The effects of stress on working memory, inhibitory gating, and motor symptoms in Parkinson's disease

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The effects of stress on working memory, inhibitory gating, and motor symptoms in Parkinson’s disease

by

Andrew Zaman

A dissertation proposal submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Co-majors: Kinesiology; Psychology

Program of Study Committee:
Elizabeth Stegemöller, Co-major Professor
Christian Meissner, Co-major Professor
Laura Ellingson-Sayen
Jon Kelly
Daniel Russell
Ann Smiley-Oyen

The student author, whose presentation of the scholarship herein was approved by the program of study committee, is solely responsible for the content of this dissertation. The Graduate College will ensure this dissertation is globally accessible and will not permit alterations after a degree is conferred.

Iowa State University
Ames, Iowa
2020

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ACKNOWLEDGMENTS

I would like to thank my major professors, Elizabeth L. Stegemöller and Christian Meissner, whose continued support and mentorship has been unwavering and exemplary. I would also like to thank the other committee members, Laura Ellingson-Sayen, Jon Kelly, Daniel Russell, and Ann Smiley-Oyen, for all of their time, effort and mentorship throughout the course of my doctoral education at Iowa State University. I would also like to thank Elizabeth (Birdie) Shirtcliff, and Kimberley Greder, members of the ISU faculty who taught and supported me throughout this process.

In addition to the committee members, I would like to thank my parents. Frederick and Virginia Zaman, your compassion and support have allowed me to pursue my passions and this degree. I would also like to thank my fellow lab mates and friends for their emotional and academic support: Cydney Lacour who is my best friend and emotional rock, Kassandra Diaz, Jennifer Uzochukwu, and many more. I am grateful for the department of Kinesiology who has created an encouraging atmosphere that breeds success, especially Jo Ellyn Burdick and Frances Sobotka.

Finally, I would like my fiancée and soulmate Dr. Patricia Izbicki. Thankfully, some of her genius, compassion, and hard work have rubbed off on me. She makes me a better human in every way. I am so lucky and grateful to have met her, and to have been able to do my doctoral work alongside her. I am excited to see what the next chapter brings for both of us.
ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder in which the substantia nigra has suffered a severe amount of cell loss, resulting in basal ganglia dysfunction. The defining motor symptoms of PD are tremor, rigidity (stiffness of the limbs and trunk), bradykinesia (slow movements), and postural instability (impaired balance). Persons with PD also have a number of non-motor symptoms such as anxiety, depression, autonomic dysfunction, cognitive impairment, and deficits in sensory processing. Currently, there is a gap in our knowledge about how stress affects persons with PD. Anecdotally, many people with PD report that their symptoms get worse when they are stressed. However, there is only indirect and anecdotal evidence for persons with PD. Thus, the purpose of this study was to examine how stress affects motor and non-motor symptoms in persons with PD.

Fifteen persons with PD and fifteen healthy older adults were recruited for the study. We measured how an acute stressor (socially evaluated cold pressor) affected working memory (digit span tasks), sensory processing (inhibitory gating), and PD motor symptoms (UPDRS motor tests). Results showed that stress appears to have differential effects in persons with PD. In persons with PD, stress negatively impacted inhibitory gating and PD motor symptoms. However, stress had positive effects on working memory. The results also suggest that inhibitory gating is associated with PD motor symptom severity, and, thus, inhibitory gating may be a potential therapeutic target. This research provides a first step in understanding how stress impacts persons with PD. Overall, the work of this dissertation suggests that acute stress is a useful tool in understanding PD, and that stress management may be an effective therapy for managing PD motor symptoms.
CHAPTER 1. GENERAL INTRODUCTION

1.1 General Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that is characterized by severe cell death of the substantia nigra (one of the brain’s main source of dopamine). The defining motor symptoms of PD are tremor, rigidity (stiffness of the limbs and trunk), bradykinesia (slow movements), and postural instability (impaired balance). These symptoms are most noticeable in well-learned, habitual behaviors such as walking, handwriting, speaking, and eating (Redgrave, et al., 2010). In addition to the cellular loss in the substantia nigra, persons with PD also have substantia neuronal loss in other regions such as the locus coureloous (LC), a primary sources of norepinephrine (Vermeiren & De Deyn, 2017). Both dopamine and norepinephrine have an inverted-U relationship with cognitive functioning, sensory processing, and motor functioning (Arnsten, 2009; Cools, 2006; Jacob & Nienborg, 2018; Vazey & Aston-Jones, 2012; Waterhouse & Navarra, 2019), and persons with PD display non-motor symptoms, such as cognitive dysfunction and sensory processing deficits (Dirnberger & Jahanshahi 2013; Kudlicka, Clare, & Hindle, 2011; Patel, Jankovic, & Hallett, 2014). Anecdotally, many individuals with PD report that stress makes their symptoms worse, but this has not been empirically tested.

Stress causes an acute increase in dopamine and norepinephrine release in the cortex and basal ganglia (al’Absi, Petersen, & Wittmers, 2002; Finlay, Zigmond, & Abercrombie, 1995; Gresch, Sved, Zigmond, & Finlay, 1994; Imperato, Puglisi-Allegra, Casolini, & Anelucci, 1991; Kim, Choi, Change, Kim, & Hwang, 2005; Morrow, Roth, & Elsworth 2000; Nater, et al., 2006; Scott, Heitzeg, Koepppe, Stohler, & Zubieta, 2006; Thoma, Kirschbaum, Wolf, & Rohleder, 2012). In healthy individuals, stress negatively impacts cognitive (Arnsten, 2009; Eysenck & Calvo, 1992; Eysenck, Derakshan, Santos, & Calvo, 2007), sensory (Easterbrook, 1959; Johnson...
Adler, 1993; White & Yee, 1997), and motor functioning (Duffy, 1957; Nibbeling, Oudejans, & Daanen, 2012; Weinberg & John, 1978; Wilson, Vine, & Wood, 2009a; Wilson Wood, & Vine, 2009b). What remains unknown is how stress impacts persons with PD, individuals whose levels of dopamine and norepinephrine are critically lower than levels found in healthy individuals.

In addition to the complex neurotransmitter interactions that come with stress and having PD, there may also be complex interactions between the affected processes (cognitive, sensory, and motor) in persons with PD. For example, sensory processing deficits may contribute to motor symptoms and motor performance impairments in persons with PD (Conte, Khan, Defazio, Rothwell, & Beradelli, 2013; Konczak, et al., 2009; Müller, et al., 2013). It is also hypothesized that persons with PD use goal-directed cognitive processes to moderate and reduce motor performance impairment (Morris, Iansek, Summer, & Matyas, 1995; Redgrave, et al., 2010). If stress negatively impacts cognitive and sensory processes in persons with PD, then stress may also affect motor symptoms indirectly by impacting those processes.

The purpose of this study is to examine the effects of stress on persons with PD. In order to induce stress for each of the four aims, participants completed a socially evaluated cold pressor (SECP) task. The participants placed their hand in cold water (2-4⁰C) for 90 seconds while having their responses video recorded to be judged at a later time (Schwabe, Haddad, & Schachinger, 2008). Aim 1/Experiment 1 examined the effects of stress on cognitive functioning, specifically working memory, by using the digit span forward and backward. Participants listened to strings of digits and then enter the digits into a computer in the original (forward) or reverse (backward) order. I hypothesized that stress would impair working memory in both healthy older adults and persons with PD. Aim 2/Experiment 2 examined the effects of stress on
sensory processing by using the paired-click paradigm. Participants listened to identical pairs of auditory stimuli while electroencephalography (EEG) signals were recorded in order to examine p50 inhibitory gating (p50 ratio), an early sensory process. I hypothesized that stress will decrease inhibitory gating in both older adults and persons with PD. Aim 3/Experiment 3 examined the effects of stress on PD motor symptoms, specifically hypokinesia, bradykinesia, and tremor. Electromagnetic position sensors recorded participants completing the United Parkinson’s Disease Rating Scale (UPDRS) motor tests (i.e., finger tapping, hand movements, pronation-supination of the hand, postural tremor, and resting tremor). I hypothesized that stress would result in an increase in motor symptoms in persons with PD, but not in healthy controls. Aim 4/Experiment 4 examined stress related changes in motor symptoms (using the UPDRS motor tests) with changes in working memory (digit span backward) and p50 inhibitory gating (p50 ratio) using a repeated measures correlation in persons with PD. I hypothesized that the worsening of motor symptoms would be associated with an increased impairment in working memory, and inhibitory gating.

1.2 Parkinson’s Disease

Parkinson’s disease (PD) is a neurodegenerative disorder in which the substantia nigra pars compacta has suffered significant dopaminergic neuronal loss (~80%). The substantia nigra pars compacta is a distinct nuclei region in the basal ganglia which produces dopamine. The cardinal symptoms of PD are tremor, bradykinesia (slow movement), hypometria (small movement), rigidity (stiffness), and postural and gait instability. As the basal ganglia is heavily involved in motor automaticity, the most impacted motor skills are well-learned, habitual behaviors such as walking, handwriting, and speaking. (Redgrave, et al., 2010).
The traditional view of PD assumes that motor and non-motor symptoms arise out of neurodegeneration of dopaminergic cells in the substantia nigra. However, there is increasing evidence that suggests PD pathophysiology includes neurodegeneration in brain stem regions that precede substantia nigra degeneration, including the olfactory bulb, anterior olfactory nucleus, raphe nucleus, locus coeruleus, and pedunculopontine nucleus (Braak, et al., 2003; Chaudhuri, Healy, & Schapira, 2006; Seidel, et al., 2015). During the early stages of the disease secondary symptoms are present but unnoticed as PD before the cardinal motor symptoms present. These early secondary symptoms include loss of smell, fatigue, sleep disorders, and autonomic dysfunction. In the later stages after the cardinal motor symptoms present, lewy bodies and neurodegeneration in limbic and cortical structures are present, which leads to an increase in cognitive and emotional problems (Braak, et al., 2003; Chaudhuri, et al., 2006; Horvath, Herrmann, Burkhard, Bouras, & Kövari, 2013; Surmeier, Obeso, & Halliday, 2017). Cognitive and emotion problems include depression (Forsa, Larsen, Wentzel-Larsen, Herlofson, & Alves, 2008; Reijnders, Ehrt, Weber, Aarsland, & Leentjens, 2008), anxiety (Nuti, et al., 2004; Pontone, et al., 2009), impulsive behaviors (Weintraub, et al., 2010), mild cognitive impairment and generalized cognitive decline (Dirnberger & Jahanshahi, 2013). Thus, the underlying pathophysiology of PD is complex and involves many brain regions which explain both the motor and non-motor symptoms. The following sections will focus on the basal ganglia architecture and basal ganglia pathophysiology of PD.

1.2.1 Parkinson’s Motor Symptom Pathology

The basal ganglia is well-known for its role in motor control and PD. The basal ganglia is involved in selecting and implementing movement patterns via inhibition of unwanted motor
programs (programs stored in thalamocortical and brainstem structures) and activation of desired motor programs (Mink, 1996). The basal ganglia is grouped into subcortical nuclei that include the putamen, dorsal striatum (caudate nucleus and putamen), ventral striatum (nucleus accumbens and olfactory tubercle), globus pallidus, subthalamic nucleus, and substantia nigra (pars compacta and pars reticulata). Together, the basal ganglia and its associated structures receive cortical inputs through the striatum. Specifically, the striatum receives input from the substantia nigra pars compacta and the ventral tegmental area. The striatum is the beginning of the “direct” and “indirect pathways. The “direct” pathway striatal neurons project directly to the output nuclei (globus pallidus internal and substantia nigra pars reticulata) to regulate behavior via disinhibition. The “indirect” pathway striatal neurons project to the globus pallidus external, which project to the subthalamic nucleus and then finally to the output nuclei to inhibit unwanted behavior/motor programs.

The classic basal ganglia model of PD is shown in Figure 1.1 (Delong, 1990; Albin, Young, & Penney, 1989). In firing rate model of PD, the loss of dopamine in the SNc causes an imbalance between the direct and indirect pathways and leads to higher firing rates of neurons in the globus pallidus internal, resulting in excessive inhibition of the thalamus and motor areas of the frontal cortex. (Albin, et al., 1989; Alexander & Crutcher, 1990; Delong, 1990; Smith, Bevan, Shink, & Bolam, 1998). Overall, the mean firing rates of the basal ganglia output nuclei result in hypokinetic or hyperkinetic movement disorders (Delong, 1990; Albin, et al., 1989).

One criticism of the firing rate model however, is that the model doesn’t explain symptoms such as rigidity and tremor (Nambu, Tachibana, & Chiken, 2015). Another finding that is inconsistent with the model is that lesions of the different pathways (direct and indirect) and the thalamus do not create the impairments that the model would predict. For example, inactivation of the globus
pallidus internal (the main output nuclei) does not induce severe motor deficits or involuntary movements (Desmurget & Turner, 2008; Inase, Buford, & Anderson, 1996). Instead, inactivation of the globus pallidus internal eliminates only dyskinesias (Baron, et al., 1996). Similarly, thalamus inactivation does not produce akinesia and instead reduces PD symptoms (Bhatia & Marsden, 1994). Thus, some rethinking of the firing rate model was needed, which lead to the firing pattern model.

The firing pattern model of PD suggests that the loss of dopamine disrupts the normal oscillatory patterns and synchronization between neuron, leading to disruption of information processing in the basal ganglia (Bergman, et al., 1998; Bevan, Magill, Terman, Bolam, & Wilson, 2002; Brown, 2003; Hammond, Bergman, & Brown, 2007; Wichmann & Delong, 1996). In PD bursts or a series of rapid neuronal firings happen in a short period of time and cause synchronized oscillatory activity in the low frequency range, and this synchronized oscillatory activity is associated with PD motor symptoms (Bergman, Wichmann, Karmon, & Delong, 1994; Brown, 2003; Levy, Hutchison, Lozano, & Dostrovsky, 2000; Heimer, et al., 2006; Raz, Vaadia, & Bergman, 2000; Tachibana, Iwamuo, Kita, Takada, & Nambu, 2011). Furthermore, PD medication and inactivation of the subthalamic nucleus disrupts the abnormal oscillatory patterns and reduces PD motor symptoms (Heimer, et al., 2006; Tachibana, et al., 2011; Wichmann, Bergman, & DeLong, 1994). Finally, synchronized oscillatory patterns in the high gamma frequencies (>60 Hz) which are thought promote movement, are reduced in persons with PD and improve with Parkinson’s medication (Brown, 2003; Brown & Williams, 2005). Overall though, both the firing rate and firing patterns of the basal ganglia contribute to the PD motor symptoms (Beradelli, Rothwell, Thompson, & Hallet, 2001).
Figure 1.1. The classic basal ganglia model of Parkinson’s adapted from Delong 1990 (McGregor & Nelson, 2019). The classic model (left) highlights the role of dopamine on the direct and indirect pathways. In the healthy condition (right), dopamine (blue) from the SNc (substantia nigra pars compacta) to the striatum activates the direct pathway (green) and inhibits the indirect pathway (right). In the PD model (left), loss of SNc dopamine causes hypoactivity of the direct pathway and hyperactivity of the indirect pathway, as a result there is increased inhibition of the thalamus and cortex and a suppression of movement. Figure reproduced with permission from the authors.

1.2.2 Basal Ganglia Loops and Interactions in Persons with PD

While the basal ganglia is critically involved in implementing movement patterns (Mink, 1996), it is also involved in a number of other processes as well. The basal ganglia receives information not just from cortical motor areas but from almost every cortical region. The
information is then processed in parallel and projected back to the thalamus and cortex, ultimately, forming functionally distinct loops (Alexander, DeLong, & Strick, 1986) shown in Figure 1.2. The basal ganglia is divided into three major functional loops: the sensorimotor loop, the associate loop, the limbic loop. The sensorimotor loop is thought to be more involved in motor skill learning/motor automaticity and implicit learning (Hikosaka, Nakamura, Sakai, & Nakahara, 2002; Miyachi, Hikosaka, & Lu, 2002; Redgrave, et al., 2010). The associative loop initiates and control goal-directed actions, which are often observed earlier in the skill and motor learning process (Miyachi, et al., 2002; Redgrave, et al., 2010). The limbic loop is heavily involved in processes related to learning, emotion, motivation, and reward (Cardinal, Parkinson, Hall, & Everitt, 2002). Another loop not shown in Figure 1.2, is the oculomotor loop which helps to control eye movements and maintain visual stability. In PD, the loss of dopamine is greatest in the posterior putamen and the sensorimotor loop (Pavese & Brooks, 2009), and thus persons with PD have dysfunction in motor automaticity and implicit learning (Redgrave, et al., 2010).

![Parallel Circuit Model of the Basal Ganglia](image)

Figure 1.2. Parallel Circuit Model of the Basal Ganglia (McGregor & Nelson, 2019). Sensorimotor (blue), associative (purple), and limbic (green) information from excitatory (arrows) cortical inputs are distributed in parallel to regions of the striatum. Anatomical separation of these channels is preserved in the basal ganglia. This figure shows an example, inhibitory projections (flat arrows) from sensorimotor striatum innervate sensorimotor regions of
the globus pallidus internal (GPI) through the direct (Globus Pallidus external (GPe)) or indirect (subthalamic nucleus (STN)) routes. Projections from the globus pallidus internal innervate the motor thalamus, and then project back to the sensorimotor regions of the cortex. Not shown is the oculomotor loop. Figure reproduced with permission from the authors.

The basal ganglia loops are often considered to be independent and parallel-projecting, but there is evidence to suggest more connectivity between these loops than previously thought (Joel & Weiner, 1994; Simonyan, 2019) and persons with PD may compensate for damage in the sensorimotor pathway by utilizing the associative pathway (Figure 1.3), (Redgrave, et al., 2010). The evidence suggests that persons with PD can compensate for impairments in motor performance by directing attention towards movements and using “goal-directed” executive control (Morris, et al., 1995; Morris, Iansek, Matyas, & Summers, 1994; Morris, Iansek, Matyas, & Summers, 1996). Stress negatively affects these goal-directed and sensory motor processes however, and thus may impact persons with PD differently. In the following section we will discuss how stress impacts neurotransmitter release and functioning in both the associative and sensorimotor loops.

1.3 Stress

Selye (1956) defined stress as the non-specific response of the body to any demand for change. Laboratory studies of acute stressors include physical stressors (i.e. prolonged exercise and electrical shock), psychological stressors (i.e. public speaking and mental arithmetic), and physical-psychological stressors (i.e. SECP) (Dickerson & Kemeny, 2004). The first wave of the acute stress response includes a rapid release of neurotransmitters (norepinephrine and dopamine) and hormones (corticotropin-releasing hormone and adrenocorticotropic hormone). These neurotransmitters and hormones increase sympathetic arousal, energy mobilization, cardiovascular tone, heart rate, arousal, and blood flow to the brain (Sapolsky, Romero, & Munch, 2000). Within a few minutes, the second wave of the acute stress response begins and
glucocorticoids (cortisol in humans) are released. Glucocorticoids regulate and modulate the actions of the first wave (see Sapolsky, et al., 2000).

Figure 1.3. Functional and Dysfunctional Loops Through the Basal Ganglia in Persons with Parkinson’s Disease (Redgrave, et al., 2010). Sensory information is received by both the goal-directed (associative loop) and stimulus-response habitual control (sensorimotor loop) systems. The goal directed and habitual control systems are independent and each can direct behavioral output via ‘final common motor pathways’ (Yin, Knowlton, & Balleine, 2004; Yin, Knowlton, & Balleine, 2005; Yin, Knowlton, & Balleine, 2006). While there are many brain regions where information from the two systems can converge, two are shown at the level of cortical motor output, and the brainstem. In PD, the loss of dopamine in the sensorimotor pathway (shown by the red cross) disrupts normal processing (shown by lightning symbols). It is suggested by Redgrave and colleagues (2010), that the disruption in the sensorimotor pathway, causes persons with PD to rely more heavily on the associative pathway. Figure reproduced with permission from the authors.
Overall, the rapid release of neurotransmitters in large amounts from acute stress starts to shut down and impair the associative loop, while upregulating sensorimotor loops (Arnsten, 2015; Lupien, McEwen, Gunnar, & Heim, 2009). This leads to impairments in goal-oriented processes such as attention, working memory, and executive functioning (Eysenck, et al., 2007). Conversely, upregulation of sensorimotor loops could potentially affect PD motor symptoms. In the following subsections, how stress influences neurotransmitters and neurohormones as well as the functioning of various regions of the brain related to the associative and sensorimotor loops will be reviewed.

1.3.1 Stress and Norepinephrine

Norepinephrine is one of the primary neurotransmitters released during the first wave of the acute stress response. Norepinephrine is primarily thought to modulate arousal levels, but is also involved in attentional and sensory related processes (Berridge & Waterhouse, 2003). The primary nuclei involved in producing and distributing norepinephrine is the locus coeruleus (LC). The LC distributes norepinephrine to a wide range of cortical regions and basal ganglia structures including substantia nigra, subthalamic nucleus, striatum as well as cortical regions involved in the associative and sensorimotor loops such as the thalamus, somatosensory cortex, primary motor cortex, prefrontal cortex, anterior cingulate (Aston-Jones & Waterhouse, 2016; Aston-Jones & Cohen, 2005; Benarroch, 2009). LC neurons have two modes of firing: a phasic mode and a tonic mode. The phasic mode of firing recruiters the α2 receptors, which typically have an inhibitory effect, while the tonic mode of firing release higher amounts of norepinephrine and recruit the lower affinity α1 receptors which have an excitatory effect (Waterhouse, Devilbiss, Fleischer, Sessler, & Simpson, 1997).
Acute physical and psychosocial stressors cause large increases in norepinephrine, (al’Absi, et al., 2002; Atterhög, Eliasson, & Hjemdahl, 1981; Nater, et al., 2006; Thoma, et al., 2012), which causes the release of high levels of norepinephrine via the tonic mode of firing (Abercrombie & Jacobs, 1987; Valentino & Foote, 1988). These stressors cause an even greater increase of norepinephrine in older adults (Palmer, Ziegler, & Lake, 1978). In contrast, persons with PD may however release less norepinephrine during stressors such as the cold-pressor (Shoulson, Glaubiger, & Chase, 1975), and exercise stress tests (DiFrancisco-Donoghue, Elokda, Lamberg, Bono, & Werner, 2009).

1.3.2 Stress and Norepinephrine in the Associative Loop

Overall effects of norepinephrine on the associative loop and prefrontal goal-directed processes follow an inverted U-shaped curve (Figure 1.4) (Arnsten, 2011; Aston-Jones, Rajkowski, & Cohen, 1999). Low levels of norepinephrine are associated with drowsiness while high levels are associated with attentional distractibility and anxiety.

The effects of norepinephrine agonists and antagonists demonstrate the importance of the neurotransmitter on cognitive functioning, specifically working memory. In animals, depletion of norepinephrine has been shown to impair working memory (Arnsten & Goldman-Rakic, 1985; Li & Mei, 1994), and a1 agonists impair working memory performance (Arnsten, 2011; Arnsten & Jentsch, 1997; Arnsten, Mathew, Ubrian, Taylor, & Li, 1999). Norepinephrine agonists of α2 receptors, on the other hand, improve working memory performance (Arnsten & Goldman-Rakic, 1985; Cai, Ma, Xu, & Hu, 1993; Mao, Arnsten, & Li, 1999). In humans, similar results have been revealed. Agonists of α2 receptors has also been shown to improve working memory performance (Jäkälä, et al., 1999; Swartz, McDonald, Patel, & Torgersen, 2008). As previously described, when LC neurons fire in the phasic mode they recruit α2 neurons, and when they fire
in the tonic mode they start to recruit $\alpha_1$ neurons in addition to $\alpha_2$ neurons (Waterhouse, et al., 1997). All together, the evidence suggests that working memory has an inverted-U relationship with norepinephrine, where working memory is optimized when LC neurons fire in the phasic mode and recruit higher affinity $\alpha_2$ receptors, and working memory is impaired when LC neurons fire in the tonic mode and recruit lower affinity $\alpha_1$ receptors.

Stress results in impaired cognitive functioning by pushing norepinephrine out of the optimal zone in the inverted U-shaped curve (Figure 1.4) (Arnsten, 2011; Aston-Jones, et al., 1999; Berridge & Spencer, 2016; Gamo, Wang, & Arnsten, 2010), by releasing high levels of norepinephrine via the tonic mode of firing (Valentino & Foote, 1988). The high levels of norepinephrine released during stress stimulates $\alpha_1$ receptors and impairs working memory performance, but working memory is then ameliorated by $\alpha_1$ antagonists (Birnbaum, Gobeske, Auerback, Taylor, & Arnsten 1999). In short, stress increases norepinephrine and as a result impairs working memory.

In persons with PD, it has been suggested that cognitive dysfunctions are a result of low norepinephrine levels (Vazey & Aston-Jones, 2012) due to LC neurodegeneration (Braak, et al., 2003). While relatively uninvestigated, some studies have shown that increasing norepinephrine improved clinical global impression scales of cognition in PD (Marsh, Biglan, Gerstenhaber, & Williams, 2009; Weintraub, et al., 2010). However, it is unknown if stress will actually improve cognitive functions, specifically working memory, by modulating levels into an optimal zone or if stress will increase norepinephrine enough to recruit $\alpha_1$ receptors and impair cognition.

Another important factor to consider is the relationship between dopamine and the associative circuit and the effect stress has on dopamine release in the prefrontal cortex. This will be reviewed in chapter 1.3.5. A more in depth review of the effects of stress on cognitive
functions such as working memory will be reviewed in chapter 1.4.3 (Stress and Working Memory).

![Figure 1.4](image).

Figure 1.4. Inverted-U Relationship Between Norepinephrine and Working Memory (Berridge & Spencer, 2016). Low rates of norepinephrine in the prefrontal cortex associated with sedation or following lesions impairs working memory. Stimulation of α2 receptors in the prefrontal cortex improves working memory. High rates of norepinephrine release associated with stress recruits lower affinity α1 receptors and impairs working memory. Blocking α1 receptors reverses stress-related working memory impairment. Figure reproduced with permission from the authors.

### 1.3.3 Stress and Norepinephrine in the Sensorimotor Loop

One of the main roles of norepinephrine is to modulate sensorimotor loop/processes (Sara & Bouret, 2012). In general, norepinephrine improves sensory processing in the primary somatosensory cortex (Waterhouse, Moises, & Woodward, 1980). Phasic firing of LC neurons improves sensory processing by increasing the signal-to-noise ratio of sensory-evoked responses via the inhibition of spontaneous firing activity in both the somatosensory cortex and the thalamus (Hirata, et al., 2006; McBurney-Lin, Lu, Zou, & Yang, 2019). High rates of discharge, however, such as those seen during stress may negatively impair sensory processes. For example,
high LC tonic firing decreases the signal-to-noise ratio due to increases of spontaneous firing in sensory areas and suppressed evoked responses (Devilbiss, Waterhouse, Berridge, & Valentino, 2012). Another sensory process disrupted by stress and large increases in norepinephrine is inhibitory gating (Johnson & Adler, 1993), a process in which repetitive information gets filtered out. Inhibitory gating will be reviewed in detail in chapter 1.5 (Inhibitory Gating).

The effect of norepinephrine on motor control is evidenced in studies of PD. Norepinephrine receptors in the basal ganglia have either an excitatory or inhibitory effect on locomotor activity, and influence PD symptoms such as tremor and rigidity (Colpaert, 1987; Delaville, Deurwaerdere, & Benazzou, 2011; Mavridis, Degryse, Lategan, Marien, & Colpaert, 1991; Schapira, 2005). In a study of Parkinson’s mice they found that norepinephrine loss was necessary to observe motor deficits (Rommelfanger, et al., 2007), and the loss of norepinephrine alone is able to produce sever motor deficits similar to those seen in PD rat models (Delaville, et al., 2010). As stress increases norepinephrine release, it is possible that stress could improve motor symptoms in persons with PD.

