Exploring factors that contribute to between-subject variability of reaction time

by

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Author's declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

For well over a century reaction time has provided researchers with a method to quantify information processing speed. Defined as the interval of time between the presentation of a stimulus to the onset of a response, reaction time as a proxy of the speed of central nervous system events has allowed researchers to reveal underlying mechanisms of information processing control. The differences in reaction time between individuals is an interesting phenomenon that is sometimes disregarded as biological noise but could reveal further insight into the determinants of central nervous system speed of processing. The primary aim of this work was to explore the factors that contribute to such between-subject variability in young health adults to determine if differences were reflective of trait differences or simply random fluctuations across repeated testing and task conditions. Specifically, this study investigated the performance of visual and tactile reaction time tasks over two sessions to capture the day to day stability and task generalizability of reaction time. Genetic samples and nerve conduction velocity were also collected to speculate on potential biological markers that may relate to reaction time performance. ICC results demonstrated that reaction time of individuals were more closely related between days than between individuals for a range of tasks that differed in modality (visual and tactile) and difficulty levels (simple and choice). Interestingly, reaction time performance was found to have a stronger association between tasks of varying difficulty but not across task modality. Furthermore, while this study relied heavily on central tendency it was also found that analyzing the distribution of reaction times also revealed important within subject variability. DNA results found no association between APOE or COMT allele and reaction time performance. Ulnar nerve conduction velocity at the

elbow also was not associated with reaction time. The results from this thesis support the importance of stable, person-specific traits in determining reaction time while also emphasizing the potential impact of state factors. Alternative expressions of reaction time, such as variability and distribution, are also likely to be important to understanding between subject differences that is not revealed by traditional central tendency measures. Outcomes from this work will help to inform and contribute in supporting the use of reaction time as a stable predictor of central nervous system processing speed to indicate declining or improving performance. Potentially, tracking reaction time performance may be important in identifying potential risk of injury related to decreased speed of processing or as a marker of improved performance in training.

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Chapter 1: Background

1.1 Importance of speed of processing

The time course of central nervous system (CNS) events constitutes an essential component of successful behaviour. In particular, stimulus-evoked behaviour requires external stimuli to be processed in various areas of the brain to ultimately produce an accurate and timely response. The manifestations of CNS processing speed can be seen in a number of situations that range from daily activities such as driving (D'Addario, Donmez, & Ising, 2014; Lee, McGehee, Brown, & Reyes, 2002) to urgent situations that enable safety and facilitate performance in skilled tasks such as balance control and sport performance (Bolton, 2015; Maki & McIlroy, 1997). Clinically, speed of processing performance may provide insight to the integrity of the CNS, where deficits in performance could imply a diseased or impaired system. For instance, patients suffering from neurological injury commonly suffer from decreased speed of processing (Stuss et al., 1989), which poses as a detriment to activities of daily living. Inevitably however, individuals will respond differently to the same tasks, even when they are drawn from the same population (Hultsch, MacDonald, & Dixon, 2002). Even in a young, healthy population, some individuals will react slower than others for any given task. This unique individual variability in speed of processing performance is a curious phenomenon that is sometimes ignored as data tends to treat all individuals through a homogenous approach by using central tendency measures such as mean performance across people. Typically, the standard deviation provides an indication of the variability between subjects but can be disregarded as simply the product of noise. Understanding the individual variability in addition to conventional methods could be even more revealing of the specific characteristics that mediate speed of processing. Understanding

of between subject differences in healthy adults may have several important benefits. First, between subject differences may reveal information about how the CNS processes information not seen in more traditional methods. Second, studying between subject differences may have applications in assessing individuals at risk of adverse events caused by delayed speed of processing where personalized rehabilitation interventions based on their unique reaction time performance can be developed to facilitate the best possible outcome. Therefore, the overarching goal of this work is to explore the significance and nature of between subject differences and identify the important person-specific factors that contribute to such differences revealed by central tendency and dispersion measures. In order to gain a better understanding of this topic, this document begins with a historical overview of processing speed and its basic principles.

1.2 Historical overview

The study of relating the timing of unobservable neural activity in the brain to measurable events is known as mental chronometry (Meyer, Osman, Irwin, & Yantis, 1988) and the events that encompass processing speed are represented through reaction time (RT). There are several other terms in the literature that are often used interchangeably with reaction time including pre-motor time, response time, and response latency. While they all serve to define the time between the presentation of a stimulus to the onset of a response, it should be noted that these terms may have different methods of obtaining a response (e.g. mouse click, verbal response, onset of movement). For the purposes of this work, reaction time is operationally defined as the time from the presentation of a stimulus to the moment a response is initiated as represented by the onset of muscle activity.

Attempts to quantify reaction time can be traced back to the work of Franciscus Donders in 1868 who sought to understand different mental processes of the human nervous system by measuring the timing of responses. It was found by Helmholtz that it was possible to quantify the conduction velocity of a motor nerve, contrary to the prior beliefs (Brebner & Welford, 1980) . When it came to decision making tasks, Donders believed that there existed distinct and separate stages of information processing that occurred in succession. He therefore postulated that the longer it would take to produce a stimulus-evoked response the more stages were required for that particular task. He sought to explain information processing by subtracting the reaction time to a single stimulus (task A) and the reaction time to make the same response by discriminating one of two stimuli (task B). Termed the subtraction method, Donders proposed that the time it took the nervous system to make a choice was revealed simply by the difference in reaction times of these two tasks (Donders, 1969). However, one of the criticisms toward Donders' work was the difficulty and practicality in devising tasks that completely removed a processing stage from a reaction time task (Sternberg, 1969). Therefore, Sternberg sought to propose a new method of examining reaction time by dividing information processing into three stages: sensory, comparison, and response. If a certain factor only influenced one of these stages, then their effects on reaction time would be additive to other factors that only influenced one processing stage. Therefore, Sternberg proposed that it could be revealed which processing stages were affected by a factor using the additive-factors method.

The differences in time during the performance of tasks of varying difficulty is mathematically described by Hick's law as the logarithmic relationship $RT = k*\log_2(n+1)$, where

RT is the reaction time of the task, k is the reaction time for a task with only one stimulus, and n is the number of alternative stimuli (Hick, 1952). In other words, the more potential responses an individual must make to different stimuli the longer it takes for the central nervous system to execute the correct response. Hick's law represents just one example of how reaction time research has contributed to the understanding of the human information processing.

With advances in neurophysiological research, it became possible to observe specific events in information processing. Researchers had at their disposal tools to measure the electrical potentials from the brain that could serve as latent indicators of mental processes, revealing potential mechanisms explaining reaction time results. This would help to clarify past hypotheses about the stages of information processing and extend our knowledge of mental chronometry. For instance, the latency of the P300 event related potential was shown to be associated with stimulus evaluation phase of a reaction time task (McCarthy & Donchin, 1981; Sutton, Braren, Zubin, & John, 1965) while Posner (2005) found that a visual stimulus would evoke significant electrical activity in the primary visual cortex at approximately 60ms. Functional magnetic resonance imaging (fMRI) was a tool used that provided evidence of specific brain regions associated with the performance of certain tasks(Connolly, Goodale, Goltz, & Munoz, 2005; Honey, Bullmore, & Sharma, 2000; Yarkoni, Barch, Gray, Conturo, & Braver, 2009), though by itself does not provide sufficient temporal resolution. The marriage of the high temporal resolution of event-related potentials and the spatial resolution of fMRI provided new insight onto the workings of information processing(Bledowski, 2006; Linden et al., 1999; Mulert et al., 2004; Rosen, Buckner, & Dale, 1998). However, despite all the progress in the field and advanced tools for measurement of information processing there are still some

unanswered questions. In a recent review it was noted that the role of reaction time variability and distribution and their value in explaining the neural basis of information processing is not well understood (Medina, Wong, Diaz, & Colonius, 2015). Furthermore, the stages of processing themselves have come into question, with early researchers suggesting complete successive stages while others argue for the capacity for at least some parallel processing of stimuli. Finally, one important topic that is not well understood is *how* reaction time can differ in real-life situations and the determinants of performance in these reactions. The importance of answering this question can be found in urgent situations where speed of processing is an essential determinant of behavioural success, such as balance reactions, obstacle avoidance in driving, and athletic performance. The implications of speed of processing research has extended beyond simple models presented by the early work of Donders and Sternberg. Over time, there has been a shift toward explaining the mental processes that occur during the most critical situations and how they act as a protective mechanism or facilitator of performance.

1.3 Examples of speed of processing in temporally urgent situations

The detection of dangerous or threatening stimuli is essential to human survival and demand rapid responses. From an evolutionary perspective, the ability to react quickly to threatening situations has played an important survival role in avoiding danger (Mineka & Öhman, 2002).

For example, balance recovery is a class of behaviour that is distinguished by temporal urgency (Lakhani et al., 2011). Stepping and grasping movements in response to unexpected perturbations are used to compensate for postural instability that would otherwise result in physical harm. These change-in-support reactions are initiated around 100ms yet fascinatingly,

are still able to maintain the complexity of volitional movements (Gage, Zabjek, Hill, & McIlroy, 2007; Lakhani et al., 2011). Failure to rapidly execute these reactions has been identified as an important determinant of fall risk in healthy older adults (Lajoie & Gallagher, 2004).

The importance of rapid information processing in response can also be seen in driving safety and hazard avoidance. Sudden changes in a dynamic traffic environment require a driver to quickly respond by performing movements such as steering the vehicle out of harm's way or releasing the acceleration pedal and engaging the brakes. In addition to motor-related factors, Anstey et. al (2004) revealed that central nervous system processing was one of the major factors contributing driving safety outcomes. Specifically, older adults that performed poorly in an on-road driving performance test had moderate correlations in measures of cognition and information processing (McKnight & McKnight, 1999). The results from these types of studies are useful in advancing automobile technology. For instance, algorithms used in rear-end collision avoidance systems rely on understanding driver response and use this information to provide warning signals to the driver (Lee et al., 2002).

In response to the presentation of unpleasant images, individuals were able to produce movements quicker compared to pleasant and neutral images (Coombes et al., 2009; Ohman, Flykt, & Esteves, 2001). The emotion evoked from these images has an effect on the motor system that some claim to be due to an arousal-driven corticospinal excitability increase (Hajcak et al., 2007). Other authors have suggested that fear-inducing stimuli inhibits processing of irrelevant information coupled with enhanced executive attention to rapidly process relevant and threatening stimuli (Finucane & Power, 2010). Similar results are seen in the olfactory system as unpleasant odours, which may signal unfavourable situations to an

individual's well-being that must be avoided, are responded to more rapidly than pleasant odours (Bensafi, Rouby, Farget, Vigouroux, & Holley, 2002; Jacob & Wang, 2006).

The capacity to demonstrate superior athletic performance provides an interesting challenge to central nervous system processing. The CNS must be able to recognize sport-specific situations in a fast-paced, dynamic environment. The elite perceptual-cognitive skill required for sport and the speed at which they are executed is arguably a distinct characteristic that separates expert athletes from novices. In volleyball and basketball players, experts had the ability to more quickly identify game and non-game situations in their respective sports (Allard & Starkes, 1980). A meta-analysis exploring the perceptual-cognitive skills in sport revealed an increase in performance in response accuracy and response time for experts compared to non-experts (Mann & Williams, 2007) while this difference is even more pronounced in athletes that participate in interceptive sports (Voss, Kramer, Basak, Prakash, & Roberts, 2010). Some authors also suggest that at least some of the cognitive performance attained from athletic training is transferable to everyday tasks such as multitasking during navigation of trafficked roads (Chaddock, Neider, Voss, Gaspar, & Kramer, 2011; Faubert, 2013).

1.4 Neurophysiological determinants of processing speed

A simplistic model of the stimulus-response pathway consists of an input (stimulus) that is integrated and processed by the central nervous system to reach a decision based on the stimulus. The decision is then executed (response) by the appropriate effectors. All instances of processing speed can be fundamentally described in terms of the systematic communication of

neurons in this pathway. Biologically, this can be divided into two components: conduction time and synapse time.

Conduction time refers to the time it takes for an electrical signal to propagate across all the axons in a given pathway. One way of altering conduction time is to change the length of the neural pathway, which is determined by the characteristics of the task. The longer a signal must travel, the more time must be accounted for to reach its final destination. For instance, all other factors remaining the same, a motor signal travelling from the brain to the muscles in the leg will take longer than if the signal were to reach the upper limb because of the pathway length differences. Furthermore, conduction time can be altered by changes in axonal conduction velocity where the degree of myelination will determine how fast a signal can propagate down an axon (Kandel et al., 2012). A reduction in the myelination of axons slows down the conduction of signals and in extreme cases, can lead to severe impairments in behaviour. For instance, patients suffering from multiple sclerosis, a neurodegenerative autoimmune disease that results in the breakdown of myelin, are known to have decreased reaction times compared to healthy controls (Elsass & Zeeberg, 1983; Jennekens-Schinkel, Sanders, Lanser, & Van der Velde, 1988; Reicker, Tombaugh, Walker, & Freedman, 2007). Finally, conduction time is also determined by the diameter of the axon. Larger diameter axons tend to conduct signals more rapidly due to the lower resistance to electrical current. For instance, sensory fibers in peripheral nerves are classified by their diameter. Type I fibers have the largest diameter (12-20 μm) and a conduction velocity of 72-120 m/s. Type II fibers are characterized by a smaller diameter (6-12 μm) and a conduction velocity ranging from 36-72 m/s (Kandel et al., 2012).

