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Digital Object Identifier: https://doi.org/10.13023/ETD.2016.400

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DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE: AN INVESTIGATION OF POST-SURGICAL SELF-REGULATION AND EXECUTIVE FUNCTIONING

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Arts and Sciences
at the University of Kentucky

By

Hannah Lane Combs

Lexington, Kentucky

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and Dr. Suzanne C. Segerstrom, Professor of Psychology

Lexington, Kentucky

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ABSTRACT OF DISSERTATION

DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE: AN INVESTIGATION OF POST-SURGICAL SELF-REGULATION AND EXECUTIVE FUNCTIONING

Parkinson's Disease (PD) is a common neurodegenerative disorder that attacks the basal ganglia and contributes to a range of motor, cognitive, and behavioral impairments (e.g., tremor, rigidity, and executive dysfunction). This dysfunction may contribute to self-regulatory impairment across several domains, including cognitive skills, thought processes, and emotion. Deep Brain Stimulation (DBS) is a neurosurgical procedure that allows for direct and reversible manipulation of brain activity in patients with PD. The procedure is growing in popularity and is commonly used as an adjunct or in some instances an alternative to dopaminometic medications. Preliminary studies suggest mild executive dysfunction follows DBS but as the literature is in its early stages, there is a need to examine further the range of executive deficits and self-regulatory impairment observed in PD following DBS.

In the present study, twenty-seven PD patients post-DBS completed a brief neuropsychological test battery and provided measures of heart rate variability (HRV). Patients also completed questionnaires regarding their ability to self-regulate emotions and thought patterns. Scores were compared to the patient's pre-surgical performance as well as to a group of healthy older adults.

Results suggest DBS leads to significant declines in executive function (EF) and self-regulation (SR). Patients had significantly worse scores on neuropsychological tests of EF (i.e., phonemic fluency, semantic fluency, and working memory) when compared to their preoperative performance. Similarly, DBS patients had significantly worse scores than controls on measures of EF (i.e., verbal fluency, attention, mental flexibility) and verbal memory. With regard to physiological functioning, lower baseline HRV was linked to worse EF but fewer impulsive-compulsive behaviors in DBS patients. Correlations among measures of theoretically similar constructs (i.e., EF and SR) modest and variable, challenging the idea that SR in different domains depends on a common resource.

The results of the current study suggest that PD patients are prone to a variety of self-regulatory deficits, ranging from subtle to severe. They are likely to experience small declines in EF post-DBS that may contribute to these self-regulatory impairments. However, this research suggests that both the quantity and quality of impairment varies, and that the correlates of these deficits may be different between patients. Clinically, it is important for health care professionals working with PD to recognize the presence of self-regulatory deficits and to be aware of the potential obstacles that might arise from such impairments within a patient's daily life.

KEYWORDS: Parkinson's disease, Deep Brain Stimulation,
Executive Functioning, Self-Regulation,
Heart Rate Variability

Hannah L. Combs

August, 26, 2016
Date

DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE: AN INVESTIGATION OF POST-SURGICAL SELF-REGULATION AND EXECUTIVE FUNCTIONING

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Chapter 1: Introduction

Parkinson's Disease

Parkinson's Disease (PD) is a common degenerative disorder of the central nervous system. It has been estimated that about one million people are affected in the United States alone, with about 66,000 new diagnoses made each year (Kowal, Dall, Charkabarti, Storm, & Jain, 2013). The disease is characterized by a loss of dopamine-generating cells in the substantia nigra region of the basal ganglia and the accumulation of α-synuclein protein aggregates (Lewy bodies) within neurons. As a result, individuals experience a variety of extrapyramidal symptoms including resting tremor, rigidity, slowness, gait abnormalities, cognitive impairments, depression, and other neurobehavioral concerns (Jankovic, 2008).

In general, most attention is paid to the motor symptoms of PD; however, the cognitive and psychological issues associated with the disease can be as much or even more debilitating for the patient. The most common psychopathology associated with PD is depression (Aarsland, Larsen, Lim, Janvin, Karlsen, Tandberg, & Cummings, 1999). A recent review of depression prevalence within PD has estimated that about 17% of patients with PD meet criteria for Major Depressive Disorder, 13% meet criteria for Dysthymia, and 22% endorse subclinical symptoms of depression (Reijnders, Ehrt, Weber, Aarsland, & Leentjens, 2008). The cognitive impairments associated with PD are diverse, including difficulty with attention (sustained and divided), slowed speed of mental processing, trouble with problem-solving and other executive functions, problems with memory recall, word-finding and naming abnormalities, as well as difficulties with visuospatial abilities (Dubois & Pillon, 1996). Furthermore, these deficits may be related

to problematic behaviors and thoughts across domains important to functioning. Consequently, there is a need to clarify the prevalence and pattern of cognitive and behavioral deficits in PD, which have a sizeable impact not only on the patient's health, but also on his or her sense of wellbeing.

Along with the symptoms described above, autonomic dysfunction is quite prevalent in Parkinson's disease. Autonomic dysfunction in Parkinson disease can manifest as low blood pressure upon standing (orthostatic hypotension) leading to lightheadedness or dizziness, constipation, difficulty swallowing, abnormal sweating, urinary leakage, and sexual dysfunction (abnormally decreased or increased interest in sex). These autonomic symptoms can precede the classic motor symptoms by years, are common in all stages of PD, and negatively impact patient's quality of life (Visser, Marinus, Stiggelbout, & Van Hilten, 2004). Consequently, there is a need to clarify the prevalence and understand the effect that various therapeutic modalities have on these autonomic symptoms.

The Basal Ganglia

First described by Thomas Willis in the 17th century, the basal ganglia are located deep within the brain and consist of five subcortical nuclei: globus pallidus, caudate, putamen, substantia nigra, and the subthalamic nucleus (Leisman, Melillo, & Carrick, 2013). The nuclei of the basal ganglia have long been known to serve motor functions; within the extrapyramidal motor system, they subserve motor refinement. When these areas are damaged, motor dysfunction such as tremors, dyskinesias, or rigidity emerges (Bhatia & Marsden, 1994). Within the past several decades, growing evidence has led researchers to conceptualize communication between the cortex and the basal ganglia in

terms of multiple (closed) parallel cortico-striato-thalamocortical loops (Alexander, Delong, & Strick, 1986; Middleton & Strick, 2000; Thorn, Atallah, Howe, & Graybiel, 2010). These circuits originate in the cortex, project to the basal ganglia (striatum and thalamus) and return back to the cortex. The impairments seen with motor functioning in PD are consequences of disruptions to these parallel loops.

These loops can be further divided into two pathways based on their effects on movement: the direct pathway (stimulates movement) and the indirect pathway (inhibits movement; Middleton & Strick, 2000). In the direct pathway, the motor cortex and the substantia nigra pars compacta (SNc, via the D1 Dopamine receptor) excite the striatum. When the striatum is excited, it sends inhibitory signals to the globus pallidus internla (GPi) and substantia nigra pars reticulate (SNr). At rest, GPi and SNr inhibit the thalamus, but when the GPi and SNr are inhibited, the thalamus is able to freely send excitatory signals to the motor cortex, thereby increasing movement.

In the indirect pathway, the motor cortex excites the striatum while the SNc (via D2 dopamine) inhibits the striatum. This, in turn, inhibits the globus pallidus external (GPe). When the GPe is inhibited, there is less inhibition of the subthalamic nucleus (STN) resulting in excitation of the GPi. As mentioned above, GPi sends inhibitory signals to the thalamus, so when it is excited, there is less excitation of the motor cortex and therefore, less movement. These two pathways provide a balance between the competing excitatory and inhibitory impulses; imbalance between the direct and indirect pathways results in dysfunction.

In addition to the two main basal ganglia pathways, recent research has demonstrated that several cortical areas have excitatory projections directly to the STN

(Jahanshahi, Obeso, Rothwell & Obeso, 2015). These cortical areas include the motor cortex, supplementary motor area, premotor cortex, anterior cingulate cortex, and the dorsolateral prefrontal cortex, among others (Kitai & Deniau, 1981; Hartmann-von Monakow, Akert, & Kiinzle, 1978). Together these pathways are known as the hyperdirect pathway, as it is the quickest action output route (Nambu, Tokuno, & Takada, 2002).

As mentioned earlier, PD results from the loss of dopaminergic neurons in the SNc. Because the nigrostriatal pathway excites the direct pathway and inhibits the indirect pathway, the loss of this DA input tips the balance in favor of activity in the indirect pathway. Thus, the GPi neurons are abnormally active, keeping the thalamic neurons inhibited. Without the thalamic input, the motor cortex neurons are not excited, and the motor system is less able to execute motor plans in response to the patient's volition (i.e., bradykinesia, rigidity).

Although these loops were originally studied within motor systems, Alexander, Delong, and Strick (1986) suggested the basal ganglia serves just as important a role with cognitive and affective abilities as it does with motor abilities. They hypothesized that the basal ganglia targets premotor and prefrontal cortices along with the primary motor cortex, thereby serving to "fine-tune" cognitive abilities along with motor actions. Damage to particular circuits within the basal ganglia disrupts specific cognitive abilities subserved by those circuits. For example, when the anterior cingulate circuit, which connects the cingulate cortex to the striatum, is damaged, individuals have difficulty with motivation and procedural learning; damage to the dorsolateral prefrontal circuit (connecting the prefrontal cortex to the caudate, globus pallidus interna, and substantia

nigra) results in impaired higher-order executive functions (Leisman, Melillo, & Carrick, 2013). The model of cortico-striato-thalamocortical (CSTC) circuits has begun to provide an integrated explanation for the non-motor symptoms of Parkinson's disease and the neurocognitive side effects attributed to deep brain stimulation (DBS) (discussed below).

Executive Functions

Despite the range of cognition affected by the disease, executive dysfunction seems to be the most profound impairment (Kudlicka, Clare, & Hindle, 2011). The term executive functions (EF) typically refers to a "wide range of cognitive processes and behavioral competencies which include verbal reasoning, problem-solving, planning, sequencing, the ability to sustain attention, resistance to interference, utilization of feedback, multi-tasking, cognitive flexibility, and the ability to deal with novelty" (Chan, Shum, Toulopoulou, & Chen, 2008, p. 201). Although there is general agreement that EF is a heterogenous concept (Godefroy, Cabaret, Petit-Chenal, Pruvo, & Rousseaux, 1999), there is less agreement concerning the best way to break down 'executive functions' into sub-constructs (e.g., initiating, inhibiting, switching; Alvarez & Emory, 2006).

In the absence of a fully agreed upon conceptualization (Aron, 2008), studying EF can be difficult. This theoretical uncertainty contributes to another difficulty with research on EF- "the lack of a clear gold standard measure against which putative EF measures can be compared" (Royall, Lauterbach, Cummings, Reeve, Rummans, Kaufer, LaFrance, & Coffey, 2002, p. 381). Although 'executive' and 'frontal lobe' tasks are often applied interchangeably, the use of executive function tasks as 'frontal lobe indicators' is not warranted by current research (Alvarez & Emory, 2006). While the frontal lobes may be involved in EF, other brain regions are also necessary, including

subcortical structures (e.g., basal ganglia). Furthermore, most research indicates that measures of EF have low reliability and low intercorrelations (Alvarez & Emory, 2006; Miyake, Friedman, Emerson, Witzki, Howerter, & Wagner, 2000). However, this may not be surprising when comparing such heterogeneous sub-constructs.

Given the variability within skills labeled as EF, clinically, it is useful to specify the individual EF abilities involved, especially in clinical conditions such as PD. A recent meta-analysis by Kudlicka and colleagues (2011) examined the pattern of executive dysfunction of patients with Parkinson's disease compared to healthy controls. Moderate deleterious effects were seen for phonemic fluency (e.g., FAS), working memory (e.g., Digit Span Backward), concept formation (e.g., WCST), and inhibition of unwanted responses (e.g., Stroop Test). Large effects were found for phonemic fluency (e.g., Animals), alternating fluency, and mental flexibility/divided attention (e.g., TMT B).

Executive Functions and Self-Regulation

Despite the controversial nature of EF as a cohesive neuropsychological domain, there is general agreement, that EF broadly defined "control and regulate thought and action" (Friedman, Miyake, Corley, Young, DeFries, & Hewitt, 2006, p. 172), "enable us to formulate goals and plans" (Aron, 2008, p. 124), and are important for "independent and responsible social behavior" (Lezak, Howieson, Bigler, & Tranel, 2012, p. 30). Similarly, the construct of self-regulation (SR) refers to the ability to control or override one's thoughts, emotions, impulses, and behavior and refers to processes that facilitate adaptive behavior and flexibility essential for accomplishing goals (Gailliot et al., 2007). Both EF and SR are limited resources and can be depleted, leading to difficulty in controlling and regulating behavior and trouble functioning in everyday life (Baumeister,

Bratslavsky, Muraven, & Tice, 1998; Gailliot et al., 2007; Marios & Ivanhoff, 2005; Miyake, Friedman, Emerson, Witzki, Howerter, & Wagner, 2000; Schmeichel, 2007). Conversely, both can also be strengthened or enhanced through practice (Davidson, Zacks, & Williams, 2003; Muraven, Baumeister, & Tice, 1999; Oaten & Cheng, 2006). High SR and executive control have positive outcomes (e.g., more effective coping skills, superior academic performance, less susceptibility to substance abuse, and reduced aggression; Gailliot et al., 2007).

