Response Time Consistency: Correspondence with Cognition and the Effects of Training and White Matter Lesion Volume

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
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Abstract

Response time consistency or, intraindividual variability (RT IIV) from trial to trial, is known to increase with age and is exaggerated in people with neurological dysfunction. RT IIV is thought to index the fidelity of executive control mechanisms necessary for sustaining attention. Conventionally measured RT IIV conveys variability about the entire distribution. An ex-Gaussian approach segments distributional properties into normal distribution and exponential components; evidence shows that the portion of the distribution containing only extremely slow responses (ex-Gaussian parameter tau) is elevated with executive control deficits. Thus, tau may be a critical factor in the measurement of RT IIV. In a series of studies, I examined response time distribution indices with two main goals: the first was to explore the association with cognition (Studies 1, 2, and 4), and the second was to investigate the malleability of variability (Studies 3 and 5). In Studies 1 and 2, data from healthy participants were gathered from response time tasks and neuropsychological tests and subjected to structural equation modeling (SEM). SEM revealed strong associations between distributional parameters (mu and tau) and different cognitive domains. Study 4 investigated the role of white matter lesions in response time performance, revealing that greater lesion volume was negatively association with general slowing and extremely slow responding.
For my second goal (investigating malleability of RT IIV) in Study 3, I applied a training procedure to healthy young and older adults. I found RT IIV reductions in participants who received feedback training, but not in participants who received a comparison control condition. Furthermore, the ex-Gaussian parameter tau was specifically reduced by training. Study 5 involving older adults with a range of white matter lesion severity showed non-significant effects for feedback training, likely due to low power. Visual inspection, however, revealed a pattern of tau reduction in the feedback group only. Overall, my dissertation research provides further support for the notion that RT IIV, and more specifically tau, is an indicator of executive control. The training studies suggest a potential avenue for attentional repair in both healthy and brain compromised individuals.
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Chapter 1

General Introduction

The ability to maintain focused attention is something that people can easily take for granted, as it is such an integral part of daily behavior. This seemingly basic cognitive ability allows people to accomplish a variety of tasks, such as reading a novel or even following a conversation. A disruption to this focus, however, may lead to an attention lapse. For example, while reading and being fully engaged, you suddenly realize that you do not remember the contents of what you just read from the last paragraph. In this example, your mind may have wandered, in which case you were actively thinking about other things, or you could have succumbed to a brief attention lapse in which you were momentarily disconnected from the current task. When these types of attentional errors occur in daily life, they are typically viewed as a minor annoyance, simply amounting to a break before regular behavior can be continued. If, however, a more serious lapse in attention occurred at a critical point in time, such as while driving, it could potentially lead to an accident. Furthermore, in people with attentional dysfunction, frequent disruptions to attentional engagement may lead to significant frustrations and disability during even mundane daily activities.

The literature now suggests that response time intraindividual variability (RT IIV) is an index of attentional engagement and may be an indicator of very brief attention lapses (Bunce, MacDonald, & Hultsch, 2004; Bunce, Warr, & Cochrane, 1993; West, Murphy, Armilio, Craik, & Stuss, 2002). Variability in responding from trial to trial has benefited from much research on attention in the last two decades. Prior to this surge of interest in the topic, researchers had been content to use the mean as a standard measure of performance. It has become evident, however,
that variability of responses provides unique information on performance compared to the mean level (Dixon et al., 2007; Hultsch, MacDonald, & Dixon, 2002). This relatively recent perspective has spawned several lines of research designed to learn more about response variability. Thus far it has been discovered that elevated variability is present in a variety of neurological conditions (Murtha, Cismaru, Waechter, & Chertkow, 2002; Stuss, Murphy, Binns, & Alexander, 2003; Stuss, Pogue, Buckle, & Bondar, 1994) and has been shown to be a marker of neurocognitive integrity (Strauss, Bielak, Bunce, Hunter, & Hultsch, 2007). Variability has been used to predict progression of cognitive decline (Dixon et al., 2007), but it has also been observed to increase naturally with age (Bielak, Cherbuin, Bunce, & Anstey, 2014; MacDonald, Hultsch, & Dixon, 2003). Several other lines of investigation have converged on the idea that variability represents the ability to efficiently maintain attention on task (Bunce, 2001; Stuss et al., 2003; Tse, Balota, Yap, Duchek, & McCabe, 2010; West et al., 2002). Yet there are still many gaps in our knowledge of this measure. The current body of literature has established a solid foundation from which to build our understanding of response time variability.

The present doctoral dissertation aims to identify the cognitive mechanisms behind within person variability in an aging and cerebrovascular compromised population, and also examines how the training of attention may reduce variability in responding. This chapter begins by discussing background theories of attention and executive functioning, then moves to a more detailed overview of RT IV variability, before integrating those theories with the current knowledge of cognitive training and intervention for attentional dysfunction. The last section introduces cerebral small vessel disease (CSVD), which is a cerebrovascular condition known to impact attention that afflicts a significant portion of older adults. Chapter 2 consists of my first doctoral research study examining the correspondence between response time consistency and executive functioning in aging, which has surprisingly been underexplored. Chapter 3 will detail
my second study, which explores the specificity of the correspondence between response time consistency and executive functioning relative to other cognition domains. Chapter 4 consists of my third study, investigating the effect of variability-targeted attention training in healthy aging. Chapter 5 details my fourth study, examining the degree to which white matter lesion volume is predictive of elevated IIV in older adults. Chapter 6 consists of my fifth and final study, exploring whether white matter lesion volume is predictive of success in the training of attention to reduce IIV. Lastly, Chapter 7 is dedicated to a general discussion and conclusions. These chapters address the overarching goals of exploring the relationship between cognition and response time consistency in healthy aging and cerebral small vessel disease, as well as the potential for variability reduction in these populations.

1.1 Theories of Attention and Executive Functioning

Broadly, attention can be defined as the ability to concentrate or focus on a particular event or activity. Models of attention provide unique perspectives corresponding to the research orientation of those who proposed them: cognitive, clinical, or neuroscience. From a classic cognitive perspective, Broadbent was one of the first to propose a model of selective attention, which he called the filter model, whereby the capacity to process information is limited, necessitating the early selection of information (Broadbent, 1958). According to this filter model of attention, the limited capacity for processing requires that stimuli be initially screened based on physical properties so that unattended information can be filtered out. Attended information passes through the selective filter for higher order processing and becomes available in working memory. Broadbent’s filter theory was later referred to as an early-selection model because processing does not proceed for information that was initially screened and filtered out. A
competing theory, termed a late-selection model, proposed that all stimuli are processed to activate stored memory representations, at which point information can be selected for further attentional processing (Deutsch & Deutsch, 1963; Norman, 1968). These early theories were critical for establishing foundational principles upon which attention research could build. Later, an important distinction would be made between voluntary and reflexive mechanisms that are in constant competition for the momentary focus of attentional processing. Reflexive attention is automatically activated by exogenous stimuli to redirect our attention to what is new and salient – it is a bottom-up process. In contrast, voluntary attention refers to the endogenous execution of control over attentional processing allowing for goal-directed behavior to be carried out – it is a top-down process. Broadbent believed that in order to implement voluntary control of attention, the filter is adjusted to have a high degree of selectivity towards the goal of interest (Lachter, Forster, & Ruthruff, 2004).

The clinical perspective on attention focuses more on the functional abilities of individuals with brain injury, and how their clinical presentations of behavioural impairments might be explained by theory. Individuals with attentional disorders typically have difficulties with concentration, distractibility, forgetfulness, and the ability to do more than one thing at a time, which can affect their reaction time and information processing speed on tasks. This method has led to the proposal of a five component model consisting of focused attention, sustained attention, selective attention, alternating attention, and divided attention (Sohlberg & Mateer, 2001). However, these divisions are not always practical from a research perspective in the sense that more than one of these components could be ‘engaged’ simultaneously during a given task. The clinical model aims to characterize behavioural deficits, but does not easily map on to neural mechanisms.
The modern neuroscience perspective identifies three separate, but interacting neural circuits that control attentional functions: alerting, orienting, and executive control (Petersen & Posner, 2012). Alerting refers to the regulation of attentional arousal, and is employed when attention needs to be amplified or maintained during periods without salient external stimuli. This attentional circuit involves the reticular system of the brain stem that projects to a right lateralized frontoparietal vigilance network, facilitated by connections through the thalamus (Petersen & Posner, 2012). Orienting refers to the ability to prioritize sensory input either by location or stimulus property (e.g. modality) (Petersen & Posner, 2012). This circuit has been called the posterior attention system, as it heavily involves the posterior parietal lobe, but also the superior colliculus, pulvinar, and the frontal eye fields (Petersen & Posner, 2012). Executive control describes the willful and internally driven management of attentional processing, including exerting control over alerting and orienting. Neuroanatomical areas thought to be implicated in executive control are the medial prefrontal cortex and anterior cingulate cortex. There is now evidence of two distinct executive control networks – a frontoparietal control system (distinct from the orienting circuit) responsible for moment-to-moment task feedback and adjustment, and a cingulo-opercular system (overlapping with the original executive circuit) involved in task set maintenance (Petersen & Posner, 2012).

Current theories of attention are integrative with respect to perspective - cognitive, clinical, and neuroscience orientations often inform one another. As briefly mentioned above, a critical dichotomy in the study of attention from the cognitive perspective is contrasting bottom-up and top-down processing. Bottom-up refers to the exogenous recruitment of attention systems, first detecting stimuli automatically through the sensory receptors before being processed by higher brain functions. In contrast, top-down refers to the endogenous allocation of attention such that control signals originate in the prefrontal cortex and influence the receptive
fields of sensory processing further down the neural hierarchy (Miller & Buschman, 2013). It is the endogenous control of attention that is of particular interest to the present dissertation as it represents the willful engagement on task for a prolonged period of time, and thus it is synonymous with the executive control of attention. The research included in this dissertation is also more concerned with executive control over alertness and sustained attention, rather than orienting.

Sustained attention or vigilance refers to the ability to maintain the focus of cognitive activity on a particular event or task. Originally, this cognitive ability was measured through tasks presenting a continuous stream of stimuli for a prolonged period of time with the requirement to respond only to rare targets. In these types of tasks, performance was evaluated by either classical signal detection parameters (hit, miss, false alarm, correct rejection), or by the vigilance decrement – a decrease in the number of correct rejections over time or an increase in response time over the duration of the vigil (Staub, Doignon-Camus, Després, & Bonnefond, 2013). These types of tasks, now referred to as Traditionally Formatted Tasks, were thought to reduce demands placed endogenously on the sustained attention system due to the alerting effect caused by the onset of a rare target. Thus, an alternative method was developed in the form of a Go/No-Go paradigm, demonstrated initially by the Sustained Attention to Response Task (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997), where responses to non-targets are continuous and ongoing, but responses must be withheld for occasional targets. The task is known to facilitate attention slips, represented as errors of commission (failing to withhold a response upon presentation of a target), which is the primary outcome measure. The theory behind this type of paradigm is that in order to inhibit an ongoing well-learned/automatic behaviour, one must rely heavily on the endogenous engagement of the sustained attention system.
Two theories have been proposed to account for failures of sustained attention: resource depletion/mental fatigue theory and mindlessness/boredom theory. The resource depletion theory proposes that cognitive resources are limited, and they can be depleted under conditions of high demand (Davies & Parasuraman, 1982; Grier et al., 2003; Warm, Parasuraman, & Matthews, 2008). Tasks requiring sustained attention would be sufficiently demanding to deplete these resources, and their continuous ongoing nature would prevent replenishment (Helton & Russell, 2011; Shaw et al., 2009). This decline in processing resources would lead to a corresponding decline in performance, an example of a time-on-task effect and commonly referred to as the vigilance decrement. Another possibility could be that if the task is sufficiently complex and demanding, initial resources may be inefficient to complete the task flawlessly from the outset, leading to attention related errors throughout. In contrast, mindlessness theory posits that sustained attention may fail due to a lack of exogenous support in situations that are not adequately endogenously driven due to automatization of behaviour or insufficient interest on task (Manly, Robertson, Galloway, & Hawkins, 1999; Manly et al., 2004; O’Connell et al., 2008; Robertson et al., 1997). Depending on the nature of the task, such automatization can cause an individual’s awareness of on-task behaviour to become disengaged from their current thought process leading to task unrelated thoughts (Giambra, 1995; Smallwood et al., 2004). Focusing on self-generated thoughts that are unrelated to any current activity is known as mind-wandering and has been associated with neural activity in the default network (DN) (Mason et al., 2007). Both task unrelated thoughts and activation of default network regions are correlated with increases in performance errors on concurrent behavioural tasks (Allen et al., 2013; Christoff, Gordon, Smallwood, Smith, & Schooler, 2009). The prevailing view is that the frontoparietal control network dynamically switches cognitive processing between internal and external states (Andrews-Hanna, Smallwood, & Spreng, 2014; Smallwood, Brown, Baird, & Schooler, 2012;
Regardless of the theory being applied, in order to complete a long monotonous task effectively in the absence of sufficient exogenous support, cognitive control mechanisms (top down mechanisms) must be engaged endogenously for the optimal processing of information. Cognitive control is a term that is often used synonymously with executive control or executive functions in research literature (Diamond, 2013); it describes a set of top down mental processes responsible for the overall management of behavior. However, the terms may be applied differentially to refer to more generalized attentional management (executive/cognitive control) or in the conceptualization of specific sub-processes (executive functions). A more detailed definition of cognitive control can be given as a set of superordinate operations that encode and maintain a representation of the current task (i.e. contextually relevant stimulus-response associations, action-outcome contingencies, and target states or goals), and coordinate necessary subordinate functions such as semantic/episodic memory, perceptual attention, action selection, inhibition, and working memory (Botvinick & Braver, 2015). Control can be characterized by its directionality towards specific task objectives, and by the intensity of top down input on subordinate functions (Shenhav, Botvinick, & Cohen, 2013). The current theory proposes that cognitive control is driven by desires and goals, and is thus heavily influenced by motivation (Botvinick & Braver, 2015). It is clear that cognitive control is an integral neural mechanism for enabling goal-directed behavior; its importance has stimulated investigations into subordinate functions.
This dissertation applies the above conceptualization of executive/cognitive control, and reserves the term executive functions to refer to sub-processes. Research has identified three main sub-processes that constitute executive functioning: inhibitory control, working memory, and cognitive flexibility (Diamond, 2013; Miyake et al., 2000). Inhibitory control is the ability to suppress irrelevant stimuli, whether from an external event or an internal thought or desire, in favour of exerting control over one’s attention, behavior, thoughts, or emotions (Diamond, 2013). This process allows humans to focus attention selectively on specific stimuli while ignoring others, whether they are internally or externally based. Working memory is the ability to hold information in mind and manipulate it. Working memory and inhibitory control rely heavily on one other to function. Lastly, cognitive flexibility involves changing perspectives and switching mental set, which builds on inhibitory control and working memory in that switching perspective requires the current set to be inhibited and loaded into working memory while engaging the new set, also loaded from working memory (Diamond, 2013). The interaction of these foundation sub-processes allows for the emergence of higher level functions such as reasoning, problem solving, and planning (Collins & Koechlin, 2012).

The study of executive functions emerged from standardized testing and observations of how individuals with damage to the dorsolateral prefrontal cortex (DLPFC) perform under novel task conditions. The origin of assessment for these abilities led to the term “frontal lobe functions” being used erroneously to describe executive functions. What has become clear through years of research on this topic is that the frontal lobes are necessary, but not sufficient, for executive functions to be implemented. Tests that allegedly assess frontal functions are confounded by their own complexity and multifactorial nature. Furthermore, the frontal lobes are now believed to contain more specialized subdivisions, with the DLPFC responsible for cognitive (executive) functions, and the ventrolateral prefrontal cortex (VLPFC) devoted to
affective functions (Stuss & Levine, 2002). More recent research has identified a hierarchical organization of the prefrontal lobes across the rostral/caudal axis, with regions further along the gradient responsible for synthesizing higher levels of abstract information (Badre, Hoffman, Cooney, & D’Esposito, 2009; Blumenfeld, Nomura, Gratton, & D’Esposito, 2013; Nee & D’Esposito, 2016). The hierarchical organization of the prefrontal lobes has allowed for further identification of sub-regions. At the most caudal point, the lateral prefrontal cortex is involved in higher order control processes that regulate selection among multiple competing options (Petrides, 2005). Moving rostrally, processing becomes increasingly abstract with the mid-dorsolateral prefrontal cortex being involved in online monitoring of information, and the mid-ventrolateral prefrontal region being involved in making active judgments by integrating information from posterior regions (Petrides, 2005).

The progression of research on the frontal lobes has led to an alternative conceptualization of executive functions. Offering a substantial contribution to the field, Stuss and colleagues across several studies systematically examined the behaviour of individuals with damage to the prefrontal cortex. They used a ‘hot spotting’ technique whereby all patients with similar cognitive deficits were grouped together for the purpose of lesion localization (Stuss, 2011). Their rational was that if a significant impairment to a specific cognitive process was common to all individuals with damage to the same overlapping brain region, it could be argued that the region is necessary for successful completion of that function. The culmination of this line of research led to a theory of fractionation of frontal lobe functions, consisting of the following processes: energization, monitoring, task setting, behavioural/emotional self-regulation, and metacognition/integration. Energization refers to the process of initiating and sustaining a response, and is impaired following superior medial prefrontal damage. Monitoring relates to the ability to check ongoing performance and is disrupted following right lateral
prefrontal damage. Task setting involves the application of if-then logic and the automatization of attentional processes, and is impaired following left lateral prefrontal damage. Damage to the ventromedial prefrontal cortex impairs behavioral/emotional self-regulation, resulting in altered behaviour related to motivation, risk/reward, emotion, and social aspects. Lastly, metacognition/integration describes higher order processing that is required to integrate and coordinate other frontal mechanisms (Stuss, 2011). It is the combination of monitoring and task setting processes, and perhaps energization, that allow for classically defined executive functions to emerge.

Executive control, including the management of attention, are vital to controlling behaviour, but it is known that they also decline with age. In a recent review on attentional abilities in the elderly, Staub and colleagues found that performance on attention tasks by older adults is highly dependent on task design (Staub et al., 2013). On traditionally formatted tasks, older adults frequently show larger vigilance decrements, greater response times, fewer hits, and more false alarms. In contrast, on Go\No-Go tasks older adults display a lower vigilance decrement and fewer errors compared to young, but with longer response times. The authors concluded that older adults do have decreased attentional processing abilities (whether exogenously or endogenously based), but they are able to adopt a more conservative strategy on Go\No-Go tasks to compensate for their difficulty inhibiting responses (Staub et al., 2013). There is also evidence that performance on neuropsychological measures of executive functions declines with age (Wecker, Kramer, Wisniewski, Delis, & Kaplan, 2000), with decrements linked to prefrontal cortex atrophy in the elderly (Gunning-Dixon & Raz, 2003; Raz, Gunning-Dixon, Head, Dupuis, & Acker, 1998). In fact, the documented deterioration of executive and attentional abilities with aging is supported by several converging studies, which have shown that the prefrontal cortex atrophies during the normal aging process (Fjell et al., 2009; Meguro et
al., 2001; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003; Tisserand et al., 2002). The research outlined above provides little doubt that older adults lack the efficiency of attentional processing that younger adults possess, but mean response time and signal detection indices may not convey the full picture. A newer technique to study attentional processing/executive control is to examine the consistency of responding on a given task, and this may improve our understanding of these neural processes.

1.2 Response Time Intraindividual Variability

Response time intraindividual variability (RT IIV) refers to performance fluctuations within a particular person over time. RT IIV has garnered much research attention in recent years, partially due to the realization that variability is not just noise in the data, but offers behavioural information beyond the mean (Li, Hämmerer, Müller, Hommel, & Lindenberger, 2009; Papenberg et al., 2011; Ram, Rabbitt, Stollery, & Nesselroade, 2005; Schmiedek, Lövdén, & Lindenberger, 2009). Variability can be measured between testing occasions, termed dispersion, or it can be quantified as trial-to-trial changes within a given task, known as consistency. The latter is of interest in this dissertation, and thus, any instance of RT IIV following will be in reference to consistency. This type of variability is expressed as the standard deviation (SD) of response times on a task for a specific individual. There is universal agreement, however, that SD is not an adequate measure of variability since raw SD does not account for differences in mean performance, nor time-on-task effects such as practice or fatigue. One option has been to calculate a coefficient of variation (CoV; SD/mean) to control for corresponding mean differences in response time. The downside of using the CoV is that it combines the effects of the SD with mean performance as well as their cross product. Not only
can this lead to ambiguity in results, but the method also does not factor in any control for time on task effects (Hultsch, Strauss, Hunter, & MacDonald, 2008). Alternatively, many researchers studying variability have developed a purification protocol that involves using linear regression to remove mean and time on task effects before the calculation of SD. Lastly, other investigators have fitted data to an ex-Gaussian distribution, which is the convolution of a normal Gaussian and an exponential function. Response time data typically fit this type of distribution very well, and the procedure is advantageous in that it outputs three useful metrics – mu (Gaussian mean), sigma (Gaussian SD), and tau (exponential positive skew).

A major focus of research on RT IIV has been to examine cognitive aging. Much like the literature on aging and mean RT (Fozard, Vercruyssen, Reynolds, Hancock, & Quilter, 1994; Salthouse, 1998; Schaie & Warner, 1989; Verhaeghen & Salthouse, 1997), it is commonly found that RT IIV is greater in older adults compared to middle-aged or younger adults (Bauermeister & Bunce, 2014; Bunce, 2001; Bunce et al., 2010, 2004, 1993; Hultsch et al., 2002; Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000; Hultsch et al., 2008; Williams, Hultsch, Strauss, Hunter, & Tannock, 2005), with age differences emerging even within the older group (Hultsch et al., 2002; MacDonald, Hultsch, & Dixon, 2003). One large cohort study revealed a U-shaped pattern of variability through aging, with children and older adults demonstrating heightened variability, compared to young adults who were more consistent (Williams et al., 2005). A longitudinal investigation demonstrated that RT IIV increased in as little as six years, most reliably in an oldest group (MacDonald, Hultsch, & Dixon, 2003). More recently it was shown that RT IIV increased longitudinally over eight years, and that the change was greatest in older adults compared to middle aged adults, and non-existent in young (Bielak, Cherbuin, Bunce, & Anstey, 2013). The authors concluded that RT IIV is a fundamental phenomenon of aging, but what does variability represent if not noise?
Investigations into the relevance of measuring RT IIV demonstrated that it had greater predictive ability of cognitive decline compared to the mean response time, and was superior in group differentiation of cognitive impairment severity (Bielak, Hultsch, Strauss, Macdonald, & Hunter, 2010; Lövdén, Li, Shing, & Lindenberger, 2007; Strauss et al., 2007). Although research has shown that mean response time shares up to 75% of age-related variance with a variety of cognitive abilities (Salthouse, 1996a, 1996b), a stronger association has been demonstrated between general intelligence measures and RT IIV than mean/median RT (Baumeister, 1998; Jensen, 1992; Walhovd & Fjell, 2007). Initial level of inconsistency has been shown to predict cognitive decline in older adults (Bielak, Hultsch, Strauss, MacDonald, & Hunter, 2010; Lövdén et al., 2007; Yao, Stawski, Hultsch, & MacDonald, 2015). Bielak and colleagues (2010) reported that inconsistent performance was an indicator of declining fluid abilities such as memory, speed, reasoning, and fluency, which was congruent with the more recent findings of Yao et al (2015) describing an association between greater RT IIV and declines in episodic memory and executive functioning. This link between inconsistency and cognition has been demonstrated further in research on mild cognitive impairment (MCI), a condition characterized by an objective decline in cognitive ability that is greater than would be expected for a person’s age and education, but with intact functional independence. Research has established that individuals with MCI have greater variability (McLaughlin, Borrie, & Murtha, 2010; Tse et al., 2010), and it has been shown that RT IIV can distinguish individuals with MCI from healthy older adults with greater precision than mean RT (Dixon et al., 2007). RT IIV has been shown to predict a change in cognitive status from healthy to MCI five years later (Bielak, Hultsch, Strauss, MacDonald, & Hunter, 2010). Moreover, in another study on MCI, response time inconsistency was most pronounced in individuals with more extensive cognitive impairment, with those suffering from
multiple domains of impairment being more variable than those with only an isolated domain affected (Strauss et al., 2007).

Elevated response time inconsistency is not only apparent in healthy older adults and individuals with MCI, but is present in a variety of neurocognitive conditions. Studies have identified greater RT IIV in individuals with traumatic brain injury (Collins & Long, 1996; Hetherington, Stuss, & Finlayson, 1996; Raja Beharelle, Kovačević, McIntosh, & Levine, 2012; Stuss, Pogue, Buckle, & Bondar, 1994), neurodegenerative disease (Cherbuin, Sachdev, & Anstey, 2010; Hultsch et al., 2000; Murtha et al., 2002), and prefrontal lobe lesions (Picton, Stuss, Shallice, Alexander, & Gillingham, 2006; Stuss et al., 1989; Stuss, Murphy, Binns, & Alexander, 2003). Additionally, recent research indicates that white matter integrity corresponds to RT IIV (Bunce et al., 2007, 2010; Fjell, Westlye, Amlien, & Walhovd, 2011; Jackson, Balota, Duchek, & Head, 2012; Walhovd & Fjell, 2007). Originally, it was hypothesized that elevated RT IIV was just an indicator of a general neurocognitive disturbance. Examination of these sample populations, however, provides a hint that RT IIV may reflect a more specific cognitive process. This idea derives from the commonality shared between these various brain pathologies known to elevate RT IIV, in that each one impacts the attentional networks of the brain. Further evidence supporting the notion that inconsistency is associated with reductions in the integrity of attentional systems can be gleaned from the tasks used to measure response times and calculate variability.

Studies have employed a variety of different experimental tasks to assess RT IIV including simple response time tasks, choice response time tasks, vigilance tasks, semantic and lexical decision tasks, and feature integration tasks. It has become clear that task parameters are very influential to the degree of variability observed. For example, research has attempted to
assess the impact of perceptual complexity on RT IIV by visually degrading stimuli at three levels of intensity. This research demonstrated that for older adults, RT IIV was greater for the condition with the most stimulus degradation (Bunce, 2001; MacDonald, Hultsch, & Bunce, 2006). Another study hypothesized that greater executive control demand would lead to increased RT IIV, and they tested this by comparing performance on a task that either required a standard choice response or a 1-back response, which was considered an added executive component (West et al., 2002). Older adults were shown to have heightened RT IIV in the 1-back condition compared to the immediate response indicating that placing greater demands on executive control processing leads to more inconsistent responding. More recently, a meta-analysis revealed that choice response time tasks produce greater effect sizes in RT IIV for older versus younger adults when compared to simple response time tasks (Dykiert, Der, Starr, & Deary, 2012). It is now widely understood that greater task complexity produces more performance variability, and that has been observed through tasks discussed above as well as countless others that focus on elements such as response inhibition or feature integration (Bellgrove, Hester, & Garavan, 2004; McLaughlin et al., 2010; Stuss et al., 2003; Tse et al., 2010).

Overall, the data indicate that more demanding tasks produce greater RT IIV differences. Several independent studies discussed above provide fairly convincing evidence that consistency reflects the fidelity of cognitive control processes necessary for maintaining attention on task. There are many important factors regarding RT IIV, however, that are still unknown. Firstly, the relationship between RT IIV and cognition in aging has yet to be fully established. In particular, the reasoning that consistent responding represents efficient executive control should be supported not only through experimental task manipulation (West et al., 2002), but also by correspondence with established measures of executive functioning. Secondly, it has not been
determined how cognitive features of an individual contribute to the potential reduction of inconsistency in healthy and pathological aging. Thirdly, it is important to investigate whether RT IIV can be modulated in conditions when there is damage to this network, and whether there would be an associated change to attentional performance. Understanding these processes could have an impact on the cognitive rehabilitation of attention impairment, but also inform our knowledge of IIV and cognitive control.

A recent study by Garrett et al. (2012) implemented an interactive goal-directed feedback paradigm within a four-choice reaction time task. The authors were inspired by evidence suggesting that attention can be improved with effective intrinsic (e.g. a participant’s interest in the task) and extrinsic (e.g. external incentives such as points) attentional motivation or goal direction on task (Bengtsson, Lau, & Passingham, 2009; Tomporowski & Tinsley, 1996). They reasoned that concurrent feedback during task performance with extrinsic motivators could prompt participants to adjust their strategic approach by restricting longer latencies, and thus decrease IIV. This method proved effective, and a reduction in older adults’ IIV was observed over the course of the 4-block task, after controlling for practice related improvements. Their results also suggested that older adults with higher levels of education benefited more from the feedback. This study provided support for the ability to alter response time IIV in healthy adults, but it is unknown how this paradigm might be applicable in a brain injured sample. Although healthy adults may have individual differences in cognitive abilities, they do not suffer from any significant attentional impairment that may alter the efficacy of the intervention. It is unknown whether this approach could be applied successfully to individuals with damage to the brain network supporting sustained attention. If beneficial results are produced, we may consider this type of metacognitive skills training as a component of attentional rehabilitation. But how does this approach fit in with existing research on rehabilitation strategies for attention?
Despite much research on the cognitive rehabilitation of attention, there is still no widely accepted standardized intervention for executive and attentional impairment. There may be several reasons for this gap in consensus including heterogeneous patient samples, no consistent use of control groups, limited outcome assessment, and the fact that many treatment techniques studied are not theoretically based (Levine & Downey-Lamb, 2002). There are four behavioural approaches that have been used to address difficulties in attention, which patients with brain injury typically possess – attention process training, strategies/environmental support, external aids, and psychosocial support (Sohlberg & Mateer, 2001). Attention process training involves the use of cognitive exercises based on the notion that impaired abilities can be improved by stimulating particular attention systems through practice. The use of strategies includes both those applied internally to self-management and externally to modifying the environment, and provides compensation for attention problems. The use of external aids help individuals track and organize information, with the potential for more functions through the development of personal technology. Lastly, psychosocial support targets those emotional and social aspects that can that can develop along with attentional disorders, or even exacerbate them. A comprehensive review of available treatments recommends metacognitive training as a practice standard because it has been shown to be most effective at promoting the development of compensatory strategies that can be directly applied to real world situations (Cicerone et al., 2011). The same authors indicated that attention process training may be included as an adjunct treatment, but evidence is lacking for its effectiveness as a standalone therapy.

Self-management/metacognitive strategy training is quite useful at encouraging individuals to be more deliberate at focusing their attention. The skills learned are well applied to
common complaints of previously automatic tasks that require more effortful concentration post-injury. In one strategy, orienting procedures, individuals are taught to consciously monitor their activities to avoid attention lapses, for example by asking themselves orienting questions at periodic intervals (Sohlberg & Mateer, 2001). An expansion of this method is training in behavioural self-regulation such as Goal Management Training (GMT), which is an intervention program that teaches individuals to monitor ongoing activity by stopping mid-behaviour in order to define goal hierarchies (Levine et al., 2000). GMT is based on the theory that disruption of the executive control network results in distractibility, interference between tasks in working memory, and goal neglect. Training to interrupt behaviour frequently to check whether current activity matches intended goals allows individuals to overcome attentional failures and stay on task. The program is typically administered over several sessions during which clients learn a variety of other integral components (e.g. awareness for absent minded errors, breaking down tasks into sub-goals, and mindfulness meditation) through instruction and practice. In initial studies, GMT was shown to be effective at improving complex attentional skills in brain injured and healthy adults (Levine et al., 2000; Levine et al., 2007). Further research applying a comprehensive version of GMT and similar variants of it also demonstrated success, observed through reduced attention lapses on experimental tasks, improved problem solving performance (Levine et al., 2011), as well as transfer to untrained cognitive and real world functional tasks (Novakovic-Agopian et al., 2011).