1.3.4 Stress and Dopamine

There are 3 main dopaminergic pathways in the brain which correspond with the 3 basal ganglia loops. The mesocortical pathway begins with dopaminergic neurons in the ventral tegmental area (VTA) which project to the prefrontal cortex of the associative loop. The mesolimbic pathway is a part of the limbic loop and consists of VTA dopaminergic neurons that project to the nucleus accumbens/ventral striatum. This pathway is typically thought to be involved in learning, emotion, motivation, and reward. The 3rd pathway is the nigrostriatal pathway which includes dopaminergic neurons of the substantia nigra pars compacta. This pathway extends to all parts of the striatum but most heavily to the dorsal striatum/sensorimotor...
loop. Acute stress increases dopamine release in prefrontal areas (Finlay, et al., 1995; Gresch, et al., 1994; Imperato, et al., 1991; Morrow, et al., 2000; Roth, Tam, Ida, Yang, & Deutch, 1988), and dopamine release from both the substantia nigra and the VTA into the nigrostriatal pathway (Keefe, DiFrischia, & Zigmond, 1989; Kim, et al., 2005; Scott, et al., 2006). Stress however appears to have a greater impact on PFC dopamine. The effects of stress on dopamine production in the striatum however are in general less than the response seen in the PFC and mesocortical pathway (Finlay & Zigmond, 1997).

1.3.5 Stress and Dopamine in the Associative Loop

Like norepinephrine, the relationship between dopamine and PFC function follows an inverted-U shaped curve and too much or too little dopamine impair PFC function (Arnsten, 2011; Cai & Arnsten, 1997; Gibbs & D’Esposito, 2006; Murphy, Arnsten, Goldman-Rakic, & Roth, 1996). Studies have demonstrated that too little or too much dopamine impairs working memory (Arnsten & Goldman-Rakic, 1990; Sawaguchi & Goldman-Rakic, 1991; Zahrt, Taylor, Mathew, & Arnsten, 1997). In persons with PD, dopaminergic agonists and precursors which are used to ameliorate motor symptoms may unintentionally exacerbate the negative effects of excessive dopamine in prefrontal regions (Li, Lindenberger, & Bäckman, 2010).

As previously mentioned, acute stress increases dopamine release in prefrontal areas (Finlay, et al., 1995; Gresch, et al., 1994; Imperato, et al., 1991; Morrow, et al., 2000; Roth, et al., 1988), and impairs PFC functioning via a hyperdopaminergic mechanism to possibly allow for a greater influence of the limbic and sensorimotor pathways (Arnsten, 2009; Arnsten & Goldman-Rakig, 1998; Deutch & Roth, 1991). In persons with PD, the combination of dopaminergic medication used by persons with PD, and stress is likely to overdose the PFC with dopamine, and result in cognitive impairments.
1.3.6 Stress and Dopamine in the Sensorimotor Loop

In chapter 1.2.1, the pathophysiology of PD and the effects of dopamine loss most heavily in the posterior putamen and sensorimotor loop was presented. As a result, persons with PD display motor symptoms such as bradykinesia, hypokinesia, rigidity, tremor, postural instability. In addition to motor symptoms, persons with PD also display impairments in sensory processes such as inhibitory gating, and impairments in tactile and proprioceptive perception (Boecker, et al., 1999, Conte, et al., 2013, Sathian, Zangaladze, Green, Vitek, & DeLong, 1997, Teo, et al., 1997; Zia, Cody, & O’Boyle, 2003). Thus, too little dopamine in sensorimotor basal ganglia regions impairs both motor and sensory processes.

On the other end of the spectrum, the effects of too much dopamine in sensorimotor pathways are demonstrated by individuals with Huntington’s disease (Garrett & Soares-Da-Silva, 1992). Individuals with Huntington’s display other types of motor impairment such as chorea (involuntary jerking or writhing movements), rigidity, impaired gait, posture, and balance, and difficulty with speech and swallowing. Individuals with Huntington’s also display abnormal inhibitory gating of sensory information (Uc, Skinner, Rodnitzsky, & Garcia-Rill, 2003), and proprioceptive impairments (Bollen, Arts, Roos, & Van Der Velde, 1985; Noth, Engel, Friedemann, & Lange, 1984; Schwarz, Block, Töpper, Sontag, & Noth, 1992). Overall, this suggests that like too little dopamine, too much dopamine impairs both motor and sensory processes. Thus, motor and sensory processes have an inverted-U shaped relationship with dopamine.

How dopamine affects motor automaticity is also of critical interest to this study. As previously noted, persons with PD demonstrate impairments in motor automaticity (Redgrave, et al., 2010; Wu, Hallet, & Chan, 2015). Conversely, increases in dopamine are associated with
increases in habitual and repetitive behaviors (Arnsten, 2015; Berridge & Aldridge, 2000; Everitt, et al., 2008). For example, increasing dopamine increases repetitive habitual behaviors such as grooming in rodents (Cooper & Dourish, 1990). In persons with PD, increases in dopamine via dopaminergic treatment are similarly associated with increases in habitual and repetitive behaviors (dopamine dysregulation syndrome) (Voon & Fox, 2007, Voon, et al., 2007). In conclusion, too little dopamine appears to impair motor automaticity, while increases in dopamine are associated with an increases in the propensity to demonstrate repetitive habitual behavior.

1.3.7 Stress and Cortisol

Acute stress increases the amount of glucocorticoids released into the blood stream (Dickerson & Kemeny, 2004; Palkovits, Baffi, & Pacak, 1999). Within a few minutes, glucocorticoids begin to act as a positive feedback loop on catecholamine (i.e. norepinephrine and dopamine) release by blocking glia from re-uptaking neurotransmitters (Gründemann, Schechinger, Rappold, & Schomig, 1998). This in turn exaggerates the previously described effects of dopamine and norepinephrine. For example, in animal and human models, stress mediated glucocorticoid release has been shown to impair higher order cognitive functions and goal directed actions while promoting more automatic/habitual processes (Barsegyan, Mackenzie, Kurose, McGaugh, & Roozendaal, 2010; Elzinga & Roelofs, 2005; Roozendaal, Okuda, De Quervain, & McGaugh, 2006; Schoofs, Preuss, & Wolf, 2008; Schwabe, Tegenthoff, Höfken, & Wolf, 2012).

Aging is associated with higher levels of cortisol (Raskind, Peskind, & Wilkinson, 1994). Moreover, the effects of cortisol in persons with PD may be exaggerated as cortisol is elevated in patients with PD compared to healthy age-matched controls (Charlett, et al., 1998). Overall, this
suggests that the exaggerated effects of stress on dopamine and norepinephrine release in persons with PD may likely contribute to impaired functioning of the sensorimotor and associative loops and their related functions (i.e. working memory, sensory processing, and motor performance). In the following subchapters, the effects of stress and PD on the associative and sensorimotor loops and their associated functions (executive functioning, sensory processing, and motor control) will be discussed in greater detail.

1.4 Attention, Working Memory, and Executive Functioning

The concept of working memory and executive functioning can be traced back to the theories of selective attention (Broadbent, 1958), which is the process of how we direct our attention to certain stimuli while ignoring others. In Broadbent’s filter model, there is a limited amount of attentional/processing capacity. Thus, the nervous system uses a filter to eliminate unnecessary sensory information and prevent overloading. The information that passes through the filter is processed by higher order cortical structures for meaning and is then stored in short-term memory. Broadbent demonstrated his theory by using a dichotic listening task where participants listened to simultaneous auditory messages, one presented to each ear. When asked to repeat what they heard, participants were unable to recall both messages (i.e., one of the messages was unattended to).

Building on Broadbent’s theory, Atkinson and Shiffrin (1968) created a multi-store model of memory. Their multi-store model includes 3 main types of memory: sensory memory (iconic and echoic), short-term memory, and long-term memory. Sensory information progresses through each type of memory in a linear manner. It has a large capacity with a very short duration. 0.3 seconds is the duration for iconic or visual information while 2 seconds is the duration for echoic or auditory information. If the information in sensory memory is attended to,
it will be transferred to short-term memory. Short-term memory has a limited capacity of 7 plus or minus 2 chunks of information (Miller, 1956) accompanied by a longer duration of 0-20 seconds. Short-term memories can then be transferred to long-term memory. Long-term memory theoretically has an unlimited duration and capacity. However, it is subject to forgetting. Short-term memory can also retrieve information from long-term memory and manipulate already stored information.

Baddeley and Hitch (1974, 2012) modified and extended the concept of short-term memory and designated it working memory. In short, working memory is a short-term memory storage that is capable of processing and manipulating information along with transferring information to and from long-term memory. Working memory is divided into several components including the central executive, episodic buffer, visuospatial sketchpad, and phonological loop. The visuospatial sketchpad stores visual and spatial information, while the phonological loop stores auditory information. The episodic buffer links both the visuospatial sketchpad and phonological loop to long term memory. In the most recent models, the episodic buffer is also temporary storage for integrated information from the visuospatial sketchpad and the phonological loop (Baddeley, 2012). The central executive is an attentional control system that focuses attention, divides attention when needed, switches attention between tasks, and links short-term memory with long term memory. In Baddeley & Hitch’s 1994 model, the central executive was further expanded and now includes functions such as inhibitory control and cognitive flexibility (i.e., multitasking, shifting between tasks and retrieval strategies, and inhibiting selectively). In short, these models provided the basis for development of attentional control systems.
Executive functioning has its roots in Broadbent’s selective attention theory. Like working memory, executive functioning can be thought of as an attentional control system with overlapping constructs. Miyake et al. (2000) wrote this about Baddeley’s central executive: “The central executive, which is considered responsible for the control and regulation of cognitive process (i.e., executive functions)…” Using latent variable analysis they found 3 main executive functions: updating information in working memory, set-shifting or switching between tasks or mental sets, and inhibiting competing responses or demands on attention. The commonality between the functions is that they are all mediated by the frontal lobe, and they represent “one’s ability to actively maintain task goals and goal-related information and use this information to effectively bias lower-level processing” (Miyake & Friedman, 2012).

In addition to the attentional control system, it has been theorized that there is also an exogenous, bottom-up, sensory driven, or an automatic attentional system. Functionally, this automatic, bottom-up sensory driven system can interrupt the top-down system, increasing the flexibility of the system in order to alert an individual to novel, meaningful, or potentially threatening stimuli (Corbetta & Shulman, 2002). Others have termed the system an endogenous system controlled by intentions, and a stimulus driven, exogenous system acting to shift attention (Posner, 1980).

Other theorists suggests that the two systems are better described by either automatic (bottom-up/exogenous system) or controlled (top-down/endogenous system) processing (Moors & De Houwer, 2006; Shiffrin & Schneider, 1977; Schneider & Chein, 2003). Controlled processing is flexible, requires attention, and has limits in capacity. Automatic processes on the other hand have no capacity limitations and do not require attention. In the view of most controlled and automatic processing theories, processes lie on a spectrum from more controlled
to more automatic (Moors & De Houwer, 2006). For example, early sensory processing stages that require no attention are viewed as more automatic, while later stages of information processing are more controlled and require increasing amount of attention. However, processes are not necessarily fixed. For example, practice results in a decreased need for attention suggesting that those practiced processes become more automatic (LaBerge & Samuels, 1974; Salthouse, 1986; Shiffrin & Schneider, 1977).

As previously mentioned, it has been suggested that PD affects automatic processes of the sensorimotor loop, and in order to overcome impaired motor automaticity, persons with PD try to use more controlled goal oriented processes (Morris, et al., 1995; Redgrave, et al., 2010). Thus, in order to understand how stress affects persons with PD, the following sections will review how stress affects attentional control systems and working memory, and further on there will be a review on how stress affects one of the most automatic sensory processes known as inhibitory gating.

1.4.1 Stress and Attentional Control

Stress and arousal are often used synonymously. In many studies and theories examining the effects of stress on executive functioning, authors often use pressure (i.e., pressure to complete a task quickly) and stress inducing tasks interchangeably. While there have been arguments that stress and arousal are independent constructs (King, Burrows, & Stanley, 1983), stress increases arousal. Thus, it is generally assumed that they are highly correlated.

Some other key constructs that are often used synonymously and interchangeably in the literature examining the effects stress on cognition are state and trait anxiety. Trait anxiety describes the individual personality differences in experiencing arousal, stress, and worry to a perceived threat. State anxiety can be described as the interaction of trait anxiety and situational
induced stress, and individuals with high trait anxiety typically perceive a stressful situation with greater intensity than those with low trait anxiety (Eysenck & Calvo, 1992).

One of the earliest hypotheses used to describe how stress/arousal affect cognitive and motor performance is the Yerkes-Dodson law. It states that the relation between arousal and performance is an inverted U-curve, where performance is best at a moderate level of arousal and performance suffers at extreme levels (high or low) of arousal (Yerkes & Dodson, 1908). Easterbrook (1959) hypothesized that the reason arousal affects performance is because it affects how individuals utilize task relevant and task-irrelevant cues. According to the Easterbrook’s hypothesis when arousal increases our attentional focus narrows. At low levels of arousal, attention is broad and individuals process both task-relevant and task-irrelevant cues. At moderate levels of arousal, performance is optimized because attentional focus has narrowed to the point where one is only concentrated on task-relevant cues. At high levels of arousal, attention has narrowed to the point that both task-irrelevant and task-relevant cues are under-utilized. Weltman and Egstrom (1966) provided strong evidence for this argument by showing that reaction time to peripheral stimuli was affected by a stressful/arousing environment while reaction time to central stimuli was unaffected. In this study, divers had large increases (300% to 400%) in reaction time to a peripheral light in the ocean compared to a calmer environment (i.e., swimming pool and standing next to a swimming pool).

One interpretation of Easterbrook’s hypothesis is that moderate levels of arousal should improve performance on primary tasks (i.e., where the task relevant cues are the most important) and impair performance on secondary tasks. However, a number of studies have shown that when the secondary stimuli are more salient recall for those stimuli are greater than or equal to stimuli for primary task (Dusek, Kermis, & Mergler, 1975; Dusek, Mergler, & Kermis, 1976;
Solso, Johnson, & Schatz, 1968). Other major limitations of this theory are that it does not address individual differences such as trait anxiety, and it does not address how stress and anxiety differentially affect different types of executive functions and cognitive processes. Overall, the Easterbrook’s hypothesis has a limited scope.

Thus, the processing efficiency theory was introduced by Eysenck and Calvo (1992). It attempted to account for how anxiety affects cognitive performance and focused on tasks that involve the working memory system as defined by Baddeley (1986). While their particular focus was on state anxiety (a combination of situational stress and trait anxiety), Eysenck and Calvo (1992) note that state and trait anxiety are highly correlated. However, the studies discussed in their paper rarely made any attempt to differentiate them. According to processing efficiency theory, high state anxiety results in poor processing efficiency (i.e., greater cognitive resources are needed to perform a working memory task) as compared to low state anxiety. The theory also assumes that performance depends upon the amount of cognitive resources available and the difficulty of the task. High state anxiety would require an individual to use more resources and effort. However, if the working memory task is not overly difficult, then no decrements in performance should be observed. Their proposed mechanism is worry, which is activated by state anxiety. Worrying uses up limited processing resources and working memory space, but it also increases motivation which is used to compensate for the increased cognitive load. In their review they state, “The empirical evidence permits one to draw various conclusions, including the following: (a) state anxiety is generally associated with poor processing efficiency under test conditions, as high-anxiety individuals use more processing resources than low-anxiety individuals; (b) the effects of state anxiety on performance effectiveness depend on (1) the
availability and utilization of additional resources and (2) the demands of the task on working memory.”

The limitations of the discussed theories led to the development of the attentional control theory (Eysenck, et al., 2007). It expanded upon processing efficiency theory and addressed some of its limitations. One of the major limitations addressed was the lack of specificity in identifying what central executive processes of working memory are most affected. As a foundation, they used the executive functions (i.e., inhibition, shifting, and updating) identified by Miyaki and colleagues (2000). They also integrated Corbetta and Shulman’s (2002) two competing attention systems: the top down goal-directed attention system and the bottom-up stimulus driven attentional system. According to attentional control theory, stress and anxiety impair overall working memory efficiency, inhibition, and set-shifting. More specifically stress and anxiety impair: 1) working memory processes in terms of overall efficiency, 2) attentional focus and the ability to inhibit attentional focus on salient task-irrelevant cues, 3) ability to switch tasks effectively. The theory doesn’t assume worry (i.e., internal distraction) is the primary mechanism. Instead it assumes the main culprit is impaired attentional control.

Unfortunately, there is no theory that can encompass how stress will affect attentional control and automatic processes in persons with PD. As previously discussed in chapter 1.3, persons with PD suffer from neurological degeneration in dopaminergic and norepinephrine systems which are linked to stress’s effect on attention and working memory. One of the goals of this study is to examine the theory that persons with PD use general attentional/working memory processes to overcome deficiencies in motor control, while specific executive functions such as set-shifting and inhibition are not necessarily implicated. In that light, the following sections we will review general working memory and how stress, aging, and PD effects general working
memory. Future studies that examine specific executive functions may provide further insight into how stress affects persons with PD.

1.4.2 Working Memory

Working memory, a component of executive function, is the holding of and working with information that is no longer perceptually present (Baddeley & Hitch, 1994). Working memory is used to piece together information during tasks such as reading, doing math, making plans and decisions, and reasoning (Baddeley, 2000). Manipulating information in working memory appears to be mediated by the dorsolateral prefrontal cortex while storing information is mediated by posterior parietal areas (D’Esposito, Postle, Ballard, & Lease 1999; Eldreth, et al., 2006; Smith & Jonides, 1997). One of the most common ways to assess working memory is using the digit span forward and backward tasks (Ramsay & Reynolds, 1995).

The digit span forward and backward tasks straightforward and quick assessments of working memory. They have also been validated as a diagnostic tool for determining cognitive impairment in persons with PD (Biundo, et al., 2013). During the digit span forward task, participants are sequentially given (either auditorily or visually) a number of items (such as a string of digits) and asked to repeat them in the same order given. During the digit span backward task, participants are sequentially presented with a number of items, but they must recite them in the reverse order. There has been much debate about whether or not the digit span forward and digit span backward measure the same working memory processes (i.e. short-term memory, working memory), but a factor analysis demonstrated that while there are large overlaps in the cognitive processes used, the digit span also requires a separate transformation processes (Ramsay & Reynolds, 1995). This suggests that the digit span forward task might be
more representative of short term memory which does not require any manipulation of the information, while the digit span backward task may be more representative of working memory.

More complex tasks have also been developed to test working memory such as the reading span, n-back, and operation span tasks (for review see Conway, et al., 2005). During the reading span, participants read a series of unrelated sentences aloud and must recall the final word of each sentence. The number of final words they can recall is quantified as the reading span. In the n-back task the subject is presented with a sequence of stimuli, and then the participant must indicate when the current stimulus matches the one from n steps prior. The larger the n the more difficult the task. In the operation span, task participants try to remember sequentially presented words in their correct order while simultaneously solving simple math equations. However, these measures of working memory are considered complex span tasks because they also require multi-tasking. Their performance may be influenced by their reading (reading span) or math abilities (operation span) (Conway, et al., 2005). The n-back paradigm is even more complex because it depends on familiarity and recognition discrimination (Oberauer, 2005). Thus, the more complex measures of working memory include processes above and beyond that of working memory/short-term memory.

1.4.3 Stress and Working Memory

As previously described (chapter 1.3), stress is likely to result in impaired cognitive functioning and working memory efficiency by pushing norepinephrine and dopamine out of the optimal zone in the inverted U-shaped curve. The findings on tasks assessing the effects of stress on working memory and attentional capacity are controversial, especially with simple working memory tasks such as the digit span tasks. Schoofs, Wolf, and Smeets (2009) found that physical stress from the cold pressor task (i.e., placing a hand in ice water) reduced performance on the
digit span backward task but not the digit span forward task. Another study that used mock prisoner of war interrogation and physical restraints as a stressor also found impairment in both of the digit span tasks (Taverniers, Van Ruysseveldt, Smeets, & von Grumbkow, 2010). However, researchers that used a public speaking stressor found no effect of stress on either of the digit span tasks (Hoffman & al’Absi, 2004; Kuhlmann, Piel, & Wolf, 2005). The inconsistency of results are due to the complexity of the task.

When using working memory/updating tasks that are more complex (operation span, reading span, and the n-back paradigm), results are less ambiguous. Researchers find that stressors negatively influence performance (Luethi, Meier, & Sandi, 2009; Schoofs, et al., 2008; Schoofs, et al., 2009). A meta-analysis concluded that stress negatively affects working memory. Furthermore, other factors such as working memory load (i.e., greater working memory load results in greater impairment) and stress severity (i.e., greater stress resulted in greater impairment) also affect the impact stress has on working memory (Shields, Sazma, & Yonelinas, 2016). Overall, these studies show that stress negatively affects working memory efficiency, whether or not working memory impairment is observable will depend on the complexity of the task and severity of the stressor. In addition, other factors may also play a role such as individual working memory capacity and neurodegeneration, like that seen in persons with PD. In the follow section we will discuss how aging and PD affects working memory, and the hypothesis regarding how stress will affect working memory in persons with PD.

1.4.4 PD, Stress, and Working Memory

Aging is associated with declines in working memory capacity on tasks such as the digit span, as well as a number of visuospatial, verbal, and more complex working memory tasks (Bopp & Verhaehen, 2005; Gajewski, Hanisch, Falkenstein, Thönes, & Wascher, 2018; Park, et
A number of studies also demonstrate that compared to healthy older adults, persons with PD have an even greater decline in working memory tasks (i.e., digit span, reading span, verbal spans, and arithmetic spans) (Gabrieli, Singh, Stebbins, & Goetz, 1996; Grogan, et al., 2018; McKinlay, Grace, Dalrymple-Alford, & Roger, 2010). Overall, meta-analyses have concluded that persons with PD show impairment in working memory, specifically the digit span backward, as compared to healthy older adults (Kudlicka, et al., 2011).

Research suggests that working memory impairment in persons with PD is due to the downstream effects of dopamine depletion in the substantia nigra (Halliday, Leverenz, Schneider, & Adler, 2014). Neuroimaging studies demonstrate that cognitive performance in persons with PD is associated with dopamine loss in the caudate (Marie, et al., 1999). However, dopaminergic medications increase striatal and cortical dopamine and, thus, have been found to enhance (Beato, et al., 2008; Cooper, et al., 1992; Lewis, Slabosz, Robbins, Barker, & Owen, 2005), impair (Costa, et al., 2003, Poewe, Berger, Benke, & Schelosky, 1991), or have no effect (Fournet, Moreaud, Roulin, Naegele, & Pellat, 2000; Grogan, et al., 2018; Zokaei, Burnett Heyes, Gorgoraptis, Budhdeo, & Husain, 2015) on working memory performance in persons with PD. Researchers have argued that the contrasting effects are due to the progression of dopamine depletion in PD. In the earlier stages, there is less severe dopamine depletion and dopaminergic medication leads to a possible dopamine “over-dosing” (Cools, 2006; Cools & D’Esposito, 2011). Indeed, studies have found that those who do well in the “off” state are more impaired in the “on” state, and vice versa (Gotham, Brown, & Marsden, 1986), and those who do poorly off medication improve when on medication (Warden, Hwang, Marshall, Fenesy, & Poston, 2016). Thus, the over-dosing at an early stage impairs working memory because there is less impairment/less dopaminergic loss at this stage, so too much dopamine leads to impairment.
At later stages when there is a greater loss of dopaminergic neurons and greater impairment in working memory, increased dopamine improves performance.

Like PD medications, acute stress increases striatal and cortical dopamine (Finlay & Zigmond, 1997; Gresch, et al., 1994; Imperato, et al., 1991; Morrow, et al., 2000; Vaessen, Hernaus, Myin-Germey, & van Amelsvoort, 2015). However, it is unknown how stress will impact working memory in persons with PD. For persons with PD in the earlier stages stress would likely result in a dopaminergic ‘over-dose’ and impair working memory. For persons with PD in the later stages stress may either improve working memory by increasing dopamine into the optimal zone, or the amount of dopamine released may still be sufficient to over-dose striatal and cortical dopamine. Thus, the first aim of this study is as follows.

Aim 1: The aim of the first study was to determine how stress affects working memory in persons with PD. I hypothesize that an acute SECP stressor will impair working memory (digit span tasks) in persons with PD.

1.5 Inhibitory Gating

In addition to the cardinal motor symptoms, persons with PD also have sensory processing deficits, and it is suggested that sensory processing deficits contribute to motor impairments (Conte, et al., 2013; Konczak, et al., 2009; Müller, 2013). A specific sensory processing deficit seen in persons with PD is reduced inhibitory gating (Gulberti, et al., 2015; Lukhanina, Kapustine, Berezetskaya, & Karaban, 2009; Lukhanina, Berezetskaya, & Karaban, 2011; Teo, et al., 1997). In this subchapter, we will review inhibitory gating, how PD and stress impacts inhibitory gating, and why inhibitory gating might be involved in PD motor symptoms.

Inhibitory gating is a multistage process in which the brain’s responses to sensory information are modulated (Gjini, Arfken, & Boutros, 2010). Inhibitory gating only requires a
short period of time to fully recover (less than 10 seconds for intra-stimulus intervals and less than 1 second for inter-stimulus intervals) (Boutros & Belger, 1999). When sensory information is repetitive, the information is filtered or “gated-out”, and the associated electrical activity of the neuronal networks are reduced (Boutros & Belger, 1999). When sensory information is novel, like when repetitive stimuli are followed by a novel stimulus we see a “gating-in” effect or increased electrical activity of the neuronal networks (Gjini, et al., 2010). Inhibitory gating is an automatic active inhibitory process (Adler, et al, 1982; Boutros & Belger, 1999) rather than a passive momentary incapacity of neurons to fully respond to stimuli (Davis, Mast, Yoshie, & Zerlin, 1966). Theoretically, inhibitory gating and “gating-out” improves cognitive functioning by decreasing the number of pre-attentive and attentive cognitive resources needed (Gjini, et al., 2010; Knight, Scabini, & Woods, 1989). Thus, inhibitory gating is a pre-attentive automatic sensory process, which may affect other sensory and consciously controlled processes.

Inhibitory gating can be measured via EEG which measures the change in electrical activity of neuronal networks (via electrodes placed on the scalp) to events such as sensory stimulation. More specifically, inhibitory gating utilizes event related potentials (ERP). ERP components are the neural responses associated with specific sensory, cognitive, and motor events. ERP components are time-locked with events and represent distinct neurological processes in distinct locations of the cortex (Luck, 2005). A single event may elicit a number of different components (i.e., p30, p50, n100, p200, etc.) which are differentiated in terms of latency (the amount of time that it takes for them to occur in response to a stimulus) (30ms, 50ms, 100ms, etc.) as well as by their positive (p) or negative (n) polarity.

However, this is not always the case. At times, they are differentiated by their polarity and the ordinal position within the wave (i.e. p1,n1, p2, etc.). Some components are broken down
further as is the case with p300a and p300b where the first peak and second peak within the large positive wave represent separate components. Finally, components may be referred to with acronyms (mismatch negativity, error-related negativity, etc.). While some components may share the same name (e.g. n100 for both auditory and visual stimuli), they typically are not functionally related across sensory (somatosensory, auditory, visual, etc.), cognitive (error detection, facial recognition, etc.), and response (movement) domains (Luck, 2005). Inhibitory gating is typically evaluated using a paired click paradigm where pairs of simple auditory stimuli elicit the p50-n100-p200 auditory components (Figure 1.5). The p50 component is a mid-latency component that reflects the early processing of auditory information (Luck, 2005). During the paired-click paradigm, the first click is referred to as the S1 and is followed shortly thereafter by the second click or S2. The most common inhibitory gating measure is the S2/S1 ratio of the p50 component, often referred to as p50 inhibitory gating. The normal gating response is indicated by a low S2/S1 ratio with a large amplitude response to S1 and a reduced amplitude response to S2.