Although there are theoretical parallels between EF and SR (Kaplan & Berman, 2010), they are typically measured in different ways. EF often refers to the unpracticed ability to execute cognitive processes (as measured by standard neuropsychological tests). SR, on the other hand, is a practiced function that is better understood when interpreted within the context of real-life situations. Thus, EF likely contributes to the ability to self-regulate in diverse situations. Hence, Schmeichel (2007) proposes that depleted self-regulatory resources may more accurately be considered examples of reduced resources for executive control.

The ability to self-regulate may be heavily dependent on EF, and vice versa. People with PD who have poor EF may demonstrate decreased capacity for self-regulation in multiple areas, including cognition. The effects of self-regulatory impairment may also have a significant impact on everyday life. Patients with PD with executive impairment have been compared to patients with damage to their frontal lobes in that they may perform well on many standardized tests and show no obvious signs in structured settings but fail to perform well in everyday situations (Rogers, Sahakian,

Hodges, Polkey, Kennard, & Robbins, 1998; Owen, Roberts, Hodges, Summers, Polkey, & Robbins, 1993).

Central Autonomic Network and Physiological Self-Regulation

Autonomic resources may be important components of the capacity for executive control and SR, and may be especially vital for people with PD. Benarroch (1993) identified the Central Autonomic Network (CAN), a set of functionally reciprocal neural structures that integrate autonomic, neuroendocrine, and behavioral responses with emotion, attention, and other executive functions, thereby linking executive and self-regulatory functions of the cortex to parasympathetic control of the heart. Thayer & Lane (2000, 2009) proposed a neurovisceral integration model suggesting "individual differences in vagal function (as indexed by HRV) at rest reflect the activity of a flexible and integrative neural network and allows the organism to effectively organize emotional, cognitive, and behavioral responses in the service of goal-directed behavior and adaptation" (Gillie & Thayer, 2014, p. 1).

The CAN is thought to be the link between the autonomic nervous system (ANS) and brain areas associated with higher order cognitive functioning (e.g., prefrontal cortex). It allows the prefrontal cortex to exert inhibitory control over subcortical structures to generate cognitive, behavioral, and physiological responses that support goal-directed behavior and adaptability. The output of this inhibitory circuit extends to autonomic inputs to the heart, including the vagus nerve. When the prefrontal cortex exerts inhibitory control, vagal tone increases leading to increased heart rate variability (HRV), the physiological phenomenon of variation in beat-to-beat intervals. For this reason, examining the parasympathetic influence on the heart via HRV can provide an

index of an individual's capacity to effectively function in a complex and challenging environment and HRV can serve as an important physiological correlate of self-regulatory capacity and executive functioning (Thayer & Lane, 2009).

Supporting this theory, HRV has been associated with prefrontal activity and SR (e.g., inhibition, cognitive flexibility, delayed response). Specifically, low resting HRV may correlate with decreased prefrontal activation, impaired EF, disrupted emotion modulation (i.e., enhanced/prolonged threat response), and perseverative thoughts (Brosschot, Gerin, & Thayer, 2006; Thayer, 2007). Studies using pharmacological and neuroimaging techniques demonstrate that prefrontal cortical activity is associated with vagally mediated HRV (Lane, McRae, Reiman, Chen, Ahern, & Thayer, 2009; Thayer, Ahs, Fredrikson, Sollers, & Wagner, 2012). HRV is also associated with SR; a growing body of research has found that individuals with higher levels of HRV at rest demonstrate enhanced performance on cognitive control tasks that require working memory, attentional modulation, and inhibition (Hansen et al., 2003; Hansen et al., 2004; Park and Thayer, 2014). Low resting HRV also predicts less persistence on tasks requiring self-regulatory effort (Segerstrom & Solberg Nes, 2007) and decreased HRV was found to be associated with stress and worry after controlling for personality, mood, and demographic factors (Pieper, Brosschot, Van der Leeden, & Thayer, 2007). Thus, HRV is thought to "reflect the ability to allocate and maintain attention, which are crucial to the control of emotion and performance" (Demaree, Pu, Robinson, Schmeichel, & Everhart, 2006, p. 162).

There is converging evidence of impaired autonomic functions in PD. Patients with PD have been shown to have impaired sympathetically mediated neurocirculatory

innervation (Haensch, Herch, Jorg, & Isenmann, 2009) resulting in decreased heart rate variability (Haapaniemi, Pursianinen, Korpelainen, Hulkuri, Sotaniemi, & Myllyla, 2001). This sympathovagal imbalance is also correlated with disease severity. Individuals who have more severe PD demonstrate more severe autonomic dysfunction (e.g., decreased HRV, orthostatic hypotension).

There is evidence to suggest that SR and EF are overlapping and related constructs that have at least one common autonomic marker (e.g., HRV). In fact, Brook and Julius (2000) propose that autonomic imbalance is related to a range of cardiovascular abnormalities. These cardiovascular factors associated with SR may be particularly important for people with PD. It could be true that the relationships between physiological factors (e.g., HRV) and SR are interactive. People with PD have impaired cortical functions, which may compromise both HRV and self-regulation, thereby resulting in the range of self-regulatory deficits in PD. Successful self-regulation and executive functions rely on autonomic activity, and there is a need to study these physiological resources in relation to other forms of self-regulation.

Deep Brain Stimulation

Despite the previously mentioned neurocognitive, psychological, and autonomic dysfunction that commonly occur with PD, the majority of treatment options are focused on motor symptoms. The most common approach for treating the motor abnormalities associated with PD is administering dopaminometic medications and other pharmacologic agents (Olanow & Koller, 1998). However, patients often experience unpleasant side effects from the medications and/or require increasing doses as the disease progresses. In order to pursue an alternative and hopefully more effective

treatment, researchers have sought to find a nonpharmacologic surgical option. Over the past few decades, deep brain stimulation (DBS), specifically targeting the basal ganglia, has gained popularity in both clinical and research settings as a treatment option for idiopathic Parkinson's disease (Sironi, 2011).

DBS is a neurosurgical procedure involving the implantation of a pacemaker in the brain that sends electrical impulses to specific target sites (Benabid, Chabardes, Mitrofanis, & Pollak, 2009). DBS allows for direct and reversible manipulation of brain activity in a controlled manner. The most common targets for DBS within Parkinson's disease are the subthalamic nucleus (STN) and globus pallidus pars interna (GPi) (Pollak, Fraix, Krack, Moro, Mendes, Chabardes, Koudsie, & Benabid, 2002).

Although the exact mechanism for the effectiveness of DBS is unknown, several theories have been proposed. One theory suggests that DBS acts by reversibly inhibiting the target site, as the effects are similar to those from ablation (removal of brain tissue; Ashby & Rothwell, 1999). In support of this theory, many studies have shown that high-frequency stimulation increases the excitatory response from the implanted site which then has an inhibitory downstream effect (Hashimoto, Elder, Okun, Patrick, & Vitek, 2003; Windels, Bruet, Popuard, Feuerstein, Bertrand, & Savasta, 2003). For example, GPi stimulation may activate GPe, which results in increased GABA signals sent back to GPi, thereby inhibiting GPi (Benazzouz & Hallett). A second theory suggests DBS is effective because it blocks the depolarization of downstream myelinated axons, and a third theory postulates that DBS works through "neuronal jamming", whereby activation of a particular target site results in a surge of incoherent messages being sent to downstream nuclei, which are then ignored (Ashby, Kim, Kumar, Lang & Lozano, 1999;

Kern & Kumar, 2007). Further research is needed to better understand the mechanism of action for DBS.

Randomized controlled trials have found that stimulating the STN or GPi is equally effective at improving motor symptoms and dyskinesias (Anderson, Burchiel, Hogarth, Favre, & Hammerstad, 2005; Follett et al., 2010). However, there has been some discrepancy as to whether DBS' impact on cognitive, behavioral, and mood symptoms differs between target sites. A recent meta-analysis of the cognitive sequelae of deep brain stimulation for treatment of Parkinson's disease demonstrated that there are small declines in psychomotor speed, learning & memory, attention/concentration, executive functions, and overall cognition, and medium declines in verbal fluency following DBS of the STN (STN-DBS; Combs et al., 2015). Fewer cognitive declines were seen following DBS of the GPi (GPi-DBS), however, small effects were still found for worsened attention/concentration and verbal fluency. The results suggested that broadly speaking, GPi-DBS may be safer than STN-DBS in terms of its effect on cognition.

However, Combs et al. (2015) expressed concern over the relatively low number of studies available to examine the overall cognitive effect of GPi-DBS ($k = 9$). Since there were few studies available, it is less likely that the estimated effects found for GPi-DBS were representative of the "true effect." As such, more studies are needed to fully understand the neurocognitive profile associated with GPi-DBS.

Deep Brain Stimulation and Heart Rate Variability

As described above, HRV is often used as a proxy for autonomic control and studies have shown suppressed HRV in both untreated and treated patients with PD

(Haapaniemi, Purianinen, Korpelainen, Huikuri, Sotaniemi, & Myllyla, 2001; Devos, Kroumova, Bordet, Vodougnon, Guieu, Libersa, & Destee, 2003). Although there has been substantial investigation of the effects of DBS on both the motor and cognitive symptoms in PD, less research is available investigating the impact on autonomic control. Preliminary studies suggest that although DBS significantly decreases motor disability, it has no significant effect on autonomic function (Azevedo, Santos, Frietas, Rosas, Gago, Garrett, & Rosengarten, 2010) and more specifically, no effect on HRV (Ludwig et al, 2007; Erola, Heikkinen, Tuominen, Juolasmaa, & Myllyla, 2006). However, these studies have only included DBS with STN as the target site.

Given Thayer and Lane's (2000, 2009) compelling theory that parasympathetic influence on the heart (i.e. HRV) is reflective of the prefrontal cortex's ability to self-regulate, declines in self-regulation after DBS ought to be related to declines in HRV. Therefore, the preliminary findings that changes in executive dysfunction are independent from changes in HRV are surprising. However, current research has not yet examined this phenomenon within the context of Thayer and Lane's (2000, 2009) model, nor in the context of GPi-DBS, and more research is necessary to better understand this theory in the context of a disease state, such as PD.

Purpose of the Present Study

Given that there is no cure for PD, and that treatment options are limited in scope and effectiveness, palliative care in this disease is of utmost importance and should incorporate areas that patients report are most critical to their well being (e.g., psychological). Furthermore, there is a need to examine the full range of deficits observed in PD following DBS as the consequences of even "mild" deficits may be quite

large and may reflect an underlying pattern of self-regulatory deficits across areas important to functioning. The present study employed neurocognitive, psychological, and physiological measures to investigate the effect of DBS on SR and EF in patients with PD compared to healthy education/gender-matched controls. Based on the previous literature the following hypotheses were tested:

1. There will be individual differences in EF and SR capacity. Specifically, examining the distribution of cognitive and self-regulatory impairments (with regard to emotions and thought processes) in people with PD before and after DBS will reveal continuous distributions of scores on measures of SR and EF, supporting the idea that deficits exist on a spectrum, rather than being discrete disease entities.
2. The second aim of this study was to establish the construct validity of EF and SR by examining relationships between reports of SR mediated functions in various domains (e.g., social regulation, emotional regulation, and regulation of thought processes) and executive control. We expected convergence among measures of EF (e.g., COWA, Animals, TMT, and IGT, see below). Likewise, it was hypothesized that there will be moderate to high positive correlations among different forms of SR (e.g., emotional, social, thought processes).
3. There will be statistical evidence of overlap between EF and SR, given the theoretical linkage of constructs. Based on prior research, we expect that EF will predict self-regulatory capacity, even when controlling for potentially

confounding variables (e.g., intelligence, duration of disease, and time of testing).

4. SR and EF will correlate with physiological measures (i.e., HRV), such that HRV will be lowest in those patients reporting more self-regulatory and executive deficits.
5. Given the common cognitive, emotional, and autonomic concerns in PD, it was predicted that the DBS group would demonstrate worse scores on EF, memory, depression, and HRV when compared to healthy older adults.
6. Lastly, we hypothesized there would be a decline in EF following DBS, such that participants would have lower scores on EF measures post-DBS when compared to their Pre-DBS scores.

Chapter 2: Methods

Participants

Twenty-seven patients with Parkinson's disease who have an implanted deep brain stimulation device [five implanted in subthalamic nucleus (STN-DBS) and twenty-two implanted in globus pallidus internus (GPi-DBS)] and a baseline pre-surgical neuropsychological evaluation available were enrolled in the study. Patient groups were recruited from the University of Kentucky's Deep Brain Stimulation Clinic. Participants were informed of the study through recruitment fliers, calls from clinic staff, and letters sent out by the patient's neurosurgeon. Participants were excluded from the study if they had an implanted cardiac pacemaker, as the pacemaker would interfere with accurate HRV measurement. Twenty-seven education and gender-matched controls from an archival longitudinal study of older adults (study protocol described previously in Segerstrom, Roach, Evans, & Schipper, 2010) were used as a comparison group to evaluate differences between the patient population and healthy controls. Based on power analysis, this sample size provided adequate power (.80) to detect a large effect (d = .70) of impaired executive function in patients with PD. Demographic characteristics of the sample are provided in Table 1. The sample was representative of the population of individuals diagnosed with PD with regard to gender and age. However, the healthy older adult control group was significantly older than the DBS group. Ultimately, age was not controlled for in the present study as to allow for a more conservative comparison between the two groups on EF and SR measures. Because neurocognitive and autonomic decline is expected as people age (Salthouse, 2009; Pfeifer, Weinberg, Cook, Best, Reenan, & Halter, 1983), having an older control group would make it more difficult to

detect any potential effects. Additionally, there was a significantly greater amount of time between the two testing sessions for DBS participants compared to HC. However, months between testing sessions did not significantly correlate with any EF or SR variable, so this was not a covariate in analyses. Table 2 depicts the demographic characteristics for PD specific variables in the DBS group.

