 1.4, also Table 1-1). As outlined in Chapter 1 of this thesis, and in subsequent studies, IIV may be a biologically and clinically relevant outcome measure. If IIV is to be incorporated as an outcome measure in clinical studies, and examined more frequently in BD, determining the relationship between IIV and other impairments (e.g., neuropsychological, clinical, functional), as well as relevance within the wider bipolar pathology is necessary.

4.7 Section summary

The current chapter has presented a historical, as well as clinical, and cognitive overview of BD. Focussing on sustained attention, the chapter has described results obtained in BD from different versions of CPT, and highlighted discrepancy with findings amongst the paradigms. Moreover, a brief overview of the sustained attention literature has highlighted that RT and IIV are not typically utilised as outcome measures in BD research. The studies that follow explore the thesis themes in patients with BD during remission (Chapter 5), and in a depressive mood state (Chapter 6).

Chapter 5. IIV in BD (in remission)

The following chapter is adapted for this thesis from a manuscript accepted for publication in Frontiers in Psychiatry in June 2016 (Moss *et al.*, 2016). The work presented in the study is the work of the doctoral candidate. The doctoral candidate was responsible for data analysis and led the manuscript writing. Dr Andreas Finkelmeyer was involved in data analysis and manuscript revision. Dr Lucy J. Robinson, Dr Jill M. Thompson, Dr Stuart Watson, Professor I. Nicol Ferrier, and Dr Peter Gallagher were involved in manuscript revision.

5.1 Introduction

In the current study, the thesis themes will be explored in a clinical sample purported by some to be associated with AA (Rizzo *et al.,* 2014) in BD. The AA model highlights that many of the changes observed in BD (altered brain structure and function, cognitive deficits, altered immune system responding, as well as telomere shortening) are similar to that observed in normal ageing. The disorder itself is proposed to 'accelerate' such senescent markers. Consequently, it is argued that these senescent features associated with BD support a model of AA (Rizzo *et al.,* 2014).

The current study had several aims. Firstly, to determine whether a similar pattern of RT and IIV (Gallagher *et al.,* 2015) would be obtained using a sustained attention task with different parameters in patients with BD (in remission) and in HC. The CPT, version AX (CPT-AX; Robinson *et al.,* 2013), and the Vigil CPT (Cegalis and Bowlin 1991), were chosen as they differed in target frequency (event rate), and therefore, task environment. Across both tasks, there are common parameters. Both tasks have a high event rate (CPT-AX = 70 events/minute; Vigil = 64 events/minute), as defined by Parasuraman (1979) (more than 60 stimuli presented per minute), and both have a similar working memory load (both '1-back' cued target sequences). However, target sequences are presented frequently during the CPT-AX (~70%), compared to Vigil CPT (~ 20%).

The high rate of responding for the CPT-AX creates a task environment in which impulsive, quick responding is possible, similar to that observed within the CCPT-II (Chapter 1). In contrast, the low rate of responding for the Vigil CPT creates a task environment in which more reserved, slower and more variable responding is possible. In the current study, RT distributions were analysed by applying the ex-Gaussian distribution to observed RTs in patients with BD (in remission) and HC who had completed the CPT-AX and Vigil CPT. For both tasks, it was anticipated that an increase in ex-Gaussian tau would be observed for patients, in agreement with previous literature from BD. Moreover, that the increase ex-Gaussian tau for patients would be higher when obtained from the Vigil CPT, compared to the CPT-AX.

The current study also aims to provide evidence of whether an association between age (as well as group-related differences) and attentional RT and IIV (obtained from the CPT-AX and Vigil CPT) represents an independent impairment, or reflects an impairment in other cognitive domains (e.g., processing speed). In agreement with the AA hypothesis (Rizzo *et al*., 2014), it was hypothesised that age would predict attentional RT and IIV obtained from both the CPT-AX and Vigil CPT, but only in patients. If an association between age (as well as group) and attentional RT and IIV reflects an independent impairment, then entry of other neuropsychological processes (e.g., executive functioning, processing speed, verbal memory) will not account for any age-related, or group-related associations. However, given the results of Chapters 1 and 3, it must also be considered that attentional RT and IIV, as well as the other neuropsychological processes of interest, are not independent *per se*, but share variance.

Alternatively, if the studies outlined in section 1.4 are taken into account, then an association between age (as well as group) and attentional RT and IIV, the latter a marker of sustained attention, will be explained by variance in the multiple neuropsychological measures of interest.

Processing speed is a candidate here, given the studies outlined in section 1.4, and the high anticipated processing speed load of the tasks utilised the current study (Table 1-1). However, based on the results of the PD study, it is not anticipated that other neuropsychological processes would account for any age-related or group-related associations with attentional RT or IIV, but may well share variance with attentional RT and IIV.

5.2 Methods

All participants included in the current analyses were from studies conducted within the IoN at Newcastle University (Thompson *et al.* 2005; Robinson *et al*. 2013). Data included in the current study was collected between 2000 - 2003 (Thompson *et al.,* 2005), and 2001-2003 (Robinson *et al.,* 2013). Remission was confirmed for patients in both studies (see section 5.2.1). These participants were a subset of those reported in Gallagher *et al.* (2015) who had completed both the CPT-AX and Vigil tasks. The doctoral candidate was not involved in study design or data collection.

5.2.1 Participants

Twenty-two adult outpatients between the ages of 30 and 57 years (M = 43.13, SD = 7.78) with a SCID (First, 1995) confirmed diagnosis of BD (in remission) were included in the analysis. Clinical interviews were conducted by psychiatrists trained in SCID administration. Recruitment was via services within the Northumberland, Tyne, and Wear NHS Foundation Trust in the North East of England. Remission – defined as a score of ≤7 on the on the 21-item HAMD (Hamilton, 1960) and the YMRS (Young *et al*., 1978) – was prospectively verified over one month from the initial assessment. During the verification month, patients completed the BDI (Beck *et al.,* 1996), and the Altman Mania Rating Scale (Altman *et al*., 1997) weekly. All patients were stable and taking psychotropic medication; 16 were prescribed lithium, 10 were prescribed antidepressants, and five were prescribed antipsychotics.

Medication status was not explored/included as a covariate in subsequent analyses due to the small and uneven sample size per medication sub-group. Patients: (i) did not have another Axis I diagnosis (except anxiety); (ii) did not have any neurological/medical conditions; (iii) did not have a history of substance or alcohol abuse/dependence over the past six months; (iv) were not prescribed corticosteroids or antihypertensive medication; (v) had not received ECT within the past year.

Twenty HC, between the ages of 30 and 53 years ($M = 43.55$, $SD = 6.67$) were recruited through local advertisements. Controls did not have a psychiatric history (SCID confirmed) or have a first degree relative with a psychiatric disorder. Groups were matched on sex, age, and premorbid IQ (NART; Nelson, 1982) and did not significantly differ in these characteristics ($p > 0.050$; Table 5-1). All study protocols were approved by the appropriate NHS Local Research Ethics. Written informed consent was obtained prior to study participation.

Table 5-1. Demographic and clinical characteristics of patients with BD (in remission, *n* = 22), and HC (*n* = 20).

Variables	BD	HC	t/χ^2	*p*
	Mean ± SD	Mean ± SD		
Demographic characteristics				
Sex (F:M)	14:8	11:9	0.32	0.569
Age, years	43.13 ± 7.78	43.55 ± 6.67	0.18	0.855
Premorbid IQ (NART)	111.77 ± 8.94	110.65 ± 7.59	- 0.43	0.665
Mood ratings				
HAMD (17)	1.68 ± 1.67	0.35 ± 0.67	-	-
HAMD (21)	1.86 ± 2.05	0.35 ± 0.67	-	-
YMRS	0.50 ± 1.01	0.50 ± 1.00		
Clinical characteristics				
Age at illness onset, years	25.18 ± 7.05	-	-	-
Post onset, months	221.22 ± 98.78	-	-	-

5.2.2 Neuropsychological measures

All participants completed an extensive neuropsychological task battery. Tasks included in the current study were selected to examine executive functioning, processing speed, verbal memory, and sustained attention. The sustained attention tasks are described in the current study, whilst the executive functioning, processing speed, and verbal memory tasks are described in the normal ageing study (Chapter 2).

In the CPT-AX (programmed by Robinson *et al.,* 2013), single, randomised letters are presented sequentially on a computer screen and participants respond to a target sequence. Letters are presented in white, on a black background. In this task, participants respond to target 'X', only when it was presented after an 'A' ('AX' target trial). This task uses a stimulus presentation time of 50 ms, and an ISI of 800 ms. In addition, participants respond to an increased number of target sequences. Over 200 trials of paired stimuli (split into four blocks of 50 paired trials), 140 target pairs (35 per block) are presented in six minutes, with no breaks between blocks or practice trials. In both tasks, participants were asked to respond quickly and accurately.

The CPT-AX is programmed in a similar way to other CPT variants included in the thesis. For instance, the high proportion of targets to non-targets is similar to the CCPT-II in the normal ageing study (90% target frequency). In addition, the length of task is similar to the CPT-IP (7 mins), RVIP (7 mins), and stimuli are presented quickly, similar to the CPT-IP (< 100 ms), in the normal ageing study. However, differences also exist between the tasks included in the current and previous studies. The high target frequency of the CPT-AX differs from the low target frequency of the CPT-IP, RVIP (both included in the normal ageing study), and DV task (PD study). The CPT-AX also has a lower working memory load compared to the RVIP (normal ageing study), as only one target sequence needs to be remembered.

In the Vigil CPT (Cegalis and Bowlin, 1991), single, randomised letters are presented sequentially on a computer screen for 85 ms, followed by a 900 ms ISI. Letters are presented in white, on a black background. Participants respond when they view target 'K', only when cued by an earlier 'A' stimulus ('AK' target sequence). Targets occur infrequently in this CPT. Over the course of 480 stimuli, 100 target sequences are presented in eight minutes. These targets were pseudo-randomised, so that 25 target sequences are presented in four blocks (no breaks given between blocks).

The Vigil CPT is programmed in a similar way to other CPT variants included in the thesis. For instance, the target frequency (low) is similar to that of the CPT-IP and RVIP (normal ageing study), and DV (PD study). In addition, the length of the task is similar to the CPT-IP (7 mins), RVIP (7 mins), and CPT-AX (8 mins), and stimuli are presented quickly, similar to the CPT-IP (< 100 ms). However, differences also exist between the tasks included in the current study and previous studies included in the thesis. The low target frequency of the Vigil differs from the high frequency of the CCPT-II (normal ageing study), and CPT-AX (current study) tasks. The Vigil also has a lower working memory load compared to the RVIP, as only one target sequence needs to be remembered.

5.2.3 Data pre-processing

Data removal followed the procedures of the normal ageing study. As the response window for the CPT-AX task could not be extended, the response window for Vigil was restricted to 850 ms. The restriction was applied to ensure that differences in RT/IIV were not simply due to task-related differences in the time participants had to respond before the next stimulus. A total of 4,054 responses were analysed, and the restriction of the response window removed eight responses (0.19% of total trials). The ex-Gaussian probability density function was calculated using the method outlined in the normal ageing study. The algorithm failed to fit the distribution to three HC participants, who were then removed from analyses involving the ex-Gaussian distribution (CPT-AX $n = 18$; Vigil CPT $n = 19$). Vincentile plots were also produced, following the procedure outlined in the PD study.

5.2.4 Statistical analysis

Statistical procedures followed the methods of the normal ageing study. Demographic and clinical characteristics between groups were investigated using an appropriate between-group comparison or correlation. Sex was not included in subsequent analyses because of the small and uneven sample size between the groups.

Behavioural outcome measures (ex-Gaussian distribution) were analysed using repeated measures ANOVA, with task (CPT-AX vs. Vigil) as the within-subjects variable and group (patient vs. HC) as the between-subjects variable.Hierarchical multiple regressions were conducted using the methods outlined in normal ageing study, as well as checking of assumptions (which were met in the current study). One outlier was removed from all models for ex-Gaussian tau obtained from the CPT-AX (n = 21) in patients only. Patients and HC were analysed separately, as well as per task (CPT-AX and Vigil).

Age, executive functioning, processing speed, and verbal memory were selected as predictors to maintain consistency between the different studies included in the thesis. Executive functioning and processing speed were assessed using the same tasks as included in the normal ageing chapter. The verbal memory composite included the following outcome measures: total score from A1-A5 (REY Total), and number of words recalled following the delay (A7). The Recognition A score from the REY was not included in the current study as this was not available. As such, delayed recognition memory does not form the verbal memory composite in this study. Z-scoring was not utilised in the current study, with a higher score on all neuropsychological measures indicating better performance. All hierarchical regression models were included in the current study are reported in the normal ageing study, with the exception of the regressions examining group.

5.3 Results

5.3.1 Task differences

Response times were slower for the Vigil CPT (ex-Gaussian mu for patients and HC: $M = 327.19$, $SE = 11.11$) compared to the CPT-AX (ex-Gaussian mu: $M = 219.61$, $SE = 7.24$). Examination of the Vincentile plots (Figure 5-1) indicated that participants performed the Vigil task more slowly across the whole distribution (from $V_1 - V_8$) compared to CPT-AX ($p < 0.050$). The ex-Gaussian sigma parameter was higher in the Vigil task ($M = 38.76$, $SE = 3.40$), compared to the CPT-AX ($M = 31.05$, $SE = 2.25$). Ex-Gaussian tau did not significantly differ between tasks.

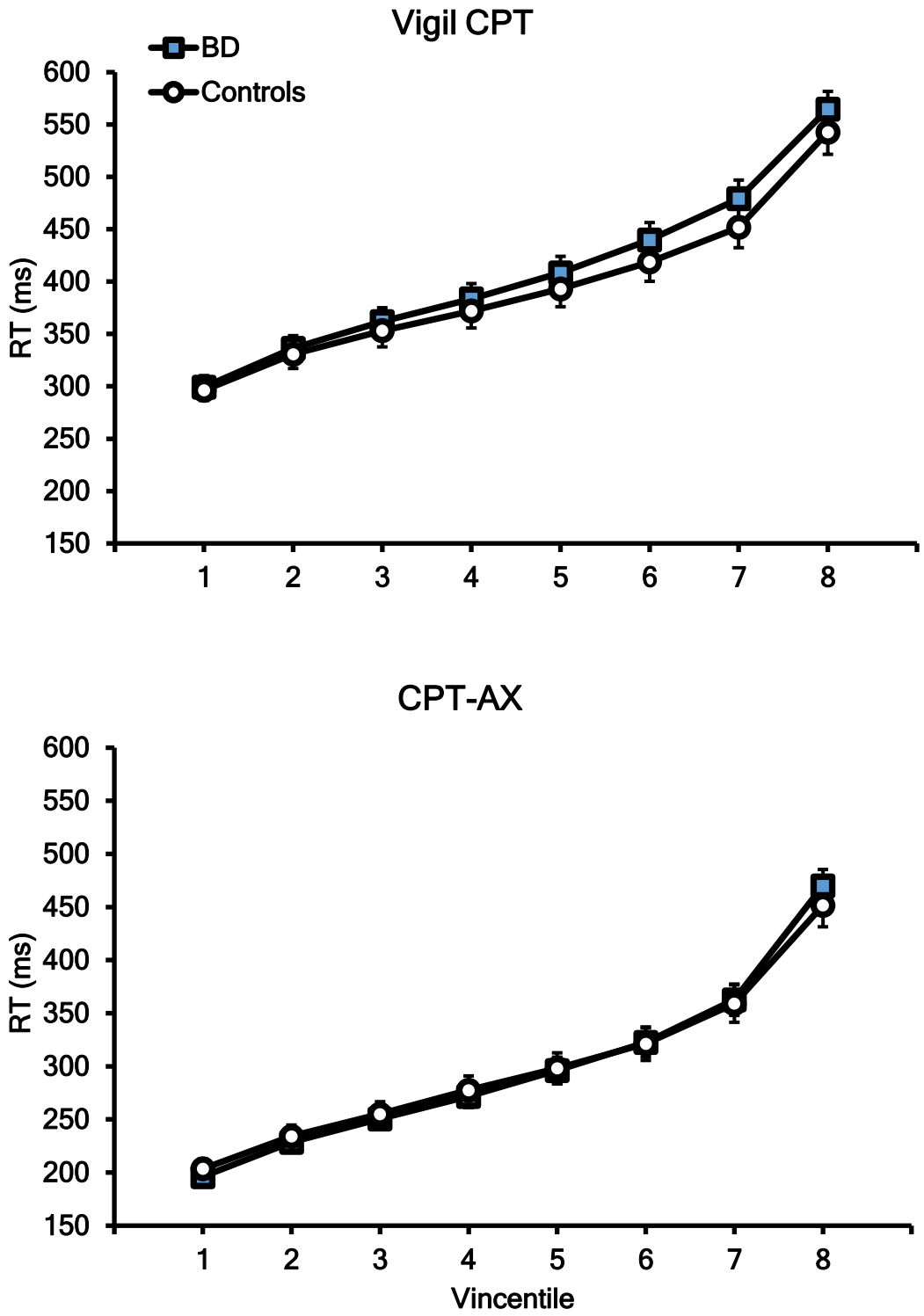

Figure 5-1. Vincentile plots (1-8) for patients with BD in remission (n = 22) and controls (n = 20) per task. Participants completed the Vigil CPT more slowly (mean RT), compared to the CPT-AX. Error bars represent Standard Error of the Mean (SEM).

5.3.2 Group differences

The between-subjects effect for group was significant for ex-Gaussian sigma (p < 0.001). Patients were more variable overall (ex-Gaussian sigma: M = 40.38, SE = 3.32), compared to HC (ex-Gaussian sigma: M = 29.43, SE = 3.78). No further between-subjects effects reached significance (see Table 5-2). A significant interaction was observed between task and diagnosis for ex-Gaussian sigma (p < 0.050; Table 5-2). The interaction was driven by differences in variability between the groups in the Vigil task ($t_{(37)}$ = -2.51, p < 0.050), but not the CPT-AX ($t_{(37)}$ = -1.052, p > 0.050). Here, patients in remission were more variable (M = 47.34, SE = 4.74) than HC (M = 30.18, SE = 4.73) (Figure 5-2).

Table 5-2. Main effects and interactions for each ex-Gaussian parameter from repeated measures ANOVA (patients n = 22, HC n = 17)

Effect	*F(df)*	*p*	*Partial* η^2
Main effect Task (mu)	198.14 $_{(1,37)}$	**0.00*** **	0.84
Main effect Task (sigma)	7.47 $_{(1,37)}$	**0.01** **	0.16
Main effect Task (tau)	2.45 $_{(1,37)}$	0.12	0.06
Main effect Diagnosis (mu)	1.225 $_{(1,37)}$	0.27	0.03
Main effect Diagnosis (sigma)	4.71 $_{(1,37)}$	**0.03***	0.11
Main effect Diagnosis (tau)	0.02 $_{(1,37)}$	0.88	0.00
Task x Diagnosis (mu)	3.67 $_{(1,37)}$	0.06	0.09
Task x Diagnosis (sigma)	4.83 $_{(1,37)}$	**0.03***	0.11
Task x Diagnosis (tau)	1.79 $_{(1,37)}$	0.18	0.04

Note. η^2 = eta-squared.