Synapse time is related to the time taken to transform the electrical signal coming from an axon into a chemical signal to communicate across the synaptic cleft to a neighbouring neuron. It encompasses all the events from the initiation of neurotransmitter release from the synaptic vesicle to the summation of the postsynaptic potentials at the axon hillock. Any delay in the time to produce an action potential in the post-synaptic neuron will slow down processing time. The time it takes to produce an action potential will be determined by the rate at which the post-synaptic membrane potential is increased to reach threshold. For instance, the generation of an action potential occurs through the attachment of neurotransmitters onto receptors on the post-synaptic neuron. If there were an increase in receptor density, this would allow more neurotransmitters to bind and generate action potentials as the faster accumulation of these signals will allow the membrane threshold to be reached sooner to trigger an action potential down an axon. It is also possible that the properties of the receptors themselves can have different levels of sensitivity to a neurotransmitter resulting in higher or lower membrane depolarization. The more sensitive a receptor is, the greater the change in membrane potential. This model serves as a basic foundation for linking modulators of reaction time to the potential biological mechanisms.

1.5 Modulators of reaction time

The extensive list of factors that influence reaction time can be divided into those that are task dependent (e.g. task difficulty) and those that are person-specific (e.g. individual factors). Task-dependent factors refer to the design of the stimulus-response paradigm. These conditions provide an environmental description of the reaction process to be completed.

These factors can often be manipulated and isolated in an experimental setting to observe the influence on reaction time. For instance, selecting the type of reaction time experiment (i.e. simple, choice, recognition) is a task-specific factor that will change reaction time based on the number of bits of information in each task. Other task specific factors known to influence reaction time include stimulus intensity (Luce, 1986), stimulus modality (Brebner & Welford, 1980), and stimulus cueing (Bertelson, 1967). **Table 1.1** summarizes several factors that have been most extensively studied.

The current study is focussed on between-subject differences and person-specific factors as these reflect unique attributes and characteristics that are distinct to each individual. Person-specific factors can be further subdivided into time-stable factors, which are defined as fixed, long term characteristics of an individual that are consistent or change slowly over a time scale of years. This may also be referred to as trait factors. In contrast, there are also time varying factors, variables that can change quickly with a day to day influence on reaction time that is dependent on the situation the individual finds themselves in. For example, quality of sleep the night before can affect performance the following day (Langner, Steinborn, Chatterjee, Sturm, & Willmes, 2010). Time varying factors are also known as state characteristics.

Given the same task conditions, a group of individuals will vary in their reaction time response based on their distinct characteristics. Saville et al. (2012) found that across visual and auditory modalities, individual differences of the onset of P3b event-related potential and reaction time were consistent and thought to be characterised by stable, pervasive factors, independent of the task. Furthermore, reaction times are consistent on a week-to-week basis,

suggesting that the determinants of performance are reliable over time and based on characteristics specific to the individual that do not change over the short term (Resch et al., 2013; Saville et al., 2011) These are considered to be the factors that will contribute to individual differences in reaction time performance. **Table 1.1** provides a list of some of the factors known to influence reaction time independent of the characteristics of the task and specific to the person.

Table 1.1: List of factors and representative studies that have been shown to influence reaction time categorized as task-dependent or person-specific.

Task dependent	Person-specific
Stimulus intensity (Luce, 1986)	Attention (Stuss et al., 1989; Weissman, Roberts, Visscher, & Woldorff, 2006)
Stimulus modality (Brebner and Welford, 1980)	Arousal (Lakhani et al., 2011; Lakhani, Miyasike-daSilva, Vette, & McIlroy, 2013)
Stimulus cueing (Bertelson, 1967)	Genetics (Saville et al., 2012; Szekely et al., 2011)
Number of stimuli and responses (Donders, 1969; Sternberg, 1969)	Personality (Corcoran, 1972; Robinson & Tamir, 2005)
Central vs. Peripheral vision of stimulus (Brebner and Welford, 1986)	Physical fitness (Spirduso, 1975)
	Gender (Adam et al., 1999; Dane & Erzurumluoglu, 2003; Noble, 1964)
	Age (Hultsch et al., 2002)
	Intelligence (Jensen & Munro, 1979; Reed & Jensen, 1992; Vernon, 1983)

As noted the current thesis is focussed on between-subject differences, and the relationship between person specific factors and reaction time. The rationale for this focus is to

explore this understudied topic as it may be valuable in identifying the unique person-specific factors that contribute to individual variability in performance that cannot be explored in more traditional studies that look at comparing between different groups and tasks. Exploring these factors may assist in defining possible biological markers for individuals at risk of decreased speed of processing with age or following neurologic injury. The following sections describe factors that can be considered to significantly contribute to between-subject differences that are person-specific.

1.5.1 Attention

Reaction time performance has often been related to an individual's level of attention to stimuli. It should be noted that attention can also be associated with the specific task conditions so it could be considered both task-dependent as well as person-specific. The concept of attention can be described as allocating cognitive resources to process relevant stimuli while suppressing irrelevant stimuli (Posner, 2011). Its contribution to influencing reaction time performance has been observed through deficits in the attention network. Stuss et. al (1989) found that deficits in attention caused by head injuries resulted in slower performance on RT tests compared to control subjects. Consistency of performance was also analyzed and revealed that head injured patients had significantly greater variability in reaction time. This led the authors to believe that while head injured patients could perform well on a task, their ability to maintain the level of performance was compromised due to deficits in sustaining attention. Weissman et. al (2006) attempted to develop a system-wide understanding of how attention might influence reaction time by observing changes in regional brain activity due to momentary lapses in attention. Of particular interest was observing the

activation of frontal areas of the brain thought to regulate and control attention. The findings suggest before stimulus presentation, decreased BOLD response in frontal areas were associated with longer reaction times. Furthermore, it was found that during slower reaction times, the default-mode network, areas of the brain thought to be associated with task-irrelevant stimuli (i.e. daydreaming) had reduced task-induced deactivation, indicating an inability to disregard processing of irrelevant stimuli. In this case, the results suggest that attention can be a person-specific factor since performance trial to trial can vary under identical conditions. It was proposed that the characteristics of the individual's attention network were determining the variability (Raichle et al., 2001)

1.5.2 Arousal

Similar to attention, arousal could be considered both a task-dependent and person-specific factor that can influence reaction time. The autonomic nervous system (ANS) is responsible for controlling activities of the body that occur unconsciously, such as breathing, regulation of blood pressure, or sweat responses (Silverthorn, 2010). Physiological arousal levels are linked to autonomic nervous system activity and may be a factor in influencing information processing. Studies have shown there to be an optimal range of arousal that produces the most benefits to reaction time performance as indicated by the parabolic relationship between the two variables
(Bagherli, Vaez-Musavi, & Mokhtari, 2011; Damanpak, Mokhtari, & Vaezmousavi, 2015).

Recent evidence has suggested that there is a potential link between reaction time performance and autonomic nervous system activity in postural control. When the nervous system is threatened with postural instability, speeded reactions are often accompanied by

increased autonomic activity measured by an electrodermal response from the fingers (Lakhani et al., 2011; Sibley, Lakhani, Mochizuki, & McIlroy, 2010). Interestingly, the speeded reactions are not restricted to stimulus-relevant responses. Lakhani et al. (2011), using a tilting chair paradigm, compared reaction times of a balance perturbation to auditory stimuli. Results indicated that regardless of congruency between stimulus and response, reaction times were always faster in the perturbation condition. Response latencies were determined by the stimulus characteristics, which were also accompanied by increased ANS activity. In a separate study, Lakhani (2013) provided further evidence for the importance of arousal in speeded reactions when he sought to pair auditory stimuli with balance perturbations to condition the nervous system to produce faster responses and greater autonomic activity to auditory stimuli alone. Immediately following 20 trials of paired auditory stimuli and perturbations, only an auditory stimulus was presented, unknowingly to the participant. The first post-pairing trial had a significantly faster reaction time and greater autonomic activity when compared to the 5^{th} post-pairing trial. Arousal as a person-specific factor may be embedded in the change in arousal that varies from person to person. In some cases, there may be non-responders who do not experience as great an increase in arousal as others. This is sometimes explained as individuals varying in their personality type, which influences their arousal response to stimuli (Griffiths & Dancaster, 1995). While the mechanisms behind how speeded reactions are achieved remains unclear, these studies have emphasized the potential importance of autonomic activity in potentially influencing information processing speed.

1.5.3 Intelligence

Individual differences in human intellect have been proposed to be linked to mechanisms involving the capacity for speed of processing. Much of the early work on this topic is attributed to Sir Francis Galton, however due to limitations in the techniques and instruments used to measure intelligence, as well as the absence of statistical inference methods such as analysis of variance, his experiments were considered unsuccessful at the time(Jensen, 2002). It was later found that there did in fact exist a negative relationship between IQ and reaction time and that tasks of greater complexity demonstrated a stronger relationship (Deary, Der, & Ford, 2001; Jensen & Munro, 1979; Vernon, 1983). However, it remains unclear why the speed of a response to environmental stimuli is related behaviours that demonstrate intelligence such as logic and reasoning.

1.5.4 Personality

Depending on the task, specific personality traits have been related to reaction time performance. Personality can be defined as the psychological structures that shape an individual's behaviour and perceptions. Personality traits are generally characterized as being stable and consistent regardless of the context of the environment Naturally, researchers have studied whether or not the psychological makeup of an individual has a profound influence on speed of processing. A popular personality theory has been to divide an individual's personality into 'traits' or "internal attributes or behavioural dispositions reflective of underlying biopsychological constructs" and relate them to other measures of cognition (Lox, Ginis, & Petruzzello, 2006). The literature shows that these traits each have a distinct difference between each other when it comes to speed of processing. For instance, introverts perform

faster in tasks considered monotonous and require long periods of sustained attention while extroverts are quicker in more active tasks (Corcoran, 1972). Neuroticism, a trait connected to variable behaviour and cognition is positively correlated to reaction time variability (Robinson & Tamir, 2005). Certainly, the psychological attributes of an individual have an effect on the biological processes of information processing.

1.5.5 Physical fitness

Studies have clearly revealed that exercise provides benefits in not just physical health, but also in a number of CNS functions (Hillman, Erickson, & Kramer, 2008). The effects of physical activity on the central nervous system implies that fitness levels are an important factor in measurements of cognition such as reaction time. Reaction times of athletes, compared to non-athletes, can be significantly faster, possibly due to their higher levels of physical activity (Spirduso, 1980). The relationship between physical activity and improved reaction time performance carries over in old age where physical activity seems to provide a protective effect to age related cognitive decline (Baylor & Spirduso, 1988; Spirduso, 1975). Specifically, long-term changes in the structure of various brain regions (Chaddock et al., 2010; Erickson et al., 2011) have been proposed as a potential mechanism to explain these benefits.

1.5.6 Genetics

Molecular genetics provides another approach to linking behavioural measures of information processing to its neurophysiological origins. While genes do not directly account for behaviour, they do provide a blueprint for the coding of proteins that can significantly influence how the CNS functions and potentially influence the speed of processing. The influence of

genetics may well be expressed through a range of possible factors that might influence reaction including the factors listed above (e.g. personality, arousal, attention).

Results from twin studies have revealed that at least part of information processing performance is heritable (Beaujean, 2005; McGue, Bouchard, Iacono, & Lykken, 1990; Spinath, Angleitner, Borkenau, Riemann, & Wolf, 2002). However, this does not provide information on which specific genes have an effect on speed of processing. Thus, studies exploring candidate genes have provided a base for potential sources of reaction time performance. Potential candidate genes including those that code for: catechol-O-methyltransferase (COMT), D_4 dopamine receptor (DRD4) and apolipoprotein E (APOE) are discussed in more detail in the next sections.

1.5.6.1 COMT

The rs4680 ($val^{158}met$) genetic variant is a well studied single nucleotide polymorphism of the COMT gene, which codes for the catechol-O-methyltransferase responsible for metabolising catecholamines. The Met variant is associated with slower enzyme action than the Val variant, which causes dopamine to be present in the synapse for longer periods of time (Grossman, Szumlanski, Littrell, Weinstein, & Weinshilboum, 1992), suggesting that COMT function influences synapse time. Its association with levels of dopamine in the frontal lobe have therefore been connected to cognitive functions such as performance of executive function (Barnett, Jones, Robbins, & Müller, 2007; M F Egan et al., 2001), and memory (Wang et al., 2013). However, previous studies have found conflicting results on the association of this gene with information processing speed suggesting better performance with both Met carriers (Stefanis et al., 2005) and Val carriers (Haraldsson et al., 2010; Saville et al., 2014).The reason

for this debate likely stems from the fact that Haraldsson et al. (2010) used an antisaccade task, which is meant to test the ability to inhibit a response that is usually compatible with the stimulus while producing an incompatible response while Saville et al. (2014) similarly used an inhibition response task in the form of an n-back test. Stefanis et al. (2005) however utilized a task that did not require response inhibition. Behaviour such as balance control or obstacle avoidance require responses that are consistent with the stimulus and therefore it is hypothesized that Met carriers are the faster performers for tasks that have high stimulus-response compatibility.