Procedure

Healthy control group. The older adult control group was made up of individuals between the ages of 60-95 who were assessed as part of a separate ongoing longitudinal study, the Thought, Stress, and Immunity Study (TSI) from August 2012-August 2014 (PI: Suzanne C. Segerstrom, Ph.D). As part of that study, neuropsychological and psychological evaluations were conducted on 147 healthy, older adults in Lexington, KY. Participants completed two-hour long visits, once every six months for ten years. During these visits they were administered a series of cognitive tasks as well as psychological questionnaires assessing their level of stress, emotional experience, and emotional expression by a clinical psychology doctoral student. All participants were English-speakers, over the age of 60, living in Lexington, KY, in good health and not being treated for any chronic medical or neurological conditions. The twenty-seven TSI participants included in the present study were matched to the DBS patient group on gender and education parameters. Furthermore, to control for potential practice effects, only data from the first two visits of the longitudinal study were used in the present sample.

Deep Brain Stimulation group. The DBS group was recruited from patients of Dr. Craig van Horne who previously underwent surgery for DBS implantation at the

Kentucky Neuroscience Institute (KNI) from January 2012 and December 2015. All patients had been referred for comprehensive neuropsychological testing prior to surgery by the attending neurosurgeon in order to evaluate the appropriateness of the surgery.

Baseline visit. Assessments included a standardized clinical interview with a licensed clinical neuropsychologist (Dr. Amelia Anderson-Mooney) and administration of a neuropsychological battery by a licensed psychometrist. The pre-surgical test battery included the following primary neuropsychological measures investigated in the current study: Trail Making Test A&B (TMT A & TMT B), FAS, Animals, Weschler Adult Intelligence Scale 4th edition Digit Span subtest (WAIS-IV Digit Span), and Geriatric Depression Scale (GDS). Several other measures were included as part of the comprehensive presurgical battery but will not be discussed as they were not included in the follow-up test battery.

Follow up visit. Approximately 6 to 18 mo. following DBS surgery, patients were mailed a letter from their neurosurgeon informing them of the current study and providing a means to contact the primary author if they were interested in participating. Approximately one month after the letters were mailed out, a clinic staff member contacted eligible patients and asked if they would be interested in speaking with the primary author to discuss the study. The primary author then contacted all interested patients and discussed the study procedures, compensation, and rationale behind the research. To be eligible for participation, the following criteria were met: diagnosis of idiopathic Parkinson's disease, having an active, implanted DBS in either STN or GPi, PD diagnosis greater than two years prior to participation, and fluency in English. Participants who were eligible and interested in participating scheduled a visit to come to

campus to complete study procedures. All attempts were made to schedule patients on the same day as other DBS-related appointments in order to allow for the most up-to-date medical information and to reduce the burden of traveling to and from campus. See Figure 1 for a flow chart depicting participant recruitment. The study took place in a quiet, isolated room within the Psychology Department building, Kastle Hall, and participants were allowed to park in a reserved research spot directly outside of the building to minimize any physical exertion. Participants were compensated $20 cash for their time.

When a participant first arrived for the study, he or she read a combined HIPAA/Consent form to allow the primary researcher (first author) to obtain relevant medical information from electronic medical records. Participants were then administered University of California, San Diego Brief Assessment of Capacity to Consent (UBACC) to assess their capacity to consent to participate. If the participant was able to sufficiently explain procedures and their rights as a study volunteer, he or she signed the combined HIPAA/Consent form. Next, participants completed a demographic questionnaire. Once completed, participants had their heart rate variability measured via a mobile EKG unit (described below). While the EKG unit was connected, the participants were asked to fill out the Behavioral Rating Inventory of Executive Functions (BRIEF) questionnaire silently (as talking can interfere with the EKG reading). Following this, a clinical psychology graduate student administered all other study measures (Geriatric Depression Scale, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease, Rey Auditory Verbal Learning Task, Trail Making Test, Controlled Oral Word Association Test, Animals, WAIS-IV Digit Span Subtest, and the Iowa Gambling Task) in a

randomized order. All together, these procedures took approximately 90 minutes.

Measures

Descriptive Measures

Demographics. As noted earlier, demographic information (e.g., age, education, marital status, gender, and ethnicity) was obtained from patients. Additionally, patients provided disease-related information (e.g., date of diagnosis, date of DBS) that was later verified in the individual's medical record. All other pertinent medical information was obtained from the electronic medical record upon the patient's written consent (e.g., pre-surgical motor function from the Unified Parkinson's Disease Rating Scale (UPDRS), medication usage before and after DBS to calculate levodopa equivalency daily dose (LEDD), DBS stimulation settings, results from pre-surgical neuropsychological testing).

Capacity to consent. Given the potential for significant cognitive impairment in patients with PD, it was important to assess the prospective participant's ability to consent to being involved in the research study. All participants were administered the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC; Jeste, Palmer, Appelbaum, et al., 2007). The UBACC is a 10-item practical instrument used to assess decision-making capacity. After the participant reviewed the consent form in detail, the research assistant explains that he or she would ask a few brief questions about the study, and proceeded with the UBACC items. Participants were given a copy of the consent form, so they did not have to rely solely on their ability to memorize the protocol details when giving consent.

Self-Regulation and Affective Measures

Behavioral Rating Inventory of Executive Functions (BRIEF; Roth, Isquith, & Gioia, 2005). The BRIEF is a 75-item measure of executive regulation of behavior that consists of nine non-overlapping empirically derived clinical scales that measure various aspects of executive functioning as applied to daily life (Inhibit, Self-Monitor, Plan/Organize, Shift, Initiate, Task Monitor, Emotional Control, Working Memory, Organization of Materials), that form two broader indices of behavioral regulation and meta-cognition. Both the scales and indexes have adequate internal consistency, ranging from .73-.90 for clinical scales and .93-.96 for indexes on the self-report form and .80-.93 for clinical scales and .95-.98 for indexes on the informant-report form. The two broad indices were used in the current study as measures of self-reported global regulation with higher scores indicating worse regulation. The internal consistence of this scale in the current sample was .94 for DBS patients and .96 for healthy older adult controls.

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS; Weintraub, Mamikonyan, Papay, Shea, Xie, & Siderowf, 2012). The QUIP is a 28-item, self-report rating scale of impulse control symptoms in PD. The QUIP was designed with the goal of having a brief, self-completed screening instrument for use in clinical care and clinical research that covered the range of impulsive-compulsive behaviors reported in PD. In the current study, the QUIP served as an indication of clinically related self-regulation deficits. The internal consistency of this scale in the current sample was .93 for DBS patients.

Geriatric Depression Scale (GDS; Yesavage, Brink, Rose, Lum, Huang, Adey, & Leirer, 1982). The GDS is a 30-item self-report questionnaire measuring depression in

older adults. The GDS is often administered to individuals with Parkinson's disease (even those younger in age) as it does not contain the physiological symptoms that other depression inventories often include. This is important because the physiological symptoms common in depression are also seen in non-depressed patients with PD, and may cause over-diagnosis of depression in this group (Hoogendijk, Sommer, Tissingh, Deeg, & Wolters, 1998). The GDS is a reliable and valid measure of geriatric depression. The scale has high degree of internal consistency (Cronbach's $\alpha = 0.94$; Split-half reliability $r = 0.94$) and strong one-week test-retest reliability ($r = 0.85$). Evidence for the validity of the GDS comes from comparisons of the mean scores associated with subjects classified as normal, mildly depressed, or severely depressed (based on Research Diagnostic Criteria) as well strong correlations found between GDS and other valid measures of depression like the Zung Self-Rating Depression Scale ($r = 0.84$) and the Hamilton Rating Scale for Depression ($r = 0.83$). The internal consistency of this scale in the current sample was .88 for DBS patients.

Neuropsychological Measures

Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996) The RAVLT is a list-learning measure of verbal learning and memory. It consists of a 15-item word list that is presented five times, always in the same order, with a test of recall immediately following each trial. The measure also includes a test of short-delay recall, long-delay recall, and recognition. The RAVLT total score and delayed recall scores have high test-retest reliability and are sensitive to brain dysfunction in a variety of neurological conditions (Strauss, Sherman, & Spreen, 2006). RAVLT raw scores were corrected based on age using meta-norms provided in the RAVLT test manual.

Trail Making Test A & B (TMT A & TMT B; Tombaugh, 2004) The TMT is one of the most well validated and widely utilized assessments of scanning and visuomotor tracking, divided attention, and cognitive flexibility (Lezak, Howeison, Bigler, & Tranel, 2012). The TMT is broken into two parts, Part A and Part B. TMT Part A is thought to tap into an individual's motor speed, visuo-motor tracking, and scanning abilities, whereas Part B incorporates a component of executive functioning (divided attention and task switching). The TMT is extremely popular among clinicians and researchers due to its high sensitivity to the presence of cognitive impairment. In addition, several studies document the effectiveness of the TMT as a predictor of instrumental activities of daily living (iADLs) among the elderly (Cahn-Weiner, Boyle, & Malloy, 2002) and of functional outcome following acquired brain injury (Acker & Davis, 1989; Ross, Millis, & Rosenthal, 1997). The test-retest reliability of the TMT varies for Part A and Part B, but for the most part is adequate. The external and discriminant validity of the test have been assessed in depth and it does seem to effectively measure the cognitive domains it purports to assess. TMT A and TMT B raw scores were corrected based on age, education, and gender according to the Revised Comprehensive Norms for the Expanded Halstead Reitan Battery.

Controlled Oral Word Association Test (COWAT; Reitan & Wolfson, 1985). The Controlled Oral Word Association Test is part of the Expanded Halstead-Reitan Neuropsychological Battery and is a test of phonemic fluency. The COWAT requires an examinee to orally produce as many words as possible beginning with a specified letter in one minute. The present study used the standard three trial version with the letters F, A, and S (Lezak et al., 2012). The COWAT is a sensitive indicator of brain dysfunction

(Lezak, Howeison, Bigler, & Tranel, 2012) and an important component in most comprehensive assessments of neurocognitive functioning. COWAT raw scores were corrected based on age, education, and gender according to the Revised Comprehensive Norms for the Expanded Halstead Reitan Battery.

Animals (Reitan & Wolfson, 1985). The "Animals" category is the most common category used to test semantic fluency. During this test the examinee is asked to produce as many animal names as possible within a one-minute interval. There is evidence that measures of semantic fluency can be more useful than other common neuropsychological measures in the detection of dementia (Heun, Papassotiropoulos, & Jennssen, 1998). The "Animals" test is sensitive to impaired verbal fluency in patients with PD (Henry & Crawford, 2004). Animals raw scores were corrected based on age, education, and gender according to the Revised Comprehensive Norms for the Expanded Halstead Reitan Battery.

Weschler Adult Intelligence Scale 4th edition Digit Span Subtest (WAIS-IV Digit Span; Weschler, 2008). The WAIS-IV (Wechsler, 2008) is a test system measuring general intellectual functioning, summarized by index scores in verbal comprehension, perceptual reasoning, working memory, and processing speed. The present study included the Digit Span (DS) subtest from the WAIS-IV. The Digit Span subtest requires participants to repeat increasing strings of digits forwards (DS Forwards), backwards (DS Backwards), and in numerical order (DS Sequencing), according to the given instructions. The Digit Span subtest has been studied extensively in neurological populations, and has demonstrated adequate sensitivity (60%) and strong specificity (87%). The Digit Span raw scores were corrected based on age using the WAIS-IV test

manual.

Iowa Gambling Task (IGT; Bechara, Damasio, Demasio, & Anderson, 1994). The IGT is a measure of executive function thought to simulate real-life decision-making. During this task, participants are instructed to choose from one of four decks (A, B, C, D; 60 cards each) until 100 selections have been made. After each selection, participants receive a reward and/or penalty in play money. The decks have pre-determined rewards and penalties (e.g., Decks A and B have a high rewards and penalties, decks C and D have low rewards and penalties). Additionally, decks A and C have more frequent penalties and decks B and D less frequent penalties. A greater selection of cards from decks A and B (disadvantaged decks) results in a net loss and a greater selection of cards from decks C and D (advantage decks) results in a net gain. The performance measures used in the current study were the number of cards chosen from each deck (A, B, C, or D), total advantaged minus disadvantaged decks, and the amount of money earned. The Iowa Gambling Task computer generated report converts raw scores to demographically corrected T scores.