*p < 0.05 ** p < 0.01 *** p < 0.001. Significant results highlighted in **bold.**

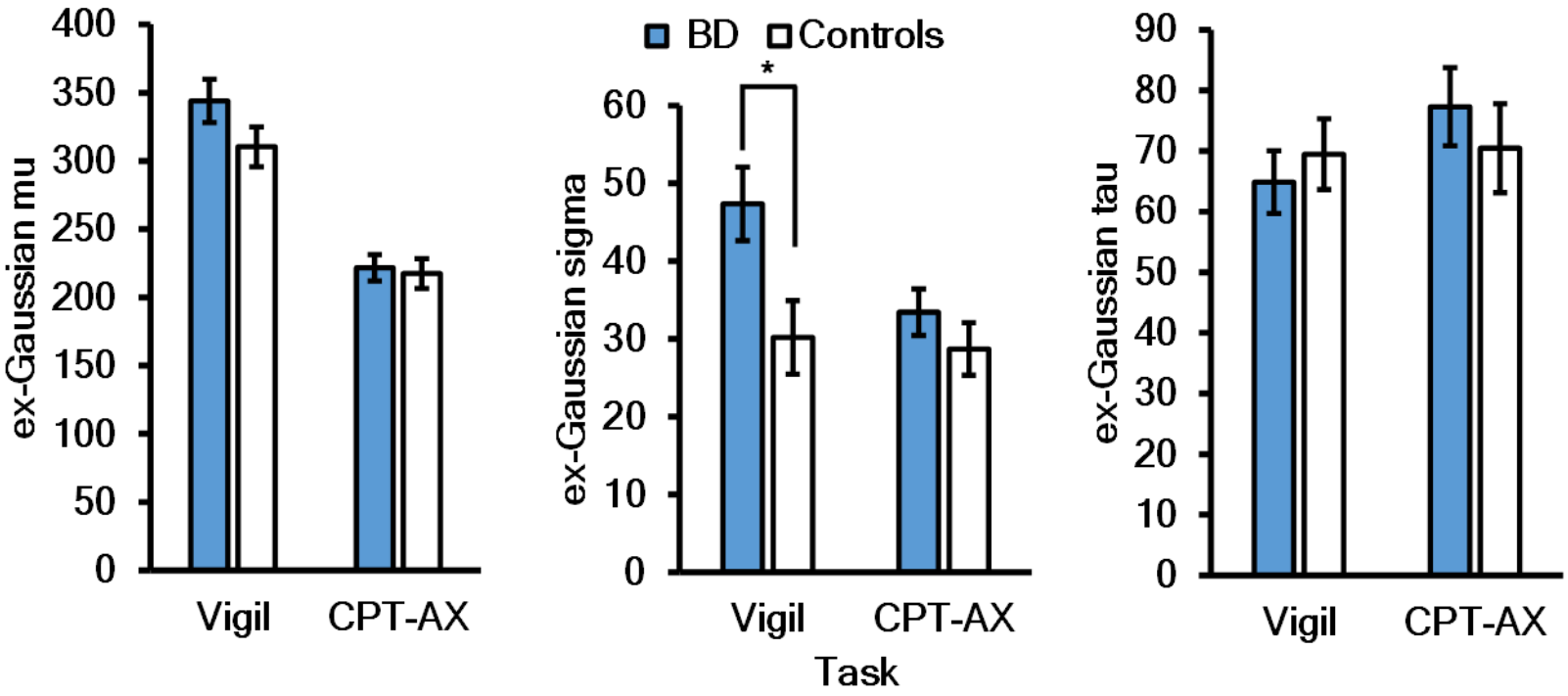

Figure 5-2. Ex-Gaussian parameters for patients with BD (in remission) and HC per task (Vigil and CPT-AX). Patients in remission were more variable than HC, as indicated by ex-Gaussian sigma (*$p < 0.050$), but only in the Vigil CPT. Error bars represent standard error of the mean (SEM).

With regard to cognitive impairment, patients and HC did not significantly differ in executive functioning ($U = 213.00$, $p = 0.852$), or verbal memory ($t_{(40)} = 0.434$, $p = 0.667$). However, patients significantly differed from HC in processing speed ($t_{(40)} = 2.45$, $p < 0.050$; patients: $M = 54.31$, $SD = 12.45$; HC: $M = 63.00$, $SD = 10.17$).

5.3.3 Relationship between age and ex-Gaussian parameters

Age was not significantly correlated with any ex-Gaussian parameter obtained from the CPT-AX or Vigil, in patients or HC (Table 9-8, Appendix C). In patients, age was significantly negatively correlated with one neuropsychological measure of interest – verbal memory (patients: $r_{s\,(22)} = -0.576$, $p < 0.010$; HC: $r_{s\,(20)} = -0.415$, $p = 0.069$), but did not correlate with executive functioning (patients: $r_{s\,(22)} = -0.343$, $p = 0.118$; HC: $r_{s\,(20)} = -0.170$, $p = 0.473$), or processing speed (patients: $r_{s\,(22)} = -0.328$, $p = 0.136$; HC: $r_{s\,(20)} = -0.048$, $p = 0.840$), in patients or HC.

The relationship between ex-Gaussian parameters and the other neuropsychological processes of interest (executive functioning, processing speed, and verbal memory) was also examined. In patients, tau obtained from the CPT-AX significantly negatively correlated with executive functioning (Table 9-10, Appendix C). No other correlation was significant for patients or HC in any ex-Gaussian parameter obtained from the CPT-AX, or Vigil CPT (Tables 9-9 to 9-10, Appendix C).

In order to examine the relationship between age and ex-Gaussian parameters (mu, sigma, and tau), whilst taking into account the multiple hypothesised cognitive demands of the CPT-AX and Vigil CPT, a series of hierarchical regressions were performed. Whilst there was a significant negative association between NART and ex-Gaussian tau (obtained from the CPT-AX) in patients ($r_{s\,(22)} = -0.489$, $p < 0.050$), NART was not included as a covariate in subsequent analyses, as a between-group difference was not observed in section 5.3.2.

In patients and HC, entry of processing speed, executive functioning, and/or verbal memory, independently (Models 1a-c), or in models examining order of entry (Models 2a-c), did not significantly predict variance in any ex-Gaussian parameter in any CPT. These results were replicated for the final entry of age into the models (Tables 9-11 to 9-16, Appendix C).

5.3.4 Relationship between group differences in ex-Gaussian parameters and cognitive impairment in other neuropsychological processes

Additional hierarchical regression models were examined, to determine whether the between-subjects differences in processing speed accounted for the group-related differences observed for ex-Gaussian sigma in the Vigil CPT. The hierarchical regression analysis indicated that group explained additional variance in ex-Gaussian sigma, after age and processing speed, which were non-significant entries, were accounted for in the model (ΔR^2 = 10%) (Table 5-3).

Table 5-3. Ex-Gaussian sigma hierarchical regression with group (BD vs. HC).

ex-Gaussian sigma (*n* = 41)					
Model		**R^2**	**ΔR^2**	**Sig. F Change**	**β**
1	Age	0.012	0.012	0.488	-0.111
	PS	0.034	0.021	0.364	-0.149
	Group: BD vs. HC	0.143	0.109	**$p < 0.050$**	0.354

Note. β = Standardised coefficients; PS = Processing Speed. Significance highlighted in bold and light blue.

5.3.5 Exploratory analysis between clinical characteristics and ex-Gaussian parameters

No significant correlations were observed between ex-Gaussian parameters mu, sigma, or tau, and any clinical characteristics ($HAMD_{21}$, YMRS, months post onset, and age of onset) in the CPT-AX or Vigil CPT (all $p > 0.050$; Table 9-17, Appendix C).

5.4 Discussion

The current study analysed RT and IIV obtained from two different sustained attention tasks (CPT-AX and Vigil CPT) in patients with BD (in remission) and HC. The sample overall (patients and HC) completed the low target frequency Vigil CPT more slowly than the high target frequency CPT-AX, as indicated by greater values of ex-Gaussian mu. In addition, variability was higher for the sample overall for ex-Gaussian sigma in the Vigil CPT, but not the CPT-AX, which was not secondary to group differences in processing speed. Variability as measured by ex-Gaussian tau between each task was similar for the sample overall. Between groups however, patients with BD in remission exhibited greater values of ex-Gaussian sigma compared to HC, but only in the Vigil CPT task. In addition, and in contrast to the previous studies of the thesis, hierarchical regression analyses indicated that the multiple neuropsychological processes theorised to be involved in CPT variants, as well as age, did not predict attentional RT or IIV obtained from the CPT-AX or Vigil tasks, in patients or HC.

5.4.1 Group differences

The variability in responding demonstrated by patients with BD in remission suggests irregular attentional engagement. However, this inconsistency is only observed under the task conditions of the Vigil CPT. Under Parasuraman's (1979) definition, both tasks included in the current study had high event rates (more than 60 stimuli presented per minute). Such tasks tend to be taxing, resulting in a sustained attention decrement (i.e. reduction in accuracy over time). The high event rate and low target frequency parameters of the Vigil CPT may have resulted in task conditions requiring more effortful processing. This level of processing would be required to maintain an adequate level of attentional task engagement in response to increased task demands (Mackworth 1948; Mackworth 1950).

Working memory load should also be considered. It should be noted that CPTs generally involve a modest contribution of working memory, namely goal maintenance (Robinson *et al.,* 2013, Thompson *et al.,* 2005). However, as both tasks required participants to maintain a target sequence of equal length ('AX' for the CPT-AX and 'AK' for the Vigil CPT), the contribution of working memory was similar between tasks. Whilst target percentage was the primary interest of the current study, other differences between the tasks, such as stimulus presentation and ISI may also have influenced results.

5.4.2 Relationship between other neuropsychological processes and attentional RT and IIV

The other neuropsychological processes examined (executive functioning, processing speed, and verbal memory) were not associated with attentional RT or IIV in patients or HC (in either CPT examined), which is in contrast to the results of the previous studies of the thesis. The STAC model (Park and Reuter-Lorenz, 2009) posits that compensatory processes are recruited in response to age-related deterioration of neural systems. As age was not associated with attentional RT and IIV in the current study, it is possible that secondary scaffolding mechanisms were not engaged. The current results may be due to the age-range of participants (combined with the small sample size of the study), as previous studies included in the thesis (normal ageing and PD), have utilised similar CPT variants, and have demonstrated an association between neuropsychological processes and attentional RT and IIV.

Alternatively, the current results may have been associated with the task demands of the Vigil CPT and CPT-AX. In Table 1-1 in Chapter 1, both tasks were hypothesised to have low levels of executive functioning load, medium for verbal memory, and high for processing speed, due to their programming characteristics. As such, it is possible that the tasks were not sufficiently difficult for engagement of other neuropsychological processes in attentional RT or IIV to be observed.

However, as these processes have been engaged in tasks with lower levels of task difficulty/load (e.g., the DV task), it is perhaps more likely that the current results were associated with the low sample size of the current study. Of note, it remains to be determined whether the results of previous studies included in the thesis reflects engagement of secondary cognitive scaffolds, or properties inherent to tasks (i.e. task demands). This will be explored in greater depth in section 8.2.1 of the General Discussion.

5.4.3 Relationship between age and attentional RT and IIV

Age was not significantly associated with ex-Gaussian mu, sigma, or tau in the Vigil CPT, or CPT-AX, in patients or HC. It is possible that this may have been due to the narrow age-range used in the current study. In the current study, patients were aged between 30 – 57 years (*M* = 43.13), and HC between 30-53 years (*M* = 43.55). Developmentally, IIV is purported to follow a U-shaped curve corresponding with an increase in age, with the nadir, or stability in responding in the fourth decade, and increasing IIV thereafter (Bielak *et al.*, 2014). As such, it is possible that a relationship between age and IIV could not be demonstrated in the current study due to the age-range of the sample. Previous studies included in the thesis have included larger age-ranges, and have demonstrated a relationship between age and ex-Gaussian parameters.

As a relationship between age and IIV was not demonstrated, the current study may not provide support for AA in the disorder (Rizzo *et al.*, 2014), if it is assumed that patients with BD should become more inconsistent in their responding as they age compared to HC. However, if the AA hypothesis is applied as a simple observation that a typical age-related marker is elevated in patients, compared to HC (i.e. IIV), then the current results may support an AA hypothesis. The inconsistency in interpretation may indicate that further refinement of the hypothesis is necessary.

It is possible that a correlation between age and IIV may be demonstrated using an older BD cohort. Indeed, IIV is likely to be higher in an older population, compared to younger age-ranges (Bielak *et al.,* 2014). The effects of AA in BD, if present, may be demonstrated in an older patient cohort. Alternatively, patients of a sufficiently wide age-range should be recruited prospectively.

5.4.4 Study limitations

Methodological considerations of the study should also be taken into account. In the data set analysed, increased ex-Gaussian tau in the Vigil CPT in patients was not observed. A sub-sample of patients with BD in remission (n = 22) and HC (n = 17) from the larger sample (n = 86 per group) in Gallagher *et al.* (2015) were included, who completed both the Vigil CPT and the CPT-AX. It is possible that the results of the current study were due to difference in the demographic and/or clinical characteristics between the samples (sample included in the current study and Gallagher *et al.,* 2015). However, this is unlikely, given similar reported characteristics between the two studies (age, IQ, depression severity), as well as lack of relationship between these characteristics and RT IIV parameters. As such, it is likely that the lack of comparison between the results of the current study, and those of Gallagher *et al.* (2015), may simply be due to the smaller sample size, as opposed to study characteristics. The small sample size of the current study can be considered a limitation.

It should be noted that a longer window for correct responses was included in the Gallagher *et al.* (2015) ex-Gaussian modelling of Vigil CPT responses. In addition to the full response window being used (985 ms), 'late' responses of up to 1970 ms were included under certain circumstances. This window was restricted in the current study to 850 ms, which may have resulted in a shift within the fitted ex-Gaussian distributional parameters. However, in the current sub-sample this only resulted in a very small number of responses that were excluded and thus is unlikely to have resulted in a large change in the group results.

In a supplementary analysis (Table 9-18, Appendix C), the possibility that use of a restricted response window removed data contributing to the positive tail of the distribution was investigated. Extension of the response window did not alter the results from analysis of the Vigil CPT, between patients and HC, as ex-Gaussian sigma remained the sole significant between-group difference.

5.4.5 Future research

Based upon the results of the current study, future research should clarify the role that other task parameters have upon RT distributions. Continuous Performance Task procedural variations such as event rate have been shown to impact on mean RTs (Parasurman, 1979; Parasuraman and Giambra, 1991; Ballard, 2001). Identifying the independent contributions of each task parameter (e.g., such as speed of stimulus presentation, working memory load etc.) would be worthwhile, as CPTs generally manipulate more than one parameter. For instance, the CPT variants included in the current study both used high event rates, yet varied on target frequency. Future work should clarify the conditions necessary for task-dependent variability in RT distributions.

5.4.6 Conclusions

To conclude, the current study has demonstrated that (1) Patients with BD (in remission) exhibit greater variability (ex-Gaussian sigma) than HC in the Vigil CPT, suggesting that IIV may have a degree of task specificity. These between-subjects results differ to Gallagher *et al.* (2015), which may be due to the smaller sample size included in the current chapter, as opposed to demographics and/or clinical characteristics (which were similar between the samples). (2) In line with the thesis aims, elevated IIV in BD is not secondary to impairment (associated with pathology) in other cognition domains (e.g., executive functioning, processing speed, and verbal memory), and does not share variance with these processes.

(3) In contrast to the previous results observed in this thesis, the current study does not provide support for an association between attentional RT and IIV, and the theorised multiple neuropsychological components of CPTs (Chapter 1, Table 1-1). However, this could be due to the types of tasks utilised (which is discussed in greater depth in Chapter 8, section 8.2.1 and 8.2.2).

To determine whether elevated IIV could be useful clinically, it is necessary to examine whether the current results indicate that IIV is a trait or state marker in BD. The study which follows (Chapter 6) analyses data obtained from the Vigil CPT in patients with BD, but during a depressive episode.

Chapter 6. IIV in BD (while depressed)

6.1 Introduction

In the study presented in this chapter, the thesis themes will be explored in a sample of patients with BD during a depressed episode, and HC. The study groups completed the Vigil CPT and the same neuropsychological tasks outlined in the previous BD study (Chapter 5).

The study aims to determine whether the results from the previous BD (in remission) study can be replicated in an acute mood state, as bipolar depression has been associated with greater severity of cognitive impairment, compared to remission (e.g., Kurtz and Gerraty, 2009). As the RT and IIV analysis of the patients and HC included in the current study is reported elsewhere (Gallagher *et al.,* 2015), predictions concerning group differences (ex-Gaussian parameters) are not made, as the Gallagher *et al.* (2015) noted elevated IIV (sigma and tau) in patients, compared to HC.

The current study also aims to provide evidence of whether an association between age (as well as group-related differences) and attentional RT and IIV (obtained from the Vigil CPT) represents an independent impairment, or reflects an impairment other cognitive domains (e.g., processing speed). Based on the results of the previous BD study(Chapter 5), it was hypothesised that age would not explain variance in attentional RT or IIV, in patients or HC. This result would be consistent with the lack of support for an AA hypothesis in BD presented in Chapter 5.

If an association between age (as well as group) and attentional RT and IIV reflects an independent impairment, then entry of other neuropsychological processes (e.g., executive functioning, processing speed, verbal memory) will not account for any age-related, or group-related associations.

However, given the results of the previous experimental chapters of this thesis, it must also be considered that attentional RT and IIV, as well as the other neuropsychological processes of interest, are not independent *per se*, but share variance. Alternatively, if the studies outlined in section 1.4 are taken into account, then an association between age (as well as group) and attentional RT and IIV, the latter a marker of sustained attention, will be explained by variance in the multiple neuropsychological measures of interest. Processing speed is a candidate here, given the studies outlined in section 1.4, and the high anticipated processing load of the Vigil CPT utilised the current study (Table 1-1). However, given the results of the PD and previous BD studies, it is not anticipated that other neuropsychological processes would account for any age-related or group-related associations with attentional RT or IIV.