1.5.6.2 DRD4

The DRD4 gene codes for the D_4 dopamine receptor. Variants of the gene are associated with attention impairments and the DRD4-7 repeat allele in attention deficit hyperactivity disorder (ADHD) patients is the most commonly studied polymorphism (Li, 2006). Its link to attention has been shown in clinical populations of patients with ADHD where the 7-repeat allele is associated with poorer performance on a sustained attention reaction time task. Specifically, more errors were made and larger moment-to-moment variability was observed (Johnson et al., 2008). It is proposed that these behavioural symptoms are a result of a decreased sensitivity to dopamine molecules in carriers of the 7-repeat allele (Szekely et al., 2011). In terms of reaction time, a decreased sensitivity would result in a neurotransmitter molecule producing a decreased amount of excitatory post-synaptic potential when binding to the receptor. The decreased rate of potential change means it would take longer to reach membrane threshold to propagate an action potential.

1.5.6.3 APOE

Apolipoprotein E (APOE) has emerged as one of the most well-studied gene in the CNS. While APOE is also produced in the periphery, its production in the CNS occurs mostly by astrocytes. The APOE gene codes for apolipoprotein E, which serves as a transporter of cholesterol by binding to neurons with APOE receptors.. In humans, there are three major isoforms that differ by 1 or 2 amino acids at position 112 and 158: APOE 2, APOE 3, and APOE4. APOE 2 has cysteine-112 and cysteine-158, APOE 3 has cysteine-112 and arginine-158, and APOE 4 has arginine-112 and arginine-158 (Liao, Yoon, & Kim, 2016). The APOE 4 allele has been identified and viewed as the strongest risk factor for developing Alzheimer's disease (Beffert et al., 1998; Kanchibhotla et al., 2013). One of the distinct characteristics of the CNS in an individual with Alzheimer's disease is the accumulation of amyloid β. It is hypothesized that there is a link related to the interaction between amyloid β and APOE that underlies the development of Alzheimer's disease that alters the accumulation and clearance of amyloid β. In relation to speed of processing, it has been shown that slowed reaction time in both the fastest and slowest components of the distribution is characteristic of individuals with Alzheimer's disease (Gordon & Carson, 1990). Therefore APOE 4 may be an important biomarker for decreased reaction time in younger adults.

In the brain, cholesterol constitutes an important element of myelin, the white matter substance that insulates axons for the purpose of increasing the speed of electrical signals down an axon. The importance of maintaining the integrity of white matter is seen in diffusion tensor imaging results that reveal structural differences in white matter of healthy adults was associated with working memory decline and cognitive instability (Charlton, Schiavone, Barrick,

Morris, & Markus, 2010; Fjell, Westlye, Amlien, & Walhovd, 2011). The role of APOE may be initially thought to play a factor considering its function as a lipoprotein. However, APOE variant may not be related to the speed of axonal signal propogation. For instance, evidence from APOE knockout mice reveal that in the periphery, there was a reduced number of unmyelinated axons only and myelinated axons remained at normal levels (Fullerton, Strittmatter, & Matthew, 1998). Therefore, while APOE is related to cholesterol transport, its effect on conduction velocity in myelinated axons of the brain does not provide a mechanism for reduced reaction times. Rather, it is possible that APOE can have influence on reaction time through its effect on synaptic acetylcholine release. One study demonstrated APOE 4 in 12-month old mice had reduced acetylcholine release in the hippocampus(Dolejší et al., 2016). Reduced acetylcholine release in the synapse may indicate that delayed reactions are due to a decrease in the amount of neurotransmitter binding to receptors on a post-synaptic cell. This would possibly lead to a reduction in the rise of membrane potential to reach action potential threshold. Considering that this can occur over synapses over an entire network, between subject variability can be accounted for biologically at the level of the synapse.

1.6 Between subject variability

As noted earlier, the focus of the current study is directed to advancing understanding of the sources of between subject variability in speed of processing. Dispersion of data points, also known as statistical variability, is an inherent characteristic of behavioural data, including reaction time. The challenge is that variability can and has been expressed in two main ways: 1) within subject variability that occurs from trial to trial typically defined as the standard

deviation and 2) traditional central tendency measures such as the mean and median. Trial to trial variation in reaction time, may appear initially to be associated with unaccountable biologic randomness, however some have made a clear argument for the biologic importance of such variation as described in the linear approach to threshold with ergodic rate model (LATER) (Noorani & Carpenter, 2016; Reddi & Carpenter, 2000). The LATER model provides a fundamental description of the mechanism for how reaction times can vary. In essence, reaction time is a process that proceeds to completion of some signal threshold (S_T) that initiates the response. The time to reach this threshold is determined by two variables: the initial value of the signal (S_0) and the rate the signal rises (r). The baseline value of the signal (S_0) will dictate how much the signal must rise to achieve threshold. The higher the initial S_0, the less time it takes to produce a response and the faster the reaction time. The linear rate, r, at which this signal rises will also determine reaction time. If 'r' is allowed to vary, then the time it takes to reach the threshold signal will change depending on the slope of the linear rise. **Figure 1.1** shows a depiction of this model (Noorani & Carpenter, 2016). Biologically, this means that varying reaction time is a product of factors that influence this model. For example, conduction velocity and synapse delay both affect the rate at which the signal rises to reach threshold. The role of genetics, specifically APOE in its function of supporting the development of myelin, and DRD4 and COMT in their functions at the synapse may be important markers of variability that work through the mechanisms described in the LATER model.

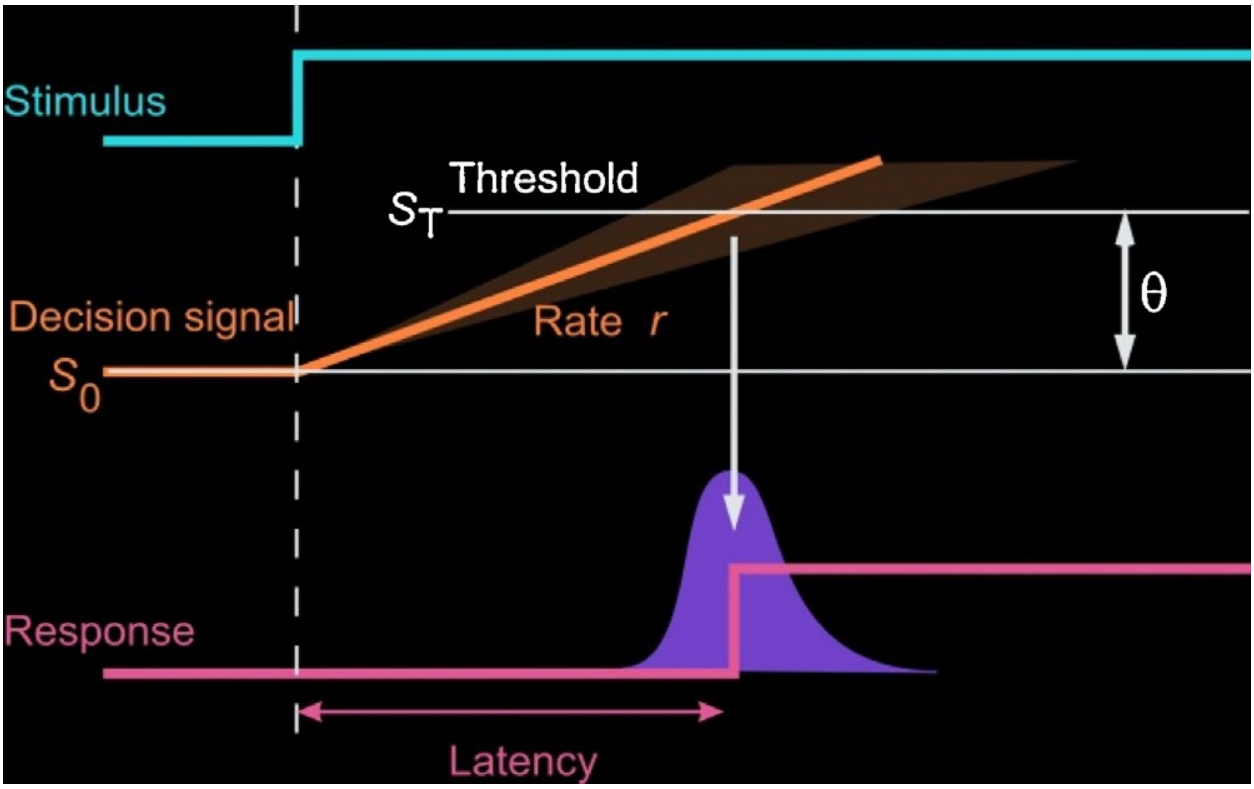


Figure 1.1: A depiction of the LATER Model. Following a stimulus, the time it takes to make a response, or reach a threshold ST is determined by the rate, r, of the signal and initial value of the signal S0. Altering one of these variables will lead to different reaction time results (Adapted from Noorani & Carpenter, 2016).

Understanding of the sources of variation is considered an important step in advancing understanding in the control of behaviour even though the primary focus comparing across tasks and groups is with respect to difference in central tendency (means/median). The importance of variability is highlighted not only by the nature of the distribution of within subject trial to trial variability but also the considerable reaction time variability seen within otherwise homogenous group of individuals suggests a potentially important person-specific contribution to speed of processing (between subject differences). For example, Hultsch et. al (2002) examined reaction time differences between individuals of the same age group on a single task and found that while the older adults group show larger standard deviations,

individual differences are pervasive throughout all age-specific populations, including young healthy adults. The implications for understanding the source for such between subject factors is important because between subject variability may provide additional insight to speed of processing not seen in more traditional methods. For example, it may explain why certain individuals are slower or faster than others in the same everyday tasks which may link to performance metrics and or injury risk. Exploring the markers that account for between subject variability may also be relevant in predicting risk of injury or cognitive decline due to decreased speed of processing. For instance, baseline performance of reaction time predicted cognitive outcomes 5 years later in a population of older adults (Bielak, Hultsch, Strauss, Macdonald, & Hunter, 2010).

Between subject variability could be accounted for from two sources as mentioned in **Section 1.5** and **Table 1.1**: 1) task-related factors specific to the attributes of a particular reaction time process and 2) person-specific factors that are connected to the characteristics of an individual that are not associated to a specific task. The challenge in observing person-specific factors influencing between subject differences is they could also be dependent on time-varying or time stable variables. Person-specific, time varying variables are defined as factors that fluctuate moment to moment on a short term basis (e.g. trial to trial and day to day). In contrast, time stable variables are factors that are person-specific as well but are fixed in their influence on a long term basis (e.g. months and years) such as age, gender, and genetics. As an example of time-varying differences, quality of sleep and stress levels which can change day to day are significant when it comes to affecting reaction time performance (Langner et al., 2010; Panayiotou & Vrana, 2004; Philip et al., 2004). Indeed, between subject

differences could be associated with differences in arousal and attention that could vary both within and between people depending on the situation. As a result, to understand the biological determinants of reaction time one must first determine the stability of repeated testing within a person under similar conditions. If between subject differences simply reflect these time-varying factors that fluctuate and change between people at different times, then the test-test reliability should be poor in comparison to between subject variability. Interestingly, reliability studies of reaction time suggest that measures are moderately consistent between weeks and seasons implying that differences are reproducible over many sessions and that they are indicative of time-stable person specific factors (Eckner et al., 2011; Resch et al., 2013; Saville et al., 2011) . However, these studies utilize either simple visual or go/no/go (response inhibition) reaction time tasks. The stability in reaction time tasks that require multiple available motor responses or different modalities is not as well documented. Furthermore, most reliability studies of reaction time however measure reaction time using imprecise methods such as button presses that incorporate movement time into the measurement. Using more precise methods such as EMG onset would allow for confirmation that reaction time is more representative of a central process. Furthermore, while it appears that reaction time is a reliable measure, there are few studies that look also at the reliability of dispersion metrics and will therefore also be confirmed in this work.

Assuming person specific and time-stable factors in reaction time are important determinants of between subject variability, and given that the modulators of reaction time appear nonspecific to task/modality, then it follows that between subject differences are generalizable across tasks within a person. There are few studies that explore comparisons

between visual and auditory tasks (Agrawal & Kumar, 1993; C. W N Saville et al., 2011; Seli, Cheyne, Barton, & Smilek, 2012) while tactile tasks have not yet been explored. As such, the reliability of the reaction times across repeated testing should be comparable across different task conditions, including tactile and choice reaction time tasks. Therefore, in addition to testing the consistency of within a person, one must also understand the generalizability of reliability across task difficulty and stimulus modality to confirm the idea that if an individual is slow in one task they will also be slow in other tasks.

Despite the evidence suggesting the importance of between-subject differences, the characterization of between subject differences have not been widely explored as typical reaction time results are reported as the mean and standard deviation (Whelan, 2008). Some authors support using a distribution analysis approach as it may reveal information that measures of central tendency are not powerful enough to show (Hervey et al., 2006; Ratcliff, 1979). Analysis of the distribution in addition to other measures of central tendency may help to uncover and explain individual differences as biologically significant information worth exploring. For example, if one argues that within subject variability is a product of time-varying factors that fluctuate moment to moment for a task and are not related to characteristics of the individual then measures of dispersion should be independent of the person as opposed to the expected differences between subjects in central tendency. In contrast, within subject variability may reflect a unique characteristic of the individuals, such as in ADHD patients with impaired attention (Castellanos & Tannock, 2002; Johnson et al., 2008) or in a healthy population that compares standard deviations of reaction time and electrocortical measures (Saville et al., 2011) and as such may parallel the between subject differences expected in

central tendencies. The proposed work will adopt the approach of exploring the between subject differences in both central tendency and dispersion measurements to explore trait specific relationship to reaction time.

