THE NEUROPSYCHOLOGICAL IMPACT OF INSULIN LEVELS: ROLES OF INSULIN IN PARKINSON'S DISEASE AND COGNITIVE FUNCTIONING

By

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Submitted to the graduate degree program in Psychology
and the Graduate Faculty of the University of Kansas in partial fulfillment of the
requirements for the degree of Master of Arts.

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Date defended: April 4, 2012

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Date approved: April 18, 2012

Abstract

Numerous studies demonstrate a relationship between insulin and Alzheimer's disease; however, little research exists on insulin's association to Parkinson's disease (PD) and Parkinson's disease dementia (PDD). The current study examined the connection between insulin and cognitive functioning in PD, PDD, and age-matched controls. A total of 22 older adult participants with PD completed the present study: 12 participants with PD (mean age = 67.50; 41.67% men; mean Mini Mental State Exam (MMSE) = 28.67) and 10 participants with PDD (mean age = 75.10; 90.00% men; mean MMSE = 22.90). Twenty-two non-demented older adults (mean age = 71.77; 63.64% men; mean MMSE = 29.23) from the University of Kansas Brain Aging Project served as the control group. Participants completed a neuropsychological assessment battery designed to represent cognitive domains of interest for individuals with PD and PDD as well as a two-hour glucose tolerance test. Total area under the curve (AUC) for blood insulin served as overall indices for insulin levels. PDD participants had lower absolute insulin values compared to PD participants and lower insulin levels were associated with decreased motor performance based on the Unified Parkinson's Disease Rating Scale (UPDRS) motor score. Contrary to predictions, higher insulin levels predicted poorer executive functioning performance for both PD and PDD participants. More research is needed to establish specific mechanisms to explain the relationship between higher insulin levels and reduced executive functioning performance. Additional research would also provide further evidence for insulin's role in cognitive changes for older adults with PD, PDD, and other neurodegenerative diseases.

Acknowledgements

The completion of this research project would not have been possible without the support of numerous people. First I would like to thank my advisor and thesis chair, Dr. David K. Johnson, who introduced me to this research project. I am extremely appreciative of his expertise, guidance, and support throughout this project and my graduate career. I would also like to thank Dr. Jeffrey M. Burns and my thesis committee member Dr. Robyn Honea for graciously allowing me to collaborate on this project. Their work with Parkinson's disease and Parkinson's disease dementia provided unparalleled opportunities for clinical and assessment experience that strengthened my clinical interests with this population and older adults. I also want to thank my thesis committee member Dr. Doug Denney for his insight and suggestions during this project. In addition, I'd like to thank my thesis committee member Dr. Sarah Kirk for her suggestions, guidance, and most importantly support throughout my graduate work.

Finally, I'd like to express my gratitude for my colleagues, friends, and family for their support throughout the often challenging journey of graduate school. I want to particularly acknowledge my mother for her continued support of my educational growth. Above all, I want to thank my husband Michael for his unwavering love and constant encouragement to achieve my goals. I am forever grateful for his continuous support in achieving this accomplishment.

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Glucose is a monosaccharide sugar within blood that serves as the brain's major energy source. Insulin is a protein hormone that metabolizes carbohydrates, proteins, and lipids. Insulin regulates blood sugar levels by assisting in the uptake of glucose into bodily tissues (White, 2003). Glucose and insulin have a direct relationship in healthy adults. Before eating, both insulin and glucose levels are low. After consuming a meal, blood glucose levels rise and initiate insulin release from the pancreas. Even a modest increase in bloodstream glucose quickly results in a noticeable increase in insulin secretion (Norman, 2009; White, 2003). When this balance is disturbed, diseases like insulin resistance occur because muscle, fat, and liver cells can no longer properly respond to insulin. Insulin resistance can lead to obesity, diabetes mellitus (Steinberger & Daniels, 2003), and cognitive decline (Arvanitakis, Wilson, & Bennett, 2006; Craft & Watson, 2004; Sandyk, 1993).

Insulin receptors play a major role in the central nervous system (CNS). These extracellular receptors act as indirect activation pathways to control intracellular activity. The indirect activation pathway and signal transduction within a cell begins when insulin molecules bind to extracellular subunits (White, 2003). Binding activates the intracellular subunit tyrosine kinase and initiates protein phosphorylation of signaling scaffold proteins IRS-1 or IRS-2. Following phosphorylation, IRS-1 or IRS-2 recruits and phosphorylates PI 3-kinase. PI 3-kinase then activates Akt kinase that continues the signaling pathway by phosphorylating several additional substrates involved in cell survival, growth, and glycogen synthesis (White, 2003). Insulin signaling also influences GABA, NMDA, and AMPA neurotransmitter receptors. These receptors contribute to learning and memory, neuronal circuitry specialization, information

storage (van der Heide, Kamal, Artola, Gispen, & Ramakers, 2005), and synaptic plasticity (Huang, Lee, & Hsu, 2004).

Hormonal reserves in the body decline as age increases. Reduction in insulin hormone and damage to glucoregulatory mechanisms trigger impaired glucose tolerance, insulin resistance, and diabetes mellitus, which are all common in older adults (Gasparini, Netzer, Greengard, & Xu, 2002; Sandyk, 1993). Inadequately regulated insulin in diabetes mellitus leads to poorer cognitive functioning and more rapid cognitive decline over time (Arvanitakis et al., 2006; Gregg et al., 2000; Messier & Teutenberg, 2005). Risk factors for diabetes mellitus and Alzheimer's disease (AD), the most common form of dementia (Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004), greatly overlap. Shared risk factors include age, family history, high blood pressure, high cholesterol, and insulin resistance (Ott et al., 1999). For this reason, it is not surprising that research suggests a close relationship between AD and insulin signaling (Burns et al., 2007; Craft & Watson, 2004; Gasparini et al., 2002).

AD and Parkinson's disease (PD) have similar biological mechanisms (Weintraub et al., 2011), so it is likely that insulin signaling impacts and exacerbates PD (Fantini & Yahi, 2010; Rodolfo, Ciccosanti, Giacomo, Piacentini, & Fimia, 2010). Numerous studies illustrate the relationship between insulin and AD; however, there is a paucity of data on insulin's association to PD and Parkinson's disease dementia (PDD). Furthermore, to our knowledge, little research has investigated insulin metabolism in PDD.

This study examined insulin's relationship with cognitive functioning in PD, PDD, and age-matched controls. We hypothesized that (1) the PDD group would have lower absolute insulin, as defined by insulin area under the curve (AUC) for a two-hour glucose tolerance test, compared to PD and control groups; (2) Lower insulin levels would significantly correlate with

decreased motor performance, as defined by the Unified Parkinson's Disease Rating Scale (UPDRS) motor score; (3) Lower insulin levels would predict poorer performance on executive functioning, memory, visuospatial, and language tasks. This research adds to the literature about the impact of insulin on cognitive performance in PD and PDD. Future use of this knowledge could streamline diagnosis of PD and PDD, improve treatment, and help to better understand the aging process.

Parkinson's disease

Parkinson's disease (PD) is the second most common degenerative neurological disorder and can affect 0.6% of the population ages 65-69 and 2.6% of those ages 85-89 (Irvine, El-Agnaf, Shankar, & Walsh, 2008). In America, prevalence rates are as high as 1.5 million individuals with 500,000 new diagnoses each year (Weintraub, 2004). Approximately 3% of the population above the age of 65 (Moghal, Rajput, D'Arcy, & Rajput, 1994) and one in ten people over the age of 80 have PD (Bennett et al., 1996).

Age is the most consistent predictor of PD (Morens et al., 1996); however, the disease is not confined to older adults. Five to ten percent of individuals experience parkinsonian symptoms before age 40. Development of PD in midlife is defined as "young-onset Parkinson's disease" (Moghal et al., 1994). The disease impacts all ethnic groups, but a greater frequency of Caucasians are diagnosed compared to Asians and African Americans. Males are diagnosed with PD at a greater frequency than females (Zhang & Roman, 1993).

PD is often associated with difficulties in movement. Classic symptoms include bradykinesia, extreme slowness in movement, or akinesia, absence of voluntary movement. Tremors, rigidity, and postural abnormalities also characterize the illness (Lang & Lozano, 1998; Slaughter, Slaughter, Nichols, Holmes, & Martens, 2001). Parkinsonian symptoms are also

associated with other causes including other neurodegenerative diseases, Wilson's disease, and antipsychotic medications such as haldol and risperdal (de Rijk et al., 1997). However, resting tremor, asymmetry of symptoms, and a positive response to the medication levodopa distinguishes PD from parkinsonian symptoms resulting from other factors (Lang & Lozano, 1998). Slight tremor in one hand and increased stiffness in the limbs are often attributed to the aging process and result in the underdiagnosis or misdiagnosis of many individuals. Parkinsonian symptoms are chronic and progressive, but the manifestation and progression of symptoms vary greatly among patients. Typically individuals do not become incapacitated from symptoms until 10-20 years after the onset of symptoms. In advanced stages, those with PD require assistance with feeding, washing, and other functions of daily living (Caballol, Marti, & Tolosa, 2007). PD symptoms gradually become more serious but are not considered fatal. Complications from the disease such as choking and falling more often lead to death. The average life expectancy after diagnosis is nine years (Lang & Lozano, 1998).

Non-motor symptoms frequently develop in PD. These include hallucinations, anxiety, complex behavioral disorders, sensory dysfunction with hyposmia or pain, disturbances of sleep-wake cycle regulation, and cognitive dysfunction (Barnes & Boubert, 2008; Poewe, 2008; van Rooden, Visser, Verbaan, Marinus, & van Hilten, 2009; Weintraub, Moberg, Duda, Katz, & Stern, 2004).

Cognitive decline in Parkinson's disease

Meta-analytic results indicate that non-demented PD patients show a relatively small decline in cognitive functioning during a 2.5-year follow-up period (Muslimovic, Schmand, Speelman, & DeHaan, 2007). Prevalence rates of individuals experiencing cognitive deficits without dementia are uncertain. However, research indicates that 36% of individuals with a

recent PD diagnosis present some form of cognitive impairment (Foltynie, Brayne, Robbins, & Barker, 2004). In addition, researchers found that 55% of a non-demented PD sample had mild cognitive impairment (Jarvin, Aarsland, Larsen, & Hugdahl, 2003).

Executive dysfunctions are typically the first cognitive deficits to occur in PD (McKinlay, Grace, Dalrymple-Alford, & Roger, 2010; Robottom & Weiner, 2009; Williams-Gray et al., 2009), and these impairments are the most sensitive neuropsychological predictors of progression of cognitive impairment in PD (Stepkina, Zakharov, & Yakhno, 2010). Executive functioning is defined as various higher-order capacities that involve the organization and prioritization of thoughts and tasks, inhibition of activity and emotions, decision making, planning, time management, shifting mental effort, short-term memory, and working memory (Barnes & Boubert, 2008; Campos-Sousa, Campos-Sousa, Ataide, de Brito Soares, & Almeida, 2010; Fernandez, Crucian, Okun, Price, & Bowers, 2005). Executive functioning is involved in the control and expansion of both cognitive and behavioral responses to environmental situations (Caballol et al., 2007; Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007). In PD, executive functioning impairments are noted through poor performance on generating mental sets, set shifting, planning, attention, and determining sequence of events (Robottom & Weiner, 2009). In some individuals, executive functioning deficits are subtle and difficult to detect with screening measures (Robottom & Weiner, 2009).

Executive dysfunctions in PD can elicit abnormalities in memorization (Baran, Tekcan, Gurvit, & Boduroglu, 2009). Difficulties in memorization can lead to disruption of sequencing and encoding new memories (Bohlhalter, Abela, Weniger, & Weder, 2009; Robottom & Weiner, 2009). Research shows non-demented PD patients experience deficits on tasks of immediate and delayed recall (Baran et al., 2009) and reduced performance on word list learning (Anderson,

2004; Caballol et al., 2007; Merims & Freedman, 2008; Williams-Gray et al., 2007). However, significant memory impairments may occur only when tasks require greater attention, learning strategies, and planning (Baran et al., 2009). Typically the ability to learn new information and recognition remains in tact (Bohlhalter et al., 2009). These data suggest that deficits involving the coding and retrieval of information are impacted more so than the storage of information (Caballol et al., 2007).