Autonomic Functioning

Heart Rate Variability (HRV). HRV is a measure of parasympathetic control over the heart that is an index of self- regulatory capacity (Segerstrom & Nes, 2007). Increased parasympathetic activity leads to more variable intervals between heartbeats, and therefore higher HRV. HRV is calculated as the root mean squared successive differences in the inter-beat interval (Camm, Malik, Bigger, Breithardt, Cerutti, & Cohen, 1996). Participants were asked to sit quietly for a period of 10 minutes. The first two minutes served as an acclimatization period, and the data for that period were discarded. The data

from the following eight minutes were analyzed to provide baseline HRV. The ECG was sampled at 1000 samples/sec. To obtain the ECG, three Ag/AgCl electrodes with shielded leads were attached in Type II configuration. These leads were connected to an ambulatory, wireless ECG monitor (MindWare Mobile Impedance Cardiograph Model# 50-2303-00). Data were analyzed using the MindWare Heart Rate Variability Analysis Software (MindWare, Cahana, OH).

Data Analysis

Alpha was set at .05, two-tailed, for all inferential tests. All neurocognitive measure raw scores were corrected based on appropriate norms (see measure descriptions). Because the normative data provided various standardized scores (e.g., T scores, standard scores), neurocognitive scores were then converted to a common metric, a standard score, with mean of 100 and standard deviation of 15.

The test of **Hypothesis 1** *(Deficits in EF and SR capacity exist on a spectrum)* primarily involved exploratory data analyses to examine the distributions of each dependent variable. First, univariate analyses (i.e., descriptive statistics and scatterplot/boxplot examination) were run to reveal any potential outliers in the data, the degree and direction of asymmetry of the distribution (skewness), and the peakedness of the distribution (kurtosis) of each variable. This examination of the distribution of values identified whether deficits exist on a continuum and informs whether there are subsequent constraints on *r* and whether the assumptions of regression analyses and ANOVA are violated with regard to linearity and normality of the dependent variable.

The test of **Hypothesis 2** *(Establish construct validity of EF and SR)* involved a Pearson product-moment correlation coefficient matrix to examine the relationships

among the various measures of SR and EF. Zero-order correlations were examined to test **Hypothesis 3** *(Evidence for overlap between SR and EF)*, that superior EF would be associated with better self-regulatory ability across domains. The possibility of a need to statistically control for some variables [e.g., intelligence, time between assessments, dopaminergic dose equivalence, and pre-surgical functional status (UPDRS On)] through partial correlations was examined, but was unnecessary given the lack of significant relationships.

The test of **Hypothesis 4** *(Predict HRV from SR and EF)* was similarly conducted by examining zero-order correlations among facets of SR and heart rate variability. Again, the possible need to statistically control for some variables (e.g., intelligence, time of assessment, respiratory functioning, and functional status) was explored, but was unnecessary given the lack of significant relationships.

The test of **Hypothesis 5** *(Demonstrate worse EF, SR, and HRV in PD),* involved the use of independent samples *t*-tests to examine mean-level differences between the DBS group and healthy older adult controls.

Lastly, to test **Hypothesis 6** *(Demonstrate decline in EF post-DBS)***,** paired sample *t*-tests were conducted to examine mean-level differences between pre-surgical and post-surgical neurocognitive performance.

Chapter 3: Results

Distribution of SR and EF in DBS Patients

Descriptive statistics revealed that most continuous variables were normally distributed. Examination of skewness statistics, scatterplots, and boxplots revealed no problematic outliers or significant skewness for most variables. However, there was 1 variable (BRIEF Behavioral Regulation Index) for which the kurtosis statistic was > 2 standard errors (Kurtosis statistic = 6.350, SE = .541), which warranted consideration for transformation. Upon examining the distribution of BRIEF Behavioral Regulation Index, three outliers were discovered (86, 87, 103). These outliers were closely examined and ultimately were removed from the dataset as they fell outside the typical range of values (i.e. < 65). The removal of these 3 outliers corrected the leptokurtic variable (Kurtosis statistic = -1.048, SE = .532), thus no transformation was performed. Therefore, normal and continuous distributions suggest that self-regulatory and executive impairments in PD do exist on a spectrum, rather than as discrete disease entities, as predicted in Hypothesis 1.

Construct Validity of EF

The first part of Hypothesis 2 aimed to examine the construct validity of EF. A correlation matrix including data from all participants (Table 3) revealed that the relationship among various domains of EF varied. A similar correlation matrix including only data from the DBS participants provided equivalent results (Table 4). There were moderate relationships between verbal fluency (FAS, Animals) and working memory (DS Forward, Backward, and Sequencing; $r \approx .27$-$.37$) and strong relationships between verbal fluency (FAS, Animals) and mental flexibility (TMT A, TMT B; $r \approx .48$-$.53$),

however, verbal fluency measures (FAS, Animals) were not significantly correlated with decision-making (IGT).

Moderate relationships were also found between working memory (DS Backward and Sequencing) and mental flexibility (TMT B; $r \approx .30$ - .39), such that greater working memory abilities predicted stronger set-shifting and flexibility of thinking. There was a strong relationship between immediate attention capacity (DS Forward) and decision-making (IGT; $r = .49$), such that greater immediate attention correlated with more greater decision-making. However, immediate attention capacity (DS Forward) was not related to mental flexibility (TMT B; $r = .09$).

Similarly, there were moderate to large relationships ($r \approx .28$ - .55) between aspects of verbal memory (e.g., encoding, retrieval, recognition) and various EF domains. Thus, there was sufficient evidence to conceptualize all EF and other cognitive measures by their distinct components (e.g., verbal fluency, working memory, flexibility, decision-making, verbal encoding, verbal retrieval, and recognition). Hypothesis 2 was not supported in that inter-correlations of EF measures varied greatly and, contrary to our hypothesis, EF measures were highly correlated with verbal memory.

Construct Validity of SR

The second part of Hypothesis 2 aimed to establish construct validity for SR by examining the bivariate correlations, including data from DBS participants (see Table 5), between self-report self-regulation (BRIEF total score, indices, and subscales) and the severity/presence of impulse control disorders (QUIP-RS). Modest relationships were seen between overall self-reported self-regulation (BRIEF Total) and impulse control symptoms ($r = .35$), similar findings were found for the BRIEF indices of Behavioral

Regulation (r = .37) and Meta Cognition (r = .26). When examining specific aspects of self reported SR, there were modest correlations between impulse control difficulties and the BRIEF subscales Inhibit, Shift, Emotional Control, Initiate, Task Monitor, and Organization of Materials. There were strong correlations ($r \approx$ .49 - .51) between impulse control difficulties and the BRIEF subscales self-monitor and Plan/Organize, such that greater impulsive-compulsive problems correlated with greater dysfunction in self-reported abilities of self-monitoring and planning. Hypothesis 2 was supported in that SR measures were related to one another. However, given that these relationships were only modest in magnitude, the use of a composite index of SR that combines measures of SR into a single index is not supported.

Evidence for Overlap between SR and EF

Hypothesis 3 proposed that EF would contribute to SR. Given the lack of support for composite SR and EF constructs, measures of EF were examined in relation to individual domains of SR (i.e., inhibition, shifting, emotional control, initiation, task monitoring, impulsivity, etc.) primarily using zero-order correlations with all participants (HC and DBS). Correlations between potential confounding variables (e.g., depression, time of assessment, LEDD, disease duration) were examined to determine whether there was a need to control for these variables. Depression was highly related to both EF and SR measures. Specifically, greater depression was related to worse working memory ($r \approx$ -.21 - .32), mental flexibility ($r \approx$ -.36 - .38), and greater global dysregulation ($r \approx$ .22 - .48). Given the significant relationships between depression and EF or SR, partial correlations were utilized to examine the relationship of EF and SR controlling for GDS score (see Table 6). Table 7 provides the partial correlations for EF and SR relationships

when controlling for GDS score with DBS participants only. There was no need to statistically control for other suspected confounds (e.g., time of assessment, LEDD, disease duration).

Correlations between EF performance and SR reports after controlling for depression were generally in the small to medium range, with a few notable exceptions. Better immediate attention (Digit Span Forward) was significantly related to self-reported shifting (r = -.48), emotional control (r = -.42), working memory (r = -.49), planning (r = -.42), and task monitoring (r = -.43), such that greater attention capacity correlated with less SR. In addition, worse immediate attention (Digit Span Forward) predicted greater number of impulse-control concerns (QUIP-RS; r = -.39). Similarly, mental flexibility (TMT) was significantly related to self-reported initiation (r = -.46) such that stronger mental flexibility correlated with less difficulties with initiation. Decision making (IGT) was significantly related to self-reported inhibition (r = -.55), shifting (r = -.52), emotional control (r = -.42), working memory (r = -.61), and task monitoring (r = -.50). Therefore, greater decision making capabilities predicted less dysregulation.

Evidence against the hypothesis that EF predicts SR functioning was found within the relationships of EF to impulse control issues (QUIP-RS). Impulse-control disorders were only modestly related to verbal fluency (FAS, Animals; $r \approx$ .24-.26) and mental flexibility (TMT A, TMT B; $r \approx$ .27-.35), such that stronger fluency and flexibility/switching predicted greater severity of impulse-control issues.

Hypothesis 3 was partially supported since generally speaking, greater EF tended to predict less reported SR difficulties. However, higher scores on specific EF subdomains (i.e., verbal fluency, and mental flexibility) may actually predict more

impulse-control concerns.

Physiological Functioning: Does EF or SR Matter?

Hypothesis 4 proposed that better EF, and better ability to self-regulate across domains, would be associated with more optimal autonomic functioning (i.e., higher HRV). As shown in Table 8, correlations between autonomic functioning (i.e., HRV) and measures of EF varied greatly. There were significant, moderate to large relationships between HRV and mental flexibility (TMT A and TMT B; $r \approx .41$-$.47$), such that stronger mental flexibility predicted better autonomic functioning (i.e., higher HRV). These relationships tended to be stronger for DBS patients than for healthy controls. Moderate relationships between HRV and working memory (DSF, DSB, and DSS; $r \approx .34$ - $.42$) were seen only in healthy controls. This relationship was practically nonexistent for DBS patients ($r \approx -.05$ - $.10$). Smaller relationships, though not significant, were seen between HRV and decision-making (IGT; $r = .12$), such that greater scores predicted higher resting HRV. HRV did not correlate well with phonemic or semantic fluency. Generally, greater EF was associated with more optimal autonomic functioning, as predicted.

Table 9 displays the correlations among autonomic functioning and measures of SR. There were no significant correlations seen between subscales of the BRIEF and HRV. However, when examining the magnitude of the Pearson correlation coefficients, small positive correlations were found between self-report SR subscales Inhibit, Shift, Self-Monitor, and Planning for DBS patients ($r = .11$ - $.28$), suggesting greater self-reported dysregulation relates to higher HRV. Similarly, small positive correlations were found between self-report SR subscales Self-monitor, Initiate, Planning, Task Monitoring, and Organization ($r \approx .12$ - $.29$) for healthy older adult controls. Unlike what

was predicted, lower SR was associated with more optimal autonomic functioning. Comparable findings were seen with impulse control concerns, as impulse control difficulties were significantly related to higher HRV (r = .40).

Initially, it was hypothesized that impulse control disorders reflected clinically severe self- regulation difficulties. Therefore, the finding that impulse control problems were significantly related to higher HRV, and not lower HRV as seen with other SR, was quite surprising. Further analyses were conducted in an attempt to explore this result. Bivariate correlations between HRV and various subscales of the QUIP-RS were examined. Large positive relationships were seen between HRV and difficulty controlling thoughts about various activities (e.g., gambling, sex, buying, eating, hobbyism (compulsive pursuit of a hobby), punding (stereotyped, ritualistic behaviors); r = .51, p = .008), having urges or desires to perform those various behaviors (r = .54, p = .004), and engaging in activities to continue behaviors (r = .40, p = .044). When examining the various behaviors related to HRV, a large significant relationship was found between higher HRV and increased hobbyism/punding (r = .46, p = .017). Moderate relationships were seen between higher resting HRV and sex (r = .36, p = .068), buying (r = .33, p =.091), and eating (r = .32, p = .105).

Cognitive, Emotional, and Autonomic Functioning in PD

Hypothesis 5 predicted that the DBS group would have worse neurocognition, greater dysregulation, greater depression, and worse autonomic functioning than healthy older adults. Initial analyses utilizing independent samples *t*-test found group differences on several variables. Table 10 presents results of post-test group differences on neurocognitive measures with effect sizes. With regards to cognitive functioning, the

DBS group performed significantly worse than HC on COWA ($t = 3.197$, $p = .002$), TMT A ($t = 4.753$, $p < .001$), TMT B ($t = 5.795$, $p < .001$), RAVLT total learning, ($t = 4.670$, $p < .001$), RAVLT short delay recall ($t = 3.730$, $p < .001$), RAVLT long delay recall ($t = 4.574$, $p < .001$), and RAVLT recognition ($t = 3.693$, $p < .001$). There were no significant differences between HC and DBS on the Digit Span subtests. For a graphical representation of the various group differences between DBS and HC, see Figure 2.