1.7 Rationale

To observe underlying central nervous events, reaction time provides a proxy to the speed at which information is processed. Its use as a behavioural measure is critical to relate our actions of daily life. The individual differences present in reaction time data suggest that there potentially exist important biological traits linked to an individual's reaction time that are task-independent and relatively stable over time. To explore the individual (person-specific) contributions to reaction time and CNS speed of processing, specifically those that are time-stable, the current study will adopt complementary approaches. First the study will confirm the consistency of between subject differences across different testing days and evaluate the generalizability of reaction time performance over different modalities and days. Collectively, test-retest reliability and generalizability of between subject differences across tasks would provide support for the importance of individual characteristics in contributing to reaction time performance. Second, the current study is interested in exploring the possible association between reaction time and specific genetic polymorphisms. The candidate genes APOE and COMT have been selected for this study because they have been previously related to performance in other cognitive tasks while also speculated to have important functions in determining conduction and synapse time. However, it is acknowledged that this is not a definitive list of genes that can influence reaction time and that the results reported in this work will require a larger sample to match previous literature. Outcomes from this work will

serve to help inform and contribute to possible interventions that predict and explain individuals at risk for injury due to decreased speed of processing or possible between subject variation in age-related or pathology related changes.

1.8 Study objectives and hypotheses

The specific objectives of this work are to 1) confirm the test-retest reliability of reaction time within subjects across different days, 2) to determine the generalizability of reaction time across tasks and within subjects, and 3) identify the possible biomarkers of individual differences that relate to reaction times.

Objective 1: It is hypothesized that similar to previous literature, test-retest reliability over 2 weeks for mean reaction time in both visual and tactile modalities will be moderate (r= 0.6-0.8) supporting the view that a significant determinant of between subject variability is associated with person specific characteristics that are task-independent.

Objective 2: It is hypothesized that there will be a positive correlation between tactile and visual reaction times across subjects, also indicating that relative performance is task-independent and that the factors influencing one task will have a similar influence on one another.

Objective 3: It is anticipated that genetics may be an important marker for reaction time performance. Although the primary aim of this work is to investigate the stability and generalizability of reaction time, there is an exploratory interest in the relationship between reaction time performance and candidate genes that have a proposed biological role in contributing to synapse and conduction times. Therefore, the results from this study are not meant to be definitive in their conclusions given the small sample size of this study. However,

future work looking into the genetic factors influencing reaction time may want to use the methods and results presented as a guide. It is hypothesized that reaction time will be significantly slower in individuals carrying one of the specific candidate genes (APOE 4, or COMT Val alleles) reinforcing the view that a portion of the between subject variability is associated with these biologic differences. While APOE might not be related to conduction velocity of axons, it is still an important component of reaction time and therefore peripheral nerve conduction velocity was measured to observe potential differences that could account for between subject variability of reaction time.

Chapter 2: Materials and Methods

2.1 Participants

This study recruited 19 young healthy adults (age range 18-31 years; median age 21), 11 females and 9 males (**Table 2.1**). All participants were graduate or undergraduate students at the University of Waterloo. A health status form was used for participants to self-report their eligibility for the study. None of the participants reported suffering from any neurological or musculoskeletal disorder at the time of the experiment that would have affected their ability to complete the reaction time tasks. All subjects provided informed, written consent for this study which was approved by a research ethics committee at the University of Waterloo.

Information about the participants was obtained through the completion of questionnaires to account for and measure other possible contributing factors to reaction time performance. Prior to completing reaction time tasks, participants completed the Godein leisure-time scale (Godin & Shephard, 1997), the Eysenck personality questionnaire (Eysenck, Eysenck, & Barrett, 1985) that measured their level of physical activity, and personality. A higher score on the respective questionnaires indicated a personality characterized by higher neurotic behaviour (Eysenck et al., 1985) and physical activity (Godin & Shephard, 1997). The purpose of these questionnaires was to screen for the relationship between these stable traits and reaction time. Specifically, individuals with higher neuroticism scores were more variable in their reaction times (Robinson & Tamir, 2005) and individuals that were more physically active were viewed as having faster reaction times (Baylor & Spirduso, 1988; Spirduso, 1975) In addition, information was recorded regarding state factors on each of the two sessions that could significantly contribute to performance. Participants were asked to provide information on their quality of sleep (Buysse et al., 1989), and stress levels (Cohen, Kamarck, &

Mermelstein, 1983) on the day of each session because of their role in moment to moment influence that may have contributed to large between day variability within a subject (Bagherli et al., 2011; Langner et al., 2010) . Individual results from each questionnaire are presented in **Table 2.1**.

Table 2.1: Participant demographics and results of the sleep questionnaire, perceived stress scale, neuroticism score for the Eysenck personality scale, and the Godin leisure-time exercise questionnaire.

Subject	Age	Sex	Quality of Sleep 1 (hours)	Quality of Sleep 2 (hours)	Perceived Stress Score 1 (/40)	Perceived Stress Score 2 (/40)	Neuroticism Score (/12)	Godin Exercise Score
1	26	M	7	7	5	16	8	30
2	25	F	7	7	14	9	4	36
3	31	F	7.5	7	16	19	7	36
4	23	M	7.5	7	14	10	3	26
5	20	F	6	5	18	22	8	54
6	27	M	8	8.5	27	8	2	35
7	23	M	8	9	18	4	3	29
8	25	M	6	7	10	13	3	67
9	18	F	9	7	12	13	1	15
10	21	F	6.5	6.5	15	17	2	73
11	20	M	6	6	13	9	3	72
12	20	F	6	7	25	17	7	47
13	21	F	8	7.5	21	15	11	40
14	20	F	8	9	20	25	1	49
15	22	M	9	9	10	7	2	36
16	21	F	7	7	27	13	10	57
17	18	F	7	7	15	18	4	51
18	21	F	7	6	23	18	6	18
19	27	M	8	8	22	25	7	45

2.2 Protocol

To test hypothesis 1 of reaction time stability over repeated testing sessions, subjects were tested over 2 days. To test hypothesis 2 of reaction time generalizability, reaction time tasks of varying difficulty (simple and choice) and modality (visual and tactile) were tested and compared across measures and within and between days.

2.2.1 Training and testing sessions

Participants attended a total of 3 sessions for this experiment. The first served as a practice session to familiarize the participant with the behavioural tasks as studies have shown that reaction time is higher in the initial trials of a task due to learning effects (Ando, Kida, & Oda, 2002; Mowbray & Rhoades, 1959). While one study suggests that at least 10 practice trials should be used in a tactile simple reaction time task (Günendi, Taskiran, & Beyazova, 2005), there is no standard number of practice trials that will ensure complete absence of learning effects in reaction time. The tasks used in this experiment were designed with the intent to have high stimulus-response compatibility to reduce the amount of learning and thus the number of practice trials required. Therefore, participants completed at a minimum 20 trials for each condition in the first session. Results were recorded and visually inspected to observe if performance has plateaued, indicating that learning had been reduced. Behavioural results of interest were taken from sessions 2 and 3 which began with 20 practice trials of each condition. Time between sessions 1 and 2 occurred within 1-3 days while the time between sessions 2 and 3 occurred within 7-9 days of each other to observe week to week stability. In each session, participants completed 4 blocks of reaction time tasks; two simple and two choice reaction tasks for each modality for a total of 8 reaction time blocks per session. The order of blocks

were randomized before the beginning of the collection. 20 trials were collected per block since inter-trial intervals are between 1-6 seconds and many trials can be collected in a short period of time without inducing fatigue in subjects. One of sessions 2 and 3 had a collection start time in the A.M. while the other session had a start time in the P.M. to account for the possibility of time of day as a state factor.

2.2.2 Reaction time tasks

Participants completed each task while seated on a height adjustable table so that their dominant arm reached 90 degrees of shoulder abduction. The starting position for the reaction time tasks was 90 degrees of elbow flexion. Participants received tactile stimulation while seated via an electrical pulse at an intensity of 1.5X perceptual threshold delivered through ring electrodes onto the middle and index fingers of the non-dominant hand. Visual stimuli in the form of right and left arrows was delivered on a computer screen in a lit room positioned in front of the participant.

Tactile condition: Prior to the beginning of the tasks, instructions were provided indicating that stimuli from the index finger are responded with elbow flexion using the biceps muscle, and stimuli from the middle finger are responded with elbow extension using the triceps muscle. After the ring electrodes were attached, stimulus intensity was determined for each finger individually by first sending low voltage single pulses and increasing the amplitude until the participant has perceived the stimulus. Participants were then asked to perform both simple (SRT) and choice reaction time tasks (CRT). In SRT, participants received tactile stimuli to only the middle or only the index finger of the supinated non-dominant hand. In these trials,

there was always one stimulus and one corresponding response. In the CRT task, participants were exposed to two possible stimuli with two possible responses. The probability of for each stimulus to occur in a trial was at 50%. After the completion of each response, participants returned their arm to the original starting position at 90 degrees of elbow flexion. Successive trials were separated by a random foreperiod of 1-6 seconds to eliminate possible anticipation of the stimulus.

Visual condition: Visual stimuli were presented on a computer screen as an arrow pointing to the right on the right side of the screen, or as a left arrow pointing to the left on the left side of the screen. Responses were designed to maintain stimulus-response compatibility with respect to the spatial location, similar to that of the tactile stimuli. Instructions were given to respond with an elbow flexion at the biceps muscle for arrows pointing to the left. Arrows pointing to the right were asked to be responded to by an elbow extension movement at the triceps. Trials in each block were separated by a random foreperiod of 1-6 seconds.

In choice reaction time tasks, participants were exposed to blocks of visual or tactile stimuli, each having two possible stimuli and two possible responses. That is, in visual blocks, participants were presented with left and right arrows and responded with an elbow flexion or extension. In tactile blocks, participants were presented with stimulation to the index and middle finger and responded with an elbow flexion or extension. In simple reaction time tasks, participants were exposed to only one possible stimuli and one corresponding response which was predetermined and described to the participant before the beginning of a testing block.

2.2.3 Nerve conduction velocity test

A nerve conduction velocity test was conducted on the non-dominant arm as a possible marker of between subject differences that contributes to reaction time performance. A stimulating electrode was placed on top of the ulnar nerve to produce a motor evoked potential recorded using EMG at the abductor digiti minimi muscle (**Figure 2.1**). The distance between the stimulating electrode and the recording electrode was measured in order to calculate conduction velocities. The ulnar nerve was stimulated at 1.5X motor threshold for 10 trials with random foreperiods of 1 to 6 seconds between trials.

2.3 Measurements

2.3.1 Electromyography

Electromyography (EMG) was collected from the biceps brachii muscle and the triceps for the reaction time task, and from the abductor digiti minimi muscle for the conduction velocity test (**Figure 2.1**). The skin over these muscles were cleaned with Nuprep and alcohol to reduce dirt, oil, and dead skin cells that may have impeded the signal. Silver/silver chloride electrodes were placed over each muscle belly. Data was collected at a frequency of 1000 Hz.

EMG data was filtered using a 2^{nd} order dual pass Butterworth filter from 30-300Hz and full wave rectified. Reaction times and conduction velocities were obtained by a custom-made Labview program. EMG onset was defined as when the amplitude exceeds 3 standard deviations of the previous 100ms of activity for more than 25 milliseconds. Trials where there appears to be significant pre-stimulus EMG activity or co contraction of the recorded muscles were eliminated due to effect that muscular tension has on shortening reaction times (Araki &

Choshi, 2006; Etnyre & Kinugasa, 2002). Errors were denoted as the occurrence of pattern of EMG activity that was not consistent with the stimulus (e.g. initial muscle contraction was observed ion the wrong muscles). These trials were removed from the analysis.