6.2 Methods

6.2.1 Participants

The data presented here represents baseline data from a multicentre treatment trial (Watson *et al.*, 2012). Fifty-three patients aged between 22 and 63 years (M = 47.25, SD = 9.59), had a SCID confirmed DSM-IV (First, 1995) diagnosis of BD - current episode depressed. Psychiatrists conducted the clinical assessment of patients including clinical ratings, illness and medication history, and review of case notes. Depressive symptoms were assessed using the HAMD (Hamilton, 1960), Montgomery and Asberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979), and BDI (Beck *et al.,* 1996); manic symptoms using the YMRS (Young *et al.*, 1978); and functioning via the Global Assessment of Functioning scale (Hall, 1995). Patients were recruited from outpatient services in the Northumberland, Tyne, and Wear NHS Foundation Trust in the North East of England and from clinics linked to Otago University in Christchurch, New Zealand. Seven patients (13%) were classified as rapid cycling, 26 (53%) had a history of suicide attempts, and 12 (25%) had current suicide ideation.
All patients were stable on medication for a minimum of four weeks prior to study participation.

Forty-two patients (79%) were prescribed at least one mood stabiliser, 39 (74 %) prescribed at least one antidepressant, 24 (45%) at least one antipsychotic, 13 (25%) at least one sedative, and 16 (32%) were prescribed lithium. Medication status was not explored/included as a covariate in subsequent analyses due to the small and uneven sample size per medication sub-group. Eleven patients had received previous ECT. Patients: (i) did not have another current Axis I diagnosis (except anxiety); (ii) did not have a neurological or medical condition; (iii) did not have a history of substance or alcohol abuse/dependence over the past six months; (iv) were not prescribed corticosteroids or antihypertensive medication; (v) had not received ECT within the past year; (vi) had not been abusing substances, or dependence on alcohol/drugs over the past 12 months.

Forty-seven HC, between the ages of 18 and 64 years (M = 44.96, SD = 13.73) and without a personal (SCID confirmed) or family (first-degree) history of psychiatric illness were recruited through local advertisement. Controls and patients were matched for age (U = 1171.00, p = 0.615), sex ($\chi^2_{(1)}$ = 0.076, p = 0.783), years of education (U = 663.50, p = 0.687), and NART IQ, missing values replaced with the mean (Nelson, 1982) (U = 981.00, p = 0.066). All study protocols were approved by local research ethics at Northumberland Tyne and Wear NHS Foundation Trust. Written informed consent was obtained prior to study participation. See Table 6-1 for demographic and clinical characteristics of patients and HC.

Table 6-1. Demographic and clinical characteristics of patients with BD and HC.

	BD		HC	
Demographics	*n*	Mean ± SD	*n*	Mean ± SD
Sex (F:M)	53	20:33	47	19:28
Age	53	47.25 ± 9.59	47	44.96 ± 13.73
NART IQ	53	108.94 ± 10.53	47	112.48 ± 11.22
Years of education (total)	52	14.40 ± 3.17	27	14.44 ± 3.96
Clinical characteristics				
BDI	36	26.03 ± 11.39	23	0.96 ± 1.49
MADRS	52	27.60 ± 8.39	37	0.27 ± 0.69
YMRS	52	1.48 ± 1.82	27	0.11 ± 0.42
GAF	51	54.31 ± 9.79	24	89.88 ± 19.02
$HAMD_{(21)}$	53	22.40 ± 5.65	25	0.12 ± 0.33
Age of onset (years)	49	27.38 ± 13.09	-	-
Length of current episode (weeks)	50	61.48 ± 82.71	-	-
Time on current medication (weeks)	48	25.63 ± 40.76	-	-

6.2.2 Neuropsychological measures

Tasks were selected to measure executive functioning, processing speed, verbal memory, using the same outcome indices as described in the normal ageing study (Chapter 2). Sustained attention was assessed using the Vigil CPT (Cegalis and Bowlin, 1991), which is described in the BD (in remission) study in Chapter 5. The RT data obtained using the Vigil CPT partially overlaps with Gallagher *et al.* (2015), where data was analysed from 33 patients with BD (while depressed) and 23 HC. In the current study, an additional 10 patients (total $n = 43$) and nine HC (total $n = 32$) have been included which were previously not available.

6.2.3 Data pre-processing and statistical analysis

Data were analysed according to methods outlined in the normal ageing study. No patients or HC were removed from analyses of the ex-Gaussian distributional parameters. Group differences in IIV were investigated using a Mann-Whitney U (non-parametric) or an independent t-test (parametric). Correlations were conducted to examine the relationship between RT and IIV (ex-Gaussian parameters), and clinical characteristics (symptom severity ratings (HAMD, MADRS, YMRS, BDI), functional assessment rating (GAF), as well as age of onset (years), length of current episode (weeks), and time on medication (weeks)).

Hierarchical multiple regressions, and inclusion of dependent variables are described in the normal ageing study and the previous BD study (Chapter 5), in addition to the inclusion of Recognition A for the verbal memory composite in the current study. The hierarchical regression assumptions were also met. In patients, one outlier was removed (final $n = 42$) from the hierarchical regressions involving ex-Gaussian mu for the following models: age as a single predictor of mu, Model 1a, 1b, and 2a. In HC, one outlier was removed (final $n = 31$) from the hierarchical regressions involving ex-Gaussian tau for the following models: age as a single predictor of tau, Model 1a, 1c, and 2b. No further outliers were removed from any other analyses in patients or HC.

6.3 Results

6.3.1 Group differences

The tau parameter was higher in patients with BD during a depressive episode, compared to HC (Patients: $M = 115.37$; $SD = 58.50$; Controls: $M = 68.18$, $SD = 39.05$), indicating a lengthening in the positive tail of the distribution. No other ex-Gaussian parameter significantly differed between the groups (Table 6-2).

Table 6-2. Ex-Gaussian parameters in patients with BD (while depressed, $n = 43$) and HC ($n = 32$).

	BD	**HC**	
Parameter	Mean ± SD	Mean ± SD	*t/U*
ex-Gaussian mu	290.81 ± 79.95	312.62 ± 108.86	669.00
ex-Gaussian sigma	40.49 ± 31.03	37.70 ± 25.50	674.00
ex-Gaussian tau	115.37 ± 58.50	68.18 ± 39.05	**318.00*** **

*** $p < 0.001$

With regard to cognitive impairment, patients performed more poorly than HC in the verbal memory composite ($t_{(98)} = -4.235$, $p < 0.001$; Patients: $M = 19.77$, $SD = 4.45$, HC: $M = 23.55$, $SD = 4.44$), and measure of processing speed ($t_{(98)} = -3.638$, $p < 0.001$; Patients: $M = 47.97$, $SD = 11.76$, HC: $M = 56.41$, $SD = 11.34$). However, patients and HC did not significantly differ in executive functioning ($U = 980.00$, $p = 0.06$).

6.3.2 Relationship between age and ex-Gaussian parameters

Age, NART IQ and years of education did not significantly correlate with any ex-Gaussian parameter in patients or HC (Table 9-19, Appendix D). However, age was significantly negatively correlated with the other neuropsychological processes of interest. In patients, the processing speed and the verbal memory composites significantly negatively correlated with age (processing speed: $r_{s\,(53)} = -0.370$, $p < 0.010$; verbal memory: $r_{s\,(53)} = -0.311$, $p < 0.05$), but not executive functioning ($r_{s\,(53)} = -0.006$, $p = 0.969$). In HC, the verbal memory composite significantly negatively correlated with age ($r_{s\,(47)} = -0.332$, $p < 0.050$), but not processing speed or executive functioning (processing speed: $r_{s\,(47)} = -0.154$, $p = 0.300$; executive functioning: $r_{s\,(47)} = -0.039$, $p = 0.794$).

The relationship between ex-Gaussian parameters and the other neuropsychological processes of interest (executive functioning, processing speed, and verbal memory) was also examined. In patients, ex-Gaussian mu significantly positively correlated with executive functioning. In HC, ex-Gaussian sigma significantly positively correlated with verbal memory. No other ex-Gaussian index significantly correlated with the cognitive composites in patients or HC (Table 6-3).

Table 6-3. Spearman correlations between ex-Gaussian parameters and other neuropsychological processes in patients with BD (while depressed) and HC.

Parameters	BD			HC		
	PS	EF	VM	PS	EF	VM
ex-Gaussian mu	0.125	**0.337***	0.193	- 0.015	0.047	0.115
ex-Gaussian sigma	0.187	0.271	0.117	- 0.139	- 0.209	**0.376***
ex-Gaussian tau	- 0.186	- 0.217	- 0.024	0.044	- 0.023	- 0.233

Note. PS = Processing speed, EF = Executive Functioning, VM = Verbal Memory.
*$p < 0.050$

In order to examine the relationship between age and ex-Gaussian parameters (mu, sigma, and tau), whilst taking into account the multiple theorised cognitive demands of the Vigil CPT, a series of hierarchical regressions were performed.

EX-GAUSSIAN MU: In all models and for patients only, entry of executive functioning, but not processing speed or the verbal memory composite, significantly predicted variance in mu (all $\Delta R^2 > 10\%$). In all models, the final entry of age was non-significant in patients (all $\Delta R^2 < 2\%$) and HC (all $\Delta R^2 < 3\%$) (Table 6-4).

EX-GAUSSIAN SIGMA: For both study groups, entry of processing speed, executive functioning, or the verbal memory composite, independently, or in models examining order of entry, did not significantly explain variance in sigma. In all models, the final entry of age was non-significant in patients (all $\Delta R^2 < 1\%$) and HC (all $\Delta R^2 < 4\%$) (Table 9-20, Appendix D).

EX-GAUSSIAN TAU: In all models, entry of processing speed, but not executive functioning, or the verbal memory composite, significantly predicted variance in tau in patients (all $\Delta R^2 > 9.6\%$), but not HC. In all models, the final entry of age was non-significant in patients (all $\Delta R^2 < 6.7\%$) and HC (all $\Delta R^2 < 3\%$) (Table 6-5).

Table 6-4. Hierarchical regression analysis with ex-Gaussian mu in patients with BD (while depressed) and HC.

ex-Gaussian mu		BDD				HC			
Model		R^2	ΔR^2	Sig. F Change	β	R^2	ΔR^2	Sig. F change	β
	Age	0.015	0.015	0.433	-0.124	0.001	0.001	0.861	0.032
1a	EF	0.112	0.112	**< 0.050**	0.335	0.003	0.003	0.751	0.058
	Age	0.122	0.009	0.526	-0.096	0.004	0.001	0.884	0.027
1b	PS	0.003	0.003	0.753	-0.050	0.000	0.000	0.949	0.012
	Age	0.023	0.021	0.367	-0.151	0.001	0.001	0.861	0.033
1c	VM	0.013	0.013	0.475	0.113	0.040	0.040	0.270	0.201
	Age	0.022	0.009	0.544	-0.101	0.065	0.024	0.392	0.181
2a	EF	0.112	0.112	**< 0.050**	0.335	0.003	0.003	0.751	0.058
	PS	0.120	0.008	0.563	-0.088	0.003	0.000	0.989	-0.003
	Age	0.136	0.016	0.411	-0.131	0.004	0.001	0.886	0.027
	PS	0.003	0.003	0.753	-0.050	0.000	0.000	0.949	0.012
	EF	0.120	0.118	**< 0.050**	0.345	0.003	0.003	0.760	0.059
	Age	0.136	0.016	0.411	-0.131	0.004	0.001	0.886	0.027
2b	EF	0.102	0.102	**< 0.050**	0.320	0.003	0.003	0.751	0.058
	VM	0.145	0.043	0.163	0.208	0.041	0.038	0.293	0.197
	Age	0.146	0.000	0.892	0.021	0.065	0.023	0.410	0.181
	VM	0.046	0.046	0.169	0.214	0.040	0.040	0.270	0.201
	EF	0.145	0.100	**< 0.050**	0.316	0.041	0.001	0.865	0.032
	Age	0.146	0.000	0.892	0.021	0.065	0.023	0.410	0.181
2c	PS	0.003	0.003	0.717	0.057	0.000	0.000	0.949	0.012
	VM	0.046	0.042	0.190	0.216	0.049	0.049	0.233	0.249
	Age	0.046	0.000	0.971	-0.006	0.083	0.034	0.317	0.221
	VM	0.046	0.046	0.169	0.214	0.040	0.040	0.270	0.201
	PS	0.046	0.000	0.957	-0.009	0.049	0.008	0.617	-0.103
	Age	0.046	0.000	0.971	-0.006	0.083	0.034	0.317	0.221

Note. β = Standardised coefficients; EF = Executive Functioning; PS = Processing Speed; VM = Verbal Memory. Significance highlighted in bold and light blue.

Table 6-5. Hierarchical regression analysis with ex-Gaussian tau in patients with BD (while depressed) and HC.

ex-Gaussian tau		BDD				HC			
Model		R^2	ΔR^2	Sig. F Change	β	R^2	ΔR^2	Sig. F change	β
	Age	0.023	0.023	0.327	-0.153	0.002	0.002	0.809	0.045
1a	EF	0.065	0.065	0.099	-0.255	0.013	0.013	0.537	-0.115
	Age	0.095	0.030	0.255	-0.174	0.016	0.003	0.776	0.054
1b	PS	0.114	0.114	**< 0.050**	-0.338	0.016	0.016	0.495	0.125
	Age	0.175	0.061	0.092	-0.256	0.034	0.019	0.459	0.137
1c	VM	0.003	0.003	0.744	-0.051	0.039	0.039	0.288	-0.197
	Age	0.032	0.029	0.280	-0.175	0.043	0.004	0.745	-0.070
2a	EF	0.065	0.065	0.099	-0.255	0.001	0.001	0.841	- 0.037
	PS	0.161	0.096	**< 0.050**	-0.312	0.021	0.019	0.458	0.143
	Age	0.228	0.067	0.074	-0.268	0.041	0.021	0.440	0.146
	PS	0.114	0.114	**< 0.050**	-0.338	0.016	0.016	0.495	0.125
	EF	0.161	0.047	0.143	-0.218	0.021	0.005	0.707	-0.072
	Age	0.228	0.067	0.074	-0.268	0.041	0.021	0.440	0.146
2b	EF	0.065	0.065	0.099	-0.255	0.013	0.013	0.537	- 0.115
	VM	0.067	0.002	0.762	-0.047	0.046	0.033	0.333	- 0.184
	Age	0.103	0.036	0.217	-0.196	0.048	0.002	0.806	- 0.054
	VM	0.003	0.003	0.744	-0.051	0.039	0.039	0.288	- 0.197
	EF	0.067	0.065	0.104	-0.254	0.046	0.007	0.644	- 0.087
	Age	0.103	0.036	0.217	-0.196	0.048	0.002	0.806	- 0.054
2c	PS	0.114	0.114	**< 0.050**	-0.338	0.016	0.016	0.495	0.125
	VM	0.117	0.003	0.719	0.057	0.132	0.116	0.058	- 0.384
	Age	0.175	0.059	0.104	-0.254	0.135	0.004	0.735	- 0.072
	VM	0.003	0.003	0.744	-0.051	0.060	0.060	0.177	- 0.245
	PS	0.117	0.114	**< 0.050**	-0.355	0.132	0.072	0.132	0.303
	Age	0.175	0.059	0.104	-0.254	0.135	0.004	0.735	- 0.072

Note. β = Standardised coefficients; EF = Executive Functioning; PS = Processing Speed; VM = Verbal Memory. Significance highlighted in bold and light blue.

6.3.3 Relationship between group differences in ex-Gaussian parameters and cognitive impairment in other neuropsychological processes

Additional hierarchical regression models were examined, to determine whether the between-subjects differences in processing speed accounted for the group-related differences observed for ex-Gaussian tau.

EX-GAUSSIAN TAU: Whilst age and processing speed were significant predictors of variance in tau, group explained additional variance, after age and processing speed were accounted for in the model (ΔR^2 = 2%) (Table 6-6).

Table 6-6. Ex-Gaussian tau hierarchical regression with group (BD vs. HC).

ex-Gaussian tau (*n* = 75)					
Model		**R^2**	**ΔR^2**	**Sig. F Change**	**β**
1	Age	0.001	0.001	0.762	0.035
	PS	0.122	0.121	***p* < 0.010**	- 0.355
	Group: BD vs. HC	0.211	0.089	***p* < 0.010**	- 0.334

Note. β = Standardised coefficients; EF = Executive Functioning; PS = Processing Speed; VM = Verbal Memory. Significance highlighted in bold and light blue.

6.3.4 Exploratory analysis between clinical characteristics and ex-Gaussian parameters

In patients, age of onset significantly negatively correlated with ex-Gaussian ex-Gaussian tau ($r_{s\,(40)}$ = - 0.317, p < 0.050). No other relationship between IIV and clinical characteristics was observed (Table 9-21, Appendix D).

6.3.5 Exploratory analysis between ex-Gaussian parameters obtained from the Vigil CPT in HC

A further analysis was conducted to determine whether the RT distributions of the HC included in both BD studies were similar, as the studies utilised the Vigil CPT. The control samples did not differ in terms of ex-Gaussian parameters with all data included (Mu: $U = 245.00$, $p = 0.260$; Sigma: $U = 252.00$, $p = 0.322$; Tau: $U = 302.00$, $p = 0.979$), or when the age-range of participants from the current study was restricted to match the age-range of participants from the previous bipolar study in this thesis (Mu: $U = 149.00$, $p = 0.370$; Sigma; $U = 178.00$, $p = 0.954$; Tau: $U = 166.00$, $p = 0.691$). In addition, age was not associated with any ex-Gaussian parameter when the age-range of controls from the current study was restricted (Mu: $r_{s\,(19)} = 0.027$, $p = 0.912$; Sigma: $r_{s\,(19)} = -0.135$, $p = 0.585$; Tau: $r_{s\,(19)} = 0.258$, $p = 0.287$).

6.4 Discussion

The current study confirmed that IIV is elevated in patients with BD while depressed, as assessed by ex-Gaussian tau, in a larger sample from that reported in Gallagher *et al.* (2015). In addition, the relationship between other neuropsychological processes and attentional RT and IIV was explored. Results indicated that better executive functioning predicted slower overall RT (mu), and better processing speed with reduced inconsistency in responding (tau), in patients only. Moreover, that other neuropsychological processes (e.g., processing speed) did not account for the between-group differences observed in ex-Gaussian tau, despite sharing variance. In addition, age was not associated with attentional RT or IIV in patients or HC.