Although metacognitive training is currently regarded as the most successful intervention for attentional dysfunction, there has been promising research using external aids. In one study, participants with traumatic brain injury demonstrated improved performance on an executive control task simply with the introduction of brief auditory alerts (Manly, Hawkins, Evans, Woldt, & Robertson, 2002). The auditory alerts were unrelated to the experimental task, only serving to
signal participants to become more aware of what they were doing. Similar alerting techniques have demonstrated beneficial results in healthy individuals (Manly et al., 2004), as well as children with ADHD (O’Connell, Bellgrove, Dockree, & Robertson, 2006). This approach is based on the idea that failures of sustained attention, or attention lapses, may occur when there is a transient decrease in endogenous control of behaviour permitting the occurrence of goal-neglect and distraction by irrelevant stimuli (O’Connell et al., 2008). Further research has supported this notion demonstrating that tones can reduce reliance on top-down control processes and act as an attentional prosthetic (O’Connor, Robertson, & Levine, 2011). This external alerting research reveals that bottom-up exogenous cueing can compensate for a deficit in self-initiated internal top-down control of attention.

Unfortunately, the use of external alerts/aids in real world settings has not always been practical in the past. With advancements being made in technology, however, external aids are becoming a more viable option, as can be seen in the memory rehabilitation literature (Svoboda, Richards, Leach, & Mertens, 2012). In the meantime, a more feasible method would be if modulation of alerting systems could be achieved internally with top-down control, allowing for application in a variety of settings – transforming the external aid into an internal metacognitive strategy. This idea was implemented in a group of stroke patients with sustained attention deficits (Robertson, Tegnér, Tham, Lo, & Nimmo-smith, 1995). Patients were given a selection of routine everyday tasks to perform (e.g. reading, sorting), and the experimenter would sporadically introduce a loud noise (clapping) with the instruction to attend in order to redirect the patients’ attention. Patients were then trained to self initiate this alerting procedure with a self-generated verbal signal. Following training, patients were able to endogenously activate their sustained attention systems without any external cue, and without even generating their own
verbal signal. Importantly, these participants showed significant improvements to trained and untrained attention tasks.

More recently, O’Connell et al. (2008) elaborated on this self-alert training (SAT) by incorporating biofeedback to facilitate the training process and to confirm training at a biological level. Participants were now able to gauge change in alertness levels in real time through electrodermal activity (EDA). Skin conductance responses (SCRs) have been widely used in psychological research and are thought to be indicative of attentional engagement (Frith & Allen, 1983). There is evidence that the volitional modulation of SCRs may activate prefrontal regions that are implicated in the top-down control of sustained attention (Critchley, Melmed, Featherstone, Mathias, & Dolan, 2002; Nagai, Critchley, Featherstone, Trimble, & Dolan, 2004). To capitalize on the link between sustained attention and arousal, participants were taught to internally generate an increase in arousal at regular intervals to offset periodic decreases in endogenous control. They found that SAT led to increased levels of autonomic arousal and improved performance on the SART in participants with ADHD.

The training procedure reported by O’Connell et al. (2008) lasted a maximum of 40 minutes, and thus does not represent an attempt to implement long term behavioural change. This SAT paradigm, however, demonstrates the potential for the rapid investigation of the cognitive mechanisms underlying attention remediation. With relevance to the present dissertation, a relatively simple paradigm was sought and already found to be successful by Garrett and colleagues (2012), focusing on providing performance feedback and motivation to improve. Research examining the effect of feedback training on RT consistency and the potential for variability reduction has been severely limited. It is also unknown whether this type of cognitive
rehabilitation technique will result in improved performance in patients with acquired neurological dysfunction such as from cerebrovascular disease.

1.4 Cerebral Small Vessel Disease

Cerebral small vessel disease (CSVD) is a cerebrovascular condition referring to a variety of pathological processes that affect small penetrating arteries, arterioles, capillaries, and even small veins in the brain. In contrast to large vessels that are typically involved in stroke, current technology does not allow small vessels to be visualized. As a result, brain lesions thought to be caused by pathological changes to these small vessels are taken as indicators of CSVD. Current brain imaging methods reveal corresponding neuropathology in the form of white matter lesions (formerly referred to as leukoaraiosis or rarefaction of white matter), lacunar infarcts (small covert ischaemic lesions 3–15 mm$^3$ in size), and cerebral microbleeds (small covert haemorrhagic lesions); however, white matter lesions tend to be the most prevalent. They are detectable on MRI using T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, and appear as hyperintense foci. Rating scales have been developed to characterize the lesion severity (Wahlund et al., 2001), which goes from isolated foci to confluence, describing the blending and expansion of multiple lesions. White matter lesions typically occur symmetrically and bilaterally across hemispheres, showing prominence around the ventricular horns and periventricular white matter.

Current theory suggests that when small vessels are compromised, blood flow in these regions becomes restricted, leading to a state of chronic hypoperfusion of the white matter, and eventual axonal loss and secondarily, degeneration of myelinated fibres (Fazekas et al., 1993).
This process represents a form of incomplete infarction, which can be contrasted with an acute occlusion of a small vessel, leading to complete infarction and more immediate tissue necrosis, which forms a lacune (Pantoni, 2010). CSVD can occur from a variety of causes including arteriolosclerosis and hereditary precursors (see Pantoni, 2010 for review). The most common type is due to arteriolosclerosis, also known as age-related and vascular risk-factor-related small vessel disease. For this reason, small vessel disease is highly related to aging, hypertension, and diabetes (Furuta, Ishii, Nishihara, & Horie, 1991), and contributes to cognitive decline, stroke, and dementia (Pantoni, 2010; Wardlaw, Smith, & Dichgans, 2013).

Regardless of the origin of cerebrovascular abnormalities, the deterioration of these small vessels commonly produces neuronal damage of subcortical brain structures, often leading to cognitive impairment. A disruption to fronto-subcortical pathways is thought to be a substantial contribution to cognitive dysfunction in CSVD (Cummings, 1998). Damage can occur at various points along the fronto-subcortical network, disconnecting communication between different cortical regions via long association white matter fibres, or affecting those pathways that connect cortical and subcortical regions (i.e. internal capsule and corona radiata). Lacunes or microbleeds may damage the subcortical nodes of this network such as the pons, thalamus, and basal ganglia, which are also dependent on small vessels for blood supply (Charidimou & Werring, 2012; Mohr, 1982; Román, Erkinjuntti, Wallin, Pantoni, & Chui, 2002). Although a significant localized disturbance to this network may cause differing effects depending on the size and site of the lesion, it is generally believed that CSVD on its own produces a consistent cognitive presentation (Erkinjuntti et al., 2000).

CSVD represents a significant health concern to society, as it is one of the most prevalent neurological conditions and many believe it may be the most common cause of vascular
pathology leading to vascular cognitive impairment no dementia (VCIND) (Esiri, Wilcock, & Morris, 1997; Pantoni, 2010; Román et al., 2002). The risk of cerebrovascular disease is known to increase with age, and is clearly demonstrated in research showing that the prevalence of vascular neuropathology increases from age 64 (11-12%) to the age of 82 (up to 94%) (Garde, Mortensen, Krabbe, Rostrup, & Larsson, 2000; Ylikoski et al., 1995). It is not completely understood, however, how cerebrovascular lesion burden translates to behavioural changes. That is, we can assume a direct correspondence between brain integrity and alterations in cognitive performance, but it is not yet known the degree of cerebrovascular lesion severity that can be endured before declines can be observed behaviourally. Studies have found at least a mild degree of white matter lesions in over 90% of purportedly healthy elderly participants sampled (de Leeuw et al., 2002; Longstreth et al., 1996), suggesting substantial cognitive resiliency. The research alludes to a continuum of cerebrovascular compromise, leading to cognitive changes that may be classified as either subclinical/covert, or overt impairments. The observation that cognitively healthy adults can possess cerebrovascular pathology suggests that neural compromise does not necessarily lead to behavioural changes; there may be compensatory processes allowing for preserved functioning with minimal cognitive consequences. It can be logically assumed that without intervention, progressive CSVD will precipitate continued deterioration until clinically relevant changes are eventually found. Individuals with VCIND have a high risk of progressing to either vascular or mixed dementia as neuropathology worsens, leading to decline of cognitive and functional abilities (Serrano, Domingo, Rodríguez-Garcia, Castro, & del Ser, 2007; Wentzel et al., 2001).

The literature suggests that CSVD is a major aetiological cause of cognitive deficits that can evolve into vascular cognitive impairment (VCI) with and without dementia (Aguero-Torres, Kivipelto, & von Strauss, 2006). In theory, since CSVD is known to affect brain structures of the
fronto-subcortical network, the observed behavioural deficits should often lead to a dysexecutive syndrome (Cummings, 1998). Neuropsychological evaluation of patients with CSVD has revealed deficits that are consistent with this reasoning, demonstrating deficits primarily in processing speed, attention, and executive functions (Román et al., 2002; Tierney et al., 2001). Studies with the non-demented elderly offer some support by identifying a relationship between white matter lesions and impairments in global functioning and psychomotor speed (de Groot et al., 2000; Garde et al., 2000; Longstreth et al., 1996). There have been some inconsistencies, however, among studies as to whether impairments to speed and executive abilities are core features, and whether memory decline is significant. Quantitative reviews of cognition in healthy older adults with signs of CSVD have attempted to clarify this discrepancy. One group analysed 16 studies using Pearson’s $r$ as a measure of effect size and found that the strongest correlations with white matter lesions were for executive, speed, and global functioning domains (Gunning-Dixon & Raz, 2000). Not long after, a similar approach using Pearson’s $r$ was applied to independent neuropsychological tests rather than overall domains (Oosterman, Sergeant, Weinstein, & Scherder, 2004). The authors found that the only significant relationship for white matter lesions was with lower performance on timed tests of executive functioning. These previous reviews did not limit their sample to individuals with cognitive impairment due to CSVD, and as a result could only rely on correlational data. In a recent meta-analysis, I contrasted the mean $d$ of cognitive test performance between individuals with vascular cognitive impairment (not demented) due to CSVD and healthy older adults (Vasquez & Zakzanis, 2015). We concluded that individuals with VCIND due to CSVD have weaknesses across all cognitive domains compared to healthy older adults, and that the most impaired domains were processing speed, then memory, followed by executive functioning. Given that individuals with CSVD typically have mild attentional dysfunction, evident from both neuropsychological and RT IIV.
research discussed above, this population provides an exceptional model of neurological
dysfunction with which to ascertain a link between executive functions and RT IIV.

1.5 Thesis Overview

This thesis is comprised of four research themes designed to characterize the cognitive
factors that yield consistent and inconsistent responding from trial to trial, and whether
intervention can alter this aspect of the response profile for healthy adults with and without
cerebrovascular disease (i.e. CSVD). The primary objectives of this PhD dissertation are: to 1)
examine how age-related changes in cognition are associated with response time consistency
measured through classical ISD and ex-Gaussian parameters (Studies 1 and 2); 2) explore the
potential for improvement in response time consistency in younger and older adults using an
attention training paradigm (Study 3); 3) investigate whether white matter lesions due to cerebral
small vessel disease are predictive of indices of response time consistency in older adults (Study
4); and 4) to examine whether the degree of white matter lesion burden contributes to the
successful improvement of response time consistency in older adults following training (Study
5). The focus of this dissertation is on RT IIV, given its association with executive control as
described above.

It has previously been shown that response time consistency is associated with an
experimental measure of working memory in older adults (Tse et al., 2010). Thus, it is predicted
that there will be a significant correspondence between executive/working memory abilities and
attentional maintenance indexed through intraindividual response time variability. Given the
knowledge that response time inconsistency is elevated in older adults (Hultsch et al., 2002), it is
suspected that the relationship with executive functioning will vary with age. Furthermore, the extent to which healthy individuals will benefit from attention training in terms of improvements in consistency will likely be dependent on age as well. Research has demonstrated that white matter integrity is associated with elevations in response time variability (Bunce et al., 2007, 2010; Fjell et al., 2011; Jackson et al., 2012; Walhovd & Fjell, 2007), and thus I expect to find that the volume of white matter lesions is predictive of variability. I also expect that white matter lesion volume will play a role in training success – I predict that stronger white matter integrity will permit greater control over improving consistency.

Please note that my first dissertation study has already been published and that the rest are in preparation to be submitted for publication. Thus, the thesis is organized as manuscripts with formatting preserved, and some methodological details will be repeated between chapters.
Chapter 2

Staying on task: Age-related changes in the relationship between executive functioning and response time consistency


2.1 Introduction

Inconsistency, or intraindividual variability in response time (RT IIV), is increasingly being recognized as an important marker of central nervous system integrity and is thought to be a useful measure of neurocognitive function. The measure is typically expressed either as the standard deviation calculated within each participant’s response time data set (intraindividual standard deviation; ISD), or as a coefficient of variation (ISD/mean RT). Research employing a variety of experimental tasks (e.g. simple RT, choice RT, lexical decision, and semantic decision) has shown that RT IIV is greater in healthy older adults compared with younger adults (Hultsch, MacDonald, & Dixon, 2002; Williams, Hultsch, Strauss, Hunter, & Tannock, 2005; Hultsch et al., 2008). Age stratification within older adult groups (e.g. young-old, mid-old, and old-old) reveals that inconsistency continues to increases with age, even in the later part of life (Hultsch et al., 2002). The evidence from more extensive cross-sectional lifespan research further supports the idea that aging is accompanied by a linear increase of within-person RT variability from the mid 20s to mid 80s at least (Williams et al., 2005).
One approach that researchers have taken to understand the source of elevated variability with age is to fit individuals’ data to an ex-Gaussian distribution, which permits the analysis of specific distribution components (West et al., 2002). An ex-Gaussian distribution is the convolution of a normal (Gaussian) function and an exponential function. The distribution is specified by three parameters: mu and sigma representing the mean and standard deviation of the Gaussian component respectively, and tau representing the right tail of the distribution, with a larger tau value indicating greater positive skew. Larger tau has been interpreted as an indicator of brief attention lapses (West et al., 2002).

A potential contributing factor to age-related increases in RT IIV and tau is the age-related deterioration of the frontal lobes (Resnick et al., 2003), responsible for the top-down influence that enables sustained attention (i.e. cognitive control). Support for this connection comes from research on brain damaged individuals, neuroimaging research on healthy individuals, and research on healthy older adults. First, the literature has shown that focal lesions to the frontal lobes impair stability of cognitive performance (Stuss, Murphy, & Binns, 1998; Stuss et al., 2003). Second, evidence from functional neuroimaging has confirmed an association between RT IIV and activation of brain regions involved in sustained attention, including the frontal lobes (Bellgrove et al., 2004). Third, and most relevant to the current investigation, studies have shown that older adults have higher tau values (Spieler, Balota, & Faust, 1996; West et al., 2002), and adult age differences in inconsistency have been reported to be primarily due to attention lapses, detected by changes in the slow end of the RT distribution (Anderson, 1999; Williams et al., 2005).

Another approach to understanding the source of age-related increases in variability is to relate observed differences in IIV and/or ex-Gaussian parameters with executive functions.
Studies that have explored this relationship, however, have been limited by the measures used, or by conceptualization of executive function. One study examined how the influence of age on variability was modulated by varying demands on executive control processes (West et al., 2002). The rationale was that if aging results in greater fluctuations in executive control efficiency, then age-related increases in IIV would be more pronounced in tasks with higher executive control requirements. Indeed, their results showed that RT variability was greater in older adults in high executive control demand conditions, but similar to younger adults in conditions requiring minimal executive control. Their study used a choice response time task involving the identification of one of 4 digits in a current display (non-executive), contrasted with a condition requiring identification for the previous display (1-back; executive). Although this manipulation elicited RT differences in relation to executive demand, it did not include assessment of a wider range of cognitive processes that constitute executive functioning. It is possible that individual differences in discrete executive abilities (e.g. flexibility, inhibition, and working memory) could differentially be related to variability in performance. Lastly, it is unclear whether the effects found were indeed due to increased executive demand, or simply a result of differences in task difficulty between choice RT and 1-back conditions. More recently, intervals on a continuous tapping task were manipulated to differentially engage attentional control systems (Bangert & Balota, 2012). The authors found that healthy older adults sped up their tapping at the slowest target rate compared to younger adults, which they reasoned was due to a breakdown in attentional control affecting the ability to maintain a synchronous response pattern independent of an auditory pacer.

A study combining both experimental and clinical tests showed that tau, computed from a composite of Stroop, Simon, and switching tasks, significantly correlated with several neuropsychological measures of cognition in a healthy older adult sample (Tse et al., 2010). The
relationships existed across several domains examined, but the strongest associations were with those tasks tapping speed of processing and executive/working memory abilities. In contrast, mu and sigma displayed fewer and weaker correlations with cognitive test performance, with no link to executive/working memory ability. Another study found that inconsistency in RT was associated with poorer everyday problem-solving abilities (Burton, Strauss, Hultsch, & Hunter, 2009). The authors demonstrated that this remained true after accounting for age, education, and mean level of performance. The problem-solving abilities studied in this research were instrumental activities of daily living (IADLs), and we know that these activities have a strong executive requirement, with established associations between certain neuropsychological tests of executive functioning and IADL measures (Bell-McGinty, Podell, Franzen, Baird, & Williams, 2002; Cahn-Weiner, Boyle, & Malloy, 2002; Jefferson, Paul, Ozonoff, & Cohen, 2006; Tomaszewski Farias et al., 2009). Together, this literature indicates a connection between executive functions and increased variability. However, neither of these two studies included a younger adult sample, and so they could not evaluate whether the relationship between intraindividual variability and executive functioning differs between old and young.

The goals of this study were: 1) to replicate the findings of age-related differences in mean RT, target misses, RT ISD, and ex-Gaussian parameters during an engaging touch-screen attention task, in young, young-old, and old-old samples; and 2) to investigate age-related changes in the relationship between performance on neuropsychological tests of executive functioning and RT distribution indices (ISD, mu, sigma, and tau). There is only one known study that previously examined the relationship between individual differences in various aspects of executive functioning and ex-Gaussian parameter estimates in older adults (Tse et al., 2010). However, their investigation focused on pathological differences, including both healthy older adults and those with mild cognitive impairment, rather than the healthy aging process.
Additionally, Tse et al. (2010) did not contrast ex-Gaussian distribution parameters with an established measure of intraindividual variability (i.e. ISD).

We developed a task in which stimuli scroll continuously across a touch screen, with the goal being to tap a specified target as quickly as possible. The rationale was to have a task that was more engaging and relatable to the real world than typical RT tasks, which is a direction that has recently been taken in RT IIV studies by employing driving and flight simulators (see Bunce, Young, Blane, & Khugputh, 2012; Kennedy et al., 2013). The recording of response time data from each tap allowed us to calculate ISD and estimate ex-Gaussian parameters. The recording of on-screen tap location also enabled the analysis of strategic differences. Here, an example of a strategy that would produce more consistent performance would be to position one’s hand over a specific section of the screen and tap each time a target passed beneath. This strategy is in contrast to a strategy that may produce greater variability in which the participant’s hand is not fixed over a certain section of the screen, promoting tapping to various locations. This analysis involved computing an x-coordinate ISD (i.e., variability in the location at which participants tapped). X-coordinate ISD is invariably linked to RT as touching a card further along the x-axis leads to a greater amount of time elapsed, but still provides separate information on response style. No prior study has explored whether strategy differences contribute to age-related increases in IIV. Potentially, the greater IIV observed in older adults could be partially explained by age differences in strategic approaches to tasks, a possibility that is supported by research demonstrating that older adults use different strategies compared to young adults (Brebion, Smith, & Ehrlich, 1997; Touron & Hertzog, 2004; Velanova, Lustig, Jacoby, & Buckner, 2007).

We anticipated an age-related increase in response time (Salthouse, 1996b), and a linear increase in performance variability (ISD, sigma, tau) from young to young-old to old-old
(Hultsch et al., 2002, 2008; West et al., 2002). We hypothesized that there would be no difference in strategy application between the groups as the literature has converged on attentional changes being the primary source of RT variability differences between young and old. Lastly, we expected that poorer performance on executive measures would be related to greater ISD and tau, reflecting the impact of decreased cognitive control on tests of executive functioning.

### 2.2 Methods

**Participants**

We recruited 24 healthy young adults (aged 18-30 years; M = 24.4, SD = 3.1; 3 males) and 48 healthy older adults (aged 65-85 years; age M=74.4, SD=6.1; 13 males) from the Rotman Research Institute participant database. The older adult group was recruited to comprise two subgroups with 24 participants each: young-old (aged 65-74; M = 69.1, SD = 3.2; 6 males) and old-old (aged 75-85; M = 79.7, SD = 2.6; 7 males). Participants were excluded on the basis of the following criteria: a history of head injury resulting in a loss of consciousness, neurological impairment or other major medical illnesses (e.g. stroke, dementia, and heart disease), radiation to the head, drug abuse, current use of psychiatric medication, or a lack of fluency in English. Older adults also had to achieve a score greater than 30 points on the modified Telephone Inventory of Cognitive Status (Welsh, Breitner, & Magruder-Habib, 1993) to be eligible to participate. Written informed consent was obtained from all volunteers, and monetary compensation was provided for participating in the study. This research was approved by Baycrest’s Research Ethics Board.
**Procedures**

After informed consent, a selected neuropsychological battery was administered to each participant. At the approximate midway point of the battery, participants completed the computerized attention task. Following the attention task, they resumed neuropsychological testing. The entire session lasted approximately two hours.

**Attention task**

This task was designed to be more ecologically valid than more commonly used experimentally based simple and choice response time tasks by incorporating dynamic movement and a feature identification requirement. Our task borrowed from naturalistic activities requiring the maintenance of selective attention over a prolonged period of time, such as observing items moving along a conveyor belt and identifying specific targets. On a production line these targets might be defective products, whereas at airport security targets would be restricted or dangerous articles.

The task involved images of playing cards scrolling continuously from left to right or from right to left (depending on the participant’s dominant hand) on a touch screen, with the goal being to tap the target (8 of spades) as quickly as possible using a stylus. The program was run on a Hewlett Packard Touchsmart-tm2 tablet PC with 13-inch screen (resolution 1280x800) placed face up on a table, slightly angled towards the participant to reduce screen glare. Before the participant began the task, they watched the experimenter demonstrate what was required with 5 target cards. The experimenter then handed the stylus to the participant for practice interacting with the touch screen. Successfully registered touches were indicated when the stimulus turned grey. Once the participant touched 10 targets the practice ended. The task took
approximately 20 minutes with 3 evenly placed breaks dividing the task into 4 blocks. Breaks were very short intermissions, only given for participants to rest their eyes briefly. Both response time and position (in pixel x-y coordinates) were recorded.

The attention task consisted of 1728 images of playing cards, 144 of which were the target 8 of spades. The remaining cards included numbers 5 through 9 in each of the 4 suits (spades, hearts, clubs, and diamonds). For each participant, the program first constructed four blocks of 432 cards. The cards within each block were ordered into 108 sets of four cards each, with the target present in 36 sets per block (33%). Selection of the non-target cards was controlled, such that cards within a set shared a certain number of attributes (colour, suit, number) in common with the target. Specifically, the non-target sets contained two 2-feature, one 1-feature, and one 0-feature overlap non-target cards (Figure 2.1)\(^1\). Target sets contained one 2-feature overlap non-target card, one 1-feature overlap non-target card, and one 0-feature overlap non-target card (Figure 2.1). Within each block, the sets were randomly ordered with the restriction that no more than three sets containing targets occurred consecutively. Once the trial set generation was completed, which only took a few seconds, the program began. It is important to note that although the cards were grouped into sets for the purpose of stimulus order selection, this grouping was not apparent to the participant while the program was running. All cards were evenly spaced, thus eliminating the appearance of preconceived organization.

\(^1\) Note that playing cards do not permit full factorial combinations of feature overlap with the target (i.e., the 1-feature overlap cards shared the number only, or the colour only, but could not share the suit).
Cards were presented on a white background. They moved from left to right for right-handed participants and in the opposite direction for left-handed participants. The cards moved at a speed of 714.3 pixels/s (or 0.146 m/s), which resulted in them being on the screen for approximately 1.79 seconds. The card images were 200 by 250 pixels in size, subtending visual angles of 5.8 by 7.3 degrees at an approximate viewing distance of 40 cm. At this speed and size, with preset spacing between cards, no more than 4 cards were visible on the screen at a given time.
**Data Preparation**

Mean response time and IIV were calculated only from ‘hit’ responses, excluding false alarms. Hit responses for the first target in each block were excluded from all analyses to accommodate task “warm-up” effects. Instances of unusually quick responses (faster than possible to carry out decision and motor action components) were unlikely to occur because the task demanded more thoughtful responding, compared to a simple button press. Accidental screen taps were rare, and typically represented false alarms (a frequency of .001%). Upper value outliers representing extremely slow responses were not possible because cards moved off the screen in 1.79 seconds, making that the upper limit for a response. If the participant was too slow to respond in that time, it was counted as a miss. Values for missing data points were not imputed.

**Estimating Intraindividual Variability and Ex-Gaussian Distribution Parameters**

There are different indices of intraindividual variability and some researchers have chosen to use the intraindividual coefficient of variation (ICV) to control for systematic group differences in mean performance. However, this method combines effects of the ISD and mean performance, as well as their cross-product, which can lead to ambiguity in results (Hultsch et al., 2008). Thus, we employed the intraindividual standard deviation (ISD) with preceding data “purification” steps as a measure of IIV based on consensus from the field (Hultsch et al., 2008). This method ensures that systematic trends in performance (practice effects, fatigue, etc.), as well as other deterministic variations in mean performance are eliminated before calculation of ISD. First, the data were checked for linear, quadratic, and cubic trends, which revealed a small but significant negative linear slope. Next, individual trial RTs were regressed on trial number for each participant and residuals saved. Lastly, intraindividual standard deviations were
calculated from the unstandardized residuals. We did not include block in the regression as preliminary analyses did not reveal differences across blocks.

Ex-Gaussian parameters were computed separately for each individual using a MATLAB toolkit (Lacouture & Cousineau, 2008). The MATLAB script estimated mu, sigma, and tau parameters for each participant.

Neuropsychological Battery

The following tests were administered to each participant: Mini Mental State Examination (MMSE), Shipley’s Institute of Living Scale, The Boston Naming Test (30-item form), Wechsler Memory Scale III (WMS-III) Logical Memory I and II, WMS-III Digit Span forwards and backwards, Wechsler Adult Intelligence Scale III (WAIS-III) Digit Symbol Coding, and the Wisconsin Card Sorting Test (WCST). In addition, Trail Making, Colour-Word Interference, and Fluency subtests from the Delis Kaplan Executive Function System (DKEFS) were administered. Of note, one of the five Trail Making subtests, number-letter switching, is analogous to the traditional timed Trail Making test part B, except that it is spread across a sheet of paper measuring 11X17 inches. Similarly, Colour-Word Interference inhibition subtest is analogous to a timed version of the Stroop test – inhibition, and DKEFS Fluency consists of phonemic (FAS), semantic (animals and boys names), and switching (fruits/furniture) subtests.

Statistical Analysis

Bivariate correlation was applied to all RT variables (mean, ISD, mu, sigma, and tau) and x-coordinate ISD in order to examine the relation between them. To confirm the effect of decreasing attention abilities with age, mean response time, target misses, RT ISD, ex-Gaussian parameters (mu, sigma, tau), and x-coordinate ISD were analyzed in separate one-way linear
contrast ANOVAs with age group (young, young-old, old-old) as the between-subject independent variable. To test the hypothesis that poorer performance on executive measures would be related to greater ISD and tau, a structural equation model (SEM) was created using neuropsychological measures of executive functioning and RT indices. The SEM was created using IBM SPSS Amos 20.0. Age-related differences in the association between executive functioning and tau were examined by creating a composite executive score (informed from SEM regression weights) and running a bivariate correlation within age groups separately.

2.3 Results

Demographics and Neuropsychological Functioning

Demographic information on the sample (i.e. age and education), as well as neuropsychological test scores, are summarized in Table 2.1. Inspection of the three age groups (young, young-old, and old-old) revealed similar levels of education, and general functioning as measured by the MMSE. Consistent with much prior research, younger adults performed slightly worse on the vocabulary subtest of Shipley’s Institute of Living Scale compared to both older participant groups. Although not present for every test, there was a tendency for younger adults to outperform young-old, who in turn outperformed old-old on cognitive measures.
Table 2.1. Group differences on demographic and neuropsychological measures.

<table>
<thead>
<tr>
<th></th>
<th>Young (n=24)</th>
<th>Young-Old (n=24)</th>
<th>Old-Old (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(aged 18 – 30)</td>
<td>(aged 65 – 74)</td>
<td>(aged 75 – 85)</td>
</tr>
<tr>
<td>Age</td>
<td>24.38 (3.08)</td>
<td>69.13 (3.15)</td>
<td>79.67 (2.65)</td>
</tr>
<tr>
<td>Education</td>
<td>16 (2.36)</td>
<td>16.13 (2.59)</td>
<td>14.79 (3.44)</td>
</tr>
<tr>
<td>MMSE (/30)</td>
<td>29.71 (0.55)</td>
<td>29.25 (1.03)</td>
<td>28.58 (1.25)</td>
</tr>
<tr>
<td>Shipley’s (/40)</td>
<td>32.17 (4.09)</td>
<td>35.96 (2.40)</td>
<td>35.17 (2.71)</td>
</tr>
<tr>
<td>Digit Symbol Coding</td>
<td>94.46 (17.63)</td>
<td>65.00 (12.83)</td>
<td>57.17 (12.23)</td>
</tr>
<tr>
<td>WCST % Perseverative Errors</td>
<td>9.21 (5.93)</td>
<td>12.63 (8.29)</td>
<td>17.04 (12.04)</td>
</tr>
<tr>
<td>DKEFS Number Sequencing</td>
<td>24.46 (7.45)</td>
<td>37.75 (9.98)</td>
<td>44.29 (12.26)</td>
</tr>
<tr>
<td>DKEFS Letter Sequencing</td>
<td>24.00 (10.22)</td>
<td>36.33 (12.53)</td>
<td>45.58 (11.51)</td>
</tr>
<tr>
<td>DKEFS Number-Letter Switching</td>
<td>53.63 (18.21)</td>
<td>93.04 (42.92)</td>
<td>127.42 (68.91)</td>
</tr>
<tr>
<td>DKEFS Color-Word Interference Inhibition</td>
<td>42.00 (8.65)</td>
<td>57.71 (18.79)</td>
<td>60.63 (11.02)</td>
</tr>
<tr>
<td>DKEFS Color-Word Interference Switching</td>
<td>46.71 (10.71)</td>
<td>60.96 (15.46)</td>
<td>67.79 (16.28)</td>
</tr>
<tr>
<td>DKEFS Phonemic Fluency (FAS)</td>
<td>42.58 (11.07)</td>
<td>48.50 (13.78)</td>
<td>44.46 (11.04)</td>
</tr>
<tr>
<td>DKEFS Categorical Fluency</td>
<td>46.79 (10.39)</td>
<td>42.75 (11.98)</td>
<td>37.00 (8.06)</td>
</tr>
<tr>
<td>DKEFS Switching Fluency</td>
<td>15.54 (2.59)</td>
<td>14.42 (3.32)</td>
<td>13.58 (2.96)</td>
</tr>
</tbody>
</table>

Significant differences between groups at p<.05 - a = Y-YO, b = Y-OO, c = YO-OO
Attention Task Performance

An age-regressed correlation matrix of attention task measures can be found in Table 2.2. Mean RT was significantly correlated with mu and sigma, which is not surprising given that the two parameters reflect the mean and standard deviation of the Gaussian distribution component. Mean RT also significantly correlated with x-coordinate ISD, and misses, but not RT ISD or tau. A significant association was found between RT ISD and the following measures: tau, x-coordinate ISD, misses, and false alarms. Tau was significantly correlated with all measures except mean RT, with the strongest relationship being with RT ISD ($r = .786$, $p < .001$).