While executive dysfunctions are the first cognitive impairments to occur in PD, visuospatial deficits are reported with greater frequency (Robottom & Weiner, 2009). In addition, research demonstrates that those PD patients with severe visuospatial deficits have a quicker progression of cognitive impairments compared to those with less visuospatial deficits (Stepkina et al., 2010). Visuospatial function is the ability to manipulate and synthesize graphic, geographic, or non-verbal information (Fernandez et al., 2005). In PD, visuospatial abnormalities present during visual orientation, visual attention, spatial planning, and spatial memory tasks (Robottom & Weiner, 2009). Along with memory impairments, visuospatial deficits are thought to relate to executive functioning and disruption of information integration (Robottom & Weiner, 2009). However, some research suggests visuospatial abilities are independent of executive function. In one study, problem solving deficits were apparent only in tasks with high visuospatial content (e.g., Matrix Reasoning; McKinlay et al., 2010).

Language impairments also occur in PD. Deficits present through speech hesitation and perseveration intrusions during word fluency tasks. Individuals can experience these difficulties in category, letter (Robottom & Weiner, 2009), and semantic fluency (Baran et al., 2009; Caballol et al., 2007). Research also has shown that PD patients have trouble with verb naming (Caballol et al., 2007). Language deficits likely result from an inability to plan and implement

motor aspects of language, capacities that are connected to executive functioning, thereby strengthening the argument that executive functioning deficits are primary in PD. In general, language is preserved and there is little evidence of aphasia in PD. (Robottom & Weiner, 2009).

Parkinson's disease dementia

Prevalence rates of Parkinson's disease dementia (PDD) range from 20-80% (Anderson, 2004; Galvin, 2006; Lang & Lozano, 1998; Merims & Freedman, 2008; Williams-Gray et al., 2007). Researchers found that within five years following a PD diagnosis, 17% of a United Kingdom study cohort had dementia (Williams-Gray et al., 2009). Another study surveying the population of Norway found that 65% of a surviving cohort with PD had dementia (Mayeux et al., 1990). If higher prevalence rates are accurate, PDD is the second most common type of dementia (Fernandez et al., 2005). Patients with PD are diagnosed with dementia at a frequency of 2 to 6.6 times greater than that of healthy older adults (Caballol et al., 2007; Mayeux et al., 1990; Robottom & Weiner, 2009). Risk factors for developing PDD include advanced age at the onset of motor symptoms, severe motor symptoms, male sex, depression, smoking, and early development of l-dopa related confusion or psychosis (Anderson, 2004; Galvin, 2006; Merims & Freedman, 2008; Muslimovic et al., 2007; Williams-Gray et al., 2007).

One study found that out of 100 PD patients, 31 patients had well-documented dementia. Nine PD patients met criteria for AD (29%), three patients met criteria for diffuse Lewy body disease (10%), and two PD patients had possible vascular dementia (6%). The researchers reported that the remaining 17 PD patients with dementia (55%) had no definite pathological explanation for the cognitive decline other than PD (Hughes, Daniel, Blankson, & Lees, 1993). These results highlight how symptom similarities among PD, AD, and dementia with Lewy bodies cause difficulty in exact diagnoses. Also, the Diagnostic and Statistical Manual of Mental

Disorders Fourth Edition (DSM-IV) defines PDD as "cognitive and motoric slowing, executive dysfunction, and impairment in memory retrieval" (American Psychiatric Association, 2000). The requirement of memory retrieval difficulties is one result of using the DSM-IV definition. While this is a common impairment, it may not be a prominent characteristic of PDD. This generalized definition of dementia could be one factor contributing to the wide prevalence ranges and controversial nature of PDD.

Cognitive decline in PDD is insidious with a slow progression. PDD commonly begins with slowing thoughts. However, researchers concluded that slowing thoughts were not a simple byproduct of motor symptoms (Berardelli et al., 2001, as cited in Gavin, 2006). PDD later progresses to increased difficulties in memory, visuospatial skills, language, abstract thinking, behavioral regulation, and motivation (Anderson, 2004; Caballol et al., 2007; Muslimovic et al., 2007). PDD patients have increasing trouble with housework or finances due to the extra time needed to complete tasks. Reduced participation in social gatherings as well as avoidance of decision-making or initiation of activities is common. PDD patients experience visual and auditory hallucinations, delusions, and depression more frequently compared to non-demented PD patients (Caballol et al., 2007; Galvin, 2006).

Similar to PD, PDD patients demonstrate greater impairment on executive functioning tasks compared to individuals with AD (Robottom & Weiner, 2009). Individuals with PDD also demonstrate reduced performance on attentional tasks and in motor reaction time (Galvin, 2006). Some researchers report that PDD and AD have similar attentional impairments (Robottom & Weiner, 2009); however, attention may fluctuate more in PDD. Reaction time and vigilance likely contribute to attentional deficits. In addition, PDD causes difficulties in set switching,

concept formation, problem solving, and speed of information processing (Robottom & Weiner, 2009).

Researchers found that 67% of PDD patients experience memory deficits (Emre, 2003). Memory deficits result from failing to retrieve information rather than trouble encoding information. Unlike non-demented PD patients, PDD patients show greater recognition deficits (Bohlhalter et al., 2009). Cueing may help reduce impairments in semantic and episodic memory (Robottom & Weiner, 2009). Compared to semantic and episodic memory deficits, a lack of evidence exists for an association between PDD and verbal memory deficits (Stepkina et al., 2010).

Visuospatial deficits also present in PDD. These impairments are subtle at first but often appear before an official dementia diagnosis is given. Visuospatial deficits in PDD are more severe compared to similar dementia severity in AD (Robottom & Weiner, 2009).

In PDD, the extent of language impairments varies, but aphasia typically does not develop. Verbal fluency deficits often emerge before an official dementia diagnosis is given. Reduced speech, shorter phrase length, trouble naming objects, and dysarthria also occur in PDD (Robottom & Weiner, 2009). Compared to AD, those with PDD have greater motor speech difficulties (Robottom & Weiner, 2009). At a six-month follow-up, researchers found that deterioration of cognitive functions was associated with trouble actively reproducing verbal material; however, prompting enhanced reproduction of material (Stepkina et al., 2010). In addition, PDD patients can experience comprehension difficulties with metaphors or ambiguous language content (Lewis, Lapointe, Murdoch, & Chenery, 1998).

Neuroanatomy of Parkinson's disease

Numerous brain structures contribute to the symptomatology of PD and PDD. Structures of the basal ganglia play a key role in PD by regulating movement and motor control (Higgins & George, 2007). The basal ganglia consist of the putamen, globus pallidus, and caudate nucleus that lay under the anterior portion of the forebrain cortex. The basal ganglia share connections with other structures including the cerebral cortex. One pathway begins as regions of the cortex send neural signals to the caudate nucleus. The neural signals pass through the caudate nucleus and continue through the putamen, globus pallidus, and thalamus until they reach frontal regions of the cortex (DeLong & Wichmann, 2009; Higgins & George, 2007; Pliszka, 2004). Disruptions to the basal ganglia including deterioration in the connections to the substantia nigra pars compacta cause difficulties in initiating or executing movements and impact the speed and amplitude of movements. In addition, postural changes and increased or decreased muscle tone result from damage to the basal ganglia (DeLong & Wichmann, 2009).

The nigrostriatal dopamine pathway is another crucial component to the neuroanatomy of PD and PDD. This important midbrain pathway comprises the substantia nigra's connections to the basal ganglia. Darkly pigmented neurons of the substantia nigra regulate initiation and orientation of critical movement (Uversky & Eliezer, 2009). The substantia nigra consists of two parts, pars reticulata and pars compacta, with contrasting functions (Pliszka, 2004). The pars reticulata continuously fires the inhibitory neurotransmitter GABA. As the pars reticulata releases GABA, eye, trunk, and walking movements are stopped. Initiation of these movements requires removal of GABA's inhibitory influence. Dopaminergic neurons in the pars compacta withdraw the inhibitory influence and allow initiation of new movement (Pliszka, 2004).

In PD, connections between the substantia nigra pars compacta and the basal ganglia deteriorate and result in dopaminergic cells loss (Pliszka, 2004; Uversky & Eliezer, 2009). Cell

loss of the nearly 400,000 dopaminergic cells of the substantia nigra is estimated to occur at a rate of approximately 2,400 cells per year. This rate of cell loss is capable of producing PD in an otherwise healthy 120-year-old individual. However, PD accelerates the typical rate of cell death and causes idiopathic onset around age 70 (Uversky & Eliezer, 2009). Neuronal death in the nigrostriatal dopamine pathway initiates classic hypokinetic symptoms of PD including tremors, bradykinesia, and difficulty maintaining balance (Uversky & Eliezer, 2009).

Cortical and subcortical structures contribute to dementia in PD. One theory proposes that disruption to the connections between the basal ganglia and frontal cortex leads to cognitive impairments associated with PDD (Stepkina et al., 2010). Research suggests that disturbances in the frontal lobe result in executive dysfunction (Caballol et al., 2007). Other theories focus on dopaminergic cell loss. Studies suggest that greater substantia nigra cell loss along with augmented involvement of caudate nucleus projections generate enhanced cognitive dysfunction (Caballol et al., 2007; Gibb & Lees, 1991). Dopamine impacts higher cognitive functions. Consequently, reduced dopamine receptors and decreased dopamine transporter density diminishes executive function and working memory performance (Seidler et al., 2009).

Molecular basis of Parkinson's disease

Along with brain structures, components at the molecular level play a role in PD and PDD. Dopamine's important role in PD requires additional discussion at the neurotransmitter level. Dopamine is a monoamine neurotransmitter formed by the decarboxylation of dopa. Dopa is an amino acid produced in the liver during melanin and epinephrine synthesis. Dopamine has five different receptors, D_1 through D_5, and is essential for normal CNS functioning (Pliszka, 2004). Voluntary movement is controlled by dopamine and a lack of the neurotransmitter causes

difficulty in the execution of smooth, controlled movements. Dopamine also plays a part in controlling motivation, sleep, mood, attention, cognition, and learning (Brooks & Piccini, 2006).

Dopamine receptors D_1 and D_2 are reduced in the aging brain, with a 5-10% loss each decade (Seidler et al., 2009). Over 70% of total dopaminergic neurons are lost by the time Parkinsonian symptoms become evident (Irvine et al., 2008; Uversky & Eliezer, 2009). Lab analyses on brains of deceased PD patients revealed that dopamine amounts were diminished by over 90% and to undetectable levels in some cases (Fearnley & Lees, 1991). Even though PD is characterized by dopaminergic cell loss, not all dopaminergic projections are impacted equally. In general, loss is greatest in the ventrolateral tier of the substantia nigra with decreasing loss in the medial ventral tier and dorsal tier. The substantia nigra pars compacta loses 0.5-0.7% of dopaminergic cells annually (Seidler et al., 2009). This dopamine neurotransmitter degradation pattern is specific to PD and can defer the loss pattern seen in typical aging (Fearnley & Lees, 1991). Research lacks clear answers for why dopaminergic neuron vulnerability leads to PD.

One neurotransmitter with a role in PD is glutamate. Glutamate is synthesized from glucose (Higgins & George, 2007; Pliszka, 2004) and acts as the major excitatory neurotransmitter in the CNS, accounting for over half of all excitatory neurons (Reis et al., 2009; Riedel, Platt, & Micheau, 2003). Glutamate has three ionotropic receptors: α-amino-3-hydroxy-5-methyl-4-isoazole propionic acid (AMPA), *N*-methyl-*D*-aspartate (NMDA), and 2-carboxy-3-carboxy-methyl-4-isopropenyl-pyrrolidine (kainate), (Higgins & George, 2007; Reis et al., 2009).

AMPA receptors are located throughout the brain and have high concentrations within the neocortex, basal ganglia, thalamus, hypothalamus, hippocampus, cerebellum, and spinal cord (Riedel et al., 2003). AMPA and NMDA control the majority of excitatory post-synaptic effects

at cell synapses. AMPA and kainate receptors provide quick and immediate postsynaptic responses to glutamate release (Riedel et al., 2003). Glutamate attaches to AMPA and kainate receptors and causes ligand-gated ion channels to open. This opening allows an exchange of sodium (Na^+) into a cell and subsequent exit of potassium (K^+) out of a cell. Na^+ and K^+ exchange leads voltage-gated Na^+ channels to open, resulting in an action potential (Pliszka, 2004).

NMDA receptor concentrations are uneven with higher concentrations within the hippocampus, thalamus, and cortex and lower concentrations within the basal ganglia, cerebellum, and spinal cord (Riedel et al., 2003). The complex NMDA channel allows calcium (Ca^{2+}) into a cell (Higgins & George, 2007). To allow Ca^{2+} into a cell, glutamate and glycine, an amino acid, must bind to a NMDA receptor site. However, resting neurons have a magnesium (Mg^{2+}) ion blocking Ca^{2+} channels. AMPA and kainate receptors displace the Mg^{2+} ion through depolarization and permit the calcium influx through the ionophore. The resulting calcium influx stimulates a series of enzymes to act as second messengers (Higgins & George, 2007).