6.4.1 Group differences

The current study indicates that patients with BD (while depressed) are more inconsistent in their responding than HC, in the positive tail of the RT distribution (tau). This result partially agrees with Gallagher *et al.* (2015), who also noted increased inconsistency in sigma, as well as tau, in a sample of 33 patients with BD (while depressed) and 23 HC. The RT data obtained from the Vigil CPT in the current study partially overlaps with Gallagher *et al.* (2015), and included an additional 10 patients (total $n = 43$) and nine controls (total $n = 32$), whose data was not previously available. The results of the current study may differ to Gallagher *et al.* (2015) due to differences in the demographic, clinical characteristics and/or IIV indices between the samples in the studies. However, demographic and clinical characteristics between the current study and Gallagher *et al.* (2015) were similar (age, NART, HAMD, and age of onset), as well as between the HC (age and NART). Ex-Gaussian parameters were also examined, and were similar between the studies, although IIV (sigma) was reduced in the sub-sample for both patients and HC, compared to the overall sample and that included in Gallagher *et al.* (2015) (Table 9-22, Appendix D). As such, the results of the current study may reflect the instability of ex-Gaussian sigma as a metric of IIV in BD, and/or the possibility of type I error in the original Gallagher *et al.* (2015) study.

6.4.2 Relationship between other neuropsychological processes and attentional RT and IIV

The positive association between better executive functioning and slowed responding (mu) is surprising, and disagrees with Salthouse (1991), who argued that age-related reductions in processing speed (which may be reflected by mu) are linked to reductions in working memory. Whilst the results may reflect the effortful processing of patients in completing the Vigil CPT, patients and HC did not differ in terms of mu or executive functioning.

Therefore, alternative accounts exist. It is possible that the results reflect an ineffective secondary compensatory scaffold (see STAC model; Park and Reuter-Lorenz, 2009), which may be a state phenomenon in BD, as the same results were not observed for HC in the current study, nor in BD patients in remission in Chapter 5. Park and Reuter-Lorenz (2009) argue that pathology, such as seen in AD, may limit the ability to effective scaffold cognitive operations, eventually leading to the collapse of this otherwise beneficial process. This may apply to BD. Alternatively, whilst anticipated to be of a low loading, the current result may reflect the executive component of the Vigil CPT (see Table 1-1). However, it is also possible that given the small sample size of the current study, the association between executive functioning and mu in patients may be due to type I error.

The current results also demonstrated an association between processing speed and ex-Gaussian tau (in patients only). Researchers have previously suggested that ex-Gaussian tau may reflect information processing capacity, with this interpretation described in ADHD (Tamm *et al.,* 2012), and schizophrenia (Kieffaber *et al.,* 2006; Rentrop *et al.,* 2010; Karantinos *et al.,* 2014). Applied to the current study, processing speed was indexed via the DSST, a measure of information processing/processing speed (Wechsler, 1998). As such, an information processing capacity account could be applied to BD. Alternatively, the association between processing speed and attentional IIV could reflect compensatory secondary scaffolding mechanisms (Park and Reuter-Lorenz, 2009), typically associated with older age, but engaged by BD patients at an earlier age.

Another interpretation of the current results concerns task demands. In Table 1-1 (Chapter 1), the Vigil CPT was hypothesised to have low levels of executive functioning load, medium for verbal memory, and high for processing speed, due to its programming characteristics.

It is possible that the association between processing speed and ex-Gaussian tau in patients with BD reflects the high processing speed component of the CPT utilised, rather than engagement of a cognitive scaffold *per se*. However, this result was not replicated in the control sample, nor in the control sample of the previous BD study described in this thesis, which suggests that the engagement of processing speed in attentional IIV may reflect scaffolding specific to pathology. The notion of whether the results of the thesis reflects engagement of secondary cognitive scaffolding, or reflects properties inherent to the particular CPT utilised (therefore, task demands), is explored in great depth in section 8.2.1 in the General Discussion.

Interestingly, processing speed did not account for the group-related differences in ex-Gaussian tau, which suggests that elevated attentional IIV in BD could be a trait marker of the illness, in agreement with the results of Chapter 5. The clinical implications of this are discussed in section 8.2.1 of Chapter 8 (General Discussion).

6.4.3 Relationship between age and attentional RT and IIV

Age was not significantly associated with ex-Gaussian mu, sigma, or tau in the Vigil CPT, in patients or HC, which corroborates the results of the previous BD study included in this thesis. As highlighted by the exploratory analysis involving the HC from both BD studies, the RT distributions between the samples did not differ. It is likely that the results from the current study are a consequence of the restrictive age-range utilised. In the previous BD study presented in this thesis, 22 BD patients (in remission) between the ages of 30-57 (M = 43.13), and 20 HC between the ages of 30-53 (M = 43.55) were included. In the current study, 47 patients between the ages of 22 and 63 (M = 47.85), and 39 HC between the ages of 19-64 (M = 44.92) were included. In analyses that exhibited age-related associations with ex-Gaussian parameters, a wider-age range was utilised, as well as larger sample sizes.

In the normal ageing study, 81 individuals, between the ages of 21 – 90 years (*M* = 53.90) were included, with 147 patients with PD, between the ages of 41 – 87 (*M* = 66.38), and 190 HC between the ages of 48- 89 (*M* = 69.97) included in PD study. When comparing across analyses, observing age-related associations with ex-Gaussian parameters may be more likely in samples that utilise a wider-age range than included in the bipolar studies. In agreement with the previous BD study presented in this thesis, the current study does not provide support for the AA hypothesis in BD (Rizzo *et al.,* 2014), if it is assumed that patients with BD should become more inconsistent in their responding as they age compared to HC.

6.4.4 Study limitations and future research

Methodological limitations of the current study should be considered. For instance, the study is limited in the investigation of the relationship between age and ex-Gaussian parameters, due to the restricted age range utilised (similar to the previous BD study reported in the thesis). In future, researchers interested in studying age-related effects in BD should consider recruiting patients from an older age-range (Depp and Jeste, 2004). The effects of AA (Rizzo *et al.*, 2014), if at all present, may be demonstrated in an older patient cohort, in combination with a larger age-range.

6.4.5 Conclusions

In conclusion, the results suggest the following: (1) The RT distributions of patients with BD (while depressed) were more variable than HC, with variability characterised by infrequent and slow RTs (ex-Gaussian tau). The between-subjects results differ to Gallagher *et al.* (2015), which may be due to the instability of IIV (ex-Gaussian sigma) as a metric of IIV in BD, and/or the possibility of type I error within Gallagher *et al.* (2015), as demographic, clinical, and IIV parameters, aside from ex-Gaussian sigma, were similar between the samples.

(2) In line with the thesis aims, the results support the involvement of other neuropsychological processes such as executive functioning and processing speed in attentional RT and IIV (these processes share variance), which may reflect engagement of cognitive scaffolding, or the intrinsic properties of the CPT examined. (3) In addition, these neuropsychological processes did not account for group-related differences in ex-Gaussian tau.

Thesis results thus far suggest that impairment in other neuropsychological processes associated with CPTs do not account for group-related differences in attentional RT or IIV, but may do so for age-related variance in attentional RT and IIV. However, using the current methodology, it is not possible to determine whether these processes mediate the relationship between age and IIV. As such, an appropriate methodology to investigate this is mediation analysis, which is utilised in the next Chapter (7).

Chapter 7. Attentional IIV: A mediation analysis

7.1 Introduction

The results of the thesis suggest that the multiple neuropsychological processes theorised to be involved in CPTs may account for age-related, but not group-related, associations with attentional RT and IIV. The involvement of other neuropsychological processes in attentional RT and IIV may reflect cognitive scaffolding, or the intrinsic properties of the CPTs examined. Within the thesis, the involvement of other neuropsychological processes in attentional RT and IIV is apparent in samples with larger sample sizes, and wide age-ranges, suggesting that the association may be age-dependent, and reflect age-related deterioration in attentional RT and IIV. If the association between other neuropsychological processes and attentional RT and IIV is age-related, it is unclear whether the relationship between age and attentional RT and IIV simply reflects age and is a direct association or reflects age-related changes in the multiple cognitive processes supporting attentional RT and IIV (see Chapter 1, section 1.4). Determining this relationship may have implications for the development of behavioural strategies (in ageing, as well as pathology), which could promote efficient scaffolding, and faster/more consistent responding (Park and Reuter-Lorenz, 2009). As hierarchical regression modelling, utilised in the thesis does not enable variables of interest and the relationship between them to be examined in a single model, mediation analysis will be utilised in the current study.

Mediation analysis is a regression-based analysis that enables researchers to determine how an independent variable (*x*) exerts its effects on a dependent variable (*y*), where there is one or more proposed mediating variables (*m*) between *x* and *y*. As such, mediation analyses suggests that variations in *x*, cause variations in *m*, which then cause variations in *y*. In contrast to hierarchical regression, mediation modelling tests two paths of influence between the *x* and *y*; Direct (*x* to *y*), or Indirect (*x* to *y*, through m) (Hayes, 2013).

Researchers have frequently utilised a causal steps approach to mediation, popularised by Baron and Kenny (1986). In a causal steps approach, the null hypothesis must be rejected in order to progress to the next step; (1) the causal and outcome variables are correlated (path *c*); (2) The causal variable is correlated with the mediator (path *a*); (3) The mediator is correlated with the outcome, after controlling for the causal variable (path *b*); (4) The relationship between the causal and outcome variable is zero, after controlling for the mediator (path *c'*) (Figure 7-1). In addition, results are discussed in terms of full, and partial mediation.

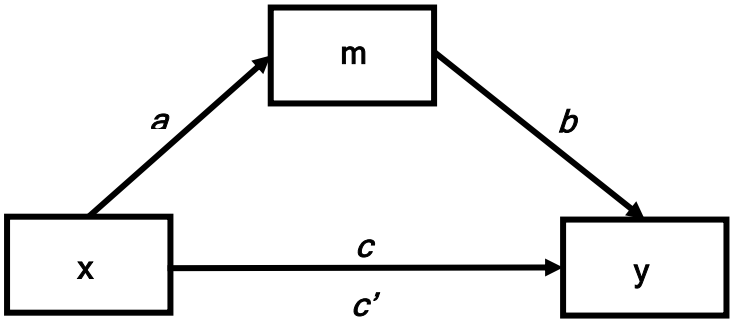

Figure 7-1. Simple mediation model example. The independent variable, or causal variable is represented by X, the dependent, or outcome variable is represented by Y, and the mediator variable is represented by M.

However, Hayes (2013) argues that the causal steps approach is flawed and has several caveats; (1) Mediation is inferred; (2) Claiming mediation is dependent on the rejection of three null hypotheses increases the potential for error; (3) There are circumstances in which the causal and outcome variables are not related, and it is still possible that *x* exerts an effect on *y*, indirectly via *m*; (4) The terms 'indirect' and 'mediation' are considered in qualitative terms, rather than quantitative. Due to these caveats, a causal approach to mediation analysis will not be utilised in the current study, and will instead, follow recommendations from Hayes (2013).

In the current study, mediation analysis will be completed for data from the normal ageing and PD studies. Data from the normal ageing and PD studies was selected because the CPTs in both studies were similar in design (e.g., digit modality, low target frequency, fast presentation).The outcome variable (*y*) of focus will be ex-Gaussian tau, due to its potential clinical significance/utility as identified in previous literature and the results of the thesis. The analysis will focus on executive functioning and processing speed, as they may be 'core' processes that underlie cognitive impairment in other domains (e.g., age-related deterioration in attentional RT and/or IIV). The aims of the current exploratory analysis was to examine whether the multiple cognitive processes (*m*) theorised to be involved versions of the CPT mediates the relationship between age (*x*) and ex-Gaussian tau (*y*).

7.2 Methods

Participants from the normal ageing and PD studies were selected for the current analysis. Participants included in the current analysis completed either the RVIP or DV paradigms. From the normal ageing study, the measures of executive functioning and processing speed were selected. From the PD study, the measure of executive functioning was selected. Processing speed was not examined in patients with PD and PD controls due to the limitations of its measurement. In the PD study, processing speed was assessed using mean RT from the SRT, rather than the DSST (which was not available in the study). Results obtained from the SRT are confounded by the motor symptoms of PD. As such, it is not an adequate measure of processing speed in this study population, and has not been included in the analysis of the current chapter. Please see individual studies for detailed Methods descriptions.

7.2.1 Mediation analyses

Mediation analysis utilised the PROCESS macro in SPSS (Hayes, 2013). A simple mediation model (Model 4) was examined to determine whether the relationship between age (*x*) and ex-Gaussian tau (*y*) was mediated by executive functioning or processing speed (*m*). The approaches described were adopted as the analysis of the current chapter is exploratory, with no *a priori* hypothesis regarding the nature of mediation.

The indirect effect (product of paths *a***b*) was tested in a single model using bias-corrected, 95% Confidence Intervals (CI) based on 10,000 bootstrap samples to increase power, as recommended by Hayes (2013). The indirect effect was considered significant if the CI value ranges did not include zero, consistent with Hayes (2013). For each model, the completely standardized effect (ab_{cs}) was selected as the measure of effect size, as recommended by MacKinnon (2008). Data has previously been checked for assumptions and processed for hierarchical regression analyses.

7.3 Results

7.3.1 Normal ageing: The relationship between age and ex-Gaussian tau

There was a significant indirect effect of age on tau obtained from the RVIP, which was fully mediated via executive functioning (ab_{cs} = 0.09, a*b (95% CI) = 0.01 to 0.86), as the direct effect between age and tau was no longer significant (Figure 7-2). Processing speed did not significantly mediate the effect of age on tau (ab_{cs} = 0.09, a*b (95% CI) = - 0.32 to 0.98) (Figure 9-1, Appendix E).

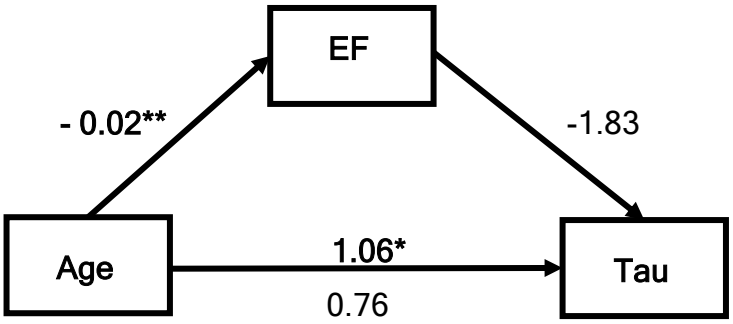

Figure 7-2. Mediation model for the impact of executive functioning (EF) on the relationship between age and tau in participants who completed the RVIP (n = 52). *p < 0.050, **p < 0.010.

7.3.2 PD: The relationship between age and ex-Gaussian tau

For patients with PD, there was a significant indirect effect of age on tau obtained from the DV, partially mediated via executive functioning (ab_{cs} =0.06, a*b (95% CI) = 0.01to0.35), as the direct effect of age on tau was still significant (Figure 7-3).

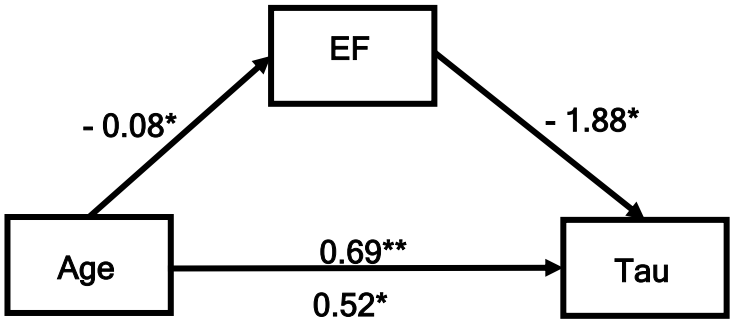

Figure 7-3. Mediation model for the impact of executive functioning (EF) on the relationship between age and ex-Gaussian tau in patients with PD (n =125). *p < 0.050, **p < 0.010.

For controls, there was a significant indirect effect of age on tau obtained from the DV in PD controls, partially mediated via executive functioning (ab_{cs} = - 0.03, a*b (95% CI) = -0.27 to 0.00), as the direct effect between age and tau was still significant (Figure 7-4).

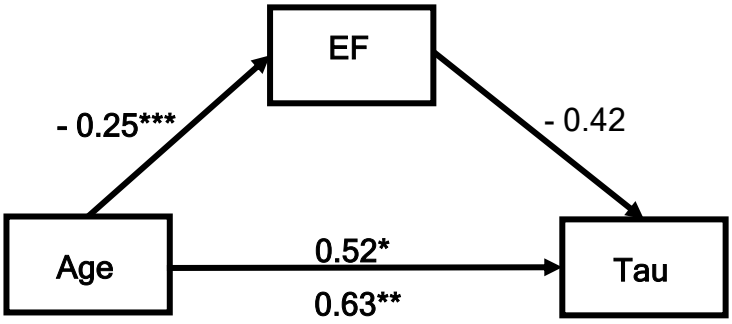

Figure 7-4. Mediation model for the impact of executive functioning (EF) on the relationship between age and ex-Gaussian tau in PD controls (n = 179). *p < 0.050, **p < 0.010, ***p < 0.001.

7.4 Discussion

The current study examined whether the other neuropsychological processes, theorised to be involved in CPTs, mediated the relationship between age and ex-Gaussian tau. For participants completing the RVIP, executive functioning fully mediated the relationship between age and tau. Similar results were obtained in patients with PD and HC completing the DV, and with a different measure of executive functioning. However, the relationship between age and ex-Gaussian tau was also direct in PD.

7.4.1 The relationship between age and ex-Gaussian tau

In the RVIP, age-related variance in tau was not due to age *per se*. In contrast, age-related deterioration in executive control processes (despite different tasks included in each analysis) fully mediated the relationship between age and ex-Gaussian tau. These results fit with the interpretation that ex-Gaussian tau may be sensitive to the deterioration of general executive control processes, which have been highlighted in normal ageing (e.g., Jackson *et al.,* 2012), as well as in clinical disorders such as mild dementia of the Alzheimer's type (Jackson *et al.,* 2012; Tse *et al.,* 2010), in ADHD (Sergeant, 2005), and in schizophrenia (Kieffaber *et al.,* 2006; Rentrop *et al.,* 2010; Karantinos *et al.,* 2014).

In the PD analysis, the relationship between age and ex-Gaussian tau also remained direct. The discrepancy between the normal ageing and PD mediation analyses could be due to the different tasks used, and consequently, task demands. In the PD study, ex-Gaussian tau was obtained from the DV, a task with lower working memory demands compared to the RVIP, with one target digit to be remembered by participants, combined with a shorter task duration (four minutes vs. seven minutes in the RVIP). Therefore, executive functioning may not completely mediate this relationship between of low task demands. Alternatively, the results obtained from the PD sample (patients and HC) may be due to the elevated study numbers included in the sample (Patients with PD n = 119; HC = 172), compared to the normal ageing study (n = 52).

7.4.2 Study limitations and future research

The current analysis is limited by only examining a simplistic mediation model, with one mediating variable. Hayes (2013) also specified mediation models whereby more than one mediator may influence the relationship between the causal and outcome variables. In the thesis, executive functioning, processing speed, and verbal memory were examined across studies where data would allow.