Table 2.2. Attention task measures correlation matrix

<table>
<thead>
<tr>
<th></th>
<th>RT ISD</th>
<th>mu</th>
<th>sigma</th>
<th>tau</th>
<th>X-ISD</th>
<th>misses</th>
<th>false alarms</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean RT Pearson r</td>
<td>.108</td>
<td>.941&quot;</td>
<td>.616&quot;</td>
<td>-.089</td>
<td>.471&quot;</td>
<td>.389&quot;</td>
<td>.146</td>
</tr>
<tr>
<td>Sig.</td>
<td>.368</td>
<td>.000</td>
<td>.000</td>
<td>.458</td>
<td>.000</td>
<td>.001</td>
<td>.222</td>
</tr>
<tr>
<td>RT ISD Pearson r</td>
<td>1</td>
<td>-.169</td>
<td>.021</td>
<td>.786&quot;</td>
<td>.615&quot;</td>
<td>.399&quot;</td>
<td>.414&quot;</td>
</tr>
<tr>
<td>Sig.</td>
<td>.155</td>
<td>.864</td>
<td>.000</td>
<td>.000</td>
<td>.001</td>
<td>.000</td>
<td>.000</td>
</tr>
<tr>
<td>mu Pearson r</td>
<td>1</td>
<td>.706&quot;</td>
<td>-.421&quot;</td>
<td>.315&quot;</td>
<td>.250&quot;</td>
<td>.009</td>
<td></td>
</tr>
<tr>
<td>Sig.</td>
<td>.000</td>
<td>.000</td>
<td>.007</td>
<td>.035</td>
<td>.942</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sigma Pearson r</td>
<td>1</td>
<td>-.426&quot;</td>
<td>.395&quot;</td>
<td>.318&quot;</td>
<td>.142</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sig.</td>
<td>.000</td>
<td>.001</td>
<td>.007</td>
<td>.234</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tau Pearson r</td>
<td>1</td>
<td>.336&quot;</td>
<td>.309&quot;</td>
<td>.365&quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sig.</td>
<td>.004</td>
<td>.008</td>
<td>.002</td>
<td>.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-ISD Pearson r</td>
<td>1</td>
<td>.496&quot;</td>
<td></td>
<td>.476&quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sig.</td>
<td>.000</td>
<td>.000</td>
<td></td>
<td>.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>misses Pearson r</td>
<td>1</td>
<td>.439&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sig.</td>
<td>.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).
**Mean Response Time.** There was a significant linear effect of age group on mean RT, \(F(1, 69) = 13.16, p = .001, \eta^2 = .16 \) (\(B = 90.93\), standard error = 25.07). Younger adults were fastest (\(M(SD) = 1004.24 \text{ ms (207.28)}\)), followed by the young-old group (1143.25 ms (145.52)), and then the old-old group (1186.11 ms (162.26)).

**Target Misses.** The contrast ANOVA revealed a significant linear effect of age group on target misses, \(F(1, 69) = 25.42, p < .001, \eta^2 = .27 \) (\(B = 4.40\), standard error = .87). Younger adults missed the fewest number of targets (\(M(SD) = 1.33(1.63)\)), followed by the young-old group (4.67(3.88)), who missed fewer than the old-old group (10.13(9.58)). It should be noted, that the number of target misses was low, and not substantial enough to affect the RT distribution analyses.

**False Alarms.** The contrast ANOVA revealed a significant linear effect of age group on false alarms, \(F(1, 69) = 11.63, p = .001, \eta^2 = .14 \) (\(B = 1.90\), standard error = .55). Younger adults had the fewest number of false alarms (\(M(SD) = .71(.91)\)), followed by the young-old group (1.96(4.29)), and then the old-old group (4.50(5.03)).

**Intraindividual Variability.** The analysis of ISD revealed a significant linear effect of age group on RT ISD (see Figure 2.2), \(F(1, 69) = 6.18, p = .015, \eta^2 = .08 \) (\(B = 16.71\), standard error = 6.72). Younger adults were the most consistent with the lowest ISD (\(M(SD) = 129.66 \text{ ms (48.75)}\)), followed by the young-old group with greater ISD (141.24 ms (43.85)), and then the old-old with the highest ISD (163.07 ms (46.89)).

**Ex-Gaussian parameters.** A linear effect of age group was observed for mu, \(F(1, 69) = 6.00, p = .017, \eta^2 = .08 \) (\(B = 67.32\) standard error = 27.61). Younger adults had the lowest mu (\(M(SD) = 905.57 \text{ ms (231.29)}\)), followed by the young-old and old-old groups with higher mu
respectively (1034.99 ms (167.29) and 1040.21 ms (165.03)). Tau demonstrated a significant linear effect of age group, $F(1, 69) = 6.672, p = .012, \eta^2 = .09$ (B = 23.61, standard error = 9.13). Younger adults had the lowest tau (M(SD) = 98.69 ms (52.30)), followed by the young-old group with greater tau (108.05 ms (63.54)), and then the old-old with the highest tau (145.90 ms (72.49)). The effect for sigma was not significant, $F(1, 69) = 2.844, p = .096$.

Figure 2.2. Response time variability indices as a function of age group

![Graph showing response time variability](image)

Note: error bars are standard error

**Tap x-Coordinate IIIV.** A strategy one could employ to improve speed and reduce variability on our task is to keep the stylus near the edge at which the cards first appeared, tapping the target as early as possible. Using a touch screen enabled the recording of positional
data of where participants touched the screen to make their response. We computed ISDs for the x-coordinates (based on pixels) using the same method as outlined above for response time. The effect of age group on x-coordinate ISD was not significant, $F(2, 69) = 1.26$, $p = .290$, $\eta^2 = .03$. We did not examine y-coordinates because all cards scrolled across the same vertical plane.

Relationships among IIV, ex-Gaussian parameters, and Executive Functioning

Because we know that age is related to executive function ability, IIV, and ex-Gaussian parameters, any correlations between these variables could reflect simply aging, and not a true relationship between these measures. Therefore, in order to examine the relationship between executive functioning and RT distribution indices, we first regressed out age from all measures of interest – purified RT ISD, mu, sigma, tau, and selected tests of executive functioning, and then saved the standardized residuals using the complete sample of younger and older adults. We chose to include five executive function measures that are commonly used in neuropsychological research and clinical practice: WCST percent perseverative errors, DKEFS Trail Making number-letter switching (time to complete), DKEFS Color-Word Interference inhibition (time to complete), and Verbal Fluency (total words generated; FAS), and Digit Span (total span). These tests cover a range of executive abilities such as problem solving, switching, inhibition, fluency, and working memory.

Next, we constructed a structural equation model (SEM) of the executive function measures and RT distribution parameters. The model was composed of the four RT distribution indices, all leading to a single component, which then predicted each of the five executive function measures. Covariance between variables was established according to modification indices in the SEM output to achieve good model fit, based on $CFI > .95$, $TLI > .90$, and $RMSEA < .08$, and the chi-square ($p > .05$). After modification of the model guided by covariance and
regression weight recommendations, the present model demonstrated a good fit to the data, CFI = .961, TLI = .918, RMSEA = .087, chi-square = 26.173, p = .071 (Figure 2.3). Inspection of the model indicates that the age-residualised ex-Gaussian variability parameters (sigma and tau) account for much more of the relationship with aspects of executive functioning than ISD or mu. The combined effect of all RT indices is related to WCST percent perseverative errors, Trail Making number-letter switching, and Color-Word Interference inhibition, with less weight to Verbal Fluency and Digit Span.
Figure 2.3. Structural equation model: Executive functions and RT distribution indices

Fit Indices: Chi square= 26.173, p=.071, CFI= .961, TLI=.918, RMSEA= .087

WCST = Wisconsin Card Sorting Test percent perseverative errors, N-L Switching = DKEFS Number-Letter Switching, Verbal Fluency = DKEFS FAS, C-W Inhibition = DKEFS Color-Word Interference Inhibition, Digit Span = WMS-III Digit Span total; All neuropsychological measures and response time distribution indices were age regressed Z-scores.
As a final step, we investigated age-related differences in the relationship between the most prominent RT parameter (tau) and executive functions. We used the regression weights from the SEM to construct executive function factor scores by multiplying the standardized regression weights by the raw neuropsychological scores (for a similar procedure see Souchay, Isingrini, & Espagnet, 2000; Taconnat et al., 2006). An executive function composite score was then created by adding these weighted scores together. Note that the standardized regression coefficients for this composite score were first multiplied by -1 to convert the latent variable from an executive dysfunction representation to that of an executive functioning characterization. The composite scores were also re-scaled to present all values with positive valence. Bivariate correlations were then calculated, separately for each age group, between our executive function composite score and tau. The results yielded a significant relationship only for the old-old group, $r = -.543, p = .006$, but not for the young, $r = .044, p = .839$, or young-old, $r = .131, p = .543$ (Figure 2.4).²

² The correlation between the EF composite and the other ex-Gaussian parameters was not significant at any age group independently. Only when the whole sample was combined did the association between the EF composite and mu and tau reach statistical significance.
Figure 2.4. Correlation between tau and executive function composite score by age group

Young

Young-Old

Old-Old
2.4 Discussion

Aging Effects

In the present study, we replicated prior findings of age-related declines in sustained selective attention using measures of mean response time, accuracy, and response time IIV. Our data showed age-related differences in RT, target misses, and in false alarms, which are in line with prior research on attention declines in healthy aging (Giambra, 1993; Parasuraman & Davies, 1977; West et al., 2002). We found a significant aging effect, with greater RT ISD in each successive age group from the young through the young-old, to the old-old group with the highest RT ISD. This is in agreement with the literature on aging and within-person variability (Hultsch et al., 2002, 2008). Several studies have reported greater within-person variability with age across a multitude of attention tasks, including finger tapping, simple RT, choice RT, and choice one-back (Bielak, Hultsch, Strauss, MacDonald, et al., 2010; Hultsch et al., 2002; Williams et al., 2005). More relevant to the present study is that research involving vigilance tasks has also confirmed the variability and aging effect (Bunce, 2001; MacDonald, Hultsch, & Bunce, 2006; O’Halloran, Finucane, Savva, Robertson, & Kenny, 2014). Similar to the observed effects on mean RT and ISD, significant linear age differences were found for the ex-Gaussian parameters mu and tau, but not sigma. Again, this is consistent with the literature demonstrating elevated mu and tau in older adults compared to younger adults (West et al., 2002).

We inferred that strategy differences in tapping the cards could be detected by examining x-coordinate ISD. By this logic, a low x-coordinate ISD could represent a response profile of locking one’s hand over a specific region of the screen and tapping a similar location each time a card passed beneath. No significant aging effect was found for x-coordinate ISD. This finding suggests that young adults were no more likely to employ such a strategy than were older adults.
As far as we are aware, this is the first attempt to examine whether strategy differences account for age-related increases in IIV. Our data do not suggest that group strategy preferences in completing the present attention task play a role in age-related differences in RT IIV.

*Executive Functions & Response Time Distribution Indices*

The structural equation model indicates that combined RT distribution indices (RT-ISD, mu, sigma, and tau) contribute distinct associations with neuropsychological measures of executive functioning. The SEM shown in Figure 2.3 reveals that the ex-Gaussian parameters tau and sigma are most strongly associated with poor performance on WCST PPE, Trail Making number-letter switching, and Color-Word Interference inhibition. The present findings reveal a significant association between RT-ISD/tau and aspects of executive functioning individually. However, the inclusion of all four distribution indices into the SEM led to a weak contribution of RT-ISD to executive functioning in terms of standardized units. In contrast, tau evinced a strong association with executive performance. This finding is supported by research suggesting that the driving force of RT-ISD as a measure of interest is derived from the tau distribution component (Williams et al., 2005). These results indicate that ex-Gaussian variability (sigma and tau), and particularly those slow RTs at the tail of the distribution, is linked to aspects of executive functioning, such that greater variability is associated with higher perseverative tendencies, lower switching efficiency, and inferior inhibition ability.

Our results are broadly similar to Tse et al. (2010) who also reported an SEM and correlations between tau and neuropsychological tests. First, in terms of their SEM, Tse and colleagues used working memory capacity exclusively as their cognitive measure, which was evaluated through reading span, letter span, and computation span tasks. Our data replicated their finding of a stronger SEM regression weight for tau, compared to sigma and mu. Moreover, the
present findings extend this greater tau relationship to a broader range of executive function abilities, beyond just working memory. Second, in terms of correlations, Tse et al. (2010) detected significant associations of tau with Digit Span, Word Fluency, and Trail Making Test part B. Comparatively, the present analysis revealed a significant correlation between tau and our executive function composite score, but only in the oldest age group. The examined relationship differs in that our weighted executive function composite contained measures from the WCST and Color-Word Interference test, which were not tested by Tse et al. Furthermore, Digit Span and Verbal Fluency in our composite were included with relatively weak contributions to the final score. It should be noted that disparity in the range of executive scores between the age groups could have contributed to the correlation differences observed.

In both the SEM and the correlations presented by Tse et al. (2010), their analyses suggest a stronger association between tau and working memory measures than in the present study. A first plausible explanation for this discrepancy is that complex span tasks, such as those used by Tse et al. (2010), are more sensitive measures of working memory than Digit Span. Secondly, in the creation of our SEM, we removed the effects of age prior to establishing the relationships between variables. Thus, it is possible that the outcome would have been different had a sample composed strictly of older adults been used. Lastly, their study had greater power to detect significant effects, with a sample size of over 200 in their healthy older adult group. Regardless, we have shown that the relationship between RT distribution parameters and cognition extends beyond just working memory to include other aspects of executive functioning. Future research may benefit from the inclusion of both experimental measures of cognition, along with traditional neuropsychological tests in evaluating the correspondence between the variables discussed.
It is worth considering how the effects we found in healthy older adults might compare to those in seniors with brain pathology. Presumably, our findings would be strengthened with such a participant group. In fact, Tse et al. (2010) found stronger relationships between tau and most neuropsychological measures in their cognitively impaired group compared to healthy older adults. Another study on mild cognitive impairment found that participants with multiple domains of impairment were more variable in their RT performance compared with those who were deficient in only a single domain (Strauss et al., 2007). For older adults with difficulties in two or more non-memory domains, increased variability was most evident on the more cognitively demanding tasks requiring executive control. These tasks required manipulation of information, switching cognitive set, or inhibiting automatic responses. The same authors reported a modest correlation between executive measures (reasoning and fluency) and response time inconsistency in their group of non-memory multiple domain impaired participants. Moving along a range from healthy to significant cognitive impairment may be accompanied by increases in response time IIV, more specifically in tau. Future research is required to explore this hypothesis.

Frontal lobe integrity may be an important link between executive functions and tau. Not only is the literature in agreement that the prefrontal cortex endures atrophy through the normal aging process (Fjell et al., 2009; Meguro et al., 2001; Resnick et al., 2003; Tisserand et al., 2002), but there is also considerable evidence of a brain-behaviour relationship between the prefrontal lobes and executive function decrements in the ageing literature. In the context of age-related brain changes, aspects of executive functioning have been linked to prefrontal cortex atrophy (Gunning-Dixon & Raz, 2003; Raz et al., 1998), volume of prefrontal white matter hyperintensities (Gunning-Dixon & Raz, 2003; Van Petten et al., 2004), and prefrontal fractional anisotropy (a measure of white matter integrity) (Grieve, Williams, Paul, Clark, & Gordon,
2007). Even more convincing is that recent research has shown that greater white matter volume was associated with less IIV and smaller tau, especially in frontal and default network regions (Jackson et al., 2012).

Ratcliff’s diffusion model for one-choice RT tasks may also provide unique insights into the present data set (Ratcliff & Van Dongen, 2011). According to this diffusion model, response time is composed of encoding time, decision time, and response execution time. When engaging in a one-choice RT task, evidence is accumulated in the decision process, from a starting point to a decision criterion, prior to making a response. The rate of accumulation of evidence is termed the drift rate, which varies across trial. Applying a computational cognitive process model such as this one may allow for the separation of these different processing aspects and account for both response time measures and accuracy in performance. This alternate approach could provide additional insights into differences between how older and younger adults process information in an attentionally demanding RT task.

Conclusions

This study confirmed age-related elevations in RT ISD as well as in ex-Gaussian parameters (mu and tau). The motivation behind designing the present task was to achieve a greater level of ecological validity in measuring cognitive control. Our findings are suggestive of real world consequences to heightened variability in older adults, but we do not yet have the data to confirm this. Ongoing research in our lab includes measures of predictive validity. Importantly, the present results showed that aspects of executive functions are most strongly associated with RT distribution indices sigma and tau, after controlling for the effects of age. When the relationships were examined between age groups, however, tau and executive functioning demonstrated a significant correspondence only in older adults between 75 and 85
years. We suggest that those neural processes involved in the cognitive control of attention, leading to greater rightward skew, overlap with those responsible for at least a subset of executive mechanisms. Research has demonstrated the utility of IIV in discriminating healthy aging from cognitive impairment as in early Alzheimer’s disease (Duchek et al., 2009a). The present results more specifically could have important clinical significance in terms of diagnosing executive impairment based on RT inconsistency in addition to classical neuropsychological measures.
Chapter 3

Response time consistency is an indicator of executive control rather than global cognitive ability

3.1 Introduction

Intraindividual variability (IIV), or inconsistency, refers to fluctuations in performance from trial to trial within a given task. We now know from several studies using a variety of tasks, and also from a meta-analytic review, that response time (RT) IIV is greater in healthy older adults compared with younger adults (Dykiert et al., 2012; Hultsch et al., 2002, 2008; Williams et al., 2005). Two longitudinal studies provide additional evidence that RT IIV increases through the aging process (Bielak et al., 2014; Bielak, Hultsch, Strauss, MacDonald, et al., 2010).

A cross-sectional study by Williams et al. (2005) found a U-shaped RT IIV function from childhood to old age – variability decreases to middle adulthood where it reaches a nadir before increasing once again into old age. This may correspond to the rise and fall of executive control abilities throughout the lifespan. It is known that the frontal lobes, which play a large role in cognitive control processes, deteriorate with age (Kennedy & Raz, 2015). Further evidence of this brain-behaviour correspondence is the elevated RT IIV in neurological populations known to have disrupted cognitive control abilities. For example, heightened variability has been observed in individuals with white matter lesions (Bunce et al., 2007), traumatic brain injury (Stuss et al., 1994), and frontal lobe lesions (Stuss, Murphy, & Binns, 1998; Stuss, Murphy, Binns, & Alexander, 2003). Lastly, functional neuroimaging has also confirmed a positive association between RT IIV and activation across a distributed neural network known to be involved in
sustained attention and inhibitory processing including the inferior parietal, thalamic, and prefrontal regions (Bellgrove et al., 2004). One theory of RT IIV proposes that intact and efficient top-down allocation of attention results in a more consistent response pattern, whereas disrupted attentional deployment leads to variable responses (Duchek et al., 2009; West, Murphy, Armilio, Craik, & Stuss, 2002).

Impairment in the ability to sustain attention may lead to a greater proportion of longer latency responses, which can inflate conventional measures of RT IIV. Fitting response time data to an ex-Gaussian distribution provides a way to test this hypothesis. An ex-Gaussian distribution is the convolution of a normal (Gaussian) function with an exponential function, and has three parameters: $\mu$ (mu) and $\sigma$ (sigma) representing the mean and standard deviation of the Gaussian component, respectively, and $\tau$ (tau) representing the right tail of the distribution. Greater $\mu$ values signify general slowing and greater $\sigma$ describes elevated variability, both while excluding the positively skewed portion of the distribution. Larger $\tau$ values indicate greater positive skew, and thus a greater proportion of slowed responses. In RT IIV research, $\tau$ has been viewed as a measure of attentional inefficiency, indicating brief attention lapses (Vasquez, Binns, & Anderson, 2016; West et al., 2002).

Current understanding of the precise cognitive underpinnings of RT IIV is sparse. One line of research has examined RT IIV as a predictive factor for cognitive decline. The first study to investigate a coupling between RT IIV and cognition was a longitudinal study over six years in a large sample of individuals from middle to old age, and demonstrated an association between inconsistency at baseline and a change in cognitive performance six years later (MacDonald et al., 2003). The authors assessed cognition across the domains of perceptual speed, working memory, fluid reasoning, episodic memory, and crystalized verbal ability; all
showed a negative relationship with RT IIV and concomitant decline of both cognitive abilities and consistent RT performance. Similar results were also shown in a study of older adults that measured RT IIV along with perceptual speed and categorical fluency over a thirteen year span (Lövdén et al., 2007). These findings were also supported more recently in another longitudinal study on older adults, which found that RT IIV was predictive of cognitive change three years later in fluid abilities including memory, speed, reasoning, and fluency (Bielak, Hultsch, Strauss, MacDonald, et al., 2010). In contrast, the same authors observed no such decline in verbal performance, reflecting the crystalized domain. Together, these data established a cognitive association with RT IIV, and that inconsistency actually precedes cognitive decline in aging. These studies did not use typical neuropsychological tests from clinical practice, and they did not distinguish between σ and τ in their analysis of the response time distribution. The previous longitudinal studies discussed thus far did not place priority on determining any cognitive specificity in the association with RT IIV, and as a result it has often been concluded that elevated RT IIV reflects compromised neurocognitive integrity broadly.

A parallel line of research has specifically targeted the role of executive processes in RT IIV. In one experiment, West et al. (2002) manipulated demand for executive control processing by having participants perform a choice RT task with or without a 1-back component. They found that RT IIV and τ were greater in older than younger adults in the 1-back condition, but similar across groups in the single-task 0-back condition. It was reasoned that older adults had decreased efficiency of executive control processing, leading to elevated variability when greater cognitive control was required. It has also been shown that quantitatively increasing the attentional demands on a response time task (i.e. simple vs. choice) increases RT IIV (Dykiert et al., 2012). Another study showed that the ex-Gaussian parameter τ was more strongly related than μ or σ to a latent working memory construct in a sample of younger adults (Schmiedek,
Oberauer, Wilhelm, Süß, & Wittmann, 2007). These findings were complemented by further research in older adults, again showing that $\tau$, computed from a composite of Stroop, Simon, and switching tasks, was most strongly correlated with tasks tapping processing speed and aspects of executive functioning (Tse et al., 2010). By comparison, the ex-Gaussian parameters $\mu$ and $\sigma$ exhibited weaker correlations with cognitive test performance, and no specific association with those aspects of executive functioning. These studies indicate a connection between executive functions and response time consistency. West et al. (2002), however, did not correlate RT measures with standardized measures of cognition, and the combined efforts of Tse et al. (2010) and Schmiedek et al. (2007) were not able to evaluate relations in the context of other important cognitive abilities. Thus, we do not know whether executive demand or task difficulty was responsible for observed effects in West et al. (2002), and we do not know whether variability-cognition associations are specific to executive functions as in Tse et al. (2010).

In a recent study (Vasquez et al., 2016), we examined indices of the RT distribution from an attention task in three age groups – young, young-old (65 – 74 years), and old-old (75-85). A structural equation model revealed that $\tau$ was associated with executive functioning, indexed by common neuropsychological tests, to a much greater degree than $\mu$ or $\sigma$, as well as a typical measure of variability based on intrasubject standard deviation (ISD). This association was established independent of age. Once age was factored in, however, we found that $\tau$ was significantly correlated with an executive function composite score only in the oldest group of adults. The data suggested that the cognitive control of attention (represented by $\tau$) is associated with executive functioning. A question that still remained was whether $\tau$ corresponds to executive functioning preferentially or to cognition more generally. This could not be addressed in our previous study as the neuropsychological tests we included did not cover multiple cognitive domains.
In the present study, we tested younger adults (18-30), young-old adults (65-74), and old-old adults (75-85) with a more comprehensive battery of neuropsychological tests, as well as a reaction time task from which we derived mean RT, number of Target misses, RT ISD, and ex-Gaussian parameters. The goal of this study was to investigate how aspects of the response time distribution (defined by ex-Gaussian parameters) relate to different cognitive domains. We anticipated higher mean RT (Salthouse, 1996b), as well as higher ISD and τ, with increasing age (Hultsch et al., 2002, 2008; Vasquez et al., 2016). We hypothesized that greater τ, rather than μ or σ, would be related more strongly to poorer performance on executive measures, reflecting the role of cognitive control in tests of executive functioning. We expected that with the inclusion of multiple domains, a structural equation model would demonstrate a stronger link between τ and executive functioning relative to other neuropsychological abilities. Lastly, we predicted that precision in describing the response time distribution, such as with an ex-Gaussian analysis, would yield data that are sensitive to differences in cognitive ability not fully accounted for simply by age.

3.2 Methods

Participants

We recruited 40 healthy young adults (aged 18-30 years; M = 22.78, SD = 3.32; 11 males) and 81 healthy older adults (aged 65-85 years; age M=74.42, SD=6.25; 22 males) from the Rotman Research Institute participant database. The older adult group was comprised of two subgroups: young-old (aged 65-74 years; n = 40; M = 68.88, SD = 2.72; 11 males) and old-old (aged 75-85; n = 41; M = 79.83, SD = 3.18; 11 males). Participants were excluded on the basis of
the following criteria: history of head injury resulting in loss of consciousness, neurological impairment or other major medical illnesses (e.g. stroke, dementia, and heart disease), chemotherapy, radiation to the head, or drug abuse; current use of psychiatric medication; or lack of fluency in English. To be eligible, older adults also had to achieve a score greater than 30 points on the modified Telephone Inventory of Cognitive Status (Welsh et al., 1993). Written informed consent was obtained from all volunteers, and monetary compensation was provided. This research was approved by Baycrest’s Research Ethics Board.

**Procedures**

After informed consent was obtained, a neuropsychological battery was administered to each participant. Computerized attention tasks and questionnaires were interspersed between cognitive tests to fill in time between memory delay tasks. The main task of interest was a feature integration task designed to measure response time and capture RT IIV. The entire session lasted approximately three hours.

**Feature Integration task**

The Feature integration task used in this study is an altered version of the attention task from Study 1 explained in Chapter 2. The stimuli were maintained, but the presentation was changed to be static and self-paced rather than having continuous dynamic movement. Each trial involved the simultaneous presentation of four playing cards in random non-overlapping locations on a touch screen, with the goal being to tap the Target (8 of spades) as quickly as possible using a stylus. In the event that there was no Target card present, participants were instructed to tap the Next button located at the bottom centre of the screen as quickly as possible. These non-target trials were referred to as ‘Next trials’. The task was self-paced, when the screen
was tapped, the display was refreshed with a new array of four playing cards. Before participants began the task, the experimenter demonstrated what was required with two Target trials and two Next trials (presented in random order). Participants were then given the opportunity to practice, which ended after 10 Targets were tapped.

The feature integration task consisted of 108 trials. The Target 8 of spades was present on 36 of these trials (33%). Cards included numbers 5 through 9 in each of the four suits (spades, hearts, clubs, and diamonds). Selection of the non-Target cards was controlled, such that cards within a trial shared a certain number of attributes (colour, suit, number) in common with the Target. Specifically, the non-Target sets contained two 2-feature, one 1-feature, and one 0-feature overlap non-Target cards. Target sets contained one 2-feature overlap non-Target card, one 1-feature overlap non-Target card, and one 0-feature overlap non-Target card. Trials were randomly ordered for each participant with the restriction that no more than three trials containing Targets occurred consecutively. Cards were presented on a white background. The card images were 180 by 225 pixels in size, subtending visual angles of 5.26 by 6.56 degrees at an approximate viewing distance of 40 cm.

The number of Target misses and false alarms was low; participants missed an average of 0.86% of Targets and pressed incorrect cards (false alarms) on 0.22% of trials. Moreover, there were no significant effects of age group for Target misses or false alarms. Thus, error trials are not discussed further.

3 Note that playing cards do not permit full factorial combinations of feature overlap with the Target (i.e., the 1-feature overlap cards shared the number only, or the colour only, but could not share the suit).
Data Preparation

Error responses and outlying RTs were removed. RTs shorter than 150 ms were removed (Dixon et al., 2007; Garrett, MacDonald, & Craik, 2012; MacDonald et al., 2006); these were exceptionally infrequent, representing none of the Target responses and 0.03% of Next responses from all age groups. Outliers representing extremely slow responses were characterized as exceeding the 3rd quartile + (3 x interquartile range). This method removed RTs that were clearly outside of the RT distribution for that individual, without removing those that were part of the tail of slow responses; these made up only 0.92%, 0.54%, and 0.75% of Target trials for young, young-old, and old-old groups respectively. Trimmed upper bound Next responses amounted to 1.61%, 1.16%, and 1.29% of trials for the same groups. Values for removed data points were not imputed.

Estimating Intraindividual Variability and Ex-Gaussian Distribution Parameters

There are different indices of intraindividual variability. Some researchers have chosen to use the intraindividual coefficient of variation (ICV) to adjust for systematic group differences in mean performance; however, this method combines effects of the ISD and mean performance, as well as their cross-product, which can lead to ambiguity (Hultsch et al., 2008). We employed the intraindividual standard deviation (ISD), with following steps, as a measure of IIV based on consensus from the field (Hultsch et al., 2008). This method reduces any effect of mean RT and systematic trends in performance (practice effects, fatigue, etc.) before calculation of ISD. First, the raw RT data were checked for linear, quadratic, and cubic trends across trials, which revealed a small but significant negative linear slope across trials. Next, individual trial RTs were regressed on trial number, block, and the interaction of trial by block for each participant and the
unstandardized residuals were saved. Lastly, intraindividual standard deviations were calculated from these residuals.

Ex-Gaussian parameters were computed separately for each individual using the MATLAB toolkit distrib v2.3 (Lacouture & Cousineau, 2008). The MATLAB script estimated \( \mu \), \( \sigma \), and \( \tau \) parameters for each participant, separately for correct Target and Next responses on the feature integration task because preliminary analyses showed that their distributions were non-overlapping.