Another neurotransmitter involved in PD is synthesized from glutamate, gamma (g)-aminobutyric acid (GABA). GABA is highly concentrated in the substantia nigra and the globus pallidus portion of the corpus striatum, with slightly lower concentrations in the hypothalamus, periaqueductal grey matter, and hippocampus (Reis et al., 2009). Unlike glutamate, GABA is the main inhibitory neurotransmitter in the central nervous system (Higgins & George, 2007). Inhibition is an important mechanism that requires precise control for optimal functioning. Too little inhibition can produce seizures. Too much inhibition results in a generalized depression of brain activity and may cause loss of consciousness (Higgins & George, 2007; Pliszka, 2004).

GABA interacts with both ionotropic receptors ($GABA_A$) and metabotropic receptors ($GABA_B$), (Pliszka, 2004). Activation of $GABA_A$ elicits a conformational change and opens ion channels to allow an influx of chlorine (Cl^-) into the postsynaptic cell. This results in hyperpolarization and thus an inhibitory postsynaptic effect (Reis et al., 2009). GABA creates mainly inhibitory responses; however, the neurotransmitter can control output of neurons responsible for excitatory functions through increased Cl^- concentrations and membrane depolarization (Matsuyama, Taniguchi, Kadoyama, & Matsumoto, 2008).

Insulin

Insulin is a polypeptide hormone necessary for adequate health that plays a key role in the CNS and neurodegenerative diseases like PD (Gasparini et al., 2002). The majority of studies focus on insulin located outside the CNS. In the periphery, β-cells within the pancreatic islet produce insulin (Norman, 2009). As individuals consume carbohydrates or sugars, the molecules are absorbed through intestinal walls and travel into the bloodstream. When pancreatic islets detect increased blood sugar, insulin is synthesized and secreted. As insulin circulates in the bloodstream, it attaches to insulin receptors located on most cells. Once insulin binds to a cell's surface, other receptors are activated to absorb glucose into the cell (Norman, 2009). Glucose and insulin act in concert; modest increases in plasma glucose result in marked increases in insulin secretion into the bloodstream. Healthy individuals achieve homeostasis when plasma glucose levels are maintained within a narrow range (Norman, 2009; White, 2003).

Disrupted glucose and insulin levels cause diseases such as heart disease, high blood pressure, high cholesterol, and obesity. Diabetes mellitus is the most common disease resulting from a glucose and insulin imbalance (Arvanitakis et al., 2006; White, 2003). Type I diabetes is the body's inability to sense glucose or secrete insulin. An autoimmune-mediated process

destroys β-cells in the pancreas and leads to total insulin deficiency. Type II diabetes occurs when the body has diminished sensitivity to peripheral insulin at the receptor level. In contrast to Type I diabetes, insulin resistance characterizes Type II diabetes. Insulin resistance is the body's inability to respond properly to insulin (White, 2003). Type II diabetes' prevalence is rapidly increasing in the United States due to the increased prevalence of obesity (White, 2003) and leading to numerous health care complications and risks including coronary heart disease, learning and memory deficits, and PD and PDD (Arvanitakis, Wilson, Bienias, & Bennett, 2007; Hu, Jousilahti, Bidel, Antikainen, & Tuomilehto, 2007). Type II diabetes accounts for approximately 90% of all diabetic cases, with higher prevalence in older adults (Arvanitakis et al., 2006).

Insulin Signaling Pathway

To provide increased understanding of insulin's role in the body and its connection to PD, a microscopic analysis is warranted. Insulin receptors are located and expressed in all regions of the brain and act as a model for integral membrane proteins (White, 2003). Domains on each insulin receptor are extracellular and act as indirect activation pathways to control activity of intracellular tyrosine kinase. To control the activity of tyrosine kinase, translation is necessary. In genetics, translation is a process where messenger RNA creates a string of amino acids on a ribosome to act as a template for protein formation. During translation, two corresponding pro-receptors form a dimer, a molecule comprised of two identical and simpler molecules, linked by two disulfide bonds. The disulfide bond is cleaved to create a tetramer of two αβ dimers (White, 2003). The indirect activation pathway and signal transduction within a cell begins when an insulin molecule binds to the extracellular α subunits. This binding activates tyrosine kinase, located on the β subunits inside the lipid bilayer membrane. Tyrosine kinase

activation leads to recruitment and phosphorylation of signaling scaffold proteins known as insulin receptor substrate protein one (IRS-1) or insulin receptor substrate protein two (IRS-2). IRS-1 is responsible for activating peripheral insulin and body growth. IRS-2 plays a role in regulating body weight, glucose homeostasis, female fertility, and brain growth. The tyrosine phosphorylation of IRS-1 or IRS-2 mediates production of most, and potentially all, signals through the insulin pathway (White, 2003).

After IRS-1 or IRS-2 is phosphorylated, it recruits and phosphorylates phosphatidylinsitol (PI) 3-kinase, an effector protein. Effector proteins are molecules that bind to other proteins and alter their functioning (Philpott, McCarthy, Klippel, & Rubin, 1997). Once PI 3-kinase is phosphorylated, it activates protein kinase B, also known as Akt kinase. Following Akt kinase activation, the insulin signaling pathway continues by phosphorylating several additional substrates. Examples of such substrates include BAD that is responsible for cell survival, and GSK3β that controls growth and glycogen synthesis (White, 2003).

Positive insulin consequences in the brain

Researchers believe that through the insulin signaling pathway, insulin promotes neuronal survival. One study showed that Akt kinase plays a role in cerebellar granule neurons survival and protects from fibroblast cell death (Philpott et al., 1997). Also, research found that inhibition of PI 3-kinase does not cause apoptosis, programmed cell death, if cells are supplied with nerve growth factor (Philpott et al., 1997). Furthermore, activated and over-expressed Akt kinase is both necessary and sufficient to activate insulin-like growth factor-1 (IGF-1). IGF-1 can prevent nitric oxide toxicity apoptosis (Matsuzaki et al., 1999) or hypoxia (Yamaguchi et al., 2001) within hippocampal cells.

In addition to protecting against programmed cell death, the insulin signaling pathway acts as a go-between for various mechanisms responsible for learning and memory (Huang et al., 2004). Recent studies have demonstrated that PI 3-kinase and Akt kinase are involved in long-term potentiation (LTP) and long-term depression (LTD). Both LTP and LTD are key steps for specialization of neuronal circuitry and information storage in the brain (van der Heide et al., 2005). LTP is a long-lasting strengthening in a post-synaptic neuron's response resulting from repeated stimulation (van der Heide et al., 2005). LTD is a use-dependent decrease in effectiveness of post-synaptic neurons (Huang et al., 2004). LTP also accounts for many forms of learning and shares features with long-term memory (Lynch, 2004). Nasally administered insulin improves memory in humans (Benedict et al., 2007). More specifically, intranasal insulin showed both acute and long-lasting positive effects on declarative memory (Reger et al., 2006). Also, intracerebroventricular insulin injections were shown to enhance performance on avoidance tasks (Park et al., 1995, as cited in Messier & Teutenberg, 2005). Giving insulin or insulin analogs may reduce cognitive decline resulting from inflammation and oxidative stress, and for this reason may potentially provide clinical benefits for dementia patients (Torres-Aleman, 2007).

Furthermore, the insulin signaling pathway may influence GABA, NMDA, and AMPA neurotransmitter receptors. Along with the PI 3-kinase and Akt kinase pathway, these receptors are associated with synaptic plasticity (Huang et al., 2004; van der Heide et al., 2005). Synaptic plasticity is the continual changing of neuronal pathways in the brain in response to experience or injury. This process is crucial for learning and memory because as new experiences are encountered, certain neuronal pathways are strengthened while others are modified or eliminated (van der Heide et al., 2005). Insulin also has a regulatory role in neuronal excitation and control

over ion channel activity. Insulin can recruit $GABA_A$ receptors to postsynaptic regions and augment NMDA synaptic transmission in hippocampal neurons. Overall, insulin along with dopamine, GABA, NMDA, and AMPA receptors influence synaptic changes and impact learning and memory.

Neurotransmitters' role in learning and memory

In terms of learning and memory processes, activation of D_1 receptors in the nucleus accumbens regulates attainment and performance of instrumental learning (Hernandez et al., 2009). Also, research suggests that this dopamine receptor has more motor performance involvement early in the learning period, but participation decreases once proficiency is achieved (Hernandez et al., 2009). Similar to AMPA and NMDA receptors, D_1 receptors are primarily involved in encoding task-related information rather than memory consolidation. Furthermore, D_1 receptors allow attainment of and action to environmental stimuli as well as the ability to process actions results (Hernandez et al., 2009).

NMDA receptors play a primary role in the learning and memory process of encoding, but little evidence suggests function in memory consolidation and retrieval (Hernandez, Andrezejewski, Sadeghian, Panksepp, & Kelley, 2009; Riedel et al., 2003). Rats born with higher hippocampal NMDA receptor levels show a higher learning capacity (Keller, Borghese, Carrer, & Ramirez, 1992). Evidence demonstrates that blocking NMDA receptors during learning prevents conditioning and results in amnesia. However, NMDA receptor blockage does not consistently result in negative consequences. Older adults may benefit from NMDA receptor blockage because previously learned information is protected from retroactive interference or forgetting (Norris & Foster, 1999). Furthermore, NMDA receptors impact the functions of instrumental learning (Hernandez et al., 2009), spatial learning, fear conditioning, olfactory and

taste memories, and locomotion activities (Riedel et al., 2003). Evidence that AD patients have reduced NMDA and glutamate binding in the hippocampus compared to healthy age-matched controls supports NMDA's role in memory. Synaptic plasticity is thought to be a process that allows the brain to store memories. Evidence exists that NMDA receptors play unique roles in regulating genes required for long-term maintenance of changes in the strength of synaptic connections (Rao & Finkbeiner, 2007) in addition to triggering learning-related plasticity (Zhuo, 2009).

Compared to NMDA receptors, relatively little evidence demonstrates AMPA receptors' function in memory formation (Riedel et al., 2003). A difficulty encountered when attempting to block AMPA receptor sites is one reason for the research gap. Blocking AMPA receptor sites reduces NMDA receptor activation due to reduced postsynaptic depolarization. When AMPA receptors are blocked, neuronal communication and essential learning components are terminated (Riedel et al., 2003). Data suggests that AMPA receptor activation is crucial for memory consolidation and recall (Jerusalinsky, et al, 1992, as cited in Riedel, et al., 2003), but other studies contradict this finding (Hernandez et al., 2009). AMPA receptor activation is necessary for spatial learning. If hippocampal AMPA substrate (GluR2) is lacking, the stability and accuracy of cell firing and spatial learning is compromised (Yan et al., 2002).

While a paucity of data exist to support AMPA's position in the process of learning and memory, some evidence shows learning-induced changes to the receptor (Tocco et al., 1991). Researchers argue that learning results in new AMPA receptor membrane sites within neuronal pathways that increase excitation and increase receptor expression. This was demonstrated through increased AMPA receptor binding in the hippocampus within 48 hours of receiving classical conditioning (Tocco et al., 1991). AMPA receptors also have a distinct role in

controlling short-term changes in synaptic plasticity strength (Rao & Finkbeiner, 2007). Overall, it appears AMPA receptors regulate learning-induced neuronal excitation and strengthen event encoding and memory enhancement (Riedel et al., 2003).

Ideal human brain activity relies on a balance of excitation, largely provided by glutamate receptors, and inhibition, usually resulting from GABA-mediated neurotransmission (Reis et al., 2009). Because GABA balances excitation and inhibition, dysfunction of GABA-related pathways can lead to psychiatric and neurological disorders including PD (Reis et al., 2009). GABA interneurons modify information flow through cortical circuits. If an excess or lack of GABA signaling exists, faulty communication and disturbances in the CNS result. These alterations or disturbances impact learning, memory, and attentional processes (Reis et al., 2009).

$GABA_A$ receptors in the CNS are important for hippocampal long-term potentiation. Evidence demonstrates that both feedforward and feedback hippocampal interneuron circuits limit the response to synaptic pathway activation (Matsuyama et al., 2008). Blocking $GABA_A$ receptors disables these circuits and allows for unchecked neuronal excitation. Researchers concluded that $GABA_A$ receptor blockage contributes to learning and memory processes by improving lost functions in age-related cognitive disorders (Matsuyama et al., 2008). This study suggests that treatment of cognitive disorders like PDD could target $GABA_A$ receptors. Furthermore, $GABA_B$ receptors perform an important role in age-related learning impairment (Lasarge, Banuelos, Mayse, & Bizon, 2009). Treatment with a $GABA_B$ antagonist ameliorated discrimination learning deficits that reliably occur in aged rats. Improvement in learning discrimination was not demonstrated in young rats without learning deficits. These results indicate that $GABA_B$ receptors require an optimal level of signaling in order to show maximal cognitive performance in young and aged rats (Lasarge et al., 2009).