For example, in the hierarchical regression models examining ex-Gaussian tau in the normal ageing study (Chapter 2), Model 2a indicates that executive functioning significantly accounts for variance in ex-Gaussian tau obtained from the RVIP, irrespective of model order, whereas processing speed only loads onto the RVIP when presented before executive functioning. Given the hierarchical nature of the other neuropsychological processes examined in the thesis (Chapter 1, section 1.4), and the data obtained, future analyses should incorporate multiple cognitive mediators in future models to examine this hierarchy.

The current chapter is further limited by the low sample sizes included in the analyses, combined with low effect sizes in all significant mediation models, which is at risk of type I and type II error. Fritz and MacKinnon (2007) conducted a simulation study with different conditions (utilising different a and b path values), designed to offer sample size guidelines to achieve adequate power (0.8) in the most common and recommended tests of mediation. The authors highlighted that in the bias-corrected bootstrapping mediation method, the type utilised in the current chapter, was consistently the most powerful test in their analyses. Fritz and Mackinnon (2007) recommended that when a and b path values are small (e.g., 0.14), the minimum sample size required to achieve a power value of 0.8 is 462. However, this recommended minimum sample size decreases, depending on the values of the a and b path. For instance, this minimum sample size decreases to 34 when the path values are large (e.g., 0.59). Taking the bias-corrected bootstrapping results of Fritz and MacKinnon (2007) into account, it is highly likely that the current study was underpowered, given that a minimum sample size of over 300 per contrast would be required to achieve adequate power for the analyses (0.8, although not a guarantee), based on the achieved a and b path values in the current study. As such, the results of the exploratory current study should be interpreted with caution, given the small sample size and low effect sizes of significant mediation models.

In addition, utilising mediation analysis does not indicate when, or how the circumstances in which a variable, such as a mediator, influences the relationship between the causal and the outcome variable. As such, interpretation of mediation can be limited. It is possible that a neuropsychological process, such as executive functioning, may *moderate* the relationship between age and ex-Gaussian tau, or that ex-Gaussian tau as a potential marker of white matter integrity (see Chapter 1), may moderate the relationship between age and the neuropsychological processes of interest. The effect of a causal variable (*x*) on an outcome variable (*y*) can be said to be moderated if the relationship between *x* and *y* varies according to the size, sign, or strength of the moderator variable, or can be predicted by it (Hayes, 2013).

The thesis has highlighted that RT distributions (e.g., ex-Gaussian tau) differ between patients and HC (patients with PD, and in BD during a depressive episode). Moreover, that cognitive impairment differs in these populations, compared to HC. As such, these could be sources of variances, which could be explored in future research via moderation analysis.

7.4.3 Conclusions

In summary, the current study demonstrated (1) executive functioning fully mediated the relationship between age and ex-Gaussian tau in normal ageing, and (2) executive functioning only partly mediated the relationship between age and ex-Gaussian tau in PD. These results suggest that age-related increases in attentional IIV are not secondary to deterioration in other cognitive domains in PD. However, in normal ageing, age-related increases in attentional IIV could be secondary to age-related decreases in executive control (as assessed by the RVIP). However, these results need to be interpreted with caution, due to the low power for the contrasts. The wider implications of the results presented in this chapter, and results presented in the thesis thus far, are discussed in greater depth in the General Discussion (Chapter 8).

Chapter 8. General Discussion

The following chapter will provide a summary of the results (section 8.1) obtained from the studies included in the thesis, as well as a discussion of their implications (sections 8.2 and 8.3), strengths and limitations (section 8.4), and recommendations for future research (section 8.5). The chapter will end with a conclusion of the current body of work (section 8.6).

8.1 Summary of results

This section summarises the results of each study included in the thesis. The interpretations and implications of these results are explored in greater depth in section 8.2.

In the normal ageing study (Chapter 2), participants completed three versions of CPT with differing task parameters – the CCPT-II, CPT-IP, and RVIP. In addition, participants completed other neuropsychological measures, which included executive functioning (working memory), processing speed, and verbal memory. The results indicated that neuropsychological measures were associated with attentional RT and IIV across the tasks – in that better performance was associated with faster RT (mu), and/or reduced inconsistency in responding (sigma and/or tau). In terms of the effect of age on attentional RT and IIV, age predicted slower speed of responding (mu) across all CPTs examined, despite mu sharing variance with the other neuropsychological measures examined. However, age effects on IIV differed per CPT. Age was associated with increased variability across the entire distribution in the CCPT-II, and CPT-IP (sigma), and in the positive tail for the RVIP (tau). The results indicated that the association between age and sigma was not accounted for by other neuropsychological measures (despite sharing variance) for the CCPT-II, but the association may have been secondary to processing resources such as processing speed and executive functioning for the CPT-IP, and similarly for the RVIP and ex-Gaussian tau.

In Chapter 3, patients with PD and HC completed the DV task – a task similar to the RVIP included in Chapter 2, but with lower working memory requirements. Participants completed additional neuropsychological measures, but this study focussed on an executive functioning composite, which comprised of accuracy scores from the OTS and FAS. Patients completed the DV more slowly (ex-Gaussian mu), and were more variable (ex-Gaussian sigma and tau) than HC, which was not secondary to a between-groups difference in executive functioning and processing speed, despite IIV sharing variance with these other neuropsychological processes. Moreover, better executive functioning in patients with PD was associated with lowered inconsistency in responding in the positive tail of the distribution (tau), but not in HC. Similar to that observed in the normal ageing study for the RVIP, age was associated with slower RTs (mu), and increased inconsistency in the positive tail of the distribution (tau), in patients and HC.

In Chapter 5, patients with BD (remission) and HC completed two sustained attention tasks which differed in target frequency – a low target frequency task (Vigil CPT), and high (CPT-AX), in addition to similar neuropsychological measures included in Chapter 2. Patients were more variable than HC (sigma), but only in the Vigil CPT, which was not accounted for by a between-groups difference in processing speed. The other neuropsychological processes examined did not predict variance in attentional RT or IIV, in either task, in patients or HC. In contrast to Chapters 2 and 3, age did not predict variance in attentional RT or IIV, in patients or HC.

In Chapter 6, patients with BD (while depressed) and HC, completed the low target frequency Vigil CPT, and the same neuropsychological measures reported in Chapter 5. Patients were more variable than HC (tau), which was not secondary to a between-groups difference in processing speed, despite IIV and processing speed sharing variance. Moreover, in patients, better processing speed was associated with reduced inconsistency in the positive tail of the distribution (tau), but better executive functioning was associated with slower RTs (mu). Similar to Chapter 5, age did not predict variance in attentional RT or IIV, in patients or HC.

The final study of the thesis, presented in Chapter 7, utilised mediation analysis to determine whether other neuropsychological processes (theorised to be involved in versions of CPT) mediated the relationship between age and ex-Gaussian tau. In normal ageing, executive functioning fully mediated the relationship between age and ex-Gaussian tau. The relationship in PD was partially mediated. These results indicate that age-related variance in tau, obtained from the RVIP in normal ageing, and the DV in PD, may in part reflect age-related deterioration in executive control. However, a direct relationship between age and ex-Gaussian tau remained for patients with PD who completed the DV, which may reflect the sample size and/or lowered task difficulty compared to the RVIP utilised in normal ageing.

8.2 Interpretation and implications of results

8.2.1 Relationship between other neuropsychological processes and attentional RT and IIV

Two key interpretations of the results reported in the thesis will be explored in this section. It is possible that the involvement of other neuropsychological processes in attentional RT and IIV represents: (1) Cognitive scaffolding, or (2) Intrinsic task properties of the CPT examined.

In the thesis studies where other neuropsychological processes predicted attentional RT and IIV, the direction of the relationship indicated that better performance on these measures 'supported' faster (mu), and more consistent (sigma and tau) responding. Given that these associations were mostly noted in studies (normal ageing and PD, but not the BD studies) where age was associated with slower responding (mu) and /or increased inconsistency (sigma and/or tau), it seems reasonable to suggest that the association is linked to the age of participants. In which case, the results may reflect the engagement of secondary cognitive scaffolds to support task performance, in response to age-related deterioration of attentional RT or IIV (Park and Reuter-Lorenz, 2009).

In their STAC theory, Park and Reuter-Lorenz (2009) posit that in response to the neural challenges associated with increasing age (e.g., reductions in white matter integrity, dopamine transmission etc.), adaptive compensatory strategies are developed at a structural (increased prefrontal activation/recruitment of additional neural circuitry) and functional level which can preserve, or 'scaffold' some cognitive abilities. The other neuropsychological processes examined in the thesis, which principally engage the frontal lobes, could be amenable to cognitive scaffolding, as their involvement in scaffolding has been reported within the literature (Cabeza *et al.*, 2002).

In addition to evidence of age-related cognitive scaffolding, evidence for pathology-related cognitive scaffolding was provided in the PD and BD (while depressed) studies. In the PD study, the results indicated that better executive functioning was associated with reduced inconsistency in responding (ex-Gaussian tau), whilst this relationship was not observed in HC. Similarly, in patients with BD (while depressed), better processing speed was associated with reduce inconsistency in responding (ex-Gaussian tau), and again, this relationship was not observed in HC. For both studies, the engagement of these cognitive processes did not account for the age-related associations with IIV and/or the between-group differences.These relationships provide further support for a secondary compensatory scaffolding account of the current results.

The results also indicated that the involvement of other neuropsychological processes in attentional RT and IIV varied according to CPT, which may indicate that recruitment of secondary compensatory scaffolding varied in response to task difficulty, or in response to challenge. The idea that recruitment of compensatory scaffolds could vary according to task difficulty is predicted by the CRUNCH model (Reuter-Lorenz and Cappell, 2008). The CRUNCH model hypothesises that inefficient processing causes an ageing brain to recruit more resources to achieve equivalent performance to that of a younger individual.

The compensatory activation is effective when the task demands are low (specific categorisation of task demands seems to be researcher led, rather than explicitly identified in the model). However, when task demands increase, a ceiling is reached, and processing becomes inefficient, and age-related decrements in performance are the result (such as attentional RT or IIV, if applied in the context of the thesis).

It must be noted that the thesis is not able to determine whether the relationship between other neuropsychological processes and attentional RT and IIV represents engagement of compensatory cognitive scaffolding associated with age. In order to do so, data between a younger and older cohort could be compared in a cross-sectional study. In agreement with the STAC model (Park and Reuter-Lorenz, 2009), secondary compensatory cognitive scaffolding should be observed in the older, compared to younger cohort, consistent with the notion that scaffolding is engaged in response to age-related neural challenges. The study could also be replicated in clinical disorders, to investigate how compensatory scaffolding may occur in response to cognitive impairment associated with pathology.

If the role of scaffolding in sustained attention can be established, then it is possible that behavioural strategies which may promote efficient scaffolding could be developed (Park and Reuter-Lorenz, 2009), and applied in clinical disorders where cognitive impairment is a core feature.

Alternatively, it is possible that the results of the thesis may reflect the intrinsic task properties of the CPTs examined, rather than compensatory scaffolding *per se*. Central to this thesis and outlined in Table 1-1, it was theorised that due to variations in versions of the CPT and their task parameters, the associated cognitive load may differ (or task complexity), with varying demands on attentional, executive, and memory systems (Riccio *et al.*, 2003). For instance, in the normal ageing study, processing speed, as assessed via the DSST, was associated with ex-Gaussian mu, irrespective of CPT.

As mentioned previously, this could reflect the high processing load inherent to most CPTs examined in the thesis (Table 1-1), which may be associated with their task parameters (linked to a high event presentation, defined as more than 60 stimuli per minute; Parasuraman, 1979). This result is also supported clinically in the PD study, with an association between processing speed and ex-Gaussian mu in the DV observed in both patients and HC.

The question here is whether engagement of processing speed, or indeed, other neuropsychological processes of interest, across the CPTs examined reflects engagement of compensatory scaffolding, or is simply a by-product of processing the load across the tasks. As mentioned previously, further research which analyses data by comparing groups (e.g., younger vs. older) may be able to answer the questions posed here.

8.2.2 Relationship between age and attentional RT and IIV

The results of the thesis indicated that the effect of age on attentional RT and IIV, as measured by the ex-Gaussian distribution, differs across different versions of CPT. In the normal ageing and PD studies, the association between age and speed of responding (ex-Gaussian mu) may reflect the high event rates (more than 40 events or stimuli presented per minute; Parasuraman and Giambra, 1991) of the CPT variants examined. These results may also reflect the developmental deterioration of processing speed with age (Brockmole and Logie, 2013), although it is worth noting that processing speed did not account for age-related variation in ex-Gaussian mu in any study. Under the definition proposed by Parasuraman and Giambra (1991), the CPT-AX task utilised in Chapter 5 and the Vigil CPT utilised in Chapters 5 and 6, also have high event rates, but an association between age and speed of responding was not observed in these studies.

With regard to attentional IIV, the association with age was inconsistent across the studies included in the thesis. Age predicted greater inconsistency in responding (sigma) in the CPT-IP and CCPT-II (normal ageing study), as well as in inconsistency characterised by infrequent and long responses (tau) in the RVIP (normal ageing study), and DV (PD study). The pattern of age-related associations with attentional IIV (sigma and tau), could be linked with the type of task RTs were obtained from.

The CPT-IP and CCPT-II are the only tasks in the thesis which include three individual conditions – two, three, and four digit presentations for the CPT-IP, and one, two, and four second ISI presentations for the CCPT-II. These conditions were collapsed, and an average score used to represent mu, sigma, and tau for these particular tasks. The alteration in task demands and/or cumulative task demands may lead to inconsistency in responding across the entire distribution with an increase in age, rather than infrequent inconsistency in responding, indexed by ex-Gaussian tau. It is worth noting that age-related associations with ex-Gaussian sigma, may depend on type of task. For instance, the association between age and sigma in the CPT-IP was accounted for when processing speed and executive functioning were included in the hierarchical regression models. The result may reflect unique CPT-IP parameters, compared to the other CPTs included in the thesis. These parameters include an increased working memory load (with two, three and four digit conditions collapsed to produce averaged values for ex-Gaussian distributional parameters), combined with the random, and quick (50 ms stimulus presentation and one second ISI), presentation of targets.

With regard to attentional IIV indexed by ex-Gaussian tau, it is possible that age effects can only be demonstrated in tasks similar to the RVIP and DV – tasks with fast sequential presentation of digits, without an ISI. However, existing research does not provide supporting evidence for this, with McAuley *et al.* (2006), Tse *et al.* (2010), and Jackson *et al.* (2012), all demonstrating associations between age and ex-Gaussian tau, utilising a number of attentional/executive control tasks, in non-pathological populations. It is also worth noting that other neuropsychological processes such as executive functioning, processing speed, and verbal memory may have accounted for the age-related association with ex-Gaussian tau in the RVIP. Despite this, the results may place doubt on whether age is the best predictor of attentional RT and IIV (sigma and tau) obtained from variants of the CPT.

Taken together, the lack of association between age and attentional IIV may indicate that IIV is more sensitive to clinical pathology and/or neuronal integrity, rather than the general brain changes reflecting by individual age, which as a marker, lacks specificity (Rabbitt *et al.,* 2007). The underlying neurobiology of attentional RT and IIV, as assessed by the ex-Gaussian distribution, is discussed in greater depth in section 8.5.2. Clinically, ex-Gaussian tau may be sensitive marker of clinical pathology – perhaps a behavioural representation of the *p factor*, or general psychopathology factor proposed by Caspi *et al.* (2014). Under this theory, increasing severity of underlying psychopathology (vulnerability) linked to worse outcomes on indicators such as disorder duration and brain functioning. Caveats of the studies included in the thesis must also be discussed, and these limit the overall interpretation and implications of the current results. Firstly, the age-ranges of samples included in several studies may be obscuring the relationship between age and attentional RT and IIV. This argument is best reflected in the BD studies included in the thesis. It is unlikely that the lack of age-related associations with ex-Gaussian parameters was due to use of the Vigil CPT/CPT-AX, as alternative CPTs with similar parameters were used in other studies included in the thesis and age-related effects noted.

Whilst the samples included in Chapters 5 and 6 involved age-ranges between 18-60 years, the mean age for patients and HC in both studies was in the fourth decade. Developmentally, IIV (as measured by ISD) is characterised by a U-shaped curve, with reduced inconsistency associated with increased age throughout childhood and adolescence (6-17 years), and increased inconsistency with age throughout adulthood (18-81 years) (Williams *et al.*, 2005). If BD follows the developmental progression associated with 'normal' cognitive ageing rather than 'accelerated', then the lack of association between age and attentional RT and IIV is to be expected. As such, the results do not support the AA hypothesis (Rizzo *et al.,* 2014), if it is assumed that patients with BD should become more inconsistent in their responding as they age compared to HC.

The findings are consistent with Cardoso *et al.* (2015) and Schouws *et al.* (2016), who reported a lack of association between age-related cognitive decline and progression of BD. However, caution is warranted here as the data is cross-sectional and could be obscuring the longitudinal course of age-related deterioration in attentional RT and IIV in BD. This thesis recommends that researchers interested in exploring the relationship between age and RT and IIV in BD should utilise samples with wider age-ranges, and recruit prospectively, rather than investigating the effects of age retrospectively.

In addition to limited age-ranges, utilising cross-sectional data limits the exploration of age and attentional RT and IIV, as studies of this kind are unable to index the continuous, long-term development and deterioration of IIV. Moreover, low sample sizes in the studies (particularly in the BD studies) may also have contributed to the current results, leading to type II error.

8.2.3 Relationship between group and attentional RT and IIV

The results of the thesis also indicate that elevated attentional RT and IIV in PD and BD is not accounted for (i.e. secondary) by deterioration in more general cognitive domains (e.g., processing speed), despite sharing variance. These results are in contrast to evidence from studies with non-pathological populations (adults) and clinical studies with LLD and BD indicating that cognitive impairment in broad domains may be secondary to a 'core' impairment in processing speed (Nebes *et al.*, 2000; Butters *et al.*, 2004; Kieseppa *et al.*, 2005; Sheline *et al.*, 2006; Antila *et al.*, 2011; Dybedal *et al.*, 2013).Although one study in MDD (Nilsson *et al.*, 2016) did report that broad cognitive impairment was secondary to an impairment in attention. It is worth noting however, that Nilsson *et al.* (2016) did not include attentional measures of RT and IIV, as this thesis has.

Taken together, these results may highlight that elevated IIV in a number of clinical disorders could represent a general psychiatric vulnerability (*p* factor) (Caspi *et al.*, 2014), or trans-diagnostic phenotype (Gottesman and Gould, 2003; Nolen-Hoeksema and Watkins, 2011), and could be a biomarker per clinical disorder. In terms of further research, it is imperative that the underlying neurobiology of elevated IIV is explored, and to determine what this represents. This is explored in greater detail in sections 8.5.1 and 8.5.2.