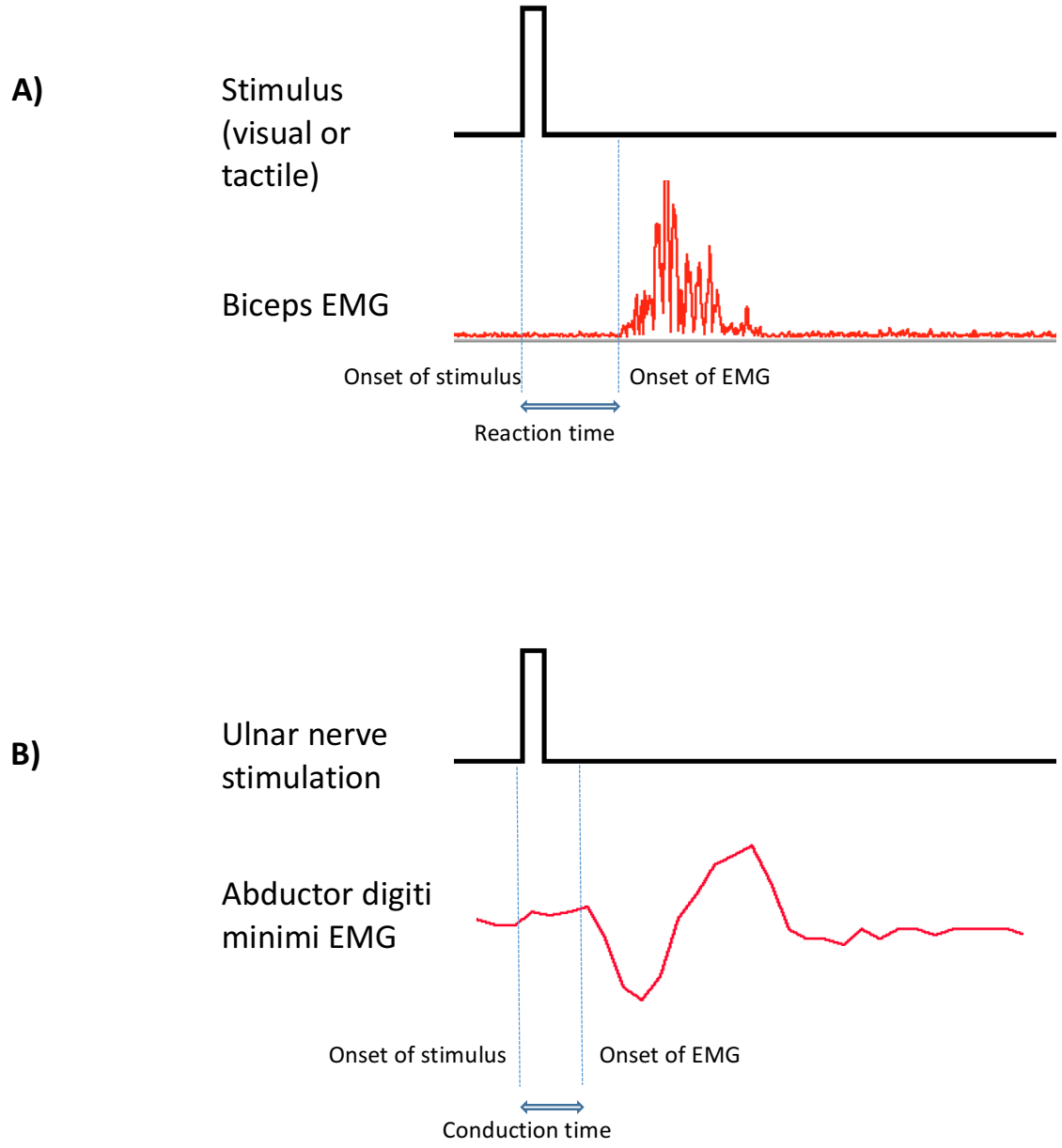


Figure 2.1: A sample time series trace for the collection of one trial of reaction time and conduction time. **A**: A sample trace of the reaction time task depicting a biceps EMG response following the presentation of a tactile or visual stimulus. Reaction time is calculated as the period of time between the onset of a stimulus to the onset of an EMG response. **B**: A sample trace of the nerve conduction velocity task. Following ulnar nerve stimulation at the elbow, an EMG response is elicited at the abductor digiti minimi muscle. Conduction time is calculated as the period of time between the onset of a stimulus to the onset of an EMG response. To calculate conduction velocity, the distance between the elbow and the proximal EMG electrode is divided by the conduction time.

2.3.2 Genotyping

Saliva samples were collected in anonymized spit cards and genotyped for apolipoprotein E (APOE) polymorphisms (rs429358, rs7412) and catechol-o-methyl transferase (COMT) Val^{158}Met polymorphisms (rs4680). While this study initially intended to genotype the DRD4 7-repeat allele, assays were not available at the time the study was conducted. DNA samples were amplified using polymerase chain reaction with TaQMan single nucleotide genotyping. This process was used to amplify specific DNA sequences and using fluorescence to quantify the amount of the sequence of interest. A solution of DNA, primers, Taq polymerase, free nucleotides, and probes containing fluorescent dyes (FAM and VIC) were combined. The solution is then heated to 94°C to allow for the DNA to unwind. This is followed by a cooling stage that reaches 60°C that is then heated to 72°C to allow for the annealing of primers and the attachment of nucleotides to single strand DNA by Taq polymerase. These steps are then repeated for 20-40 cycles to obtain multiple copies of DNA. The probes with fluorescent dye are annealed to their respective sequence and emit a fluorescent signal once they have been cleaved by Taq polymerase. The recording of this fluorescent signal allows for the quantification of which sequence is present in the DNA sample. **Table 2.1** provides a summary of the VIC/FAM labelling system used and **Table 2.2** shows the corresponding gene variants.

Table 2.1: VIC/FAM labelling system for APOE 429358, APOE 7412, and COMT 4680

Gene	Signal	Base
APOE 429358	VIC	C
	FAM	T
APOE 7412	VIC	C
	FAM	T
COMT 4680	VIC	A
	FAM	G

Table 2.2: List of possible gene variants for APOE and COMT

Gene	Base	Variant
APOE	TT/CC	3/3
	CC/CC	4/4
	CT/CC	3/4
	CT/CT	2/4
	TT/TT	2/2
	TT/CT	2/3
COMT	AA	Met/Met
	AG	Met/Val
	GG	Val/Val

2.4 Statistical analyses

Reaction time was used as the primary dependent variable. In total there were 80 trials collected on each task per person over the two sessions for a total of 320 trials. Trials were excluded if there was an error in responding with the correct movement. Individual error rates were found to range from 0 – 8.75% of all trials for the choice tactile task, and 0-6.25% for the choice visual task. Note that trials in which an error occurred were removed only from choice reaction time trials (no errors coded in simple reaction time).

2.4.1 Primary analysis

To address objective 1, test-retest reliability scores of mean and standard deviation of reaction time was determined by calculating the intra class correlation between days for all tasks (simple visual, choice visual, simple tactile, choice tactile). The minimum required sample size for this study (12 subjects) was based on recommendations outlined by Walter et. al (1998) for test-retest reliability studies for an alpha level of .05 with 80% power.

To address objective 2 a Pearson product moment coefficient correlation was calculated to observe the potential relationship between performance of simple and choice reaction time tasks within the same modality as well as across different modalities. This was conducted to determine whether between subject variability was consistent and generalizable across different tasks. Statistical significance was set at an alpha level of 0.05.

To address objective 3, to explore possible contributions of genetics as biological markers of speed of processing and their potential roles in determining conduction and synapse time in speed of processing as described in objective 3, separate two-way mixed ANOVAs were calculated to determine differences in mean and standard deviation of reaction time between carriers of each allele for COMT and APOE. Statistical significance was set at an alpha level of 0.05.

2.4.2 Secondary analysis

A secondary analysis was set out to determine if peripheral conduction velocity is also associated with the APOE gene as there is speculation it may influence conduction velocity, one of the neurophysiological determinants of reaction time. APOE genotyping would be complemented by conduction velocity results to also investigate the efficacy of using peripheral nerve conduction velocity to predict central conduction velocity. Therefore, a Pearson product moment correlation coefficient was calculated to observe the possible association between conduction velocity and reaction time. Statistical significance was set at an alpha level of 0.05.

Chapter 3: Results

3.1 Reaction time performance across tasks

Figure 3.1 displays mean reaction times across the different tasks. Note that participants' performance for each task includes the results from session 1 and session 2. Overall, choice reaction times were significantly slower than simple reaction times (CRT – 310.3 ms; SRT 237.9 ms; $F_{(1,18)} = 286.05$, $p > .0001$). Overall, there were no statistically significant differences when comparing reaction times evoked by an auditory versus a visual stimulus (Auditory – 280.2 ms; Visual – 268.1 ms; $F_{(1,18)} = 2.29$, $p = 0.15$). However, as evident in **Figure 3.1**, there was a significant interaction effect between tasks (simple/choice) and modality (auditory/visual) ($F_{(1,18)} = 87.66$, $p > 0.0001$). A post-hoc Tukey's honestly significance difference test revealed tactile reaction time was faster than the visual modality for simple reaction time while tactile reaction times were slower than visual reaction times in the choice task condition ($p < 0.05$).

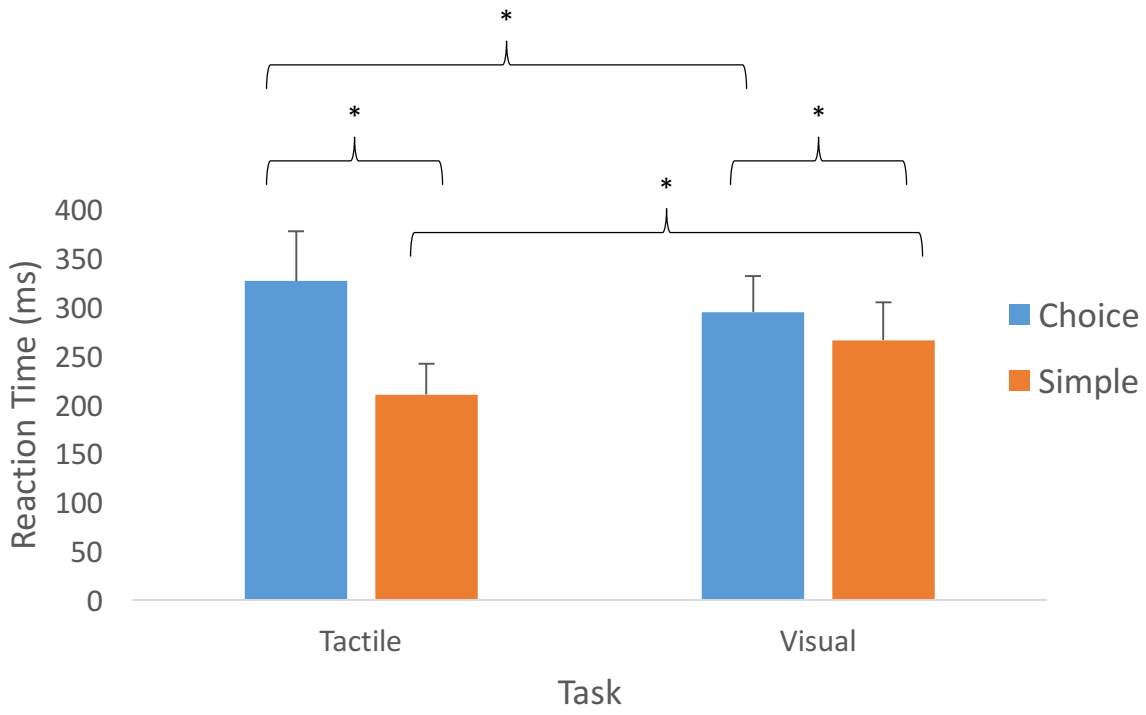


Figure 3.1: Average reaction times across both post-training sessions across all participants for tactile and visual reaction time tasks. Error bars display the standard deviation. Asterisk denotes a statistical significance (p>.05).

3.2 Between day consistency

Between day intra class correlations (ICC) of reaction time means for each task are presented in **Table 3.1**. The range of each task indicates the large between subject variability that is present in this sample of young, healthy adults. ICC values were 0.82, 0.77, 0.78, and 0.82 for CRT tactile, SRT tactile, CRT visual, and SRT visual, respectively. In addition, ICCs on the coefficient of variation for the same set of tasks were found to be 0.25, 0.54, 0.57, and 0.53. **Figure 3.2** provides a graphical representation of day to day changes in reaction time for each subject on each of the 4 tasks ordered by subject in ascending order of speed, displaying the both the spread of unique performance differences across individuals as well as within-individual reaction time differences over the two testing periods. In addition, **Table 3.2**

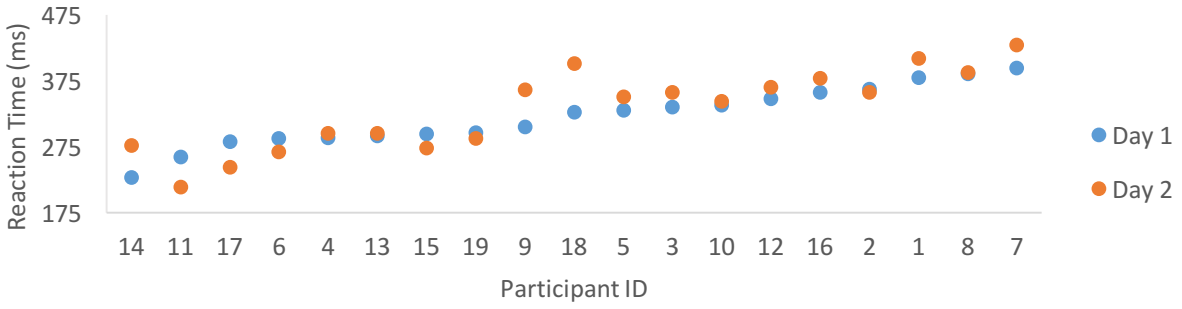
summarizes all individuals' between day differences for each task and demonstrates the inconsistent pattern of reaction time changes for within subject variability across tasks. For instance, Subject 1's between day differences for the choice visual task reaction time performance was faster on day 1 than it was on day 2 (28.6 ms faster day 1). However, the opposite trend is seen for the simple visual task (73.1 ms faster on day 2).

In addition to the ICCs that summarize the test-retest reliability for all participants, a secondary informal analysis was conducted to better understand why certain individuals varied more between sessions than others as well as highlight the large within subject variability of reaction times from moment to moment. In order to observe the portion of participants with the largest differences between days for each task, the top 5 participants (75^{th} percentile) with the largest reaction time difference between days were analyzed to see how different parts of the distribution changed. Individual trials from both sessions were then sorted from fastest to slowest. Individual examples of this analysis is summarized in **Figure 3.3**. Visual inspection approximated that distribution changes occurred either through a large increase in the slowest trials only or through a large increase in all parts of the distribution.