Figure 1.5. Event-Related Potential EEG Waveform. An example of an auditory EEG waveform showing P1 (p50), N1 (n100), P2 (p200), P3(p300). Figure reproduced with permission from the

The inhibitory gating of the p50 component is considered pre-attentive because it is uninfluenced by attentional manipulations (Hillyard, Hink, Schwent, & Picton, 1973; Jerger, Biggins, & Fein, 1992; Kho, et al., 2003). For example, Yee and White (2001) demonstrated that compared to a passive relining task there was no difference in p50 ratios when participants were 1) in an upright posture (muscular interference), 2) counted silently (cognitive interference), 3) listened passively (auditory interference), or 4) counted out loud (cognitive, auditory, and muscular interference). These results suggest that p50 inhibitory gating is largely unconscious and are not affected by competing auditory stimulation, performing cognitive tasks, performing motor tasks, and attentional manipulations. Overall, these studies demonstrate that the p50 inhibitory gating is an automatic sensory driven process. Thus, it may reflect how stress and PD affect automatic processes described in chapter 1.4.

1.5.1 Neural Components of Inhibitory Gating

One of the main mediators of inhibitory gating appears to be regions of prefrontal lobe specifically the dorsolateral prefrontal cortex (DLPFC) (Boutros, Gjini, Eickhoff, Urbach, & Pflieger, 2013; Garcia-Rill, et al., 2008; Grunwald, et al., 2003; Korzyukov, et al., 2007; Tregellas, et al., 2007). One study showed that cathodal-tDCS on the DLPFC impairs p50 inhibitory gating (Terada, Kurayama, Nakazawa, Matsuzawa, & Shimizu, 2015). However, other studies also implicate the thalamus, somatosensory, supplementary motor, anterior cingulate, and parietal areas (Boutros, et al., 2013; Grunwald, et al., 2003; Tregellas, et al., 2007). Recordings from intracranial evoked potentials in epilepsy patients showed that other cortical areas of the sensorimotor loop are also involved such as the primary somatosensory cortex, premotor and
supplementary motor areas, and anterior cingulate cortex (Grunwald, et al., 2003). Overall, many cortical brain regions are involved in mediating inhibitory gating.

The basal ganglia has not been directly implicated in inhibitory gating, but evidence suggests that the basal ganglia may also be involved. The basal ganglia is involved in modulating sensory information (Juri, Rodríguez-Oroz, & Obeso, 2011) and is functionally connected to prefrontal and parietal regions via subcortical loops (McHaffie, Stanford, Stein, Coizet, & Redgrave, 2005). In addition, impaired inhibitory gating is observed in disorders of the basal ganglia such as PD (Gulberti, et al., 2015; Teo, et al., 1997), and Huntington’s disease (Uc, et al., 2003). Finally, involvement of the basal ganglia is also demonstrated by studies that show both subthalamic nucleus deep brain stimulation (Gulberti, et al., 2015) and ablative pallidal surgery restore normal inhibitory gating in persons with PD (Mohamed, Iacono, & Yamada, 1996, Teo, Rasco, Skinner, & Garcia-Rill, 1998). Overall, this evidence suggests that the basal ganglia and sensorimotor loop are involved in inhibitory gating, and that inhibitory gating may be associated with the functioning of sensory and motor processes.

1.5.2 Inhibitory Gating and Parkinson’s Disease

In an expansive literature search, only one study was found that examined inhibitory gating of the p50 component in persons with PD using traditional measures (p50 ratio). Teo and colleagues (1997) examined inhibitory gating in 24 moderate to severe (Hoehn and Yahr (H&Y) III-V) PD subjects and ten age matched controls. They found that persons with PD had impaired or decreased inhibitory gating compared to the age matched controls, but this was driven by those in the later stages. Stage V (83±43%) had the most impaired gating followed by stage IV (76±51%), stage III (54±35), and controls (31+24%). Thus, this study demonstrates that p50
inhibitory gating is impaired in persons with PD in the later stages of the disease, and inhibitory gating gets worse (declines) as the disease progresses.

Three other studies have examined measures that are related but significantly differ from the traditional inhibitory gating ratio (p50 ratio). For example, one study examined only the amplitude of the p50 response in 12 mild to severe (H&Y 3±1) subjects with PD. The participants completed four separate trials: off medication, on medication, post-operative subthalamic nucleus-deep brain stimulation (STN-DBS) off (while off medication), and post-operative STN-DBS on (while off medication). Results showed a significant difference for the peak-to-peak amplitude for all conditions compared to age matched controls, no difference between those on or off medication, and no difference between those with their DBS turned on and those with their DBS turned off (Gulberti, et al., 2015). Overall, this suggests that S1 and S2 amplitudes are greater in persons with PD, and that PD medication or STN-DBS does not affect S1 and S2 amplitudes.

Another study used the ratio of the n100-p200 complex. They found that the ratio of the n100-p200 complex was higher than age-matched controls suggesting that inhibitory gating was worse in the PD group (Lukhanina, et al., 2009). This study also found that inhibitory gating was positively associated with p300 latency, a neurophysiological correlate of attention and memory. In other words, better gating was associated with better attention and memory. In addition, they found that levodopa helped to significantly improve the n100-p200 ratio and p300 latency in persons with PD. A follow up study found that the inhibition ratio of the n100-p200 complex was correlated with age (r = -0.29), age of onset (r = 0.28), and body bradykinesia (r = -0.35) (Lukhanina, et al., 2011). This study suggests that the later components of inhibitory gating may be associated with PD motor symptoms. However, there are limited to no studies that have
examined how stress affects inhibitory gating, nor the relationship between p50 inhibitory gating and PD motor symptoms.

1.5.3 Stress and Inhibitory Gating

Acute stressors have repeatedly been shown to impair inhibitory gating in healthy populations, presumably through increasing levels of norepinephrine (Ermutlu, Karamürsel, Ugur, Senturk, & Gokhan, 2005; Johnson & Adler, 1993; White & Yee, 1997). Inhibitory gating has an inverted-U shaped relationship with norepinephrine, where agonists and antagonists have been shown to disrupt normal gating (Adler, et al., 1991; Stevens, Meltzer, & Rose, 1993). One of the most common stressors used to look at the effects of stress on inhibitory gating is the cold-pressor task. During the cold-pressor task participants place their hand into very cold water (0-10°C), for a short period of time (60-300 seconds). Using the cold-pressor, inhibitory gating gets worse for about 30 minutes after exposure (Ermutlu, et al., 2005; Johnson & Adler, 1993). Other stressors such as mental arithmetic or preparing to give a speech have also been effective at decreasing inhibitory gating (White & Yee 1997; Yee & White, 2001). Overall, acute stressors have been found to influence inhibitory gating in healthy populations.

While stress negatively impacts inhibitory gating in healthy populations, it is unknown how stress will affect persons with PD. As a review, the literature shows 1) that persons with PD in the later stages demonstrate impaired inhibitory gating, but have comparative gating levels in the earlier stages (Teo, et al., 1997), 2) stress disrupts inhibitory gating presumably through increasing levels of norepinephrine (Johnson & Adler, 1993), and 3) older adults release more norepinephrine during a cold stressor than young adults (Palmer, et al., 1978). Thus, the second aim of this study is as follows.
Aim 2: The second aim was to determine how stress impacts p50 inhibitory gating in persons with PD. I hypothesized that an acute Socially Evaluated Cold Pressor (SECP) will decrease inhibitory gating (larger p50 ratio) in both HOAs and persons with PD.

1.6 Stress, Motor Performance, and Parkinson’s Disease

The cardinal PD motor symptoms include tremor, bradykinesia (slow movement), hypometria (small movement), rigidity (stiffness), postural instability, and gait instability. These primary symptoms most commonly impact well-learned, automatic behaviors such as walking, handwriting, speaking, and eating (Redgrave, et al., 2010). Currently, there is limited literature examining how stress can affect PD motor symptoms. In the PD rat model, researchers demonstrated that restraint stress negatively impacts fine motor skills such as reaching and grasping (Smith, Jadavi, Colwell, Pehrudoff, & Metz, 2008). In persons with PD, a more stressful environment, such as walking on a plank over an open pit in a virtual reality setting, negatively impacted gait (Ehgoetz Martens, Ellard, & Almeida, 2015). Stress was not measured however, and changing the visual environment was a confounding factor. Anxiety has also been positively correlated with gait impairment (Martens, Ellard, & Almeida, 2015), self-reported motor symptoms (Siemers, Shekhar, Quaid, & Dickson, 1993), and clinical tests (Henderson, Kurlan, Kersun, & Como, 1992). Furthermore, the stress related neurohormone cortisol has also been associated with gait deficits (Charlett, et al., 1998). All together, there is limited evidence, but that evidence suggests that stress may negatively impact motor symptoms in persons with PD.

While the research does appear to suggest that stress negatively impacts motor performance in persons with PD, the underlying mechanisms have not been fully explored. Additionally, no specific hypotheses about how stress would impact persons with PD differently
than healthy individuals has been put forward. In the following sections, we will review what is known about the stress motor performance relationship and theories as to how stress will impact persons with PD.

1.6.1 Inverted-U Hypothesis

The relationship between stress and motor performance generally follows an inverted-U shaped curve. Duffy (1962) referred to this as the “inverted-U principle”. The premise behind the inverted-U principle is that stress influences arousal levels. When arousal is either too high or too low, the result is a degradation in motor performance. Weinberg and John (1978) demonstrated this principle in junior high school males. To manipulate stress levels, they told participants that their performance on throwing a tennis ball was either better than 70% (low), 40% (moderate), or 10% (high) of the overall population. The researchers discovered that the low-stress and high-stress groups performed worse than the moderate-stress group, resulting in an inverted-U curve. Finally, the study also showed that there was a significant trait anxiety by stress interaction. Low-anxiety participants performed the best when in the high-stress condition and vice-versa for high-anxiety participants. There are a number of theories that explain the mechanisms underlying how stress affects motor performance either directly or indirectly. The most relevant theories will be reviewed in the following sections.

1.6.2 Self-Focus Theories

Self-focus theories (also referred to as execution focus models) suggest that stress, particularly stress about performing well “raises self-consciousness and anxiety about performing correctly, which increases the amount of attention paid to skill processes and their step-by-step control” (Nieuwenhuys & Oudejans, 2012). This may be especially true for well learned skills. For example, Beilock, Carr, MacMahon, & Starkes (2002) demonstrated that
experienced golfers were significantly more off target (distance from the hole) when focused on the follow through of the club head when compared to listening to secondary auditory-tone monitoring task or when practicing without instruction. This same study also found that expert soccer players dribbled slower (worse) when using their preferred foot and attending to that foot compared to when they had to dual-task with their preferred foot. However, the performance of less well learned skills may be improved by attending to the skill processes and step-by-step control. For example, novices dribbled faster and experts performed better with their non-dominant foot when attending to the skill (Beilock, et al., 2002). This demonstrates that focusing on the skill process negatively affects well learned skills and motor automaticity, but it helps less well learned skills.

One issue with studies like Beilock and colleagues (2002), however, is that participants were told to attend to the skill and the step-by-step control. Qualitative studies that have examined retrospective verbal reports of attentional focus in 70 elite athletes showed that their attention was focused on movement execution only 4% of the time (Oudejans, Kuijpers, Kooijman, & Bakker, 2011). Thus, how often performers actually engaged in self-focus under stressful conditions is debatable. Overall though, the evidence from self-focus theories shows that conscious control of motor skills negatively influences skills that have been automatized.

In persons with PD, automatized skills are already impaired due to basal ganglia damage. However, persons with PD may benefit from using more conscious control of movements (Redgrave, et al., 2010). Thus, if self-focus were the only mechanism involved, then stress may actually improve motor performance in individuals with PD. However, self-focus may not be the only mechanism involved. In the following sections some of the other mechanisms involved will be reviewed, such as the effect of stress on attention and motor automaticity.
1.6.3 Capacity Model of Attention

So far theories that specifically address how stress might affect motor performance via distraction, reduced cue-utilization, and self-focus have been reviewed. While those theories each capture a portion of the picture, they have some limitations in scope. Some of the broader theories of motor control and attention may better illuminate how stress impacts motor control. One of the earliest theories, and one that is still taught in motor control and learning classes is Kahneman’s capacity model of attention (1973), which is an example of a central-resource theory. Like Broadbent (1958), Atkinson and Shifferin (1968), and Baddeley and Hitch (1974, 2012) discussed in chapter 1.4, Kahneman’s capacity model of attention views attention as a limited pool, for which all cognitively demanding tasks must draw their resources from. In many ways it may make some similar predictions as cue-utilization theory, and the distraction model, yet it also highlights some important considerations that should be accounted for when making predictions about how stress will impact motor performance.

The capacity model of attention has three general rules for how people divide their attention. The rule relevant to this discussion concerns how attention is involuntarily recruited, according to this theory each of us has “enduring disposition” to become distracted by novel and personally meaningful stimuli. As stressors pose a challenge or threat they would be considered personally meaningful stimuli, and thus stressors demand cognitive resources either voluntarily or involuntarily. As stressors demand limited attentional resources, less resources are left to complete cognitive and motor tasks, possibly resulting in impaired performance.

Not only do stressors attract attention, but the capacity model of attention also suggests that the central-resource pool capacity is influenced by arousal (Kahneman, 1973). When arousal is too high or too low, attentional capacity is reduced. As previously reviewed (chapter 1.3), stress
increases arousal (via norepinephrine) and impairs attention/working memory. Thus in addition to requiring attentional resources stress reduces attentional capacity. Overall, the capacity model of attention would predict that during stress, less attentional resources are available for cognitive and motor tasks, and thus performance will be compromised.

One thing the capacity model of attention does better than some of the previously discussed theories, is take into account automaticity, and how learning reduces the attentional demands of the task. Thus while stress demands attention, and reduces attentional capacity, it would predict that well learned tasks don’t demand much attention and thus well learned skills will be left unaffected by stress. For example, it would predict the findings of Nibbeling and colleagues (2012) and recognize that well learned skills are more automatic, and therefore are not as susceptible to impairment via reduced attentional capacity that comes with stress. It would also predict the findings of Fuchs (1962), because interpreting and reacting to acceleration may be more demanding on our attentional resources, and thus when our attentional resources are impaired we regress to using velocity or positional cues, skills which were well learned. Finally, it would predict that stress would negatively affect explicit learned skills while implicitly learned skills would be preserved (Masters, 1992), as implicitly learned skills are performed more automatically. Overall, the evidence and theories put forth thus far suggest that stress negatively impacts attention as well as conscious control of movement. More automatic processes which are less attention demanding, however, should be left unaffected. In the next section, theories that suggest that stress may actually upregulate these automatic processes will be reviewed.

1.6.4 Drive Theory and Response Dominance Hypothesis

Drive Theory (Spence, 1956; Spence & Spence, 1966), and the response dominance hypothesis (Zajonc, 1965) are based off of social facilitation research and more specifically how
social facilitation affects motor performance. It is important to remember when reviewing the social facilitation literature that social evaluation is one of the most effective stressors (Dickerson & Kemeny, 2004). Drive theory states that the presence of others will facilitate dominant responses and impair performance of non-dominant responses. Similarly, Zajonc’s (1965) response dominance hypothesis (Figure 1.6) postulates that an audience increases arousal levels and increases the probability of using a dominant reaction. In terms of motor performance this suggests that social facilitation improves performance on well-learned tasks (simple tasks) and impairs performance on tasks that are not well-learned (complex tasks). Overall, social facilitation would suggest that stress should lead to using more automated control of movements.

![Diagram](image)

Figure 1.6. The Zajonc model (1965) (Strauss, 2002). The presence of others increases activation and arousal, which in turn increases the probability of dominant reactions and decreases the probability of subordinate reactions. Thus, the presence of others will facilitate or improve performance on simple (well-learned) tasks because the dominant response is often the correct one. Performance on complex (not well-learned) will often be impaired because the dominant response is often incorrect. Figure reproduced with permission from the authors.

A number of studies have tested drive theory and the response dominance hypothesis, and in general they find that people perform complex motor tasks worse in front of an audience during skill acquisition and perform better after sufficient practice (Landers, Bauer, & Feltz...
1978; Martens, 1969). Similarly, Haas and Roberts (1975) found that performance was hindered by social evaluation when learning a complex motor task, but once learned performance was enhanced by social evaluation. Similar results have been demonstrated in a balancing task (MacCracken & Stadulis, 1985), and karate kicks (Bell & Yee, 1989). Overall, a meta-analysis of social facilitation on motor performance in 241 studies found that an audience improved performance on simple tasks and hindered performance on complex tasks (Bond & Titus, 1983). Therefore, the evidence suggests that stress can improve performance on automatic well-learned simple skills, and hinder performance on more complex attention demanding skills. In the following sections the implications that this has for persons with PD will be reviewed.

1.6.5 Stress and PD Motor Symptoms

In general, stress negatively affects attention and motor performance of less well learned skills. For more automatic skills, however, stress has less of an effect or may actually improve performance. The effects of stress on motor performance in persons with PD may be different. As previously discussed, persons with PD have damage to the substantia nigra, primarily in the posterior striatum and sensorimotor loop, and as a result show the cardinal motor symptoms and impairment of well learned automatic skills (i.e. handwriting, walking, postural stability) (Redgrave, et al., 2010). Limited research has shown that more stressful inducing situations such as walking on an elevated plank led to greater gait impairment in persons with PD (Ehgoetz Martens, et al., 2015), and stress decreased skilled reaching in PD rat models (Smith, et al., 2008). Still, it is unknown how stress will affect motor symptoms in persons with PD. How stress will affect PD motor symptoms may depend in part on the characteristics of the motor tests performed, which we will review next.
The UPDRS motor tests include upper limb movements such as finger tapping (tapping of the index finger), hand movements (opening and closing of the fingers), and pronation-supination of the hand (rotating the palm to the sky, then to the ground, and back again). The finger tapping, hand movements, and pronation-supination tests examine motor symptoms such as bradykinesia (slow movements), and hypokinesia (small movements) by examining the speed and amplitude of these movements. The instructions for testing these movements are for the individual to complete these movements as fast and as large as possible. Part of the reason for these instructions is that impairment of these upper limb movements are speed dependent with greater impairment at movement rates above 2Hz (Freeman, Cody, & Schady, 1993; Nakamura, Nagasaki, & Narabayashi, 1978; Yahalom, Simon, Thorne, Peretz, & Giladi, 2004; Stegemöller, Simuni, & MacKinnon, 2009). Movement at higher rates is more automatic and less consciously controlled (Wu, et al., 2015), and thus faster movements may be more likely be affected by stress than slower movements. The other two tests that are examined are postural tremor, and resting tremor. Similar to moving at faster rates, postural control is seen as being largely automatic and unconscious (Park, Kang, & Horak, 2015), and thus stress may increase postural and resting tremor. As previously described, the third aim of this study is as follows.

Aim 3: The third is to determine how stress affects PD motor symptoms (tremor, upper extremity bradykinesia, and upper extremity hypokinesia). I hypothesize that stress will negatively impact the following UPDRS motor tests: finger tapping, hand movements, pronation-supination of the hand, postural tremor, and resting tremor in persons with PD, but not in HOAs.

The fourth aim of this study is to examine some of the possible mechanisms involved in stress’s effect on PD motor symptoms. Research has demonstrated that dual tasks requiring
working memory/attention have a greater negative impact on persons with PD compared to HOAs (Hackney & Earhart, 2010; O'Shea, Morris, & Iansek, 2002; van Gemmert, Teulings, & Stelmach, 1998). Conversely, studies have also demonstrated that bringing attention via visual cues (lines) and auditory cues (verbal reminders to pay attention) improve motor performance in persons with PD (Morris, et al., 1996; Oliveira, Gurd, Nixon, Marshall, & Passingham, 1997). Mechanistically, this suggests that persons with PD may use attention/working memory to override impairments of automatized motor control. Stress negatively impacts attention via increases in norepinephrine and dopamine, and thus, stress may make it more difficult for persons with PD to override the impaired sensorimotor pathway. In order to test this, how stress affects the relationship between working memory and motor symptoms will be examined.

Another possibility is that stress is affecting sensory processes and in general the sensorimotor pathway, which may contribute to stress’s effect on PD motor symptoms. As previously discussed, stress decreases inhibitory gating, which is the filtering of sensory signals in the sensorimotor pathway. Thus, stress’s effect on inhibitory gating may reflect how stress is affecting automatic sensorimotor processes, and inhibitory gating may be either a biomarker or involved in mediating stress’s effect on PD motor symptoms. How stress affects the relationship between inhibitory gating and motor symptoms will also be examined. Aim 4 is as follows.

Aim 4: The fourth is to determine how stress induced changes in cognitive functioning and sensory processing are associated with changes in motor symptoms. Experiment 4 will examine the relationship between stress induced changes in motor symptoms (UPDRS motor tests) with changes in working memory (digit span backward) and inhibitory gating (p50 ratio) using a repeated measures correlation in persons with PD. I hypothesize that the worsening of
motor symptoms would be associated with an increased impairment in working memory (smaller
digit span scores), and inhibitory gating (increased p50 ratio) in persons with PD.

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CHAPTER 2. THE EFFECTS OF A SOCIALLY EVALUATED COLD PRESS STRESSOR ON WORKING MEMORY IN PERSONS WITH PARKINSON’S DISEASE

Andrew Zaman¹, Elizabeth L. Stegemöller¹

¹Department of Kinesiology, Iowa State University

Modified from a manuscript to be submitted to Movement Disorders.

2.1 Abstract

Persons with Parkinson’s disease (PD) can have a number of non-motor symptoms such as executive function impairment, even at the earliest stages. In healthy populations, stress negatively affects executive functions such as working memory. However, there is a gap in our knowledge about how stress affects working memory in persons with PD. Thus, the purpose of this study was to examine how stress affects motor and non-motor symptoms in persons with PD.

Fifteen persons with PD and fifteen healthy older adults (HOAs) completed the digit span forward and digit span backward tasks following an acute stressor (socially evaluated cold pressor) and after a non-stressful control condition. The two-error maximum length (TE-ML) method was used as the working memory capacity outcome measure for each of the tasks. Response time was also recorded for accurately completed trials. A repeated measures factorial ANOVA was used to examine statistical differences.

Following the non-stressful condition, persons with PD had a smaller digit span backward capacity compared to HOAs. However, following the stress condition, persons with PD performed similarly to HOAs on the digit span backward task. The acute stressor reduced working memory capacity in HOAs, and surprisingly increased working memory capacity in persons with PD, making their performance statistically equivalent. The results also revealed that stress had a negative influence on the amount of time it took to manipulate information on the
digit span backwards task in both groups. Stress did not appear to influence digit span forward capacity or response time for either group.

The results of this study suggest that stress does not have a universally negative effect on executive functioning in persons with PD. Stress may actually help improve working memory capacity in persons with PD. However, the results did show that stress negatively impacted the time it took to manipulate information in working memory. Overall, this demonstrates the need for studying stress in persons with PD, as stress may affect them differently than healthy older adults.

2.2 Introduction

Impairments in cognitive functioning are evident at the earliest stages of Parkinson’s disease (PD) (Dubois & Pillon, 1996; Owen, 2004), and it has been estimated that up to 80% of individuals with PD will develop dementia (Hely, Reid, Adena, Halliday, & Morris, 2008). Moreover, cognitive impairment is a strong predictor of quality of life in persons with PD (Lawson, et al., 2016; Schrag, Jahanshahi, & Quinn, 2000). Impairments in cognitive function in persons with PD are diverse and include changes in attention, executive functions, memory, language, and visuospatial abilities (Zgaljardic, Borod, Fold, & Mattis, 2003). However, executive functions (i.e. working memory), appear to be the most affected cognitive domain in persons with PD (Zgaljardic, et al., 2003), and are highly associated with difficulties in completing common daily activities (Foster & Hershey, 2011). Persons with PD demonstrate working memory deficits (Gabrieli, Singh, Stebbins, & Goetz, 1996; Grogan, et al., 2018; Kudlicka, Clare, & Hindle, 2011; McKinlay, Grace, Dalrymple-Alford, & Roger, 2010; Siegert, Weatherall, Taylor, & Abernethy, 2008), and have more difficulty manipulating information in working memory (Bublak, Müller, Grön, Reuter, & von Cramon, 2002; Siegert, et al., 2008;
Zgaljardic, et al., 2003). Yet, there remains a need to better understand how common factors, such as stress, influence impairments in working memory in persons with PD.

Stress is a common experience that has been shown to negatively impact working memory in healthy populations (Arnsten, 2009; Eysenck & Calvo, 1992; Eysenck, Derakshan, Santos, & Calvo, 2007). Results from a meta-analysis concluded that stress negatively affects working memory tasks with higher working memory loads (Shields, Sazma, & Yonelinas, 2016). The effect of stress on working memory in healthy adults may be explained by an over-dosing of prefrontal regions with the catecholamines, dopamine and norepinephrine (Arnsten, 2009; Arnsten, 2011; Arnsten 2015; Arnsten & Goldman-Rakig, 1998; Berridge & Spencer 2016; Deutch & Roth 1990). In persons with PD, medications including dopaminergic agonists and precursors, which are used to ameliorate motor symptoms, may unintentionally exacerbate the negative effects of excess dopamine in prefrontal regions (Cools, 2006). However, the effects of stress on working memory in persons with PD remain unknown.

Given the relationships among stress, dopamine, and working memory in healthy populations, it is likely that stress would negatively influence the already impaired working memory performance in persons with PD. Thus, the purpose of this study was to examine the effects of an acute stressor (socially evaluated cold pressor (SECP)) on a simple working memory task (digit span forward and backward) in persons with PD compared to healthy older adults (HOAs). We hypothesized that stress would negatively impact working memory capacity (digit span forward and backward two error maximum length (TE-ML)) in both HOAs and persons with PD. We also hypothesized that persons with PD would, in general, have lower working memory capacity than HOAs.
2.3 Methods

2.3.1 Participants

Fifteen participants diagnosed with idiopathic PD (mean age 67.8 ± 4.7 years; 5 males and 10 females), and 15 age-, and gender-matched HOAs (mean age 68.7± 5.0 years) completed this study. Participants with PD were recruited via the Iowa State University Neurophysiology Lab PD Database, which consists of a list of individuals diagnosed with PD who have indicated interest in research opportunities. HOAs were recruited via word of mouth; the primary inclusion criterion for this group was being between the ages of 50 and 80 (the general age of a person with PD). Participants were also excluded if they demonstrated any cognitive impairment (Mini-Mental Status Exam < 25). Participants were further excluded if they had 1) severe hearing loss, 2) any metallic objects in your head (outside the mouth), 3) any implanted objects such as a pacemaker 4) brain surgery, 5) been diagnosed with a mental disorder besides anxiety or depression, 6) any musculoskeletal disorders, 7) any other brain-related conditions, 8) were pregnant or take birth control, 9) used tobacco, illicit drugs, or excessive amounts of alcohol, 10) or had either a systolic blood pressure (SBP) above 140 mmHg, or a diastolic blood pressure above 90 mmHg during the initial screening. One HOA was excluded during the initial blood pressure screening to avoid any potential cardiac events during the SECP. All participants provided written informed consent. All procedures were approved by the Iowa State University Institutional Review Board (see Chapter 2.9 Appendix B).