Table 11 depicts the group differences with effect sizes for measures of self-regulation, HRV, and depression. The DBS group had a significantly higher rate of depressive symptoms on GDS when compared to HC ($t = -4.972$, $p < .001$). With regards to physiological functioning, DBS group had significantly lower HRV than HC ($t = 2.350$, $p = .023$). Lastly, on a measure of reported self-regulation (i.e., BRIEF), DBS group endorsed significantly more difficulties with inhibition ($t = -2.591$, $p = .012$), emotional control ($t = -2.385$, $p = .021$), initiation, ($t = -3.478$, $p = .001$), working memory ($t = -3.189$, $p = .002$), planning/organizing ($t = -2.714$, $p = .009$), and task monitoring ($t = -2.041$, $p = .046$).

Post-surgical Executive Functioning in PD

Hypothesis 6 proposed there would be significant decline between DBS pre-surgical and post-surgical performance on executive function measures. Paired samples t-tests were utilized to examine the differences between testing sessions. Figure 3 presents a graphical representation of differences between DBS pre- and post-surgical scores and Table 12 depicts the differences between testing sessions with effect sizes. There was significant decline on FAS (phonemic fluency; $t = 2.689$, $p = .013$), Animals (semantic fluency; $t = 2.505$, $p = .020$), and Digit Span Backwards subtest (working memory; $t =$

2.290, p = .032). There was a trend towards decline on Digit Span Sequencing (working memory; t = 1.751, p = .093) and TMT B (mental flexibility; t = 1.727, p = .099). Effect size examinations of these pre-test, post-test differences revealed small effects of DBS on EF measures. As a control comparison, there was no significant decline between testing sessions for the healthy older adults. Thus, hypothesis 6 was supported in that post-DBS patients experienced significant declines in verbal fluency and working memory, which would not be expected in normal aging.

Chapter 4: Discussion

Overview of Findings

Although classically viewed as a movement disorder, the cognitive, emotional, and autonomic symptoms of PD have been increasingly identified; and these extra-motor symptoms can be quite distressing for the patient. As there is no cure for PD, greater understanding of the available treatment options (such as DBS) on these extra-motor symptoms is of the utmost importance. The current study aimed to elucidate the prevalence and pattern of executive deficits and behavioral dysregulation in patients with PD after DBS. The present study used neuropsychological, behavioral, and physiological methods to examine dysfunction associated with DBS and PD. An innovative aspect of this project was the exploration of self-regulatory domains in patients with PD using a healthy older adult comparison group.

Relationships between SR and EF

This research revealed that the scope of extra-motor impairment in PD can be wide, with deficits existing on a continuum such that some, but not all, patients evidence deficits in self-regulatory abilities to effectively manage emotions and thought processes. This informs research and clinical work with PD as self-regulatory and executive deficits may be part of the disease process, but the severity will vary between patients.

Of particular interest in this study was the lack of convergence of self-regulatory deficits across domains. Given prior research that suggests executive control and behavioral self-regulation rely on a similar resource, and that depletion of this resource on one task can impair subsequent performance on others (Thayer & Lane, 2009), it was surprising that there was not a consistent pattern that emerged among domains of SR and

EF. However, this likely was a consequence of poor convergence among the individual measures of EF and SR. For example, individual EF abilities of verbal fluency, working memory, attention capacity, and mental flexibility correlated well with one another, however a measure of decision-making (IGT) was only related to immediate attention capacity. Though decision-making was included as a neuropsychological measure of EF, the finding that the IGT was not highly related to other neuropsychological measures is consistent with a recent review by Toplak and colleagues (2010). In their paper, they demonstrate that decision-making on the IGT is highly separated from other cognitive abilities and more consistent with a test of rationality than our traditional tests of intelligence.

Additionally, there were significantly strong relationships between aspects of verbal memory and EF measures, suggesting significant overlap between these abilities in patients with PD. Given the related yet distinct nature of the various components of EF, conceptualizing EF as a non-unitary construct is informative and important, especially for future studies. This may be particularly true in PD as deficits may influence clinically important outcomes.

Similarly, among the nine aspects of self-reported self-regulation assessed in the current study (BRIEF subscales: Inhibition, Shifting, Emotional Control, Initiation, Task Monitoring, Impulsivity Organization of Materials, Self-Monitoring, Planning/Organizing) only self-monitoring and planning were related to clinical dysregulation (i.e., Impulsive Compulsive Symptoms), suggesting that the impulsive-compulsive concerns (as measured by the QUIP-RS) account for only a small variance of potential self-regulatory difficulties.

Another interesting finding of the present study was that self-reported SR (as measured by the BRIEF) and clinical impulsive-compulsive concerns (QUIP-RS) related to EF in opposing ways, suggesting the relationship between EF and SR varies based on the individual abilities examined. Thus, it is necessary to examine these relationships at the individual level as opposed to broader constructs. As hypothesized, worse immediate attention (DSF), poor decision-making (IGT), and poor mental flexibility (TMT B) were strongly related to poor self-reported SR abilities. However, contrary to our hypothesis, clinical impulsive-compulsive concerns were inversely related to EF. Impulse-control concerns were originally included in the present study to serve as a clinical indicator of poor SR. Greater verbal fluency and mental flexibility were strongly predictive of worse impulse-control issues. This finding persisted even when examining the specific actions involved (e.g., thinking about activity, urges/desires, engaging in activity) or breaking down impulse-control issues into various types of behaviors (e.g., hobbyism/punding, sex, buying, and eating).

Again, the results from the present study imply that impulse-control issues related to PD and DBS are related to stronger EF. One possible explanation of this finding is that stronger EF and SR predispose an individual with PD to develop impulse-control issues, or more likely, patients with greater impulse-control issues may develop stronger EF and HRV as a means to compensate for impulsive and compulsive difficulties.

Relationship of Physiological Resources to EF and SR

The current study partially converges with research linking vagally-mediated HRV to prefrontal activity and EF (Thayer, 2006; Thayer, Hansen, Saus-Rose, & Johnsen, 2009; Segerstrom & Nes, 2007). Higher resting HRV was associated with

greater psychomotor speed and attention (TMT A), mental flexibility, (TMT B), phonemic fluency (FAS), and working memory (DSB & DSS), which converges with research linking decreased EF to decreased (i.e., worse) HRV (Thayer et al., 2009). However, the pattern of association among measures of SR and HRV was unexpected, such that poorer self-reported SR (BRIEF) and greater clinical impulse-control issues (QUIP-RS) were significantly associated with greater HRV.

This study suggests the mechanisms by which HRV indexes the capacity for self-regulation in PD patients may differ from other "healthy" samples. If decreased HRV is in fact associated with the disease process of PD, examining individual differences in HRV may be particularly informative to self-regulatory processes. Alternatively, HRV could be more dynamic in PD patients than in "healthy" samples, which may suggest both theoretical and methodological adaptations for non-healthy samples.

Another surprising finding is the inverse relationship seen between the QUIP-RS and HRV. Perhaps, impulse-control concerns seen in patients with PD are unrelated to disruptions of prefrontal circuitry and are not reflective of SR as it has been previously conceptualized. It is possible that Thayer and Lane's (2000) model pertains to egosyntonic behaviors such as rumination, emotional dysregulation, and addiction, but does not translate to explaining egodystonic behaviors, such as those seen with impulse-control issues or obsessive-compulsive disorders. Another possible explanation is that stronger EF and SR predispose an individual with PD to develop impulse-control issues, or alternatively, patients with greater impulse-control issues develop stronger EF and HRV as a means to compensate for impulsive and compulsive difficulties. Future studies that include a non-DBS PD control group would be useful in expounding upon this

finding. More research is needed to deconstruct this novel outcome and to examine the limitations of Thayer and Lane's model.

Post-surgical Cognitive, Emotional, and Physiological Functioning in PD

Consistent with what was hypothesized, patients with PD were more depressed and had worse neurocognitive, self-regulatory, and physiological functioning than healthy older adults. With regards to neurocognitive functioning, patients with PD had worse scores on tests of phonemic fluency (FAS), psychomotor speed and attention (TMT A), mental flexibility (TMT B), and verbal memory (RAVLT). Patients with PD endorsed more difficulties with inhibition, emotional control, initiation, working memory, planning/organizing, and task monitoring and had significantly lower HRV than older adults. These findings replicate previous research and highlight the prevalence and severity of extra-motor symptoms in PD.

Based on previous research it was predicted that there would be significant declines in executive functioning in patient's post-DBS when compared to their presurgical test scores. As hypothesized patient's post-DBS had significantly worse scores on tests of phonemic fluency (FAS), semantic fluency (Animals), and working memory (DS) with marginal declines in mental flexibility (TMT B). These declines were small in magnitude, consistent with what was found in a recent meta-analysis of post-DBS cognitive functioning (Combs et al., 2015). No differences were seen with regard to executive functioning changes between patients who received STN-DBS to those who were implanted in GPi, consistent with recent literature suggesting no differences between cognitive profiles of the two target sites (Okun et al., 2009). The present study supports the notion that DBS is relatively well tolerated from an executive standpoint.

However, the functional significance of these declines remains unclear. A small decrement in verbal fluency and working memory may or may not impact an individual's daily life, hence the conclusion that DBS is considered to be neurocognitively benign.

Limitations

While this study provides an important contribution to the current body of literature on self-regulatory, emotional, and executive functioning in patients with PD after DBS, limitations must be acknowledged. Though care was used to arrange a demographically equivalent healthy older adult control group, matching based on age and time between testing sessions was not possible. In addition, the sample of patients was both small and varied. Although there was sufficient power to detect large effects, which had been previously obtained in research on EF, a larger sample would have increased the power to detect small to moderate effects, which may be clinically important in PD. A related methodological concern is Type 1 error due to multiple comparisons. The current study did not involve a correction (e.g., Bonferroni) for Type I error. Given the limited sample size, the caution in relying on *p* – values in small samples, the risk of neglecting Type 2 error, and the absence of theoretically guided a priori hypotheses (in many instances); preservation of power was a priority. Another major limitation for the study is the absence of presurgical measures of SR (i.e., BRIEF and QUIP-RS) and HRV. As a result, it was not possible to investigate changes in SR and HRV due to DBS surgery. Future research needs to include such measures in both pre-and post-surgical assessments to investigate the impact of DBS on these domains.

Conclusions

In summary, if cross-validated, the results of the current study suggest that PD

patients are prone to a variety of self-regulatory deficits, ranging from subtle to severe. They are also likely to experience small declines in executive functioning post-DBS that may contribute to self-regulatory impairments. However, this research suggests that both the quantity and quality of impairment varies, and that the correlates of these deficits may be different between patients. Clinically, it is important for health care professionals working with PD to recognize the presence of self-regulatory deficits and to be aware of the potential obstacles that might arise from such impairments within a patient's daily life.

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Table 2.1. Descriptive Statistics by Group

		DBS *n = 27*	*HC* *n = 27*	*t or* X^2	*p*
Age	M (SD)	66.07 (9.93)	75.63 (3.44)	4.72	<.001
Education	M (SD)	15.74 (3.19)	15.70 (2.80)	0.05	0.96
Months between testing	M (SD)	20.69 (9.13)	13.56 (1.27)	4.02	<.001
Gender	% Male	63.0%	63.0%	0.00	1.00
Race	% Caucasian	100%	100%	0.00	1.00
Marital Status	% Married	50%	50%	0.00	1.00

Table 2.2. Descriptive statistics of DBS on PD specific variables

		N	*M*	*SD*
Time	Months Since DBS	27	19.766	22.861
	Years Since Diagnosis	27	11.185	5.561
Motor Function	Pre UPDRS Off Meds	21	50.524	17.730
	Pre UPDRS On Meds	18	26.611	17.614
Dopaminergic Medications	Pre LEDD	26	879.250	555.405
	Post LEDD	27	425.833	311.466
DBS Stimulation Settings	Left DBS Voltage (V)	26	3.921	0.717
	Left DBS Pulse width (μs)	26	93.077	34.382
	Left DBS Frequency (Hz)	26	178.654	27.697
	Right DBS Voltage (V)	26	3.877	0.736
	Right DBS Pulse width (μs)	26	93.462	22.617
	Right DBS Frequency (Hz)	26	172.692	20.844

Note: *N* = Sample Size, *M* = Mean, *SD* = Standard Deviation**;** DBS, deep brain stimulation patient group; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; LEDD, levodopa equivalency daily dose

Figure 2.1. Flow chart depicting participant recruitment and final enrollment for DBS Patient Group