Insulin and Parkinson's disease

Following discussion of how insulin and neurotransmitters are connected to learning and memory, it is necessary to provide description of insulin's relationship to PD. Physiological hormone reserves gradually decline as age increases. Impaired hormonal homeostasis, particularly glucose homeostasis, is one potential cause of hormonal declines (Sandyk, 1993). Damage to glucoregulatory mechanisms are seen through impaired glucose tolerance, insulin resistance, and diabetes mellitus, all common disorders in older adults. Approximately 40-83% of older adults experience glucose intolerance or diabetes (Gasparini et al., 2002; Sandyk, 1993), and over 50% of older adults could have undiagnosed diabetes mellitus. Diagnosing glucose intolerance and diabetes mellitus is challenging because glucose tolerance may not become significant until the age of 70 (Gasparini et al., 2002; Lipman, Boykin, & Flora, 1974). Glucose intolerance is found in various neurological disorders including Huntington's chorea, tardive dyskinesia, and Parkinson's disease. Furthermore, PD patients have higher rates of glucose intolerance compared to healthy older adults (Lipman et al., 1974; Morris, Seim, Bomhoff, Geiger, & Stanford, 2011; Sandyk, 1993), and having diabetes is associated with a 36% increased risk of developing Parkinson's disease (Schernhammer, Hansen, Rugbjerg, Wermuth, & Ritz, 2011).

Despite knowledge of the connections among insulin resistance and Alzheimer's disease (Burns et al., 2007; Gasparini et al., 2002) and stroke (Hu et al., 2007), there is a relative paucity of research establishing the relationship between PD, insulin resistance, and diabetes mellitus. One study demonstrated that diabetes mellitus was associated with parkinsonian symptoms including postural reflex impairments and gait disturbances (Arvanitakis et al., 2007). Diabetic older adults scored 0.20 points higher on a measure of global parkinsonian signs compared to

non-diabetic older adults. This is equivalent to increasing the impact of parkinsonian symptoms by three years. Conversely, tremor, rigidity, and bradykinesia symptoms lacked connections to diabetes mellitus (Arvanitakis et al., 2007). A national survey of older adults found elevated diabetes mellitus prevalence rates in older adults with PD compared to healthy older adults (Pressley et al., 2003). In addition, Type II diabetes strongly correlates with an increased risk of PD. Therefore, researchers propose that Type II diabetes mellitus act as a risk factor for the development of PD (Hu et al., 2007; Sandyk, 1993).

Insulin's relationship to cognitive decline and dementia

Both Type I and Type II diabetes mellitus are associated with deficits to the CNS and impairments in learning and memory. Most studies report that diabetes mellitus negatively impacts cognition and leads to a more rapid decline in cognitive functioning (Arvanitakis et al., 2006; Gregg et al., 2000; Messier & Teutenberg, 2005). While the majority of studies have focused on the connections among diabetes mellitus, cognitive decline, and AD (Arvanitakis et al., 2006; Leibson et al., 1997), as previously stated a lack of research investigating the connection among diabetes mellitus, PD, and PDD exist. The higher dementia rates observed in those with both PD and diabetes mellitus highlight the significance of this research area (Sandyk, 1993).

Diabetes mellitus influences some cognitive abilities over others. Diabetes mellitus related impairments typically involve verbal memory and complex information processing (Awad, Gagnon, & Messier, 2004; Fontbonne, Berr, Ducimetiere, & Alperovitch, 2001; Gasparini et al., 2002). One study reported poorer performance on serial learning tasks in older adults with diabetes mellitus compared to non-diabetic older adults. Ending trials requiring storage and information retrieval presented the greatest difficulty. In addition, diabetic older

adults scored lower on the Benton Visual Retention Test (Mooradian, Perryman, Fitten, Kavonian, & Morley, 1988). Another study found that individuals with diabetes mellitus scored 15-20% lower on memory and attentional tasks compared to individuals without diabetes mellitus (Arvanitakis et al., 2006). Diabetic women reported increased memory problems compared to non-diabetic women. Also, diabetic women showed poorer baseline performances on Digit Symbol, Trails B, and m-MMSE measures (Gregg et al., 2000). One longitudinal study demonstrated a 40% perceptual speed reduction in individuals with diabetes mellitus compared to those without diabetes mellitus. However, no executive dysfunctions or semantic memory declines were presented (Arvanitakis et al., 2004). Furthermore, another longitudinal study showed that individuals with Type II diabetes mellitus had reduced facial recognition, processing speed, and motor function scores (Fontbonne et al., 2001).

Diabetes mellitus might act as a risk factor for dementia (Fontbonne et al., 2001; Gasparini et al., 2002; Leibson et al., 1997) and could increase dementia risk by approximately two-to-threefold (Arvanitakis et al., 2006; Ott et al., 1999). Diabetic individuals using insulin treatments had significantly higher risks for cognitive decline compared to those not using insulin treatments. Also, women with diabetes mellitus for 15 or more years had a 1.4 to 3.2-fold increase in cognitive impairments at baseline and a 1.6 to 2.1-fold increased risk of cognitive decline compared to non-diabetics (Gregg et al., 2000). These data indicate that patients with severe diabetes mellitus or longer disease durations are at greater risk for cognitive dysfunctions (Gregg et al., 2000; Ott et al., 1999).

This study examined insulin's relationship with cognitive functioning in PD, PDD, and age-matched controls. We hypothesized that (1) the PDD group would have lower absolute insulin, as defined by insulin area under the curve (AUC) for a two-hour glucose tolerance test,

compared to PD and control groups; (2) Lower insulin levels would significantly correlate with decreased motor performance, as defined by the Unified Parkinson's Disease Rating Scale (UPDRS) motor score; (3) Lower insulin levels would predict poorer performance on executive functioning, memory, visuospatial, and language tasks. This research enhances literature on the impact of insulin on cognitive performance in PD and PDD.

Methods

Participants

Eligible participants were ages 55 to 85 with a diagnosis of PD based on the United Kingdom Parkinson's Disease Society brain bank diagnostic criteria. These criteria require bradykinesia and at least one of the following: muscular rigidity; four to six Hertz resting tremor; or postular rigidity not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction. Diagnostic criteria for PDD participants stemmed from recommendations from the Movement Disorder Society Task Force for level I testing (Dubois et al., 2007). These criteria require: a PD diagnosis as described above; PD motor symptoms that developed prior to the onset of dementia; decreased global cognitive functioning defined by a score of 25 or below on the Mini Mental Status Examination (MMSE); cognitive deficits severe enough to impair daily life; impairment in more than one cognitive domain including executive function, memory, visuoconstructive ability, and attention.

The study sample included 22 older adult participants with PD: 12 participants with PD and 10 participants with PDD. The University of Kansas Parkinson's Disease and Movement Disorder Center collected basic demographic information, history of onset and symptoms of PD, current medications, type of assistive devices used, and living arrangements for all participants. The KU Parkinson's Disease and Movement Disorder Center evaluated individuals using the

Unified Parkinson's Disease Rating Scale (UPDRS), Mini Mental Status Examination (MMSE), and additional assessments as part of another study protocol. MMSE scores in addition to the criteria described above determined dementia status. The PD group consisted of individuals with MMSE scores above 25, and the PDD group consisted of individuals with MMSE scores of 25 or below.

Non-demented older adults from the University of Kansas Brain Aging Project served as the control group. Participant recruitment was conducted from the KUMC Brain Aging Project using an established patient registry (Burns et al., 2007). These individuals were evaluated with neuroimaging and insulin measures including intravenous glucose tolerance testing procedures similar to those the PD and PDD groups completed. Dementia status was determined using the Clinical Dementia Rating (CDR) scale that assessed cognitive function across multiple domains (Morris, 1993). A global CDR score was based on ratings from each domain, with a CDR score of 0 indicating no dementia. Control group participants received a neurological evaluation to assess for abnormalities in visual fields, cranial nerves, motor strength, sensation, reflexes, plantar responses, coordination, praxis, and gait. The control group consisted of 22 participants matched on age and gender to PD and PDD participants.

Neuropsychological Measures

The neuropsychological assessment battery examined executive functioning, memory, working memory, visuospatial ability, language, and simple motor speed. These widely used measures represented the cognitive domains of interest for PD and PDD participants. The current battery contained tests recommended by the Clinical Task Force of the Alzheimer Disease Centers (Weintraub et al., 2009) as well as several well-known tests sensitive to visuospatial deficits occurring in PD. Many measures were gathered from the Wechsler Adult Intelligence

Scale III (WAIS-III), Wechsler Adult Intelligence Scale IV (WAIS-IV), and the Wechsler Memory Scale - Revised (WMS-R). These measures were selected because they did not demonstrate floor or ceiling effects and showed sensitivity to change over two years in a trial of mild cognitive impairment in AD.

Mini Mental State Examination (MMSE). This screening scale consisted of 30 items that evaluated participants' orientation to place and time, registration, attention and concentration, recall, language, and visual construction. Lower MMSE scores indicated poorer performance and greater cognitive impairment (Folstein, Folstein, & McHugh, 1975).

Logical Memory I and II. Logical Memory I examined memory and assessed recall of a short story. Logical Memory II investigated delayed recall of episodic memory (Groth-Marnat, 2003). Participants were read a short story and immediately asked to retell the story from memory. After a period of at least 20 minutes, but no more than 30 minutes from the initial reading, participants were asked to recall as much of the story as they could remember. Total scores for both immediate and delayed measures were calculated based on the total number of accurately recalled story segments.

Digit Span (Forwards and Backwards). Digit Span Forward evaluated rote learning and memory, attention, and auditory processing. Digit Span Backward examined working memory, mental manipulation, and visuospatial imaging. Shifting from one Digit Span task to another required cognitive flexibility and mental alertness (Groth-Marnat, 2003; Reynolds, 1997). In Digit Span Forward, participants were read a sequence of numbers and asked to recall the numbers in the same order as presented. In Digit Span Backward, participants were read other number sequences and asked to recall the number sequences in reverse order. Both tasks contained 12 items with two trials of the same number span length. Digit Span Forwards and

Digit Span Backwards total scores were calculated based on the number of correctly recalled sequences.

Category Fluency. Category Fluency examined semantic memory, executive functioning, verbal fluency, and language (Weintraub et al., 2009). In this task, participants were given a semantic category (e.g., animals and vegetables) and instructed to provide different examples of the category as quickly as possible. Each trial was one minute in duration. Scores were calculated based on the total number of correct category examples within the time limit.

Trail Making Test. Trail Making Test evaluated executive functioning and processing speed. Part A required visuomotor and perceptual-scanning skills, while Part B required visuomotor and perceptual-scanning skills in addition to cognitive flexibility to complete the task within a specified time limit (Weintraub et al., 2009). Part A consisted of 25 circles numbered 1 through 25 scattered across a sheet of paper. Participants were instructed to connect the circles in ascending numerical order by drawing a line as quickly as possible without making mistakes. Part B consisted of 25 circles containing either numbers (1 through 13) or letters (A through L). Participants were instructed to connect the circles in ascending order alternating between numbers and letters (i.e., A to 1; 1 to B; B to 2; 2 to C). Total completion time and the number of errors were recorded.

Digit Symbol. This task investigated cognitive flexibility, attention, concentration, motivation, processing speed, psychomotor speed, short-term visual memory, learning ability, and visual-motor coordination (Groth-Marnat, 2003). Participants were shown boxes where each number was associated with a unique symbol. Participants were instructed to quickly copy the symbols associated with each number while going in order across the sheet. Total score was based on the number of symbols correctly paired with each number within a specific time limit.

Boston Naming Test. This measure examined language and was sensitive to aphasia and object recognition deficits (Mack, Freed, Williams, & Henderson, 1992; Weintraub et al., 2009). Participants were shown pictures of items in order of recognition frequency, from most frequent (e.g., house) to least frequent (e.g., palette) and asked to name each pictured item. Participants were administered the Boston Naming short form containing 15 pictured items.