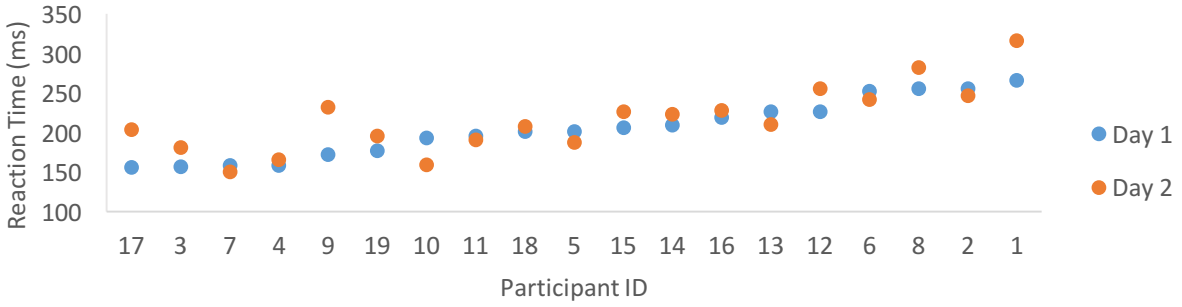
Table 3.1: Summary of performance for all participants. Mean, standard deviation, and range are calculated separately for day 1 and day 2 for each task. Separate intraclass correlations were calculated using the mean and coefficient of variation.

Task		Mean (ms) ± SD	Range (ms)	ICC	
				$\overline{x}$	CV
CRT Tactile	**1**	320.7 ± 44.5	165.4	0.82	0.25
	2	331.5 ± 60.6	215.4		
SRT Tactile	**1**	204.3 ± 35.9	109.3	0.77	0.54
	2	215.7 ± 41.7	165.2		
CRT Visual	**1**	292.5 ± 29.2	137.4	0.78	0.57
	2	296.7 ± 37.5	164.9		
SRT Visual	**1**	267.1 ± 46.0	214.4	0.82	0.53
	2	264.4 ± 35.4	142.7		

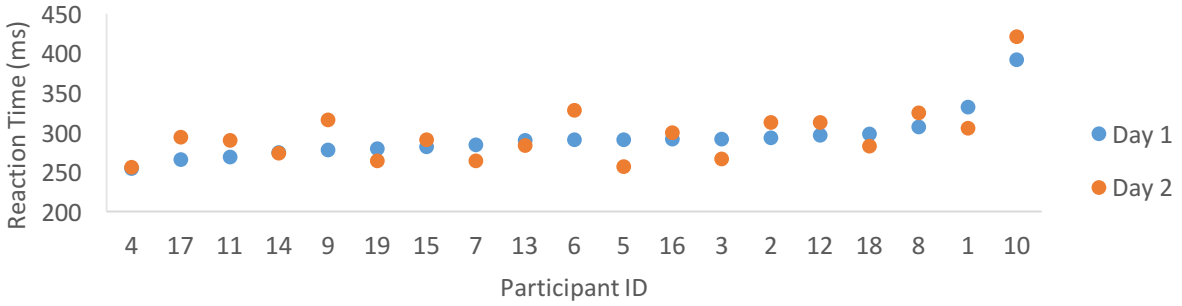
A) Choice reaction time - tactile stimulus



B) Simple reaction time - tactile stimulus



C) Choice reaction time - visual stimulus



D) Simple reaction time - visual stimulus

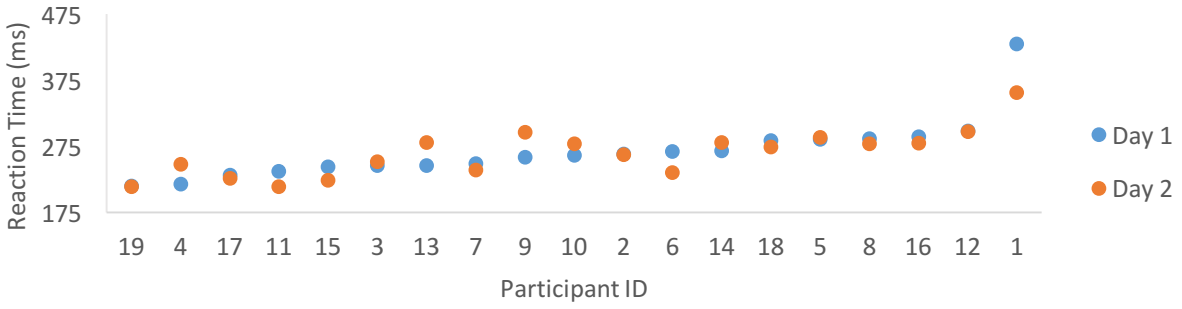
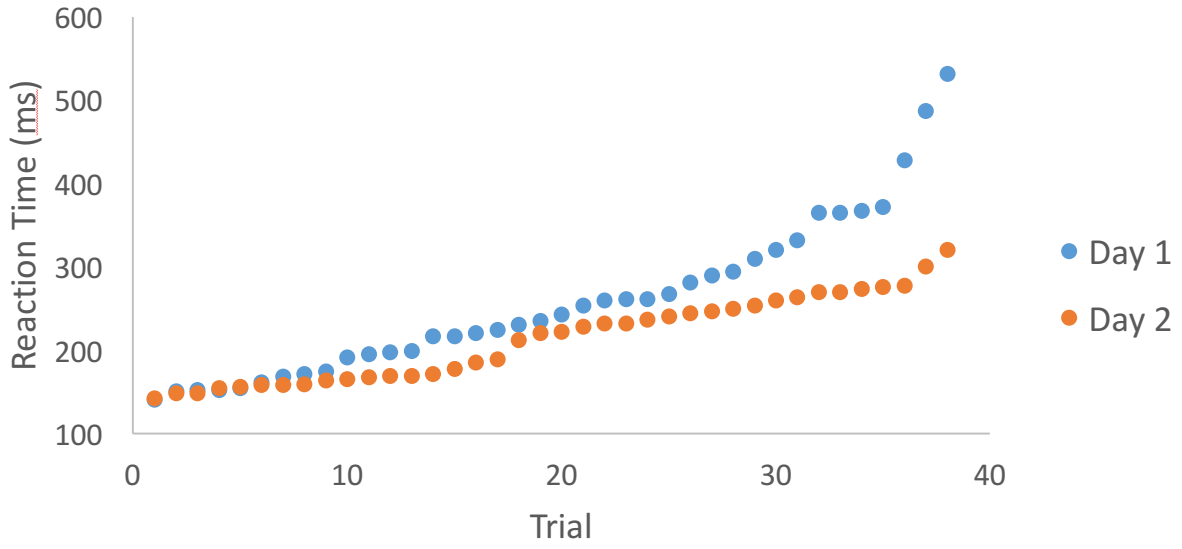


Figure 3.2: Mean reaction time for day 1 and day 2 for each individual participant. Participants are ordered from fastest to slowest based on their performance on the first day for A) Choice tactile, B) Simple tactile, C) Choice visual and D) Simple visual tasks.

A)



B)

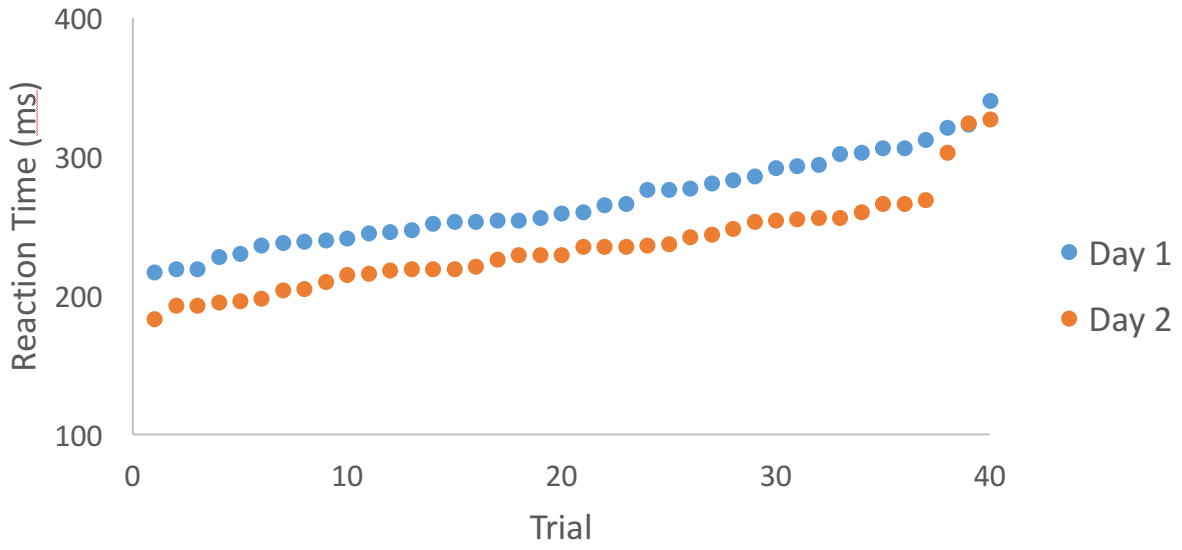


Figure 3.3: The top 5 subjects for each task with the largest difference between days had their reaction time performance expressed as individual trials ordered from fastest to slowest. The above graphs depict a summary of how differences between days are characterized. A) The fastest trials do not change between days and the large difference is due to differences in the slowest tail of the distribution. B) Systematic differences in reaction time across all trials.

Table 3.2: Individual differences in average reaction time (ms) from day 1 to day 2 across all tasks. A negative value indicates that performance was faster on day 1.

	Average change in reaction time (ms) from day 1 and day 2			
Subject	**CRT visual**	**SRT visual**	**CRT tactile**	**SRT tactile**
1	-28.6	73.1	-29.1	8.8
2	26.3	0.3	4.9	16.2
3	-27.7	-6.0	-23.0	-8.5
4	0.7	-30.1	-6.1	-47.4
5	-37.2	-3.0	-20.6	-20.1
6	15.4	31.8	20.0	13.5
7	-21.8	10.0	-35.7	4.7
8	-17.6	7.9	-2.2	-26.9
9	-37.9	-37.5	-55.7	-59.5
10	-8.4	-17.6	-5.9	-50.1
11	20.0	23.2	45.4	7.9
12	-15.8	0.7	-18.0	-29.0
13	-19.3	-34.7	-3.6	-6.7
14	-8.1	-12.3	-48.6	-6.9
15	33.4	20.6	20.9	33.5
16	25.8	9.8	-20.7	-13.8
17	-1.1	4.2	38.4	-24.7
18	6.6	10.2	-73.5	10.7
19	15.5	1.4	8.0	-18.7

3.3 Association of reaction times between tasks

To reveal the association of reactions between tasks Pearson product moment correlation coefficients were conducted for each combination of task (**Table 3.3**). The data shows that there are positive relationships when comparing any two tasks. Within modality comparisons all reached significance of $p<.05$ (**Table 3.3A, C**). The correlation coefficients range from r= 0.62-0.87 for tactile comparisons and visual comparisons. However, comparisons did not all reach significance. Of the 16 cross-modality comparisons calculated, 4 did not reach significance. Furthermore, the range of significant correlation coefficients were weaker than the within modality comparisons (r= 0.39 – 0.62) (**Table 3.3B)**.

Table 3.3: Pearson product moment correlation coefficients for all task comparisons. The number on the task name indicates the session the task was completed in. P-values are shown beneath the correlation coefficient (n= 19).

A) Within-tactile comparisons

Task	CRT tactile 1	CRT tactile 2	SRT tactile 1	SRT tactile 2
CRT tactile 1	-	0.87 <.0001	0.73 0.0004	0.62 0.0046
CRT tactile 2	0.87 <.0001	-	0.70 0.0011	0.64 0.0030
SRT tactile 1	0.73 0.0004	0.69 0.0011	-	0.81 <.0001
SRT tactile 2	0.62 0.0046	0.64 0.0030	0.81 <.0001	-

B) Cross-modal comparisons

Task	CRT Tactile 1	CRT Tactile 2	SRT Tactile 1	SRT Tactile 2
CRT Visual 1	0.39 0.10	0.35 0.14	0.52 0.024	0.24 0.32
CRT Visual 2	0.46 0.046	0.54 0.017	0.51 0.027	0.45 0.054
SRT Visual1	0.49 0.031	0.54 0.016	0.60 0.0070	0.41 0.083
SRT Visual 2	0.43 0.066	0.62 0.0047	0.55 0.014	0.61 0.0058

C) Within-visual comparisons

Task	CRT Visual 1	CRT Visual 2	SRT Visual 1	SRT Visual 2
CRT Visual 1	-	0.80 <.0001	0.73 0.0004	0.62 0.0046
CRT Visual 2	0.80 <.0001	-	0.69 0.0011	0.64 0.0030
SRT Visual1	0.86 <.0001	0.86 <.0001	-	0.81 <.0001
SRT Visual 2	0.67 0.0017	0.87 <.0001	0.81 <.0001	-

3.4 Genetics

To assess the genetic contribution of APOE and COMT polymorphisms to reaction time, separate two-way mixed ANOVAs were conducted with factors of polymorphism (between factor) and task (within factor). The performance of each polymorphism is shown in **Figure 3.4**. The observed genotype frequencies are presented in **Table 3.5**. In this study and population, there was no significant difference for APOE polymorphism ($F_{(4,13}$=0.58, p=0.6782) nor was there an APOE x Task interaction ($F_{(12,39)}$ = 0.33, p = 0.98). In addition to the APOE results, nerve conduction velocity results revealed that there was no significant correlation associated with any of the reaction time tasks (**Table 3.4**). Analysis on COMT shows there was a significant difference for polymorphism at a 95% level of significance ($F_{(2,14)=}$=3.35, p=.0412). However, a Tukey post-hoc analysis showed no significant difference between any COMT group. There was no significant COMT x Task interaction ($F_{(12,42)}$ = 0.62, p = 0.71) . Individual genetic and nerve conduction velocity results are summarized in **Table 3.6**. Reference values from **Table 3.7** show that the majority of the conduction velocity results are within the range of previous literature.