Neuropsychological Battery

Shipley’s Institute of Living Scale Vocabulary subtest was included to obtain an estimate of verbal intellectual functioning. The Boston Naming Test (30-item form) was used as a language measure. For later analysis with structural equation modeling, the following tests were grouped into three cognitive domains (memory, speed of processing, executive functioning). For the memory domain we used the California Verbal Learning Test – II (CVLT-II) delayed free recall, Wechsler Memory Scale III (WMS-III) Logical Memory II, and Rey-Osterrieth Complex Figure immediate recall. For the speed of processing domain we used Wechsler Adult Intelligence Scale III (WAIS-III) Digits Symbol Coding, DKEFS Trail Making Number Sequencing (time to complete), and the DKEFS Colour-Word Interference Word Reading (time to complete). For the executive functioning domain we used Wisconsin Card Sorting Test (WCST) percent perseverative errors, DKEFS Trail Making Number-Letter switching (time to complete), and DKEFS Color-Word Interference Inhibition (time to complete). Additional questionnaires were administered that are not discussed here.
**Statistical Analysis**

To confirm age differences in RT performance, individual RT summary statistics (mean, ISD, $\mu$, $\sigma$, $\tau$) for Target and Next responses were first separately analyzed in multivariate ANOVAs with age group (young, young-old, old-old) as a between subjects factor. Where there were significant multivariate effects, follow-up univariate analyses were performed. Prior to analysis, estimates of ISD and $\tau$ for one participant with extreme values were winsorized.

As a first step in examining how different cognitive domains are associated with age and RT distribution indices, we used structural equation modeling (SEM) to establish age-independent relations between variables. In a second step, we applied these unbiased values to an analysis examining the degree to which both age and RT distribution indices are simultaneously associated with cognitive functioning. The benefit of the secondary analysis was that it allowed us to examine whether additional variance in cognitive performance would be explained by ex-Gaussian parameters, over and above age. To start, we took the same approach from previous work (Vasquez et al., 2016) by first regressing age from all measures of interest – mean, ISD, and ex-Gaussian parameters ($\mu$, $\sigma$, $\tau$) for Target responses, in addition to the memory, processing speed, and executive function tests. The standardized residuals from the regression were saved and used to build two structural equation models (SEMs) of three cognitive latent variables and the RT distribution indices – one with the mean and ISD, and the other with the ex-Gaussian parameters. The age-regression technique enabled us to isolate the relationships between RT distribution indices and neuropsychological measures of cognition, independent of the influence of age. The construction of each model was guided by covariance and regression weight recommendations and modified to achieve the best possible model fit (as in Vasquez et al., 2016). IBM SPSS Amos 20.0 was used for the SEM analysis.
Given our interest in the relative importance of age vs. RT indices in accounting for differences in cognition, we then investigated how age group and the ex-Gaussian parameters predicted performance in the three cognitive domains (memory, processing speed, executive functioning). Note that we only pursued the following analysis with ex-Gaussian parameters, not mean and ISD, in accordance with the ex-Gaussian model demonstrating better fit. We used raw data from the tests contributing to each cognitive domain in the SEM, rather than age-regressed residuals, then multiplied them by SEM standardized regression weights and summed the resultant values to create cognitive domain factor scores (for a similar procedure see Vasquez et al., 2016; Souchay, Isingrini, & Espagnet, 2000; Taconnat et al., 2006). Note that to facilitate comparison with our previous results (Vasquez et al., 2016), standardized regression coefficients for certain tests (e.g. timed tasks) were multiplied by -1 so that higher composite scores represented better processing speed and executive functioning. Linear regression was performed separately for each of the three cognitive composites. Predictors were entered in two steps: first age group and second the ex-Gaussian parameters (i.e. $\mu$, $\sigma$, and $\tau$).

### 3.3 Results

**Demographics and Neuropsychological Functioning**

Demographic information and neuropsychological test scores are summarized in Table 3.1. One participant from the young-old group had to leave the testing session before completing the neuropsychological battery; data from this participant are missing for the Boston Naming test, the WMS-III Logical Memory II, and WAIS Digit Symbol Coding. Multivariate ANOVA was used to identify differences between age groups in terms of demographics and cognitive test
variables, which yielded a significant model using Pillai’s trace, $V = 1.028$, $F(48, 188) = 4.15$, $p < .001$, $\eta^2 = .514$. Main effects were examined with univariate ANOVA, revealing significant age group differences across most variables, with the exception of the Boston Naming test (see Table 3.1). The older adult groups had acquired more years of formal education than the young group. Consistent with much prior research, younger adults performed slightly worse on the vocabulary subtest of Shipley’s Institute of Living Scale compared to older adults. Although not present for every test, there was a tendency for younger adults to outperform young-old, who in turn outperformed old-old on cognitive measures.
Table 3.1. Demographic and Neuropsychological Measures (mean, SD, and effect size)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Young (n=40) (18-30)</th>
<th>Young-old (n=40) (65-74)</th>
<th>Old-old (n=41) (75-85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>22.78(3.32)</td>
<td>68.88(2.72)</td>
<td>79.83(3.18)</td>
</tr>
<tr>
<td>Education*</td>
<td>.06</td>
<td>15.25(2.23)</td>
<td>16.93(3.45)</td>
</tr>
<tr>
<td>Shipley's Vocab*</td>
<td>.38</td>
<td>30.5(4.33)</td>
<td>36.25(3.26)</td>
</tr>
<tr>
<td>Boston Naming Test*</td>
<td>.05</td>
<td>26.85(2.24)</td>
<td>27.92(2.16)</td>
</tr>
<tr>
<td>WMS_III Logical Memory I*</td>
<td>.09</td>
<td>45.15(8.61)</td>
<td>42.55(8.35)</td>
</tr>
<tr>
<td>WMS_III Logical Memory II*</td>
<td>.13</td>
<td>60.45(6.52)</td>
<td>27.85(6.41)</td>
</tr>
<tr>
<td>RCFT copy*</td>
<td>.06</td>
<td>31.60(3.13)</td>
<td>30.58(3.62)</td>
</tr>
<tr>
<td>RCFT recall*</td>
<td>.23</td>
<td>21.86(4.76)</td>
<td>16.15(6.66)</td>
</tr>
<tr>
<td>CVLT-II SDFR*</td>
<td>.11</td>
<td>12.95(2.52)</td>
<td>11.53(3.31)</td>
</tr>
<tr>
<td>CVLT-II LDFFR*</td>
<td>.15</td>
<td>13.75(1.66)</td>
<td>11.80(2.98)</td>
</tr>
<tr>
<td>WAIS-III Digit Symbol Coding*</td>
<td>.44</td>
<td>86.45(14.38)</td>
<td>67.82(13.50)</td>
</tr>
<tr>
<td>WCST Percent Perseverative Errors*</td>
<td>.12</td>
<td>7.70(3.57)</td>
<td>13.03(12.39)</td>
</tr>
<tr>
<td>DKEFS Trail Making Num. Sequence*</td>
<td>.25</td>
<td>27.85(11.32)</td>
<td>38.27(12.33)</td>
</tr>
<tr>
<td>DKEFS Trail Making N-L Switching*</td>
<td>.29</td>
<td>59.45(16.95)</td>
<td>90.60(30.66)</td>
</tr>
<tr>
<td>DKEFS C-W Colour Naming*</td>
<td>.07</td>
<td>27.05(5.14)</td>
<td>30.20(5.13)</td>
</tr>
<tr>
<td>DKEFS C-W Word Reading*</td>
<td>.08</td>
<td>19.68(4.10)</td>
<td>22.35(4.79)</td>
</tr>
<tr>
<td>DKEFS C-W Inhibition*</td>
<td>.22</td>
<td>42.75(9.03)</td>
<td>58.60(18.11)</td>
</tr>
</tbody>
</table>
Feature Integration Task Performance

**Target Responses.** A significant multivariate effect was found for age group using Pillai’s trace ($V = .265, F(10, 230) = 3.52, p < .001, \eta_p^2 = .133$). There was a significant univariate effect of age group on all Target response measures except $\sigma$, $F(2, 118) = 1.36, p = .262, \eta^2 = .02$. Target mean, $F(2, 118) = 13.25, p < .001, \eta^2 = .18$, Target ISD, $F(2, 118) = 7.00, p = .001, \eta^2 = .11$, and Target $\tau$, $F(2, 118) = 5.28, p = .006, \eta^2 = .08$ all showed the pattern of better performance (faster, less variable, fewer slowed responses) with decreasing age. A significant linear contrast revealed higher values in the RT indices escalating with each age group from the young to the young-old group, and from the young-old to the old-old group (Table 3.2). Target $\mu$, $F(2, 118) = 8.69, p < .001, \eta^2 = .13$, was lower in the young compared to the young-old and old-old groups. A significant quadratic contrast was found for Target mean and Target $\mu$, suggesting an attenuated aging effect within older adults.

**Next Responses.** A significant multivariate effect was also found for age group using Pillai’s trace ($V = .257, F(10, 230) = 3.39, p < .001, \eta_p^2 = .128$). There was a significant univariate effect of age group on all Next response measures except $\tau$, $F(1, 118) = 1.43, p = .245, \eta^2 = .02$. Linear contrasts revealed that Next mean, $F(1, 118) = 14.83, p < .001, \eta^2 = .20$, Next $\mu$, $F(1, 118) = 14.67, p < .001, \eta^2 = .20$, Next ISD, $F(1, 118) = 5.97, p = .003, \eta^2 = .09$, and Next $\sigma$, $F(1, 118) = 3.66, p = .029, \eta^2 = .06$, all declined (slower, more variable) moving from the young group, to the young-old group, to the old-old group (Table 3.2). No significant quadratic contrasts were detected.
### Table 3.2. RT distribution indices by age group (mean and standard deviation)

<table>
<thead>
<tr>
<th></th>
<th>mean RT</th>
<th>ISD</th>
<th>μ</th>
<th>σ</th>
<th>τ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target Responses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>young</td>
<td>1346.79</td>
<td>263.22</td>
<td>1148.70</td>
<td>146.09</td>
<td>197.99</td>
</tr>
<tr>
<td></td>
<td>(228.88)</td>
<td>(72.62)</td>
<td>(207.86)</td>
<td>(86.05)</td>
<td>(121.85)</td>
</tr>
<tr>
<td>young-old</td>
<td>1597.36</td>
<td>324.71</td>
<td>1355.30</td>
<td>178.41</td>
<td>242.11</td>
</tr>
<tr>
<td></td>
<td>(285.99)</td>
<td>(104.97)</td>
<td>(262.75)</td>
<td>(87.71)</td>
<td>(154.08)</td>
</tr>
<tr>
<td>old-old</td>
<td>1628.34</td>
<td>346.19</td>
<td>1325.49</td>
<td>165.56</td>
<td>302.51</td>
</tr>
<tr>
<td></td>
<td>(287.61)</td>
<td>(127.41)</td>
<td>(245.69)</td>
<td>(95.86)</td>
<td>(154.63)</td>
</tr>
<tr>
<td><strong>Next Responses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>young</td>
<td>1463.89</td>
<td>234.62</td>
<td>1269.93</td>
<td>131.50</td>
<td>193.96</td>
</tr>
<tr>
<td></td>
<td>(357.55)</td>
<td>(105.20)</td>
<td>(310.61)</td>
<td>(90.51)</td>
<td>(126.90)</td>
</tr>
<tr>
<td>young-old</td>
<td>1767.39</td>
<td>260.04</td>
<td>1568.55</td>
<td>161.73</td>
<td>198.85</td>
</tr>
<tr>
<td></td>
<td>(336.10)</td>
<td>(88.64)</td>
<td>(318.42)</td>
<td>(84.24)</td>
<td>(86.80)</td>
</tr>
<tr>
<td>old-old</td>
<td>1905.11</td>
<td>310.22</td>
<td>1671.51</td>
<td>188.41</td>
<td>233.62</td>
</tr>
<tr>
<td></td>
<td>(417.62)</td>
<td>(106.00)</td>
<td>(399.90)</td>
<td>(107.57)</td>
<td>(127.77)</td>
</tr>
</tbody>
</table>

Note: values are in milliseconds

**Age, RT parameters, and cognition**

Two structural equation models were created to examine the relationship between RT indices and neuropsychological measures of cognition covering the domains of memory, processing speed, and executive functioning. The first model used mean and ISD, whereas the second model included the ex-Gaussian parameters to describe RT performance. The resulting model for mean and ISD demonstrated a poor fit to the data, CFI = .930, TLI = .868, RMSEA = .095, chi-square = 60.22, p = .001. Conversely, the ex-Gaussian SEM exhibited good model fit, CFI = .974, TLI = .944, RMSEA = .056, chi-square = 72.68, p = .083 (Figure 3.1). Inspection of the model indicates that the episodic memory latent variable was most strongly related to the
parameter $\mu$, whereas the processing speed and executive functioning latent variables were most strongly associated with the parameter $\tau$.

Figure 3.1. Structural Equation Model Relating Reaction Time Distribution Parameters and Cognition

Good model fit - CFI = .974, TLI = .944, RMSEA = .056, chi-square = 72.68, $p = .083$, based on the following fit statistic criteria; CFI > .95, TLI > .90, RMSEA < .08, and the chi-square $p > .05$.

Regression weights are standardized

Trails NS = DKEFS Trail Making Test - Number Sequencing (time to complete); C-W Reading = DKEFS Colour-Word Interference Word Reading (time to complete); Digit Symbol = Wechsler Adult Intelligence Scale III (WAIS-III) Digits Symbol Coding; CVLT LDFR = California Verbal Learning Test – II (CVLT-II) Long Delay Free Recall; Logical Mem II = Wechsler Memory Scale III (WMS-III) Logical Memory II; Rey Figure recall = Rey-Osterrieth Complex Figure immediate recall; WCST PE = Wisconsin Card Sorting Test (WCST) percent perseverative errors; Trails N-L Switch = DKEFS Trail Making Number-Letter switching (time to complete); C-W Inhibition = DKEFS Color-Word Interference Inhibition (time to complete).
Linear regression was applied to examine the influence of age on the relationship between RT indices and each cognitive domain separately. Age group was entered in a first step, followed by the ex-Gaussian parameters (i.e. \( \mu, \sigma, \) and \( \tau \)) in a second step. The resulting regression model for memory was significant \([F(4, 115) = 12.95, p < .001]\), indicating that age group was a significant predictor. However, the coefficients for the ex-Gaussian parameters were not significant (see Table 3.3); the R-square change for the addition of ex-Gaussian parameters was .045. A significant regression model was generated in the prediction of processing speed \([F(4, 115) = 39.68, p < .001]\). For this processing speed model, age group was the strongest predictor; \( \mu \) and \( \tau \) also had significant coefficients, but \( \sigma \) did not (Table 3.3). The \( R^2 \) change for the ex-Gaussian parameters in the processing speed model was 0.175, indicating that the parameters explained a significant amount of variance, over and above age group \((\Delta F p < .001)\). Lastly, the regression model predicting executive functioning was significant \([F(4, 116) = 32.22, p < .001]\), again with age group explaining most of the variance. Coefficients for both \( \mu \) and \( \tau \), but not \( \sigma \), were again significant in the prediction of executive functions (Table 3.3). The \( R^2 \) change for the inclusion of ex-Gaussian parameters into the executive functioning model was 0.222, also demonstrating significant variance explained, over and above age group \((\Delta F p < .001)\).
Table 3.3. Hierarchical regression of age group and ex-Gaussian parameters predicting cognitive composites

A. Regression Predictors of Memory Composite

<table>
<thead>
<tr>
<th>Step</th>
<th>β</th>
<th>ΔR²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age Group</td>
<td>-0.52*</td>
<td>.265*</td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age Group</td>
<td>-0.43*</td>
<td></td>
</tr>
<tr>
<td>Target Mu</td>
<td>-0.21</td>
<td></td>
</tr>
<tr>
<td>Target Sigma</td>
<td>-0.00</td>
<td></td>
</tr>
<tr>
<td>Target Tau</td>
<td>-0.09</td>
<td>.045</td>
</tr>
</tbody>
</table>

Total R²: .311, * p < .01

B. Regression Predictors of Processing Speed Composite

<table>
<thead>
<tr>
<th>Step</th>
<th>β</th>
<th>ΔR²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age Group</td>
<td>-0.64*</td>
<td>.405*</td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age Group</td>
<td>-0.46*</td>
<td></td>
</tr>
<tr>
<td>Target Mu</td>
<td>-0.28*</td>
<td></td>
</tr>
<tr>
<td>Target Sigma</td>
<td>-0.12</td>
<td></td>
</tr>
<tr>
<td>Target Tau</td>
<td>-0.28*</td>
<td>.175*</td>
</tr>
</tbody>
</table>

Total R²: .580, * p < .01

C. Regression Predictors of Executive Functioning Composite

<table>
<thead>
<tr>
<th>Step</th>
<th>β</th>
<th>ΔR²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age Group</td>
<td>-0.55*</td>
<td>.304*</td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age Group</td>
<td>-0.35*</td>
<td></td>
</tr>
<tr>
<td>Target Mu</td>
<td>-0.28*</td>
<td></td>
</tr>
<tr>
<td>Target Sigma</td>
<td>-0.12</td>
<td></td>
</tr>
<tr>
<td>Target Tau</td>
<td>-0.38*</td>
<td>.222*</td>
</tr>
</tbody>
</table>

Total R²: .526, * p < .01
3.4 Discussion

Variability in Aging

The present study supports prior literature indicating age-related slowing as mean RT was observed to increase across the three age groups (Gianglia, 1993; Parasuraman & Davies, 1977; West et al., 2002). As predicted, within-person variability indexed by ISD was lowest in young adults and higher in each successive age group (young-old through to old-old), a result which is in agreement with RT IIV research in general (Bielak, Hultsch, Strauss, MacDonald, et al., 2010; Bunce, 2001; Hultsch et al., 2002; MacDonald et al., 2006; O’Halloran et al., 2014; Williams et al., 2005), as well as with studies specifically examining RT IIV age-related effects within an older adult group (i.e. old-old more variable than young-old) (Hultsch et al., 2002, 2008; Vasquez et al., 2016). Lastly, an aging effect was also found for ex-Gaussian parameters. Target response \( \mu \) and \( \tau \), but not \( \sigma \), increased linearly with age, whereas the same linear age effect for Next responses was only observed for \( \mu \) and \( \sigma \). The discrepancy found between these response types could be due to Target responses requiring greater attentional control, reflected in age differences in Target, but not Next \( \tau \). The aging effect observed for Target response \( \tau \) is in agreement with research that evaluated ISD in both tails of the RT distribution, showing that inconsistency in adulthood is due to factors that specifically influence the slow end of the RT distribution, such as attention lapses (Williams et al., 2005; Williams, Strauss, Hultsch, & Hunter, 2007). The present findings are also congruent with what has been found previously in terms of elevation of \( \tau \) in older compared to younger adults, suggestive of an age-related decrease in cognitive control (Vasquez et al., 2016; West et al., 2002).
Cognition and the Response Time Distribution

The current study demonstrates for the first time that various components of the response time distribution correspond, with differential priority, to different cognitive domains, in this case memory, speed, and executive functioning. These observations are in contrast to previous literature suggesting that response time consistency is a general indicator of neurocognitive integrity. We fit an SEM that incorporated episodic memory and processing speed, in addition to executive functioning, to capture more fully the spectrum of cognitive domains and contrast the strength of relations of these domains with RT distribution indices. The current results provide further evidence that the association between $\tau$ and executive functioning is higher than for other ex-Gaussian parameters, but now in context with other cognitive domains. An additional novel aspect of our findings highlights the importance of $\mu$ in the association with cognitive variables.

The best fitting SEM presented here builds on prior research that identified relationships between response time distribution indices and cognition. Tse and colleagues (2010) took two approaches to examining the relation between RT distribution parameters and cognition, first using correlation with cognitive tests covering several domains, and then focusing on working memory with a SEM. The latter established a connection between $\tau$ and a working memory composite that was stronger than the other parameters $\mu$ and $\sigma$. More recently, we expanded upon this idea by including other aspects of executive functioning (e.g. switching, inhibition, fluency) into an SEM, which further supported the connection with $\tau$ (Vasquez et al., 2016). Our prior study also demonstrated that executive functioning was more strongly connected to $\tau$ than to ISD or the other ex-Gaussian parameters.

The present results identified that $\tau$ was more strongly associated with processing speed and executive functioning than with memory. We suggest that fluctuating attention may lead to
the occurrence of brief attention lapses (i.e. sporadic slowed responses) during speeded cognitive tasks (e.g. Digit Symbol Coding or Trails A), which would negatively contribute to overall completion time; this aspect of performance is not captured directly by scoring on standardized tests. Similarly, brief attention lapses would be detrimental to performance on neuropsychological tests of executive functioning (e.g. Trails B, WCST, etc.). Although some of the tests we used to assess executive functioning, particularly DKEFS Trail Making and Color-Word Interference, were speeded tasks that theoretically could have exaggerated the τ-executive relation, we do not believe this to be the case. Most importantly, the executive function latent variable included a non-speeded task (WCST). It should also be noted that previous work from our lab demonstrated a model of executive functioning, in which the highest-weighted measure was the WCST percent perseverative errors, which is not speeded (Vasquez et al., 2016). Lastly, research has shown a strong relation between τ and measures of non-speeded working memory in another SEM (Tse et al., 2010). Together, this suggests that brief attentional lapses not only inflate the completion time, but also cause individuals to lose set, thereby disrupting performance on executive tests of concept formation (WCST) and working memory. Exceptionally slow responses directly correspond to the efficiency with which attention is maintained on task, and thus can be viewed as an index of cognitive control.

General latency, estimated by μ, also evinced a strong association with all cognitive domains included, which is not unanticipated for speed of processing and to some extent the executive domain, as a subset of tests have a speeded component and slower RTs should logically be related. The association between memory and μ, however, was unexpected given that memory test performance is not directly dependent on the speed of response. Moreover, the regression weight between the memory latent variable and μ was the strongest of the entire model, a finding which diverges from Tse et al. (2010) in which no significant correlation was
observed between $\mu$ and memory variables. The strong memory-$\mu$ relation in the current study may be explained by the theory that optimal cognitive processing requires speeded neural transmission. The proposal is that neural processing speed mediates cognition, including memory, through the principles of limited time and simultaneity mechanisms (Salthouse, 1996b) - processing information at a slower rate could disrupt cognition if sub-operations cannot all be completed in time, or if a mechanism is interrupted by decay of early sub-operations. Following this proposal, the Gaussian mean may provide an index of network efficiency and neural processing speed. Alternatively, the $\mu$-memory relationship could have resulted from individual differences in level of ability – those who can respond quickly may also have better memory, representing superior performers in the sample.

A coupling between response time consistency and cognition has been shown to exist for fluid cognitive domains such as reasoning and processing speed (Bielak, Hultsch, Strauss, MacDonald, et al., 2010; Grand, Stawski, & MacDonald, 2016), which is consistent with the finding of age-related declines in fluid abilities (Salthouse, 2004). Bielak et al. (2010) and Grand et al. (2016) used a conventional measure of consistency (ISD), which captures both the rightward distributional tail ($\tau$) and the variability of observations closer to the mean ($\sigma$). Using ex-Gaussian analysis, the present data do not demonstrate a specific role for $\sigma$, indicating that the ‘active ingredient’ in the relationship between ISD and fluid abilities is likely the slow responses reflected in $\tau$.

The suggestion that isolating the distributional component $\tau$ offers a purer measure of cognitive control is also supported by our present findings that $\tau$ presents a stronger association with aspects of executive functioning compared to memory. Cognitive specificity of ex-Gaussian parameters had previously been hinted at in the data from Tse et al. (2010), which showed
stronger correlations between τ and tests of processing speed and executive functions compared to memory. Including all variables into one unified structural equation model provides more direct evidence for the preferential association of τ with processing speed and executive functions over memory.

Regression analyses showed that age group and the inclusion of all three ex-Gaussian parameters yielded significant models in the prediction of memory, processing speed, and executive functions. Regression models revealed that age group explained the majority of variance in cognitive performance across all of the three domains. The addition of ex-Gaussian parameters provided a significant increase in the predictive ability of the models for processing speed and executive functioning, but not memory. Inspection of the model coefficients indicated that Gaussian mean and extremely slow RTs represented significant contributions to processing speed and executive functioning. Thus, these findings demonstrate that differences in processing speed and executive functioning may be partially attributed to elevations in attention lapses (depicted in τ) and a general slowing of response (Gaussian mean), in addition to age group. The data suggest that deterioration of cognitive control mechanisms through aging is responsible for alterations in related cognitive abilities such as information processing speed and executive functioning.

The relationship between executive functions and τ is supported by research linking elevated RT IIV to damaged brain structures involved in cognitive control, such as prefrontal and white matter regions (Bunce et al., 2007; Stuss et al., 2003). Degradation to this network is known to occur through normal aging – the prefrontal cortex undergoes atrophy with age (Fjell et al., 2009; Meguro et al., 2001; Resnick et al., 2003; Tisserand et al., 2002) as does prefrontal white matter (Grieve et al., 2007; Gunning-Dixon & Raz, 2003; Van Petten et al., 2004). These
age-related brain changes to frontal grey and white matter have been linked to performance changes on tests of executive functioning (Gunning-Dixon & Raz, 2003; Raz et al., 1998). There is now evidence that greater (healthy) white matter volume is associated with less IIV and smaller $\tau$, especially in frontal and default network regions (Bunce et al., 2007, 2010; Fjell et al., 2011; Jackson et al., 2012).

It is worth noting that these findings are reported from a response time task involving not only complex attention through the requirement of feature integration, but also limb movement to correct target locations. This task contrasts with more conventional response time tasks simply requiring a button press. It has been shown that when components of a response are dissociated, that RT IIV is attributed to the decision, rather than movement, component (Bunce et al., 2004). Thus, the present findings further support the universality of measuring attentional fluctuations through RT IIV and $\tau$ using different task designs. As a result, the task implemented here is a step closer to being a more ecologically valid measurement of response time performance.

Conclusions

This study demonstrated, with SEM, that ex-Gaussian RT parameters are differentially associated with different cognitive domains. The data support the theory that $\tau$ reflects the fidelity of cognitive control systems, which are recruited for classic tests of executive functioning (Vasquez et al., 2016; West et al., 2002), but also that these attentional failures impact measurement of speed of processing on neuropsychological testing. The model replicated a stronger association of $\tau$ than other ex-Gaussian parameters $\mu$ and $\sigma$ with neuropsychological measures of executive functioning independent of age. The model also indicated a particularly strong connection between $\mu$ (the Gaussian mean) and memory, suggesting that general speed of processing may be an essential component to effective memory performance. It is also important
to note that μ was strongly related to all cognitive domains, potentially supporting the theory that speed of processing mediates several cognitive operations. When the regression models were created for each of the three cognitive domains, the data revealed that in addition to age, general slowing and extremely slow responses (indicative of attention lapses) are predictive of performance on tests of processing speed and executive functioning. We propose that cognitive specificity exists in the relative contribution of RT distribution parameters to neuropsychological performance based on the neural processes from which they are derived. Our data provide evidence for the role of attention lapses in neuropsychological tests of processing speed and executive functioning, and also identify Gaussian mean RT as a relevant variable to multiple domains of cognitive processing.
Chapter 4

Slow and steady: Training induced improvements to response time consistency are due to elevations in the ex-Gaussian parameter mu, but reductions in the parameter tau

4.1 Introduction

Response time intraindividual variability (RT IIV) or inconsistency refers to fluctuations in performance from trial to trial within a given task. Evidence from multiple sources strongly suggests that intact and efficient top down allocation of attention will result in a more consistent response pattern, whereas disrupted attentional deployment will lead to variable responses (Stuss et al., 2003; West et al., 2002). Indirect support for the relationship between cognitive control and RT variability comes from RT IIV literature on individuals with white matter lesions, traumatic brain injury, and frontal lobe lesions (Bunce et al., 2007; Stuss et al., 2003, 1994), in that each of these participant populations exhibit deficits to executive attention, as well as documented elevations in RT IIV. In comparison to healthy young adults, elevated RT IIV on a variety of tasks can reliably be observed in healthy older adults, which is a group that could be considered to have the mildest alteration of cognitive control, compared to patients with overt brain injury. The majority of studies have contrasted age cohorts, even finding differences within the older adult group, with those above age 75 displaying greater variability than those aged 65-74 (Hultsch et al., 2002; Vasquez et al., 2016). A more detailed examination of response time consistency across the lifespan indicated that RT IIV follows a U-shaped function from childhood into old age – variability decreases to middle adulthood where it reaches a low point
before increasing once again into old age (Williams et al., 2005). Furthermore, a recent longitudinal evaluation of consistency in young, middle, and older adulthood found that RT IIV increased most prominently over 8 years in the oldest group (Bielak et al., 2014).

Research has suggested that the degree of positive skew within the response distribution is largely responsible for the observed differences in typical measures of RT IIV (Vasquez et al., 2016; West et al., 2002; Williams et al., 2005). In other words, RT IIV combines distributional properties such as standard deviation and rightward skew to give an imprecise metric of variability. Analyzing distributional components, such as positive skew, has been accomplished by fitting response time data to an ex-Gaussian distribution. An ex-Gaussian distribution is the convolution of a normal (Gaussian) function with an exponential function, and consists of three parameters: mu and sigma representing the mean and standard deviation of the Gaussian component respectively, and tau representing the right tail of the distribution. Importantly, larger tau values reflect greater positive skew, which is indicative of a higher proportion/magnitude of responses with a longer latency. As a result, tau has been interpreted as an indicator of brief attention lapses or momentary task disengagement, leading to occasional unusually slowed responses (West et al., 2002). This notion has been supported by recent research from our lab, which showed that tau was very strongly associated with cognitive measures of executive control (Vasquez et al., 2016; See also Tse, Balota, Yap, Duchek, & McCabe, 2010).

A critical issue that has remained underexplored is whether RT IIV is beyond endogenous control, or whether it is modifiable. Only a single paper has addressed this question by promoting improvements in consistency with the integration of feedback during a four choice response time task in healthy younger and older adults (Garrett et al., 2012). The reasoning was that if greater RT IIV reflects a deficit in cognitive control, applying methods to specifically
target such deficiencies in older adults may limit longer response latencies, thereby reducing overall RT IIV. During breaks in the task participants were shown interactive goal-directed feedback on their performance from the preceding block and encouraged to become more consistent over time. The authors found that in the older adult group RT IIV was reduced over blocks to a greater extent in the feedback compared to a no-feedback control condition. Older adults with higher levels of education were observed to benefit the most from the feedback training. Surprisingly, a younger adult comparison group did not show a similar effect from the training, maintaining their level of consistency across the experimental blocks regardless of condition.