However, there are caveats to the results that should be discussed. The neuropsychological task battery in the PD study was limited in its scope, and the study included an inadequate measure of processing speed that was confounded with the motor symptoms of the disorder (see section 3.4.4). The current result would need to be replicated using an extensive neuropsychological task battery, similar to that employed in BD studies (e.g., Thompson *et al.*, 2006, 2009).

With reference to the BD studies, patients had preserved cognitive functioning, aside from processing speed, which is in contrast to previous reports of cognitive impairment in the disorder (Robinson *et al.*, 2006; Kurtz and Gerraty, 2009). It is possible that the results do not reflect patients with BD whom experience severe cognitive impairment. The results would need to be replicated in this population. Despite the limitations described, the current results remain promising, and warrant further detailed investigation.

8.3 Thesis strengths and limitations

Strengths (8.3.1), and limitations (8.3.2, 8.3.3, and 8.3.4) of the work presented in the thesis will now be discussed. Limitations that apply to all studies included in the thesis will be discussed in the section below.

8.3.1 Strengths of the thesis

Analysis of RT distributions in all thesis studies was examined using ex-Gaussian modelling. Utilising ex-Gaussian modelling can be considered a strength of the thesis, given the limitations of existing RT and IIV measures, and the additional information obtained about an individual's/clinical group's responding. In addition, the novel application of the ex-Gaussian distribution to RTs obtained from the CPT-AX, CPT-IP and RVIP in the normal ageing study, and the DV in the PD study.

The latter of which places PD amongst other neurodegenerative and psychiatric disorders characterised by elevations in ex-Gaussian tau, which may represent a general psychiatric vulnerability (*p* factor) (Caspi *et al.*, 2014), or trans-diagnostic phenotype (Gottesman and Gould, 2003; Nolen-Hoeksema and Watkins, 2011). Of further support, this body of work has demonstrated that elevated IIV, of biological and clinical utility, is not secondary to cognitive impairment in other cognitive domains, despite sharing variance, in PD and BD. Therefore, these results emphasise the need for investigating its potential as a biomarker per clinical disorder.

8.3.2 Application and reliability of the ex-Gaussian distribution

There are methodological limitations of utilising the ex-Gaussian distribution that should be considered. For instance, the ex-Gaussian distribution lacks a solid theoretical underpinning to its parameters (it is simply a mathematical convolution of a normal 'Gaussian' distribution and exponential tail). As such, researchers have emphasised that it should be considered descriptive (Schmiedek *et al.*, 2007), and use of this model in isolation cannot account for the cognitive factors that drive behavioural performance (Luce, 1986; Healthcote *et al.*, 1991). As such, the thesis is limited by its focus on the ex-Gaussian distributional parameters.

It is unclear at present, what the relationship between the ex-Gaussian parameters, and 'traditional' measures of sustained attention is (e.g., hit rate, commission/omission errors), the latter of which are typically used to define sustained attention impairments in normal ageing and clinical populations. This lack of clarity may also be contributing to the assertion that the ex-Gaussian distribution should be considered as simply a descriptive tool, as it is not clear what the ex-Gaussian represents cognitively. Without empirical evidence of the association between attentional RT and IIV, as measured by the ex-Gaussian distribution, and traditional measures of sustained attention impairment, the parameters should not be used in isolation in clinical studies. Utilising the ex-Gaussian may prove to be more informative, if in future, it was examined alongside traditional markers of sustained attention to obtain a 'global' view of an individual's responding. Examination of outcome measures in parallel may serve to elevate the ex-Gaussian from a descriptive tool of RT distributions, to a model for explaining cognitive phenomena.

The stability and reliability of IIV, and the ex-Gaussian distribution is also a limitation. The ex-Gaussian distribution can be applied to RT distributions with as few as 40 RTs (McAuley *et al.,* 2006). However, Lacouture and Cousineau (2008) recommend 100 RTs and above, to reduce the likelihood of biases, and improve stability. All data included in the studies of the thesis included a minimum of 40 RTs per individual, where possible. However, it remains a possibility that biases and reduced stability of fit may be present within the data. As such, the results presented in this thesis would need to be replicated.

This thesis recommends that further studies wishing to utilise the ex-Gaussian distribution in their RT data should seek to increase the number of RTs analysed per participant. Increasing the number of RTs obtained per individual would increase the likelihood of stable and reliable data. In order to do so, task parameters need to be taken into account, preferably *a priori*. To gain further RT data, stimuli could be presented more quickly, a higher target frequency could be utilised, and/or participants complete the task over a longer period of time. However, the theoretical implications of altering task parameters needs to be taken into account.

A further challenge to IIV and the ex-Gaussian distribution is whether obtained parameters (e.g., mu, sigma, and tau) are temporally stable. The cross-sectional data presented in this thesis is unable to provide supporting evidence for the temporal stability of attentional RT and IIV, as measured by the ex-Gaussian distribution. Despite measuring performance inconsistency, IIV is reported to remain consistent within an individual (Bielak and Anstey, 2015).

For instance, Hultsch *et al.* (2000) noted that inconsistency in RT measured by ISD and CoV in older adults remained stable across four different testing sessions (between two – nine days apart), and in four different cognitive tasks. The results of Hultsch *et al.* (2000) are also supported by Hultsch *et al.* (2002), who noted that individuals who were inconsistent across different cognitive tasks, were also inconsistent over time, demonstrating stability in their inconsistency (Hultsch *et al.*, 2002). Stability in inconsistent responding is consistent with the idea that IIV reflects underlying, endogenous (i.e. neurobiological) mechanisms, rather than exogenous sources, such as fatigue and/or stress (Hultsch *et al.,* 2002).

However, data concerning the stability of the parameters obtained from the ex-Gaussian distribution are not available at present. It remains to be seen whether IIV obtained from these indices represent stable, enduring symptoms and potential biomarkers of distinct clinical disorders, or simply represent transitory endogenous changes. To circumvent the challenges described above, future studies should examine the temporal stability of the ex-Gaussian distribution. It is possible that diurnal effects may influence attentional IIV, given that attention may vary according to time of day (Valdez *et al.*, 2008), but this may depend on paradigm utilised (Valdez *et al.*, 2005; Schmidt *et al.*, 2007). Future work investigating the temporal stability of the ex-Gaussian distribution should take possible diurnal effects into account, with multiple testing sessions throughout the day. Weekly, as well as monthly assessment of IIV would be useful.

Ideally, ex-Gaussian analysis would be incorporated into existing longitudinal studies, to examine its long-term course, and potential as a biomarker, given the limitations of incorporating the parameters in cross-sectional studies. Indeed, analysis of the ex-Gaussian distribution in the long-term may be incorporated into the ICICLE-PD study (Yarnall *et al.*, 2014) - a sub-set of data was presented in Chapter 3.

Finally, consideration needs to be given as to the appropriateness of applying the ex-Gaussian distribution to RT data – is RT data best fitted to this function? As mentioned in Chapter 1, models tend to describe RT distributions using exponential tails (van Zandt *et al.,* 2000), with the ex-Gaussian distribution applied in the thesis due to its relevance to the aims. Moreover, researchers have argued that the ex-Gaussian distribution is a good fit to the RT data generally (e.g., Heathcote *et al.,* 1991).

It is possible that the application of the ex-Gaussian distribution was not an appropriate model for data sets included in the thesis. For example, in the PD study, all ex-Gaussian parameters were elevated in patients with PD, compared to HC. However, significance of all parameters has limited interpretive value. The raw RTs in this patient population were excessively slow (some due to a recording error), and outliers needed to be removed in order to fit the data to the ex-Gaussian distribution in the study. As such, it is possible that the exponential tail of RTs for patients with PD were longer than could be characterised accurately using the ex-Gaussian distribution, and therefore another model may have been more appropriate for this data. Alternative models argued to fit RT data accurately include the Diffusion, Gamma, Shifted-Wald, and Weibull (see van Zandt *et al.,* 2000 for a review). Alternative models could be investigated in future analyses of the data included in the thesis.

Consequently, this thesis recommends that studies apply more than one RT model to data obtained from cognitive tasks, to determine which model(s) best characterise the data from the study population(s) included, which would improve the *a priori* researcher selection of RT models for future work. Although requiring additional conceptualisation, the proposed methodology would enable a data-driven approach to selecting RT models of best fit to the data, rather than a researcher-selected, model-down approach, which may not accurately characterise the data obtained.

8.3.3 Sample sizes

Sample sizes throughout each thesis study varied, and per hierarchical regression model in some instances, due to incomplete data (see Chapters 2 and 3). The lack of age-related associations with ex-Gaussian parameters in Chapter 2, and in BD (Chapter 5 and 6), may be due to low sample size. Future studies should maximise the data available, and maintain full data sets per participant where possible.

8.3.4 Neuropsychological measures

There was also a lack of comparison between studies presented in the thesis with the neuropsychological measures utilised. Whilst every effort was made to use similar tasks throughout the thesis, the lack of comprehensive neuropsychological battery in the PD study indicates a limitation. Similar tasks measuring similar concepts were used where available however.

In addition, three out of the five studies in the thesis are also limited by only analysing one component of executive functioning, working memory. Miyake (2000) also specifies that set-shifting, and inhibition are also components of executive functioning. These could be included in future studies to investigate their contributions to attentional RT and IIV from variants of the CPT.

Theoretically, the Digit Span backwards relies on an executive-phonological loop interface, as outlined by the Baddeley and Hitch (1974) model of working memory. The task involves the short term maintenance of items on the digit list, which is managed by two 'slave' systems involved in the temporary storage and rehearsal of information (phonological loop), as well as the integration of information (visuospatial sketchpad). Additionally, an individual is required to mentally manipulate the digit list to achieve the correct order. As such, the task requires the resources of the Central Executive, which is a system that maintains attentional control of working memory (Baddeley, 1996; Monaco *et al.,* 2013). It would be interesting to include assessment of the two 'slave' systems in Baddeley and Hitch's (1974) model, such as the forward digit span (phonological loop), and spatial span (visuo-spatial sketchpad), to determine their contribution to the assessment of sustained attention via the CPT.

In addition to issues surrounding executive functioning, use of the DSST may also be considered a limitation. Although the DSST is considered a standard tool in the assessment of processing speed (Salthouse, 1992b), it also measures a collection of cognitive processes such as sustained attention, visual scanning, motor speed, and coordination (Lezak *et al.*, 2012; Cepeda *et al.*, 2013), all of which echo the requirements of CPTs generally. As such, it is difficult to determine whether the contribution of processing speed to attentional RT and IIV, is due to speed *per se*, or the additional processes involved in its assessment.

8.3.5 Medication

The relationship between medication status and cognitive impairment (e.g., IIV) should also be considered. It is possible that the between-subjects differences observed in Chapters 5 and 6 in BD were due to the medication status (as well as dosage) of patients, with medication including lithium, antidepressants, as well as antipsychotics. Whilst researchers have argued for the independence of medication status (such as lithium and antidepressant use) and cognitive impairment (Clark and Goodwin, 2004; Martínez-Arán *et al.*, 2004; Bourne *et al.*, 2013), others have suggested that antipsychotic medication may have a detrimental effect on cognition in BD (Frangou *et al.*, 2005). Of note, there is a paucity of data examining the effects of medication status/dosage on attentional IIV in BD, as assessed by the ex-Gaussian distribution. In sum, the long-term effects of medication and dosage on cognitive impairment in BD remain to be determined (Lee *et al.*, 2014; Samamé *et al.*, 2014), and should be a focus for future research.

8.4 Future directions

The results from the thesis have highlighted directions for future research, which will now be discussed.

8.4.1 Alternative forms of RT modelling

The thesis has emphasised the potential clinical utility of the analysis of RTs using the ex-Gaussian distribution, particularly as elevated IIV was not accounted for by pathology-related deterioration of other cognitive domains (e.g., executive functioning, processing speed, verbal memory). Whilst the thesis has demonstrated elevated ex-Gaussian tau in PD and explored the task-specificity of RT and IIV, as well as differences in mood states in BD, use of ex-Gaussian modelling generally does not fully characterise the periodic nature of IIV.

Analysis using the ex-Gaussian does not indicate how often y slow, and infrequent RTs occur over the course of a task, or indeed, whether they are transitory, or frequent. Of note, increases in IIV could represent faster moment-to-moment top-down control fluctuations across a task, or more slowly-evolving fluctuations, and may provide an underlying neurobiological explanation for sustained attention impairments in a variety of clinical populations (Castellanos *et al.*, 2005). Indeed, the idea that sustained attention ability oscillates is not new (Buck, 1966).

Further research could combine analysis of the ex-Gaussian distribution with examining the temporal components of IIV. With use of the FFT, periodic patterns of responding that are specific to certain time scales (temporal frequency bands), can be detected, manifesting as peaks in the (spectral) power at the specific frequency band (Johnson *et al.*, 2007). Analysis of the temporal nature of IIV has been investigated primarily in ADHD. Studies have reported that increases in behavioural performance variability (indexed by ex-Gaussian tau) occur every 15-40 seconds (in the frequency band slow-4: 0.027-0.074Hz) (Penttonen and Buzsáki, 2003) for children with ADHD compared to HC (Castellanos *et al.*, 2005; Johnson *et al.*, 2007; Di Martino *et al.*, 2008). However, increased spectra in specific frequency bands may differ due to task parameters (Vaurio *et al.*, 2009; Yordanova *et al.*, 2011). More recently, the relationship between mental health and IIV was investigated using FFT in a cohort of young, healthy adults (Bastiaansen *et al.*, 2015). The authors reported that temporal fluctuations in RT within the slow-4 frequency band 0.027-0.074Hz were predictive of attention and externalising problems.

In addition to further characterising IIV, analysis of RTs using FFT may have clinical utility. Interestingly, analysis of FFT may indicate underlying abnormalities, such as inefficient processing in specific neural and/or resting-state networks such as the Default Mode (e.g., as used in ADHD; Johnson *et al.*, 2007; Vaurio *et al.*, 2009). As altered network activity (e.g., Default Mode) has been reported in BD (Vargas *et al.*, 2013), and PD (Li *et al.*, 2016) analysis of the oscillatory pattern of RTs warrants further investigation. This may shed light on the underlying pathophysiology associated with clinical disorders and diseases, which may provide novel targets for psychopharmacological interventions.

Given the potential benefits, this thesis recommends that FFT be analysed in future studies, in addition to the ex-Gaussian distribution. A proposed bandwidth for investigation in clinical populations such as BD and PD would be slow wave 4 (0.027-0.074 Hz) (Penttonen and Buzsáki, 2003), due to the reported relationship between this bandwidth and ex-Gaussian tau noted in ADHD (Castellanos *et al.*, 2005; Johnson *et al.*, 2007; Di Martino *et al.*, 2008). Slow-wave 4 is a proposed candidate for exploration, not because of the clinical similarities between the three disorders, but is instead related to the hypothesis that increases in IIV (in particular ex-Gaussian tau) may represent a *trans-diagnostic phenotype* (Gottesman and Gould, 2003; Nolen-Hoeksema and Watkins, 2011).

Moreover, this may be related to the *p* factor, or general psychopathology factor proposed by Caspi *et al.* (2014), with increasing severity of underlying psychopathology (vulnerability) linked to worse outcomes on indicators such as disorder duration and brain functioning. However, it is also possible that the pattern of IIV and association with its temporal components analysed via FFT may be distinct per clinical disorder, as IIV is likely to be the result of different developmental, functional, neurological, as well as neuropsychological processes (i.e. the concept of *equifinality*) (Willcutt *et al.*, 2008; Kofler *et al.*, 2013).

As such, a consideration of the task used to obtain IIV would be needed, as the ability to capture both fast and slow variability (higher or lower FFT bandwidths) varies depending on the task and associated parameters employed (e.g., target frequency, stimulus presentation time etc.).

As task parameters need to be considered in relation to outcome measures, researchers would need to adjust individual tasks to maximise the temporal resolution available in analysis of FFT. Ideally, tasks would be developed *a priori*, if appropriate tasks are not already available, and developed through a series of pilot studies. For instance, Castellanos *et al.* (2005) noted that temporal task parameters (e.g., ISI) constrain the temporal frequencies that can be examined, and recommended that longer tasks, with more frequent sampling be utilised.

The thesis also highlighted that age accounted for variance in attentional RT and IIV, across a number of tasks, and in clinical disorders. Whilst hierarchical regression models were significant, the predictive power was poor, suggesting that RT and IIV may not reflect global alterations in underlying neurobiology indexed by age. This begs the question what does elevated IIV, as measured by the ex-Gaussian distribution, in normal ageing, as well as in clinical disorders, reflect? The relationship between IIV and neurobiology will be discussed in the next section.

8.4.2 DTI

Intra-individual variability may be a behavioural marker of neuronal integrity (e.g., Fjell *et al.*, 2011). Future research could confirm the link between ex-Gaussian parameters and underlying neurobiology by analysing white matter tract integrity, via DTI, to determine the source of IIV in normal ageing and clinical disorders. White matter microstructure can be quantified in vivo using DTI, by measuring the rate and direction of water diffusion through tissue (Madden *et al.*, 2012).

Frequently used indices of white matter damage include FA and MD (Mahon *et al.*, 2009), measuring diffusion directionality and tissue breakdown respectively (Beaulieu, 2009). Alterations in FA and MD may be linked to loss of neurons and axonal density, as well as reduced myelination (Chaddock *et al.*, 2009; Mahon *et al.*, 2010).

Clinically, reduced FA has been reported in BD, in addition to elevation of MD (Barysheva *et al.*, 2013). Alterations in white matter integrity has also been reported in early-stage PD (Auning *et al.*, 2014), with a reduction of FA in the corpus callosum (genu), and superior longitudinal fasciculus (SLF) (Gattellaro *et al.*, 2009). Moreover, in adults with ADHD, higher ex-Gaussian tau was associated with reduced FA in the right SLF (Wolfers *et al.*, 2015). The SLF forms part of a frontoparietal attention network that is proposed to underpin attention deficits in ADHD (Makris *et al.*, 2009), but is also implicated in BD (Sprooten *et al.*, 2016), and PD (Jiang *et al.*, 2015). As such, the SLF may represent a target for future DTI studies to examine its relationship with elevated IIV (sigma or tau) in clinical disorders. Moreover, it would be useful for future studies to clarify what IIV (sigma or tau) obtained from particular cognitive tasks (such as the CPT) represents neurally, as few studies have examined the ex-Gaussian distribution and its neural underpinnings.

It is also worth noting that alternative methods of examining white matter microstructure exist, as there are limitations to use of DTI. Whilst DTI assumes that water diffusion subscribes to a Gaussian pattern, DKI assumes that that diffusion is in fact, non-Gaussian (Szczepankiewicz *et al.*, 2013).
Diffusion Kurtosis Imaging is considered a mathematical extension of DTI (Veraart and Sijbers, 2016), and assesses the non-Gaussian diffusion of water, which is thought to be more sensitive to the microstructural integrity of underlying neural structures (Helpern *et al.*, 2011). Whilst a number of kurtosis indices exist (e.g., axial kurtosis, kurtosis anisotropy, and radial kurtosis; Veraart and Sijbers, 2016), research studies have frequently utilised mean kurtosis (MK).
A higher MK value indicates that the underlying tissue has more diffusion barriers (typically the case in complex tissue), which causes water to deviate from a Gaussian distribution.