Block Design. This measure investigated the ability to analyze and synthesize abstract visual stimuli. Successful completion involved nonverbal concept formation and reasoning, simultaneous processing, visuospatial ability, and learning (Carroll, 1993; Groth-Marnat, 2003). Participants were shown pictures and asked to recreate presented designs using red- and white-sided blocks. Total score was based on the number of correctly assembled designs within a time limit.

Stroop Color-Word Test. The Stroop Color-Word Test evaluated executive functioning, cognitive flexibility, ability to suppress a habitual response in favor of an unusual one, and selective attention (Fisher, Freed, & Corkin, 1990). This task had three subtests, each with a unique stimulus card. In the first subtest, participants were presented a stimulus card and instructed to name the colors of each box (e.g., red, green, or blue). In the second subtest, participants were presented with a stimulus card and asked to read the names of colors (e.g., red, green, or blue) appearing in black ink. In the third subtest, participants were shown a stimulus card, the interference card, where color words were printed in non-corresponding color inks (e.g., the word “red” printed in blue ink). Participants were instructed to ignore the printed words and report only the color of ink for each printed word. Each subtest was 45 seconds. Total scores were based on the number of correct responses within the time allowed minus response errors.

Free and Cued Selective Reminding Test (SRT). SRT investigated memory, learning, self-organized retrieval, encoding, and retention (Grober, Ocepek-Welikson, & Teresi, 2009). This task consisted of 16 pictures from unique categories. Participants were shown a set of four pictures and instructed to identify and name each picture when its category cue was presented (i.e., "What is the Animal?"…"An Elephant"). Once all 16 pictures and category cues were presented, participants were instructed to count down from 98 for a total of 20 seconds to prevent picture rehearsal. Following the interference, memory of pictures was tested by free recall. If any items were not retrieved by free recall, the same category cues for those items were provided to test cued recall. If participants were unable to recall cued items, they were immediately reminded of that item (selective reminding). There were three trials of free and cued recall, each trail preceded by 20 seconds of interference. Total score was calculated based on the number of retrieved items during free recall and the number of recalled cued items.

Letter-Number Sequencing. Letter-Number Sequencing examined working memory, sequential processing, mental manipulation, attention, concentration, cognitive flexibility, and short-term auditory memory (Groth-Marnat, 2003). Participants were read number and letter sequences and asked to recall the numbers in ascending order and the letters in alphabetical order. Sequences ranged from two to eight letter and number combinations with three trials for each sequence length. Total score was based on the number of correct sequences.

Visual Puzzles. Visual Puzzles investigated nonverbal reasoning and the ability to analyze and synthesize abstract visual stimuli. This test also examined simultaneous processing, spatial visualization and manipulation, and the ability to anticipate relationships among parts (Carroll, 1993; Groth-Marnat, 2003). Participants were shown a puzzle constructed from three shapes and instructed to select three response options that reconstructed the puzzle when

combined. Total score was determined based on the number of correct combinations chosen within a specified time limit.

Matrix Reasoning. Matrix Reasoning measured classification and spatial ability, broad visual intelligence, simultaneous processing, and knowledge of part-whole relationships (Groth-Marnat, 2003). Participants were shown an incomplete series or matrix and instructed to select a picture response option that completes each series or matrix. Total score was based upon the number of correctly selected pictures.

Geriatric Executive Interview (EXIT). This interview contained a variety of items designed to detect deficits in executive functioning including frontal release signs (e.g., grasp reflex), motor or cognitive perseveration (e.g., echopraxia), verbal intrusions, imitation behavior, loss of spontaneity (e.g., word fluency), and environmental dependence (Juby, Tench, & Baker, 2002). This 25-item face-to-face interview took approximately 15-20 minutes to administer. Total score was determined by participant responses, where correct answers received fewer points. Higher total scores indicated poor performance and greater cognitive impairment in executive functioning.

Crossing-Off. Crossing-Off evaluated simple motor speed. This task contained 96 horizontal lines on one sheet of paper. Participants were instructed to place vertical line marks on top of each horizontal line as quickly as possible without making mistakes. Total score was based upon the number of correct marks completed within one minute.

Procedure

Investigators contacted initially eligible individuals for this study, in addition to collateral sources of those with PDD, by phone and provided a brief description of the study. Individuals were asked questions regarding medical history to verify any existing exclusion criteria including

concurrent diagnosis of AD, Type I, or Type II diabetes mellitus. Investigators mailed additional study information including consent forms, directions to each study site, parking passes, and the investigators' contact information to individuals interested in participation.

All participants were consented by an investigator. Each participant was asked to bring a collateral source to the initial visit. Investigators reviewed consent forms describing the study background and purpose, procedures, and potential benefits and risks to participants. The University of Kansas Medical Center Institutional Review Board (IRB) approved all procedures and consent forms. Participant questions and any areas of concern were addressed. After consent forms were signed, participants in both groups underwent a neuropsychological assessment as described below. Investigators scheduled participants for glucose tolerance testing following the initial meeting.

Neuropsychological Assessment. This visit took place at the University of Kansas Alzheimer's and Memory Program and lasted approximately 1.5 to 2 hours. Participants completed paper and pencil tests of memory and general cognitive functioning administered by one trained psychometrician. Cognitive testing was administered one-on-one to both PD and PDD participants. Investigators minimized potential distractions to the testing process. Participants in the control group were tested previously and not evaluated using Visual Puzzles, Matrix Reasoning, EXIT, and Crossing-Off tasks.

Glucose Tolerance Testing. This visit took place at the General Clinical Research Center at the University of Kansas Medical Center and lasted approximately 2 to 2.5 hours. Methods used during this portion of the study were similar to the KU Brain Aging Project (Burns et al., 2007). Nursing staff performed a 13-sample intravenous glucose tolerance test (IVGTT) at 8:00

am after participants completed a 12-hour overnight fast of food and drink. Investigators encouraged participants to drink water before this visit but abstain from morning medications.

Nursing staff placed a small, temporary catheter into a vein in the participant's desired arm that was used for administering glucose and drawing blood samples. An IV glucose bolus of 0.3 g/kg of body weight (approximately 20 grams) was delivered at Time 0. Nursing staff collected 13 blood samples at -5, 1, 3, 5, 10, 15, 20, 30, 40, 50, 60, 90, and 120 minutes after administration of the glucose bolus. Blood samples were used to determine glucose and insulin levels. A total of approximately 100 cc of blood was sampled from each participant. When the IVGTT was complete, participants were able to take personal medications and were provided with a light breakfast as well as a meal voucher for lunch at the KU Medical Center cafeteria. Blood samples were sent to Denver, Colorado for insulin analysis. The 2006 American Diabetic Association criteria was used to classify participants as having impaired fasting glucose (fasting glucose > 100 mg/dL) or impaired glucose tolerance (2-hour postload glucose level of 140 to 199 mg/dL).

Data Analysis

Analyses were conducted using PASW Statistics 18.0. Important covariates of age and gender were controlled for on all statistical tests. Covariates are variables that may have an influence on the criterion variables; however, the effects are not of interest (Witte & Witte, 2007).

Student's *t* test was used to make comparisons between the means of the PD, PDD, and healthy ND control groups on demographic and clinical information. Pearson correlations were used to assess relationships between cognitive measures of executive functioning, visuospatial ability, memory, language, attention, learning, and problem solving for the PD and PDD groups.

Total area under the curve (AUC) for blood concentration over time for both glucose and insulin served as overall indices for glucose and insulin levels. This measurement is commonly used in diabetes research to evaluate how insulin secretion is impacted following administration of glucose (Allison, Paultre, Maggio, Mezzitis, & Pi-Sunyer, 1995; Walker, 1994; Tai, 1994). Rather than investigating the body's insulin response to glucose at a single time point, the AUC value is an integrated assessment that evaluates response over a specific amount of time. A single insulin measurement is not an accurate depiction of how insulin levels increase after a glucose load. Additionally, examining only the peak level of insulin is an inaccurate evaluation because insulin secretion might be rapid at first in response to administered glucose, and then might decrease quickly. Therefore, an integrated representation of insulin levels over time using the AUC may provide the most accurate assessment of how insulin levels respond to administered glucose (Walker, 1994).

When evaluating insulin, a larger AUC value is ideal. A larger insulin AUC value would indicate the body is properly responding to an increased amount of administered glucose (Allison et al., 1995; Norman, 2009). In diabetes mellitus, the body cannot produce enough insulin or properly use insulin to control for the increased glucose following consumption of food or during a glucose tolerance test (Norman, 2009; White, 2003).

Secondary measures included fasting baseline, 30-minute, 1-hour, and 2-hour post-load insulin and glucose levels. This study aimed to examine differences in insulin AUC across the three study groups. Differences among group means were evaluated using analysis of variance (ANOVA). Correlations between insulin measures and neuropsychological measures as well as correlations between insulin measures and motor performance were determined.

Linear regression analysis describes how the value of a criterion variable changes when any one of the predictor variables is varied (Witte & Witte, 2007). Linear regression was used to examine the presence of any group x metabolic variable interactions in predicting overall cognitive performance and performance on executive functioning, visuospatial ability, memory, language, attention, learning, and problem solving tasks. Analyses were conducted within diagnostic groups (ND control, PD, and PDD) separately as opposed to all participants combined.

Because of the relatively small sample sizes due to the rarity of the well characterized PD and PDD samples, all tests were conducted using bootstrap confidence interval estimation. Participants in this study were older and had Parkinson's disease or Parkinson's disease dementia. Traditional statistics that uphold certain assumptions such as a normal distribution, equal variances among samples, and large sample sizes (Sahiner, Chan, Hadjiiski, 2008) may not accurately portray results for means and correlations in neuropsychological test performance, the differences between groups on insulin AUC, and the presence of group x metabolic variable interactions. Bootstrapping is a method for gaining a true estimation of performance when a sample does not follow traditional statistical assumptions.

In bootstrapped estimation, a subset of sample observations are randomly selected with replacement until the number of re-sampling observations equals the number of observations in the original sample (Daw et al., 2001). This re-sampling process is repeated a large number of times, and test statistics such as mean, standard deviation, and confidence intervals are calculated for each repetition. This information is used to more accurately estimate the characteristics of the original sample, and can be used to determine bias that may be inherent in the sample (Daw et al., 2001).

In this study, the bootstrapped values were compared to the *t*-test, ANOVA, and linear regression values calculated directly from the data in order to evaluate the amount of bias present in the original statistical procedures (e.g., non-normal distribution, unequal variance, and small sample size).

Results

A total of 22 older adult participants with PD completed the present study: 12 participants with PD and 10 participants with PDD. The groups differed significantly on all demographic variables with the PDD participants being older on average, having lower average MMSE scores representing greater cognitive impairment, and higher average UPDRS motor scores representing greater motor impairment.

Twenty-two non-demented (ND) older adults from the University of Kansas Brain Aging Project (Burns et al., 2007) served as the control group. Control participants were chosen for the present study to match on demographic information including age, gender, and MMSE scores. Demographic information for participants in the ND control, PD, and PDD groups are shown in Table 1. The ND control participants did not differ from the PD and PDD group participants with respect to gender. However, the control group differed significantly with respect to age compared to the PD group and differed significantly from the PDD group with respect to MMSE scores. The significant difference in MMSE scores between the ND control group and the PDD group is expected, as this score is representative of cognitive decline inherent in participants with PDD.

Table 1
Demographic information for participants in the ND, PD, and PDD groups

	ND Participants (N = 22)		*t* (df = 20)	PD Participants (N = 12)		*t* (df = 20)	PDD Participants (N = 10)	
	M	*SD*		*M*	*SD*		*M*	*SD*
Gender (M/F)	14/8			5/7			9/1	
Age	71.77	6.22	**– 2.14***	67.50	4.01	**– 3.99****	75.10	4.93
MMSE	29.23	1.69	– 0.92	28.67	1.72	**6.04****	22.90	2.73
UPDRS	-	-	-	19.58	7.09	**– 4.59****	32.40	5.74

*. Significant at the 0.05 level (2-tailed).
**. Significant at the 0.01 level (2-tailed).
Note. UPDRS not calculated for the non-demented participants

Neuropsychological measures

Participants in the ND control, PD, and PDD groups completed a 1.5 to 2 hour neuropsychological battery. The battery was consistent across the three groups with the addition of Visual Puzzles, Matrix Reasoning, Geriatric Executive Interview (EXIT), and Crossing-Off for the PD and PDD groups only. Each participant in the PD group was able to complete all tests; however, some individuals in the PDD group were unable to complete tests (e.g., Trails B, Digit Symbol, Block Design, Stroop Color-Word, SRT, Visual Puzzles, Matrix Reasoning) due to difficulties comprehending instructions. Participants unable to complete tests received a score of zero on those tests, with the exception of Trails B where the maximum value of 300 seconds was assigned.