Table 3.4: Pearson product moment correlation coefficients comparing nerve conduction velocity to reaction time performance in all tasks. P-values are shown beneath the correlation coefficient.

Task	Correlation (r) (n= 19)	P - value
CRT Tactile	-0.04	0.88
CRT Visual	-0.01	0.95
SRT Tactile	-0.10	0.68
SRT Visual	0.01	0.97

Table 3.5: Summary of the number of carriers of each allele for the APOE and COMT genes. Note that one participant's sample was unable to be genotyped for APOE allele and is not included in the count.

	APOE					COMT		
	2/3	2/4	3/3	3/4	4/4	AA	AG	GG
n	1	2	11	3	1	3	10	6

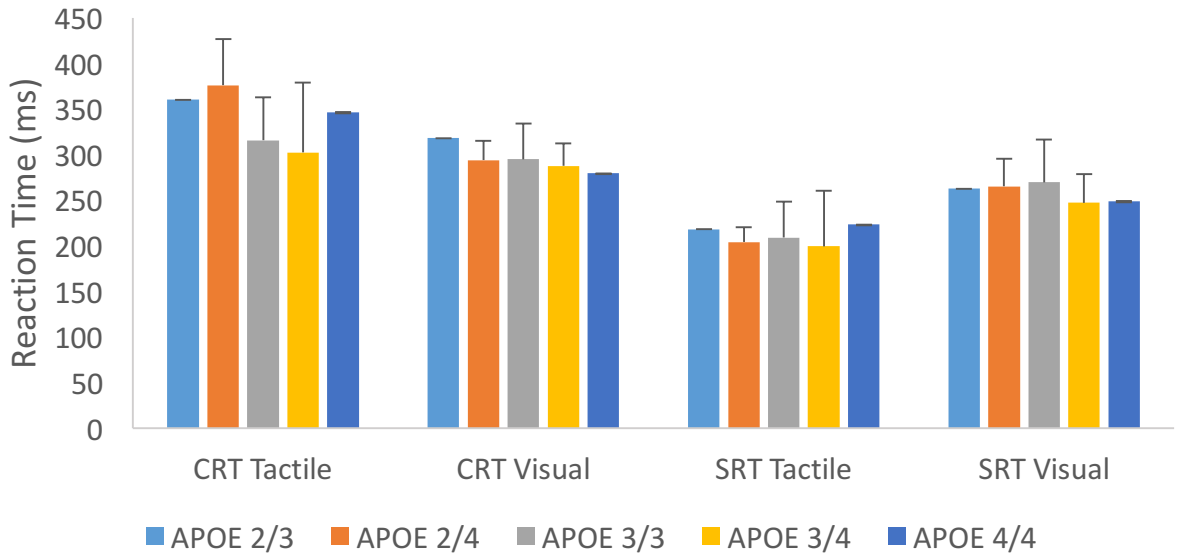
Table 3.6: Individual genetic (APOE and COMT) and nerve conduction velocity results. Note that for subject 12 the sample was unable to be genotyped for APOE allele.

Subject	APOE	COMT	Conduction velocity (m/s)
1	3/3	AG	59.3 ± 5.3
2	2/3	GG	48.6 ± 5.4
3	4/4	AG	52.8 ± 4.4
4	3/3	AG	51.6 ± 5.0
5	2/4	GG	52.5 ± 3.7
6	3/3	AG	50.3 ± 4.4
7	2/4	AG	42.2 ± 3.0
8	3/4	AG	47.6 ± 6.4
9	3/3	AA	28.7 ± 3.5
10	3/3	AG	47.1 ± 3.1
11	3/4	GG	48.7 ± 3.9
12	-	GG	38.7 ± 3.0
13	3/3	GG	43.8 ± 4.5
14	3/3	AA	32.5 ± 1.4
15	3/4	AA	47.3 ± 4.5
16	3/3	AG	50.7 ± 2.3
17	3/3	GG	38.1 ± 2.4
18	3/3	AG	39.1 ±3.1
19	3/3	AG	40.0 ± 4.4

Table 3.7: Reference ulnar nerve conduction velocities cited in previous literature. All values presented in the table are reported as the mean ± standard deviation with the exception of the McKnight study that reported median values.

Study	Conduction Velocity (m/s)
Azma et. al 2007	62.65 ± 7.62
Kimura & Butzer 1975	55.9±5.1
Thomas, Sears, Gilliat 1959	56.2±4.6
McKnight et. al 2010	58.25 (males) 58.04 (female)

A) APOE allele



B) COMT Allele

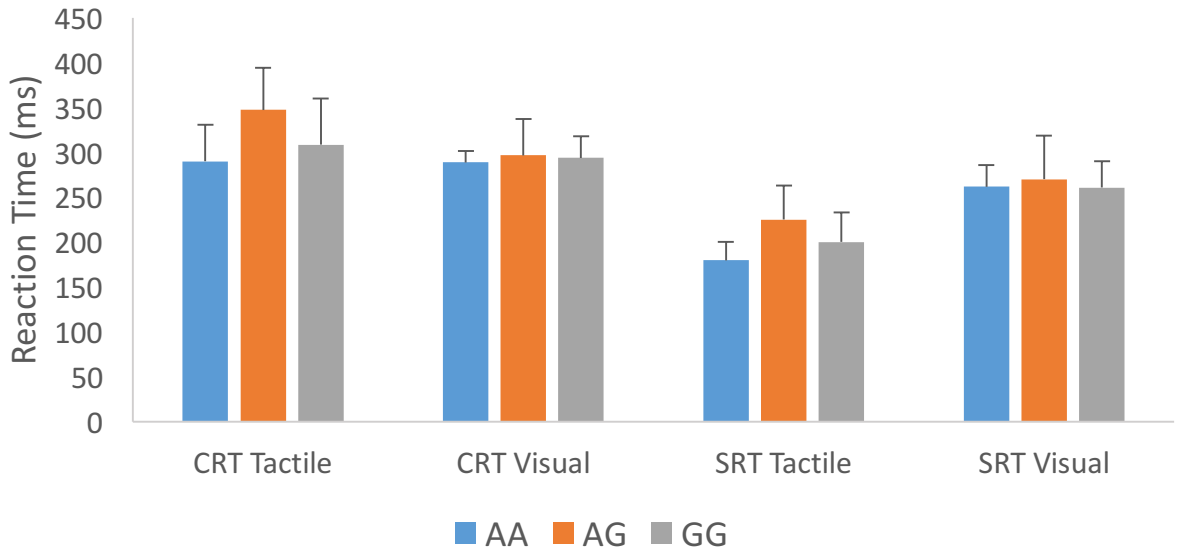


Figure 3.4: Mean reaction time, and standard deviation of all tasks comparing all participants grouped by **A**: APOE allele and **B**: COMT allele

Chapter 4: Discussion

4.1 Summary of findings

Overall, this thesis looked to further understand between subject differences as a product of two variables: stable, person-specific characteristics (trait) and transient, time-varying factors (state). The main findings suggest:

1) Reaction time results, expressed as the mean supports hypothesis 1 in that the intraclass correlation (ICC) is consistent with the findings of previous literature for tactile and visual tasks as well as simple and choice tasks.
2) Hypothesis 2 is not supported. While mean reaction time is generalizable when comparing performance between task challenges within a modality (i.e. simple vs. choice reaction time), it does not carry over across modalities (i.e. visual vs. tactile).
3) Hypothesis 3 is not supported as there is no present evidence for association between reaction time performance and the proposed genetic biomarkers to influence conduction velocity or synapse time.
4) In addition, the study reinforced the view that other expressions for speed of processing besides central tendency should be considered.

4.2 Within-subject, between day stability of reaction time performance

The unique finding in the present study demonstrate that ICCs of reaction time over 1 week were within the range of previous results in the literature across tasks of varying difficulty (simple and choice) and also across different modalities (visual and tactile). Testing average reaction times on different days over a 1-week time period and at different times in the day revealed stable reaction time performance within-subjects compared against between subject

differences. On average individuals maintained similar performance regardless for specific task conditions despite being tested over multiple sessions. This finding resulted in similar consistency to previous experiments focussed on simple visual reaction time tasks to explore reliability across days and months (Eckner et al., 2011; Resch et al., 2013; Saville et al., 2011). The findings of the current study are novel in that it extends the observation to other modalities (i.e. haptic) and task challenges (choice reaction times) where the literature has been primarily focused on simple visual tasks.

However, while the results are encouraging and appear to reflect the stable nature of reaction time, the interpretation of these results should also consider the limitations of the ICC calculation, specifically the variables used to estimate the ICC's magnitude. In essence, as described by Weir (2005) the ICC is an index of relative consistency, that is a ratio of the between subject variability relative to the total variability and the magnitude can be misleading based on heterogeneity of the subjects. Therefore, a high ICC may be a result of larger between subject variability in reaction time compared to the variability within a subject. This means that while this study observed ICCs that appear to suggest high reliability due to trait characteristics, there is nevertheless important contributions from state factors causing reaction time to fluctuate that may go unnoticed. For instance, breaking down the day to day differences from each individual across all tasks provides insight into the role of state factors. **Table 3.2** shows that the magnitude and direction of changes in average reaction time performance between days are not always constant across all tasks. While an individual may be faster at a specific task one day, the opposite pattern may be seen in another task. Further breakdown of individual reaction time trials (**Figure 3.3**) also indicate potential fluctuations in the fastest and slowest

reactions can occur from day to day. In fact, the literature clearly reveals the important state dependent influences on speed of processing including arousal, stress, and attention (Lakhani et al., 2013; Langner et al., 2010; Panayiotou & Vrana, 2004; Weissman et al., 2006).

This is not to suggest that reaction time is determined exclusively by state factors or that the ICC of reaction time is not a reliable measurement but rather the intent is to acknowledge the profound influence that state factors have on reaction time. What the ICC does well is reveal that reaction times within a participant are more closely related than times between individuals despite day to day differences. In fact, additional ICC analysis conducted on the stability of different measures of reaction time, including the median, fastest 10 trials, and the slowest 10 trials found that ICCs were similar to values found using the mean of all trials. So, while mean reaction time can be biased and is typically observed as a non-normal distribution (Whelan, 2008), the between subject variability is present not just through the mean which includes all trials and can be biased, but also through different expressions of the data.

4.3 Generalizability

It was originally hypothesized that relative performance would be similar across tasks because of a common speed of processing trait shared by all sensory modality networks within an individual. This study implemented multiple tasks that varied in difficulty (simple and 2-choice tasks) as well as in modality (visual and tactile) to observe an individual's relative performance. Therefore, even though there would be absolute differences between tasks of varying difficulty or modality, it was expected that individuals who were slow or fast in one task would demonstrate a similar level of performance in a different task and serve as a reflection of

trait specific differences in speed of processing. Within modalities, simple and choice reaction times were relatively consistent across subjects (moderate to high correlations) suggesting the hypothesis was supported when comparing across task difficulty. This finding is in agreement with Agrawal's (1992) and Seli et. al (2012) assessment of generalizability between reaction time task difficulty. It is noteworthy that these studies compared modalities as well (visual versus auditory) and revealed a significant association. In contrast, we observed a lack of association between visual and tactile modalities. It should also be noted that the previous studies revealed the weaker associations when comparing modalities as opposed to task difficulty.

There are several possible explanations that may account for the differences in reaction times between visual and tactile modalities seen in the present study as compared to the similarities seen in previous literature. First, the differences between tactile and visual tasks may be attributable to differences in relative stimulus intensity. This experiment attempted to standardize stimulus intensity by using a voltage that was 1.5X a subjective, perceived threshold for tactile tasks and a standardized visual stimuli situated in identical locations. It was assumed that the stimulation of sensory neurons would be the same for each trial across participants. However, there was no way of measuring and ensuring the precise magnitude of the sensory volley or number of sensory fibers activated of each trial, especially in the tactile condition. As a result, it is possible that the absolute intensity of stimulus was different for subjects due to differences in perceptual judgements . Variation in absolute stimulus intensity has the potential to impact reaction times due to the inverse relationship between stimulus intensity and reaction time (Lakhani et al., 2011; Vaughan, Costa, & Gilden, 1966). To control for this in

the future it may be beneficial to choose a stimulus intensity based on each individual's stimulus response curve. As the intensity increases, reaction time decreases eventually reaching a plateau (Luce, 1986) providing a range of possible scores. Using this stimulus-response curve as a guide, a consistent stimulus intensity comparable to all participants can be selected based on a percentage of the entire range rather than based on a perceptual judgment threshold (e.g. the stimulus intensity delivered to each participant will correspond to the median reaction time in the stimulus-response curve).