The study by Garrett et al. (2012) was unique in demonstrating that RT IIV is malleable, but their results have also stimulated numerous new research questions. In particular, since we know that RT IIV is higher in successive age groups of older adults (Hultsch et al., 2002; Williams et al., 2005), it is unknown whether older adult cohorts of different ages respond to feedback training in the same way. Secondly, given the strong association between tau and aspects of executive functioning (Tse et al., 2010; Vasquez et al., 2016), it would be interesting to identify how training differentially affects ex-Gaussian distribution parameters. Thirdly, if RT IIV reflects the integrity of cognitive control processes, then would training induced improvements transfer to other tasks requiring cognitive control? Further investigation into the effects of feedback training on RT IIV is warranted to accurately characterize the mechanism of improvement in the context of the response time distribution (i.e. mu, sigma, and tau). A more fulsome understanding of the beneficial training effects is important theoretically for the conceptualization of RT IIV, and to determine whether there is potential for application to cognitive rehabilitation of attentional dysfunction. In this study, we set out to answer these questions.
In a previous study, we identified that tau derived from a feature integration response time task was more strongly associated with executive functioning and speed of processing than episodic memory (Chapter 3). In the present paper, we used data from the same study to examine the effects of feedback training on RT distribution indices compared to an active control. Participants also completed a four-choice RT task before and after the training task to assess near transfer. We anticipated that feedback training would result in a reduction of RT IIV across blocks of trials to a greater degree compared to a control condition without feedback. Given that RT IIV can be dependent on task complexity and that we applied a relatively novel task design, we were uncertain whether younger and older adults would show differential effects of feedback training, as they had in Garrett et al.’s (2012) study. We did expect, however, that both groups of older adults would benefit from the training paradigm. We predicted that analysis of ex-Gaussian parameters would reveal that feedback training would specifically reduce tau rather than mu or sigma. We anticipated that the feedback training would result in significant near transfer effects to an untrained response time task.

4.2 Methods

Participants

We recruited 40 healthy young adults (aged 18-30 years; M = 22.78, SD = 3.32; 11 males) and 81 healthy older adults (aged 65-85 years; age M=74.42, SD=6.25; 22 males) from the Rotman Research Institute participant database. The older adult group was recruited to comprise two subgroups with 40 and 41 participants each, respectively: young-old (aged 65-74; M = 68.88, SD = 2.72; 11 males) and old-old (aged 75-85; M = 79.83, SD = 3.18; 11 males).
Participants were excluded on the basis of the following criteria: a history of head injury resulting in a loss of consciousness, neurological impairment or other major medical illnesses (e.g. stroke, dementia, and heart disease), radiation to the head, drug abuse, current use of psychiatric medication, or a lack of fluency in English. Older adults also had to achieve a score greater than 30 points on the modified Telephone Inventory of Cognitive Status (Welsh et al., 1993) to be eligible to participate. Written informed consent was obtained from all volunteers, and monetary compensation was provided for participating in the study. This research was approved by Baycrest’s Research Ethics Board.

**Procedures**

Participants were assigned to condition (Feedback or Standard) in an alternating pseudorandom fashion – alternating between the two options within each age group. Thus, half of participants received feedback training and the other half did not. Feedback training was integrated between blocks of a feature integration task, whereas the Standard condition involved the same feature integration task, but without feedback provided between blocks. After informed consent, participants completed a pre-training baseline four choice response time task, followed by the ‘training’ task (the feature integration task either with or without feedback), and then the four-choice response time task again as a post-training assessment of transfer. Transfer was evaluated by comparing pre- to post-training performance on the four choice RT task. A selection of neuropsychological tests was also administered to characterize the sample.

**Feature Integration task**

**Task Overview.** The task involved the simultaneous presentation of 4 playing cards in random non-overlapping locations on a touch screen, with the goal being to tap the Target (8 of
spades) as quickly as possible using a stylus. In the event that there was no Target card present, participants were instructed to tap the Next button located at the bottom centre of the screen as quickly as possible. The format of the task was self-paced, and upon tapping either the Target or the Next button, or incorrectly tapping a non-Target card, the display would be refreshed with a new array of 4 playing cards. Before the participants began the task the experimenter demonstrated what was required with two Target trials and two Next trials (presented in a random order). The experimenter then handed the stylus to the participant for practice interacting with the touch screen. Once the participant touched 10 Targets the practice ended. The recording of response time data from each Target and Next response tap allowed us to calculate a measure of RT IIV and estimate ex-Gaussian parameters.

**Stimuli Details.** The feature integration task consisted of 432 trials (1728 images of playing cards) evenly divided into 4 blocks of 108 trials each. 144 trials contained the Target 8 of spades, while 288 did not (i.e. ‘Next’ responses). That is, in each block, the Target was present on 36 trials and absent on 72 trials, which required a ‘Next’ response. The cards included numbers 5 through 9 in each of the 4 suits (spades, hearts, clubs, and diamonds). Within each block, the trials were randomly ordered with the restriction that no more than three trials containing Targets occurred consecutively. Cards were presented on a white background. The card images were 180 by 225 pixels in size, subtending visual angles of 5.26 by 6.56 degrees at an approximate viewing distance of 40 cm.

**Feedback Training Condition.** Participants assigned to the feedback condition received feedback immediately following each block of 108 trials. Based upon the study by Garrett et al. (2012), feedback was presented on one screen graphically, and displayed performance in 4 different ways (Figure 4.1). The top left quadrant contained a line graph of response times to
each of the 36 Targets tapped in the preceding block only. This feedback plot gave participants a visual sense of trial-to-trial variability (i.e. less variability would result in a flatter line, whereas more variability would lead to larger spike amplitudes). The top right quadrant showed a bar graph of the median response times and standard deviations for Target hits of each block that had been completed. This plot allowed participants to gauge their progress in improving speed and consistency across blocks. The bottom right quadrant provided a bar graph of the number of false alarm responses given by the participant in each block that had been completed. Note that false alarms were rare, fewer than one per person - averaging .38, .30, and .83, for the young, young-old, and old-old groups, respectively, F(2, 118) = 1.40, p=.251, and this element of feedback was not believed to contribute to feedback related effects. The bottom left quadrant showed a bar graph of points earned for consistently quick responses in each block that had been completed. Participants received 10 points for any response +0.5 standard deviations (SDs) or quicker in relation to their median on the preceding block (for the first feedback it was necessary to use the block 1 median). Participants lost 10, 20, or 50 points for responses that were +0.5 to +2 SDs, +2 to +4 SDs, and greater than +4 SDs, respectively than their median in the preceding block. No point deductions were made for missed Targets. Implementing the preceding median as a basis for calculating point allocation was designed to encourage continuous improvement throughout the task. Participants were told that they would be awarded points for improved performance at being consistently quick, but they were not told how many points.
After the completion of the first block of trials, the experimenter explained what was being shown in each quadrant and the reason for providing the feedback – to aid participants in becoming more consistent going forward. Participants were not permitted to continue to block 2 until they understood the task instructions and feedback related to becoming more consistent in responding. The experimenter provided support throughout feedback and participants were encouraged to evaluate the effectiveness of their strategy before moving forward at each feedback break. The experimenter provided minimal intervention, only serving as a positive and encouraging guide, without overtly suggesting any specific strategy for improvement.

Standard (no Feedback) Condition. Participants in the Standard condition received a control version of the feature integration task in which no feedback was given between blocks, and there was no instruction on consistent responding or support provided by the experimenter.
In place of feedback, a blank screen was presented with instructions to take a brief break. The duration of the breaks with and without feedback provided were similar. The task was self-paced, and as a result the total time was dependent on how fast the individual responded on each trial, but generally took between 20 and 25 minutes, with the Feedback version taking slightly more time than the control version.

**Four Choice Response Time task**

The numbers one through four were randomly presented in the centre of the screen, preceded by a blank background for 200 ms and then a fixation cross for 500 ms. Participants were instructed to press a numbered key corresponding to the number on the screen using designated fingers (index through to little finger) on their preferred hand. The task was self-paced in that the next trial began only once a key press had been made in response to the numeric stimuli. Participants were given 8 practice trials, which provided feedback (correct or incorrect) following each response. The main experimental task consisted of 208 trials divided into 4 blocks of 52 trials, with no feedback shown. Participants were given a brief rest between blocks. Stimuli were presented in 30-point black Courier New Type font on a white background. The task took approximately five minutes to complete.

**Neuropsychological Battery**

A selection of commonly used neuropsychological tests was administered to all participants. Shipley’s Institute of Living Scale Vocabulary subtest was included to obtain an estimate of verbal intellectual functioning. The Boston Naming Test (30-item form) was used as a language measure. For later analysis of predictors of training success, the remaining tests were grouped into four critical domains: Memory (California Verbal Learning Test – II (CVLT-II)
delayed free recall, Wechsler Memory Scale III (WMS-III) Logical Memory II, and Rey-Osterrieth Complex Figure test immediate recall). speed of processing (Wechsler Adult Intelligence Scale III (WAIS-III) Digits Symbol Coding, DKEFS Trail Making Number Sequencing (time to complete), and the DKEFS Colour-Word Interference Word Reading (time to complete)) executive functioning (Wisconsin Card Sorting Test (WCST) percent perseverative errors, DKEFS Trail Making Number-Letter switching (time to complete), DKEFS Color-Word Interference Inhibition (time to complete), and Verbal Fluency (total words generated; FAS)), and working memory (WMS-III Number-Letter Sequencing (total span) and a computerized test of reading span (total correct) (Unsworth, Heitz, Schrock, & Engle, 2005)). Composite scores were created for each cognitive domain (memory, processing speed, executive functioning) by multiplying each test by regression weights derived from a previous study (Chapter 3). Note that prior to composite score calculation, the directionality of certain tests was adjusted (multiplying by -1) to have compatible performance metrics with one another. Additional questionnaires were administered that are not discussed here.

Data Preparation

Prior to RT IIIV calculation, RT data for the four choice RT task (pre and post) and the feature integration task (Next and Target responses) were subject to identical pre-processing steps. RT IIIV was calculated only for correct Next responses and correct Target cards (8 of spades) tapped. Extremely fast or slow responses could reflect different types of errors, such as an accidental key press or screen tap, or an unexpected interruption on task. To correct for these types of errors we removed outliers from upper and lower bounds through the following methods. A lower bound representing instances of unusually quick responses (faster than possible to carry out decision and motor action components) was set at 150 ms based on
consensus from the field (Dixon et al., 2007; Garrett et al., 2012; MacDonald et al., 2006). Responses meeting our lower bound requirement were exceptionally infrequent, representing 0% of Target responses and .03% of Next responses from all age groups. The same low frequency of lower bound responses was observed for the first presentation of the 4 choice RT task (0.004%) and the second presentation (0%). Outliers representing extremely slow responses were characterized as an upper bound of the 3rd quartile + (the interquartile range x 3). This method removed RTs that were clearly outside of the RT distribution for that individual, without removing those that were part of the tail of slow responses. Outliers removed for exceeding the upper bound for correct Target detections on the feature integration task made up less than 1% of trials (0.92%, 0.54%, and 0.75% of Target trials for young, young-old, and old-old groups respectively). Trimmed upper bound Next responses amounted to 1.61%, 1.16%, and 1.29% of trials for the same groups. Lastly, 4 choice RT responses that exceeded the upper bound and were trimmed amounted to 0.14%, 0.23%, and 0.79% of trials for the first presentation and 0.10%, 0.24%, and 0.50% of trials for the second presentation. Values for missing data points were not imputed.

Estimating Intraindividual Variability and ex-Gaussian Distribution Parameters

There are different indices of intraindividual variability and some researchers have chosen to use the intraindividual coefficient of variation (ICV) because of its simplicity in controlling for systematic group differences in mean performance, while others prefer the intraindividual standard deviation (ISD). The coefficient of variation can be considered less precise as the trends in ISD and mean performance are combined through its calculation (Hultsch et al., 2008). Thus, we employed ISD with preceding data “purification” steps as a measure of IIV based on consensus from the field (Hultsch et al., 2008). This method removes mean RT and
systematic trends in performance (practice effects, fatigue, etc.) before calculation of ISD. First, the data were checked for linear, quadratic, and cubic trends, which revealed a small but significant negative linear slope. Next, individual trial RTs were regressed on trial number, block, and the interaction of trial by block for each participant with unstandardized residuals saved. Lastly, ISDs were calculated from these residuals.

Ex-Gaussian parameters were computed separately for each individual using the MATLAB toolkit distrib v2.3 (Lacouture & Cousineau, 2008). The MATLAB script estimated mu, sigma, and tau parameters for each participant, separately for the CRT task, and for Target and Next responses on the feature integration task.

Statistical Analysis

In order to examine the effects of feedback training in the different age groups, mean response time, RT ISD, and ex-Gaussian parameters (mu, sigma, tau) were first analyzed in a repeated measures multivariate ANOVA with age group (young, young-old, old-old) and condition (Feedback or Standard) as between-subject independent variables, and block (1 and 4) as a within-subject variable. If significant multivariate effects were found, they were followed up with a univariate analysis. These analyses were conducted separately on data from Target and Next responses of the feature integration task.

The potential for transfer of effects from feedback training in the different age groups was examined by comparing pre- and post-training performance on the four-choice response time task. Mean response time, errors, RTISD, and ex-Gaussian parameters (mu, sigma, tau) were analyzed in a mixed repeated measures multivariate ANOVA with age group (young,
young-old, old-old) and condition (Feedback or Standard) as the between-subject independent variables, and pre/post as the within-subject variable.

4.3 Results

Demographics and Neuropsychological Functioning

Demographic information and neuropsychological test scores are summarized in Table 4.1. One participant from the young-old group had to leave the testing session before completing the neuropsychological battery; data from this participant is missing for the Boston Naming test, the WMS-III Logical Memory II, WMS-III Letter-Number Sequencing, WAIS Digit Symbol Coding, and the DEX. Demographics and cognitive test variables were contrasted across groups using MANOVA followed up with Sidak post-hoc tests. Although not in every case, there was a general pattern for young adults to perform better than older adults, sometimes just compared to the young-old group and other instances only compared to the old-old group. One exception was for education in which young-old adults had significantly more years of education compared to young. Also, younger adults performed slightly worse on the vocabulary subtest of Shipley’s Institute of Living Scale compared to both older participant groups, which was expected from prior investigations.
## Table 4.1. Demographic and neuropsychological test performance in the young, young-old, and old-old groups.

<table>
<thead>
<tr>
<th></th>
<th>post-hoc Sidak</th>
<th>Young (n=40) (18-30)</th>
<th>young-old (n=40) (65-74)</th>
<th>old-old (n=41) (75-85)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td>22.78(3.32)</td>
<td>68.88(2.72)</td>
<td>79.83(3.18)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>a</td>
<td>15.25(2.23)</td>
<td>16.93(3.45)</td>
<td>15.76(2.65)</td>
</tr>
<tr>
<td><strong>Shipley's Vocab</strong></td>
<td>ab</td>
<td>30.5(4.33)</td>
<td>36.25(3.26)</td>
<td>36.41(2.99)</td>
</tr>
<tr>
<td><strong>Boston Naming Test</strong></td>
<td></td>
<td>26.85(2.24)</td>
<td>27.92(2.16)</td>
<td>27.88(2.04)</td>
</tr>
<tr>
<td><strong>WMS_III Logical Memory I</strong></td>
<td>b</td>
<td>45.15(8.61)</td>
<td>42.55(8.35)</td>
<td>38.51(8.38)</td>
</tr>
<tr>
<td><strong>WMS_III Logical Memory II</strong></td>
<td>b</td>
<td>60.45(6.52)</td>
<td>27.85(6.41)</td>
<td>24.15(7.02)</td>
</tr>
<tr>
<td><strong>RCFT copy</strong></td>
<td>b</td>
<td>31.6(3.13)</td>
<td>30.58(3.62)</td>
<td>29.61(2.93)</td>
</tr>
<tr>
<td><strong>RCFT recall</strong></td>
<td>ab</td>
<td>21.86(4.76)</td>
<td>16.15(6.66)</td>
<td>14.27(6.06)</td>
</tr>
<tr>
<td><strong>CVLT-II SDFR</strong></td>
<td>b</td>
<td>12.95(2.52)</td>
<td>11.53(3.31)</td>
<td>10.33(3.42)</td>
</tr>
<tr>
<td><strong>CVLT-II LDFR</strong></td>
<td>ab</td>
<td>13.75(1.66)</td>
<td>11.80(2.98)</td>
<td>10.76(3.67)</td>
</tr>
<tr>
<td><strong>WMS-III Letter-Number Sequencing</strong></td>
<td>b</td>
<td>12.33(2.39)</td>
<td>11.44(2.72)</td>
<td>10.10(2.23)</td>
</tr>
<tr>
<td><strong>Reading Span Absolute Score</strong></td>
<td>b</td>
<td>33.38(19.11)</td>
<td>26.10(19.00)</td>
<td>17.12(13.34)</td>
</tr>
<tr>
<td><strong>Reading Span Total Correct</strong></td>
<td>ab</td>
<td>52.70(14.12)</td>
<td>42.40(19.75)</td>
<td>35.59(17.96)</td>
</tr>
<tr>
<td><strong>WAIS-III Digit Symbol Coding</strong></td>
<td>abc</td>
<td>86.45(14.38)</td>
<td>67.82(13.50)</td>
<td>57.54(13.10)</td>
</tr>
<tr>
<td><strong>WCST Percent Perseverative Errors</strong></td>
<td>abc</td>
<td>7.70(3.57)</td>
<td>13.03(12.39)</td>
<td>15.37(8.27)</td>
</tr>
<tr>
<td><strong>DKEFS Trail Making Number Sequencing</strong></td>
<td>abc</td>
<td>27.85(11.32)</td>
<td>38.27(12.33)</td>
<td>47.83(18.11)</td>
</tr>
<tr>
<td><strong>DKEFS Trail Making Letter Sequencing</strong></td>
<td>abc</td>
<td>26.38(8.63)</td>
<td>35.85(10.79)</td>
<td>46.78(18.33)</td>
</tr>
<tr>
<td><strong>DKEFS Trail Making N-L Switching</strong></td>
<td>ab</td>
<td>59.45(16.95)</td>
<td>90.60(30.66)</td>
<td>105.61(40.57)</td>
</tr>
<tr>
<td><strong>DKEFS C-W Interference Colour Naming</strong></td>
<td>ab</td>
<td>27.05(5.14)</td>
<td>30.20(5.13)</td>
<td>30.88(7.73)</td>
</tr>
<tr>
<td><strong>DKEFS C-W Interference Word Reading</strong></td>
<td>ab</td>
<td>19.68(4.10)</td>
<td>22.35(4.79)</td>
<td>22.78(5.22)</td>
</tr>
<tr>
<td><strong>DKEFS C-W Interference Inhibition</strong></td>
<td>ab</td>
<td>42.75(9.03)</td>
<td>58.60(18.11)</td>
<td>59.95(18.81)</td>
</tr>
<tr>
<td><strong>DKEFS C-W Interference Inhibition/Switching</strong></td>
<td>ab</td>
<td>49.75(10.36)</td>
<td>62.35(13.04)</td>
<td>70.68(27.60)</td>
</tr>
<tr>
<td><strong>DKEFS Letter Fluency (FAS)</strong></td>
<td></td>
<td>47.50(11.38)</td>
<td>46.33(13.08)</td>
<td>49.12(13.60)</td>
</tr>
<tr>
<td><strong>DKEFS Category Fluency</strong></td>
<td></td>
<td>45.88(9.15)</td>
<td>43.00(8.88)</td>
<td>41.49(8.77)</td>
</tr>
<tr>
<td><strong>DKEFS Category Switching</strong></td>
<td>b</td>
<td>15.05(2.90)</td>
<td>14.28(2.73)</td>
<td>13.22(3.48)</td>
</tr>
</tbody>
</table>

**Note:** a: Young ≠ Young-Old; b: Young ≠ Old-Old; c: Young-Old ≠ Old-Old

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**Feature Integration Task Performance**

**Target Responses.** Repeated measures MANOVA revealed that there were significant multivariate effects for condition (V = .246, F(5, 111) = 7.26, p < .001, η² = .246), age group (V = .250, F(10, 224) = 3.20, p = .001, η² = .125), block (V = .170, F(5, 111) = 4.53, p = .001, η² = .
and the interaction between block and condition (V = .140, F(5, 111) = 3.63, p = .004, \( \eta^2_p = .140 \)). Confirming the effect of our experimental manipulation, univariate analyses demonstrated a significant block X condition interaction for RTISD (F(1, 115) = 12.57, p = .001, \( \eta^2_p = .099 \)), mu (F(1, 115) = 7.38, p = .008, \( \eta^2_p = .060 \)), and tau (F(1, 115) = 7.93, p = .006, \( \eta^2_p = .065 \)), but not sigma (F(1, 115) = .03, p = .857, \( \eta^2_p = .000 \)) or mean RT (F(1, 115) = .62, p = .434, \( \eta^2_p = .005 \)). RT ISD reduced from block 1 to block 4 in the Feedback condition, but this reduction was not observed in the Standard condition (Figure 4.2). Participants in the Standard condition showed a decrease in mu from block 1 to block 4, whereas those in the Feedback condition showed the reverse over the same period. Tau reduced from block 1 to block 4 in the Feedback condition, but not in the Standard condition (Figure 4.2). The lack of an age group x condition x block interaction indicates that all three age groups benefitted comparably from feedback training.
Next Responses. Repeated measures MANOVA revealed that there were significant multivariate effects for condition ($V = .172, F(5, 111) = 4.62, p = .001, \eta_p^2 = .172$), age group ($V = .280, F(10, 224) = 3.65, p < .001, \eta_p^2 = .140$), block ($V = .283, F(5, 111) = 8.77, p < .001, \eta_p^2 = .283$), the interaction between block and condition ($V = .149, F(5, 111) = 3.89, p = .003, \eta_p^2 = .149$), and a block X condition, X age group three-way interaction ($V = .158, F(10, 224) = 1.92, p < .05, \eta_p^2 = .079$). Univariate analyses demonstrated a significant block X condition interaction for RTISD ($F(1, 115) = 16.59, p < .001, \eta_p^2 = .126$), and sigma ($F(1, 115) = 4.66, p < .05, \eta_p^2 = .039$), but not mean RT ($F(1, 115) = .66, p = .417, \eta_p^2 = .006$), mu ($F(1, 115) = .01, p = .909, \eta_p^2 = .000$) or tau ($F(1, 115) = 1.43, p = .235, \eta_p^2 = .012$). Lastly, the block X condition X age group interaction was significant for one of the three indices of consistency – RT ISD ($F(2, 115) =$)
6.66, p = .002, \eta^2_p = .104), which was not present for sigma (F(2, 115) = .614, p = .543, \eta^2_p = .011) or tau (F(2, 115) = 2.47, p = .089, \eta^2_p = .041). The data for tau displayed a similar pattern of interaction as the results observed for Next response RTISD, but it failed to reach significance.

Further univariate analysis of the three-way interaction in RTISD Next responses revealed significant block X condition interactions for young F(1, 38) = 26.53, p = .000, \eta^2_p = .41 and young-old adults F(1, 38) = 7.14, p = .01, \eta^2_p = .16, but not for old-old F(1, 39) = .17, p = .685, \eta^2_p = .004. Younger adults showed a reduction in RT ISD from block 1 to block 4 in the Feedback condition compared to an increase in RT ISD in the Standard condition. Although the magnitude of decrease was not as large, young-old adults also showed a similar effect for Feedback with RTISD reducing from block 1 to block 4, but increasing across the same blocks in the Standard condition.
Table 4.2. Feature Integration Task RT Indices (mean and standard deviation)

<table>
<thead>
<tr>
<th></th>
<th>mean RT</th>
<th>ISD</th>
<th>mu</th>
<th>sigma</th>
<th>tau</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target Responses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 1</td>
<td>1530.50</td>
<td>325.07</td>
<td>1281.76</td>
<td>178.10</td>
<td>248.71</td>
</tr>
<tr>
<td>(316.65)</td>
<td>(131.46)</td>
<td>(256.42)</td>
<td>(93.48)</td>
<td>(180.09)</td>
<td></td>
</tr>
<tr>
<td>Block 4</td>
<td>1481.02</td>
<td>332.60</td>
<td>1215.37</td>
<td>159.34</td>
<td>265.45</td>
</tr>
<tr>
<td>(275.46)</td>
<td>(104.70)</td>
<td>(301.06)</td>
<td>(114.04)</td>
<td>(149.87)</td>
<td></td>
</tr>
<tr>
<td>Feedback</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 1</td>
<td>1519.46</td>
<td>298.03</td>
<td>1271.97</td>
<td>150.45</td>
<td>247.26</td>
</tr>
<tr>
<td>(274.30)</td>
<td>(79.76)</td>
<td>(255.26)</td>
<td>(85.46)</td>
<td>(111.87)</td>
<td></td>
</tr>
<tr>
<td>Block 4</td>
<td>1500.42</td>
<td>243.66</td>
<td>1330.48</td>
<td>135.45</td>
<td>169.64</td>
</tr>
<tr>
<td>(346.40)</td>
<td>(82.51)</td>
<td>(329.47)</td>
<td>(77.73)</td>
<td>(107.18)</td>
<td></td>
</tr>
</tbody>
</table>

| **Next Responses** |         |       |       |        |        |
| Standard          |         |       |       |        |        |
| Block 1           | 1733.21 | 288.12| 1502.88| 163.96 | 230.34 |
| (435.72)          | (120.47)| (400.37)| (107.18)| (136.00)|        |
| Block 4           | 1634.22 | 300.74| 1397.51| 158.50 | 237.90 |
| (378.93)          | (97.68) | (378.12)| (87.24)| (113.30)|        |
| Feedback          |         |       |       |        |        |
| Block 1           | 1693.92 | 248.84| 1506.59| 157.53 | 187.33 |
| (391.51)          | (81.32) | (368.32)| (85.79)| (87.07) |        |
| Block 4           | 1564.64 | 214.11| 1396.80| 116.36 | 167.84 |
| (370.78)          | (97.92) | (349.84)| (73.30)| (99.77) |        |

Note: values are in milliseconds

FourChoiceResponseTimeTaskPerformance

Repeated measures MANOVA revealed that there were significant multivariate effects for condition (V = .136, F(5, 111) = 3.49, p = .006, η² = .136), age group (V = .430, F(10, 224) = 6.14, p < .001, η² = .215), and pre/post (V = .317, F(5, 111) = 10.33, p < .001, η² = .317).

Univariate analyses showed that there was a significant effect of pre/post for RTISD (F(1, 115) = 44.06, p < .001, η² = .277) and tau (F(1, 115) = 27.17, p < .001, η² = .191). However, the fact that pre/post did not interact with condition (or group) suggests that reductions in both measures of variability were unrelated to feedback training, and likely reflected practice effects (Figure 4.3).
Figure 4.3. Evaluation of Transfer – 4-Choice RT task

- **young**
  - Pre and Post measures for young subjects for standard and feedback conditions.

- **young-old**
  - Pre and Post measures for young-old subjects for standard and feedback conditions.

- **old-old**
  - Pre and Post measures for old-old subjects for standard and feedback conditions.
4.4 Discussion

The first objective of the present study was to investigate whether the malleability of RT IIV through feedback training differed depending on age cohort within older adults. Similar to Garrett et al. (2012), it was believed that response time consistency could be improved over the course of a response time task. Our data corroborated this effect, with participants in the feedback group showing significant decreases in RT ISD for Target responses. This effect was significant for the young, young-old, and old-old - all three age groups showed comparable reductions in variability from block 1 to block 4. This finding differed from Garrett et al.’s (2012) in that they found no effect of feedback training in their young adults. Garrett et al. (2012) advanced two hypotheses to explain why their younger adults did not benefit from training: 1) the feedback paradigm that they applied was not optimized for younger adults to improve above their already excellent levels of performance, and 2) the choice RT task was too simple for feedback training to have a considerable effect. Data from the present study suggest that the latter provides a more accurate interpretation as we were able to show an effect for this group using the same feedback paradigm, but using a different training task. We know from the literature that task types differ in their sensitivity to measuring differences in RT IIIV (Dykiert et al., 2012). It is likely that the choice RT task employed by Garrett et al. (2012) allowed them to perform at optimal levels without feedback, leaving little practical room for improvement. The feature integration task used in the present study was designed explicitly to be sensitive to changes in RT IIIV. Indeed, exploratory analyses revealed that RT IIIV and tau values were higher on the first block of the feature integration task compared to the pre-training four-choice RT task (data not shown). Thus, young adults may have benefited from training in our study but not in Garrett et al. (2012) because they had more room to improve.
Participants in the Feedback condition were encouraged to become more consistent in responding to Targets, but the alteration in performance also extended to Next responses in the young and young-old groups, but not the old-old group. The differential effects observed for Target and Next responses in the old-old suggest that there may be a limit to training effects in this group. Participants in the old-old group displayed the weakest attentional abilities, and although they were able to benefit from feedback training directed to Target responses, they may not have been able to implicitly transfer this improvement to the embedded measure of Next responses, which was not specifically trained in that the feedback pertained only to the Target responses. The improvements observed for RT consistency cannot be explained by practice related effects as both experimental and control conditions received the same amount of task exposure. Not only did participants in the Standard condition fail to reduce their variability across blocks of the task, but in some instances they became more variable. Mean RT for Target responses was not affected by the Feedback training, but a decrease was observed across blocks for the Next responses.

It was hypothesized that RT IIV feedback training causes improvements in response time consistency by specifically targeting overly slow responses. It has previously been proposed that the right tail of the response time distribution is the most important component of RT IIV because of its correspondence with aspects of executive functioning (Vasquez et al., 2016), and so we examined this possibility by fitting response time data to an ex-Gaussian distribution. The results indicate that feedback lead to reductions in Target response tau, whereas mu increased with feedback. These results are actually consistent with the fact that mean RT was unchanged by feedback, given that mean RT can be estimated by the sum of mu and tau. With feedback, participants’ typical responses became slower, but their atypical slow responses became faster, much like the aphorism “slow and steady wins the race”. There was no effect of condition for
sigma. Our findings support the theory that reductions in RT IIV for trained responses are due to changes in the tau portion of the distribution. Participants diminished their tendency towards occasional slow responding, likely due to improved attentional efficiency. Together, the results support the conclusion that response time consistency is modifiable. Response time consistency appears to reflect attentional efficiency on a task that can be adjusted through the implementation of cognitive control. As our data indicate, the ability to exert cognitive control may change with age, but there appears to be the chance for functional compensation given the appropriate conditions - in this instance environmental support provided through feedback. Inspection of Next response data identified a different pattern – mu was not affected by condition, and the decreasing trend observed with tau did not reach statistical significance, but sigma decreased following feedback training. Although Next responses were not specifically the focus of training, they were affected as a by-product, as sigma was seen to diminish in the feedback condition. Together, the ex-Gaussian results indicate that while feedback training primarily targets reductions in tau, other task parameters not specifically trained may show a corresponding improvement through decreases in sigma.

Another objective was to evaluate whether the effects of feedback training transferred to an untrained task. A four-choice response time task was used to assess transfer, comparing pre- and post-training measures of consistency. Although consistency improved from pre- to post-training, measured by both ISD and tau, no effect of condition was observed. Thus, there was no significant transfer effect as individuals showed reduced variability post-assessment regardless of which condition they were in. Perhaps the four-choice response time task was not appropriate to assess near transfer, possibly because it was lacking in complexity. Recent research on training to improve cognitive control abilities in young adults suggests a positive effect on RT performance from an untrained task following a more in depth training paradigm (Shahar &
Meiran, 2015). In this study, participants were trained over a period of 19 days on an adaptive working memory (n-back) task, which involved switching between two different choice RT requirements (object and spatial classification). Pre-post testing was conducted using a shape classification task where participants either categorized the stimuli by shape type (diamond vs. triangle) or filling (empty vs. full). The authors found that tau, measured from the shape classification task, was reduced from pre to post, but only in the training group (Shahar & Meiran, 2015). Current evidence indicates that transfer and the maintenance of beneficial effects occur most often when the intervention is adaptive and consists of multiple training sessions (Kelly et al., 2014). More work is required to examine fully the potential for transfer of training in healthy aging when it comes to measures of response time consistency.