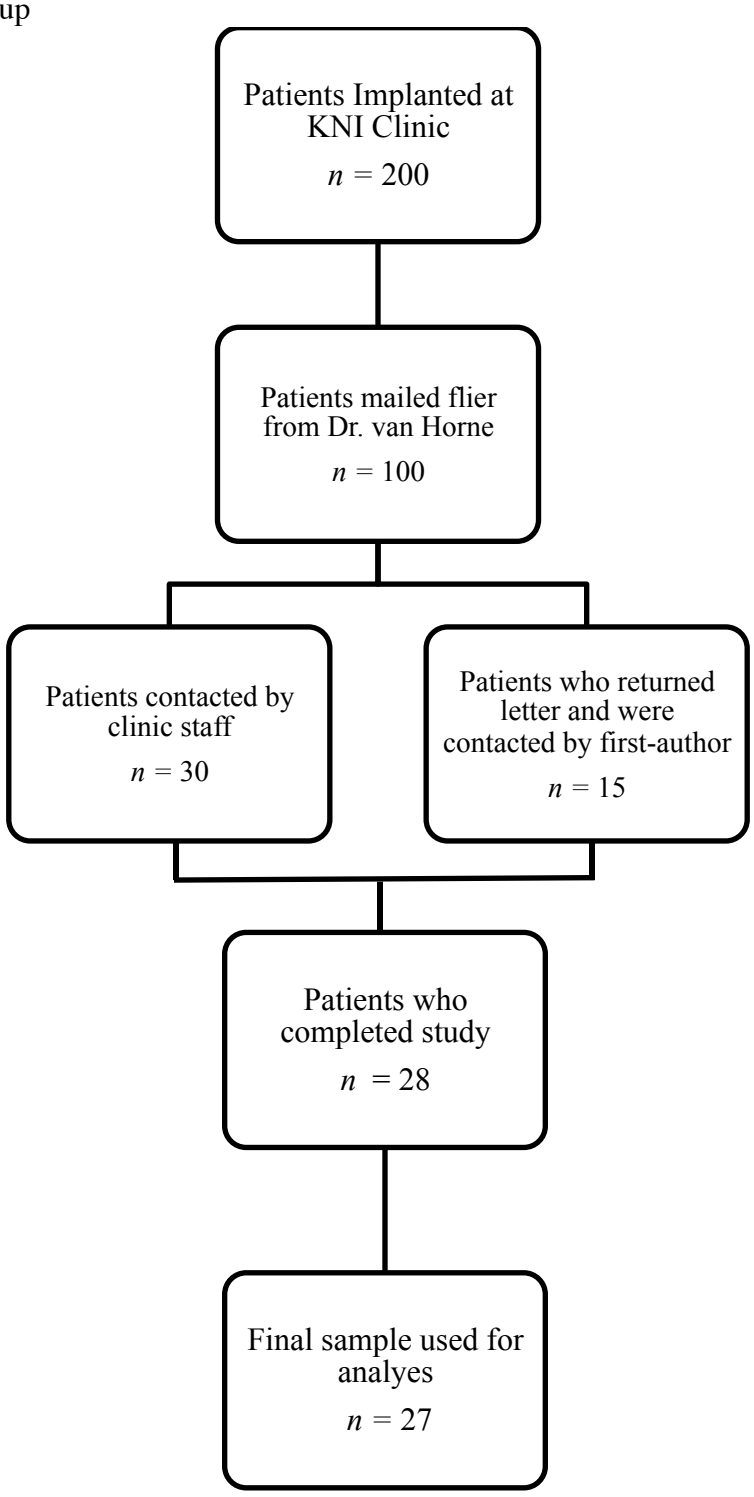


Table 3.1. Inter-correlations among cognitive measures for all participants

	COWA	Animals	DSF	DSB	DSS	TMT A	TMT B	TMT B-A	IGT Total	IGT Money	RAVLT Total Learning	RAVLT SD Recall	RAVLT LD Recall	RAVLT Recog.
COWA	-													
Animals	.825**	-												
DSF	.268**	.286*	-											
DSB	.368**	.279*	.557**	-										
DSS	.366**	.307*	.491**	.517**	-									
TMT A	.527**	.484**	.233*	.380**	.394**	-								
TMT B	.476**	.459**	.097	.300**	.340**	.776**	-							
TMT B-A	-.051	.172	-.002	-.161	-.255*	-.286**	-.425**	-						
IGT Total	-.119	-.019	.488**	.106	-.123	-.069	-.183	-.233*	-					
IGT Money	-.064	.020	.693**	.382*	.128	.064	-.025	-.112	.868**	-				
RAVLT Learning	.457**	.407*	.322**	.449**	.482**	.549**	.550**	-.165	-.228	.057	-			
RAVLT SD Recall	.446**	.370	.286*	.401**	.338**	.517**	.487**	-.076	.010	.200	.822**	-		
RAVLT LD Recall	.395**	.409*	.162	.292*	.267*	.464**	.468**	.474*	-.164	-.016	.746**	.809**	-	
RAVLT Recog.	.520**	.544**	.068	.197	.237*	.619**	.556**	.314	-.239	-.081	.588**	.596**	.619**	-

Note: COWA, Controlled Oral Word Association Test, DSF, Digit Span Forward, DSB, Digit Span Backward; DSS, Digit Span Sequencing; TMT, Trail Making Test; IGT, Iowa Gambling Task; RAVLT; Rey Auditory Verbal Learning Task
*$p < .05$, **$p < .01$

Table 3.2. Inter-correlations among cognitive measures for DBS Group

	COWA	Animals	DSF	DSB	DSS	TMT A	TMT B	TMT B-A	IGT Total	IGT Money	RAVLT Total Learning	RAVLT SD Recall	RAVLT LD Recall	RAVLT Recog.
COWA	-													
Animals	.825**	-												
DSF	.313*	.286*	-											
DSB	.297*	.279*	.627**	-										
DSS	.389**	.307*	.597**	.601**	-									
TMT A	.499**	.484**	.228	.368**	.405**	-								
TMT B	.403**	.459**	.015	.307*	.367**	.781**	-							
TMT B-A	.136	.172	.135	-.048	-.145	-.293*	-.311*	-						
IGT Total	-.119	-.019	.488**	.106	-.123	-.069	-.183	.474*	-					
IGT Money	-.064	.020	.693**	.382*	.128	.064	-.025	.314	.868**	-				
RAVLT Learning	.459*	.407*	.312	.527**	.554**	.510**	.469*	-.266	-.228	.057	-			
RAVLT SD Recall	.379	.370	.331	.204	.249	.387	.260	-.006	.010	.200	.742**	-		
RAVLT LD Recall	.455*	.409*	.153	.126	.202	.404*	.287	-.103	-.164	-.016	.702**	.815**	-	
RAVLT Recognition	.604**	.544**	.059	.058	.269	.624**	.496*	-.047	-.239	-.081	.481*	.545**	.634**	-

Note: COWA, Controlled Oral Word Association Test, DSF, Digit Span Forward, DSB, Digit Span Backward; DSS, Digit Span Sequencing; TMT, Trail Making Test; IGT, Iowa Gambling Task; RAVLT; Rey Auditory Verbal Learning Task
*$p < .05$, **$p < .01$

Table 3.3. Correlations between DBS ratings of SR and severity of ICDs

		QUIP-RS
BRIEF Subscales	Inhibit	.261
	Shift	.298
	Emotional Control	.282
	Self-Monitor	.506**
	Initiate	.284
	Working Memory	.176
	Plan/ Organize	.487*
	Task Monitor	.274
	Organization of Materials	.236
BRIEF Indices	Behavioral Regulation	.369
	Meta Cognition	.260
BRIEF Total	Total Score	.347

Note: DBS, deep brain stimulation patient group; SR, self-regulation; ICD, impulse control disorder; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease Rating Scale; BRIEF, Behavior Rating Inventory of Executive Function

* $p < .05$, ** $p < .01$

Table 3.4. Partial correlations among measures of EF and SR controlling for depression for all participants

		COWA	Animals	DSF	DSB	DSS	TMT A	TMT B	TMT B-A	IGT°
BRIEF Subscales	Inhibit	-.077	-.234	-.341	-.055	.067	.081	-.125	-.045	-.550**
	Shift	-.149	-.309	-.480*	-.240	-.055	.055	-.101	.119	-.515**
	Emotional Control	-.069	-.184	-.422*	-.316	.146	.129	-.066	-.129	-.422*
	Self-Monitor	.111	.088	-.330	-.145	.128	.114	.111	-.051	-.232
	Initiate	-.154	-.265	-.327	-.271	-.103	-.334	-.456	.247*	-.347
	Working Memory	-.169	-.306	-.490*	-.209	-.114	-.172	-.280	.207	-.608**
	Plan/ Organize	.063	.043	-.420*	-.250	-.225	-.111	-.161	.213	-.106
	Task Monitor	-.025	-.186	-.431*	-.204	-.012	-.019	-.179	.189	-.502*
	Organization of Materials	.064	.090	-.188	-.086	-.115	-.113	-.189	-.013	-.023
BRIEF Indices	Behavioral Regulation	-.079	-.076	-.434*	-.280	-.034	-.111	.008	-.051	-.309
	Meta Cognition	-.072	-.085	-.347	-.221	-.297	-.444*	-.368	.194	-.238
BRIEF Total	Total SR	-.082	-.091	-.415*	-.266	-.233	-.370	-.270	.103	-.289
QUIP-RS°	Impulse-Control Symptoms	.263	.238	-.393	-.160	-.171	.354	.274	.057	-.019

Note: EF, Executive Functioning; SR, Self-Regulation; COWA, Controlled Oral Word Association Test; DSF, Digit Span Forward; DSB, Digit Span Backward; DSS, Digit Span Sequencing; TMT, Trail Making Test; IGT, Iowa Gambling Task; BRIEF, Behavior Rating Inventory of Executive Function; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease, Rating Scale

* $p < .05$, ** $p < .01$

º Correlations calculated for DBS patient group only

Table 3.5. Partial correlations among measures of EF and SR controlling for depression for DBS Group

		COWA	Animals	DSF	DSB	DSS	TMT A	TMT B	TMT B-A	IGT[o]
BRIEF Subscales	Inhibit	-.028	-.040	-.156	.111	-.022	-.106	-.067	.177	-.306
	Shift	-.160	-.166	-.507*	-.297	-.284	-.143	.008	.111	-.176
	Emotional Control	-.058	-.040	-.287	-.356	.107	-.020	-.001	-.159	-.134
	Self-Monitor	.047	.048	-.219	-.116	.057	-.062	.094	-.021	-.282
	Initiate	-.180	-.185	-.145	-.260	-.253	-.678**	-.574**	.330	-.053
	Working Memory	-.166	-.178	-.425*	-.180	-.272	-.435*	-.301	.166	-.420*
	Plan/ Organize	-.017	-.031	-.361	-.252	-.369	-.319	-.256	.260	-.131
	Task Monitor	.098	.089	-.364	-.199	-.168	-.287	-.163	.227	-.168
	Organization of Materials	-.024	-.037	-.165	-.086	-.180	-.234	-.291	.088	-.172
BRIEF Indices	Behavioral Regulation	-.079	-.091	-.415*	-.266	-.233	-.370	-.270	.009	-.289
	Meta Cognition	-.072	-.076	-.434*	-.280	-.034	-.111	.008	.238	-.309
BRIEF Total	Total SR	-.082	-.085	-.347	-.221	-.297	-.444*	-.368	.179	-.238
QUIP-RS[o]	Impulse-Control Symptoms	.237	.231	-.327	-.137	-.267	.277	.278	.057	.008

Note: EF, Executive Functioning; SR, Self-Regulation; COWA, Controlled Oral Word Association Test; DSF, Digit Span Forward; DSB, Digit Span Backward; DSS, Digit Span Sequencing; TMT, Trail Making Test; IGT, Iowa Gambling Task; BRIEF, Behavior Rating Inventory of Executive Function; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease, Rating Scale.
* $p < .05$, ** $p < .01$

Table 3.6. Correlations between HRV and cognitive measures

	Total Sample HRV	DBS Patients HRV	HC Group HRV
COWA	.166	.070	.030
Animals	.079	.079	-
DSF	.164	-.054	.353
DSB	.178	-.035	.417*
DSS	.203	.102	.340
TMT A	.466**	.594**	.248
TMT B	.414**	.556**	.226
TMT B-A	-.126	-.186	-.059
IGT	-.121	-.121	-

Note: HRV, Heart Rate Variability, COWA, Controlled Oral Word Association Test; DSF, Digit Span Forward; DSB, Digit Span Backward; DSS, Digit Span Sequencing; TMT, Trail Making Test; IGT, Iowa Gambling Task
* $p < .05$, ** $p < .01$