2.3.2 Procedure

Participants were scheduled for two lab visits within a one week timespan. The initial visit lasted approximately 1 hour. Participants were first screened for cognitive impairment with the Mini-Mental Status Exam (MMSE) and high blood pressure using an automated Omron
blood pressure cuff. Participants then provided demographic information and completed a battery of questionnaires that have been found to be reliable and valid measures for persons with PD including the Montreal Cognitive Assessment (MOCA) (Gill, Freshman, Blender, & Ravina, 2008), Geriatric Depression Scale (GDS) (Ertan, Ertan, Kızıltan, & Uygucgil, 2005), and the State and Trait Anxiety Inventory (STAI) (Yang, et al., 2019). The Perceived Stress Scale (PSS) was also used, while it is has not been tested for its psychometric properties in persons with PD, it has been shown to be reliable and valid in older adults (Lee, 2012; Jiang, et al., 2017)

Participants with PD also completed the Unified Parkinson’s Disease Rating Scale (UPDRS) with a trained researcher. Table 2.1 shows the means and standard deviations of demographic and questionnaire data. All of the participants also completed 2 practice trials of the digit span forward and 2 practice trials of the digit span backwards to familiarize themselves with the working memory tasks during the initial visit. Finally, participants were reminded to adhere to dietary and medical restrictions prior to their second lab visit which included limiting their caffeine intake to one cup (8 oz.) of a caffeinated beverage finished at least 3 hours prior to the start of the second visit, and refraining from alcoholic beverages during the 24 hours prior to the start of the second visit. If they were non-compliant with any of these restrictions, participants were asked to reschedule. Participants were also asked to eat 1-2 hours before and to take their Parkinson’s medication 1 hour prior to the beginning of the second visit. The second visit was scheduled to align with their normal medication times. All of the second visit starting times were scheduled between 12PM and 3PM.

The second visit lasted approximately 2.5 hours and began by reviewing adherence to the dietary and medical restrictions and recommendations. During the first half hour of the visit electroencephalogram (EEG), and electromagnetic sensors were fitted on the participants, the
electromagnetic sensors were used to examine the effects of stress on PD motor symptoms. Electromagnetic sensors were placed on the tip of the index finger, the metacarpophalangeal joint index finger, and the metacarpophalangeal joint of the pinky finger on the most affected side. Next, the participants completed either the stress intervention (SECP) or the control intervention (warm water hand bath). The order was counter balanced. After completing either the stress task or the control task, participants blood pressure was taken with an automated Omron blood pressure cuff. Then, they verbally reported how stressful they thought the task was on a Likert scale from 1 to 10, with respective response anchors of “not stressful at all”, and the “most stressful thing I can imagine”. Within 1-2 minutes of completing the stress and control tasks participants completed digit span backward task. Between 5-10 minutes after completing the SECP and control condition, participants completed a sub-section of the UPDRS motor tests.

Participants then completed 80 trials of the paired click paradigm to examine inhibitory gating. Details regarding the UPDRS motor tests and the paired click paradigm will be discussed in chapters 3 and 4. Following this, participants rested or read a magazine/book for half an hour. After the rest period, participants completed the same series of steps and tasks again with the uncompleted intervention (i.e., warm water bath or SECP). See Figure 2.1.

### 2.3.3 Stress and Control Tasks

The stress intervention was a SECP task where the participants placed their hand up to the wrist in an ice water bath (2-4°C) for 90 seconds. Participants were also made aware that this task was being video recorded and that their facial expressions were to be judged by trained experimenters at a later time. During the control condition, participants placed their hand in warm water (36-38°C) for 90 seconds. During the control condition participants were reminded that they were not being videotaped and the camera was moved out of sight.
2.3.4 Digit Span Forward and Backward

E-Prime (Psychology Software Tools, Pittsburgh, PA) was used to present the digit span tasks to the participants. Digits were auditorily presented at a rate of 1 per second. The string of digits used in the task did not include the digit 0, sequences (e.g. 1-2, or 2-1) or single digit repetition (e.g. 1,5,1) (Woods, et al., 2011). When beginning the tasks participants were presented a three-digit number and asked to type the digits back into the computer in the forward or reverse (backward) order. If they got the sequence correct, the number of digits increased by one. Accuracy and response time were recorded via E-Prime. After 2 consecutive mistakes, the task ends. The number of trials correct prior to two successive misses was recorded. This is referred to as the two-error maximum list length (TE-ML) (Woods, et al., 2011). For correct trials, the response time was the amount of time the participant took to enter the digits back into the computer after the computer completed presenting the digits.

2.3.5 Cortisol Analysis

On the day of collection, salivary cortisol samples were stored in -20°C freezer within 30 minutes. Cortisol was analyzed with the Salimetrics® Cortisol Enzyme Immunoassy Kit. The kit uses a competitive immunoassay in which cortisol competes with cortisol conjugated to horseradish peroxidase for the antibody binding sites. To determine the cortisol reactivity, the area under the curve was calculated using the baseline and the 25 min post intervention samples for each condition.

2.3.6 Statistical Analysis

For all variables, outliers above or below two standard deviations were winsorized (Ruppert, 2004). This criterion resulted in 4 of the 106 response time data values of the digit
span backwards, 14 of the 178 response time data values of the digit span forwards and 4 of the 60 cortisol data values being winsorized.

An independent samples $t$-test was used to examine any group differences on demographic and questionnaire outcome measures. To confirm that the SECP initiated an increase in stress for participants, a 2 condition (stress, control) x 2 group (PD, HOA) repeated measures ANOVA was completed for measures of stress (perceived stress, blood pressure, and cortisol). To test the hypothesis that stress will negatively impact working memory capacity, and that persons with PD will in have a lower working memory capacity than HOAs, a 2 condition (stress, control) x 2 group (PD, HOA) repeated measures ANOVA was used to determine differences on digit span forward TE-ML, and digit span backward TE-ML.

When examining digit span response time, an additional factor of digit length was also included in our repeated measures ANOVA. For the digit span forward 96.7% of our participants successfully completed both trials for the 5 digit length, while only 60% of participants successfully completed the 6 digit length. Thus, digit lengths 3, 4, and 5 were used to examine response time on correct trials using a 2 condition (stress, control) x 2 group (PD, HOA) x 3 digit length (3, 4, 5) repeated measures ANOVA. For the digit span backwards, 93.3% of our participants successfully completed both trials for the 3 digit length, 73.3% successfully completed both trials of the 4 digit length, and 50% completed both trials of the 5 digit length. For our analysis digit span backwards response time, a 2 condition (stress, control) x 2 group (PD, HOA) x 2 digit length(3, 4) repeated measures ANOVA was used. For all repeated measures ANOVAs, partial eta squared ($\eta^2_p$) effect sizes were calculated. Planned post hoc mean comparison $t$-tests were then used for response time measures when analyzing within and between subjects in each intervention at each digit length. A Pearson correlation was performed
on all working memory measures and can be found in the chapter 2.8 Appendix A. Significance was set at \( \alpha = 0.05 \). For all post hoc analyses, a Bonferroni correction was used to interpret statistical significance.

2.4 Results

Table 2.2 shows the means, and standard deviations for all stress measures (perceived stress, blood pressure, and cortisol). Table 2.3 shows the means, standard deviations, and pre-planned post hoc comparisons for all working memory measures.

2.4.1 Participants

Participants with PD had higher trait anxiety than the HOAs \( (t_{(28)} = 3.086, p = 0.005, \text{Mean Difference (MD)} = +9.2, d = 1.126) \). No other demographic variables were significantly different (Table 2.1).

2.4.2 Perceived Stress

There was a main effect of condition \( (F_{(1,28)} = 147.393, p < 0.001, \eta^2_p = 0.840) \). The participants found that the SECP was more stressful than the control condition \( (MD = +5.2, d = 2.256) \). There was no main effect for group \( (F_{(1,28)} = 0.267, p = 0.609, \eta^2_p = 0.009) \), or an interaction effect for group x condition \( (F_{(1,28)} = 0.006, p = 0.938, \eta^2_p = 0.000) \).

2.4.3 Blood Pressure

There was a main effect for condition both systolic \( (F_{(1,28)} = 8.003, p = 0.009, \eta^2_p = 0.222) \) and diastolic blood pressure \( (F_{(1,28)} = 5.543, p = 0.026, \eta^2_p = 0.165) \). The participants had higher systolic blood pressure after the SECP compared to the control condition \( (MD = +6.4 \text{ mmHg}, d = 0.518) \). Participants also had higher diastolic blood pressure after the SECP compared to the control condition \( (MD = +2.8 \text{ mmHg}, d = 0.430) \). There was no main effect for group systolic blood pressure \( (F_{(1,28)} = 2.138, p = 0.155, \eta^2_p = 0.071) \), no main effect for group
diastolic blood pressure ($F_{(1,28)} = 0.360, p = 0.553, \eta_p^2 = 0.013$), and no interaction effect of group x condition for systolic blood pressure ($F_{(1,28)} = 0.889, p = 0.354; \eta_p^2 = 0.031$) or diastolic blood pressure ($F_{(1,28)} = 0.767, p = 0.388; \eta_p^2 = 0.027$)).

2.4.4 Cortisol

There was a main effect of condition for cortisol ($F_{(1,28)} = 6.780, p = 0.015 \eta_p^2 = 0.195$). Participants had a higher cortisol AUC values during the SECP compared to the control condition ($MD = +13.4 \text{ ng/dl/hr}, d = 0.479$). There was no main effect for group ($F_{(1,28)} = 0.187, p = 0.699, \eta_p^2 = 0.007$) and no interaction effect of group x condition ($F_{(1,28)} = 0.596, p = 0.447, \eta_p^2 = 0.021$).

2.4.5 Digit Span Forward and Backward Two Error Maximum Length

Figure 2.2A and 2.2B shows results for digit span forward and backward TE-ML.

For the digit span forward TE-ML, there were no main effects of condition ($F_{(1,28)} = 0.086, p = 0.771, \eta_p^2 = 0.003$), group ($F_{(1,28)} = 0.565, p = 0.459, \eta_p^2 = 0.020$), or interaction effects ($F_{(1,28)} = 0.345, p = 0.562, \eta_p^2 = 0.012$).

For the digit span backward TE-ML, no main effect for condition was found ($F_{(1,28)} = 0.000, p = 1.000, \eta_p^2 = 0.000$). However, there was a trend for group ($F_{(1,28)} = 3.632, p = 0.067, \eta_p^2 = 0.115$). In general, HOAs had a larger digit span backward TE-ML than persons with PD ($MD = 0.8, d = 0.617$). There was also an interaction trend for group x condition ($F_{(1,28)} = 3.429, p = 0.075, \eta_p^2 = 0.109$). Persons with PD increased their digit span backward TE-ML ($MD = +0.4, d = 0.356$) score following the SECP, while HOAs demonstrated a decrease ($MD = -0.4, d = 0.322$). Post hoc analysis did not show any differences between persons with PD and HOAs following the SECP ($p = 0.418, MD = 0.4, d = 0.301$). However, following the control condition,
persons with PD had a lower digit span backward TE-ML score than HOAs ($p = 0.014, MD = -1.2, d = 0.957$).

**2.4.6 Digit Span Forward Response Time**

Figure 2.2C shows results for digit span forward response time. There was no main effect of condition for digit span forward response time ($F_{(1,28)} = 0.398, p = 0.533, \eta^2_p = 0.014$). A main effect of group ($F_{(1,28)} = 5.579, p = 0.025, \eta^2_p = 0.166$) was seen. HOAs had a faster response time compared to persons with PD ($MD = -0.9s, d = 0.493$). There was a main effect of digit length after applying a Greenhouse-Geisser correction for lack of sphericity ($F_{(1.628,45.575)} = 12.517, p < 0.001, \eta^2_p = 0.309$). After applying a Bonferroni correction, post hoc analysis showed that there was a significant difference in response time with a 5 digit length compared to the 3 digit length ($p = 0.008, MD = 1.03s, d = 0.413$), and the 4 digit length ($p <0.001, MD = 1.21s, d = 0.641$). There was no difference between the 3 digit length and the 4 digit length ($p = 1.0, MD = 0.18s, d = 0.119$).

The results revealed a length x group interaction effect ($F_{(1.628, 45.575)} = 6.245, p = 0.007 \eta^2_p =0.182$). Post hoc analysis showed that there were significant differences between HOAs and persons with PD at the 3 digit length ($p < 0.001, MD = 1.7s, d = 1.346$) and 4 digit length ($p < 0.001, MD = 1.1s, d = 1.098$), where persons with PD had a slower response time. There was no significant difference at the 5 digit length ($p = 0.881, MD = -0.1s, d = 0.049$). Post hoc analysis also revealed that HOAs had a slower response time at the 5 digit length compared to the 3 digit length ($p <0.001, MD = +1.9s, d = 0.904$) and 4 digit length ($p <0.001, MD = +1.8s, d = 0.802$), while there was no difference between the 3 and 4 digit lengths ($p = 0.654, MD = 0.1s, d = 0.082$). For persons with PD, post hoc analysis revealed no significant differences among any of the digit lengths.
No condition x group ($F_{(1,28)} = 0.057, p = 0.813, \eta^2_p = 0.002$), condition x length ($F_{(1.933, 54.124)} = 1.295, p = 0.282, \eta^2_p = 0.044$), or condition x length x group ($F_{(1.933, 54.124)} = 1.842, p = 0.168, \eta^2_p = 0.062$) interaction effects were found. Post hoc comparisons showed that persons with PD had a slower response time than HOAs during the SECP for 3 digit length ($p = 0.021$, $MD = +1.6s$, $d = 0.890$), and 4 digit length ($p < 0.001$, $MD = +1.6s$, $d = 1.594$), and during the control condition at the 3 digit length ($p = 0.014$, $MD = +2.0s$, $d = 0.957$). Post hoc comparisons also demonstrated that HOAs had a slower response during the control condition compared to the SECP at the 4 digit length ($p = 0.028$, $MD = +0.9s$, $d = 0.632$). No other post hoc comparisons were statistically significant.

2.4.7 Digit Span Backward Response Time

Figure 2.2D shows results for digit span backwards response time. There was a main effect of condition ($F_{(1,20)} = 4.558, p = 0.045, \eta^2_p = 0.186$) and length ($F_{(1,20)} = 28.645, p < 0.001, \eta^2_p = 0.589$). In general, participants had a slower response time during the SECP compared to the control condition ($MD = +0.8s$, $d = 0.314$), and had a slower response time at 4 digits compared to 3 digits ($MD = +3.5s$, $d = 0.984$). There was no main effect for group ($F_{(1,20)} = 0.717, p = 0.407, \eta^2_p = 0.035$). There were no interaction effects for condition x group ($F_{(1,20)} = 0.072, p = 0.791, \eta^2_p = 0.004$), length x group ($F_{(1,20)} = 0.085, p = 0.774, \eta^2_p = 0.004$), condition x length ($F_{(1,20)} = 0.086, p = 0.772, \eta^2_p = 0.004$), and condition x length x group ($F_{(1,20)} = 0.434, p = 0.518, \eta^2_p = 0.021$). No post hoc comparisons were statistically significant.

2.5 Discussion

Our results revealed that the SECP was successful in increasing stress, both perceptually and physiologically (perceived stress, blood pressure, and cortisol) in both HOAs and persons with PD. Under non-stressful conditions, persons with PD had a smaller digit span backward
capacity and were slower during the digit span forward task ($MD = +0.9s$) compared to HOAs. However, contrary to our hypothesis, during the stress condition, persons with PD performed similarly to HOAs on the digit span backward task. Thus, as expected stress reduced capacity in HOAs ($MD = -0.4$), but surprisingly increased capacity in persons with PD ($MD = +0.4$), equalizing performance. The results also revealed that stress had a negative influence on the amount of time it took to manipulate information (response time) on the digit span backwards task ($MD = +0.9s$) in both groups. Stress did not appear to influence digit span forward capacity or response time for either group, but stress did shorten the response time in HOAs during for 4 digit length.

Consistent with much of the previous research in this area, these results showed that persons with PD had smaller working memory capacity on the digit span backward task during the control condition (no stress) (Grogan, et al., 2018; Kudlicka, et al., 2011; Siegert, et al., 2008). While some studies have found no differences in digit span backward capacity, this may have been due to testing newly diagnosed persons (Zokaei, Burnett Heyes, Gorgoraptis, Budhdeo, & Husain, 2015), small sample size (8 participants) (Dalrymple-Alford, Kalders, Jones, & Watson, 1994), and those in the earlier stages of the disease (motor UPDRS = 19.81) (Warden, Hwang, Marshall, Fenesy, & Poston, 2016). The participants in this study were in the middle stages of the disease (H&Y = 2.3; UPDRS = 66.9) and thus may be more likely to display lower digit span capacity scores. In contrast, there were no differences between persons with PD and HOAs on the digit span forward task. While a meta-analysis showed that persons with PD have a smaller digit span forward capacity, the effect size was small (Hedges’ $g = 0.18$) (Siegert, et al., 2008), and we were unlikely to find any group differences due to being underpowered. Overall, more complex working memory tasks such as the digit span backward
are more likely to be negatively impacted in persons with PD during periods of time without undue stress.

The results also showed that performance in persons with PD was worse than HOAs during the no stress condition, and that the acute stressor equalized performance between the two groups by improving scores in persons with PD and decreasing scores in HOAs. The two prevailing theories of why persons with PD have impaired working memory are due to either 1) dopaminergic medication ‘over-dosing’ of prefrontal regions, or 2) reduced striatal dopamine (Cools, 2006; Halliday, Leverenz, Schneider, & Adler, 2014; Marie, et al., 1999). By inducing acute stress, both prefrontal and striatal dopamine levels presumably increased (Finlay & Zigmond, 1997; Gresch, Sved, Zigmond, & Finlay, 1994; Imperato, Puglisi-Allegra, Casolini, & Angelucci, 1991; Morrow, Roth, & Elsworth, 2000; Vaessen, Hernaus, Myin-Germeys, & van Amelsvoort, 2015). The positive effect of stress on working memory capacity in our sample of persons with PD who were in the middle stages of the disease (H&Y = 2.3), suggests that their impaired working memory may have been due to reduced striatal dopamine.

The results revealed that stress had no effect on the digit span forward task for either persons with PD or HOAs. While a few studies report that stress negatively influences digit span forward capacity (Taverniers, Van Ruysseveldt, Smeets, & von Grumbkow, 2010), most studies find that stress does not influence simple working memory tasks that do not require manipulation of information (i.e. digit span forward) (Hoffman & al’Absi, 2004; Kuhlmann, Piel, & Wolf, 2005; Schoofs, Wolf, & Smeets, 2009; Shields, et al., 2016). Overall, the lack of differences between HOAs and persons with PD, and the lack of an effect of the acute stressor, suggest that the updating function of working memory may be less sensitive to dopaminergic modulation.
compared to more complex working memory tasks that require manipulation of information (i.e. digit span backward).

Measuring response time of the digit span is an uncommon measure of working memory or other cognitive processes, but it has been employed by some researchers (Cowan, et al., 2003; Thomas, Milner, & Haberlandt, 2003). For this task, response time is thought to reflect general processing speed (Kail & Salthouse, 1994). Thus, the digit span forward response time may be more representative of simple processing speed, as reordering of the digits was unnecessary. Other studies find that stress improves response time on working memory tasks such as the Sternberg working memory task in healthy adults (Duncko, Johnson, Merikangas, & Grillon, 2009). In this study, HOAs had a quicker response time on the digit span forward during the stress condition, which suggests that stress improved processing speed for this group. Interestingly, persons with PD did not see this same decrease in response time following the SECP stressor. One possible explanation for this is that stress negatively impacted PD motor symptoms and how quickly persons with PD were able to reenter the digits on the keyboard. While the literature on how stress effects PD motor symptoms is limited, stress has been shown to negatively affect skilled reaching in PD rat models (Smith, Jadavi, Colwell, Perrehudoff, & Metz, 2008). Thus, more studies are needed to disentangle the effects stress has on motor symptoms and processing speed in persons with PD.

For the digit span backward task, response time would include both the time needed to reenter the digits as well as the time needed to reorder the digits. In our study, the results showed that stress had a negative impact on response time in both HOAs and persons with PD. These consistent findings for both groups, and the opposite effect in HOAs during the forward digit span (i.e. quicker response time), suggests that stress negatively influenced the time needed to
manipulate/reorder the digits. Thus, while stress appeared to improve working memory capacity in persons with PD, it may have hindered the speed at which they were able to manipulate the information. Another possibility is that stress improved the speed of both general processing and manipulating information in persons with PD, but improvements were masked by the worsening of motor symptoms and impairment in fine motor skills. Future studies that use a different response measure (e.g. something not reliant on motor skills) are needed to separate motor and cognitive components to better understand how stress affects response time in persons with PD.

2.5.1 Limitations

A major limitation of this study was the small sample size and consequent increased risk for Type II errors. While there was a statistical trend for improvements in persons with PD following stress and decrements in HOAs, this may have been significant with a larger sample. Similarly, no differences between HOAs and persons with PD on the digit span forward capacity were found. With a larger sample size, there may have been group differences and an interaction similar to what was seen in the digit span backwards. Another major limitation was using the keyboard, while this is unlikely to affect TE-ML measures, it could have had differential effects on the response times of persons with PD. Response times may have been inflated in persons with PD compared to processing/cognitive speed due to PD motor symptoms such as bradykinesia (slowness of movement). Additional studies using verbal report of digits which may be less affected by bradykinesia may be a better indicator of processing/cognitive speed in persons with PD. Another limitation is that the stress intervention used in this study was primarily a physical stressor, which has more of an impact on dorsal striatal dopamine than psychological stressors (Vaessen, et al., 2015). Future studies are needed to differentiate the effects of different types of stress. Finally, dopamine and other neurotransmitters were not measured in this study, which will
be needed to confidently conclude the mechanisms involved in the influence of stress on working memory in persons with PD.

2.5.2 Conclusions

Taken together, these results suggest that stress does not have a universally negative effect on persons with PD. In fact, even those with impaired working memory capacity may actually see improvements following stress. While the mechanisms involved in this cannot be examined with this study, the results suggest that improvement in working memory capacity may be mediated by increases in striatal dopamine due to the stress response. Results also demonstrated that stress may have improved simple processing speed in HOAs. It is less clear how stress affected processing speed in persons with PD. Stress may have improved simple processing speed in persons with PD, but improvements may have been masked by the worsening of motor symptoms. Further research is needed to determine how stress affects PD motor symptoms. Overall, this study showed that in persons with mild to moderate PD, stress may actually improve some executive functioning abilities. This demonstrates that there may be benefit in studying the complex neurotransmitter interactions between PD and stress related neurotransmitters.
2.6 Figures and Tables

**Figure 2.1. First and Second Visit Procedure**

- **1st Visit**
  - Check Residency, Compliance, and Setup
  - SECP or Control Intervention
  - Baseline cortisol sample is taken and then participants complete either the SECP or control intervention
  - Digit Span Tasks
    - Finger tapping, hand movements, pronation-supination of the hand, postural tremor, and resting tremor. In that order.
  - UPDRS Motor Tasks
  - Paired Click Paradigm
  - Cortisol Sample
  - 25 min post-intervention cortisol sample

- **2nd Visit**
  - Check Residency and setup Electromagnetic Sensors, and EEG
  - Participants complete either the SECP or control intervention
  - Digit span forward followed by digit span backward
  - Finger tapping, hand movements, pronation-supination of the hand, postural tremor, and resting tremor. In that order.
  - Participants listen to 80 pairs of paired clicks
  - 30 Minute Rest Period
  - End of Experiment

Demographic Questionnaire, MMSE, MoCa, PSS, UPDRS (PD only), GDS, STAI, review restrictions, practice digit span tasks
Figure 2.2. The Effects of Stress on Working Memory

A) Digit span forward TE-ML for both groups during the control and stress conditions. B) Digit span backward TE-ML for both groups during the control and stress conditions. C) Digit span forward response time for both groups with conditions (control, stress) collapsed at each digit length. D) Digit Span Backward response time for the control and stress condition and groups (HOA, PD) collapsed at digit lengths 3 and 4. Standard error bars shown. Small horizontal bars show between group differences. Long horizontal bars show within group differences. Long horizontal bars connected with short horizontal bars shows a main effect of condition. \( *p<0.05, **p<0.01, ***p<0.001 \)
Table 2.1. Demographic and Questionnaire Information

<table>
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<th>PD</th>
<th>HOA</th>
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<tr>
<td>Age (Years)</td>
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<td>68.7 ± 5.0</td>
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<td>N/A</td>
</tr>
<tr>
<td>Years since diagnosis</td>
<td>9.9 ± 1.7</td>
<td>N/A</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.3 ± 0.7</td>
<td>29.7 ± 0.6</td>
</tr>
<tr>
<td>MOCA</td>
<td>26.1 ± 2.2</td>
<td>26.5 ± 2.5</td>
</tr>
<tr>
<td>GDS</td>
<td>6.5 ± 4.5</td>
<td>3.8 ± 3.7</td>
</tr>
<tr>
<td>PSS</td>
<td>13.5 ± 5.6</td>
<td>9.2 ± 6.6</td>
</tr>
<tr>
<td>STAI1</td>
<td>33.3 ± 8.5</td>
<td>28 ± 10.9</td>
</tr>
<tr>
<td>STAI2</td>
<td>38.3 ± 8.7**</td>
<td>29.1 ± 7.6**</td>
</tr>
</tbody>
</table>

Note. Means and standard deviations for all demographic measures, and cognitive questionnaires. For between subjects comparisons **p<0.01. HOA; healthy older adult; PD: persons with PD; UPDRS: Unified Parkinson’s Disease Rating Scale; H&Y: Hoehn and Yahr; MMSE: Mini-Mental Status Exam; MOCA: Montreal Cognitive Assessment; GDS: Geriatric Depression Scale; PSS: Perceived Stress Scale; STAI1: State and Trait Anxiety Inventory (State); STAI2: State and Trait Anxiety Inventory (Trait).