To assess the relationship among task performance on cognitive measures for the ND, PD, and PDD groups, bivariate correlations were computed separately for each group. For the

PD group, performance was significantly related on tests evaluating memory, working memory, executive functioning, visuospatial ability, language, and processing speed. Simple motor speed (Crossing Off) was not significantly related to other neuropsychological measures. Table 2 shows the intercorrelation matrix for the PD group. For the PDD group, performances were significantly related on tests evaluating memory, working memory, executive functioning, visuospatial ability, processing speed, and simple motor speed. Language performance (Boston Naming Test – Short Form) was not significantly related to other neuropsychological measures in this group. The intercorrelation matrix for the PDD group is shown in Table 3. Simple independent *t* tests were used to compare the means for the PD and PDD groups on each neuropsychological measure and results are presented in Table 4.

Table 2: *Correlation matrix for neuropsychological measures in PD group.*

	LM-I	LM-II	SRT T1-FR	SRT T1-CR	SRT T2-FR	SRT T2-CR	SRT T3-FR	SRT T3-CR	DSF	DSB	LNS	CFAn	DFVeg	Trail A	Trail B	Str-Col	Str-W	Str-It	EXIT	BD	VP	MR	BN	Dig Sym	CO
Memory																									
Logical Mem I	1.00																								
Logical Mem II	0.85**	1.00																							
SRT																									
T1-FR	−.05	−.26	1.00																						
T1-CR	0.11	0.32	−0.99**	1.00																					
T2-FR	0.42	0.20	0.56	−0.56	1.00																				
T2-CR	−0.42	−0.20	−0.56	0.56	−1.00**	1.00																			
T3-FR	0.52	0.27	0.29	−0.30	0.30	−0.30	1.00																		
T3-CR	−0.52	−0.27	−0.29	0.30	−0.30	0.30	−1.00**	1.00																	
Working Memory																									
Digit Span F	−.047	−.160	0.06	−0.06	0.03	−0.03	−0.24	0.24	1.00																
Digit Span B	−.154	−.342	0.29	−0.31	0.21	−0.21	−0.22	0.22	0.70*	1.00															
Letter-Number Seq	0.37	0.20	0.47	−0.48	0.61*	−0.61*	0.52	−0.52	0.19	0.29	1.00														
Exec. Functioning																									
Category Flu Ani	0.68*	0.47	0.34	0.23	0.35	−0.35	0.31	−0.31	0.07	−0.07	0.48	1.00													
Category Flu Veg	0.31	0.30	0.26	−0.27	0.49	−0.49	0.29	−0.29	0.24	0.41	0.62*	0.09	1.00												
Trails A	−0.25	0.17	−0.74**	0.72**	−0.67*	0.67*	−0.43	0.43	−0.05	−0.22	−0.43	−0.47	−0.20	1.00											
Trails B	−0.26	0.08	−0.33	0.38	−0.26	0.26	−0.73**	0.73**	−0.06	−0.38	−0.50	−0.03	−0.39	0.50	1.00										
Stroop (# correct)																									
Color	0.15	0.18	0.16	−0.12	−0.02	0.02	0.08	−0.08	0.10	0.15	0.12	0.21	0.29	−0.35	−0.26	1.00									
Word	0.53	0.58*	−0.10	0.17	0.18	−0.18	−0.2	0.02	0.35	0.29	0.34	0.46	0.42	−0.11	−0.09	0.70*	1.00								
Interference	0.40	0.23	0.04	−0.06	0.27	−0.27	0.74**	−0.74**	0.11	0.08	0.61*	0.15	0.36	−0.34	−0.73**	0.36	0.40	1.00							
EXIT-25	−0.15	−.131	0.21	−0.17	−0.07	0.07	−0.27	0.27	−0.35	−0.39	−0.63*	0.05	−0.59*	−0.08	0.49	−0.27	−0.49	−0.71**	1.00						
Visuospatial																									
Block Design	0.26	−0.09	0.60*	−0.58*	0.26	−0.26	0.64*	−0.64*	0.15	−0.05	0.28	0.45	−0.12	−0.62*	−0.43	−0.06	−0.24	0.30	0.22	1.00					
Visual Puzzles	0.27	0.06	0.39	−0.40	0.37	−0.37	0.61*	−0.61*	−0.26	−0.22	0.58*	0.37	0.38	−0.61*	−0.48	0.34	0.04	0.48	−0.29	0.37	1.00				
Matrix Reasoning	0.33	0.15	0.60*	−0.59*	0.58*	−0.58*	0.15	−0.15	0.04	0.46	0.38	0.28	0.63*	−0.50	−0.38	0.19	0.17	−0.08	0.02	0.14	0.31	1.00			
Language																									
Boston Naming	0.42	0.34	0.30	−0.17	0.11	−0.11	0.01	−0.01	0.06	−0.06	0.05	0.80**	−0.04	−0.31	0.26	0.30	0.42	−0.19	0.36	0.27	0.00	0.20	1.00		
Processing Speed																									
Digit Symbol	0.47	0.21	0.31	−0.31	0.44	−0.44	0.48	−0.48	−0.11	0.03	0.30	0.35	−0.11	−0.64*	−0.54	0.35	0.24	0.56	−0.03	0.51	0.39	0.18	0.66*	1.00	
Simple Motor Speed																									
Crossing-Off	−0.25	−0.52	0.34	−0.35	0.13	−0.13	−0.30	0.30	0.35	0.31	0.06	0.18	−0.28	−0.45	−0.00	−0.03	−0.19	−0.23	0.18	0.32	0.20	0.17	−0.02	0.26	1.00

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

*. Correlation is significant at the 0.05 level (2-tailed).

Table 3: *Correlation matrix for neuropsychological measures in PDD group.*

	LM-I	LM-II	SRT T1-FR	SRT T1-CR	SRT T2-FR	SRT T2-CR	SRT T3-FR	SRT T3-CR	DSF	DSB	LNS	CFAn	DFVeg	Trail A	Trail B	Str-Col	Str-W	Str-It	EXIT	BD	VP	MR	BN	Dig Sym	CO
Memory																									
Logical Mem I	1.00																								
Logical Mem II	0.61	1.00																							
SRT																									
T1-FR	−0.01	0.04	1.00																						
T1-CR	0.54	0.62	0.20	1.00																					
T2-FR	0.13	0.27	0.94**	0.34	1.00																				
T2-CR	0.47	0.48	0.27	0.97**	0.35	1.00																			
T3-FR	0.09	0.53	0.79**	0.49	0.86**	0.49	1.00																		
T3-CR	0.54	0.24	0.26	0.85**	0.33	0.89**	0.24	1.00																	
Working Memory																									
Digit Span F	0.31	0.16	0.55	0.25	0.50	0.29	0.28	0.45	1.00																
Digit Span B	0.67*	0.57	0.06	0.70*	0.15	0.65*	0.30	0.53	−0.02	1.00															
Letter-Number Seq	0.08	0.39	0.58	0.33	0.62	0.34	−0.75*	0.11	0.20	0.29	1.00														
Exec. Functioning																									
Category Flu Ani	0.38	0.27	0.61	0.65*	0.61	0.70*	0.53	0.71*	0.51	0.69*	0.42	1.00													
Category Flu Veg	0.32	0.13	0.85**	0.44	0.82**	0.46	0.64*	0.54	0.60	0.19	0.36	0.59	1.00												
Trails A	−0.39	−0.44	−0.80**	−0.29	−0.86**	−0.27	−0.73*	−0.26	−0.65*	−0.29	−0.71*	−0.62	−0.70*	1.00											
Trails B	0.26	−0.27	−0.56	−0.14	−0.61	−0.18	−0.71*	0.04	−0.20	−0.04	−0.84**	−0.36	−0.16	0.60	1.00										
Stroop (# correct)																									
Color	0.04	0.07	0.76*	0.30	0.77**	0.35	0.59	0.39	0.42	0.38	0.59	0.83**	0.55	−0.73*	−0.65*	1.00									
Word	0.43	0.52	0.60	0.65*	0.58	0.69*	0.72*	0.53	0.60	0.36	0.43	0.56	0.71*	−0.58	−0.26	0.27	1.00								
Interference	0.32	0.14	0.69*	0.51	0.70*	0.54	0.51	0.62	0.48	0.56	0.57	0.91**	0.64*	−0.73*	−0.45	0.93**	0.38	1.00							
EXIT-25	−0.28	−0.05	−0.83**	−0.47	−0.81**	−0.50	−0.57	−0.62	−0.55	−0.38	−0.45	−0.82**	−0.87**	0.74*	0.33	−0.84**	−0.50	−0.93**	1.00						
Visuospatial																									
Block Design	0.11	0.48	0.70*	0.34	0.78**	0.33	0.78**	0.22	0.63	0.08	0.79**	0.49	0.50	−0.86**	−0.83**	0.64*	0.58	0.56	−0.54	1.00					
Visual Puzzles	0.15	0.54	0.79**	0.51	0.86**	0.52	0.94**	0.33	0.49	0.32	0.82**	0.66*	0.60	−0.84**	−0.82**	0.72*	0.71*	0.65*	−0.64*	0.92**	1.00				
Matrix Reasoning	0.22	0.64*	0.42	0.69*	0.55	0.65*	0.72*	0.45	0.44	0.29	0.77**	0.46	0.40	−0.60	−0.68*	0.42	0.64*	0.47	−0.42	0.84**	0.82**	1.00			
Language																									
Boston Naming	0.46	0.29	0.36	0.42	0.42	0.41	0.37	0.42	0.05	0.58	−0.14	0.54	0.53	−0.26	0.22	0.30	0.42	0.36	−0.44	−0.06	0.23	−0.10	1.00		
Processing Speed																									
Digit Symbol	0.01	−0.02	0.23	0.50	0.24	0.53	0.19	0.57	0.04	0.49	−0.17	0.67*	0.31	0.02	0.07	0.49	0.15	0.50	−0.47	−0.10	0.15	−0.01	0.66*	1.00	
Simple Motor Speed																									
Crossing-Off	0.24	0.51	0.68*	0.28	0.73*	0.28	0.76*	0.15	0.58	−0.03	0.39	0.27	0.65*	−0.69*	−0.39	0.24	0.80**	0.18	−0.35	0.71*	0.73*	0.53	0.33	−0.11	1.00

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

*. Correlation is significant at the 0.05 level (2-tailed).

Table 4
Comparison of means of neuropsychological measures for ND, PD, and PDD groups

	Non-Demented (N = 22)		*t*	PD Participants (N = 12)		*t*	PDD Participants (N = 10)	
	M	*SD*	ND vs PD	*M*	*SD*	PD vs PDD	*M*	*SD*
Memory								
Logical Mem I	14.64	4.22	– 1.24	12.75	4.33	4.67**	4.50	3.87
Logical Mem II	13.82	4.07	– 1.57	11.50	4.19	4.85**	3.60	3.27
SRT								
T1-FR	8.95	1.91	.06	9.00	2.09	5.28**	3.70	2.63
T1-CR	7.05	1.91	– .18	6.92	2.02	– 1.36	9.20	4.98
T2-FR	10.77	2.05	– .65	10.42	1.17	6.21**	4.90	2.60
T2-CR	5.23	2.05	.65	5.58	1.17	– 1.24*	8.30	4.32
T3-FR	10.50	2.76	.63	11.08	2.28	4.53**	5.50	3.47
T3-CR	5.05	2.01	– .17	4.92	2.28	– 2.16*	7.80	3.91
Working Memory								
Digit Span F	8.77	2.22	– .45	8.42	2.11	1.92	6.90	1.45
Digit Span B	5.77	2.16	– .15	5.67	1.78	1.53	4.40	2.12
Letter-Number Seq	9.55	3.04	– .31	9.25	1.77	4.76**	4.50	2.88
Executive Functioning								
Category Flu Ani	20.36	5.15	1.12	22.50	5.68	4.54**	12.20	4.80
Category Flu Veg	14.45	3.69	– .03	14.42	4.60	4.33**	7.10	2.96
Trails A	30.23	9.27	– .75	27.92	7.17	– 4.66**	96.10	45.84
Errors A	.05	.21	.89	.17	.58	– 1.89	.80	.92
Trails B	83.36	29.34	– .39	79.25	28.60	– 6.22**	240.60	77.77
Errors B	.64	.90	– .41	.50	1.00	– 1.46	1.50	1.96
Stroop (# correct)								
Color	72.48	9.72	– .33	71.08	14.81	4.27**	37.90	21.55
Word	94.36	13.03	– .62	91.42	13.73	3.97**	58.80	24.29
Interference	37.57	8.25	.38	38.67	7.23	6.83**	13.80	9.84
EXIT-25	--	--	--	3.42	1.24	– 5.69**	13.30	5.38
Visuospatial								
Block Design	36.24	13.04	– 1.07	31.67	9.09	2.99*	16.90	13.99
Visual Puzzles	--	--	--	13.08	3.70	3.59*	6.80	4.52
Matrix Reasoning	--	--	--	13.42	3.87	3.84**	6.50	4.58
Language								
Boston Naming	14.52	.68	1.39	14.83	.58	3.38*	13.00	1.63
Processing Speed								
Digit Symbol	50.55	8.11	– 25.29**	4.08	.97	3.37*	1.90	1.97
Simple Motor Speed								
Crossing-Off	--	--	--	90.42	11.99	2.83*	61.50	30.46