Table 3.7. Correlations between HRV and SR measures

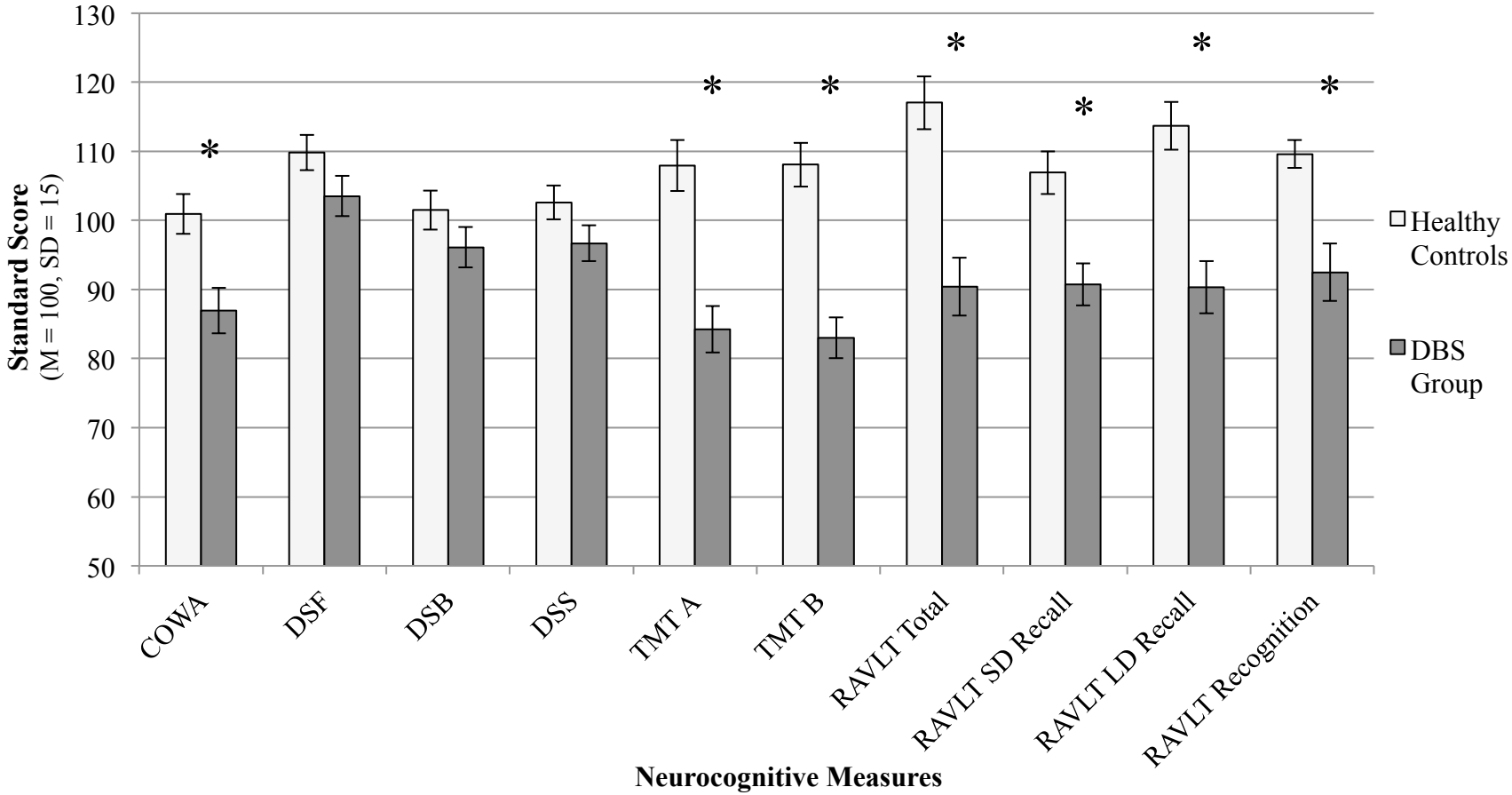
		Total Sample HRV	DBS Patients HRV	HC Group HRV
BRIEF Subscales	Inhibit	-.038	.134	.022
	Shift	-.016	.109	-.010
	Emotional Control	-.057	.046	.053
	Self-Monitor	.142	.275	.124
	Initiate	-.045	-.040	.260
	Working Memory	-.162	.037	-.175
	Plan/ Organize	.046	.152	.223
	Task Monitor	-.030	-.070	.288
	Organization of Materials	-.009	-.046	.166
BRIEF Indices	Behavioral Regulation	-.017	.027	.053
	Meta Cognition	-.050	.012	.191
BRIEF Total	Total Score	-.034	.072	.139
QUIP-RS^{o}	Impulse-Control Symptoms	.399**	.399**	-

Note: HRV, Heart Rate Variability; SR, Self-Regulation; BRIEF, Behavior Rating Inventory of Executive Function; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease, Rating Scale

** $p < .01$

^{o} Correlations calculated for DBS patient group only

Figure 3.1. Bar graph depicting group differences on neurocognitive measures



Note: M = Mean, SD = Standard Deviation; Errors bars denote +/- SE_M; COWA, Controlled Oral Word Association Test; DSF, Digit Span Forward; DSB, Digit Span Backward; DSS, Digit Span Sequencing; TMT, Trail Making Test; RAVLT, Rey Auditory Verbal Learning Task; DBS, Deep Brain Stimulation
* $p < .05$

Table 3.8. Post-test group differences on neurocognitive measures

		DBS *n = 27*	*HC* *n = 27*	*d*
COWA (Standard Score)	M (SD)	86.926 (17.151)	100.944 (14.995)	0.870
DSF (Standard Score)	M (SD)	103.519 (15.052)	109.815 (13.408)	0.442
DSB (Standard Score)	M (SD)	96.111 (15.212)	101.481 (14.598)	0.411
DSS (Standard Score)	M (SD)	96.667 (13.445)	102.593 (12.662)	0.454
TMT A (Standard Score)	M (SD)	84.231 (17.072)	107.962 (18.882)	1.318
TMT B (Standard Score)	M (SD)	83.000 (14.991)	108.056 (16.422)	1.594
TMT B-A (Raw- Seconds)	M (SD)	49.722 (33.230)	59.046 (67.347)	0.176
RAVLT Total (Standard Score)	M (SD)	90.429 (21.407)	117.031 (19.629)	1.295
RAVLT SD Recall (Standard Score)	M (SD)	90.735 (15.479)	113.705 (17.681)	1.382
RAVLT LD Recall (Standard Score)	M (SD)	90.312 (19.169)	113.705 (17.681)	1.269
RAVLT Recognition (Standard Score)	M (SD)	92.481 (20.845)	109. 598 (10.135)	0.920

Note: *M,* Mean, SD DBS, Deep brain stimulation group; HC, Healthy older adult controls; COWA, Controlled Oral Word Association Test; DSF, Digit Span Forward; DSB, Digit Span Backward; DSS, Digit Span Sequencing; TMT, Trail Making Test; RAVLT, Rey Auditory Verbal Learning Task

Table 3.9. Post-test group differences on measures of SR, HRV, and depression

				DBS *n = 27*	*HC* *n = 27*	*d*
Self- Regulation	BRIEF Subscales	Inhibition	M (SD)	14.296 (4.445)	11.815 (2.237)	0.705
		Shift	M (SD)	11.148 (5.067)	9.519 (2.408)	0.411
		Emotional Control	M (SD)	16.889 (5.918)	13.704 (3.625)	0.649
		Self-Monitor	M (SD)	9.889 (3.017)	9.370 (1.904)	0.206
		Initiate	M (SD)	13.519 (3.867)	10.370 (2.677)	0.947
		Working Memory	M (SD)	16.333 (5.657)	12.519 (2.578)	0.868
		Plan/ Organize	M (SD)	17.482 (4.964)	14.333 (3.419)	0.739
		Task Monitor	M (SD)	11.482 (4.847)	9.407 (2.099)	0.555
		Organization of Materials	M (SD)	14.111 (4.774)	12.667 (2.922)	0.365
	BRIEF Indices	Behavioral Regulation	M (SD)	47.250 (7.571)	44.537 (8.765)	0.331
		Meta Cognition	M (SD)	72.926 (20.080)	59.889 (11.177)	0.802
	BRIEF Total	Total Score	M (SD)	125.148 (34.774)	104.426 (18.903)	0.740
Physiological	RSA	HRV	M (SD)	3.735 (1.274)	4.771 (1.903)	0.640
Depression	GDS	Depression	M (SD)	9.889 (6.925)	2.852 (2.476)	1.353

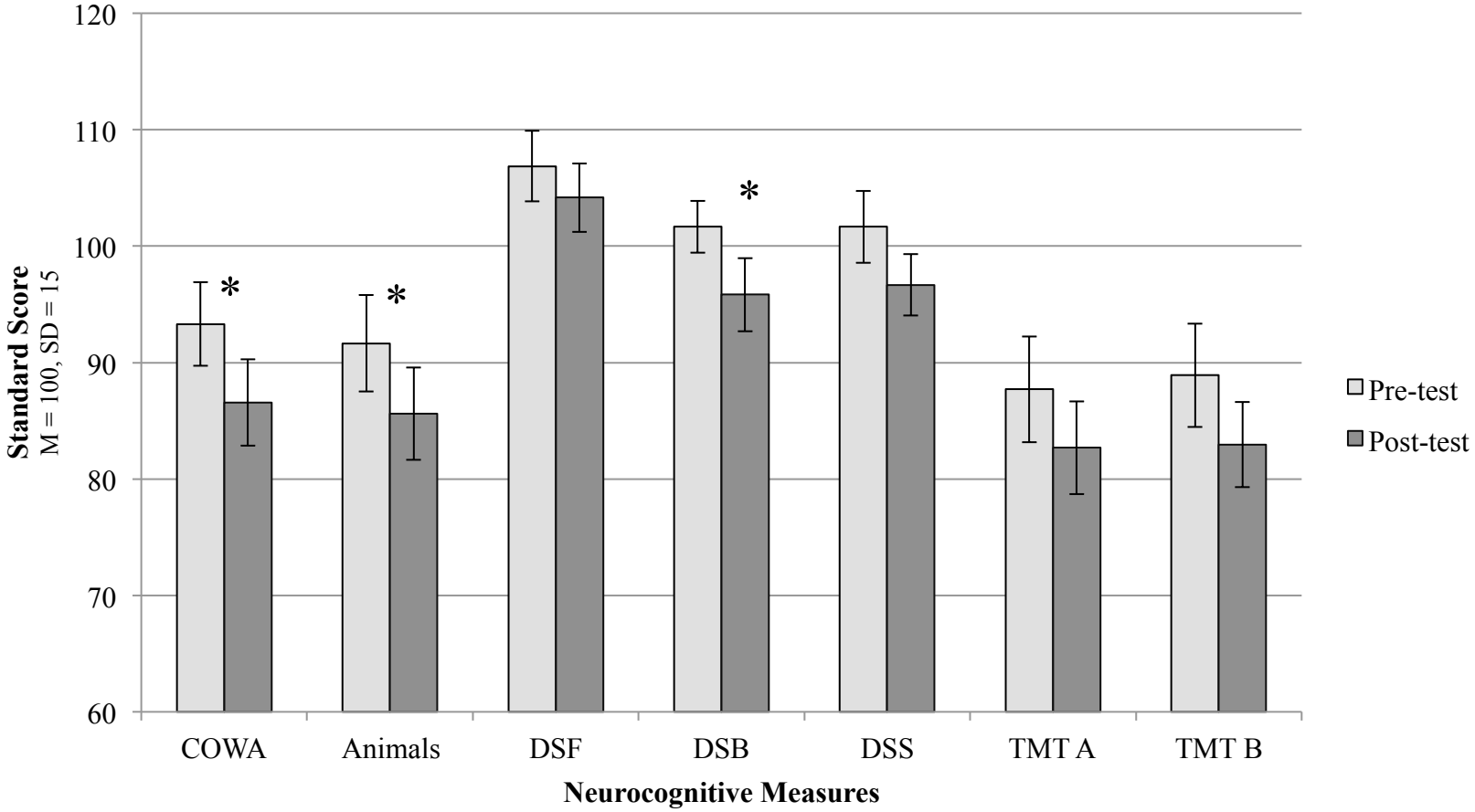
Note: SR, self-regulation; DBS, Deep brain stimulation group; HC, Healthy older adult controls; COWA, Controlled Oral Word Association Test; DSF, Digit Span Forward; DSB, Digit Span Backward; DSS, Digit Span Sequencing; TMT, Trail Making Test; BRIEF, Behavior Rating Inventory of Executive Functions; RSA, respiratory sinus arrhythmia; HRV, heart rate variability; GDS, Geriatric Depression Scale

Table 3.10. Differences between pre- and post-test DBS neurocognitive scores

		Pre- Test *n = 22*	*Post-Test* *n = 24*	*d*
COWA	M	93.304	86.565	- 0.39
	(SD)	(17.256)	(17.738)	
Animals	M	91.652	85.609	- 0.31
	(SD)	(19.821)	(18.989)	
DSF	M	106.875	104.167	- 0.19
	(SD)	(14.804)	(14.421)	
DSB	M	101.667	95.833	- 0.44
	(SD)	(10.901)	(15.440)	
DSS	M	101.667	96.667	- 0.36
	(SD)	(15.156)	(12.910)	
TMT A	M	87.696	82.696	- 0.24
	(SD)	(21.743)	(19.139)	
TMT B	M	88.909	82.955	- 0.31
	(SD)	(20.810)	(17.126)	
VLT* Total Recall	M	82.696	90.429	0.45
	(SD)	(11.640)	(21.407)	
VLT* Long Delay Recall	M	78.636	90.312	0.64
	(SD)	(16.989)	(19.169)	
VLT* Recognition	M	87.522	92.481	0.26
	(SD)	(16.892)	(20.845)	

Note: DBS, Deep brain stimulation patient group; COWA, Controlled Oral Word Association Test; DSF, Digit Span Forward; DSB, Digit Span Backward; DSS, Digit Span Sequencing; TMT, Trail Making Test; Verbal Learning Test (VLT)
*DBS patients were administered the Hopkins Verbal Learning Test (HVLT) on pre-test and the Rey Auditory Verbal Learning Task (RAVLT) on post-test. Scores were normed on a standard metric to compare across tests.