Of note, MK can quantify the microstructural integrity of grey and white matter in the presence of crossing fibres, unlike FA (Helpern *et al.*, 2011; Lu *et al.*, 2016).

Research utilising DKI is promising, with reports suggesting that kurtosis indices have higher sensitivity and specificity of detecting underlying white matter microstructural alterations, compared to DTI, in a non-pathological adult population (Jensen *et al.*, 2005; Van Cauter *et al.*, 2012). These results have also been reported clinically. For instance, Wang *et al.* (2011) noted that patients with idiopathic PD had higher MK values in all basal ganglia regions, compared to HC. Mean kurtosis values were also compared with conventional DTI indices of MD and FA for diagnostic comparison using ROC. Interestingly, Wang *et al.* (2011) reported that the MK value for the ipsilateral substantia nigra had the best diagnostic performance compared to other DTI indices – with 92% sensitivity and 87% specificity. The purported sensitivity of DKI indices, compared to DTI, has also been reported in ADHD (Helpern *et al.*, 2011).

The studies described suggest that DKI is a promising tool for future neuroimaging research, for normal ageing and clinical populations. At present, there are a paucity of studies utilising DKI to replicate previous work, but also, across a wide range of clinical populations (e.g., BD). In addition, few studies have investigated the relationship between DKI indices and cognitive impairment (e.g., IIV). If DKI indices are more sensitive and specific in characterising underlying microstructural integrity, compared to DTI, then they may be more sensitive indices of cognitive impairment. This could have diagnostic implications, particularly as cognitive impairment may precede clinical symptoms in some disorders (e.g., PD; Bhidayasiri and Truong, 2012). It would be useful for future studies to examine the sensitivity/specificity of DTI and DKI indices, diagnostically, as well as in relation to neuropsychological performance

8.5 Thesis conclusions

This thesis has explored the relationship between other neuropsychological processes, theorised to be involved in CPT variants, and attentional RT and IIV, as assessed by the ex-Gaussian distribution. The relationship between age (as well as pathology) and attentional RT and IIV was also examined. The thesis themes were explored in normal ageing, PD, and BD (in remission and while depressed). This body of work highlights that other neuropsychological processes supported faster RTs (mu) and reduced inconsistency in responding (sigma and/or tau). The results may indicate use of secondary compensatory scaffolding, engaged as a result of age and/or pathology, or represent the cumulative effects of task difficulty on attentional RT and IIV. The results also indicated that the effect of age on attentional RT and IIV, as measured by the ex-Gaussian distribution, differs per CPT variant. Age may not be the most sensitive index of attentional IIV, with attentional IIV perhaps better reflecting clinical pathology and/or underlying neuronal vulnerability, rather than the global changes represented by age. Of clinical utility, elevated IIV in PD and in BD is not secondary to impairments in other cognitive domains such as executive functioning and processing speed, despite sharing variance. Strengths of the approach adopted here include utilising the ex-Gaussian distribution to describe attentional RT and IIV, and the novel application of the ex-Gaussian distribution to a variety of CPTs in normal ageing, as well as PD. Limitations of such approaches include the stability and reliability of the ex-Gaussian distribution, in addition to the quality of data (incomplete data sets, sample size across studies, lack of neuropsychological comparison across studies included, which are common in assessments of this nature). Future work should examine the stability and reliability of the ex-Gaussian distribution, explore further analysis of IIV such as the application of FFT, or data-driven modelling, and investigate the neurobiological origins of IIV via the analysis of white matter integrity (DTI and/or DKI). This would further our understanding on the use of secondary cognitive scaffolding in relation to the CPT, as well as the stability, reliability, and neurobiological origins of cognitive intra-individual variation.

Chapter 9. Appendices

9.1 Appendix A

SAMPLE CHARACTERISTICS QUESTIONNAIRE

1. Demographics

Date of birth: _____

Sex *(Please circle):* MALE/FEMALE

2. Physical health

Do you have any physical health problems?

_____

_____

3. Menstrual cycle (applicable to female participants)

Are you taking hormonal contraception? *(Please circle)* YES/NO

If **YES**, which brand? *(Indicate here whether you are receiving Hormone Replacement Therapy)*

_____

If **NO**, what day/date did you finish your last period? *(Please indicate if this is a guess)*

_____

4. Substance use

Alcohol _____ units per *week (e.g. 1 unit = 1/3 pint of beer; half a standard measure of red wine (175ml); 25ml single measure of whiskey)*

Cigarettes _____ per day

Prescribed/Over-the-counter medicines None _____
(Please circle if NONE and
*Provide details if **CURRENT**)*

Current _____

5. Education

What is your highest level of education? (e.g., GCSE's, A-Levels etc)

_____

How many years of formal education have you received?

_____

6. Employment

What is your employment status? (please circle)

- Employed, full-time
- Employed, part-time (or zero-hours contracted)
- Unemployed
- Sick leave
- Retired
- Other (please indicate)

  _____

Table 9-1. Total *n*, outliers removed, per CPT for each model in the hierarchical regression analysis for ex-Gaussian mu. Total *n*, without outliers removed, are presented in brackets (Normal ageing study).

ex-Gaussian mu	CCPT-II	CPT-IP	RVIP
Age	74	70 (71)	54
Model 1a	68 (69)	64 (65)	52
Model 1b	72 (73)	68 (69)	54
Model 1c	43	41	43
Model 2a	67 (68)	62 (63)	52
Model 2b	41	39	41
Model 2c	43	41	43

Note. Model 1a = executive functioning and age; Model 2a = processing speed and age; Model 2c = verbal memory and age; Model 2a = processing speed, executive functioning, and age; Model 2b = verbal memory, executive functioning, and age; Model 2c = verbal memory, processing speed, and age.

Table 9-2. Total *n*, outliers removed, per CPT for each model in the hierarchical regression analysis for ex-Gaussian sigma. Total *n*, without outliers removed, are presented in brackets (Normal ageing study).

ex-Gaussian sigma	CCPT-II	CPT-IP	RVIP
Age	74	71	54
Model 1a	69	65	52
Model 1b	73	69	54
Model 1c	43	41	43
Model 2a	68	63	52
Model 2b	41	39	41
Model 2c	43	41	43

Note. Model 1a = executive functioning and age; Model 2a = processing speed and age; Model 2c = verbal memory and age; Model 2a = processing speed, executive functioning, and age; Model 2b = verbal memory, executive functioning, and age; Model 2c = verbal memory, processing speed, and age.

Table 9-3. Total *n*, outliers removed, per CPT for each model in the hierarchical regression analysis for ex-Gaussian tau. Total *n*, without outliers removed, are presented in brackets (Normal ageing study).

ex-Gaussian tau	CCPT-II	CPT-IP	RVIP
Age	72	70	54
Model 1a	67 (69)	65	52
Model 1b	71 (73)	69	54
Model 1c	43	41	43
Model 2a	66 (68)	63	52
Model 2b	41	39	41
Model 2c	43	41	43

Note. Model 1a = executive functioning and age; Model 2a = processing speed and age; Model 2c = verbal memory and age; Model 2a = processing speed, executive functioning, and age; Model 2b = verbal memory, executive functioning, and age; Model 2c = verbal memory, processing speed, and age.

9.2 Appendix B

Table 9-4. Total *n*, outliers removed in the hierarchical regression analysis for ex-Gaussian mu. Total *n*, without outliers removed, are presented in brackets (PD study).

ex-Gaussian mu	PD	HC
Age	142 (143)	187 (188)
Model 1a	127	180
Model 1b	143	187 (188)
Model 2a	127	180

Note. Model 1a = executive functioning and age; Model 2a = processing speed and age; Model 2a = processing speed, executive functioning, and age.

Table 9-5. Total *n*, outliers removed in the hierarchical regression analysis for ex-Gaussian sigma. Total *n*, without outliers removed, are presented in brackets (PD study).

ex-Gaussian sigma	PD	HC
Age	142 (143)	183 (188)
Model 1a	126 (127)	176 (180)
Model 1b	142 (143)	183 (188)
Model 2a	126 (127)	176 (180)

Note. Model 1a = executive functioning and age; Model 2a = processing speed and age; Model 2a = processing speed, executive functioning, and age.

Table 9-6. Total *n*, outliers removed in the hierarchical regression analysis for ex-Gaussian tau. Total *n*, without outliers removed, are presented in brackets (PD study).

ex-Gaussian tau	PD	HC
Age	143	187 (188)
Model 1a	125 (127)	179 (180)
Model 1b	141 (143)	187 (188)
Model 2a	125 (127)	179 (180)

Note. Model 1a = executive functioning and age; Model 2a = processing speed and age; Model 2a = processing speed, executive functioning, and age.

Table 9-7. Hierarchical regression analysis with ex-Gaussian sigma in patients with PD and HC.

ex-Gaussian sigma		PD				HC			
Model		R^2	ΔR^2	Sig. F Change	β	R^2	ΔR^2	Sig. F change	β
	Age	0.012	0.012	0.193	0.110	0.001	0.001	0.649	-0.034
1a	EF	0.000	0.000	0.960	-0.005	0.000	0.000	0.970	-0.003
	Age	0.011	0.011	0.251	0.106	0.003	0.003	0.461	-0.058
1b	PS	0.003	0.003	0.527	0.053	0.011	0.011	0.154	0.106
	Age	0.014	0.011	0.207	0.107	0.015	0.004	0.425	-0.061
2a	EF	0.000	0.000	0.960	-0.005	0.000	0.000	0.970	-0.003
	PS	0.001	0.001	0.681	-0.038	0.005	0.004	0.378	0.068
	Age	0.013	0.011	0.244	0.108	0.010	0.005	0.346	-0.076
	PS	0.001	0.001	0.693	-0.036	0.004	0.004	0.382	0.066
	EF	0.001	0.000	0.896	-0.012	0.005	0.000	0.893	0.010
	Age	0.013	0.011	0.244	0.108	0.010	0.005	0.346	-0.076

Note. β = Standardised coefficients; EF = Executive Functioning; PS = Processing Speed.

9.3 Appendix C

Table 9-8. Spearman correlations between ex-Gaussian parameters and age for the Vigil CPT and CPT-AX in patients with BD (n = 22) and HC (Vigil n = 19, CPT-AX n = 18).

	Vigil CPT		CPT-AX	
	BD	**HC**	**BD**	**HC**
ex-Gaussian mu	-0.027	-0.054	-0.174	-0.061
ex-Gaussian sigma	0.033	-0.321	0.024	-0.116
ex-Gaussian tau	-0.094	0.185	-0.086	0.079

Table 9-9. Spearman correlations between ex-Gaussian parameters obtained from the Vigil CPT and other neuropsychological processes in patients with BD (in remission) and HC.

	BD			HC		
	EF	**PS**	**VM**	**EF**	**PS**	**VM**
ex-Gaussian mu	- 0.026	- 0.142	- 0.050	- 0.068	0.023	- 0.105
ex-Gaussian sigma	- 0.137	- 0.079	0.025	0.078	0.154	- 0.098
ex-Gaussian tau	0.089	- 0.050	0.035	- 0.291	0.340	0.041

Note. EF = Executive Functioning, PS = Processing Speed, VM = Verbal Memory.

Table 9-10. Spearman correlations between ex-Gaussian parameters obtained from the CPT-AX and other neuropsychological processes in patients with BD (in remission) and HC.

	BD			HC		
	EF	**PS**	**VM**	**EF**	**PS**	**VM**
ex-Gaussian mu	0.303	-0.041	0.303	0.033	0.265	-0.007
ex-Gaussian sigma	0.097	-0.107	-0.174	-0.038	0.239	0.156
ex-Gaussian tau	**-0.428***	-0.224	0.097	-0.037	0.418	0.173

Note. EF = Executive Functioning, PS = Processing Speed, VM = Verbal Memory.

* $p < 0.050$.

Table 9-11. Hierarchical regression analysis with ex-Gaussian mu in patients with BD and HC (Vigil CPT).

ex-Gaussian mu		VIGIL BD (*n* = 22)				VIGIL HC (*n* = 19)			
Model		R^2	ΔR^2	**Sig. F Change**	**β**	R^2	ΔR^2	**Sig. F change**	**β**
	Age	0.001	0.001	0.866	-0.038	0.062	0.062	0.303	-0.250
1a	EF	0.002	0.002	0.855	-0.041	0.005	0.005	0.784	-0.067
	Age	0.005	0.003	0.803	-0.062	0.075	0.071	0.285	-0.271
1b	PS	0.003	0.003	0.804	-0.056	0.017	0.017	0.600	-0.129
	Age	0.007	0.004	0.796	-0.064	0.078	0.062	0.317	-0.248
1c	VM	0.000	0.000	0.959	-0.012	0.000	0.000	0.937	-0.019
	Age	0.002	0.002	0.867	-0.048	0.075	0.075	0.272	-0.292
2a	EF	0.002	0.002	0.855	-0.041	0.005	0.005	0.784	-0.067
	PS	0.004	0.003	0.825	-0.052	0.017	0.012	0.662	-0.122
	Age	0.010	0.006	0.745	-0.088	0.083	0.066	0.316	-0.262
	PS	0.003	0.003	0.804	-0.056	0.017	0.017	0.600	-0.129
	EF	0.004	0.001	0.880	-0.035	0.017	0.000	0.954	- 0.016
	Age	0.010	0.006	0.745	-0.088	0.083	0.066	0.316	- 0.262
2b	EF	0.002	0.002	0.855	-0.041	0.005	0.005	0.784	- 0.067
	VM	0.002	0.000	0.942	0.017	0.005	0.000	0.965	- 0.011
	Age	0.006	0.003	0.804	-0.079	0.087	0.082	0.264	- 0.309
	VM	0.000	0.000	0.959	0.012	0.000	0.000	0.937	- 0.019
	EF	0.002	0.002	0.852	-0.044	0.005	0.004	0.796	- 0.066
	Age	0.006	0.003	0.804	-0.079	0.087	0.082	0.264	- 0.309
2c	PS	0.003	0.003	0.804	-0.056	0.017	0.017	0.600	- 0.129
	VM	0.005	0.002	0.867	0.043	0.017	0.000	0.945	- 0.018
	Age	0.007	0.002	0.845	-0.058	0.090	0.074	0.288	- 0.289
	VM	0.000	0.000	0.959	0.012	0.000	0.000	0.937	- 0.019
	PS	0.005	0.005	0.772	-0.074	0.017	0.016	0.612	- 0.128
	Age	0.007	0.002	0.845	-0.058	0.090	0.074	0.288	- 0.289

Note. β = Standardised coefficients; EF = Executive Functioning; PS = Processing Speed; VM = Verbal Memory.

Table 9-12. Hierarchical regression analysis with ex-Gaussian sigma in patients with BD and HC (Vigil CPT).

ex-Gaussian sigma		VIGIL BD (n = 22)				VIGIL HC (n = 19)			
Model		R^2	ΔR^2	Sig. F Change	β	R^2	ΔR^2	Sig. F change	β
	Age	0.002	0.002	0.862	0.039	0.138	0.138	0.118	- 0.371
1a	EF	0.038	0.038	0.385	-0.195	0.009	0.009	0.700	0.095
	Age	0.039	0.001	0.874	-0.039	0.139	0.130	0.140	- 0.366
1b	PS	0.000	0.000	0.906	-0.011	0.001	0.001	0.892	0.034
	Age	0.002	0.001	0.871	0.040	0.139	0.138	0.129	- 0.372
1c	VM	0.002	0.002	0.838	0.046	0.001	0.001	0.901	- 0.031
	Age	0.009	0.007	0.724	0.101	0.167	0.166	0.093	- 0.435
2a	EF	0.038	0.038	0.385	-0.195	0.009	0.009	0.700	0.095
	PS	0.038	0.000	0.957	0.012	0.009	0.000	0.978	- 0.008
	Age	0.039	0.001	0.885	-0.038	0.139	0.130	0.152	- 0.369
	PS	0.000	0.000	0.960	-0.011	0.001	0.001	0.892	0.034
	EF	0.038	0.038	0.397	-0.196	0.009	0.008	0.726	0.098
	Age	0.039	0.001	0.885	-0.038	0.139	0.130	0.152	- 0.369
2b	EF	0.038	0.038	0.385	-0.195	0.009	0.009	0.700	0.095
	VM	0.043	0.005	0.753	0.072	0.011	0.002	0.866	- 0.043
	Age	0.043	0.000	0.975	0.010	0.168	0.158	0.112	- 0.428
	VM	0.002	0.002	0.838	0.046	0.001	0.001	0.901	- 0.031
	EF	0.043	0.041	0.378	-0.204	0.011	0.010	0.696	0.100
	Age	0.043	0.000	0.975	0.010	0.168	0.158	0.112	- 0.428
2c	PS	0.000	0.000	0.960	-0.011	0.001	0.001	0.892	0.034
	VM	0.003	0.003	0.808	0.062	0.002	0.001	0.902	- 0.031
	Age	0.009	0.006	0.741	0.098	0.169	0.167	0.103	- 0.436
	VM	0.002	0.002	0.838	0.046	0.001	0.001	0.901	- 0.031
	PS	0.003	0.001	0.883	-0.038	0.002	0.001	0.893	0.034
	Age	0.009	0.006	0.741	0.098	0.169	0.167	0.103	- 0.436

Note. β = Standardised coefficients; EF = Executive Functioning; PS = Processing Speed; VM = Verbal Memory.