A second possible explanation for modality specific differences may link back to stable trait differences linked to person specific differences in processing specific sensory information. Sensory processing networks may have the capability to develop independently of one another, resulting in specialized networks. Indeed, evidence that information processing is not equivalent across sensory modalities can come from ontogenetic and phylogenetic examples. While they may not provide direct evidence to explain why the speed of processing across modalities is so different, it does highlight the concept that the development of processing networks is unique. The independent relationship between the speed of processing of one sensory modality to another is important to understand because it changes the predictive outcomes of speed of processing behaviour For instance, the Colavita effect demonstrates that responses to the simultaneous presentation of visual and auditory or tactile stimuli are biased towards visual information in adults (Koppen, Levitan, & Spence, 2009; Posner, Nissen, & Klein, 1976; Rock & Victor, 1964). Furthermore, use-dependent plasticity in certain modalities might cause structural changes in the development of specific neurons to increase firing efficiency. Thus, the speed of processing capabilities of neurons that are used would be disproportionately

faster for that modality. Tasks probing the same sensory modality would see a correlation in speed for simple and choice reactions because they share a common network with the same speed of processing capabilities. This is evident in certain populations such as video game players and musicians who are required to frequently respond to visual or auditory stimuli and develop a 'specialized' ability for processing visual stimuli relative to other modalities resulting in faster reactions (Dye, Green, & Bavelier, 2009; Landry & Champoux, 2017). Finally, adaptation to sensory impairment also illustrates the unique development of sensory processing. Individuals with congenital deafness compensate for their lack of auditory stimuli processing by using areas Heschl's gyrus to process other intact senses such as somatosensation or vision (Finney, Fine, & Dobkins, 2001; Karns, Dow, & Neville, 2012). The interpretation of performance on a given task can only be expected to extend to other tasks of the same modality and the interpretation of performance of one modality may tell a different story than performance on another modality. As a result, despite efforts to correlate tactile and visual reaction times, direct comparisons between different modalities may be difficult to assess because of the independent development of their respective processing networks. Further research is required to determine how specific trait variables may have separate influences on modality-specific processing.

4.4 Genetic variability

The within subject consistency of reactions times across days and across some task conditions (e.g. simple versus choice) led indirectly to the view that there may exist important trait specific determinants of reaction time. This was further explored by conducing a preliminary investigation into the relationship between reaction time and specific genetic

variants that may be associated with neural speed of processing. The results did not support the hypothesis of the proposed relationship between APOE and COMT variants and reaction time for this specific study and sample population. In addition, the related hypothesis of the association between conduction velocity of the ulnar nerve and APOE variant was not supported in this study.

There are several possible explanations for the absence of a relationship. First, the small sample size undoubtedly limits the interpretation of the results but may serve as a guide for future research into the genetic contributions of speed of processing. Therefore, non-significant results from this work should not be interpreted as an indication of a reduced role of genetics in driving reaction time. Typically such studies require samples on the scale of hundreds of participants (Saville et al., 2014; Stefanis et al., 2005; Szekely et al., 2011). A second explanation for an absence of association is that these specific variants do not relate to speed of processing. The current experiment chose to analyze genes that were 1) known to be associated with cognitive function and 2) related to potential synapse and conduction time changes. It was hypothesized that APOE's function as related to conduction velocity would impact speed of processing where the e4 variant would result in slower reaction times across tasks. It was also proposed that COMT's function in metabolizing dopamine would have an effect on synapse time and the val/val variant, which results in increased dopamine metabolization would be associated with slower RTs compared to the met/met variant. While there was no statistical significance it is interesting to note however that the met/met variant was faster in tactile tasks compared to the met/val and val/val variants. This trend is in line with previous research that suggests met/met carriers perform better in cognitive tasks that do not

test for response inhibition (Saville et al., 2014; Stefanis et al., 2005). Biologically, more dopamine present in the frontal cortex for met/met carriers would suggest more neurotransmitter readily available at the synapse, increasing the membrane potential leading to less time needed to reach action potential threshold. In contrast, this mechanism would lead to more errors in a response inhibition paradigm where the intent is to withhold a response. Therefore, it is important to consider the stimulus-response relationship of any task when attempting to relate processing performance to any gene.

Genetic variation found between individuals can facilitate our understanding of the biological mechanisms that determine an individual's unique speed of processing capabilities. From a single nucleotide polymorphism, the function and properties of our central nervous system can be altered. The fundamental physiology of conduction velocity and synapse time that mediate speed of processing can be revealed behaviourally as reaction time performance. The role of our genetic blueprint, although not a major objective for the present work, was an important exploratory interest in understanding the potential biological mechanisms that influence reaction time. The preliminary findings warrant further investigation through the recruitment of more subjects.

It was also found that ulnar nerve conduction velocity was not associated with RT, suggesting that at least peripheral CV does account for much of the differences in between subject differences in reaction time. The current study relied on peripheral conduction velocities due to accessibility and speculation that peripheral CV would reflect central CV. In reality, some of the processes linked to the production and development of myelin may differ for oligodendrocytes and Schwann cells (Brinkmann et al., 2008). Future work may consider a

more direct method for measuring central conduction velocities using transcranial magnetic stimulation (TMS)(Fietzek et al., 2000; Samii, Luciano, Dambrosia, & Hallett, 1998). Central conduction velocity would be obtained by calculating the difference between the latency of a motor evoked potential elicited by TMS and the approximated peripheral conduction time from the muscle to the spinal cord

Furthermore, it may also be argued that variability in processing speed may be less attributed to conduction time and more to synapse time. The earlier sections of this thesis described conduction time and synapse time as the two fundamental processes that determine reaction time. However, the proportion of reaction time performance associated with synapse time is greater than conduction time. The conduction velocity of an alpha motor neuron measures at 72-100 m/s (Kandel 2013). Therefore, the time it takes for a motor neuron to activate a muscle in the foot 1 meter away takes approximately 10-13 ms. While the conduction velocity in the brain is slower due to the smaller diameter of CNS axons (Aboitiz et al. 1992, Liewald et al. 2014), the distance an electrical signal has to travel within the brain is shorter. Furthermore, connections between neurons require chemical synaptic transmission that result in delays ranging from 0.3ms – 2 ms in mammals (Yamada 1992, Bennett 2004, Kandel 2013) and relative would be expected to be larger relative to the conduction time of the respective axon.

There are a number of other candidate genes that may be associated with reaction time performance in addition to ones proposed in this work. For instance, the brain derived neurotrophic factor gene (BDNF) and the kidney and brain associated protein (KIBRA) were also genotyped in this study but were not included in the primary analysis because their association

with reaction time was not as strongly supported as APOE and COMT. Nonetheless, one of the roles of BDNF is to support synaptic plasticity and the development and growth of neurons (Huang & Reichardt, 2001). Its role in cognition may be an indication that it is related to speed of processing as well. Specifically, the Val66Met polymorphism has been reported to be related to memory and learning where the Met allele was associated poorer memory performance (Michael F. Egan et al., 2003) and a more rapid decline in cognitive abilities for Alzheimer's patients (Boots et al., 2017) and older adults (Ghisletta et al., 2014). KIBRA's interaction with various other proteins in the central nervous system has also been reported to be associated with memory recall. Studies investigating the single nucleotide polymorphism rs17070145 have found that the T allele is related to better performance on memory recall tasks (Kauppi, Nilsson, Adolfsson, Eriksson, & Nyberg, 2011; Papassotiropoulos et al., 2006).

4.4.1 Epigenetics influence

In addition to the influence of single nucleotide polymorphisms, the role of epigenetics adds another layer to the biological determinants of speed of processing behaviour. The epigenome refers to the modulation of DNA gene expression through histone modifications and DNA methylation that result in a facilitation or suppression of gene transcription. So while the specific DNA sequence is fixed, the epigenome is much more dynamic and can be altered based on certain environmental factors. For instance, rats who were given high frequency of licking and grooming (high LG) by their mothers within the first week of being born were shown to have an altered epigenome at the glucocorticoid receptor in the hippocampus compared to rats who received a low frequency of licking and grooming (low LG) (Weaver et al., 2004). This result is linked to a decrease in DNA methylation of the glucocorticoid receptor promotor region.

Behaviourally, high LG rats responded to stress with lower hypothalamic-pituitary-adrenal activity compared to low LG rats, suggesting that that maternal behaviour has the ability to modify behaviour through epigenetic changes. Similarly, a growing body of literature suggest that gene expression as a result of environmental factors through epigenetic mechanisms are important (Franklin & Mansuy, 2010; Zhang & Meaney, 2010) and may have profound impact on cognitive development (Fagiolini, Jensen, & Champagne, 2009; Gräff & Mansuy, 2009). Furthermore, differences in speed of processing have even been related to the efficiency of DNA methylation in children (Voelker, Sheese, Rothbart, & Posner, 2017). Future research will be challenged with exploring the link between specific environmental factors and cognitive health. The implications of understanding the epigenome has the potential to dictate our behaviour despite what our DNA sequence might say. Clinically, the profile an individual, including environmental interactions and diet choices can serve as a biomarker that is equally as important as genotyping DNA samples for speed of processing related risk assessment. Identification of these biomarkers are important for informing preventative interventions such as drug therapy and lifestyle changes.

4.5 The utility of distribution analysis

Reaction time data is commonly represented using central tendency measures that describe the entire distribution of data points. Statistics such as the mean and median are valuable in describing scores that occur near the middle of the distribution. Typical dispersion metrics such as the standard deviation also aim to describe the entire distribution by indicating the spread of these scores. However, examining the different parts of the distribution as

separate units may be worthwhile in providing more in-depth interpretation into speed of processing.

Despite the results pointing to a high intra class correlation of mean reaction time, there were still certain individuals that appeared to perform inconsistently day-to-day, possibly masked by the large between subject variability given the limitations of ICC as described in **Section 4.2**. Therefore, a secondary informal analysis was conducted to better understand why these individuals appeared to vary more than others. Five participants from each task with the largest difference between days were analyzed to see how different parts of the distribution changed. This analysis revealed that there are various distributions that can lead to changes in central tendency each having a different impact on our interpretation of speed of processing mechanisms. This type of analysis allows for the examination of the biological significance of different portions of the distribution. Rather than treating the entire distribution of individual trials as coming from the same source, the best performance and worst performance may be indicative of different speed of processing mechanisms. The first is characterized by a larger shift in the slowest trials driving the reaction times changes. This mechanism may be indicative of moment-to-moment state changes that more frequently alter the slowest reactions without altering the best performance level. Therefore, changes in mean reaction time from day to day were due to a few aberrant trials. In fact, previous studies have linked the worst performance on cognitive tasks as a better predictor of variables such as general intelligence (Larson & Alderton 1990, Baumeister & Kellas, 1968). The neurophysiological causes for changes in the slowest reactions may be a result of lapses in attention influencing reaction time performance, similar to the mechanisms described above by Weissmann (2006). From the perspective of the

LATER model Noorani and Carpenter (2003) attributes the slower reactions as a change in the rate of rise for a decision signal. In agreement with the model, evidence from single trial magnetoencephalography signals from motor cortical areas relate the slope of the signal preceding a motor response as being co-varied randomly with the variability of reaction times (Smyrnis et al., 2011). In other words, the variability of trial to trial reaction time was explained by the rate of rise of a pre-motor signal. It is possible that the large increase in reaction time from one day to another is explained by larger lapses in attention moment-to-moment on a particular session. The second is characterized by a seemingly equal shift in both the fastest and slowest trials driving these changes. This pattern indicates that the large difference in mean performance from day to day were driven by changes in reactions from both the fastest and slowest parts of the distribution. Changes in both parts of the distribution may be explained by motivation of individuals to respond as quickly as possible. In particular, it has been shown that trial to trial variability can be reduced by providing feedback on an individual's performance (Garrett, MacDonald, & Craik, 2012). While participants in the present study were instructed to respond as quickly as possible, there was no consequence or feedback for delayed responses which may lead to increased variability in the fastest reaction times. This pattern reinforces the potential impact that state factors can have on the reliability of reaction time.

4.6 Conclusions

The overarching purpose of this work looked to develop a better understanding of the factors that account for between subject differences in reaction time. In summary, the results indicate that mean reaction time is: stable day-to-day for a variety of tasks, generalizable within a modality. This study did not support an association in performance with with APOE or COMT

alleles. However, it is important to note that there are considerable state factors contributing to reaction time as evident when looking at both within subject day to day differences and trial to trial variability. Furthermore, reaction time expression may reveal separate underlying sources of variability than central tendency measures.

Similar to previous findings in pilot results, this experiment shows considerable range of between subject performance across all tasks even after subjects have been familiarized with the tasks in a practice session, reducing the likelihood of any learning effects influencing the results. Relative to between subject variability he stability of within subject reaction time is upheld for tasks that present stimuli in different modalities (visual and tactile) as well as for tasks with varying difficulty (simple and choice) indicating the involvement of person-specific, time stable factors.

In regards to the generalizability of reaction time, there appears to be a strong association between reaction time in tasks that are of the same modality. Cross-modal comparisons however, do not display the same relationship and is perhaps indicative of stimulus intensity variability or independent speed of processing characteristics for each modality.

A larger number of participants is required to more confidently interpret the relationship that APOE and COMT alleles may serve as factors that influence conduction time and synapse time. In addition, utilizing peripheral nerve conduction velocity may not provide an accurate representation for conduction time of central processing speed.

Analyzing different components of the reaction time distribution (e.g. slowest and fastest trials) helped to better understand how certain individuals may vary greatly from one

day to another that was not captured by central tendency measurements. The large range of reaction times seen within an individual's distribution may be as revealing than traditional central tendency measurements in terms of understanding between subject differences. The separate sources for the variability in different parts of the distribution may be a topic for future studies to investigate.

The outcomes of this work indicate the ability for reaction time to be used as a biomarker that reflect the stable, person-specific factors of CNS speed of processing. Monitoring reaction time performance across the lifespan, in addition to tracking relevant person-specific factors could potentially assist in the prediction of injury risk associated with deficits in speed of processing. However, because of the differences in performance across modalities shown in this work, deciding the characteristics of a task that best predict the intended outcome will be a topic for future investigation. Moving forward, it will also be critical for future studies to examine strategies to 'train' speed of processing in individuals to improve performance once deficits have been identified. Finally, rather than ignoring variability measurements that may be conventionally viewed as biological noise, it is important to embrace the mentality that these expressions of performance may deepen our understanding of the nature of the speed of stimulus-evoked behaviour.

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