Table 2.2. Stress Measures

<table>
<thead>
<tr>
<th></th>
<th>PD Control</th>
<th>HOA Control</th>
<th>PD Stress</th>
<th>HOA Stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived Stress***</td>
<td>1.20±0.56</td>
<td>1.00±0.00</td>
<td>6.40±2.53</td>
<td>6.13±2.27</td>
</tr>
<tr>
<td>SBP (mmHg)**</td>
<td>121.3±13.0</td>
<td>130.5±16.2</td>
<td>129.7±15.4</td>
<td>134.7±13.8</td>
</tr>
<tr>
<td>DBP (mmHg)*</td>
<td>75.6±9.3</td>
<td>74.9±8.0</td>
<td>79.5±8.7</td>
<td>76.7±8.3</td>
</tr>
<tr>
<td>Cortisol (ng/dl/hr)*</td>
<td>66.7±26.4</td>
<td>58.8±23.2</td>
<td>76.1±27.0</td>
<td>76.3±34.2</td>
</tr>
</tbody>
</table>

Note. Means and standard deviations for all measures of stress for both groups and both conditions. For a main effect of condition *p<0.05, **p<0.01, ***p<0.001. DBP: Diastolic blood pressure; HOA: healthy older adult; PD: persons with Parkinson’s disease; SBP: Systolic blood pressure.
Table 2.3. Working Memory Measures

<table>
<thead>
<tr>
<th></th>
<th>PD Control</th>
<th>HOA Control</th>
<th>PD Stress</th>
<th>HOA Stress</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Digit Span</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Forward</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TE-ML</td>
<td>6.20 ± 0.94</td>
<td>6.60 ± 0.99</td>
<td>6.27 ± 1.34</td>
<td>6.40 ± 1.30</td>
</tr>
<tr>
<td><strong>Backward</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TE-ML</td>
<td>4.20 ± 1.15(^b)</td>
<td>5.40 ± 1.35(^b)</td>
<td>4.60 ± 1.30</td>
<td>5.00 ± 1.36</td>
</tr>
<tr>
<td><strong>Forward</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT 3 Digits(s)</td>
<td>6.81 ± 2.36(^{bb})</td>
<td>4.65 ± 1.72(^{bb})</td>
<td>6.02 ± 2.08(^b)</td>
<td>4.42 ± 1.15(^b)</td>
</tr>
<tr>
<td><strong>Digit Span</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Forward</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT 4 Digits(s)</td>
<td>5.79 ± 1.24</td>
<td>5.11 ± 1.54(^a)</td>
<td>5.88 ± 1.30(^{bbb})</td>
<td>4.25 ± 0.73(^{a,bbb})</td>
</tr>
<tr>
<td><strong>Digit Span</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Forward</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT 5 Digits(s)</td>
<td>6.48 ± 1.85</td>
<td>6.87 ± 1.81</td>
<td>6.32 ± 1.32</td>
<td>6.09 ± 3.19</td>
</tr>
<tr>
<td>**Backward 3 Digits(s)</td>
<td>5.88 ± 2.25</td>
<td>4.77 ± 1.64</td>
<td>6.19 ± 2.00</td>
<td>5.86 ± 2.01</td>
</tr>
<tr>
<td>**Backwards 4 Digits(s)</td>
<td>9.18 ± 3.80</td>
<td>8.26 ± 2.72</td>
<td>10.32 ± 5.51</td>
<td>9.03 ± 4.35</td>
</tr>
</tbody>
</table>

Note. Means and standard deviations for all working memory measures for both groups and both conditions. For within subjects intervention comparisons \(^a\)\(p<0.05\), \(^{aa}\)\(p<0.01\), \(^{aaa}\)\(p<0.001\). For between subjects comparisons for a particular condition \(^b\)\(p<0.05\), \(^{bb}\)\(p<0.01\), \(^{bbb}\)\(p<0.001\). HOA; healthy older adult; PD: persons with Parkinson’s disease; RT: Response Time; TE-ML Two Error-Maximum Length
2.7 References


Berridge, C. W., & Spencer, R. C. (2016). Differential cognitive actions of norepinephrine a2 and a1 receptor signaling in the prefrontal cortex. *Brain research, 1641*, 189-196.


## 2.8 Appendix A: Additional Material

Table A1. Working Memory Correlation Table

<table>
<thead>
<tr>
<th>Stress</th>
<th>TE-ML</th>
<th>Forward</th>
<th>Back</th>
<th>3 Digits</th>
<th>4 Digits</th>
<th>5 Digits</th>
<th>3 Digits</th>
<th>4 Digits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Forward</td>
<td>.402*</td>
<td>.029</td>
<td>.124</td>
<td>.294</td>
<td>-.125</td>
<td>-.144</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Back</td>
<td>.029</td>
<td>.321</td>
<td>.248</td>
<td>.360</td>
<td>-.160</td>
<td>.206</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 Digits</td>
<td>-.125</td>
<td>.075</td>
<td>.143</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 Digits</td>
<td>-.144</td>
<td>.206</td>
<td>.192</td>
<td>.378</td>
<td>.458*</td>
<td>.407*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 Digits</td>
<td>-.125</td>
<td>.075</td>
<td>.143</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>TE-ML</td>
<td>Forward</td>
<td>.440*</td>
<td>.280</td>
<td>-.020</td>
<td>-.235</td>
<td>-.071</td>
</tr>
<tr>
<td></td>
<td>Back</td>
<td>.484**</td>
<td>.584**</td>
<td>-.358</td>
<td>-.403*</td>
<td>.003</td>
<td>-.233</td>
<td>-.043</td>
</tr>
<tr>
<td></td>
<td>3 Digits</td>
<td>-.081</td>
<td>-.070</td>
<td>.133</td>
<td>.353</td>
<td>.017</td>
<td>.205</td>
<td>.538**</td>
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<tr>
<td></td>
<td>4 Digits</td>
<td>.060</td>
<td>-.218</td>
<td>.469**</td>
<td>.468**</td>
<td>.149</td>
<td>-.005</td>
<td>.288</td>
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<tr>
<td></td>
<td>5 Digits</td>
<td>.021</td>
<td>-.041</td>
<td>.052</td>
<td>.470**</td>
<td>.226</td>
<td>.045</td>
<td>.526**</td>
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<tr>
<td></td>
<td>3 Digits</td>
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<td>-.262</td>
<td>.157</td>
<td>.537**</td>
<td>.439*</td>
<td>.283</td>
<td>.647**</td>
</tr>
<tr>
<td></td>
<td>4 Digits</td>
<td>-.208</td>
<td>.043</td>
<td>.030</td>
<td>.082</td>
<td>.440*</td>
<td>.372</td>
<td>.812**</td>
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</table>
Table A1 continued.

<table>
<thead>
<tr>
<th>Stress</th>
<th>TE-ML</th>
<th>Forward RT</th>
<th>Backward RT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Forward</td>
<td>Back</td>
</tr>
<tr>
<td></td>
<td>Forward</td>
<td>.440*</td>
<td>.484**</td>
</tr>
<tr>
<td></td>
<td>Back</td>
<td>.280</td>
<td>.584**</td>
</tr>
<tr>
<td>Forward RT</td>
<td>3 Digits</td>
<td>-.020</td>
<td>-.358</td>
</tr>
<tr>
<td></td>
<td>4 Digits</td>
<td>-.235</td>
<td>-.403*</td>
</tr>
<tr>
<td></td>
<td>5 Digits</td>
<td>-.071</td>
<td>.003</td>
</tr>
<tr>
<td>Back RT</td>
<td>3 Digits</td>
<td>-.202</td>
<td>-.233</td>
</tr>
<tr>
<td></td>
<td>4 Digits</td>
<td>-.059</td>
<td>-.043</td>
</tr>
<tr>
<td>Control</td>
<td>TE-ML</td>
<td>Forward</td>
<td>Back</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>.528**</td>
</tr>
<tr>
<td></td>
<td>Back</td>
<td>.528**</td>
<td>1</td>
</tr>
<tr>
<td>Forward RT</td>
<td>3 Digits</td>
<td>-.170</td>
<td>-.426*</td>
</tr>
<tr>
<td></td>
<td>4 Digits</td>
<td>.043</td>
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</tr>
<tr>
<td></td>
<td>5 Digits</td>
<td>.003</td>
<td>-.062</td>
</tr>
<tr>
<td>Back RT</td>
<td>3 Digits</td>
<td>-.104</td>
<td>-.292</td>
</tr>
<tr>
<td></td>
<td>4 Digits</td>
<td>.033</td>
<td>-.091</td>
</tr>
</tbody>
</table>

*Note.* Pearson’s r for correlations between all digit span measures. *p* < 0.05, **p** < 0.05. Back: Digit Span Backward; Forward: Digit Span Forward; RT: Response Time; TE-ML: Two-Error Maximum Length.
2.9 Appendix B: Informed Consent/ IRB Approval

Date: 6/16/2016
To: Andrew Zaman
238 Forker Bldg
Ames, IA

From: Office for Responsible Research

Title: Working Memory, Sensory Processing, and Motor Performance Study

IRB ID: 16-257

Approval Date: 6/16/2016
Date for Continuing Review: 6/6/2018

Submission Type: New
Review Type: Full Committee

The project referenced above has received approval from the Institutional Review Board (IRB) at Iowa State University according to the dates shown above. Please refer to the IRB ID number shown above in all correspondence regarding this study.

To ensure compliance with federal regulations (45 CFR 46 & 21 CFR 50), please be sure to:

- Use only the approved study materials in your research, including the recruitment materials and informed consent documents that have the IRB approval stamp.
- Retain signed informed consent documents for 3 years after the close of the study, when documented consent is required.
- Obtain IRB approval prior to implementing any changes to the study by submitting a Modification Form for Non-Exempt Research or Amendment for Personnel Changes form, as necessary.
- Immediately inform the IRB of any serious and/or unexpected adverse experiences involving risks to subjects or others, and any other unanticipated problems involving risks to subjects or others.
- Stop all research activity if IRB approval lapses, unless continuation is necessary to prevent harm to research participants. Research activity can resume once IRB approval is reestablished.
- Complete a new continuing review form at least three to four weeks prior to the date for continuing review as noted above to provide sufficient time for the IRB to review and approve continuation of the study. We will send a courtesy reminder as this date approaches.

Please be aware that IRB approval means that you have met the requirements of federal regulations and ISU policies governing human subjects research. Approval from other entities may also be needed. For example, access to data from private records (e.g., student, medical, or employment records, etc.) that are protected by FERPA, HIPAA, or other confidentiality policies requires permission from the holders of those records. Similarly, for research conducted in institutions other than ISU (e.g., schools, other colleges or universities, medical facilities, companies, etc.), investigators must obtain permission from the institution(s) as required by their policies. IRB approval in no way implies or guarantees that permission from those other entities will be granted.

Upon completion of the project, please submit a Project Closure Form to the Office for Responsible Research, 1138 Pearson Hall, to officially close the project.

Please don't hesitate to contact us if you have questions or concerns at 515-294-4566 or IRB@iastate.edu.
CHAPTER 3: THE EFFECTS OF A SOCIALLY EVALUATED COLD PRESS STRESSOR ON INHIBITORY GATING IN PERSONS WITH PARKINSON’S DISEASE

Andrew Zaman\textsuperscript{1}, Patricia Izbicki\textsuperscript{1}, Elizabeth L. Stegemöller\textsuperscript{1}

\textsuperscript{1}Department of Kinesiology, Iowa State University

Modified from a manuscript to be submitted to Movement Disorders.

3.1 Abstract

Persons with Parkinson’s (PD) disease have a variety of non-motor symptoms including sensory processing impairments. One such processing impairment seen in persons with PD is inhibitory gating which is a pre-attentional sensory filter that eliminates repetitive information. Acute stress can negatively impact inhibitory gating. However, there is a gap in knowledge about how stress affects inhibitory gating in persons with PD. The purpose of this study is to examine how an acute stressor affects inhibitory gating in persons with PD.

Fifteen persons with PD and fifteen healthy older adults (HOAs) completed a paired click paradigm following an acute stressor (socially evaluated cold pressor) and after a non-stressful control condition. The amplitudes of p50 response to the first (S1) and second (S2) stimuli were analyzed, and the p50 ratio (S1/S2) was our measure for inhibitory gating. A repeated measures factorial ANOVA was used to examine statistical differences.

Both HOAs and persons with PD showed decreased inhibitory gating following the acute stressor compared with the non-stress control condition. While not significant, the stressor appeared to decrease inhibitory gating to a greater degree in persons with PD compared to HOAs with a condition x group interaction showing a medium to large effect size ($\eta_p^2 = 0.104$). The results also demonstrated a group trend ($p < 0.1$) where persons with PD had larger S1 and S2 amplitudes.
Overall, the results suggest that acute stress has a negative impact on inhibitory gating in persons with PD and HOAs. Although it was not statistically significant, persons with PD may have a larger decrease in inhibitory gating following an acute stressor. While more evidence is needed to confirm, impairment of sensory processes such as inhibitory gating may contribute to PD motor symptoms. Thus, pharmacological treatment of inhibitory gating may be a potentially effective target for reducing PD motor symptoms. In addition, the larger p50 amplitudes seen in persons with PD suggests an over-activation/compensation by the reticular activating system. Hence, the p50 component may be a potential biomarker useful for examining interactions between the cholinergic and dopaminergic systems in persons with PD.

3.2 Introduction

Motor decrements are the hallmark symptoms of Parkinson’s disease (PD). However, in addition to motor symptoms, persons with (PD) also have a number of secondary non-motor symptoms, including sensory processing impairments (Boecker, et al., 1999, Gulberti, et al., 2015; Kaji, 2001; Patel, Jankovic, & Hallett, 2014; Teo et al., 1997). One sensory processing impairment seen in persons with PD is reduced inhibitory gating (Gulberti, et al., 2015; Lukhanina, Berezetskaya, & Karaban, 2011; Lukhanina, Kapustina, Berezetskaya, & Karaban, 2009; Teo, et al., 1997), which has been associated motor symptoms such as bradykinesia (Lukhanina, et al., 2011). Inhibitory gating is a natural pre-attentional sensory process that filters out repetitive information (Buotros & Belger, 1999; Gjini, Arfken, & Boutros, 2010). Acute stress negatively influences inhibitory gating (Ermutlu, Karamürsel, Uğur, Senturk, & Gokhan, 2005; Johnson & Adler, 1993; White & Yee, 1997). However, it is unknown how stress will impact inhibitory gating in persons with PD.
Inhibitory gating is typically evaluated using a paired click paradigm where pairs of simple auditory stimuli elicit the electroencephalography (EEG) p50-n100-p200 auditory components. During the paired-click paradigm, the first click is referred to as the S1 and is followed shortly thereafter by the second click or S2. The most common inhibitory gating measure is the S2/S1 ratio of the p50 component (p50 ratio). The normal gating response is indicated by a low S2/S1 ratio, with a large amplitude response to S1 and a reduced amplitude response to S2.

There is no general agreement about the brain regions involved in p50 inhibitory gating but most studies find that the prefrontal cortex is heavily involved (Boutros, Gjini, Eickhoff, Urbach, & Pflieger, 2013; Garcia-Rill, et al., 2008; Grunwald, et al., 2003; Korzyukov, et al., 2007; Tregellas, et al., 2007; Williams, Nuechterlein, Subotnik, & Yee, 2011). Studies also implicate the thalamus, somatosensory, supplementary motor, anterior cingulate, and parietal areas (Boutros, et al., 2013; Grunwald, et al., 2003; Tregellas, et al., 2007; Williams, et al., 2011). Although the basal ganglia has not been directly implicated in inhibitory gating, evidence suggests it is also involved. For example, the basal ganglia is involved in modulating sensory information (Juri, Rodriguez-Oroz, & Obeso, 2011) and is functionally connected to prefrontal and parietal regions via subcortical loops (McHaffie, Stanford, Stein, Coizet, & Redgrave, 2005). Furthermore, impaired gating is seen in disorders of the basal ganglia such as PD (Gulberti, et al., 2015; Teo, et al., 1997), Huntington’s disease (Uc, Skinner, Rodnitzsky, & Garcia-Rill, 2003), and focal dystonia (Lim, Bradshaw, Nicholls, & Altenmueller, 2005). Finally, involvement of the basal ganglia is also demonstrated by studies that show both subthalamic nucleus deep brain stimulation (Gulberti, et al., 2015) and ablative pallidal surgery restore normal inhibitory gating in persons with PD (Mohamed, Lacono, & Yamada, 1996, Teo, Rasco, Skinner, & Garcia-Rill, 1998). Overall, this evidence suggests that the basal ganglia and
sensorimotor loop are involved in inhibitory gating, and that inhibitory gating may be associated with the functioning of sensory and motor processes.

One might assume that since persons with PD have disrupted inhibitory gating that dopamine is mechanistically involved. However, Levodopa does not appear to modulate inhibitory gating in persons with PD (Gulberti, et al., 2015; Lukhanina, et al., 2009; Teo, et al., 1997). A more likely modulatory neurotransmitter in persons with PD is norepinephrine. Inhibitory gating appears to have an inverted-U shaped relationship with norepinephrine, where both agonists and antagonists have been shown to disrupt normal gating (Adler, et al., 1991; Stevens, Meltzer, & Rose, 1993). Persons with PD suffer cellular loss in the locus coeruleus, a region the produces and projects norepinephrine (Vermeiren & De Deyn, 2017). Thus, impaired gating in persons with PD may be mediated by neuronal death in the locus coeruleus and decreased levels of norepinephrine.

Acute stressors such as the cold-pressor and public speaking have repeatedly been shown to impair inhibitory gating, proposedly by increasing the release of norepinephrine (Ermutlu, et al., 2005; Johnson & Adler, 1993), and the amount of norepinephrine released during a cold stressor is greater in older adults compared to young adults (Palmer, Ziegler, & Lake, 1978). Given the cellular death in the locus coeruleus in persons with PD, and increased norepinephrine release during a cold stressor in older adults, it is unknown how SECP will impact inhibitory gating in persons with PD. Thus, the main purpose of this study is to examine how an acute stressor [Socially Evaluated Cold Pressor (SECP)] impacts p50 inhibitory gating (p50 ratio) in persons with PD. Given the aforementioned gaps in knowledge, we hypothesize that the SECP task will impair inhibitory gating (higher p50 ratios) in both persons with PD and healthy older adults (HOAs).
3.3 Methods

3.3.1 Participants

The same participants used in Chapter 2 were used for this study. See Chapter 2.3.1 Participants. All participants provided written informed consent to participate in the study as approved by the Iowa State University Institutional Review Board (see chapter 3.8 Appendix).

3.3.2 Procedure

The same participants used in Chapter 2 were used for this study. See Chapter 2.3.2 Procedure.

3.3.3 Stress and Control Tasks

The same stress and control tasks were used in Chapter 2 were used for this study. See Chapter 2.3.3 Stress and Control Tasks.

3.3.4 EEG Data Acquisition and Analysis

The subjects were sitting comfortably in a semi-reclined armchair in a quiet well lit room. Participants were instructed to keep their movement to a minimum and their eyes open and focused on a piece of tape stuck to a desk 5 feet in front of them. Participants were also instructed to refrain from falling asleep.

To collect the potentials, a 64 electrode EEG cap was fitted according to the international 10-20 system (Biosemi, Amsterdam, Netherlands). Eye movements were monitored with electrodes placed above and below the right eye for filtering purposes. A single common reference electrode was placed over the mastoid process ipsilateral to the participants most affected side (HOAs were matched) and the ground electrode was placed on the forehead just above the nose and between the eyebrows. The electrode of interest is Cz which is located in the midline at the ‘vertex’ or top of the head. Impedances were checked to make sure they are below...
5k ohms prior to beginning the data collection. Signals were recorded at 2kHz and amplified. During the task, auditory clicks were presented through speakers at 80dB hearing level. The auditory stimuli were pairs of identical auditory clicks (1000-Hz tone) with a duration of 20ms and an interval of 500ms between clicks. 80 trials were presented with a 7 second interval between trials. The time for each recording epoch was 300ms before the first pair of clicks until 1s following the second click. The auditory tones were collected simultaneously by the EEG data collection system to ensure synchronization. Overall, these are the recommended methods for collecting the p50 response (Dalecki, Croft, & Johnstone, 2011).

EEG data were processed using standard methods in the Krigolson Laboratory (http://www.kirolsonlab.com/data-analysis.html). Signals were re-referenced offline using a bipolar montage (Cz-Iz) and filtered using a 0.5-45Hz 4th order dual-pass butterworth band-pass and a 60Hz notch filter. Next, data was divided into smaller epochs (-200ms to 300ms) around each auditory tone. Finally, a trial was discarded if the voltage on any channel exceeded 10 μV/ms gradient and an absolute voltage difference > 100 μV.

The P50 ratio (S2/S1) was our measure of habituation (Dalecki, et al., 2011). S1 (peak-to-peak method) was the difference in amplitudes in the positive deflection between 35 - 65ms and the most negative deflection between 15-45ms of the first stimulus. S2pp was the difference of those amplitudes for the second stimulus. In addition, latency measures were also calculated for S2 and S1 where the latency value reflected the timing difference between the maximum positive deflection and the auditory stimulus. Due to technical difficulties, EEG was not collected for 4 of the participants with PD. A clear p50 component was interpretable in both the S1 and S2 in both conditions (SECP and control) for 19 participants (8 PD and 11 HOAs). These were used for statistical analysis.
3.3.5 Cortisol Analysis

The same Cortisol methods used in Chapter 2 were used for this study. See Chapter 2.3.5 Cortisol Analysis.

3.3.6 Statistical Analysis

An independent samples $t$-test was used to examine any group differences on demographic and questionnaire outcome measures. A 2 condition (stress, control) x 2 group (PD, HOA) repeated measures ANOVA was completed for measures of stress (perceived stress, blood pressure, and cortisol) to confirm that the SECP initiated an increase in stress for participants. To test the hypothesis that the SECP task will impair inhibitory gating (higher p50 ratios) in both persons with PD and HOAs, a 2 condition (stress, control) x 2 group (PD, HOA) repeated measures ANOVA was used to determine differences on inhibitory gating (p50 ratio) and measures of early auditory processing (amplitude and latency of S1 and S2). For all repeated measures ANOVAs, partial eta squared ($\eta_p^2$) effect sizes were calculated. Significance was set at $\alpha = 0.05$. For all post hoc analyses, a Bonferroni correction was used to interpret statistical significance.

3.4 Results

Table 3.2 shows the means and standard deviations for all stress related measures (perceived stress, blood pressure, and cortisol). Table 3.3 shows the means and standard deviations for all auditory processing measures.

3.4.1 Participants

Participants with PD had higher trait anxiety than the HOAs ($t_{(28)} = 3.086, p = 0.005$, Mean Difference ($MD$) = +9.2, $d = 1.126$). No other demographic variables were significantly different (Table 3.1).
3.4.2 Perceived Stress

There was a main effect of condition ($F_{(1,28)} = 147.393, p < 0.001, \eta^2_p = 0.840$). The participants found that the SECP was more stressful than the control condition ($MD = +5.2, d = 2.256$). There was no main effect for group ($F_{(1,28)} = 0.267, p = 0.609, \eta^2_p = 0.009$), or an interaction effect for group x condition ($F_{(1,28)} = 0.006, p = 0.938, \eta^2_p = 0.000$).

3.4.3 Blood Pressure

There was a main effect for condition both systolic ($F_{(1,28)} = 8.003, p = 0.009, \eta^2_p = 0.222$) and diastolic blood pressure ($F_{(1,28)} = 5.543, p = 0.026, \eta^2_p = 0.165$). The participants had higher systolic blood pressure after the SECP compared to the control condition ($MD = +6.4 \text{ mmHg}, d = 0.518$). Participants also had higher diastolic blood pressure after the SECP compared to the control condition ($MD = +2.8 \text{ mmHg}, d = 0.430$). There was no main effect for group systolic blood pressure ($F_{(1,28)} = 2.138, p = 0.155, \eta^2_p = 0.071$), no main effect for group diastolic blood pressure ($F_{(1,28)} = 0.360, p = 0.553, \eta^2_p = 0.013$), and no interaction effect of group x condition for systolic blood pressure ($F_{(1,28)} = 0.889, p = 0.354; \eta^2_p = 0.031$) or diastolic blood pressure ($F_{(1,28)} = 0.767, p = 0.388; \eta^2_p = 0.027$).

3.4.4 Cortisol

There was a main effect of condition for cortisol ($F_{(1,28)} = 6.780, p = 0.015 \eta^2_p = 0.195$). Participants had a higher cortisol AUC values during the SECP compared to the control condition ($MD = +13.4 \text{ ng/dl/hr}, d = 0.479$). There was no main effect for group ($F_{(1,28)} = 0.187, p = 0.699, \eta^2_p = 0.007$) and no interaction effect of group x condition ($F_{(1,28)} = 0.596, p = 0.447, \eta^2_p = 0.021$).
3.4.5 Inhibitory Gating

Figure 3.1A shows results for inhibitory gating. Results revealed a main effect for condition \( (F_{(1,17)} = 12.813, p = 0.002, \eta_p^2 = 0.430) \). In general, there was less inhibitory gating following the SECP compared to the control condition (MD = +0.20, \( d = 0.760 \)). No main effect for group \( (F_{(1,17)} = 0.736, p = 0.403, \eta_p^2 = 0.042) \) or interaction for condition x group \( (F_{(1,17)} = 1.971, p = 0.178, \eta_p^2 = 0.104) \) was found.

3.4.6 Early Auditory Components

Figure 3.1C and 3.1D show the results for S1 amplitude and S2 amplitude. No main effects for condition were found [S1 amplitude \( (F_{(1,17)} = 0.261, p = 0.616, \eta_p^2 = 0.015) \); S2 amplitude \( (F_{(1,17)} = 1.527, p = 0.233, \eta_p^2 = 0.082) \)]. However, there was a group trend for S1 amplitude \( (F_{(1,17)} = 3.560, p = 0.076, \eta_p^2 = 0.173) \), and S2 amplitude \( (F_{(1,17)} = 4.109, p = 0.059, \eta_p^2 = 0.195) \). Persons with PD had a greater S1 amplitude (\( MD = +4.1 \mu V, d = 0.672 \)) and S2 amplitude (\( MD = +3.0 \mu V, d = 0.675 \)). No condition x group interactions were found [S1 amplitude \( (F_{(1,17)} = 0.206, p = 0.656, \eta_p^2 = 0.012) \); S2 amplitude \( (F_{(1,17)} = 0.376, p = 0.548, \eta_p^2 = 0.022) \)].

3.5 Discussion

This present study aimed to test the effects of SECP on inhibitory gating in persons with PD. The results revealed that the SECP was successful in increasing stress related measures (perceived stress, blood pressure, and cortisol). The results supported our hypothesis. SECP decreased inhibitory gating in HOAs and persons with PD. While not significant, the SECP appeared to decreased inhibitory gating to a greater degree in persons with PD (\( MD = +0.293 \)) compared to HOAs (\( MD = +0.127 \)), with the interaction condition x group showing a medium to large effect size (\( \eta_p^2 = 0.104 \)). Similar to previous research (Teo, et al., 1997), the results
showed that persons with PD had larger, though not significantly different, S1 ($MD = +4.1 \, \mu V$) and S2 ($MD = +3.0 \, \mu V$) amplitudes, suggesting that PD may affect early auditory processing as well.

During the control condition, persons with PD and HOAs had similar inhibitory gating ratios which was expected given the mild to moderate disease severity of our subjects with PD (Hoehn and Yahr (H&Y) = 2.3). Previous researchers have found that compared to HOAs persons with PD have more impaired inhibitory gating (Teo, et al., 1997). However, differences were driven by those in later stages of the disease (H&Y = 4 & 5). No differences in inhibitory gating were seen between HOAs and persons with PD in the middle stages of the disease (H&Y = 3). The inhibitory gating ratios were greater (p50 ratio = 0.60) than might be expected in healthy young adults however, where ratios are on average typically less than 0.4 (Adler, et al., 2004; Dalecki, et al., 2011; Yadon, Bugg, Kisley, & Davalos, 2009). This is not entirely unexpected as age-related impairments of inhibitory gating have previously been documented (Kisley, Davalos, Engleman, Guinther, & Davis, 2005).

Consistent with our hypothesis, stress decreased inhibitory gating in both HOAs and persons with PD. Given that during the control condition inhibitory gating was likely lower than what might be considered normal gating levels in healthy young adults (Adler, et al., 2004; Dalecki, et al., 2011; Yadon, et al., 2009), this is somewhat surprising as a floor effect was more likely to be observed. Statistically the decrease in inhibitory gating was similar between both groups. However, there was a medium to large condition x group interaction effect size ($\eta^2 = 0.104$), and persons with PD had a decrease in inhibitory gating that was more than double what was observed in the HOAs. This suggests that stress is more likely to impair inhibitory gating in persons with PD.
Similar to other studies that observe larger auditory event-related potentials in persons with PD (Gulberti et al., 2015; Tanaka et al., 2000; Teo et al. 1997), there was a trend ($p < 0.1$) for p50 amplitudes to be greater in persons with PD. Others have suggested that this indicates an over-activation of the ascending cholinergic reticular activating system within persons with PD (Skinner, Miyazato, & Garcia-Rill, 2002; Teo, et al., 1997), which may be a compensatory mechanism to attenuate cognitive and motor deficits due to nigrostriatal dopamine loss (Bohnen, et al., 2015; Kucinski, de Jong, & Sarter, 2017). Thus, the auditory p50 amplitude may be a useful biomarker to examine the interaction between dopaminergic and cholinergic systems in persons with PD. Similar to previous research (Johnson & Adler, 1993), the SECP had no effect on p50 amplitudes. Overall, this suggests that the SECP had a greater impact on the gating of S2 and a reduced impact on the ascending reticular activating system in persons with PD.