Table 9-13. Hierarchical regression analysis with ex-Gaussian tau in patients with BD and HC (Vigil CPT).

ex-Gaussian tau		VIGIL BD (n = 22)				VIGIL HC (n = 19)			
Model		R^2	ΔR^2	Sig. F Change	β	R^2	ΔR^2	Sig. F change	β
	Age	0.024	0.024	0.494	-0.154	0.043	0.043	0.397	0.206
1a	EF	0.014	0.014	0.601	0.118	0.100	0.100	0.186	- 0.317
	Age	0.028	0.014	0.606	-0.128	0.123	0.023	0.527	0.154
1b	PS	0.001	0.001	0.893	-0.030	0.123	0.123	0.141	0.351
	Age	0.031	0.030	0.451	-0.184	0.164	0.041	0.390	0.202
1c	VM	0.019	0.019	0.545	0.137	0.016	0.016	0.609	0.125
	Age	0.027	0.008	0.691	-0.113	0.087	0.071	0.281	0.285
2a	EF	0.014	0.014	0.601	0.118	0.100	0.100	0.186	- 0.317
	PS	0.016	0.002	0.845	-0.045	0.385	0.285	**< 0.050**	0.588
	Age	0.035	0.019	0.555	-0.158	0.395	0.010	0.629	0.101
	PS	0.001	0.001	0.893	-0.030	0.123	0.123	0.141	0.351
	EF	0.016	0.015	0.597	0.123	0.385	0.262	**< 0.050**	- 0.564
	Age	0.035	0.019	0.555	-0.158	0.395	0.010	0.629	0.101
2b	EF	0.014	0.014	0.601	0.118	0.100	0.100	0.186	- 0.317
	VM	0.029	0.015	0.594	0.124	0.128	0.027	0.490	0.166
	Age	0.032	0.003	0.806	-0.077	0.176	0.048	0.365	0.237
	VM	0.019	0.019	0.545	0.137	0.016	0.016	0.609	0.125
	EF	0.029	0.010	0.659	0.102	0.128	0.112	0.171	- 0.337
	Age	0.032	0.003	0.806	-0.077	0.176	0.048	0.365	0.237
2c	PS	0.001	0.001	0.893	-0.030	0.123	0.123	0.141	0.351
	VM	0.028	0.027	0.475	0.182	0.138	0.015	0.611	0.121
	Age	0.039	0.011	0.662	-0.128	0.205	0.068	0.276	0.278
	VM	0.019	0.019	0.545	0.137	0.016	0.016	0.609	0.125
	PS	0.028	0.009	0.673	-0.107	0.138	0.122	0.152	0.349
	Age	0.039	0.011	0.662	-0.128	0.205	0.068	0.276	0.278

Note. β = Standardised coefficients; EF = Executive Functioning; PS = Processing Speed; VM = Verbal Memory. Significance highlighted in bold and light blue.

Table 9-14. Hierarchical regression analysis with ex-Gaussian mu in patients with BD and HC (CPT-AX).

ex-Gaussian mu		CPT-AX BD (n = 22)				CPT-AX HC (n = 18)			
Model		R^2	ΔR^2	Sig. F Change	β	R^2	ΔR^2	Sig. F change	β
	Age	0.016	0.016	0.580	-0.125	0.007	0.007	0.738	- 0.085
1a	EF	0.108	0.108	0.136	0.328	0.002	0.002	0.859	- 0.045
	Age	0.108	0.000	0.992	-0.002	0.011	0.009	0.724	- 0.094
1b	PS	0.000	0.000	0.945	-0.016	0.009	0.009	0.709	0.095
	Age	0.019	0.019	0.552	-0.146	0.017	0.008	0.735	- 0.088
1c	VM	0.003	0.003	0.805	-0.056	0.002	0.002	0.866	- 0.043
	Age	0.041	0.038	0.398	-0.240	0.013	0.011	0.684	- 0.114
2a	EF	0.108	0.108	0.136	0.328	0.002	0.002	0.859	- 0.045
	PS	0.111	0.003	0.799	-0.056	0.017	0.015	0.644	0.130
	Age	0.111	0.000	0.928	-0.023	0.028	0.011	0.695	- 0.107
	PS	0.000	0.000	0.945	-0.016	0.009	0.009	0.709	0.095
	EF	0.111	0.111	0.141	0.335	0.017	0.008	0.738	- 0.094
	Age	0.111	0.000	0.928	-0.023	0.028	0.011	0.695	- 0.107
2b	EF	0.108	0.108	0.136	0.328	0.002	0.002	0.859	- 0.045
	VM	0.118	0.010	0.652	-0.100	0.003	0.001	0.895	- 0.035
	Age	0.123	0.005	0.742	-0.098	0.015	0.012	0.684	- 0.118
	VM	0.003	0.003	0.805	-0.056	0.002	0.002	0.866	- 0.043
	EF	0.118	0.114	0.133	0.341	0.003	0.001	0.887	- 0.038
	Age	0.123	0.005	0.742	-0.098	0.015	0.012	0.684	- 0.118
2c	PS	0.000	0.000	0.945	-0.016	0.009	0.009	0.709	0.095
	VM	0.003	0.003	0.815	-0.060	0.012	0.003	0.838	- 0.054
	Age	0.041	0.038	0.410	-0.242	0.025	0.013	0.671	- 0.123
	VM	0.003	0.003	0.805	-0.056	0.002	0.002	0.866	- 0.043
	PS	0.003	0.000	0.970	0.010	0.012	0.010	0.703	0.100
	Age	0.041	0.038	0.410	-0.242	0.025	0.013	0.671	- 0.123

Note. β = Standardised coefficients; EF = Executive Functioning; PS = Processing Speed; VM = Verbal Memory.

Table 9-15. Hierarchical regression analysis with ex-Gaussian sigma in patients with BD and HC (CPT-AX).

ex-Gaussian sigma		CPT-AX BD (n = 22)				CPT-AX HC (n = 18)			
Model		R^2	ΔR^2	Sig. F Change	β	R^2	ΔR^2	Sig. F change	β
	Age	0.005	0.005	0.765	0.068	0.008	0.008	0.724	-0.089
1a	EF	0.024	0.024	0.495	0.153	0.032	0.032	0.475	-0.180
	Age	0.042	0.018	0.555	0.145	0.046	0.014	0.647	-0.119
1b	PS	0.008	0.008	0.694	-0.089	0.021	0.021	0.566	-0.145
	Age	0.010	0.002	0.860	0.043	0.028	0.007	0.745	-0.084
1c	VM	0.068	0.068	0.240	-0.261	0.006	0.006	0.761	0.077
	Age	0.079	0.011	0.638	-0.130	0.010	0.004	0.799	-0.071
2a	EF	0.024	0.024	0.495	0.153	0.032	0.032	0.475	-0.180
	PS	0.035	0.012	0.637	-0.109	0.039	0.007	0.748	-0.090
	Age	0.047	0.011	0.649	0.121	0.051	0.012	0.679	-0.112
	PS	0.008	0.008	0.694	-0.089	0.021	0.021	0.566	-0.145
	EF	0.035	0.027	0.472	0.167	0.039	0.018	0.602	-0.146
	Age	0.047	0.011	0.649	0.121	0.051	0.012	0.679	-0.112
2b	EF	0.024	0.024	0.495	0.153	0.032	0.032	0.475	-0.180
	VM	0.104	0.080	0.208	-0.286	0.046	0.013	0.654	0.118
	Age	0.105	0.001	0.867	-0.050	0.053	0.007	0.750	-0.091
	VM	0.068	0.068	0.240	-0.261	0.006	0.006	0.761	0.077
	EF	0.104	0.035	0.397	0.190	0.046	0.040	0.442	-0.203
	Age	0.105	0.001	0.867	-0.050	0.053	0.007	0.750	-0.091
2c	PS	0.008	0.008	0.694	-0.089	0.021	0.021	0.566	-0.145
	VM	0.069	0.061	0.279	-0.272	0.030	0.009	0.720	0.094
	Age	0.080	0.011	0.653	-0.128	0.033	0.003	0.838	-0.059
	VM	0.068	0.068	0.240	-0.261	0.006	0.006	0.761	0.077
	PS	0.069	0.001	0.916	0.026	0.030	0.024	0.554	-0.155
	Age	0.080	0.011	0.653	-0.128	0.033	0.003	0.838	-0.059

Note. β = Standardised coefficients; EF = Executive Functioning; PS = Processing Speed; VM = Verbal Memory.

Table 9-16. Hierarchical regression analysis with ex-Gaussian tau in patients with BD and HC (CPT-AX).

ex-Gaussian tau		CPT-AX BD (n = 21)				CPT-AX HC (n = 18)			
Model		R^2	ΔR^2	**Sig. F Change**	**β**	R^2	ΔR^2	**Sig. F change**	**β**
	Age	0.012	0.012	0.641	0.108	0.040	0.040	0.425	0.200
1a	EF	0.196	0.196	**< 0.050**	-0.442	0.001	0.001	0.923	0.024
	Age	0.200	0.004	0.769	-0.068	0.043	0.043	0.426	0.209
1b	PS	0.060	0.060	0.284	-0.245	0.196	0.196	0.066	0.443
	Age	0.061	0.001	0.905	0.029	0.230	0.034	0.427	0.185
1c	VM	0.002	0.002	0.866	-0.039	0.061	0.061	0.325	0.246
	Age	0.012	0.011	0.663	0.125	0.154	0.093	0.218	0.326
2a	EF	0.196	0.196	**< 0.050**	-0.442	0.001	0.001	0.923	0.024
	PS	0.233	0.037	0.362	-0.194	0.220	0.220	0.058	0.506
	Age	0.250	0.017	0.545	-0.148	0.246	0.026	0.502	0.163
	PS	0.060	0.060	0.284	-0.245	0.196	0.196	0.066	0.443
	EF	0.233	0.173	0.059	-0.419	0.220	0.024	0.507	-0.167
	Age	0.250	0.017	0.545	-0.148	0.246	0.026	0.502	0.163
2b	EF	0.196	0.196	**< 0.050**	-0.442	0.001	0.001	0.923	0.024
	VM	0.196	0.000	0.937	0.017	0.061	0.061	0.341	0.251
	Age	0.200	0.004	0.770	-0.084	0.154	0.093	0.236	0.326
	VM	0.002	0.002	0.866	-0.039	0.061	0.061	0.325	0.246
	EF	0.196	0.194	0.052	-0.444	0.061	0.001	0.921	-0.026
	Age	0.200	0.004	0.770	-0.084	0.154	0.093	0.236	0.326
2c	PS	0.060	0.060	0.284	-0.245	0.196	0.196	0.066	0.443
	VM	0.067	0.007	0.721	0.093	0.236	0.040	0.390	0.201
	Age	0.073	0.006	0.742	0.095	0.163	0.075	0.237	0.293
	VM	0.002	0.002	0.866	-0.039	0.061	0.061	0.325	0.246
	PS	0.067	0.065	0.276	-0.288	0.236	0.176	0.083	0.421
	Age	0.073	0.006	0.742	0.095	0.311	0.075	0.237	0.293

Note. β = Standardised coefficients; EF = Executive Functioning; PS = Processing Speed; VM = Verbal Memory. Significance highlighted in bold and light blue.

Table 9-17. Spearman correlations between ex-Gaussian parameters and clinical characteristics for the Vigil task and CPT-AX (patients only, $n = 22$).

	Parameter	Age of onset (years)	Months post onset (years)	$HAMD_{(21)}$	YMRS
Vigil	ex-Gaussian mu	0.011	-0.058	0.003	- 0.305
	ex-Gaussian sigma	0.121	-0.016	0.119	- 0.363
	ex-Gaussian tau	-0.318	0.212	-0.231	- 0.040
CPT-AX	ex-Gaussian mu	-0.007	-0.199	-0.219	-0.104
	ex-Gaussian sigma	0.279	-0.097	0.333	-0.070
	ex-Gaussian tau	-0.072	0.076	-0.113	-0.148

Table 9-18. Main effects and interactions for each ex-Gaussian parameter using the extended Vigil window (1970 ms) from repeated measures ANOVA.

Effect	*F(df)*	*p*	*Partial* η^2
Main effect Task (mu)	194.84 $_{(1,37)}$	**0.00*** **	0.84
Main effect Task (sigma)	8.17 $_{(1,37)}$	**0.00** **	0.18
Main effect Task (tau)	3.53 $_{(1,37)}$	0.06	0.08
Main effect Diagnosis (mu)	1.17 $_{(1,37)}$	0.28	0.03
Main effect Diagnosis (sigma)	4.54 $_{(1,37)}$	**0.04***	0.10
Main effect Diagnosis (tau)	0.04 $_{(1,37)}$	0.83	0.00
Task x Diagnosis (mu)	3.43 $_{(1,37)}$	0.07	0.08
Task x Diagnosis (sigma)	4.64 $_{(1,37)}$	**0.03***	0.11
Task x Diagnosis (tau)	1.37 $_{(1,37)}$	0.24	0.03

Note. η^2= Eta-squared.
*$p < 0.050$ **$p < 0.010$ *** $p < 0.001$

9.4 Appendix D

Table 9-19. Spearman correlations between age, NART, years of education, and ex-Gaussian parameters in patients with BD.

	Age[a]		NART[b]		Years of education[c]	
	BD	HC	BD	HC	BD	HC
ex-Gaussian mu	- 0.157	0.156	0.249	0.135	0.097	0.030
ex-Gaussian sigma	0.045	- 0.089	0.000	0.074	- 0.268	0.028
ex-Gaussian tau	- 0.202	0.036	- 0.074	0.241	- 0.180	0.007

[a] BD *n* = 43; HC *n* = 32

[b] BD *n* = 41; HC *n* = 42

[c] BD n = 29; HC *n* = 25

Table 9-20. Hierarchical regression analysis with ex-Gaussian sigma in patients with BD and HC.

ex-Gaussian sigma		BD				HC			
Model		**R^2**	**ΔR^2**	**Sig. F Change**	**B**	**R^2**	**ΔR^2**	**Sig. F change**	**β**
	Age	0.000	0.000	0.951	-0.010	0.003	0.003	0.767	- 0.055
1a	EF	0.064	0.064	0.101	0.253	0.018	0.018	0.465	- 0.134
	Age	0.064	0.000	0.947	0.010	0.020	0.002	0.816	- 0.043
1b	PS	0.015	0.015	0.440	0.121	0.028	0.028	0.364	- 0.166
	Age	0.015	0.000	0.890	0.023	0.031	0.004	0.735	- 0.063
1c	VM	0.030	0.030	0.264	0.174	0.070	0.070	0.142	0.265
	Age	0.031	0.001	0.835	0.034	0.079	0.009	0.605	0.108
2a	EF	0.064	0.064	0.101	0.253	0.018	0.018	0.465	- 0.134
	PS	0.072	0.008	0.553	0.092	0.037	0.019	0.457	- 0.142
	Age	0.074	0.001	0.827	0.035	0.040	0.003	0.777	- 0.053
	PS	0.015	0.015	0.440	0.121	0.028	0.028	0.364	- 0.166
	EF	0.072	0.058	0.122	0.242	0.037	0.009	0.601	- 0.099
	Age	0.074	0.001	0.827	0.035	0.040	0.003	0.777	- 0.053
2b	EF	0.064	0.064	0.101	0.253	0.018	0.018	0.465	- 0.134
	VM	0.093	0.029	0.267	0.169	0.100	0.082	0.115	0.289
	Age	0.096	0.003	0.736	0.053	0.116	0.016	0.482	0.149
	VM	0.030	0.030	0.264	0.174	0.070	0.070	0.142	0.265
	EF	0.093	0.063	0.105	0.250	0.100	0.029	0.338	- 0.173
	Age	0.096	0.003	0.736	0.053	0.116	0.016	0.482	0.149
2c	PS	0.015	0.015	0.440	0.121	0.028	0.028	0.364	- 0.166
	VM	0.035	0.021	0.358	0.151	0.176	0.149	**< 0.050**	0.435
	Age	0.038	0.002	0.763	0.050	0.208	0.032	0.297	0.214
	VM	0.030	0.030	0.264	0.174	0.070	0.070	0.142	0.265
	PS	0.035	0.005	0.649	0.075	0.176	0.106	0.063	- 0.367
	Age	0.038	0.002	0.763	0.050	0.208	0.032	0.297	0.214

Note. β = Standardised coefficients; EF = Executive Functioning; PS = Processing Speed; VM = Verbal Memory. Significance highlighted in bold and light blue.

Table 9-21. Spearman correlations between ex-Gaussian parameters and clinical characteristics for the Vigil task.

	$HAMD_{(21)}$	GAF	MADRS	YMRS	BDI	Meds	Length	Onset
ex-Gaussian mu[a]	- 0.136	-0.052	0.027	- 0.063	-0.021	- 0.162	0.119	- 0.029
ex-Gaussian sigma[a]	- 0.007	-0.027	0.068	- 0.175	0.091	- 0.138	0.051	-0.284
ex-Gaussian tau[a]	- 0.129	-0.082	- 0.260	- 0.033	-0.165	- 0.074	0.243	**- 0.317***

Note. Meds = Time on current medication (weeks); Length = Length of current episode (weeks); Onset = Age of onset (years). * $p < 0.050$.

[a] n (in order of presentation): 43, 42, 43, 43, 43, 31, 40, 40, 40

Table 9-22. Demographic, clinical and IIV parameter comparison between the BDD and HC samples included in Gallagher *et al.* (2015), the current study (Chapter 6), and the sub-sample of BDD and HC included within the current study.

	Gallagher *et al.* (2015)		**Current study**		**Sub-sample**	
	BDD[a]	HC[b]	BDD[c]	HC[d]	BDD[e]	HC[f]
Age	47.0 (8.64)	46.7 (8.42)	47.25 (9.59)	44.96 (13.73)	47.30(13.80)	51.56 (10.66)
NART	109.0 (10.21)	109.8 (8.44)	108.94 (10.53)	112.48 (11.22)	113.0 (6.66)	109.00 (16.00)
Age of onset	25.8 (3.23)	-	27.38 (13.09)	-	34.60 (13.68)	-
HAMD	21.9 (5.75)	-	22.40 (5.65)	-	21.70 (5.51)	-
Mu	296.0 (87.66)	324.6 (82.76)	290.81 (79.95)	312.62 (108.86)	273.77 (45.76)	281.85 (46.51)
Sigma	45.2 (33.85)	29.8 (18.46)	40.49 (31.03)	37.70 (25.50)	24.89 (8.27)	26.86 (14.20)
Tau	117.3 (59.40)	66.3 (22.32)	115.37 (58.50)	68.18 (39.05)	108.92 (58.02)	59.83 (24.19)

Note. Mean and (standard deviation) presented.
[a] $n = 33$
[b] $n = 33$
[c] $n = 53$
[d] $n = 47$
[e] $n = 10$
[f] $n = 9$

9.5 Appendix E

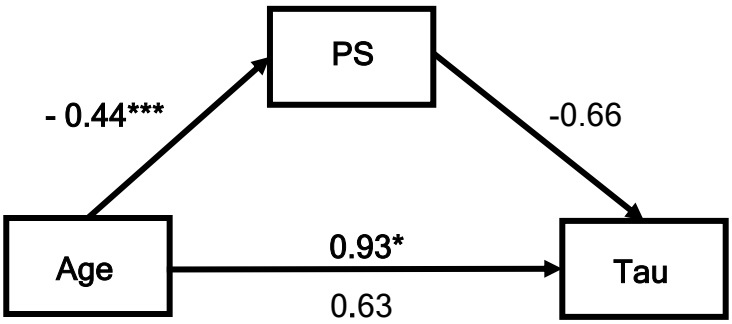

Figure 9-1. Mediation model for the impact of processing speed (PS) on the relationship between age and ex-Gaussian tau in participants (normal) who completed the RVIP (n = 54). *p < 0.050, ***p < 0.001

Chapter 10. References

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