Garrett et al. (2012) found that older adults with higher levels of education benefited most from the feedback training, but our data did not replicate this finding (data not shown). Education is often taken as a proxy of cognitive reserve, a concept referring to individual differences in the ability to functionally compensate for pathological brain changes. It has been observed that older adults with higher education are able to maintain higher levels of cognitive performance than lower educated peers (Stern, 2002). In the case of Garrett et al. (2012), there could have been other factors related to education level that were responsible for differences in training effects such as pre-existing ability, motivation, and intelligence (Jaeggi, Buschkuehl, Shah, & Jonides, 2014).

Conclusions

This study confirmed that response time consistency can be reduced in healthy adults through an interactive feedback paradigm, and indicated that online modifications to responding were driven by changes in the ex-Gaussian parameter tau. The findings add support for tau as an
indicator of the efficiency with which cognitive control can allocate and maintain attention on task, and that even with diminished cognitive resources, older adults still have the ability to amplify attention at will to minimize brief attention lapses. Although near transfer was not observed, future research should explore whether transfer effects are evident when adaptive training is delivered or when a more complex transfer task is used. The current results suggest that even a rather short training exposure may induce functional compensation to improve cognitive control on task in healthy older and young adults.
Chapter 5

Slow and skewed: Effects of white matter lesion volume on response time distributions and cognition

5.1 Introduction

Cerebral small vessel disease (CSVD) affecting smaller penetrating arteries (Pantoni, 2010) restricts the supply of oxygen and nutrients to white matter and subcortical structures leading to ischemic lesions. Early stages of CSVD may involve few or several isolated lesion foci, but if the condition worsens, lesions expand and become confluent. The main predictors of CSVD are vascular risk factors and age, which is highlighted in research showing that 90% of purportedly healthy older adult participants had at least a mild degree of white matter lesions (de Leeuw et al., 2002; Longstreth et al., 1996). Several studies corroborate the susceptibility of white matter to deteriorate with age, particularly in anterior brain regions (Bartzokis et al., 2003; Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Head et al., 2004; Salat et al., 2009).

Given that CSVD is a common form of cerebrovascular disease in older adults, it is important to study how white matter lesions influence cognition. Research has shown that age-related white matter changes are associated with cognitive dysfunction (Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Raz et al., 2008; Raz, Rodrigue, Kennedy, & Acker, 2007), most notably impairments in processing speed, executive functioning, and memory (Gunning-Dixon & Raz, 2000; Vasquez & Zakzanis, 2014). Whereas early research on the effects of brain injury on cognition placed emphasis on the cortex, there are many that advocate equal importance for studying white matter due to its role in facilitating functional connectivity.
between large-scale brain systems (Andrews-Hanna et al., 2007; He et al., 2012; Lockhart et al., 2015; Mišić et al., 2014, 2016).

Research has indicated that disruption to white matter impairs stability of performance, perhaps because those routes can no longer transmit signals as efficiently as they once did. Axons of the white matter are insulated by myelin, which increases the speed and efficiency of signal conduction (Hartline, 2008). Areas affected by brain ischemia due to CSVD will primarily exhibit axonal loss and also demyelination (Fazekas et al., 1993), leading to network disconnection and slower speeds of transduction across the affected network. Variability in behaviour may reflect random oscillation between optimal and disrupted routes of transmission as cognitive mechanisms fluctuate in their recruitment of neural pathways (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008). As a result, disturbance to white matter effectively creates neural noise (Russell et al., 2006).

The importance of studying response time variability has been highlighted by data indicating its sensitivity as a marker for cognitive change over and above central tendency (Bielak, Hultsch, Strauss, MacDonald, et al., 2010; Dixon et al., 2007; Lövdén et al., 2007). Current theories suggest that response time variability may correspond to cognitive control processes that are implemented to maintain attention on task (Duchek et al., 2009b; Rabbitt, Osman, Moore, & Stollery, 2001). Some studies have analyzed the integrity of healthy white matter using volumetric quantification or diffusion tensor imaging approaches (Fjell et al., 2011; Jackson et al., 2012; Walhovd & Fjell, 2007), while others have focused on quantifying lesions within the white matter (Bunce et al., 2007, 2010, 2013). Bunce et al. (2007) found that the degree of white matter lesions in the prefrontal regions was positively associated with response time intraindividual variability (RT IV), or fluctuations in speed of performance from trial to
trial within a task, in adults aged 60-64. These results have been extended to include younger and middle aged adults, and a broader range of brain regions (prefrontal, temporal, and parietal areas) using both white matter integrity and lesion load approaches (Bunce et al., 2010; Fjell et al., 2011; Ullén, Forsman, Blom, Karabanov, & Madison, 2008). The association between response time indices and neuroanatomical quantification is robust; in fact RT IIV reliably predicts the extent of frontal lobe white matter lesions (Bunce et al., 2013). Others have contrasted grey and white matter volumes, and found that cortical grey matter volume was negatively associated with mean RT, whereas white matter volume was negatively associated with RT IIV (Walhovd & Fjell, 2007).

A more precise examination of the response time distribution can provide additional information about variability in performance. RT IIV represents variability throughout the RT distribution – both in the faster portion of the Gaussian curve, and in the positively skewed portion of slower RTs. An alternative to RT IIV analysis is to fit the data to an ex-Gaussian distribution, which is a convolution of a normal (Gaussian) distribution and an exponential function. The ex-Gaussian distribution has the following parameters: mu (Gaussian mean), sigma (Gaussian SD), and tau (exponential positive skew). It is believed that the longer latency responses observed through tau more precisely reflect the cognitive control processes thought to be embodied by RT IIV (Vasquez et al., 2016; West et al., 2002). That is, when cognitive control on task is weakened, individuals may sporadically respond slowly, resulting in positively skewed distribution (indexed by tau). Fitting RT data to the ex-Gaussian distribution can be extremely useful in characterizing response time patterns and identifying cognitive operations that are drawn upon during a task.
Jackson et al. (2012) examined how total and regional white matter volumes were related to RT IIV and ex-Gaussian parameters in healthy and cognitively impaired seniors. They found that larger total cerebral white matter volumes were associated with less RT IIV, and this effect was amplified in frontal regions. Furthermore, the ex-Gaussian parameter tau displayed an even stronger association with white matter volume, particularly in their cognitively impaired group. These data support the hypothesis that elevated long latency responses described by tau are important in the assessment of RT consistency and can be attributed to less prefrontal white matter.

An important consideration is that white matter volume and white matter lesions are not necessarily complementary, as an individual could have reduced white matter volume due to atrophy. Lesions in the white matter are likely to have a more direct effect on cognition, compared to the relationship between individual differences in healthy white matter volume and cognition. Thus, we were interested in the role of white matter lesion volume in response time performance (RT IIV and the ex-Gaussian distribution). No study has specifically investigated the correspondence between quantified white matter lesions and response time consistency using ex-Gaussian distributional parameters. Given the high prevalence of white matter lesions in the elderly, and the fact that CSVD significantly contributes to stroke and dementia (vascular and mixed) (Gorelick et al., 2011; Pantoni, 2010), new assessment methods that can tap into these cognitive changes are desperately needed. With previous research indicating specific cognitive connections with RT parameters (Chapter 3), an ex-Gaussian analysis holds great potential for application as a screening tool for cognitive impairment. In particular, the ex-Gaussian parameters mu and tau may be highly relevant and sensitive indices of attentional impairments initially present in CSVD. Early detection of cognitive changes related to CSVD would allow for the treatment of modifiable risk factors.
The primary objective of this study was to examine whether classical RT measures and ex-Gaussian parameters are dependent on the degree of white matter lesion burden in older adults. The secondary objective was to investigate the effect of white matter lesions on cognition, as well as the relationship between ex-Gaussian parameters and cognition, in the context of white matter lesion burden. Structural equation modeling was used to examine these brain-behaviour relationships. We predicted that greater white matter lesion volume would correspond to greater inconsistent performance in terms of a classical measure of RT IIV, and to increases in the ex-Gaussian parameter \( \tau \). We also hypothesized that greater white matter lesion volume would correspond most conspicuously with processing speed and executive functioning. Lastly, we expected that the ex-Gaussian parameter \( \tau \) would be associated with neuropsychological measures of executive functioning, as the susceptibility for slowed responses is known to be indicative of the efficiency of cognitive control on task (Vasquez et al., 2016; West et al., 2002). The results from this study will provide foundational knowledge towards the ultimate goal of developing sensitive markers of cognitive changes related to CSVD.

5.2 Methods

Participants

We recruited 54 healthy community dwelling older adults (aged 65-87 years; age \( M = 75.59, SD = 6.33; 17 \) males) from the Rotman Research Institute participant database who had participated in a previous neuroimaging study unrelated to the present study (\( M = 1.80 \) years, \( SD = 1.65 \), range = 0 to 7), with the particular goal of having most of the sample have some degree of white matter lesions based on initial visual inspection. Scans from the Rotman Research
Institute Neuroimaging Database were later reviewed by a stroke neurologist [JW] experienced in the assessment of white matter and other brain pathology to confirm suitability for inclusion and rule out potential incidental findings. Participants were excluded on the basis of the following criteria: a history of head injury resulting in a loss of consciousness, neurological impairment or other major medical illnesses (e.g. stroke, dementia, and heart disease), radiation to the head, drug abuse, current use of psychiatric medication, lack of fluency in English, or scoring less than 31 points on the modified Telephone Inventory of Cognitive Status (Welsh et al., 1993). Demographic variables and neuropsychological test performance characterizing the sample can be found in Table 5.1. Written informed consent was obtained from all volunteers, and monetary compensation was provided for participating in the study. This research was approved by Baycrest’s Research Ethics Board.
Table 5.1. Demographics and neuropsychological test scores.

<table>
<thead>
<tr>
<th></th>
<th>Mean(SD)</th>
<th>Mean Standard Score (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>75.59 (6.33)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>16.33 (3.23)</td>
<td></td>
</tr>
<tr>
<td>White Matter Lesion Volume Ratio</td>
<td>0.32 (0.40)</td>
<td></td>
</tr>
<tr>
<td>Shipley's Vocab</td>
<td>36.3 (2.49)</td>
<td>12.74 (2.34)</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>27.39 (2.22)</td>
<td>12.00 (3.02)</td>
</tr>
<tr>
<td>WMS-III Logical Memory I</td>
<td>42.93 (9.82)</td>
<td>13.11 (2.66)</td>
</tr>
<tr>
<td>WMS-III Logical Memory II</td>
<td>27.63 (8.74)</td>
<td>14.09 (2.94)</td>
</tr>
<tr>
<td>RCFT copy</td>
<td>29.33 (3.88)</td>
<td>WNL</td>
</tr>
<tr>
<td>RCFT recall</td>
<td>14.31 (6.38)</td>
<td>11.15 (4.20)</td>
</tr>
<tr>
<td>CVLT-II SDFR</td>
<td>11.04 (3.47)</td>
<td>12.30 (2.88)</td>
</tr>
<tr>
<td>CVLT-II LDFR</td>
<td>11.78 (3.73)</td>
<td>12.11 (3.41)</td>
</tr>
<tr>
<td>WMS-III Letter-Number Sequencing</td>
<td>10.30 (2.45)</td>
<td>12.57 (2.49)</td>
</tr>
<tr>
<td>Reading Span Absolute Score</td>
<td>17.55 (14.45)</td>
<td>n/a</td>
</tr>
<tr>
<td>Reading Span Total Correct</td>
<td>34.47 (18.13)</td>
<td>n/a</td>
</tr>
<tr>
<td>WAIS-III Digit Symbol Coding</td>
<td>60.96 (13.12)</td>
<td>12.74 (2.40)</td>
</tr>
<tr>
<td>WCST Percent Perseverative Errors</td>
<td>11.99 (6.88)</td>
<td>13.43 (3.12)</td>
</tr>
<tr>
<td>DKEFS Trail Making Number Sequencing</td>
<td>38.65 (15.26)</td>
<td>12.93 (2.30)</td>
</tr>
<tr>
<td>DKEFS Trail Making Letter Sequencing</td>
<td>39.26 (16.86)</td>
<td>12.63 (2.03)</td>
</tr>
<tr>
<td>DKEFS Trail Making N-L Switching</td>
<td>91.74 (35.00)</td>
<td>12.60 (1.84)</td>
</tr>
<tr>
<td>DKEFS C-W Interference Colour Naming</td>
<td>29.26 (4.06)</td>
<td>11.89 (1.63)</td>
</tr>
<tr>
<td>DKEFS C-W Interference Word Reading</td>
<td>22.50 (4.03)</td>
<td>11.56 (2.13)</td>
</tr>
<tr>
<td>DKEFS C-W Interference Inhibition</td>
<td>59.30 (12.91)</td>
<td>12.63 (1.77)</td>
</tr>
<tr>
<td>DKEFS C-W Switching</td>
<td>66.63 (19.09)</td>
<td>12.33 (2.19)</td>
</tr>
<tr>
<td>DKEFS Letter Fluency (FAS)</td>
<td>46.07 (11.06)</td>
<td>13.50 (3.04)</td>
</tr>
<tr>
<td>DKEFS Category Fluency</td>
<td>40.96 (7.54)</td>
<td>13.30 (2.74)</td>
</tr>
<tr>
<td>DKEFS Category Switching</td>
<td>13.61 (3.02)</td>
<td>12.15 (3.50)</td>
</tr>
</tbody>
</table>

Note. WNL = within normal limits. Normative data are not available for Reading Span.

Abbreviations:

CVLT LDFR = California Verbal Learning Test – II (CVLT-II) Long Delay Free Recall; Logical Mem II = Wechsler Memory Scale III (WMS-III) Logical Memory II; Rey Figure recall = Rey-Osterrieth Complex Figure immediate recall; Trails NS = DKEFS Trail Making Test - Number Sequencing (time to complete); C-W Reading = DKEFS Colour-Word Interference Word Reading (time to complete); Digit Symbol = Wechsler Adult Intelligence Scale III (WAIS-III) Digits Symbol Coding; Verbal Fluency = DKEFS Verbal Fluency (FAS; total words generated); WCST %PE = Wisconsin Card Sorting Test (WCST) percent perseverative errors; Trails N-L Switch = DKEFS Trail Making Number-Letter switching (time to complete); C-W Inhibition = DKEFS Color-Word Interference Inhibition (time to complete); Reading Span = computerized Reading Span (total correct).
Brain Image Analyses

Participants’ T1 [MPRAGE, field-of-view (FOV)=256 mm, 192 x 256 acquisition matrix, 1.0 mm³ voxels, bandwidth=200 Hz/Pixel, TI/TE/TR=1100/2.63/2000 ms, flip angle=9 degrees, 160 slices, averages=1, 1 concat, ipat/ref lines = 3/48, scan duration 4:16] and T2-weighted fluid-attenuated inversion recovery [FLAIR, FOV=256 mm, 256 x 256 acquisition matrix, 1 x 1 x 3 mm voxels, TI/TE/TR=2500/94/9000 ms, 32 slices, Turbo factor=2, flip angle=165 degrees, scan duration = 3:38] scans collected in prior studies were downloaded.

Total intracranial volume (TIV) was calculated to account for differences in brain size in the analysis of white matter lesion load. Brain volumes from T1 images were segmented using SPM 12, generating separate segmentation maps for grey matter, white matter, cerebrospinal fluid (CSF), and skull. The tissue volume utility in SPM was then used to calculate volumes of grey matter, white matter, and CSF, which were summed to provide an estimate of TIV in ml.

White matter lesion volume was calculated using the Lesion Segmentation Tool (LST) version 2.0.11 (http://www.statistical-modelling.de/lst.html) in SPM12. LST provides an automated solution to the segmentation of white matter hyperintensities, which has the advantage of high reliability (Schmidt et al., 2012). The lesion prediction algorithm (LPA) was implemented in LST, entering FLAIR images for the main analysis, along with a T1 as a reference image. Values of interest representing white matter lesions were then extracted by creating a binary file based on the probability lesion map with a threshold of 0.9. The algorithm output total white matter lesion volume in ml, which was then divided by TIV and multiplied by 100 to provide a white matter lesion percentage. LST has been validated against manual tracing in a group of healthy controls (Schmidt et al., 2012). More recent investigations have established
the application of LST in the context of healthy aging and mild cognitive impairment (Birdsill et al., 2014; Fujishima et al., 2014).

**Procedures**

After informed consent, a selected neuropsychological battery was administered to each participant. Computerized attention tasks and questionnaires were interspersed between cognitive tests and to fill in time between memory delay tasks. The main task of interest was a feature integration task (described below) designed to measure response time and capture RT IIV. The entire session lasted approximately three hours.

**Neuropsychological Assessment**

The Shipley’s Institute of Living Scale Vocabulary subtest was included to obtain an estimate of verbal intellectual functioning, and the Boston Naming Test (30-item form) was included as a language measure. Tests were grouped into four cognitive domains for later analysis with structural equation modelling (memory, speed of processing, executive functioning, and working memory). The **memory** domain consisted of the California Verbal Learning Test – II (CVLT-II) delayed free recall, Wechsler Memory Scale III (WMS-III) Logical Memory II, and Rey-Osterrieth Complex Figure immediate recall. For the **speed of processing** domain we grouped the Wechsler Adult Intelligence Scale III (WAIS-III) Digits Symbol Coding, DKEFS Trail Making Number Sequencing (time to complete), and the DKEFS Colour-Word Interference Word Reading (time to complete). The **executive functioning** domain consisted of Wisconsin Card Sorting Test (WCST) percent perseverative errors, DKEFS Trail Making Number-Letter switching (time to complete), DKEFS Color-Word Interference Inhibition (time to complete), Verbal Fluency (FAS; total words generated), and computerized reading span (total
correct) (Unsworth, Heitz, Schrock, & Engle, 2005). The selection of tests in each domain was based on our prior research using structural equation modeling with the same variables, but in a healthy adult sample (Chapter 3).

**Feature Integration task**

The feature integration task is described in detail elsewhere (Chapter 3). In brief, the task involved the simultaneous presentation of 4 playing cards in random non-overlapping locations on a touch screen, with instructions to tap the target (8 of spades) as quickly as possible using a stylus. In the event that there was no target card present, participants were instructed to tap the ‘Next’ button located at the bottom centre of the screen as quickly as possible. The task was self-paced, and upon tapping the screen, the display was refreshed with a new array of 4 playing cards. Before the participants began the task the experimenter demonstrated what was required with two target trials and two ‘Next’ trials (presented in a random order). The experimenter then handed the stylus to the participant to practice interacting with the touch screen. Once the participant touched 10 targets the practice ended. The task consisted of 108 trials (432 images of playing cards). The target 8 of spades was present on 36 of these trials (33%). Cards included numbers 5 through 9 in each of the 4 suits (spades, hearts, clubs, and diamonds). Selection of the non-target cards was controlled, such that cards within a trial shared a certain number of attributes (colour, suit, number) in common with the target. The trials were randomly ordered for each participant with the restriction that no more than three target trials occurred consecutively.

**Data Preparation**

The number of target misses (M = 1.02) and false alarms (M = 0.07) was low, and those trials were not included in the RT distribution analyses. In addition, outlying RTs were removed.
A lower bound for extreme values was set at 150 ms as in prior research (Dixon et al., 2007; Garrett, MacDonald, & Craik, 2012; MacDonald, Hultsch, & Bunce, 2006; Vasquez et al., 2016), as faster responses are considered too quick to carry out decision and motor action components of a response. Responses meeting our lower bound requirement were exceptionally infrequent, representing 0% of Target responses and 0.02% of Next responses. An upper bound for extreme values was defined as responses above the 3rd quartile + (the interquartile range x 3). Visual inspection confirmed that removing these outliers eliminated responses that were clearly outside of the RT distribution for that individual, while preserving those that were part of the slow response tail. Outliers removed for exceeding the upper bound for correct target detections on the feature integration task made up only 1.29% of Target trials and 1.46% of Next trials. Values for missing data points were not imputed.

**Intraindividual Variability and Ex-Gaussian Distribution Parameters**

We employed the intraindividual standard deviation (ISD) with preceding data “purification” steps as a measure of IIV based on consensus from the field (Hultsch et al., 2008). This method ensures that mean RT and systematic trends in performance (practice effects, fatigue, etc.) are eliminated before calculation of ISD. First, the data were checked for linear, quadratic, and cubic trends, which revealed a small but significant negative linear slope across trials. Next, individual trial RTs were regressed on trial number with unstandardized residuals saved. Lastly, intraindividual standard deviations were calculated from these residuals.

Ex-Gaussian parameters were computed separately for each individual using the MATLAB toolkit distrib v2.3 (Lacouture & Cousineau, 2008). The MATLAB script estimated mu, sigma, and tau parameters for each participant, separately for target and next responses on the feature integration task.
Statistical Analysis

To investigate the effect of white matter lesion volume on RT performance, a multivariate analysis of variance (MANOVA) was conducted on all response time variables of interest (mean RT, ISD, mu, sigma, and tau) with white matter lesion volume adjusted for total intracranial volume (TIV) entered as a covariate. This analysis was performed for Target hits and Next correct responses on the feature integration task separately as preliminary analyses indicated that these two response types had different RT distributions. The significant MANOVA was followed-up with univariate analysis for each RT distribution variable.

Structural equation modeling (SEM) was used to examine the relation between RT distribution indices and cognition, in the context of white matter integrity. RT distribution indices from the feature integration task Target hits, neuropsychological tests covering three cognitive domains (memory, processing speed, and executive functions), and white matter lesion volume (corrected for TIV) were applied to the construction of the model. As past research has identified ex-Gaussian parameters as more precise and salient response time distribution metrics compared to mean and ISD (Chapter 3; Jackson et al., 2012; Tse, Balota, Yap, Duchek, & McCabe, 2010; Vasquez et al., 2016), only mu, sigma, and tau were applied to the model. The covariance between variables in the model was adjusted according to recommendations from modification indices in the SEM output to improve model fit. The SEM was created using IBM SPSS Amos 20.0.
5.3 Results

**Neuropsychological and White Matter Lesion Measures**

Participants performed within normal limits across all neuropsychological tests administered (Normative performance is $M = 10$, $SD = 3$; Table 5.1). The automated segmentation procedure (adjusted for brain volume) yielded white matter lesion ratios ranging from 0 to 1.56 ($M = 0.32$, $SD = 0.40$).

**Feature Integration Task**

For ‘Target’ responses, the average values for RT indices were the following: mean RT 1614.58 ms ($SD = 273.45$), ISD 333.32 ms ($SD = 129.24$), mu 1342.43 ms ($SD = 221.92$), sigma 168.35 ms ($SD = 80.30$), and tau 271.89 ms ($SD = 146.34$). For ‘Next’ responses, the average values for RT indices were the following: mean RT 1935.21 ms ($SD = 442.15$), ISD 325.39 ms ($SD = 138.52$), mu 1709.11 ms ($SD = 409.25$), sigma 201.27 ms ($SD = 124.62$), and tau 226.12 ms ($SD = 120.80$).

**Target Responses.** Using Pillai’s trace, there was a significant multivariate effect of white matter lesion volume (corrected for TIV), ($V = .283, F(5, 48) = 3.78, p = .006, \eta^2_p = .283$). Univariate analysis indicated that individuals with greater white matter lesion volume had higher mean RT ($F(1,52) = 11.54, p = .001, B = 292.59, \eta^2_p = .182$), ISD ($F(1,52) = 12.22, p = .001, B = 141.53, \eta^2_p = .190$), mu ($F(1,52) = 7.20, p = .01, B = 194.33, \eta^2_p = .122$), and tau ($F(1,52) = 4.05, p < .05, B = 98.72, \eta^2_p = .072$), but not sigma ($F(1,52) = 1.59, p = .213, B = 34.72, \eta^2_p = .030$).

**Next Responses.** Analysis of Next responses also yielded a significant multivariate effect using Pillai’s trace for white matter lesion volume (corrected for TIV), ($V = .285, F(5, 48) = \ldots$)
3.82, p < .01, \eta^2_p = .285). Follow-up univariate analysis indicated that greater white matter lesion volume was associated with higher mean RT (F(1,52) = 8.01, p < .01, B = 405.47, \eta^2_p = .133), ISD (F(1,52) = 16.63, p < .001, B = 171.20, \eta^2_p = .242), mu (F(1,52) = 7.98, p < .01, B = 374.87, \eta^2_p = .133), and sigma (F(1,52) = 16.47, p < .001, B = 153.44, \eta^2_p = .241), but not tau (F(1,52) = 0.53, p = .468, B = 30.59, \eta^2_p = .010).

Correspondence between RT Distribution Indices and Cognition

Structural equation modeling was applied to the data to examine the correspondence between RT performance and cognition while also factoring in white matter lesion severity. Following recommendations from modification indices, the final model demonstrated good fit to the data (CFI = .936, TLI = .903, RMSEA = .061, chi-square = 82.252, p = .132). The model indicated that mu and tau had relatively stronger relationships with cognitive latent variables compared to sigma, which had weaker regression weights (Figure 5.1). Additionally, mu most strongly corresponded to the processing speed latent variable, whereas tau related most strongly to the executive functioning latent variable. Lastly, white matter lesion volume (corrected for TIV) had the strongest regression weight to mu, followed by tau, and then sigma.
Figure 5.1. Structural Equation Model – ex-Gaussian RT Parameters (mu, sigma, tau), Cognition, and White Matter Lesion Volume

Good Model Fit - CFI =.936, TLI =.903, and RMSEA =.061, and the chi-square (.132)

Note: regression weights are standardized

For explanations of abbreviations, see Table 5.1.

5.4 Discussion

The primary objective of the present investigation was to examine, in a group of older adults, the relationship between degree of white matter lesion volume and response time distribution indices (both classical RT measures and ex-Gaussian parameters). No prior study had specifically examined the effects of white matter lesion volume on ex-Gaussian distributional parameters, although previous evidence indicates that tau may be more sensitive to executive impairment than typical RT measures (mean and RT IIV). The secondary objective
was to investigate how neuropsychological measures of cognition, representing different domains, are related to white matter lesions and ex-Gaussian parameters. We discuss the results in relation to these objectives in turn below.

*White Matter Lesions and Response Time*

The current results showed that greater white matter lesion volume was associated with slower response speed (mean and mu), greater variability across the entire RT distribution (ISD), and a greater degree of exceptionally slow responses (tau). The analysis, however, revealed no significant effect of white matter lesion volume on the RT variability within the Gaussian component of the distribution (sigma). Given that ISD captures both sigma and tau, we can conclude that the classical measure of RT IIV is primarily reflecting a greater propensity for extremely slow responses, albeit less precisely. Lesions to the white matter may disrupt the neural network responsible for cognitive control, degrading the ability to maintain optimal performance on task, and permitting the susceptibility to subtle brief ‘attention lapses’. These momentary attentional delays manifest as a greater degree of longer latency responses, leading to a positive distributional skew. Interestingly, white matter lesion volume corresponded only with Target tau, but not Next response tau. This fits well with the concept that responding to rare targets (which also involved a feature integration component) is more taxing to executive control processes, compared to the high frequency Next responses.

The structural equation model revealed a pattern of relative contribution of white matter lesion volume to RT distribution indices. In particular, the data showed that white matter lesions correspond most strongly to the Gaussian mean (mu), followed by positively skewed responses (tau), and finally, Gaussian standard deviation (sigma), consistent with the pattern identified in the ANOVA. These data suggest that white matter lesions most highly impact general speed of
responding by reducing network connectivity and integration (Kim et al., 2015; Tuladhar et al., 2017) and effectively delaying neural transmission, and to a slightly lesser degree are responsible for exceptionally slow responses that likely reflect waning executive control due to a network disconnection.

Our data complement existing research on white matter and response time indices, which has been explored from two perspectives - through quantification of white matter lesion volume (Bunce et al., 2007, 2010, 2013) and the measurement of healthy white matter integrity (Fjell et al., 2011; Jackson et al., 2012; Walhovd & Fjell, 2007). In reference to studies using white matter lesion volume, the present data are compatible, showing a positive relationship between white matter lesion volume and RT IIV. In particular, Bunce and colleagues have shown both in middle-aged (Bunce et al., 2010) and older adults (Bunce et al., 2007) that white matter lesions, uniquely in the frontal lobes, were associated with elevated RT IIV. Our findings on white matter lesion volume also support existing research that takes an individual differences perspective by studying healthy white matter integrity. Using diffusion tensor imaging, Fjell and colleagues (2011) examined white matter microstructure in a group of healthy adults (aged 20 – 83) and found a significant negative association of white matter integrity with RT IIV that was independent of mean RT. More closely related to the present investigation, Jackson et al. (2012) included an ex-Gaussian analysis and found that RT IIV, mu, and tau, but not sigma, demonstrated a robust relationship with total cerebral white matter. The authors also found specific regional effects, with RT IIV and tau exhibiting associations with frontal and posterior white matter regions. The same study involved an examination of relations in healthy older adults and a cognitively impaired group, which notably revealed a stronger association with white matter for tau than RT IIV in both samples. Similarly to Jackson et al. (2012), we also found notable effects for overall speed of response (i.e. mean and mu), indicating that white
matter lesions affect more than just consistency of responding. Bridging these two areas of the literature, it is evident that greater white matter lesion volume (Bunce et al., 2007, 2010, 2013), or weaker healthy white matter integrity (Fjell et al., 2011; Jackson et al., 2012; Walhovd & Fjell, 2007) relates to more variable responses and corresponds to a greater degree of exceptionally slow responses (tau).

Some of these previous studies have identified specific brain regions that exhibit a particularly strong correspondence with variability measures, for instance frontal white matter (Bunce et al., 2007, 2010; Jackson et al., 2012). White matter regions involved in the default network such as the posterior cingulate and precuneus have also been implicated (Jackson et al., 2012). The automatic segmentation algorithm implemented in the present study provided white matter lesion quantification over the entire brain, and not by region. We do not believe this detracts from our findings – although executive abilities are known to rely on the prefrontal cortex, connections with other brain regions through white matter tracts are critical. Disruption to executive control processing can occur at any point along this network (Grambaite et al., 2011; Grieve et al., 2007; Hedden et al., 2012), which is congruent with our findings of the greater cognitive decline with escalating whole-brain white matter lesion severity. The literature on the role of white matter in cognition supports the notion that multiple regions provide important network contributions. For instance, white matter integrity in the frontal, parietal and temporal lobes has been implicated in tasks of attentional control and executive functioning (Grieve et al., 2007), with further evidence indicating that degeneration of white matter in frontal and cingulate regions (both anterior and posterior) contributes to executive dysfunction in mild cognitive impairment (Grambaite et al., 2011). Furthermore, total white matter lesions have been shown to affect the ability to modulate attentional control systems leading to impaired executive performance (Hedden et al., 2012).
The present study focused on the spectrum of CSVD in older adults, which is unique among studies on RT IIV. A strength of the research design was the attempt to capture a range of severity of sporadic CSVD by including the most at risk age range and having a relatively wide distribution of lesion volumes. Our sample consisted of older adults between the ages of 65 and 87, who had lesion volumes ranging from none to severe. This was a noteworthy divergence compared to previous studies on white matter lesions and RT IIV, which attempted to control for potential confounding age effects by restricting participant inclusion to adults aged 60 to 64 (Bunce et al., 2007) and 44 to 48 (Bunce et al., 2010). Applying an age restriction was successful at identifying the importance of white matter lesions and their contribution to response time consistency regardless of age. These limited age ranges, however, also likely constrained the degree of white matter disruption (Pantoni, 2010) and RT IIV (Hultsch et al., 2002). The authors acknowledged this limitation in their 2010 paper, explaining that due to the young age of the sample, there were few participants with substantial white matter lesion load.