It has also been suggested that inhibitory gating prevents sensory overload, which may impair cognitive functioning by competing for limited cognitive resources (Croft, Lee, Bertolot, & Gruzelier, 2001; Desimone & Duncan, 1995; Yadon, et al., 2009). Similarly, it has been suggested that disrupted sensory processing contributes to motor impairments (Chudler & Dong, 1995; Conte, Khan, Defazio, Rothwell, & Berardelli, 2013; Konczak, et al., 2009; Müller, et al., 2013; Nieuwboer & Giladi, 2013). In healthy populations inhibitory gating is associated with motor inhibition (Cheng, et al., 2016; Liu, Xiao, Shi, & Zhao, 2011; Yadon, et al., 2009), which is impaired in persons with PD (Obeso, Wilkinson, & Jahanshahi, 2011). Inhibitory gating has also been associated with PD motor symptoms such as bradykinesia (Lukhanina, et al., 2011). In this study we found that stress negatively influenced inhibitory gating in persons with PD. Overall, this suggests that stress could negatively influence PD motor symptoms by impairing inhibitory gating.
3.5.1 Limitations

While our sample size was large enough to support our initial hypothesis that the SECP reduced in inhibitory gating in both HOAs and persons with PD, we were likely underpowered to find a group x condition interaction. Effect sizes suggest that those with PD have a larger decrement in inhibitory gating. Another major limitation is that neurotransmitters that are thought to mediate changes in inhibitory gating were not measured. Thus, while there is an assumption that stress induced changes in gating are mediated by norepinephrine, other transmitters such as acetylcholine and dopamine may have been involved. Similarly, the involvement of the basal ganglia and other neural regions involved in acute stress effect on inhibitory gating is speculative. Future studies will need to try and examine the neurotransmitter mediators of stress on inhibitory gating in persons with PD and HOAs. More studies are also needed to examine the relationship between inhibitory gating and cognitive and motor functioning in persons with PD. Nonetheless, this study demonstrated that stress impairs inhibitory gating in persons with PD.

3.5.2 Conclusion

The acute SECP stressor decreased inhibitory gating in persons with PD and HOAs. Although non-significant, the decrease appeared to be larger in persons with PD. Impairments in sensory processing may have contributed to motor deficits in PD, but future studies are needed to examine if and how p50 inhibitory gating is associated with PD motor symptoms. If p50 inhibitory gating contributes to motor deficits, then it may also be a potential neuropharmacological target to help improve functioning in persons with PD. We also found a statistical trend (p <0.1) for persons with PD to have larger S1 and S2 amplitudes, suggesting an over-activation/compensation by the reticular activating system. Thus, S1 and S2 amplitudes
may be a potential biomarker which can be used to examine the interaction of cholinergic and dopaminergic systems in persons with PD.
3.6 Figures and Tables

Figure 3.1. The Effects of Stress on Inhibitory Gating and the p50 Response

A) p50 ratio for both groups and both conditions. B) Example EEG waveform from one person with PD in both conditions. C) S1 Amplitude for both groups and both conditions. D) S2 Amplitude for both groups and both conditions. Standard error bars shown. In Figure 3.1A long horizontal bars show a main effect of condition, ** $p<0.01$
Table 3.1. Demographic and Questionnaire Information

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>HOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>67.8 ± 4.7</td>
<td>68.7 ± 5.0</td>
</tr>
<tr>
<td>Gender (% Male)</td>
<td>33.3 ± 50.0</td>
<td>33.3 ± 50.0</td>
</tr>
<tr>
<td>UPDRS</td>
<td>66.9 ± 5.8</td>
<td></td>
</tr>
<tr>
<td>H&amp;Y</td>
<td>2.3 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Years Diagnosed</td>
<td>9.9 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>29.3 ± 0.7</td>
<td>29.7 ± 0.6</td>
</tr>
<tr>
<td>MOCA</td>
<td>26.1 ± 2.2</td>
<td>26.5 ± 2.5</td>
</tr>
<tr>
<td>GDS</td>
<td>6.5 ± 4.5</td>
<td>3.8 ± 3.7</td>
</tr>
<tr>
<td>PSS</td>
<td>13.5 ± 5.6</td>
<td>9.2 ± 6.6</td>
</tr>
<tr>
<td>STAI1</td>
<td>33.3 ± 8.5</td>
<td>28 ± 10.9</td>
</tr>
<tr>
<td>STAI2**</td>
<td>38.3 ± 8.7</td>
<td>29.1 ± 7.6</td>
</tr>
</tbody>
</table>

Note. Means and standard deviations for all demographic measures, and cognitive questionnaires. For between subjects comparisons **p < 0.01. HOA; healthy older adult; PD: Parkinson’s disease; UPDRS: Unified Parkinson’s Disease Rating Scale; H&Y: Hoehn and Yahr; MMSE: Mini-Mental Status Exam; MOCA: Montreal Cognitive Assessment; GDS: Geriatric Depression Scale; PSS: Perceived Stress Scale; STAI1: State and Trait Anxiety Inventory (State); STAI2: State and Trait Anxiety Inventory (Trait).

Table 3.2. Stress Measures

<table>
<thead>
<tr>
<th></th>
<th>PD Control</th>
<th>HOA Control</th>
<th>PD SECP</th>
<th>HOA SECP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived Stress***</td>
<td>1.20 ± 0.56</td>
<td>1.00 ± 0.00</td>
<td>6.40 ± 2.53</td>
<td>6.13 ± 2.27</td>
</tr>
<tr>
<td>SBP (mmHg)**</td>
<td>121.3 ± 13.0</td>
<td>130.5 ± 16.2</td>
<td>129.7 ± 15.4</td>
<td>134.7 ± 13.8</td>
</tr>
<tr>
<td>DBP (mmHg)*</td>
<td>75.6 ± 9.3</td>
<td>74.9 ± 8.0</td>
<td>79.5 ± 8.7</td>
<td>76.7 ± 8.3</td>
</tr>
<tr>
<td>Cortisol (ng/dl/hr)*</td>
<td>66.7 ± 26.4</td>
<td>58.8 ± 23.2</td>
<td>76.1 ± 27.0</td>
<td>76.3 ± 34.2</td>
</tr>
</tbody>
</table>

Note. Means and standard deviations for all measures of stress for both groups and both conditions. For a main effect of condition *p < 0.05, **p < 0.01, ***p < 0.001. DBP: Diastolic blood pressure; HOA: healthy older adult; PD: persons with Parkinson’s disease; SBP: Systolic blood pressure.
### Table 3.3. p50 Measures

<table>
<thead>
<tr>
<th></th>
<th>PD Control</th>
<th>HOA Control</th>
<th>PD SECP</th>
<th>HOA SECP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>p50 Ratio</strong></td>
<td>0.61 ± 0.28</td>
<td>0.60 ± 0.12</td>
<td>0.90 ± 0.47</td>
<td>0.72 ± 0.16</td>
</tr>
<tr>
<td>S1 Amplitude (μV)</td>
<td>10.42 ± 5.73</td>
<td>6.04 ± 2.86</td>
<td>9.82 ± 7.56</td>
<td>6.01 ± 3.00</td>
</tr>
<tr>
<td>S2 Amplitude (μV)</td>
<td>6.31 ± 4.27</td>
<td>3.71 ± 2.16</td>
<td>7.59 ± 5.50</td>
<td>4.14 ± 2.00</td>
</tr>
</tbody>
</table>

*Note.* Means and standard deviations for all p50 measures for both groups and both conditions. For a main effect of condition, **p < 0.01. HOA: healthy older adult; PD: Parkinson’s disease; S1: stimulus 1; S2: stimulus 2.*
3.7 References


3.8 Appendix: Informed Consent/IRB Approval

The project referenced above has received approval from the Institutional Review Board (IRB) at Iowa State University according to the dates shown above. Please refer to the IRB ID number shown above in all correspondence regarding this study.

To ensure compliance with federal regulations (45 CFR 46 & 21 CFR 50), please be sure to:

- Use only the approved study materials in your research, including the recruitment materials and informed consent documents that have the IRB approval stamp.
- Retain signed informed consent documents for 3 years after the close of the study, unless documented consent is required.
- Obtain IRB approval prior to implementing any changes to the study by submitting a Modification Form for Non-Exempt Research or Amendment for Personnel Changes form, as necessary.
- Immediately inform the IRB of (1) all serious and/or unexpected adverse experiences involving risks to subjects or others; and (2) any other unanticipated problems involving risks to subjects or others.
- Stop all research activity if IRB approval lapses, unless continuation is necessary to prevent harm to research participants. Research activity can resume once IRB approval is reestablished.
- Complete a new continuing review form at least three to four weeks prior to the date for continuing review as noted above to provide sufficient time for the IRB to review and approve continuation of the study. We will send a courtesy reminder as this date approaches.

Please be aware that IRB approval means that you have met the requirements of federal regulations and ISU policies governing human subjects research. Approval from other entities may also be needed. For example, access to data from private records (e.g., student, medical, or employment records, etc.) that are protected by FERPA, HIPAA, or other confidentiality policies requires permission from the holders of those records. Similarly, for research conducted in institutions other than ISU (e.g., schools, other colleges or universities, medical facilities, companies, etc.), investigators must obtain permission from the institution(s) as required by their policies. IRB approval in no way implies or guarantees that permission from those other entities will be granted.

Upon completion of the project, please submit a Project Closure Form to the Office for Responsible Research, 1138 Pearson Hall, to officially close the project.

Please don't hesitate to contact us if you have questions or concerns at 515-294-4566 or IRB@iastate.edu.
CHAPTER 4. THE EFFECTS OF A SOCIALLY EVALUATED COLD PRESS STRESSOR ON PARKINSON’S DISEASE MOTOR SYMPTOMS

Andrew Zaman\textsuperscript{1}, Elizabeth L. Stegemöller\textsuperscript{1}

\textsuperscript{1}Department of Kinesiology, Iowa State University

Modified from a manuscript to be submitted to Movement Disorders.

4.1 Abstract

Persons with Parkinson’s disease have reported that their motor symptoms get worse with stress, but research is in this area is very limited. In the PD rat model, restraint stress has been shown to negatively impact skilled reaching and grasping. No studies however, have examined the effects of an acute stressor on motor performance in persons with PD. The purpose of this study was to examine how an acute stressor affects bradykinesia, hypokinesia, and tremor of the upper extremities in persons with PD.

Fifteen persons with PD and fifteen healthy older adults (HOAs) completed the a subset of the Unified Parkinson’s Disease Rating Scale (UPDRS) motor tests including: finger tapping, hand movements, pronation-supination of the hand, postural tremor of the hands, and resting tremor of the hands. This was done following an acute stressor (socially evaluated cold pressor) and after a non-stressful control condition. Positional data was recorded from the most affected side using electromagnetic sensors. A repeated measures factorial ANOVA was used to examine statistical differences.

The results showed that compared to the non-stress control condition, the acute stressor resulted in decreased finger tapping amplitude in both persons with PD and HOAs. Interestingly, the stressor resulted in decreased finger tapping amplitude variability in HOAs and increased finger tapping amplitude variability in persons with PD. Similarly, the acute stressor increased postural tremor amplitude in both groups, but the increase in postural tremor amplitude was
greater in persons with PD. Stress did not affect movement rate for any of the tasks, nor did it affect amplitude or amplitude variability for the hand movements, pronation-supination of the hand, or resting tremor tests.

Overall, the results suggest that acute stress can have a negative impact on PD motor symptoms such as hypokinesia and tremor. More specifically, finger tapping and postural tremor were negatively impacted by stress. Correlation studies have shown that finger tapping is associated with performance of more complex tasks such as buttoning, handwriting, and postural instability. While more research is necessary, this suggests that stress may also negatively impact the ability of persons with PD to complete more complex tasks. Moreover, this suggests that helping individuals with PD manage their stress may also help in reducing PD motor symptoms.

4.2 Introduction

In general, the relationship between acute stress and motor performance is described as an inverted-U shaped curve, with the performance of motor skills being worst at either end of the stress spectrum (Duffy, 1957). Anecdotally, persons with Parkinson’s disease (PD) report that their motor symptoms worsen with stress, but research is very limited. Animal research shows that restraint stress negatively impacts skilled reaching and grasping in a PD rat model (Smith, Jadavji, Colwell, Pehrudoff, & Metz, 2008). In persons with PD, gait performance worsens when they are asked to walk on an virtual elevated plank in as compared to a virtual plank on the ground. Although, the authors interpret this as stress negatively impacting gait, no stress responses were measured (Ehgoetz Martens, Ellard, & Almeida, 2015). No other studies have examined the relationship between stress and motor performance in PD. A better
understanding of the influence of stress on motor symptoms may contribute to the development of therapeutic strategies for persons with PD.

PD is a neurodegenerative disorder in which neuronal cell death in the substantia nigra results in basal ganglia dysfunction. This neurodegeneration is thought to underlie the defining motor symptoms of PD. Symptoms include tremor, rigidity (stiffness of the limbs and trunk), bradykinesia (slow movements), and postural instability. PD also negatively impacts well-learned, automatic behaviors such as walking, handwriting, speaking, and eating (Redgrave, et al., 2010). It has been suggested that persons with PD compensate for impairment in motor automaticity by directing attention towards movements and using executive control (Morris, Iansek, Matyas, & Summers, 1996; Redgrave, et al., 2010; Wu, Hallett, & Chan, 2017). The positive effects of directing attention and using executive control have been demonstrated by studies implementing visual and auditory cues to improve handwriting and gait (Morris, et al., 1996; Oliveira, Gurd, Nixon, Marshall, & Passingham, 1997). However, when attention is occupied during dual-task procedures, there is a disproportionately negative effect on motor performance in persons with PD (Hackney & Earhart, 2010; O'Shea, Morris, & Iansek, 2002; van Gemmert, Teulings, & Stelmach, 1998). Taken together, there is supporting evidence that suggests attentional processes are used to overcome impairments in motor automaticity in PD.

However, using attentional processes to overcome impairments in motor automaticity in PD may not be effective during stressful events. Acute stressors have repeatedly been shown to impair attention and goal-directed processes (Eysenck, Derakshan, Santos, & Calvo, 2007). Mechanistically, stress is thought to impair motor performance by impairing cue-utilization and attentional goal-directed processes (Easterbrook, 1959; Wilson, 2008). However, the negative effects of stress are typically only seen in the performance of less well learned skills, while
performance on well learned/automatic skills are preserved (Nibbeling, Oudejans, & Daanen, 2012). As previously discussed, persons with PD rely more heavily on goal-directed attentional processes to overcome deficits in motor automaticity (Morris, et al., 1996; Redgrave, et al., 2010; Wu, et al., 2017). In other words, stress is likely to exaggerate impairment in well learned motor skills and motor symptoms in persons with PD. However, there is a lack of literature empirically examining this phenomenon.

Thus, the goal of this study was to examine how stress influences PD motor symptoms. Movement tasks were taken from the Unified Parkinson’s Disease Rating Scale (UPDRS) motor subsection. Participants performed simple repetitive movements, such as finger tapping, open and closing of the fist, and pronation-supination of the hand, as quickly as possible to examine upper extremity bradykinesia and hypokinesia. These tasks are relatively simple and automatic (Wu, et al., 2015). Other unconsciously controlled motor symptoms such as resting and postural tremor were also tested. A socially evaluated cold pressor (SECP) was applied before the completion of these tasks. It was hypothesized that a SECP will negatively impact motor behaviors in PD including finger tapping, hand movements, pronation-supination of the hand, postural tremor, and resting tremor in persons with PD but not in healthy older adults (HOAs).

4.3 Methods

4.3.1 Participants

The same participants used in Chapter 2 were used for this study. See Chapter 2.3.1 Participants. All participants provided written informed consent to participate in the study as approved by the Iowa State University Institutional Review Board (see chapter 4.8 Appendix).
4.3.2 Procedure

The same procedure used in Chapter 2 were used for this study. See Chapter 2.3.2 Procedure.

4.3.3 Stress and Control Tasks

The same stress and control tasks used in Chapter 2 were used for this study. See Chapter 2.3.3 Stress and Control Tasks.

4.3.4 UPDRS Motor Data Acquisition and Analysis

The subjects were sitting comfortably in a semi-reclined armchair in a quiet well lit room. The UPDRS motor tests were examined in the following order for all participants UPDRS sections: 3.4 finger tapping, 3.5 hand movements, 3.6 pronation-supination movements of the hands, 3.15 postural tremor of the hands, and 3.17 rest tremor of the hands. For the UPDRS motor tests, instructions to examiner were followed when instructing participants, with the exception that participants were instructed to complete each of the tests for 10 seconds instead of 10 repetitions for finger tapping, hand manipulation, and pronation-supination of the hand. Participants completed all 3 of the non-tremor tasks on both sides starting with the side with the most affected side (or matched side for HOAs). However, data was only recorded on the most affected side (i.e., the side not entrenched in water). Positional data was collected using electromagnetic sensors placed on the tip of the index finger, the metacarpophalangeal joint index finger, and the metacarpophalangeal joint of the pinky finger on the most affected side (Figure 4.1A).

For all motor tests, the primary outcome measures were movement rate and amplitude. Movement rate was measured in cycles per second (Hz), with the end of each cycle marked by: 1) when the index finger reached a minimum on the y-axis (i.e., touched the thumb for the finger
tapping task or palm of the hand) for finger tapping and hand movements (Figure 4.1B and Figure 4.1C) or 2) reached the maximum rotation when pointing the palm to the floor (pronation-supination of the hand) (Figure 4.2D). For finger tapping and hand movements, amplitude was analyzed by examining the magnitude of movement of the index finger in relation to the metacarpophalangeal joint index finger. For pronation-supination movements of hands, the amplitude of the movement was analyzed by examining the degree of rotation between the metacarpophalangeal joints of the index and pinky fingers. For the tests of postural and resting tremor, the amplitude of tremor was measured by examining the magnitude of tremor frequency movements (3-8 Hz) using tip of the index finger. The largest tremor seen during the tremor recording periods was recorded as max amplitude. In order to measure interruptions, decrements in amplitude, and slowing, variability of movement was examined by calculating the coefficient of variation (CV) for each of our outcome measures with the exception of max amplitude.

4.3.5 Cortisol Analysis

The same cortisol analysis used in Chapter 2 were used for this study. See Chapter 2.3.5 Cortisol Analysis.

4.3.6 Statistical Analysis

Data from finger tapping in one participant with PD was excluded because they did not complete the task correctly (participant was completing full hand movements during finger tapping task). Data for one HOA participant was excluded in the analysis of postural tremor because no tremor was detectable during the control condition. An independent samples t-test was used to examine any group differences on demographic and questionnaire outcome measures. A 2 condition (stress, control) x 2 group (PD, HOA) repeated measures ANOVA was completed for measures of stress (perceived stress, blood pressure, and cortisol) to confirm that
the SECP initiated an increase in stress for participants. To test the hypothesis that a SECP will negatively impact UPDRS motor symptoms in persons with PD but not in HOAs, a group (PD, HOA) x 2 (control, SECP) repeated measures factorial ANOVA was used to determine differences on tremor and upper extremity bradykinesia. For all repeated measures ANOVAs, partial eta squared \( (\eta_p^2) \) effect sizes were calculated. Significance was set at \( \alpha=0.05 \). For all post hoc analysis, Bonferroni correction was used to interpret statistical significance.

4.4 Results

Table 4.2 shows the means, standard deviations, for all stress related measures for both conditions and in both groups. Table 4.3 shows the means, standard errors, for all quantitative motor UPDRS measures.

4.4.1 Participants

Participants with PD had higher trait anxiety than the HOAs \( t_{(28)} = 3.086, p = 0.005 \), Mean Difference \( (MD) = +9.2, d = 1.126 \). No other demographic variables were significantly different (Table 4.1).

4.4.2 Perceived Stress

There was a main effect of condition \( F_{(1,28)} = 147.393, p <0.001, \eta_p^2 = 0.840 \). The participants found that the SECP was more stressful than the control condition \( (MD = +5.2, d = 2.256) \). There was no main effect for group \( F_{(1,28)} = 0.267, p = 0.609, \eta_p^2 = 0.009 \), or an interaction effect for group x condition \( F_{(1,28)} = 0.006, p = 0.938, \eta_p^2 = 0.000 \).

4.4.3 Blood Pressure

There was a main effect for condition both systolic \( F_{(1,28)} = 8.003, p = 0.009, \eta_p^2 = 0.222 \) and diastolic blood pressure \( F_{(1,28)} = 5.543, p = 0.026, \eta_p^2 = 0.165 \). The participants had higher systolic blood pressure after the SECP compared to the control condition \( (MD = +6.4 \).
mmHg, $d = 0.518$). Participants also had higher diastolic blood pressure after the SECP compared to the control condition ($MD = +2.8$ mmHg, $d = 0.430$). There was no main effect for group systolic blood pressure ($F_{(1,28)} = 2.138, p = 0.155, \eta^2_p = 0.071$), no main effect for group diastolic blood pressure ($F_{(1,28)} = 0.360, p = 0.553, \eta^2_p = 0.013$), and no interaction effect of group x condition for systolic blood pressure ($F_{(1,28)} = 0.889, p = 0.354; \eta^2_p = 0.031$) or diastolic blood pressure ($F_{(1,28)} = 0.767, p = 0.388; \eta^2_p = 0.027$)).

4.4.4 Cortisol

There was a main effect of condition for cortisol ($F_{(1,28)} = 6.780, p = 0.015, \eta^2_p = 0.195$). Participants had a higher cortisol AUC values during the SECP compared to the control condition ($MD = +13.4$ ng/dl/hr, $d = 0.479$). There was no main effect for group ($F_{(1,28)} = 0.187, p = 0.699, \eta^2_p = 0.007$) and no interaction effect of group x condition ($F_{(1,28)} = 0.596, p = 0.447, \eta^2_p = 0.021$).

4.4.5 Finger Tapping

Figure 4.2A shows the results for finger tapping amplitude, and Figure 4.2B shows the results for finger tapping amplitude CV. A main effect of condition on finger tapping amplitude ($F_{(1,27)} = 7.420, p = 0.011, \eta^2_p = 0.216$) was revealed. Participants had smaller finger taps following the SECP ($MD = -0.4$ cm, $d = 0.496$). No main effect of condition was found for movement rate ($F_{(1,27)} = 2.006, p = 0.168, \eta^2_p = 0.069$), amplitude CV ($F_{(1,27)} = 0.815, p = 0.375, \eta^2_p = 0.029$), or movement rate CV ($F_{(1,27)} = 0.495, p = 0.488, \eta^2_p = 0.018$).

A main effect of group on amplitude CV ($F_{(1,27)} = 7.552, p = 0.011, \eta^2_p = 0.219$) was revealed. The variability in amplitude was greater in persons with PD ($MD = +3.4$, $d = 0.739$). There was a group trend on amplitude ($F_{(1,27)} = 3.238, p = 0.083, \eta^2_p = 0.107$) where persons with PD had smaller finger taps than HOAs ($MD = -0.8$ cm, $d = 0.652$). No main effect of group was
found for movement rate \( (F_{1,27} = 0.402, p = 0.531, \eta^2_p = 0.015) \) or movement rate CV \( (F_{1,27} = 1.147, p = 0.294, \eta^2_p = 0.041) \).

The results revealed a condition x group interaction for amplitude CV \( (F_{1,27} = 5.501, p = 0.027, \eta^2_p = 0.169) \) where the finger tapping amplitude CV increased in persons with PD \( (MD = +4.6, d = 0.519) \) and decreased in HOAs \( (MD = -2.0, d = 0.326) \) following the SECP. Post hoc analysis found that persons with PD had a significantly higher amplitude CV than HOAs during the SECP \( (t_{27} = 3.516, p = 0.002, MD = 7.6, d = 1.305) \), but amplitude CV was similar between the two groups during the control condition \( (t_{27} = 0.386, p = 0.702, MD = 0.8, d = 0.175) \). No condition x group interaction effects were found for amplitude \( (F_{1,28} = 1.161, p = 0.291, \eta^2_p = 0.041) \), movement rate \( (F_{1,28} = 0.071, p = 0.793, \eta^2_p = 0.003) \), movement rate CV \( (F_{1,28} = 2.526, p = 0.123, \eta^2_p = 0.083) \).

### 4.4.6 Hand Movements

No main effects of condition were found for any of the hand movement measures (amplitude \( (F_{1,28} = 0.429, p = 0.518, \eta^2_p = 0.015) \); movement rate \( (F_{1,28} = 0.071, p = 0.793, \eta^2_p = 0.003) \); amplitude CV \( (F_{1,28} = 0.059, p = 0.809, \eta^2_p = 0.002) \); movement rate CV \( (F_{1,28} = 2.526, p = 0.123, \eta^2_p = 0.083) \).

The results revealed a group trend for amplitude CV \( (F_{1,28} = 3.242, p = 0.083, \eta^2_p = 0.104) \), where participants with PD had a higher amplitude CV \( (MD = 4.7, d = 0.597) \). No other main effects of group were found (amplitude \( (F_{1,28} = 1.450, p = 0.239, \eta^2_p = 0.049) \); movement rate \( (F_{1,28} = 0.231, p = 0.634, \eta^2_p = 0.008) \); movement rate CV \( (F_{1,28} = 1.299, p = 0.264, \eta^2_p = 0.044) \)).
No condition x group interaction effects were found (amplitude ($F_{(1,28)} = 1.034, p = 0.318, \eta^2_p = 0.036$); movement rate ($F_{(1,28)} = 1.195, p = 0.284, \eta^2_p = 0.041$); amplitude CV ($F_{(1,28)} = 0.000, p = 0.991, \eta^2_p = 0.000$); movement rate CV ($F_{(1,28)} = 0.020, p = 0.887, \eta^2_p = 0.001$)).

### 4.4.7 Pronation-Supination of the Hand

There were no main effects of condition on any of the pronation-supination of the hand outcome measures (amplitude ($F_{(1,27)} = 2.820, p = 0.105, \eta^2_p = 0.095$); movement rate ($F_{(1,27)} = 2.309, p = 0.140, \eta^2_p = 0.079$); amplitude CV ($F_{(1,27)} = 0.159, p = 0.694, \eta^2_p = 0.006$); movement rate CV ($F_{(1,27)} = 0.320, p = 0.576, \eta^2_p = 0.012$)).

The results revealed a main effect of group for amplitude ($F_{(1,27)} = 7.148, p = 0.013, \eta^2_p = 0.209$) and movement rate ($F_{(1,27)} = 9.086, p = 0.006; \eta^2_p = 0.252$), where persons with PD had less pronation-supination of the hand rotation ($MD = -24.4^\circ, d = 0.926$), and slower rotations ($MD = -0.4$ Hz, $d = 1.001$) than HOAs. No main effect of group was found for amplitude CV ($F_{(1,27)} = 0.073, p = 0.788, \eta^2_p = 0.003$), or movement rate CV ($F_{(1,27)} = 0.047, p = 0.829, \eta^2_p = 0.002$).

The results revealed no condition x group interaction effects (amplitude ($F_{(1,27)} = 1.535, p = 0.226; \eta^2_p = 0.054$); movement rate ($F_{(1,27)} = 0.092, p = 0.764, \eta^2_p = 0.003$); amplitude CV ($F_{(1,27)} = 0.660, p = 0.424; \eta^2_p = 0.024$); movement rate CV ($F_{(1,27)} = 0.764, p = 0.390; \eta^2_p = 0.028$)).