*. Independent *t* test is significant at the 0.05 level (2-tailed).
**. Independent *t* test is significant at the 0.01 level (2-tailed).
Note. Visual Puzzles, Matrix Reasoning, EXIT, and Crossing-Off not calculated for the non-demented participants

Insulin

Total area under the curve (AUC) for blood glucose and insulin concentration over time served as overall indices for glucose and insulin levels. The AUC values were calculated based on the 120-minute glucose tolerance test. Simple independent *t* tests were used to compare the average insulin AUC for the PD group and PDD groups. The average insulin AUC for the PD group ($M = 4682.40$) did not significantly differ from the PDD group ($M = 4301.15$, $t = .45$, $p = .66$). However, the average insulin AUC for the PD group significantly differed from the average insulin AUC for the ND control group ($M = 3126.30$, $t = -2.53$, $p = .016$). The average insulin AUC for the PDD group did not differ significantly from the ND control group ($M = 4301.15$, $t = 1.81$, $p = .08$). Insulin AUC values were not significantly related to age, MMSE scores, or UPDRS motor scores for all three groups. Correlations between insulin AUC values and demographic information for the three groups are shown in Table 5.

Table 5
Correlations between demographic information and insulin AUC

	Insulin AUC					
	Non-Demented		PD Participants		PDD Participants	
	R	*p*	*R*	*p*	*R*	*p*
Age	– .141	.532	.097	.765	.200	.579
MMSE	– .079	.725	– .224	.483	.149	.681
UPDRS	--	--	– .369	.238	– .446	.196

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

One-way between subjects analysis of variance (ANOVA) was used to compare the means of the ND control, PD, and PDD groups on insulin levels at each of the 13 time points of the glucose tolerance test. The mean insulin levels at each time point of the glucose tolerance test are shown in Table 6. The three groups differed significantly on baseline insulin levels (i.e., -5 minute time point), $F(2,41) = 5.25$, $p = .009$. Bonferroni post hoc procedure was used because it is a conservative approach that reduces the opportunity for Type I errors. Post hoc analysis indicated that participants in the PD group ($M = 15.83$, $SD = 4.13$, $p = .03$) and the PDD group ($M = 15.80$, $SD = 7.05$, $p = .04$) had significantly higher baseline insulin levels compared to participants in the ND control group ($M = 10.95$, $SD = 4.26$). Baseline insulin levels did not significantly differ between the PD and PDD groups. Figure 1 illustrates the means for the baseline insulin levels for the three groups. The three groups also differed significantly on insulin levels at the one-minute time point, [$F(2,41) = 4.73$, $p = .014$], the 30-minute time point, [$F(2,41) = 5.69$, $p = .007$], the 40-minute time point, [$F(2,41) = 6.62$, $p = .003$], the 50-minute time point, [$F(2,41) = 3.92$, $p = .028$], the 90-minute time point, [$F(2,41) = 3.75$, $p = .032$], and the 120-minute time point, [$F(2,41) = 3.45$, $p = .041$]. The PD group had the highest insulin value at 120 minutes ($M = 18.30$). The three groups differed significantly on the insulin AUC value, $F(2,41) = 3.46$, $p = .041$. Figure 2 illustrates the insulin AUC for the three groups at the 120-minute time point.

Table 6
Mean insulin levels at each time point of glucose tolerance test

	Insulin					
	Non-Demented		PD Participants		PDD Participants	
	M	*SD*	*M*	*SD*	*M*	*SD*
Time points						
- 5 minute (baseline)	10.95	4.26	15.84	4.13	15.80	7.05
1 minute	44.59	47.37	80.17	52.79	24.30	10.32
3 minute	109.86	83.32	143.75	89.54	105.00	45.92
5 minute	100.23	67.18	114.33	74.73	89.80	44.81
10 minute	53.45	37.37	59.08	36.25	63.30	25.56
15 minute	37.18	22.83	53.17	30.41	53.70	23.23
20 minute	31.73	18.09	47.54	25.97	46.00	22.58
30 minute	25.91	13.38	44.00	19.74	40.70	18.49
40 minute	23.05	11.52	42.58	22.07	39.70	19.19
50 minute	23.14	13.76	38.75	18.90	34.80	19.77
60 minute	21.86	13.93	36.33	19.31	32.50	22.10
90 minute	15.14	6.97	23.83	11.87	24.20	15.47
120 minute	12.00	5.82	16.92	6.08	18.30	10.29

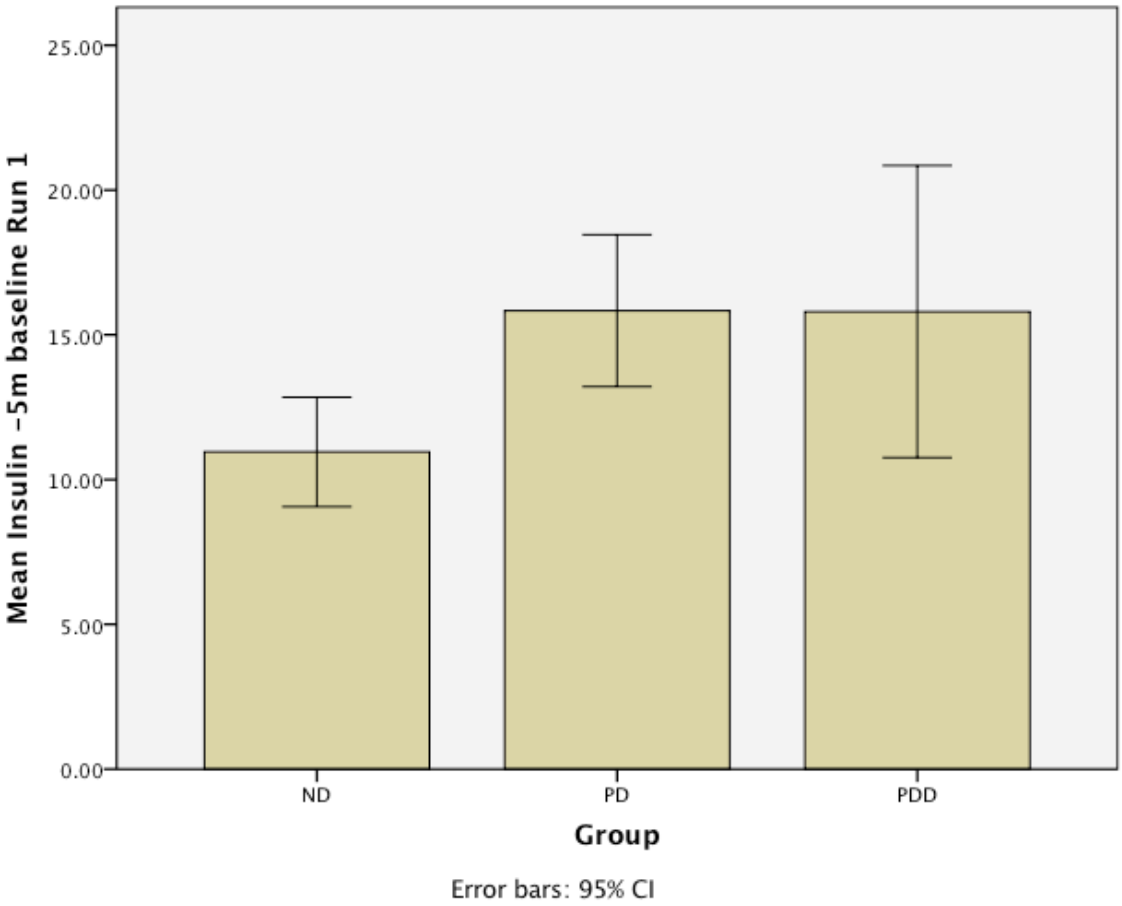

Figure 1. *Means for baseline insulin values for the ND, PD, and PDD groups.*

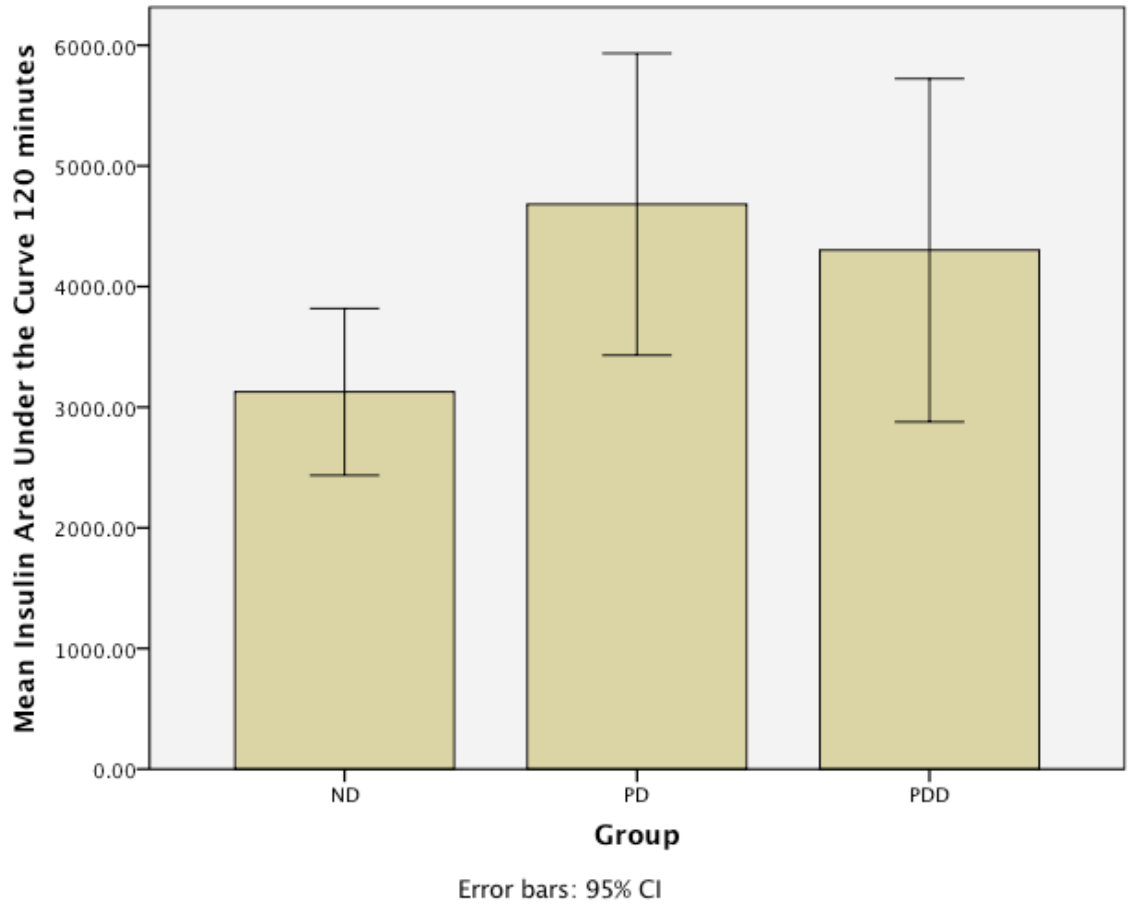

Figure 2. *Means for insulin AUC values at the 120-minute time point for the ND control, PD, and PDD groups.*

Using bivariate correlations, insulin AUC values for participants in the PD group were significantly related to performance on measures of executive functioning [i.e., Stroop Word subtest (r = – .65, p = .022) and EXIT (r = .65, p = .022)]. In the PDD group, performance on executive functioning [i.e., Category Fluency - Vegetables (r = .631, p = .050)] was also significantly related to insulin AUC values. In the ND control group, insulin AUC was also significantly correlated with measures of executive functioning [i.e., Trail Making A (r = – .53, p = .011) and Stroop Interference subtest (r = .55, p = .009)] and processing speed [Digit Symbol (r = - .50, p = .024)]. Insulin AUC values were not significantly related to measures of memory,

working memory, language, visuospatial ability, or simple motor speed in the three groups. Table 7 shows the correlations between performance on neuropsychological measures and insulin AUC.