**White Matter Lesions and Cognition**

Structural equation modeling was applied to characterize the relation between white matter lesions, cognition and response time together, which is a novel approach to synthesizing RT and cognitive performance data. The white matter lesion latent variable corresponded with differential priority to cognitive domains. Greater white matter lesion volume was most strongly related to worse memory, followed by weaker executive functioning, and lastly slower processing speed, suggesting a differential impact on cognition. Although, previous research indicates that white matter lesions significantly contribute to performance in all these cognitive domains, processing speed is known to be the most affected (Gunning-Dixon & Raz, 2000; Vasquez & Zakzanis, 2015). Interacting model components may account for why we found
memory to have the strongest association with white matter lesion volume, rather than the expected domain of processing speed. Of the ex-Gaussian parameters, mu had the highest regression weight from white matter lesion volume and to the processing speed latent variable. Thus, it is possible that individual differences in processing speed can be explained by lower mu, which is influenced by the presence of white matter lesions. In contrast, memory performance may not be as well described by the ex-Gaussian parameters, but is still affected by white matter lesion severity. The widespread neuropsychological relationships demonstrate the importance of white matter integrity to cognitive processing, regardless of any overt reliance of these mechanisms on speed of mental processing.

Tau was most strongly associated with executive functioning, which is congruent with the theory that exceptionally slow responses index executive control efficiency, also supported by prior research from our lab (Chapter 3; Vasquez et al., 2016). Sigma provided minor contributions to cognitive latent variables by comparison. The relative weightings of cognitive variables differed from our prior study’s data with healthy adults (Chapter 3) in that mu no longer had a very strong association with cognitive domains. It should be noted that the prior SEM from Chapter 3 did not incorporate white matter lesion volume, which could explain relative differences compared to the present model.

*The Importance of White Matter*

The present findings, in conjunction with previous research described above, suggest that white matter is critical to both speed of responding and consistency - specifically minimizing exceptionally slow responses. This holds true both from an individual differences perspective, looking at healthy brains with variation in white matter integrity, or from a pathological process perspective, quantifying white matter lesions. The purpose of white matter is to maintain
functional connectivity between distant and adjacent brain regions to create large-scale brain systems (Andrews-Hanna et al., 2007). Thus, white matter is directly related to the speed at which information is processed (Magistro et al., 2015). Differences in the intactness of white matter likely correspond to the speed of signal transduction across a given neural network, which has repercussions on mean behavioural response speed. A similar logic can be applied to behavioural variability – as signals are transmitted across the white matter, lesions may influence the routes that are accessed. Fluctuations between optimal and suboptimal neural pathways create variability in the efficiency of signal transduction, which may correspond to behavioural consistency (Kelly et al., 2008). Furthermore, disrupting the efficiency of signal transduction across the white matter likely affects cognitive processes differently. Elevations in ex-Gaussian tau may reflect a disturbance in cognitive control circuitry, necessitated by intact white matter, such that attention cannot be continuously sustained at efficient levels.

Limitations

Some brain scans were taken a significant amount of time before behavioural testing was done - up to 7 years prior (the mean time difference was 1.80 years). Thus, there was a margin of error in our brain-behaviour connection. Due to the progressive nature of cerebrovascular disease, however, it is quite unlikely that brain integrity would have improved over time. Use of these dated scans would only have underestimated participants’ white matter lesion volumes, suggesting that the associations of white matter lesions volumes with speed and variability reported here may actually be higher. Another limitation may exist relating to the locations in which CSVD typically exerts effects. The organization of the cerebrovascular system dictates that CSVD will lead to white matter lesions in similar brain regions between individuals (Pantoni, 2010). If the networks responsible for certain cognitive processes are affected by
CSVD more than others, then *locations* of white matter loss would also be relevant in addition to *volume* of white matter loss. Severity of CSVD is likely to implicate a greater amount of white matter across distributed regions, which may disrupt more domains of cognition. Unfortunately, the lesion segmentation algorithm used in the present study was not able to quantify lesions within specific brain regions, preventing any control for this factor. Lastly, we were not able to control for a variety of confounding variables such as age, education, or medical conditions (e.g. hypertension/diabetes) due to insufficient power, which may have affected the results.

**Conclusions**

We found that white matter lesion volume in otherwise healthy older adults significantly predicts response time speed, indexed by mean RT and mu, and intraindividual variability measured through ISD and tau, but not sigma. White matter lesions were also shown to influence cognitive performance in the domains of memory, executive functioning, and processing speed, in declining order of magnitude, respectively. Examination of cognitive relations confirms that, in a selection of older adults with varying degrees of white matter lesion severity, Gaussian mean reflects speed of processing, and that exceptionally slow responses are related to executive control processes. The present study provides further evidence for the importance of intact white matter in producing quick and consistent behavioural performance. The results strongly suggest that white matter lesions due to CSVD compromise cognitive and response time performance owing to interruptions in the transmission of signals across white matter tracts. More specifically, disordered signal transmission may increase the time required for cognitive operations to complete, directly impacting speed and potentially indirectly impacting other processes such as memory (Salthouse, 1996b), and disrupt cognitive control processing via diffuse executive network disconnections. These findings identify a brain-behaviour connection
that is relevant to many older adults, stressing the importance of targeting vascular risk factors in order to maintain brain and cognitive health in aging. Future research should investigate whether elevations in RT parameters, such as tau, are predictive of later functional decline and dementia.
Chapter 6

The effect of white matter lesion burden on the training of response time consistency

6.1 Introduction

Cerebral small vessel disease (CSVD) is a vascular condition affecting small penetrating arteries in the brain that supply oxygen and nutrients to white matter and subcortical regions. The most common and easily visible indicators of CSVD on neuroimaging are ischemic white matter lesions caused by a breakdown in the health of these small vessels. Noteworthy predictors of developing CSVD are vascular risk factors and age. In fact, evidence of at least early stages of CSVD have been shown to be present in over 90% of older adults sampled, visible as mild to severe white matter lesions (de Leeuw et al., 2002; Longstreth et al., 1996). It has been shown that cognition is affected in CSVD across all domains typically examined, with the most notorious impairment being in processing speed, followed by memory and executive functioning (Vasquez & Zakzanis, 2015).

White matter tracts provide connective pathways between processing centres of different cortical regions, as well as between cortical and subcortical structures. White matter consists of neurons that are myelinated, which provides insulation to promote efficient and rapid signal conduction (Kivipelto, Soininen, & Tuomilehto, 2002). Furthermore, the high degree of myelination in white matter creates superior isolation of electrical currents in dendrites and axons (Russell et al., 2006). Disturbance to white matter may have a wide effect on brain function as it can interrupt transmission of information across networks (Grambaite et al., 2011;
Hedden et al., 2012). Instead, brain regions must communicate through variable alternate paths, leading to excess neural noise (MacDonald, Li, & Bäckman, 2009). This hypothesis could explain findings that weaker white matter integrity corresponds to elevations in response time intraindividual variability (RT IIV; Fjell, Westlye, Amlien, & Walhovd, 2011; Jackson, Balota, Duchek, & Head, 2012), also known as response time inconsistency, which describes within task fluctuations in performance from trial to trial. Current theories propose that response consistency represents a functionally more efficient system, with the ability to more effectively engage cognitive control (Stuss et al., 1994; West et al., 2002). In contrast, inconsistent responding relates to a subtle breakdown in this ability, and may directly convey brief attention lapses through observed increases in longer latency responses (Bunce et al., 1993; West et al., 2002).

Research has shown that the degree of white matter lesions in the prefrontal lobes is associated with elevated RT IIV, both in adults aged 60-64 (Bunce et al., 2007), as well as in adults in their mid 40s (Bunce et al., 2010). Over a larger age range, from healthy young to healthy older adults, it has been shown that white matter integrity is significantly correlated with RT IIV, independent of processing speed (Fjell et al., 2011; Walhovd & Fjell, 2007). Another study examined the relationship between white matter volume and ex-Gaussian parameters reflecting response time consistency (Jackson et al., 2012). The ex-Gaussian distribution fits reaction time data well, as it is the convolution of a Gaussian distribution, with parameters mu and sigma reflecting the mean and standard deviation of the faster reaction times, and an exponential distribution with the parameter tau reflecting the rightward tail of slower responses. Jackson et al. (2012) found a robust relationship between RT IIV and total cerebral white matter, especially in frontal regions. Furthermore, the ex-Gaussian parameter tau displayed an even stronger relationship with white matter volume, a relationship which was higher still in their cognitively impaired group.
The research described above indicates that disruption to white matter is associated with instability of performance, perhaps because those routes can no longer transmit signals as efficiently as they once did. It is still unknown whether the brain can adapt functionally to counter this inefficiency. Promising evidence for such plasticity in healthy older adults comes from research on the malleability of response time consistency. One study integrated visual feedback between blocks into a four choice response time task to determine if a targeted training procedure could promote the reduction of RT IIV (Garrett et al., 2012). The feedback included graphs of performance on preceding blocks, an explanation of RT IIV, and positive reinforcement. They found that feedback training lead to a significant decrease in RT IIV over the four blocks for healthy older adults. More recently, we replicated these findings and examined the effects of feedback training on ex-Gaussian parameters, and on transfer to an independent test (Chapter 4). We found that reductions in variability are primarily due to alterations in the ex-Gaussian parameter tau. The data, however, did not support the potential for transfer of training. Together these studies suggest that RT IIV is reflective of current attentional processing resources that can be willfully influenced. These resources can be optimized to reduce variable responding, with the appropriate training. We have yet to determine, however, the neural requirements for this procedure to be effective. That is, we know that feedback can reduce healthy younger and older adults’ RT IIV, but this paradigm has not been applied to individuals with damage to the brain network supporting cognitive control – the same structural brain regions known to be affected in CSVD.

To this end we recruited 44 participants with varying levels of white matter lesion severity and asked them to complete a similar training paradigm as discussed above using a feature integration response time task. Participants were assigned to receive either feedback on their response time performance between blocks, or no feedback. Additionally, a four-choice
response time task was given before and after the feature integration task in order to evaluate the potential for transfer of training. Improvements in response time consistency were evaluated as a function of condition (feedback or no feedback) and white matter lesion volume.

The primary goal of this study was to investigate whether RT IIV feedback training could improve consistency in healthy, cognitively intact individuals with a range of white matter lesion severity, from mild to moderate. Our secondary objective was to explore the influence of white matter lesion load on training success. The third and final aim was to determine whether any training benefits would transfer to an untrained task. We predicted that individuals would be able to adapt and utilize the feedback to reduce variability across blocks of the training task, regardless of white matter lesion severity. We hypothesized, however, that beneficial effects of feedback would be greater in individuals with low white matter lesion burden. We found no significant transfer in our previous study with healthy older adults (Chapter 4), but were uncertain whether transfer would occur in a group of individuals with white matter lesions.

6.2 Methods

Participants

We recruited 44 older adults (aged 65-87 years; age M=76.09, SD=6.45; 14 males) from the Rotman Research Institute participant database who had all participated in a neuroimaging study in the past that was unrelated to the present study. Participants were excluded on the basis of the following criteria: a history of head injury resulting in a loss of consciousness, neurological impairment or other major medical illnesses (e.g. stroke, dementia, and heart disease), radiation to the head, drug abuse, current use of psychiatric medication, or a lack of
fluency in English. Participants also had to achieve a score greater than 30 points on the modified Telephone Inventory of Cognitive Status (Welsh et al., 1993).

Scans from the Rotman Research Institute Neuroimaging Database were reviewed by a stroke neurologist [JW] experienced in the quantification of white matter pathology. Participants were only included if they had significant white matter lesions visible on MRI. The Fazekas rating scale was applied to T2-weighted FLAIR sequences to classify severity level, such that 0 reflected minimal or no white matter pathology, 1 represented a mild degree of white matter pathology, and 2 in any single brain region corresponded to moderate/severe white matter lesion load (Wahlund et al., 2001). In efforts to match participants in the two study conditions for severity of white matter lesions, participants were categorized during recruitment into two severity levels (1 or 2) and alternately assigned to condition (Feedback or Standard) within each group. Individuals who received a Fazekas rating of 0 were not included in the present study as we were interested in determining the effect of white matter lesion severity on the experimental manipulation. Written informed consent was obtained from all volunteers, and monetary compensation was provided for participating in the study. This research was approved by Baycrest’s Research Ethics Board.

**Brain Imaging Acquisition**

We downloaded participants’ T1 [MPRAGE, field-of-view (FOV)=256 mm, 192 x 256 acquisition matrix, 1.0 mm$^3$ voxels, bandwidth=200 Hz/Pixel, TI/TE/TR=1100/2.63/2000 ms, flip angle=9 degrees, 160 slices, averages=1, 1 concat, ipat/ref lines = 3/48, scan duration 4:16] and T2-weighted fluid-attenuated inversion recovery [FLAIR, FOV=256 mm, 256 x 256 acquisition matrix, 1 x 1 x 3 mm voxels, TI/TE/TR=2500/94/9000 ms, 32 slices, Turbo factor=2, flip angle=165 degrees, scan duration = 3:38] scans collected in prior studies.
Intracranial Volume Calculation

In order to account for the possibility that differences in brain size could contribute to effects related to the quantity of white matter lesions, total intracranial volume (TIV) was incorporated into the measure of lesion volume. To calculate TIV, brain volumes from T1 images were first segmented in SPM 12, which created separate segmentation maps for grey matter, white matter, cerebrospinal fluid (CSF), and skull. Next, actual volumes of grey matter, white matter, and CSF were computed using the tissue volume utility in SPM. These volumes were then summed to give an estimate of TIV in ml.

White Matter Lesion Segmentation

The Lesion Segmentation Tool (LST) version 2.0.11 in SPM12 (http://www.statistical-modelling.de/lst.html) was used to estimate white matter lesion volume. LST uses an algorithm to segment white matter hyperintensities in an automated fashion. This computational protocol has the advantage of high reliability compared to manual tracing methods. The lesion prediction algorithm (LPA) was implemented in LST, using FLAIR images, as well as a T1 as a reference image. Upon completion, the algorithm generated estimates of total white matter lesion volume in mls. In order to eliminate the possibility of false positive lesions, a threshold of 0.9 was applied to the probability map before values of interest were extracted. The estimated white matter lesion volume was then divided by TIV and multiplied by 100 to achieve a white matter lesion percentage. The LST toolbox has been tested on healthy older adults and deemed to be a reliable and appropriate tool for automated white matter lesion segmentation (Schmidt et al., 2012). A few recent studies have further supported the application of LST in research on healthy aging and mild cognitive impairment (Birdsill et al., 2014; Fujishima et al., 2014).
Procedures

Feedback training was incorporated into a feature integration task, between blocks. In contrast, the Standard condition involved the same feature integration task without feedback provided between blocks. Participants were assigned to condition (Standard or Feedback) in a pseudorandom fashion. Participants completed three attention tasks: a pre-training baseline four choice response time task was followed by the ‘training’ task (the feature integration task either with or without feedback), and then the four-choice response time task again as a post-training assessment of transfer. We evaluated the possibility of near transfer by examining the effect of training condition on differences between pre- and post-training performance on the four choice RT task. A selection of neuropsychological tests was also administered to characterize the sample.

Four Choice Response Time task

The numbers one through four were presented centrally, one at a time, in random order but with each number being presented equally often. Each number was preceded by a blank screen for 200 ms, followed by a fixation cross for 500 ms. The task instructions were to press a numbered key that corresponded to the number on the screen using designated fingers assigned to each key (index through to little finger) on their preferred hand. Numbers remained on the screen until the participant made a response, at which point the next trial began, making the task self-paced. The task began with eight practice trials, for which feedback was provided immediately after each response (correct or incorrect). After practice, the experimental task consisted of 208 trials divided into 4 blocks of 52 trials, with no feedback shown. The task was divided into blocks to allow for brief rests. The stimuli were displayed in 30-point black Courier New Type font on a white background. The task took approximately five minutes to complete.
**Feature Integration task**

**Task Overview.** On each trial, four playing card images were simultaneously presented in random non-overlapping spatial locations on a touch screen. Participants were instructed to use a stylus to tap the Target card (8 of spades) as quickly as possible if it was present in the display. In the event that there was no Target card present, participants were instructed to tap the ‘Next’ button located at the bottom centre of the screen as quickly as possible. Card stimuli remained on the screen until a response was made. Upon tapping either the Target card or the Next button, or incorrectly tapping a non-Target card, the display would be refreshed with a new array of 4 playing cards. Before the experimental trials began, the experimenter demonstrated how to make responses on the touch screen in response to two Target trials and two Next trials (presented in a random order). The participant then practiced the task until he or she successfully touched 10 Targets. The responses of each Target and Next tap were recorded for the later calculation of RT IIV and the estimation of ex-Gaussian parameters.

**Stimuli Details.** The feature integration task presented four playing cards per trial, over 432 trials (equaling 1728 images of playing cards), and was evenly divided into 4 blocks of 108 trials each. The Target 8 of spades was displayed on 144 trials, and was absent on 288 trials. Card images were only those with numbers 5 through 9 in each of the 4 suits (spades, hearts, clubs, and diamonds). The trials were randomly ordered within each block, maintaining a restriction that no more than three trials containing Targets could occur consecutively. Playing card stimuli were presented on a white background. The card images were 180 by 225 pixels in size, subtending visual angles of 5.26 by 6.56 degrees at an approximate viewing distance of 40 cm.
Feedback Training Condition. Feedback was provided immediately following each block of 108 trials, as was done by Garrett et al. (2012). Feedback was presented on one screen graphically, displaying performance in 4 different ways on one screen (Figure 6.1). A line graph of response times to each of the 36 Targets tapped in the immediately preceding block appeared in the top left quadrant. This feedback plot was designed to give a visual sense of trial-to-trial variability (i.e. less variability would result in a flatter line, whereas more variability would be visible as a jagged line with many high amplitude spikes). A bar graph of Target hit median response times and standard deviations for each previously completed block appeared in the top right quadrant. The purpose of this plot was to allow participants to gauge their progress in improving speed and consistency across blocks. A bar graph of the number of false alarm responses made in each preceding block was provided in the bottom right quadrant (note that false alarms were rare, fewer than one per person - averaging .50, and it is believed that this feedback element did not contribute to feedback related effects. A bar graph of points earned for consistently quick responses in each previously completed block was contained in the bottom left quadrant. Participants received 10 points for any response +0.5 standard deviations (SDs) or quicker in relation to their median on the preceding block (for the first feedback it was necessary to use the block 1 median). Participants lost 10, 20, or 50 points for responses that were +0.5 to +2 SDs, +2 to +4 SDs, and greater than +4 SDs, respectively than their median in the preceding block. No point deductions were made for missed Targets. The preceding block median (or current median for Block 1) was used as a basis for calculating points awarded in order to encourage continuous improvement throughout the task.

Figure 6.1. Between Block Feedback during the Feature Integration Task
Once the first block of trials was completed, the first set of feedback graphs was displayed. At this point, the meaning of each feedback graph was explained and the training objective was emphasized, which was to use the feedback as a guide to becoming more consistent in the next block of trials. Participants were informed that they would be awarded points for becoming more consistent. We did not divulge more specific information on point calculation. The featured integration task was not resumed at the start of block 2 until the experimenter was confident that participants understood the task instructions and goal to become more consistent. Participants were also encouraged to evaluate the effectiveness of their strategy before continuing the task. This protocol facilitated an interactive dynamic between participant, experimenter, and feedback material. In the event that a participant was having difficulty developing a suitable strategy, the experimenter would foster a discussion to aid them. Importantly, the majority of participants did not require this added intervention component. The
role of the experimenter was to provide a minimal level of positive support and guidance throughout the provision of feedback, not to overtly suggest a specific strategy for improvement.

**Standard (no Feedback) Condition.** The Standard condition involved a control version of the feature integration task in which no feedback was given between blocks, and there was no instruction given to become more consistent. A blank screen was shown in between blocks with instructions to take a brief break. The duration of the breaks between blocks was similar for both Feedback and Standard versions of the task. Since the task was self-paced, the total completion time was dependent on how fast the participant responded on each trial, but generally took between 20 and 25 minutes, with the Feedback version taking slightly longer than the control version.

**Statistical Analysis**

To examine the effects of feedback training, mean response time, RT ISD, and ex-Gaussian parameters (mu, sigma, tau) were analyzed in a mixed repeated measures multivariate ANOVA with condition (Feedback or Standard) as a between-subject independent variable, block (1 and 4) as a within-subject variable, and white matter lesion volume (corrected for TIV) as a covariate. If significant multivariate effects were found, they were followed up with a univariate analysis. These analyses were conducted separately on data from Target and Next responses of the feature integration task, based on preliminary analyses that determined they had different RT distributions.

The potential for transfer of effects from feedback training was examined by comparing pre- and post-training performance on the four-choice response time task. Mean response time, RT ISD, and ex-Gaussian parameters (mu, sigma, tau) were analyzed in a mixed repeated
measures multivariate ANOVA with condition (Feedback or Standard) as the between-subject independent variables, and pre/post as the within-subject variable, and white matter lesion volume (corrected for TIV) as a covariate. Significant multivariate effects were followed up with a univariate analysis.

6.3 Results

Feature Integration Task Performance

Target Responses. Repeated measures MANOVA using Pillai’s trace revealed that there was no significant multivariate effect for condition ($V = .241$, $F(5, 36) = 2.28$, $p = .067$, $\eta_p^2 = .241$). There was a significant multivariate effect for white matter lesion volume ($V = .264$, $F(5, 36) = 2.59$, $p = .042$, $\eta_p^2 = .264$), and for the interaction between condition X white matter lesion volume ($V = .258$, $F(5, 36) = 2.50$, $p = .048$, $\eta_p^2 = .258$). The multivariate main effect of block was not significant ($V = .239$, $F(5, 36) = 2.27$, $p = .068$, $\eta_p^2 = .239$), and there was no significant block X condition interaction ($V = .186$, $F(5, 36) = 1.65$, $p = .173$, $\eta_p^2 = .186$), nor was there a significant block X white matter lesion volume interaction ($V = .221$, $F(5, 36) = 2.05$, $p = .095$, $\eta_p^2 = .221$). Lastly, there was no significant 3-way block X condition X white matter lesion volume interaction ($V = .182$, $F(5, 36) = 1.61$, $p = .183$, $\eta_p^2 = .182$). Univariate analyses demonstrated a significant effect of white matter lesion volume on mean ($F(1, 40) = 8.06$, $p = .007$, $\eta_p^2 = .168$), ISD ($F(1, 40) = 6.68$, $p = .014$, $\eta_p^2 = .143$), mu ($F(1, 40) = 6.36$, $p = .016$, $\eta_p^2 = .137$), and sigma ($F(1, 40) = 5.30$, $p = .027$, $\eta_p^2 = .117$), but not tau ($F(1, 40) = 2.11$, $p = .154$, $\eta_p^2 = .050$). A significant univariate interaction of condition X white matter lesion volume was only found for mu ($F(1, 40) = 7.06$, $p = .011$, $\eta_p^2 = .150$); individuals with low white matter lesion
volume in the standard condition had lower mu values than those with high white matter lesion volume, whereas individuals with low white matter lesion volume in the feedback condition had higher mu values than those with high white matter lesion volume.

The absence of a significant 3-way interaction means that the data failed to confirm our hypothesis that white matter lesion volume would interact with training effects on RT indices. After finding that the 3-way interaction was not significant at the multivariate level, the data were examined using a median split of white matter lesion volume to create low and high lesion severity groups. A median split approach allowed for a straightforward interpretation of data pattern including experimental condition, training effects, and white matter lesion volume. Viewing the data in this format revealed that there was a non-significant trend for ISD to be reduced in individuals with high white matter lesion volume following feedback (Figure 6.2). Similarly, the data also show a pattern of feedback related reductions in tau for those with low and high white matter lesion volume (Figure 6.2). Of note, when the data were split by Fazekas ratings (1 and 2), the same non-significant pattern of results was visible.
Further examination of training effects was conducted by re-analyzing RT data in another repeated measures multivariate ANOVA, but this time including all four blocks for the within-subjects variable. This analysis using Pillai’s trace revealed significant multivariate main effects of condition \((V = .267, F(5, 36) = 2.62, p = .040, \eta_p^2 = .267)\) and white matter lesion volume \((V = .340, F(5, 36) = 3.72, p = .008, \eta_p^2 = .340)\), and a significant interaction of condition X white matter lesion volume \((V = .309, F(5, 36) = 3.22, p = .017, \eta_p^2 = .309)\). There were no significant effects for block \((V = .512, F(15, 26) = 1.82, p = .087, \eta_p^2 = .512)\) or the interaction of block X condition \((V = .381, F(15, 26) = 1.07, p = .428, \eta_p^2 = .381)\). However, significant interactions were found for block X white matter lesion volume \((V = .669, F(15, 26) = 3.50, p = .002, \eta_p^2 = .669)\) and for block X condition X white matter lesion volume \((V = .552, F(15, 26) = 2.14, p = .043, \eta_p^2 = .552)\).
Univariate analyses following the 4-block repeated measures MANOVA demonstrated no significant effects of condition for any of the RT variables. A significant effect of white matter lesion volume was found for mean (F(1, 40) = 7.35, p = .010, η_p^2 = .155), ISD (F(1, 40) = 8.93, p = .005, η_p^2 = .182), mu (F(1, 40) = 5.70, p = .022, η_p^2 = .125), and sigma (F(1, 40) = 7.71, p = .008, η_p^2 = .162), but not tau (F(1, 40) = 2.47, p = .124, η_p^2 = .058). A significant univariate interaction of condition X white matter lesion volume was only found for mu (F(1, 40) = 4.38, p = .043, η_p^2 = .099). Although significant multivariate interactions were found for block X white matter lesion volume and block X condition X white matter lesion volume, there were no significant univariate results for these interactions with any of the RT variables. The absence of univariate effects was surprising, given the clear pattern that emerged as the data were inspected.

ISD showed a clear decline across the four blocks of the feedback condition for those with high white matter lesion volume, whereas individuals with low white matter lesion volume had a relatively stable level over time (Figure 6.3). In contrast, participants in the standard condition appeared to become slightly more variable over time. Viewing the results for tau reveals that individuals with low white matter lesion volume demonstrated reductions across the four blocks (Figure 6.3). Individuals with high white matter lesion volume, however, first showed a reduction in tau across the first three blocks and then a slight elevation at block 4. Mu appeared to be relatively stable, only showing a slight decrease across the four blocks, except in individuals who had low white matter lesion volume for which mu increased. No discernable pattern was observed for mean or sigma.
Next Responses. Repeated measures MANOVA using Pillai’s trace revealed that there was no significant multivariate main effect for condition (V = .188, F(5, 36) = 1.67, p = .167, $\eta_p^2 = .188$). However, there was a significant main effect for white matter lesion volume (V = .284, F(5, 36) = 2.86, p = .028, $\eta_p^2 = .284$) and the interaction of condition X white matter lesion volume (V = .438, F(5, 36) = 5.60, p = .001, $\eta_p^2 = .438$). There were no significant multivariate within-subjects main effects or interactions: block (V = .249, F(5, 36) = 2.38, p = .057, $\eta_p^2 = .
.249), block X condition (V = .227, F(5, 36) = 2.12, p = .086, η² = .227), block X white matter lesion volume (V = .081, F(5, 36) = 0.63, p = .678, η² = .081), and block X condition X white matter lesion volume (V = .125, F(5, 36) = 1.03, p = .417, η² = .125).

Univariate analyses demonstrated a significant main effect of white matter lesion volume for mean (F(1, 40) = 8.14, p = .007, η² = .169), ISD (F(1, 40) = 13.72, p = .001, η² = .255), μ (F(1, 40) = 6.94, p = .012, η² = .148), and σ (F(1, 40) = 9.58, p = .004, η² = .193), but not τ (F(1, 40) = 2.08, p = .157, η² = .050). A significant univariate interaction for condition X white matter lesion volume was only observed for τ (F(1, 40) = 9.01, p = .005, η² = .184).

Four Choice Response Time Task Performance

Repeated measures MANOVA using Pillai’s trace revealed that there was no significant multivariate main effects for condition (V = .206, F(4, 37) = 2.40, p = .067, η² = .206) or white matter lesion volume (V = .085, F(4, 37) = 0.86, p = .495, η² = .085), but there was a significant interaction between them – condition X white matter lesion volume (V = .258, F(4, 37) = 3.22, p = .023, η² = .258). With respect to within-subjects effects, there were no significant multivariate results: pre/post (V = .177, F(4, 37) = 1.99, p = .117, η² = .117), pre/post X condition (V = .185, F(4, 37) = 2.09, p = .101, η² = .185), pre/post X white matter lesion volume (V = .020, F(4, 37) = 0.19, p = .945, η² = .020), and pre/post X condition X white matter lesion volume (V = .080, F(4, 37) = 0.81, p = .528, η² = .080).

Univariate analysis of the condition X white matter lesion volume multivariate effect revealed significance only for μ (F(1, 40) = 4.68, p = .037, η² = .105), but not the other RT indices. Specific to the evaluation of near transfer, analyses demonstrated no significant pre/post
X condition interaction for any RT index, nor was there any significant 3-way interaction with white matter lesion volume.

6.4 Discussion

The main objective of this study was to determine whether RT IIV feedback training could improve consistency in older adults with a range of white matter lesion burden (mild to moderate). Previously, a training paradigm such as this had only been attempted on healthy older adults presumed to be free of cerebrovascular disease (Chapter 4; Garrett et al., 2012). In those instances, the training lead to more consistent performance attributed to availability of feedback and the participants’ motivation to improve. The question remained as to whether disruption to white matter tracts, known to be a critical component of attention networks, would affect training-related advancements in performance. The present results indicated that there was no significant effect of feedback training on any of the RT indices, and white matter lesion volume did not significantly affect training success. Given our predictions, it was most surprising that there was no significant feedback-related reduction of ISD or tau.