### 4.4.8 Postural Tremor

Figure 4.2C shows postural tremor amplitude, and Figure 4.2D show postural tremor amplitude CV.

There was a main effect of condition on postural tremor amplitude ($F_{(1,27)} = 6.676, p = 0.016, \eta^2_p = 0.198$), where postural tremor was greater following the SECP ($MD = 0.42$ mm, $d =$
0.473). We also found a trend for the max amplitude ($F_{(1,27)} = 3.064, p = 0.091, \eta^2_p = 0.102$) to be greater following the SECP ($MD = 1.00 \text{ cm}, d = 0.33$). There was no effect of condition on amplitude CV ($F_{(1,27)} = 0.818, p = 0.374, \eta^2_p = 0.029$).

There was a main effect of group on max amplitude ($F_{(1,27)} = 8.727, p = 0.006, \eta^2_p = 0.244$), and amplitude CV ($F_{(1,27)} = 5.666, p = 0.025, \eta^2_p = 0.173$). There was also a group trend effect for amplitude ($F_{(1,27)} = 3.302, p = 0.080, \eta^2_p = 0.109$). In general, persons with PD had a greater amplitude ($MD = 0.36 \text{ mm}, d = 1.48$), max amplitude ($MD = 1.88 \text{ mm}, d = 0.813$), and amplitude CV ($MD = 13.8, d = 0.677$) than HOAs.

No condition x group interaction effects were found for amplitude ($F_{(1,27)} = 2.494, p = 0.126, \eta^2_p = 0.085$), max amplitude ($F_{(1,27)} = 1.487, p = 0.233, \eta^2_p = 0.052$), or amplitude CV ($F_{(1,27)} = 0.016, p = 0.899, \eta^2_p = 0.001$).

### 4.4.9 Resting Tremor

We did not find a main effect of condition for any of our resting tremor measures (amplitude ($F_{(1,27)} = 0.015, p = 0.902, \eta^2_p = 0.001$); max amplitude ($F_{(1,27)} = 1.069, p = 0.310, \eta^2_p = 0.037$); amplitude CV ($F_{(1,27)} = 2.412, p = 0.132, \eta^2_p = 0.079$).

We found a main effect of group on amplitude ($F_{(1,27)} = 5.440, p = 0.027, \eta^2_p = 0.163$), and max amplitude ($F_{(1,27)} = 6.012, p = 0.021, \eta^2_p = 0.077$). Persons with PD had a higher amplitude resting tremor ($MD = 0.62 \text{ cm}, d = 0.749$) and a higher max amplitude resting tremor ($MD = 2.32 \text{ cm}, d = 0.862$) than HOAs. There was no main effect of group on amplitude CV ($F_{(1,27)} = 2.349, p = 0.137, \eta^2_p = 0.077$).

No condition x group interaction effects were found (amplitude ($F_{(1,27)} = 0.000, p = 0.996, \eta^2_p = 0.000$); max amplitude ($F_{(1,27)} = 0.915, p = 0.347, \eta^2_p = 0.032$); amplitude CV ($F_{(1,27)} = 0.187, p = 0.669; \eta^2_p = 0.007$)).
4.5 Discussion

The primary aim of this study was to determine if the SECP impacted motor symptom in persons with PD. The results of this study revealed that the SECP reduced finger tapping amplitude in both persons with PD and HOAs. The results also showed variability in finger tapping amplitude increased in persons with PD while variability decreased in HOAs after the SECP. Similarly, postural tremor amplitude increased following the SECP with a greater increase in postural tremor amplitude in persons with PD compared with HOAs. The SECP did not affect the amplitude or amplitude variability of hand movements, pronation-supination of the hand, or resting tremor. Finally, the SECP did not affect the movement rate at which participants completed the motor tests.

In general, compared with HOAs, persons with PD had a smaller movement amplitude for finger tapping and pronation-supination of the hand amplitude. Persons with PD also demonstrated greater hand movement amplitude variability, and slower pronation-supination of the hand. Finally, persons with PD had more postural tremor and resting tremor. These results suggest that the quantitative analysis used were sensitive enough to capture PD motor symptoms.

The results revealed the SECP decreased finger tapping amplitude in both groups. However, the difference (albeit statistically insignificant) was greater in persons with PD \((MD = -0.54 \text{ cm})\) than HOAs \((MD = -0.23 \text{ cm})\). There was also an interaction where SECP increased finger tapping amplitude variability in persons with PD while the amplitude variability in HOAs decreased. An important factor to consider when looking at the results is the speed at which the movements are made. In persons with PD, impairment of upper limb movements are speed dependent with greater impairment at movement rates above 2 Hz (Freeman, Cody, & Schady, 1993; Nakamura, Nagasaki, & Narabayashi, 1978; Stegemöller, Simuni, & MacKinnon, 2009;
Yahalom, Simon, Thorne, Peretz, & Giladi, 2004). Movement rate did not change for finger and hand movements during the stressor, which suggests that any changes (i.e. amplitude) mediated by the stressor cannot be explained by changes in movement rate. Thus, stress appeared to exacerbate finger tapping hypokinesia. Furthermore, stress increased amplitude variability in persons with PD, and decreased amplitude variability in HOAs. This suggests that stress may negatively impact motor automaticity in persons with PD, and improve motor automaticity in HOAs.

In contrast to the negative effects the SECP had on finger tapping, the SECP did not appear to impact hand movements and pronation-supination of the hand. One possible reason for this finding may be associated with movement rate differences between these tasks. In this study, participants with PD and HOAs completed finger tapping at a fast pace that was consistent for both conditions (> 3 Hz) while hand movements and pronation supination of the hand movements were considerably slower (< 2.3 Hz). As previously stated, impairment of upper limb movements are speed dependent with greater impairment at movement rates above 2 Hz (Freeman, et al., 1993; Nakamura, et al., 1978; Stegemöller, et al., 2009; Yahalom, et al., 2004). Movement rate has a positive linear relationship brain activation across a number cortical and subcortical motor regions (basal ganglia, frontal regions, and cerebellum), and a negative linear relationship with activity in the posterior putamen (Lutz, Koenke, Wüstenberg, Jäncke, 2004; Riecker, Wildgruber, Mathiak, Grodd, & Ackermann, 2003). Compared to healthy individuals, when persons with PD perform simple and well learned motor skills, they also have higher activation in the same cortical and subcortical motor regions impacted by movement rate (Wu, et al., 2015). Theoretically activation in these prefrontal regions is used for attentional control to overcome deficits in motor automaticity (Wu, et al., 2015). Thus, the negative effect of
movement rate on PD motor symptoms may be due to an additive effect and a resulting overloading of neural networks associated with conscious control of movement. Stress negatively impacts prefrontal regions and attentional mechanisms (Arnsten, 2009; Eysenck, et al., 2007), and thus may be more likely to impact movements which take greater cortical resources (i.e. fast finger tapping) compared to the other UPDRS motor tasks.

Given the previous hypothesis that stress may further exacerbate movements that take greater prefrontal resources and attention, we predict that more complex motor skills are also likely to be impacted by stress in persons with PD. As previously stated, previous research has found that stress negatively impacted skilled reaching in a PD rat model (Smith, et al., 2008), and that a stressful environment negatively impacted gait in persons with PD (Ehgoetz Martens, et al., 2015). Further support, is demonstrated by correlations between finger tapping and performance of more complex tasks such as Purdue peg board (Müller, Schäfer, Kuhn, & Przuntek, 2000), buttoning (Uzochukwu & Stegemöller, 2019), handwriting (Stegemöller, Zaman, & Uzochukwu, 2019), and posture and postural instability (Stegemöller, et al., 2016). Overall, there is reason to believe that stress will negatively impact well-learned complex motor skills in persons with PD.

The results also demonstrated stress increased postural tremor in both persons with PD and HOAs. There was also an interaction in which persons with PD had a larger increase in postural tremor than HOAs. Increases in tremor was not completely unexpected as others have shown that stress can increase postural tremor in healthy young adults (Mitchem & Tuttle, 1954), by increasing catecholamines such as norepinephrine, epinephrine, and acetylcholine (Marshall & Schnieden, 1966). Unlike postural tremor, resting tremor did not appear to be affected by the SECP. Evidence suggests that resting tremor may have a different underlying pathophysiology
(Louis, et al., 1999; Louis, et al., 2001), which is mediated by the loss of dopaminergic neurons in the retrorubral area (Hirsch, Mouatt, Faucheux, Bonnet, & Javoy-Agid, 1992; Jellinger, 1999; Oiwa, et al., 2003). While evidence is sparse, stress does not appear to impact dopaminergic output of the retrorubral area (Deutch, et al., 1991). Overall, stress may have increased postural tremor by releasing catecholamines, while the networks and neurotransmitters that mediate resting tremor were unaffected.

4.5.1 Limitations

One major limitation of this study is that we did not measure the effect of stress on more complex motor skills such as walking, handwriting, or speaking. Whether stress negatively impacts complex motor skills in persons with PD remains to be examined. However, given that hypokinesia and tremor impact functional motor skills, stress should be considered an important modifiable factor. Another major limitation is that only behavioral data were observed. Studies are still needed to delineate the underlying mechanisms of stress in persons with PD. Finally, this study needs to be replicated with a larger sample size and with persons with PD in other stages of the disease progression. Nonetheless, this data provides an initial step in better understanding the effect of stress on motor symptoms in persons with PD.

4.5.2 Conclusion

Persons with PD demonstrated that some clinical measures of motor symptoms got worse following an acute stressor. More specifically, it appears that fast paced finger tapping and postural tremor were negatively impacted by stress. Although more research is needed, this suggests that the negative impact stress has on attentional and prefrontal networks may lead to an increase in motor symptom severity, especially with more complex tasks (i.e. handwriting,
buttoning, gait). Furthermore, interventions that help reduce stress and/or help bring conscious control over motor performance may help in reducing the negative impacts of stress.
4.6 Figures and Tables

Figure 4.1. Electromagnetic Sensor Setup and Example Position Data

A) Electromagnetic sensor setup. Electromagnetic sensors were placed on the tip of the index finger, the metacarpophalangeal joint index finger, and the metacarpophalangeal joint of the pinky finger on the most affected side or the matched side for HOAs. B) Example position data for UPDRS 3.4 finger tapping task. C) Example position data for UPDRS 3.5 hand movement task. D) Example position data for UPDRS 3.6 pronation-supination of the hand task.
Figure 4.2. The Effects of Stress on PD Motor Symptoms

A) Finger tapping amplitude for both groups and both conditions. B) Finger tapping amplitude CV for both groups and both conditions. C) Postural tremor amplitude for both groups and both conditions. D) Postural tremor amplitude CV for both groups and both conditions. Standard error bars shown. Small horizontal bars show between group differences. Long horizontal bars show within group differences. Long horizontal bars connected with short horizontal bars shows a main effect of condition. *p<0.05, **p<0.01.
Table 4.1. Demographic and Questionnaire Information

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>HOA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Years)</strong></td>
<td>67.8 ± 4.7</td>
<td>68.7 ± 5.0</td>
</tr>
<tr>
<td><strong>Gender (% Male)</strong></td>
<td>33.3 ± 50.0</td>
<td>33.3 ± 50.0</td>
</tr>
<tr>
<td><strong>UPDRS</strong></td>
<td>66.9 ± 5.8</td>
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<tr>
<td><strong>H&amp;Y</strong></td>
<td>2.3 ± 0.1</td>
<td></td>
</tr>
<tr>
<td><strong>Years Diagnosed</strong></td>
<td>9.9 ± 1.7</td>
<td></td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td>29.3 ± 0.7</td>
<td>29.7 ± 0.6</td>
</tr>
<tr>
<td><strong>MOCA</strong></td>
<td>26.1 ± 2.2</td>
<td>26.5 ± 2.5</td>
</tr>
<tr>
<td><strong>GDS</strong></td>
<td>6.5 ± 4.5</td>
<td>3.8 ± 3.7</td>
</tr>
<tr>
<td><strong>PSS</strong></td>
<td>13.5 ± 5.6</td>
<td>9.2 ± 6.6</td>
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<tr>
<td><strong>STAI1</strong></td>
<td>33.3 ± 8.5</td>
<td>28 ± 10.9</td>
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<tr>
<td><strong>STAI2</strong></td>
<td>38.3 ± 8.7</td>
<td>29.1 ± 7.6</td>
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</tbody>
</table>

*Note. Means and standard deviations for all demographic measures, and cognitive questionnaires. For between subjects comparisons **p<0.01. GDS: Geriatric Depression Scale; H&Y: Hoehn and Yahr; HOA: healthy older adult; MMSE: Mini-Mental Status Exam; MOCA: Montreal Cognitive Assessment; PD: persons with Parkinson’s disease; PSS: Perceived Stress Scale; STAI1: State and Trait Anxiety Inventory (State); STAI2: State and Trait Anxiety Inventory (Trait). UPDRS: Unified Parkinson’s Disease Rating Scale.*

Table 4.2. Stress Measures

<table>
<thead>
<tr>
<th></th>
<th>PD Control</th>
<th>HOA Control</th>
<th>PD SECP</th>
<th>HOA SECP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perceived Stress</strong></td>
<td>1.20 ± 0.6</td>
<td>1.00 ± 0.0</td>
<td>6.4 ± 2.5</td>
<td>6.1 ± 2.3</td>
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<tr>
<td><strong>SBP (mmHg)</strong></td>
<td>121.3 ± 13.0</td>
<td>130.5 ± 16.2</td>
<td>129.7 ± 15.4</td>
<td>134.7 ± 13.8</td>
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<tr>
<td><strong>DBP (mmHg)</strong></td>
<td>75.6 ± 9.3</td>
<td>74.9 ± 8.0</td>
<td>79.5 ± 8.7</td>
<td>76.7 ± 8.3</td>
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<tr>
<td><strong>Cortisol (ng/dl/hr)</strong></td>
<td>66.7 ± 26.4</td>
<td>58.8 ± 23.2</td>
<td>76.1 ± 27.0</td>
<td>76.3 ± 34.2</td>
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</table>

*Note. Means and standard deviations for all measures of stress for both groups and both conditions. For a main effect of condition *p<0.05, **p<0.01, ***p<0.001. DBP: Diastolic blood pressure; HOA: healthy older adult; PD: persons with Parkinson’s disease; SBP: Systolic blood pressure.*
Table 4.3. Motor Symptom Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>PD Control</th>
<th>HOA Control</th>
<th>PD Stress</th>
<th>HOA Stress</th>
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<tbody>
<tr>
<td>Finger Amp (cm)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.15 ± 0.32</td>
<td>3.77 ± 0.32</td>
<td>2.61 ± 0.35</td>
<td>3.54 ± 0.31</td>
</tr>
<tr>
<td>Finger Amp CV&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16.08 ± 1.55**</td>
<td>15.12 ± 1.34</td>
<td>20.65 ± 1.81**</td>
<td>13.09 ± 1.22</td>
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<tr>
<td>Finger MR (Hz)</td>
<td>3.25 ± 0.20</td>
<td>3.11 ± 0.14</td>
<td>3.42 ± 0.27</td>
<td>3.24 ± 0.15</td>
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<td>Finger MR CV</td>
<td>12.72 ± 1.73</td>
<td>10.95 ± 0.99</td>
<td>13.27 ± 1.08</td>
<td>11.51 ± 1.23</td>
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<td>Hand Amp (cm)</td>
<td>6.36 ± 0.57</td>
<td>7.50 ± 0.43</td>
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<td>Hand Amp CV</td>
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<td>10.23 ± 1.93</td>
<td>14.59 ± 2.58</td>
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<td>Hand MR (Hz)</td>
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<td>2.29 ± 0.16</td>
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<td>Hand MR CV</td>
<td>16.42 ± 1.74</td>
<td>14.14 ± 1.96</td>
<td>14.11 ± 2.25</td>
<td>11.38 ± 1.67</td>
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<td>Pro-Sup Amp (deg)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>155.4 ± 6.3</td>
<td>184.5 ± 5.6</td>
<td>153.7 ± 8.3</td>
<td>173.5 ± 7.8</td>
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<td>Pro-Sup Amp CV</td>
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<td>Pro-Sup MR (Hz)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.13 ± 0.07</td>
<td>1.44 ± 0.08</td>
<td>1.18 ± 0.06</td>
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<td>Pro-Sup MR CV</td>
<td>11.31 ± 1.95</td>
<td>9.58 ± 1.73</td>
<td>10.86 ± 1.50</td>
<td>11.70 ± 1.92</td>
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<tr>
<td>Postural Tremor (mm)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.82 ± 0.11</td>
<td>0.71 ± 0.07</td>
<td>1.49 ± 0.32</td>
<td>0.87 ± 0.08</td>
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<tr>
<td>Postural Tremor Max (mm)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.97 ± 0.56</td>
<td>1.77 ± 0.21</td>
<td>4.62 ± 0.97</td>
<td>2.06 ± 0.20</td>
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<td>Postural Tremor CV&lt;sup&gt;b&lt;/sup&gt;</td>
<td>66.7 ± 6.7</td>
<td>53.5 ± 4.4</td>
<td>62.8 ± 6.6</td>
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<tr>
<td>Rest Tremor (mm)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.80 ± 0.32</td>
<td>0.18 ± 0.02</td>
<td>0.82 ± 0.30</td>
<td>0.19 ± 0.02</td>
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<tr>
<td>Rest Tremor Max (mm)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.04 ± 1.13</td>
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<td>2.43 ± 0.84</td>
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<tr>
<td>Rest Tremor CV</td>
<td>69.16 ± 12.64</td>
<td>49.21 ± 11.21</td>
<td>54.88 ± 6.54</td>
<td>41.15 ± 4.10</td>
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</tbody>
</table>

Note. Means and standard error for all quantitative UPDRS measures for both groups and both conditions. For a main effect of condition *<i>p</i>&lt;0.05, for a main effect of group **<i>p</i>&lt;0.05. For post hoc tests within subject effects of condition *** <i>p</i>&lt;0.01. Amp: amplitude; Finger: finger tapping; MR: movement rate; Hand: hand movements; HOA: healthy older adult; PD: persons with Parkinson’s disease; Pro-Sup: pronation-supination of the hand.
4.7 References


Duffy, E. (1957). The psychological significance of the concept of" arousal" or" activation.". *Psychological review, 64*(5), 265.


4.8 Appendix: Informed Consent/IRB Approval

IOWA STATE UNIVERSITY
OF SCIENCE AND TECHNOLOGY

Date: 6/16/2016
To: Andrew Zaman
238 Forker Bldg
Ames, IA

From: Office for Responsible Research

Title: Working Memory, Sensory Processing, and Motor Performance Study

IRB ID: 16-257

Date for Continuing Review: 6/6/2018
Review Type: Full Committee

Approval Date: 6/16/2016

The project referenced above has received approval from the Institutional Review Board (IRB) at Iowa State University according to the dates shown above. Please refer to the IRB ID number shown above in all correspondence regarding this study.

To ensure compliance with federal regulations (45 CFR 46 & 21 CFR 50), please be sure to:

- Use only the approved study materials in your research, including the recruitment materials and informed consent documents that have the IRB approval stamp.
- Retain signed informed consent documents for 3 years after the close of the study, when documented consent is required.
- Obtain IRB approval prior to implementing any changes to the study by submitting a Modification Form for Non-Exempt Research or Amendment for Personnel Changes form, as necessary.
- Immediately inform the IRB of (1) all serious and/or unexpected adverse experiences involving risks to subjects or others; and (2) any other unanticipated problems involving risks to subjects or others.
- Stop all research activity if IRB approval lapses, unless continuation is necessary to prevent harm to research participants. Research activity can resume once IRB approval is reestablished.
- Complete a new continuing review form at least three to four weeks prior to the date for continuing review as noted above to provide sufficient time for the IRB to review and approve continuation of the study. We will send a courtesy reminder as this date approaches.

Please be aware that IRB approval means that you have met the requirements of federal regulations and ISU policies governing human subjects research. Approval from other entities may also be needed. For example, access to data from private records (e.g., student, medical, or employment records, etc.) that are protected by FERPA, HIPAA, or other confidentiality policies requires permission from the holders of these records. Similarly, for research conducted in institutions other than ISU (e.g., schools, other colleges or universities, medical facilities, companies, etc.), investigators must obtain permission from the institution(s) as required by their policies. IRB approval in no way implies or guarantees that permission from those other entities will be granted.

Upon completion of the project, please submit a Project Closure Form to the Office for Responsible Research, 1138 Pearson Hall, to officially close the project.

Please don’t hesitate to contact us if you have questions or concerns at 515-294-4566 or IRB@iastate.edu.
CHAPTER 5. STRESS AND PARKINSON’S MOTOR SYMPTOMS: REPEATED MEASURES CORRELATIONS WITH WORKING MEMORY AND INHIBITORY GATING

Andrew Zaman¹, Elizabeth L. Stegemöller¹

¹Department of Kinesiology, Iowa State University

Modified from a manuscript to be submitted to Movement Disorders.

5.1 Abstract

Stress can negatively impact Parkinson’s disease (PD) motor symptoms such as finger tapping and postural tremor. Unknown however, are the mechanisms in which stress can impact motor functioning in persons with PD. One possible mechanism is that stress impacts PD motor symptoms via its effect on prefrontal cortices and cognition, which persons with PD utilize to compensate for impairment in automatic processes and behaviors. Another possible mechanism, is that stress impacts PD motor symptoms via its effect on sensory processes such as inhibitory gating, which are thought to contribute to motor impairments in persons with PD. The purpose of this study was to examine how stress effects the within-individual relationships between clinical motor tests and potential mediators such as working memory, and inhibitory gating in persons with PD.

Fifteen persons with PD completed the a subset of the Unified Parkinson’s Disease Rating Scale (UPDRS) motor tests including: finger tapping, hand movements, pronation-supination of the hand, postural tremor of the hands, and resting tremor of the hands. The participants also completed tests of working memory (digit span backward), and inhibitory gating of the p50 auditory component. This was done following an acute stressor (socially evaluated cold pressor) and after a non-stressful control condition. Positional data was recorded from the most affected side using electromagnetic sensors. A repeated measures Pearson’s
correlation was used to examine the relationship between changes in performance between the control and stress conditions on the UPDRS motor tasks and measures of inhibitory gating (p50 ratio) and working memory capacity (digit span backwards two-error maximum list length (TE-ML)).

Significant associations were found between p50 inhibitory gating and finger tapping amplitude, and postural tremor maximum amplitude. In general, as p50 ratio increased the finger tapping amplitude decreased and maximum postural tremor amplitude increased. The results also showed a trend correlation and many medium to large correlations between p50 ratio and the motor symptoms including resting tremor, finger tapping variability, hand movement variability, finger tapping movement rate, hand movement rate, and movement rate variability for finger tapping. All of which showed that decreases in inhibitory gating were associated with increases in motor symptom severity. One correlation was in the opposite direction however, where decreases in inhibitory gating was associated with an increase in hand movement amplitude. In general, changes in working memory capacity were not associated with changes in PD motor symptoms.

Overall, the results suggest that inhibitory gating may influence PD motor symptom severity. Inhibitory gating can be improved pharmacologically or by reducing stress, and may be a powerful therapeutic target for persons with PD. Overall, changes in working memory were not reliably correlated with changes in PD motor symptoms. However, studies are still needed to examine how working memory and other attentional and cognitive mechanisms may be involved in compensating for motor impairments in persons with PD.
5.2 Introduction

Parkinson's disease (PD) is a neurodegenerative disorder in which the substantia nigra suffers severe cell loss resulting in basal ganglia dysfunction. The defining motor symptoms of PD are tremor, rigidity (stiffness of the limbs and trunk), bradykinesia (slow movements), and postural instability (impaired balance). PD symptoms negatively impact well-learned, habitual behaviors such as walking, handwriting, speaking, and eating (Redgrave, et al., 2010). Animal PD models show that restraint stress negatively impacts skilled reaching (Smith, Jadavji, Colwell, Pehrudoff, & Metz, 2008). In persons with PD, gait performance worsens when walking in a stressful virtual environment (elevated plank over an open pit) (Ehgoetz Martens, Ellard, & Almeida, 2014). Finally, in our previous results, stress negatively impacted clinical motor tests such as finger tapping and postural tremor, while other motor tests such as hand movements, pronation-supination of the hand, and resting tremor were unaffected (Chapter 4). Yet, the underlying mechanisms mediating stress’ impact on PD motor symptoms remain unknown.

Impairments in working memory and cognitive functioning are common deficits in persons with PD (Gabrieli, Singh, Stebbins, & Goetz, 1996; Grogan, et al., 2018; Kudlicka, Clare, & Hindle, 2011; Mckinlay, Grace, Dalrymple-Alford, & Roger, 2010; Siegert, Weatherall, Taylor, & Abernethy, 2008). In healthy individuals, stress impairs cognitive abilities such as attention and working memory (Eysenck, Derakshan, Santos, & Calvo, 2007), which persons with PD utilize to compensate for impairment in automatic processes (Morris, Iansek, Summer, & Matyas, 1996; Redgrave, et al., 2010; Wu, Hallet, & Chan, 2015). This is demonstrated by directing attentional focus to the task via visual and auditory cues which improve motor performance in persons with PD (Morris, et al., 1996; Oliveira, Gurd, Nixon, Marshall,
Passingham, 1997). However, attentionally demanding secondary tasks disproportionately impair motor performance in persons with PD (Hackney & Earhart, 2009; O'Shea, Morris, & Iansek, 2002; van Gemmert, Teulings, & Stelmach, 1998). In chapter 2, the results showed that stress did not significantly impair performance on working memory capacity (digit span backwards) in persons with PD. However, there may be individual differences with some individuals working memory being negatively impacted by stress. It remains unknown, if the effect stress has clinical motor symptoms and working memory capacity are associated in persons with PD.

In addition to cognition, stress negatively impacts sensory processes such as inhibitory gating in healthy populations (Johnson & Adler, 1993; Ermutlu, Karamürsel, Ugur, Senturk, & Gokhan, 2005). In chapter 3, the results showed that stress also impairs inhibitory gating in persons with PD. Impairments in sensory processing are thought to contribute to motor impairments in persons with PD (Conte, Khan, Defazio, Rothwell, & Berardelli, 2013; Konczak, et al., 2009; Müller, 2013; Nieuwboer & Giladi, 2013). While relatively unexplored, one study found that gating of the mid-latency (n100-p200) components have been associated with bradykinesia symptoms (Lukhanina, et al., 2011). It is unknown however, if the early components (p50) which worsen with stress are associated with the effects of stress on PD motor symptoms.

The purpose of this study was to examine how stress effects the within-individual relationships between clinical motor tests and potential mediators such as working memory, and early sensory processing (inhibitory gating) in persons with PD. We hypothesized a negative association between early inhibitory gating (p50 ratio) and PD motor symptoms, where decreases in inhibitory gating will be associated with an increase in PD motor symptoms. We also hypothesized a negative association between working memory capacity (digit span backward)
and PD motor symptoms, where decreases in working memory capacity will be associated with an increase in PD motor symptoms.

5.3 Methods

5.3.1 Participants

The same participants used in Chapter 2 were used for this study. See Chapter 2.3.1 Participants. All participants provided written informed consent to participate in the study as approved by the Iowa State University Institutional Review Board (see chapter 5.8 Appendix).

5.3.2 Procedure

The same procedure used in Chapter 2 were used for this study. See Chapter 2.3.2 Procedure.

5.3.3 Stress and Control Tasks

The same stress and control tasks used in Chapter 2 were used for this study. See Chapter 2.3.3 Stress and Control Tasks.

5.3.4 UPDRS Motor Data Acquisition and Analysis

The same UPDRS motor data acquisition and analysis used in Chapter 4 were used for this study. See Chapter 4.3.4 UPDRS Motor Data Acquisition and Analysis.