Figure 3.2. Bar graph depicting DBS pre- and post-test scores on neurocognitive measures



Note: M = Mean, SD = Standard Deviation; DBS, deep brain stimulation patient group; COWA, Controlled Oral Word Association Test; DSF, Digit Span Forward; DSB, Digit Span Backward; DSS, Digit Span Sequencing; TMT, Trail Making Test

* $p < .05$

Hannah Lane Combs

Curriculum Vitae

EDUCATION

2013 **M.S., Clinical Psychology (Neuropsychology Track)**
University of Kentucky, Lexington, KY
Thesis Title: The Effects of Posttraumatic Stress Disorder, Mild Traumatic Brain Injury, and Combined Posttraumatic Stress Disorder/Mild Traumatic Brain Injury on Returning Veterans
Thesis Chair/Advisor: David T.R. Berry, Ph.D.

2011 **B.S., Psychology (Honors)**
University of Texas, Austin, TX
Honors Thesis Title: Motor Learning, Forced Exercise Rehabilitation, and Functional Motor Cortex Plasticity Following Traumatic Brain Injury in Rats
Thesis Chair/Advisor: Theresa A. Jones, Ph.D.

HONORS AND AWARDS

2016	Jesse G. Harris, Jr. Dissertation Research Award, University of Kentucky
2014	Excellence in Campus Leadership, American Psychological Association of Graduate Students
2014	Best Grassroots Project Award, American Psychological Association of Graduate Students
2013-2015	Graduate Student Travel Award, University of Kentucky
2013-2015	Department of Psychology Student Travel Award, University of Kentucky
2011	Phi Beta Kappa
2010-2011	Undergraduate Research Fellowship, University of Texas
2010-2011	Psychology Departmental Honors Program, University of Texas
2008-2011	College of Liberal Arts Dean's List, University of Texas

PUBLICATIONS

PEER-REVIEWED MANUSCRIPTS

Segerstrom, S.C., **Combs, H.L.**, Boehm, J.K., Winning, A., Kubzansky L.D. (2016). The Happy Survivor: Effects of Mortality Bias on Life Satisfaction in Older Age. *Psychology and Aging. 31,* 340-345

Segerstrom, S.C., Geiger, P.R., **Combs, H.L**., & Boggero, I.A., (2016). Time Perspective and Social Preference in Older and Younger Adults: Effects of Self-Regulatory Fatigue. *Psychology and Aging, 31,* 594-604

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Combs, H.L., Folley, B.S., Berry, D.T.R., Segerstrom, S.C., Han, D., Anderson-Mooney, A., Walls, B., & van Horne, C. (2016) Cognitive Effects of Deep Brain Stimulation on the Subthalamic Nucleus and Globus Pallidus Pars Interna in Parkinson's Disease: A Meta-Analysis. *Neuropsychology Review, 4,* 439-454

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O'Bryant, A.J., Adkins, D.L., Sitko, A. A., **Combs, H.**, Nordquist, S. K, & Jones, T. A. (2014). Enduring post-stroke motor functional improvements by a well-timed combination of motor rehabilitative training and cortical stimulation in rats. *Neurorehabilitation & Neural Repair, 30*(2), 143-154).

Williamson, K.D., **Combs, H.L.,** Berry, D.T.R., Harp, J.P., Mason, L.H., & Edmundson, M. (2014). Discriminating among ADHD alone, ADHD with a comorbid disorder, and feigned ADHD in a college sample. *The Clinical Neuropsychologist, 28*, 1182- 96.

BOOK CHAPTERS

Combs, H.L., Dunham, K.J., Walls, B., & Anderson-Mooney, A.J. (in press). Post-ABI Movement Disorders. In Han, D. Y. (Ed.), *Acquired Brain Injury: Clinical Essentials for Neurotrauma and Rehabilitation Professionals.* Springer Publishing.

Berry, D.T.R., Harp, J.P., Koehl, L.H., & **Combs, H.L.** (in press). Applying diagnostic standards to performance validity tests and the individual case. In Bowden, S. C. (Ed.), *Neuropsychological assessment in the era of evidence-based practice: Diagnostic and treatment evaluations.* New York: Oxford University Press.

Riley, E. N., **Combs, H.L.**, Davis, H.A., & Smith, G.T. (in press). Theory as evidence: Criterion validity in neuropsychological testing, In Bowden, S. C. (Ed.), *Evidence-based Neuropsychological Practice*: *National Academy of Neuropsychology*. New York: Oxford University Press.

PROFESSIONAL PRESENTATIONS

ORAL

Combs, H.L. & Susman, D.T. (2015). Healthy You: Breaking Silence on Mental Health in America. Presented at the University of Kentucky Certified Nonprofit Professional Association's Mental Health Panel, October.

Han, D.Y. & **Combs, H.L**. (2015). Neuropsychological Sequelae of Neurosurgical Cases. Presented at University of Kentucky's Neurosurgery Grand Rounds, June.

Combs, H.L., Koehl, L.H., Anderson, A. J., & Han, D. Y. (2015). Irritability and Aggression as Indicators of Persistent Post-Concussive Symptoms in Adolescent Athletes. Paper presented at the Conference of Clinical and Translational Science annual meeting, March.

Combs, H.L. (2015). State and Federal Legislative Advocacy: A Primer. Presented at University of Kentucky professional development meeting, April.

Combs, H.L., Folley, B.S., Berry, D.T.R., Segerstrom, S.C., Han, D., Anderson-Mooney, A., Walls, B., & van Horne, C. (2015) Cognitive Effects of DBS on the STN and GPi in Parkinson's Disease: A Meta-Analysis. Presented at Bluegrass Area Neuropsychology Group (BANG) Meeting, February.

Combs, H.L. (2015). Neuropsychology of Multiple Sclerosis and Other Demyelinating Disorders. Presented at University of Kentucky Functional Neuroanatomy Didactics, January.

Combs, H.L. (2014). Clinical case presentation "J": Advanced psychotherapy client. Presented at University of Kentucky professional development meeting, October.

Combs, H.L. & Folley, B.S. (2014). Case presentation of PB: Patient with left splenial arteriovenous malformation. Presented at Bluegrass Area Neuropsychology Group (BANG) meeting, September.

Combs, H.L. (2014). What is Advocacy? An Introduction to Advocacy Work for Graduate Students. Presented at University of Kentucky professional development meeting, October, May.

Combs, H.L. (2014). Mental Health and the Role of Psychology in Rehabilitation. Presentation for Medical Personnel at Cardinal Hill Rehabilitation Hospital, June.

Combs, H.L. (2013). Case presentation of K: Patient with Frontotemporal Dementia with Upper Motor Neuron Disease. Presented at Bluegrass Area Neuropsychology Group monthly meeting, October.

Combs, H.L., Berry, D.T.R., Pape, T.L., Babcock-Parziale, J., Smith, B.M., Schleenbaker, R.E., & High Jr., W.M. (2013). The Effects of Posttraumatic Stress Disorder, Mild TBI, PTSD, and Combined PTSD/mTBI on Returning Veterans. Presented at University of Kentucky professional development meeting, August.

Combs, H.L. (2013). Role of Psychology in a Disorders of Consciousness Program. Presented at the Cardinal Hill Rehabilitation Hospital Disorders of Consciousness Symposium, May.

POSTERS

Koehl, L.M., **Combs, H.L.,** Walls, B.D., Berry, D.T.R., & Han, Dong Y. (2016). Neurocognitive Measures in an Adolescent Sports Concussion Sample. Poster

presented at the Conference of Clinical and Translational Science annual meeting, Lexington, KY.

Reed, R.G., **Combs, H.L.** & Segerstrom, S.C. (2016). A latent constellation of self-regulation and its association to chronic disease in older adults. Poster presented at the American Psychosomatic Society 74th Annual Scientific Meeting, Denver, CO.

Koehl, L.M., **Combs, H.L.,** Walls, B.D., Berry, D.T.R., & Han, Dong Y. (2016). Validating Neurocognitive Measures in an Adolescent Sports Concussion Sample: ImPACT Computerized Testing versus Traditional Neuropsychological Measures. Posterpresented at the annual meeting of the International Neuropsychological Society Conference, Boston, MA.

Segerstrom, S.C., **Combs, H.L.**, Boehm, J.K., Winning, A., Kubzansky L.D. (2015). The Happy Survivor: Effects of Mortality Bias on Life Satisfaction in Older Age. Poster presented at the annual meeting of the Gerontology Society of America, Orlando, FL.

Combs, H.L., Scott, A. B., & Segerstrom, S.C. (2015), Higher HRV Predicts Stronger Performance on Executive Functioning Tasks in Older Adults. Poster presented at the annual meeting of the American Psychosomatic Society Conference, Savannah, GA.

Combs, H.L., Koehl, L. H., Anderson, A. J., Han, D. Y. (2015). Irritability and Aggression as Indicators of Persistent Post-Concussive Symptoms in Adolescent Athletes. Poster presented at the annual meeting of the International Neuropsychology Society Conference, Denver, CO.

Combs, H.L., Russell, M., & Segerstrom, S.C. (2015). "Higher Heart Rate Variability Predicts Better Performance on Executive Functioning Measures in Older Adults." Poster presented at the annual meeting of the International Neuropsychology Society Conference, Denver, CO.

Garcia, N.E., **Combs, H.L.,** & Segerstrom, S.C. (2014). "Practice Effects and Longitudinal Change in Processing Speed and Executive Functioning Among Older Adults." Poster presented at the annual meeting of the International Neuropsychology Society Conference, Seattle, WA.

Williamson, K.D., **Combs, H.L.,** Harp, J.P., Mason, L.H., Edmundson, M., & Berry, D.T.R. (2014). "Discriminating Between ADHD, ADHD with a Comorbid Psychological Disorder and Malingered ADHD in a College Sample." Poster presented at the annual meeting of the International Neuropsychology Society Conference, Seattle, WA.

Combs, H.L., Garcia, N.E., Segerstrom, S.C. (2014). "Age and IQ Moderate Practice Effects of Verbal Memory Ability in Older Adults." Poster presented at the annual meeting of the International Neuropsychology Society Conference, Seattle, WA.

Combs, H.L., Scott, A. B., & Segerstrom, S.C. (2014), "Higher Heart Rate Variability Predicts Stronger Performance on Executive Functioning Tasks in Older Adults." Poster presented at the annual Markesbery Symposium on Aging and Dementia, Lexington, KY

Combs, H.L., Berry, D.T.R., Pape, T.L., Babcock-Parziale, J., Smith, B.M., Schleenbaker, R.E., & High Jr., W.M. (2014). "Effect of severity of concussion

(mTBI) and PTSD on cognitive functioning in veterans with deployment-related mTBI." Poster presented at the annual meeting of the International Neuropsychology Society Conference, Seattle, WA.

Combs, H.L., Berry, D.T., & High, W.M. (2013). The Effects of Posttraumatic Stress Disorder, Mild Traumatic Brain Injury, and Combined PTSD/mTBI on Returning Veterans. Presentation at the 11th Annual meeting of the American Academy of Clinical Neuropsychology, Chicago, IL.

Combs, H.L., Adkins, D. L., Kozlowski, D.A., & Jones, T. A. (2011). "Skill training, exercise and constraint-like therapy together promote major functional reorganization of remaining motor cortex after controlled cortical impact injury in rats." Poster presented at the annual meeting of the National Neurotrauma Symposium, Ft. Lauderdale, FL.

Combs, H.L., Adkins, D. L., & Jones, T. A. (2011). "Motor learning, forced exercise rehabilitation, and functional neuroplasticity following controlled cortical impact." Poster presented at the annual meeting of the University of Texas' Institute of Neuroscience Symposium, Austin, TX.

O'Bryant, A., **Combs, H.,** Nordquist, S., & Jones, T. A. (2010). "Effects of transcranial cortical stimulation and motor rehabilitative training on functional recovery following unilateral cortical infarcts in rats." Poster presented at the 2010 conference of the Society for Neuroscience, San Diego, CA.

Combs, H. L., Adkins, D. L., & Jones, T. A. (2010). "Motor learning, forced exercise rehabilitation, and functional motor cortex neuroplasticity following traumatic brain injury in rats." Poster presented at the Psychology Departmental Honors Day, Austin, TX.

PUBLIC DISSEMINATION OF RESEARCH FINDINGS

Adams, E. (2014, Dec 22). UK Researchers Point to Impact of Combined Brain Injury in War Veterans. *UKnow: University of Kentucky News.* Retrieved 12/22/2014 from http://uknow.uky.edu/content/uk-researchers-point-impact-combined-brain-injury-and-ptsd-war-veterans

Davenport, L. (2015, Jan 8). PTSD and Brain Injury: Double Trouble for Veterans. *Medscape*. Retrieved 1/28/2015 from http://www.medscape.com/viewarticle/837811

TEACHING EXPERIENCE

Teaching Assistant

University of Kentucky, Lexington, KY (Fall 2011 – Fall 2012)

- PSY 100 *Introduction to Psychology*
- PSY 216 *Application of Statistics in Psychology*

Guest Lecturer

University of Kentucky, Lexington, KY (Fall 2015- Spring 2016)

- PSY 333 *Abnormal Psychology*
- PSY 399 *Community Based Education*

ACADEMIC JOURNAL PEER REVIEW ACTIVITY

Assessment

Journal of the International Neuropsychological Society

PROFESSIONAL AFFILIATIONS

American Psychological Association – Division 40
American Psychological Association of Graduate Students
Association of Neuropsychology Students in Training
Bluegrass Area Neuropsychology Group
Kentucky Psychological Association
Phi Beta Kappa
University of Kentucky Psychology Advocacy Group