Inspection of the data demonstrated that a pattern of effects consistent with decreased variability following feedback was actually present, although they did not reach statistical significance. Specifically, ISD appeared to be lower in block 4 compared to block 1 in the feedback condition, but only for individuals with higher white matter lesion volume. Individuals who received no feedback training showed no decrease in ISD, regardless of high or low white matter lesion volume. This apparent beneficial RT effect for individuals with higher white matter lesion volume is counter to what was expected. We had hypothesized that individuals with lower
lesion burden would outperform individuals with higher lesion burden because the neural
network facilitating cognitive control would have been more intact. Examination of the data at
each block (rather than the block 1-4 change) shows a non-significant pattern that supports this
rationale – in the feedback group, individuals with lower white matter lesion volume had lower
variability (ISD) than participants with higher white matter lesion volume in each of the four
blocks. Even though participants with high white matter lesion volume showed decreased
variability from training, their lowest level (the final training block) was still above that of the
low white matter volume participants. It is possible that participants with low white matter lesion
volume in the feedback condition had reached a floor effect with regard to classically measured
RT IIV.

I theorize that the prefrontal cortex is responsible for propagating cognitive control, and
that white matter is necessary for facilitating these processes through an attentional network.
Damage to white matter through ischemic lesions may impede this process, but cognitive control
could still be implemented with diminished effectiveness. It could then be proposed that damage
to the prefrontal cortex may prevent any kind of consistency training from being successful, as it
would disrupt cognitive control at the source. Further research would be necessary to test this
hypothesis. The pattern of data observed from the present study is consistent with our proposal
for the influence of white matter lesions on cognitive control.

I have argued previously that training to reduce variability actually targets the extremely
slow responses that may indicate attention lapses, and are indexed by tau (Chapter 4). The
present data, though non-significant, speak to this - individuals with high white matter lesion
volume showed apparent reductions in tau from block 1 to block 3, at which point a slight
increase was observed at block 4. In contrast, individuals with low white matter lesion volume
reduced tau steadily from block 1 to block 4. But why then did they not show a similar reduction in variability in response to training? A decrease in those exceptionally slow responses contributes to the effects observed in ISD, but does not necessarily represent a one-to-one association. Accompanying the decrease in tau with feedback was also an increase in mu in individuals with low white matter lesion volume, which is a pattern consistent with our previous work on training consistency in healthy older adults (Chapter 4). A plausible explanation for the absence of variability reduction in those with low white matter lesion volume is that they simply altered their response profile/RT distribution differently as a result of the feedback training. If the RT distribution transitions from ex-Gaussian to a frequency plot more resembling a wide Gaussian curve, it would explain the maintenance of variability, decrease in rightward skew, and an increase in overall speed. This notion is supported by the observed elevation of mu in that group. The standard condition resulted in no apparent decrease in ISD or tau, or an increase in mu, which is what we would have expected. It is likely that these effects did not reach threshold for significance due to a lack of power in the sample.

The trends in the data provide further support for the hypothesis that reductions in response time variability through training are the result of alterations in overly slow responses that make up the right tail of the distribution. Research from our lab and others has implied that tau is the critical component of the response time performance that is being captured by RT IIV measures (Tse et al., 2010; Vasquez et al., 2016; West et al., 2002). Furthermore, there is evidence that RT IIV, and perhaps more sensitively tau, reflect the reliability with which cognitive control is deployed to maintain attention on task (Tse et al., 2010; Vasquez et al., 2016; West et al., 2002). Thus, it appears that training individuals to become more consistent promotes the focusing of attention to minimize longer latency responses. The data also suggest that an optimal method for exerting control over attention involves an overall slowing of responding.
Taking extra time to fully process stimuli could be a necessary component to the amplification of attention when the goal is to minimize attention lapses.

The observation that decreases in tau occurred in the present sample indicates that disruption to white matter tracts integral to the brain’s attention networks may not prevent the willful improvement of attentional abilities. If a larger sample size had been obtained, visual patterns in the data may have reached statistical significance. One such pattern was that individuals with greater lesion volume may have had lower training gains for tau. If this were true, it would suggest that white matter lesion integrity influences the degree to which cognitive control can be modulated on task to alter behaviour. The importance of white matter to cognitive control is also supported by a narrative appraisal of training RT consistency in healthy older adults. If we compare feedback training effects on Target response tau, using Cohen’s d, in healthy older adults aged 75-85 from our previous study (Chapter 4) with the present complete dataset, we get effect sizes of 1.18 and 0.39 respectively (keeping in mind the sample size for the present study is much lower than our previous healthy older adult investigation). Although these studies used the same feedback training protocol, they were conducted separately, preventing a direct statistical comparison. Simply reviewing effect size estimates indicates that training consistency is less effective in a CSVD participant sample.

Lastly, we evaluated the possibility of transfer of effects to an untrained task using a four choice RT task given before and after the training task. As with our previous study on healthy young and older adults, no significant evidence of transfer was detected. RT IIV and tau both decreased slightly from pre- to post-assessment, though this change was not significant. More importantly, there was no interaction of pre/post with condition, meaning that becoming more consistent in the transfer task was not due to feedback specifically.
It is unknown why transfer of training could not be produced. The hypothesis given before by Vasquez et al. (2016) is that the four choice RT task could have lacked the complexity needed to separate RT IIV performance differences that were practice related compared to training related. Transfer and generalization of training are often sought after outcomes of cognitive intervention studies. This should come as no surprise as the optimal goal of cognitive rehabilitation is to give individuals the necessary skills to overcome cognitive deficits, applied functionally to real world tasks. Unfortunately, the evidence supporting transfer of training across studies has been inconsistent (Owen et al., 2010; Papp, Walsh, & Snyder, 2009). Further research is necessary to determine the optimal conditions for transfer to be successful with regard to reducing variability and extremely slow responses. It is possible that some forms of training are just not amenable to transfer effects. A recent review of cognitive interventions concluded that the prolonged effects of training and transfer of those skills was dependent on the intervention being adaptive and consisting of multiple sessions (Kelly et al., 2014). It has already been shown in younger adults that cognitive training produced improvements in the RT parameter tau on an untrained task (Shahar & Meiran, 2015). Perhaps the same outcome could be achieved in older adults with CSVD given longer training durations, multiple training sessions, and adaptive difficulty progression, all of which were included in Shahar & Meiran’s (2015) training paradigm.

Conclusions

This study found no significant effect of feedback training on RT distribution indices, nor was there any significant contribution of white matter lesion volume to training efficacy. That being said, the data showed promising trends that may have reached threshold for significance given a larger sample size. In particular, inspection of the data indicated that response time
consistency may be improved in older adults with damage to the brain network supporting sustained attention using a simple interactive feedback paradigm. The present data also suggest that a key outcome measure following attention training is the quantification of rightward distributional skew signifying exceptionally slow responses (i.e. tau). Extremely slow responses may be an important component that is incorporated into standard measures of RT IIV. Though non-significant, the pattern of data indicates that older adults were able to reduce these extremely slow responses on task regardless of the presence of white matter lesions. Individuals with high white matter lesion volume, however, were not able to maintain improvements as well as those with low white matter lesion volume. This demonstrates that having a disruption to information transmission through white matter fibres does not prevent one from amplifying cognitive control on task to reduce variability. However, white matter lesion severity may negatively influence the magnitude of improvement in tau from feedback training. The data suggest that white matter tracts are necessary for the efficient modulation of cognitive control.
Chapter 7

General Discussion

This series of experiments examined the cognitive basis of response time consistency and evaluated the effects of training promoting the improvement of consistent performance. Each study coherently integrated both the classical measurement of consistency in the form of intraindividual standard deviations with an alternative ex-Gaussian distributional analysis. The work described in chapters two and three explored the relation between neuropsychological measures of cognition and response time consistency in healthy adults, which no prior research project had thoroughly attempted. Chapter four built on the one previous study that investigated whether response time consistency could be improved through training. Chapter five uniquely explored the pathology of cerebral small vessel disease (CSVD) and its correspondence to RT distributional components, and Chapter 6 extended variability training to individuals with CSVD. Together, this dissertation produced an important collection of findings that improve our understanding of response time consistency and cognitive control in general. I first review the findings from the five studies and then discuss limitations of this research, implications for healthy aging, and implications for CSVD. Figure 7.1 provides a schematic to assist integration of the findings across the five studies.

7.1 Results of the Five Studies

The main hypothesis of Study 1 was that the ex-Gaussian parameter tau would be related to neuropsychological measures of executive functioning. The rationale was developed from prior research suggesting that response time consistency is a behavioural measure of cognitive control to maintain attention on task (West et al., 2002). Those authors found that response time
consistency was elevated in older adults under conditions of increased executive control demand, and that these effects were evident in the parameter tau, but not mu or sigma. This association was later supported using ex-Gaussian parameter estimation and structural equation modeling (SEM), with a composite measure of working memory (Tse et al., 2010), which is considered to be one aspect of executive control (Diamond, 2013). The experimental design of West et al. (2002), however, was not able to rule out increased task difficulty as an explanation for executive demand effects, and Tse et al. (2010) focused on working memory, excluding other sub-processes and preventing interpretation in the context of broader executive functioning ability. The data from Study 1 confirmed the hypothesis with a SEM, in which an executive function latent variable was associated with tau to a much greater extent compared to mu or sigma. My SEM also included intraindividual standard deviation to contrast the strength of association with executive functioning with the ex-Gaussian parameters. Comparison of SEM standardized regression weights revealed that the correspondence between tau and executive functioning (1.19) far surpassed that observed for ISD (-.10). These findings were present with age held constant, but when age was factored in using correlation, the results indicated that the association between tau and executive functioning was only present in older adults between the ages of 75 and 85. This may signify that declines in cognitive control occur most blatantly in older adults above the age of 75, and that the severity of such changes is more likely to encompass multiple aspects of attentional/executive functioning.

Study 2 aimed to explore the correspondence between ex-Gaussian distributional parameters and a broader array of cognitive domains. Within this context, I was able to test whether the relation between tau and cognition was specific to executive functioning or whether there could be involvement from other domains. Using a new response time task and participant sample, this time I included measures of episodic memory and processing speed, in addition to
executive functioning to create a new SEM. The results demonstrated that mu held robust connections with all cognitive variables, but to the greatest degree with memory. Although this finding was initially unexpected as memory performance was not dependent on speed of response, the finding can be explained by Salthouse’s (1996) theory of cognitive slowing. The proposal is that cognitive processing, regardless of domain, is dependent on speeded neural transmission, and that slowing will impact sub-operations that are necessary for higher level cognition to function at an optimal level. Sigma maintained relatively weak associations across the board. Tau was associated with executive functioning most strongly, followed by processing speed, and then the memory domain more weakly. The association between tau and processing speed is not surprising given that tau represents exceptionally slow responses, which would directly contribute to speeded tasks. The strongest link with tau, however, was the latent executive variable, which suggests that integrity of cognitive control relates to executive sub-processes and the ability to maintain attention on task. The findings regarding tau indicate a relationship between positively skewed longer latency responses and executive functions, which is congruent with my hypothesis.

Further analysis of study 2 data using linear regression revealed that age group explained more variance in cognitive performance across the three domains examined (memory, processing speed, and executive functioning) compared to ex-Gaussian distributional parameters. The ex-Gaussian parameters did provide a significant increase in predictive ability over and above age group for processing speed and executive functioning, but not memory. More specifically, it was Gaussian mean and extremely slow RTs that were related to executive functioning and processing speed, while variability about the normal distribution was much less important. These data indicate that elevations in attention lapses and a general slowing of responses are important variables that are predictive of particular cognitive functions over and above simply age group.
Overall, the results of study 2 suggest that elevated tau in aging does not simply correspond to general neurocognitive integrity, but likely reflect a disruption to cognitive control processes. Based on my research, I proposed cognitive control as the mechanism governing the maintenance of attention, which may minimally fluctuate in efficiency within a normal range. In conditions when cognitive control is not operating at optimal levels, processing efficiency may be lower, causing occasional escalation in response times.

Study 3 sought to examine how integrating feedback training into a response time task could stimulate improvement in RT consistency. The paradigm was adapted from Garrett et al. (2012) who demonstrated for the first time that RT IIV could be reduced in healthy older adults. It was found that the effect was not present in younger adults and that older adults with higher education benefited the most. The authors suggested that cognitive reserve, estimated with education level, may mitigate the effects of aging on cognition, providing functional compensation that allowed for superior task performance. In Study 3, I found that feedback training reduced RT IIV in both groups of healthy older adults (aged 65-74 and aged 75-85) and a similar outcome was also observed in a young group. Unlike the original research, there was no effect of education level. It is unknown why there were differences in the effect of cognitive reserve between studies. One hypothesis is that eligibility requirements for my study were more stringent, leading to the recruitment of a healthier population for which cognitive reserve would not exert interaction effects. This supposition is speculative as Garrett and colleagues (2012) did not provide exclusion criteria. Future research on the influence of education as a proxy measure of cognitive reserve is warranted in the context of attention training, as well as looking at alternative explanatory factors that may co-vary.
Importantly, Study 3 demonstrated that the ex-Gaussian parameter tau was reduced following feedback training, whereas mu increased, and sigma did not change. These results suggest that training induced reductions in RT IIV are not due to restricting dispersion in the normal distribution. Instead, the training to reduce variability targets tau, with an accompanying increase in mu, and provides further evidence that cognitive control processes are recruited to maintain consistent performance on task. That is, increased attentional engagement through cognitive control would be required in order to minimize longer latency responses. This may be more easily accomplished by taking more time for stimulus processing during the task, observed through increases in mu.

It is likely that a variety of factors influence training outcome. Two possible contributions to the success of training include between subject differences in time estimation ability, and the negative influence of neuropathology such as white matter lesions. The first hypothesis comes from research highlighting the importance of the parietal cortex and the cerebellum in the ability to estimate time durations (Hayashi, Kantele, Walsh, Carlson, & Kanai, 2014). This cognitive process may be required to adjust response times to ensure they are consistent from trial to trial. Unfortunately, the task designs contained in this dissertation did not allow for the assessment of this factor. The second hypothesis, that white matter lesion volume may impact the success of variability training is addressed in Study 5. Additionally, the components of having an attainable goal for which progress can be assessed at regular intervals may be critical to acquire the motivation to succeed. Unfortunately, the beneficial effects to RT performance on the training task did not transfer to an untrained task. It is possible that the task used to assess transfer was simply not sensitive enough to detect improvements, or perhaps the training procedure was not of sufficient length to allow transfer to occur. The results from Study 3, demonstrating task
improvement following performance feedback, have implications for attention rehabilitation that will be discussed below.

Study 4 focused on a highly prevalent cerebrovascular condition related to old age (cerebral small vessel disease) and the contribution of white matter lesions to RT IIV in this population. Previously, the correspondence between white matter and RT IIV had been studied from two perspectives – based on healthy white matter measures or through white matter lesion volume. Some of this prior research also used age ranges that were either quite large (20 to 83) (Fjell et al., 2011) or severely restricted (60 to 64) (Bunce et al., 2007). Study 4 examined the association between severity level of CSVD, determined by white matter lesion volume (ranging from almost none to what is considered severe pathology), and RT distribution indices in a sample of older adults between 65 and 87 years old. This study offered a unique perspective compared to prior work on RT consistency and white matter lesion volumes by incorporating an ex-Gaussian analysis of the RT distribution, which had only previously been examined in this context with a measure of healthy white matter integrity (Jackson et al., 2012). White matter lesion volumes were calculated, and ex-Gaussian parameters were derived from the feature integration attention task used in Study 2 and 3. The results indicated that white matter lesion volume predicted several RT indices – mean, ISD, mu, and tau, but not sigma. These findings imply that white matter lesions contribute to alterations in response time performance in terms of both slower speed and elevated variability, which may reflect effects that compromise rapidity of signal transduction and implementation of cognitive control. Moreover, since ISD represents a combination of both sigma and tau, the findings indicate that white matter lesions correspond to exceptionally slow responses in particular, rather than variability about the entire distribution.
As a secondary objective, Study 4 also sought to examine the correspondence of different domains of cognitive functioning with white matter lesions and ex-Gaussian parameters. I again applied SEM to examine this question and found that white matter lesion volume was differentially associated with cognitive domains—memory, executive functioning, and processing speed in decreasing order of strength respectively. The pattern of neuropsychological associations highlights the essential role of white matter to cognitive domains whether or not they intuitively depend upon mental quickness. In regards to the RT parameters, tau was most strongly associated with the executive functioning latent variable compared to other cognitive domains, which supports the idea that exceptionally slow responses represent brief attention lapses (an indicator of executive control). The strong tau relationship was also found for healthy older adults in Study 2. Inspection of the SEMs created with data from healthy adults compared to adults with a range of white matter lesions due to CSVD exposed a noteworthy difference—the strength of association between mu and cognitive domains was weaker when white matter lesions were factored in. Differences in relative weightings suggests that the presence of white matter lesions alters the connection between cognition and RT distribution indices, specifically with respect to slowing of the Gaussian mean. The alteration in the strength of the mu association could be due to a number of factors such as a specific CSVD induced impairment to speed of processing, or a form of compensation in that group compared to a healthy sample.

Study 5 sought to investigate whether the degree of white matter lesion burden would affect the ability of older adults to reduce their RT IIV following feedback training. The training paradigm was the same as was used in Study 3 with healthy older adults, and focused on improving consistency over the course of a response time task. Study 3 and the original experiment by Garrett et al. (2012) demonstrated that RT IIV was under endogenous control and could be reduced provided the proper feedback and motivation be applied. No prior research,
however, had attempted the training procedure on individuals with neuropathologic changes known to compromise attentional abilities. Contrary to expectation, there was no outcome of significant effect for the experimental manipulation of condition (i.e. feedback training) and the influence of white matter lesion volume on degree of training success. Examination of the data, however, revealed non-significant trends – individuals with high white matter lesion volume were the only group able to decrease ISD across the blocks. Unexpectedly, participants with low white matter lesion volume did not show any visible decrease in ISD, which I hypothesized was due to an alteration of other RT distributional components. Participants in the feedback condition appeared to benefit from training, observed through a non-significant trend of reducing tau across the four blocks. Again, examining the non-significant trends, individuals with low white matter lesion volume fared better, showing a steady decrease in tau with each block, whereas high white matter lesion volume participants demonstrated an initial reduction followed by a slight increase in tau from block three to four. Interestingly, the trends in the data also showed that in participants with low white matter volume reduced tau following feedback was accompanied by an increase in mu. The results replicate those of Study 3 in showing that the ex-Gaussian parameter tau reduces, while mu increases, in response to training. Moreover, these changes were found to be dependent on white matter lesion severity. Though non-significant, the trends indicated that greater volume of white matter lesions corresponded to smaller reductions in tau and no alteration of mu following feedback training. The discovery that reductions in tau were likely minimized by greater white matter lesion volume implicates these connective pathways in the efficient deployment of cognitive control. Cortical regions such as those in the prefrontal lobes may be responsible for training effects through the activation of cognitive control processes, facilitated through intact white matter, to decrease attention lapses. In this way, elevated variability (i.e. RT IIV) brought about by degraded connective white matter
pathways (shown in Study 4) may be aided by eradicating exceptionally long responses. Importantly, the benefit incurred is lessened in those with high white matter lesion load, and may actually be prevented at a sufficient lesion severity level.

7.2 Limitations

The data presented in this thesis are novel and provide a valuable contribution to the knowledge and theory of RT IIV, but certain limitations should be acknowledged. First, the sample sizes used were moderate and in the case of applying SEM, were at a minimum requirement for running such a procedure. It would be optimal to be able to replicate the findings in a larger sample size, although it is noteworthy that my research found a strong association between tau and executive functioning among healthy participants in two independent studies. Second, participants were recruited through the Rotman Research Institute database and thus consisted of a sample of self-selected volunteers, some of whom had much past experience completing cognitive tasks. Third, caution should be used when interpreting ageing effects between cohort groups as it does not directly address how cognitive variables change with age. Ideally, with more time and resources, a longitudinal design would provide a more robust investigation of factors related to cognitive aging. Fourth, considering the intended application for attention rehabilitation, the experimental tasks used in the research lacked generalizability to real world behaviour. Future research may wish to place more emphasis on this factor. Fifth, the white matter lesion analyses attempted to characterize a whole brain effect that is representative of CSVD. However, examining particular regions of interest such as prefrontal white matter and cortex may allow more specific brain-behaviour relations to be detected. Sixth, the individuals tested in these studies were healthy older adults and older adults with CSVD, and thus did not represent a population with severe attentional impairment. Further research would be required to
determine whether other types of patients would benefit and whether having longer training periods or multiple sessions has any impact on variability reduction. Seventh, Study 5 likely suffered from low power due to a small sample size.

Lastly, the research included in this thesis utilized an ex-Gaussian distributional analysis as a means to provide a more detailed examination of response time consistency. Although this technique produced novel worthwhile findings, it is possible to analyze RT data more comprehensively using computational models. In particular, the diffusion model (Ratcliff, Thapar, & McKoon, 2006) provides a more established cognitive process model that characterizes multiple components contributing to the execution of a response. The benefit of utilizing the diffusion model is that it can speak to age differences and neuropathological influences regarding aspects such as the efficiency of the decision process, variability in sensory or motor aspects of performance, and criterion setting regarding speed accuracy tradeoffs. Applying the diffusion model to the study of RT consistency may advance a deeper understanding of attention performance as a function of aging, training, and brain-behaviour relationships. As the attention tasks used in my research were not typical experimental choice response time tasks, from which the diffusion model was based, my design did not lend itself well to the model (Ratcliff, personal communication, May 17, 2013). It is still unknown how RT IIV is reflected in a diffusion model analysis, but future research should aim to integrate these two disparate approaches.

7.3 Implications for Healthy Aging

The first three studies of this dissertation uncovered new interesting findings about response time consistency that are highly relevant to the future study of cognitive control. First, my research signifies the importance of using more detailed measures of response time
consistency as they can provide useful additional information about performance. In each investigation I applied an ex-Gaussian distributional analysis, which allowed me to dissociate different response time parameters that characterize how a task is carried out at the cognitive level. Classical measures of RT IIV combine these distributional elements, and my findings suggest that observed differences between groups or conditions in previous studies may in fact be attributed to disparities in positive rightward skew (represented by ex-Gaussian tau). This signifies the importance of conducting more detailed analyses of response time data, permitting a deeper examination of behaviour.

My research builds a strong case for the correspondence between tau and executive functioning. I reliably demonstrated in two healthy aging studies that tau corresponds to neuropsychological measures of executive functioning, more than any other response time index examined. Further, the association of tau with cognition was found to be strongest with executive functioning and processing speed compared to memory. The association with processing speed can be attributed to the point that brief fluctuations in attentional performance would invariably cause performance on speeded cognitive tests to suffer. In contrast, the correspondence with executive functioning lends support to the theory that tau is a direct result of an individual’s ability to exert cognitive control on task. If cognitive control is efficiently deployed and maintained throughout task engagement, there should be fewer instances of minute ‘attention lapses’ and RT performance should not be positively skewed. Alternatively, dysfunctional cognitive control may lead to sporadic instances of waning attention, or brief ‘attention lapses’, that would present as longer latency responses and become apparent as larger tau values. Greater positive skew represented through tau should also be visible in higher values calculated for ISD. If this is in fact true, my research suggests that elevated tau and occasionally ISD reflect a disruption to cognitive control processes rather than a disturbance to general neurocognitive
integrity. This may have implications for how and why we study RT IIV. The further evidence of this tau-executive link that my research has established may lead to an increase in the use of tasks tapping cognitive control to measure RT consistency, and may stimulate new research directions and hypotheses. Previous studies have already employed RT IIV as an early marker of cognitive impairment (Dixon et al., 2007; Strauss et al., 2007) and even to predict white matter lesion burden (Bunce et al., 2013). My research on the specificity of RT distribution parameters could be applied to the development of more sensitive predictors of cognitive impairment for certain populations.

The work included in this dissertation is an important contribution to our knowledge of RT IIV. Not only do my findings suggest that aspects of the response time distribution, and variability within the distribution, can be an indicator of cognitive control integrity, but RT IIV can also be used as a target for attention training. My research was not the first to discover that RT IIV can be willfully modified, and in fact reduced in healthy older adults. I was, however, the first to show that reductions in RT IIV following training in healthy older (and younger) adults are due to diminished tau. This suggests that the training that was implemented to improve RT consistency stimulated individuals to amplify cognitive control facilitating greater focus of attention on task, and resulting in a lessening of longer latency responses. While I failed to find transfer to an untrained choice RT task, given the relation established between tau and executive performance, a question remains as to whether training to improve consistency has any transfer effects to other aspects of executive functioning. It would be interesting to explore whether training induced improvements to cognitive control also lead to better performance on tasks of cognitive flexibility, inhibitory processing, and working memory. This research may have implications for the development of cognitive rehabilitation methods for attentional dysfunction. I have provided evidence that packaging attention training into a novel task involving familiar
stimuli with an easy to use touch screen interface, and providing a goal that can be reasonably achieved, lead to statistically significant improvements over a very short duration. There is also potential for this technique to be integrated into existing intervention protocols. If future research indicated this to be a viable application, it may be important for researchers to test variability reduction training on suitable real world behaviours. Alternatively, a similar protocol could be used as an exercise to aid in focusing attention within a more comprehensive intervention program.

7.4 Implications for Cerebral Small Vessel Disease

The two studies constituting the latter part of this dissertation examined the influence of white matter lesions on behavioural variability and attention training. There are substantial implications from these projects in the finding that white matter lesion severity was predictive of ex-Gaussian distribution parameters tau and mu. This discovery suggests that degraded white matter may produce both elevated variability and slowed processing, possibly due to unreliable routes of transmission for neural signals that would accompany reductions in network connectivity and integration (Kim et al., 2015; Tuladhar et al., 2017). These data also suggest that disruption to the efficiency of large scale network function negatively impacts the implementation of cognitive control, which is supported by the correspondence between white matter lesion volume and ex-Gaussian tau. Comparison of SEMs from Studies 2 and 4 further indicate diminished effectiveness of network function through a weakening of association between mu and memory ability in the CSVD model. Moreover, white matter lesion volume was shown to have a direct effect on all three cognitive domains and all three ex-Gaussian parameters. My findings are congruent with the neuroscience literature, which specifies the involvement of a frontoparietal network (including white matter connections) in executive
control (Petersen & Posner, 2012). My research also fits with the prevailing theory describing how cognitive control is implemented through a cascade of neural signals originating in the prefrontal cortex that augments receptive fields at sensory processing centres (Miller & Buschman, 2013). That is, white matter is an integral component to the execution of cognitive control, and subcortical lesions should logically influence the efficiency of related operations.

The outcome of structural equation modeling in my studies signified that white matter disturbance alters the relation between cognition and RT distribution parameters – mu becomes less pronounced in the model compared to tau, particularly with regards to memory. The change in structural relations points to a potential mechanism through which cognitive impairment is incurred through CSVD. That is, white matter lesions may impede signal transduction throughout the brain causing the processing of information to be slowed or disrupted. This interference to the neural system may influence a variety of functions such as learning a list of words or carrying out more complex goal directed behaviour. In fact, a similar hypothesis has been proposed previously, without a neuroanatomical basis, to describe how age related changes in cognition can be attributed to slowed processing speed (Salthouse, 1996b). This theory describes two potential mechanisms; 1) cognitive performance is degraded because necessary limited time operations cannot be successfully executed due to a longer period required to complete subcomponents, and 2) for more complex operations that require several processing steps, the output of early processing may not be available by the time later processing is complete. Both principles, limited time and simultaneity, respectively, fit with the proposal that white matter lesions are a potential neuropathological agent facilitating cognitive decline. These ideas are congruent with meta-analytic approaches to examining the effects of white matter lesions on cognition, which have highlighted impaired neuropsychological test performance across multiple domains (Gunning-Dixon & Raz, 2000; Vasquez & Zakzanis, 2015).
Understanding the mechanism of cognitive impairment in CSVD will contribute to our knowledge of brain-behaviour relations and may aid in the development of intervention strategies.

In regards to the effects of training, CSVD participants did not demonstrate a significant response, nor was there an influence of white matter lesion volume. The data however, did show a pattern of decreased variability following feedback training that was similar to Study 3 with healthy older adults. When the data were examined between severity levels of white matter lesion volume, an interesting picture began to form whereby individuals with low white matter lesion volume appeared to decrease tau to a greater extent than individuals with higher white matter lesion volume. Further research would be required to confirm the significance of this pattern. In addition, the training induced decrement to tau in low white matter lesion volume participants was accompanied by an increase in mu, suggesting that effectively engagement cognitive control may require slowing down as well (this was also demonstrated in Study 3). The observation that white matter lesion severity negatively influenced the degree to which tau was reduced following training implies that intact cognitive control mechanisms can be activated to reduce minute ‘attention lapses’ and thus improve response time consistency through decreasing positive RT distribution skew. Degraded white matter introduces an impeding factor, likely making it more difficult to exert cognitive control to reduce longer latency responses, and thus works against beneficial training effects.

7.5 General Implications

Integrating my dissertation data with the literature provides support for the idea that variability can be produced by different neuropathological sources, namely damage to the prefrontal cortex (Stuss et al., 2003) and subcortical white matter (Bunce et al., 2007). As
discussed previously, both the prefrontal cortex and connective white matter are critical structures in the executive control network. Their roles, however, are quite different, as cortex is responsible for information processing and white matter facilitates communication. One could hypothesize that due to differences in function, damage to these structures may lead to distinct outcomes in terms of behavioural variability. For example, one possibility is that damage to white matter may affect variability across the entire distribution, whereas prefrontal cortical damage may inflate variability mainly through an increase in attention lapses, observed via tau. Future research will be necessary to validate this idea, but it will be an important step in confirming brain-behaviour relationships regarding RT IIV.

This dissertation identifies tau as a behavioural measure of cognitive control that corresponds to neuropsychological tests of executive functioning. Training to improve RT consistency leads to the reduction of tau and the elevation of mu in healthy younger and older adults (and potentially those with low white matter lesion volume), which can be interpreted to be the result of cognitive control enhancement. Although executive functioning capacity is reflected in baseline tau, executive functioning does not predict the modulation of cognitive control (measured through the magnitude reduction in tau), which is instead dependent on white matter integrity. There is likely a different cognitive basis for the static implementation of executive abilities and the degree to which these abilities can be dynamically adjusted. Previous research has established that the prefrontal cortex is critical for the execution of executive control processes. Based on the data included in this dissertation, I propose that the prefrontal cortex in conjunction with subcortical white matter is responsible for producing between person differences in RT consistency, reflected through tau and to a lesser extent ISD. Degradation to white matter tracts diminishes the reliability of signal transduction, thereby introducing noise to
the system in the form of general slowing and distributional variability. This impedes the successful amplification of cognitive control originating in prefrontal circuits.

My research suggests that cognitive control can be quantified through the measurement of response time, and that a simple training paradigm can lead to improvements in attentional performance that apply to both healthy young and older adults. White matter lesions are a prevalent neuropathological consequence of CSVD that impairs cognition, particularly the efficiency of cognitive control, and impedes the training of attention. It will be essential for future work to test the limits of cognitive rehabilitation in CSVD in the hopes of discovering alternative methods to circumvent the disruption of neural network communication in this population.
Figure 7.1. Schematic of relationships between ex-Gaussian parameters, cognition, white matter lesion volume, and training

Healthy

CSVD

Note: Red = positive association; Blue = negative association; thickness of lines (between ex-Gaussian parameters and cognitive domains) indicates strength of associations. Thinnest to thickest reflect the following weights [1) 0.40-0.60, 2) 0.61-0.80, 3) 0.81-1.00, 4) >1.00]
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