5.3.5 Digit Span Backward

E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA) was used to present the digit span tasks to the participants. Digits were auditorily presented at a rate of 1 per second. The string of digits used in the task did not include the digit 0, sequences (e.g. 1-2, or 2-1) or single digit repetition (e.g. 1,5,1) (Woods, et al., 2011). When beginning the tasks participants were presented a three-digit number and asked to type the digits back into the computer in the reverse (backward) order. If they got the sequence correct, the number of digits increased by one.
Accuracy was recorded via E-Prime. After 2 consecutive mistakes, the task ends. The number of trials correct prior to two successive misses will be recorded. This is referred to as the two-error maximum list length (TE-ML) (Woods, et al., 2011).

5.3.6 EEG Data Acquisition and Analysis

The same EEG data acquisition and analysis used in Chapter 3 were used for this study. See Chapter 3.3.4 EEG Data Acquisition and Analysis.

5.3.7 Statistical Analysis

Data from 1 participant in the analysis of finger tapping was excluded because they did not complete the task correctly. For all variables, outliers of 3 standard deviations were removed. This resulted in 6 outliers being removed. This included 2 rest tremor, 1 maximum rest tremor, 1 rest tremor CV, 1 postural tremor, and 1 p50 ratio data points being removed.

A repeated measures Pearson’s correlation (Bakdash & Marusich, 2017) was used to examine the relationship between changes in performance between the control and stress conditions on the UPDRS motor tasks and measures of inhibitory gating (p50 ratio) and working memory capacity (digit span backwards TE-ML). Significance was set at $\alpha=0.05$. Repeated measures correlations is used to examine within-individual associations for measures assessed on two or more occasions for multiple individuals. Repeated measures correlations do not violate the assumption of independence of observations, and estimates the association shared among individuals. Repeated measures correlation uses an analysis of covariance (ANCOVA) to adjust for inter-individual variability by removing between-participants variance and provides the best linear fit for each participant using a parallel regression lines with varying intercepts. Unlike an ANCOVA which is used to adjust for a nuisance (within-participants variance, in each individual), repeated measures correlation uses one of the paired measures to adjust for between-
participants variance. Like the Pearson correlation coefficient (r), repeated measures correlation is bounded by -1 to 1 and represents the strength of the linear association between two variables. Repeated measures correlations is similar to a null multilevel model that uses varying intercept and a common slope for each individual.

5.4 Results

Table 5.1 shows the repeated measures Pearson’s r correlations between all hypokinesia measures with p50 ratio and digit span backward TE-ML. Table 5.2 shows the repeated measures Pearson’s r correlations between all bradykinesia measures with p50 ratio and digit span backward TE-ML. Table 5.3 shows the repeated measures Pearson’s r correlations between all tremor measures with p50 ratio and digit span backward TE-ML.

Figure 5.1 shows the significant repeated measures correlations. Significant associations were revealed between p50 inhibitory gating and finger tapping amplitude \((r = -0.806, p = 0.029)\), and p50 inhibitory gating and postural tremor maximum amplitude \((r = 0.787, p = 0.020)\). In general, as p50 ratio increased the finger tapping amplitude decreased and maximum postural tremor amplitude increased. We also discovered a trend for the association between p50 inhibitory gating and resting tremor maximum amplitude \((r = 0.665, p = 0.072)\). As the p50 ratio increased the maximum resting tremor amplitude increased. Finally, there was a trend correlation between digit span backward TE-ML with hand movement rate \((r = 0.481, p = 0.070)\). Increases in digit span backward TE-ML were associated with faster hand movements. No other correlations were significant.

5.5 Discussion

The purpose of this study was to examine how stress effects the within-individual relationships between clinical motor tests and potential mediators such as working memory, and
inhibitory gating in persons with PD. Decreases in inhibitory gating was associated with decreases in finger tapping amplitude and increases in resting and postural tremor maximum amplitude. We found that as inhibitory gating decreased, motor symptoms became more impaired. There were large associations (>0.5) (Cohen, 1988) that showed decreases in p50 inhibitory gating were associated with decreases in finger tapping amplitude ($r = -0.806$), and increases in both maximum resting ($r = 0.665$) and maximum postural ($r = 0.787$) tremor amplitude. While not statistically significant there was also a medium to large correlations (>0.3) between inhibitory gating and the repetitive movement tasks in the predicted direction.

Decreases in inhibitory gating were associated with increases in movement amplitude variability (finger tapping ($r = 0.346$) and hand movement ($r = 0.403$)). Decreases in inhibitory gating were also associated with decreases in movement rate for finger tapping ($r = -0.481$), and hand movements ($r = -0.462$), and increases in movement rate variability for finger tapping ($r = 0.313$). There was one medium to large correlation in the opposite direction however, where decreases in inhibitory gating were associated with increases in hand movement amplitude ($r = 0.411$). Taken together, these results suggests that inhibitory gating may be involved in the negative effect of stress on PD motor symptoms. Improvement on the digit span backwards was associated with an increase in hand movement rate. However, the associations between working memory and PD motor symptoms were generally not present. In short, there seems to be a relationship between inhibitory gating and PD motor symptoms.

As previously described, sensory processing impairments are hypothesized to contribute to motor impairments in persons with PD (Conte, et al., 2013; Konczak, et al., 2009; Müller, 2013; Nieuwboer & Giladi, 2013). Persons with PD demonstrate impairments in inhibitory gating in early and mid-latency components (Gulberti, et al., 2015; Lukhanina, Kapustina,
Berezetskaya, & Karaban, 2009; Lukhanina, Berezetskaya, & Karaban, 2011; Teo, et al., 1997). Inhibitory gaiting has been associated with bradykinesia symptoms (point 31 of the UPDRS) but not other UPDRS motor scores (Lukhanina, et al., 2011). The results of this study are in line with the previous research. However, one of the major limitations of study put forth by Lukhanina (2011) was using the subjective ordinal UPDRS rating scale, which is unable to detect small differences in PD motor symptoms. Another difference was that this study examined how stress affected the within subjects associations in inhibitory gating and motor symptoms by using a repeated measures correlation, which significantly increases our power to detect intra-individual associations (Bakdash & Marusich, 2017). Despite the benefits of using quantitative measures of motor symptoms and repeated measures correlations, our sample size was small. Thus, the results of this study should be considered exploratory.

While the exact mechanisms of stress’ negative impact on PD inhibitory gating and motor symptoms are unknown, there are three potential pathways that could explain the results observed here. First, decreases in inhibitory gating may result in sensory overloading, which may impair cognitive functioning by competing for limited cognitive resources (Croft, Lee, Bertolot, & Gruzelier, 2001; Desimone & Duncan, 1995; Yadon, Bugg, Kisley, & Davalos, 2009). In turn, this could affect movement by negatively impacting the ability of persons with PD to use cognitive mechanisms to compensate for basal ganglia damage and the resulting movement impairments. Second, stress may negatively affect PD motor symptoms by disrupting normal sensory processing. Finally, PD motor symptoms may be negatively impacting other inhibitory processes that are associated with inhibitory gating such as motor inhibition (Cheng, et al., 2016; Liu, Xiao, Shi, & Zhao, 2011; Yadon, et al., 2009), which is also impaired in persons with PD (Obeso, Wilkinson, & Jahanshahi, 2011). In short, there are a number of possible mechanisms in
which inhibitory gating may influence PD motor symptoms. Additional research is warranted to examine these relationships.

Another aim of this study was to examine how stress affects the relationship between working memory capacity (digit span backward TE-ML) and motor symptoms in persons with PD. The only association we found for digit span backward TE-ML was with hand movement rate ($r = 0.481, p = 0.07$). The SECP caused a slight but statistically insignificant improvement in digit span backwards performance in persons with PD (Chapter 3), and improvement on the digit span backwards was associated with an increase in hand movement rate. This suggests that enhancements of working memory may be associated with the ability of persons with PD to compensate for symptoms of bradykinesia. However, the likelihood of this being a type 1 error is high given that only 1 of 18 separate correlations were significant and the others had a small ($r < 0.3$) to non-existent effect size. Overall, the evidence suggests that the stress induced changes in digit span backward capacity are unrelated to the PD motor symptoms of bradykinesia, hypokinesia, and tremor.

Attention and executive control are hypothesized to help compensate and reduce PD motor symptom impairment (Morris, et al., 1996; Redgrave, et al., 2010; Wu, et al., 2017). The exact processes that underlie the compensatory relationship between top-down cognitive processes and PD motor symptoms still need to be explored. The null findings in this experiment only suggest that the digit span backward, a measure of simple working memory capacity, was unrelated to the effects of stress on tremor, upper body bradykinesia, and upper body hypokinesia. Stress is more likely to affect attention and more complex working memory tasks that require multitasking such as the operational span, task-switching, and inhibition (Eysenck, et al., 2007; Luethi, Meier, & Sandi, 2008; Schoofs, Preuß, & Wolf, 2008; Schoofs, Wolf, &
Smeets, 2009; Shields, Sazma, & Yonelinas, 2016). Thus, future studies are needed to examine the effects of stress on other possible cognitive functions (i.e. attention, cue-utilization, distraction) that might mitigate the effects of stress on motor symptoms in persons with PD.

5.5.1 Limitations

One of the major limitations of this study was the small sample size. Despite using quantitative measures of motor symptoms and repeated measures correlation to improve the power of this study, the small sample size makes this study exploratory and underpowered. Another major limitation is that the motor symptom tasks used are not functional skills (i.e. gait, handwriting). Whether or not inhibitory gating and working memory capacity are associated with functional skill performance in persons with PD still needs to be explored. Finally, another limitation is the use of the digit span backwards TE-ML as the measure of working memory capacity. More sensitive measures of working memory abilities may more reliably detect meaningful associations.

5.5.2 Conclusion

Our hypothesis was partially supported, and decreases in p50 inhibitory gating were generally associated with and increase bradykinesia, hypokinesia, and postural tremor in persons with PD. P50 inhibitory gating can be improved pharmacologically via norepinephrine and acetylcholine (Adler, et al., 1998; Oranje & Glenthøj, 2014). Thus, a potential therapeutic treatment for persons with PD might include modulation of these neurotransmitters. Stress-induced changes in working memory were positively associated with hand movement rate, but overall working memory was not reliably correlated with changes in PD motor symptoms. While simple working memory capacity may not be associated with PD motor symptoms, more complex working memory tasks and other executive functions may still be related to PD motor
functioning. Future studies are still needed to examine how other attentional and cognitive mechanisms are involved in compensating for motor impairments in persons with PD.
Figure 5.1. Repeated Measures Correlations between Inhibitory Gating and Working Memory with PD Motor Symptoms

Each dot represents one of two separate observations for a participant. Observations from the same participant are given the same color, with corresponding lines to show the repeated measures correlation fit for each participant. Solid color lines represent intra individual correlations. The dotted gray line represents the fit of simple between subject correlations. A) Repeated Measures correlation between p50 ratio and finger tapping amplitude. B) Repeated measures correlation between digit span backward and hand movement rate. C) Repeated measures correlation between p50 ratio and maximum rest tremor amplitude. D) Repeated measures correlation between p50 ratio and maximum postural tremor amplitude. *p<0.05, **p<0.01.
<table>
<thead>
<tr>
<th></th>
<th>P50 Ratio</th>
<th>DS Backward</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Finger Amp</strong></td>
<td>-0.806 **</td>
<td>-0.008</td>
</tr>
<tr>
<td>(N = 6)</td>
<td>p = 0.029</td>
<td>p = 0.976</td>
</tr>
<tr>
<td><strong>Hand Amp</strong></td>
<td>0.411</td>
<td>-0.145</td>
</tr>
<tr>
<td>(N = 7)</td>
<td>p = 0.312</td>
<td>p = 0.593</td>
</tr>
<tr>
<td><strong>Pro-Sup Amp</strong></td>
<td>-0.412</td>
<td>-0.030</td>
</tr>
<tr>
<td>(N = 7)</td>
<td>p = 0.311</td>
<td>p = 0.913</td>
</tr>
<tr>
<td><strong>Finger Amp CV</strong></td>
<td>0.346</td>
<td>0.266</td>
</tr>
<tr>
<td>(N = 6)</td>
<td>p = 0.448</td>
<td>p = 0.339</td>
</tr>
<tr>
<td><strong>Hand Amp CV</strong></td>
<td>0.403</td>
<td>-0.214</td>
</tr>
<tr>
<td>(N = 7)</td>
<td>p = 0.322</td>
<td>p = 0.427</td>
</tr>
<tr>
<td><strong>Pro-Sup CV</strong></td>
<td>0.126</td>
<td>0.070</td>
</tr>
<tr>
<td>(N = 7)</td>
<td>p = 0.767</td>
<td>p = 0.799</td>
</tr>
</tbody>
</table>

**Note.** Pearson’s r for correlations between p50 ratio and digit span backward tasks, and all hypokinesia measures. **p<0.05. Finger: Finger Tapping; Hand: Hand Movement; Pro-Sup: Pronation-Supination of the Hand; CV: Coefficient of Variation; DS Backward: Digit Span Backward TE-ML.
Table 5.2. Bradykinesia Correlations

<table>
<thead>
<tr>
<th></th>
<th>P50 Ratio</th>
<th>DS Backward</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finger Movement Rate</td>
<td>-0.481 (N = 6)</td>
<td>-0.026 (N = 14)</td>
</tr>
<tr>
<td></td>
<td>p = 0.274</td>
<td>p = 0.926</td>
</tr>
<tr>
<td>Hand Movement Rate</td>
<td>-0.462 (N = 7)</td>
<td>0.481 (N = 15)</td>
</tr>
<tr>
<td></td>
<td>p = 0.249</td>
<td>p = 0.070</td>
</tr>
<tr>
<td>Pro-Sup Movement Rate</td>
<td>0.052 (N = 7)</td>
<td>-0.263 (N = 15)</td>
</tr>
<tr>
<td></td>
<td>p = 0.902</td>
<td>p = 0.325</td>
</tr>
<tr>
<td>Finger Movement Rate CV</td>
<td>0.313 (N = 6)</td>
<td>0.079 (N = 14)</td>
</tr>
<tr>
<td></td>
<td>p = 0.495</td>
<td>p = 0.780</td>
</tr>
<tr>
<td>Hand Movement Rate CV</td>
<td>0.114 (N = 7)</td>
<td>-0.028 (N = 15)</td>
</tr>
<tr>
<td></td>
<td>p = 0.788</td>
<td>p = 0.917</td>
</tr>
<tr>
<td>Pro-Sup Movement Rate CV</td>
<td>0.091 (N = 7)</td>
<td>0.123 (N = 15)</td>
</tr>
<tr>
<td></td>
<td>p = 0.831</td>
<td>p = 0.650</td>
</tr>
</tbody>
</table>

Note. Pearson’s r for correlations between p50 ratio and digit span backward tasks, and all bradykinesia measures. Finger: Finger Tapping; Hand: Hand Movement; Pro-Sup: Pronation-Supination of the Hand; CV: Coefficient of Variation; DS Backward: Digit Span Backward TE-ML.
Table 5.3. Tremor Correlations

<table>
<thead>
<tr>
<th></th>
<th>P50 Ratio</th>
<th>DS Backward</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rest Tremor Amp</strong></td>
<td>0.018 (N = 6)</td>
<td>0.033 (N = 13)</td>
</tr>
<tr>
<td></td>
<td>p = 0.969</td>
<td>p = 0.910</td>
</tr>
<tr>
<td><strong>Rest Tremor Max</strong></td>
<td>0.665 (N = 6)</td>
<td>0.036 (N = 14)</td>
</tr>
<tr>
<td></td>
<td>p = 0.072</td>
<td>p = 0.899</td>
</tr>
<tr>
<td><strong>Rest Tremor CV</strong></td>
<td>-0.470 (N = 6)</td>
<td>0.182 (N = 14)</td>
</tr>
<tr>
<td></td>
<td>p = 0.287</td>
<td>p = 0.517</td>
</tr>
<tr>
<td><strong>Postural Tremor Amp</strong></td>
<td>0.481 (N = 6)</td>
<td>0.333 (N = 14)</td>
</tr>
<tr>
<td></td>
<td>p = 0.275</td>
<td>p = 0.226</td>
</tr>
<tr>
<td><strong>Postural Tremor Max</strong></td>
<td>0.787* (N = 7)</td>
<td>0.093 (N = 15)</td>
</tr>
<tr>
<td></td>
<td>p = 0.020</td>
<td>p = 0.731</td>
</tr>
<tr>
<td><strong>Postural Tremor CV</strong></td>
<td>-0.188 (N = 7)</td>
<td>-0.203 (N = 15)</td>
</tr>
<tr>
<td></td>
<td>p = 0.655</td>
<td>p = 0.451</td>
</tr>
</tbody>
</table>

*Note.* Pearson’s r for correlations between p50 ratio and digit span backward tasks, and all tremor measures. *p* < 0.05. Amp: Amplitude; Max: Maximum Amplitude; CV: Coefficient of Variation; DS Backward: Digit Span Backward TE-ML.
5.7 References


5.8 Appendix: Informed Consent/IRB Approval

IOWA STATE UNIVERSITY
OF SCIENCE AND TECHNOLOGY

Date: 6/16/2016
To: Andrew Zaman
238 Farken Bldg
Ames, IA

From: Office for Responsible Research

Title: Working Memory, Sensory Processing, and Motor Performance Study

IRB ID: 16-257

Approval Date: 6/16/2016
Date for Continuing Review: 6/4/2018

Submission Type: New
Review Type: Full Committee

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- Stop all research activity if IRB approval lapses, unless continuation is necessary to prevent harm to research participants. Research activity can resume once IRB approval is reestablished.
- Complete a new continuing review form at least three to four weeks prior to the date for continuing review as noted above to provide sufficient time for the IRB to review and approve continuation of the study. We will send a courtesy reminder as this date approaches.

Please be aware that IRB approval means that you have met the requirements of federal regulations and ISU policies governing human subjects research. Approval from other entities may also be needed. For example, access to data from private records (e.g., student, medical, or employment records, etc.) that are protected by FERPA, HIPAA, or other confidentiality policies requires permission from the holders of those records. Similarly, for research conducted in institutions other than ISU (e.g., schools, other colleges or universities, medical facilities, companies, etc.), investigators must obtain permission from the institution(s) as required by their policies. IRB approval in no way implies or guarantees that permission from these other entities will be granted.

Upon completion of the project, please submit a Project Closure Form to the Office for Responsible Research, 1138 Pearson Hall, to officially close the project.

Please don't hesitate to contact us if you have questions or concerns at 515-294-4566 or IRB@iastate.edu.
CHAPTER 6. GENERAL CONCLUSION

6.1 General Conclusion

Parkinson’s disease (PD) is a neurodegenerative disorder characterized by dopaminergic cell loss in the substantia nigra and norepinephrine producing cells in the locus coeruleus. As a result, persons with PD have cardinal motor symptoms (i.e. tremor, rigidity, bradykinesia, and postural instability), impairments in motor automaticity (Redgrave et al., 2010; Wu, Hallett, & Chan, 2015), and impairments in cognitive and sensory processing (Kudlicka, Clare, & Hindle, 2011; Siegert, Weatherall, Taylor, & Abernethy, 2008; Teo, et al., 1997; Zgaljardic, Borod, Foldi, & Mattis, 2003). However, these impairments are intertwined with one another. Sensory processing deficits contribute to PD motor impairments (Conte, Khan, Defazio, Rothwell, & Berardelli, 2013; Konczak, et al., 2009; Müller, 2013). In order to overcome motor automaticity deficits, persons with PD use controlled cognitive processes (Morris, Iansek, Matyas, & Summers, 1996; Redgrave et al., 2010; Wu, et al., 2015). Thus, modifiable factors such as stress (which can impact motor performance, cognition, and sensory processing) should be of interest to both patients and clinicians.

In healthy adults, stress floods the brain with neurotransmitters such as dopamine and norepinephrine (al’Absi, Petersen, & Wittmers, 2002; Atterhög, Eliasson, & Hjemdahl, 1981; Finlay & Zigmond, 1995; Gresch, Sved, Zigmond, & Finlay, 1994; Imperato, Puglisi-Allegra, Casolini, & Angelucci, 1991; Keefe, DiFrischia, & Zigmond, 1989; Kim, Choi, Chang, Kim, & Hwang, 2005; Morrow, Roth, & Elsworth, 2000; Nater, et al., 2006; Roth, Tam, Ida, Yang, & Deutch, 1988; Scott, Heitzeg, Koepppe, Stohler, & Zubieta, 2006; Thoma, Kirschbaum, Wolf, & Rohleder, 2012). Stress also impairs cognitive functions such as working memory (Arnsten, 2009; Eysenck, Derakshan, Santos, & Calvo, 2007), sensory processing (Ermutlu, Karamürsel,
Ugur, Senturk, & Gohan, 2005; Johnson & Adler, 1993), and less-well learned motor skills (Nibbeling, Oudejans, & Daanen, 2012). In persons with PD, there is neurodegeneration in dopaminergic and norepinephrine systems (Braak, et al., 2003; Chaudhuri, Healy, & Schapira, 2006; Seidel, et al., 2015; Vermeiren & De Deyn, 2017). However, it is unknown how stress would affect persons with PD. Thus, the goal of this work was to understand how stress affects a subset of cognitive processes (i.e., working memory), sensory processing (i.e., inhibitory gating), and PD motor symptoms (i.e., tremor, and upper body bradykinesia and hypokinesia). In addition, as an exploratory analysis, we examined how changes in working memory and inhibitory gating were associated with changes in PD motor symptoms.

Aim 1: Determine if stress negatively impacted working memory in persons with PD. We hypothesized that stress will negatively impact working memory capacity (digit span forward and backward two error maximum length (TE-ML)) in both HOAs and persons with PD. We also hypothesized that persons with PD will in general have lower working memory capacity than HOAs.

Aim 2: Determine if stress reduces inhibitory gating in persons with PD. We hypothesized that the stress would impair inhibitory gating (higher p50 ratios) in both persons with PD and HOAs.

Aim 3: Determine if stress impacts the PD motor symptoms of tremor, upper body bradykinesia, and upper body hyperkinesia. We hypothesized that stress will negatively impact finger tapping, hand movements, pronation-supination of the hand, postural tremor, and resting tremor in persons with PD but not in HOAs.

Aim 4: Determine if stress induced changes in motor symptoms are associated with the changes in inhibitory gating, and working memory in persons with PD. We hypothesized that
decreases in inhibitory gating would be associated with an increase in PD motor symptoms. We also hypothesized that decreases in working memory capacity will be associated with an increase in PD motor symptoms.

The results and highlights of these experiments are as follows:

- **Experiment 1**: Stress had no effect on digit span forward capacity. There was an interaction where stress increased digit span backward capacity in persons with PD, and decreased digit span capacity in HOAs resulting in equal performance of both groups.

- **Experiment 2**: Stress negatively impacted inhibitory gating (increased p50 ratio) in both HOAs and persons with PD. There was a trend for the change to be greater in persons with PD.

- **Experiment 3**: Stress negatively impacted finger tapping amplitude and postural tremor in persons with PD and HOAs. The results also showed that stress increased finger tapping amplitude variability in persons with PD while it decreased in HOAs. Finally, stress increased postural tremor more in persons with PD than it did within HOAs.

- **Experiment 4**: A decrease in inhibitory gating was associated with an increase in PD motor symptom severity.

### 6.1.1 Implications for persons with PD

The effects of stress on persons with PD involve a complex interaction between stress which increases the release of neurotransmitters such as dopamine and norepinephrine, and PD which is associated with cell death in brain regions which distribute these neurotransmitters. In addition, stress impacts cognitive and sensory processes, both of which influence PD motor symptom severity (Conte, et al., 2013; Konczak, et al., 2009; Morris, et al., 1996; Müller, 2013;
Redgrave, et al., 2010; Wu, et al., 2015). This work provides a first step in understanding how stress impacts persons with PD, and suggests that stress may affect persons with PD differently.

Stress negatively impacted performance on some motor tests but not others possibly due to movement rate. Finger tapping was performed at a much faster movement rate than the hand movement and pronation-supination of the hand tasks. Movements at faster rates result in greater activation in cortical and subcortical motor regions (basal ganglia, frontal regions, and cerebellum). Stress negatively impacts prefrontal functioning (Arnsten, 2009), and therefore may negatively impact fast repetitive movements (i.e. finger tapping) more than the slower repetitive movements (i.e. hand movements, pronation-supination of the hand). Movement rate was not controlled for however. More studies are needed to examine other potential moderating factors such as the degrees of freedom, the size and muscles used in the different tasks, and the automaticity of those movements, all of which may also contribute to the differential effects of stress on the motor tasks.

There was also an interaction where stress increased variability in persons with PD and decreased variability in HOAs which suggests that stress may have also influenced motor automaticity differently in persons with PD. Motor automaticity is associated with decreased activation in cortical and subcortical motor regions, but not in persons with PD who rely more on attentional control to overcome deficits in automaticity (Wu, et al., 2015). Thus, by negatively impacting prefrontal functioning stress may have improved automaticity in HOAs, and impaired automaticity in persons with PD. More studies are still needed to examine the underlying factors and mechanisms involved in stress’ impact on persons with PD. Furthermore, the effects of stress on more complex skills and activities of daily living in persons with PD are needed to provide a better understanding of the clinical implications of stress and stress management.
Stress impacted working memory in persons with PD and HOAs differently. Stress and caused a slight improvement in working memory (digit span backward) in persons with PD while the opposite was true in HOAs, resulting in equal performance of the two groups. Thus, stress may help to improve working memory in persons with PD. Future studies are still needed to determine how stress and PD severity interact however, as those in the early stages may see effects similar to HOAs, due to a possible dopaminergic ‘over-dosing’ (Cools, 2006).

While the results showed that stress did not negatively affect working memory in persons with PD, and that changes in working memory were generally not associated with PD motor symptoms. The evidence suggests however that attention and other cognitive mechanisms help persons with PD overcome deficits in motor automaticity (Morris, et al., 1996; Redgrave, et al., 2010; Wu, et al., 2015), and the results of this study showed that stress negatively impacted some PD motor symptoms. Thus, more studies are needed to examine how stress effects more complex working memory tasks and other types of cognitive functioning (i.e. inhibition, set-shifting) as they may have a different response curves with stress and dopamine (Cools, Barker, Sahakian, & Robbins, 2001), and they may be more mechanistically involved in PD motor symptoms.

Inhibitory gating was identified as a potentially mechanism that may contribute to PD motor symptoms. Theoretically inhibitory gating is important for overall neurological functioning, by filtering out irrelevant sensory information (Gjini, Arfken, & Boutros, 2010; Knight, Scabini, & Woods, 1989), and inhibitory gating impairment is associated with decreases in cognitive performance (Lijffijt, et al., 2009; Yadon, Bugg, Kisley, & Davalos, 2009), and motor inhibition (Cheng, et al., 2016; Liu, Xiao, Shi, & Zhao, 2011; Yadon, et al., 2009). The evidence suggests that stress may be a modifiable factor that could help improve inhibitory gating, and PD motor symptoms. Future studies should examine if improving inhibitory gating
either through reducing stress and/or pharmacological medications can improve the physical and cognitive functioning in persons with PD.

6.1.2 Conclusion

Stress appears to have some differential effects in persons with PD. The effects of stress are more negative for some processes (i.e. inhibitory gating, PD motor symptoms), and more positive for other processes (i.e. working memory). We have also identified some potentially modifiable mechanisms such as inhibitory gating which may help to decrease PD motor symptom severity. This provides a first step in understanding how stress impacts persons with PD. Overall, the work of this dissertation suggests that acute stress is a useful tool in understanding PD, and that stress management is a potentially powerful tool for managing PD motor symptoms.

6.2 References