Table 7
Correlations between neuropsychological measure performances and insulin AUC

	Insulin AUC					
	Non-Demented		PD Participants		PDD Participants	
	R	*p*	*R*	*p*	*R*	*p*
Memory						
Logical Mem I	– .005	.981	– .243	.447	– .102	.778
Logical Mem II	.025	.914	– .126	.697	– .189	.601
SRT						
T1-FR	.134	.552	.215	.502	.593	.071
T1-CR	– .134	.552	– .220	.492	.095	.794
T2-FR	– .003	.988	– .207	.519	.477	.164
T2-CR	.003	.988	.207	.519	.214	.553
T3-FR	– .083	.714	– .097	.764	.325	.360
T3-CR	.263	.238	.097	.764	.301	.398
Working Memory						
Digit Span F	– .181	.419	– .360	.250	.522	.122
Digit Span B	– .229	.305	– .458	.135	– .245	.495
Letter-Number Seq	.159	.481	– .231	.469	– .203	.574
Executive Functioning						
Category Flu Ani	– .182	.418	.033	.919	.291	.415
Category Flu Veg	– .195	.385	– .567	.054	**.631***	**.050**
Trails A	**– .528***	**.011**	.182	.572	– .201	.578
Errors A	**.519***	**.013**	– .017	.959	.517	.126
Trails B	– .412	.056	.365	.243	.057	.875
Errors B	– .119	.599	.450	.143	.105	.773
Stroop (# correct)						
Color	– .034	.885	– .500	.098	.179	.621
Word	– .089	.660	**– .649***	**.022**	.554	.097
Interference	**.554****	**.009**	– .530	.076	.124	.734
EXIT-25	--	--	**.649***	**.022**	– .372	.290
Visuospatial						
Block Design	.260	.255	.305	.335	.176	.627
Visual Puzzles	--	--	– .104	.747	.260	.469
Matrix Reasoning	--	--	– .123	.704	– .013	.972
Language						
Boston Naming	.202	.379	.017	.959	.456	.185
Processing Speed						
Digit Symbol	**.501***	**.024**	– .045	.089	.353	.318
Simple Motor Speed						
Crossing-Off	--	--	.241	.450	.603	.065

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

Linear regressions were calculated to determine if group x metabolic interactions existed in predicting cognitive performance on neuropsychological measures. Insulin AUC was used to represent metabolic values. In the PD group, insulin AUC significantly predicted performance on measures of executive functioning, including the word-reading subtest of the Stroop Color-Word test: [$F(1,10) = 7.27$, $p = .02$, $R^2 = .42$], with higher word-reading subtests scores (i.e., less impairment) associated with lower insulin AUC. Insulin AUC also predicted performance on the EXIT: [$F(1,10) = 7.28$, $p = .02$, $R^2 = .42$], with higher EXIT scores (i.e., greater cognitive impairment) associated with higher insulin AUC. In the PDD group, insulin AUC significantly predicted performance on only one measure of executive functioning, Category Fluency – Vegetables: [$F(1,8) = 5.29$, $p = .05$, $R^2 = .40$], with lower Category Fluency – Vegetables scores (i.e., greater impairment) associated with higher insulin AUC. Based on regression results, participants in the PD and PDD groups performed better on measures of executive functioning when insulin AUC were lower and demonstrated greater cognitive impairments when insulin AUC were higher. Similar predictions of cognitive performance in the areas of memory, working memory, language, visuospatial functioning, processing speed, and simple motor speed based on insulin AUC and PD and PDD group designation were not established.

Discussion

Reductions in insulin hormone and insulin receptor expression and damage to glucoregulatory mechanisms are more common as age increases (Cardoso et al., 2009). These changes trigger impaired glucose tolerance, insulin resistance, and diabetes mellitus (Gasparini, Netzer, Greengard, & Xu, 2002; Sandyk, 1993). Inadequately regulated insulin in diabetes mellitus leads to poorer cognitive functioning and more rapid cognitive decline over time (Arvanitakis et al., 2006; Gregg et al., 2000; Messier & Teutenberg, 2005). While numerous

studies have illustrated the relationship between insulin and AD, there is a paucity of data on insulin's association to PD and PDD. We hypothesized that (1) the PDD group would have lower absolute insulin compared to PD and control groups; (2) Lower insulin levels would significantly correlate with decreased motor performance, as defined by the Unified Parkinson's Disease Rating Scale (UPDRS) motor score; (3) Lower insulin levels would predict poorer performance on executive functioning, memory, visuospatial, and language tasks. This study demonstrated a relationship between insulin and motor performance as well as a connection between insulin and executive functioning performance in the PD and PDD groups.

Hypothesis 1 – absolute insulin

Results demonstrated that participants in the PDD group had lower absolute insulin values compared to the PD group when measured by the insulin area under the curve (AUC) for a two-hour glucose tolerance test. However, insulin AUC values did not differ significantly between the PD and PDD groups. This finding was consistent with previous research that demonstrated a connection between insulin levels and reduced cognitive functioning (Cardoso et al., 2009; Gasparini et al., 2002). For example, in a study using a similar protocol, lower insulin AUC levels were associated with higher dementia severity in individuals with AD (Burns et al., 2007). Based on the nature of the diagnosis, PDD participants typically demonstrate increased dementia severity compared to individuals with only a PD diagnosis.

In addition, the link between lower insulin levels and increased dementia severity found in this study adds support to the connection between lower insulin levels and reduced performance in various cognitive domains. An established relationship exists between lower insulin levels and impaired insulin signaling, a key feature of diabetes mellitus (White, 2003). Individuals with diabetes mellitus were found to have lower scores than non-diabetic individuals

on tasks of attention, psychomotor function, and executive functioning (Nandipati, Luo, Schimming, Grossman, & Sano, 2011). Diabetes mellitus also led to rapid decline in cognitive functioning (Arvanitakis et al., 2006; Cardoso et al., 2009; Gregg et al., 2000; Messier & Teutenberg, 2005). This study and others provide convergent evidence for higher dementia rates among those with both PD and diabetes mellitus (Sandyk, 1993) and highlights the need for additional research in the area to clarify how insulin is related to PD and PDD.

Hypothesis 2 - motor

Results showed a relationship between insulin AUC and motor performance such that lower insulin was associated with reduced motor performance. This relationship was consistent with previous research that demonstrated how diabetes is connected to parkinsonian symptoms including postural reflexes and gait disturbances (Arvanitakis et al., 2007), and connected to increased motor severity (Papapetropoulos, et al., 2004). The connection between reduced motor performance and lower insulin is likely attributed to the neuroanatomy of PD and brain structures involved in the insulin signaling pathway. For example, a loss of neurons within the substantia nigra was accompanied by reduced insulin receptors in those with PD. In addition, animal studies showed that hypoinsulinemia (i.e., low insulin in blood) was associated with reduced dopamine transporters in the substantia nigra (Cardoso et al., 2009). These findings are consistent with the current study and help explain why participants showed poorer UPDRS motor performance when insulin levels were lower.

We established a relationship between insulin and motor performance; however, the relationship was clinically notable rather than statistically significant. One possible explanation for why only clinically notable results were found between insulin and motor performance is all participants were asked to take their usual PD medications before completing the UPDRS and

other screening measures. The medications, most commonly levodopa or carbidopa-levodopa, likely blunted the true impact of motor dysfunction that patients experience when not taking medications. Despite not reaching the level of statistical significance, this information is useful for individuals with PD, particularly if comorbid with diabetes mellitus. Obtaining appropriate treatments to relieve motor symptoms may become more challenging with both diseases, as participants in this study still demonstrated reduced motor performance despite being on medications aimed at controlling physical symptoms of PD. Furthermore, these findings could assist doctors in recommending exercises targeted for increased motor flexibility and safety if PD patients are diagnosed with diabetes mellitus.

Hypothesis 3 – neuropsychology performance

Results did not demonstrate that lower insulin levels predicted poorer performance on executive functioning, memory, visuospatial, and language tasks. Instead, we found that higher insulin levels predicted poorer performance only in the area of executive functioning for both the PD and PDD groups. This inverse relationship was opposite to what was expected in this population given previous evidence that associated lower insulin levels with reduced cognitive performance (Cardoso et al., 2009; Gasparini et al., 2002). Past studies found that administering optimal doses of nasal and intravenous insulin actually increased cognitive performance, particularly in the area of verbal and declarative memory (Benedict et al., 2007; Bourdel-Marchasson, Lapre, Laksir, & Puget, 2010; Reger et al., 2006). In addition, the finding that higher insulin AUC levels predicted poorer cognitive performance is opposite to what researchers found in individuals with AD. Increased insulin levels were associated with greater cognitive performance in AD (Bourdel-Marchasson et al., 2010; Burns et al., 2007). Results from the current study are surprising given the similarities among AD, PD, and PDD.

One possible explanation for the relationship between higher insulin levels and poorer executive functioning performance could be that tests measuring executive functioning activate specific pathways and structures within the brain, many of which are also connected to insulin and insulin signaling. Brain structures involved in executive functioning include the cerebral cortex, hippocampus, and hypothalamus. Tests activating the cerebral cortex, specifically the prefrontal cortex, use the frontostriatal system. Executive functioning tests that use this system require gradual learning through trial and error and is demonstrated through skill learning, planning, set shifting, and habit formation. Alternatively, some executive functioning tests use the hippocampal system that requires a rapid and flexible system of learning (Leh, Petrides, & Strafella, 2010). As individuals compete tasks of executive functioning, the frontostriatal and hippocampal systems may act independently, work together, or compete with each other depending on the demands of the specific test.

The two main brain systems participating in executive functioning abilities involve the cerebral cortex and the hippocampus, both of which are key structures concerning insulin in the brain. These two structures along with the hypothalamus are among the structures with the highest concentrations of insulin receptors (Leh et al., 2010; Weintraub et al., 2011). Because these particular structures have a high concentration of insulin receptors, the effects of increasing age and reduced insulin hormone are noticeable. In addition, chronic hyperinsulinemia (i.e., excessive insulin in blood) both increases genes responsible for inflammatory and immune pathways and decreases genes responsible for insulin signaling. These changing gene levels result in blocked glucose usage and reduced mitochondrial functioning in hippocampal neurons (Blalock et al., 2010). This reduced functioning is demonstrated through diminished activity of several mitochondrial enzymes (e.g. pyruvate and isocitrate dehydrogenases, a-ketoglutarate

dehydrogenase complex) that are components of the citric acid cycle and energy production. Researchers have found evidence for this reduced mitochondrial functioning and mitochondrial enzymes in brain tissue samples from patients with AD (Bubber et al., 2005, as cited in Aviles-Olmos, Limousin, Lees, & Foltynie, 2012). Because of similarities between AD and PD, it is possible that reduced mitochondrial functioning associated with hyperinsulinemia may explain why higher insulin levels were connected to poorer executive functioning performance. Due to the hippocampus' connections to both insulin and executive functioning, it is important to investigate this area further so see if generalizations can be applied to individuals with PD and PDD or if results from this study are unique to our sample.

While this study demonstrated connections between insulin and executive functioning, results did not support previous research that showed relationships between insulin and reduced performance on tasks of memory. In a study using magnetic resonance imaging (MRI), reduced hippocampal and prefrontal cortex volumes were associated with declarative memory in individuals with diabetes. Also, individuals with diabetes demonstrated greater difficulties in tasks of short-term memory compared to those without diabetes (Bourdel-Marchasson et al., 2010). Despite the hippocampus' involvement in both memory and insulin, it is possible that higher concentrations of insulin receptors exist in the hippocampus compared to the cerebral cortex and hypothalamus. Therefore, reductions in insulin receptors and insulin levels may result in less damage to memory performance and more damage to the cerebral cortex and hypothalamus involved in executive functioning. This could explain why executive dysfunctions are common and among the first to be seen in both PD and PDD.

Overall, even though this study supported previous research by showing a connection between insulin levels and executive functioning in PD and PDD, the exact mechanism to

explain the relationship is unknown. Furthermore, it is unknown why higher insulin levels predicted poorer cognitive performance on executive functioning measures, particularly when past research demonstrated a relationship between reduced cognitive performance, especially memory performance, and lower insulin levels. Additional research to replicate this finding and better clarify potential mechanisms for the relationship is warranted.

Limitations

This study was limited by the unique participant sample. The exclusion criteria (i.e., ages 55-85, diagnosis of PD, no diagnosis of Type I or Type II diabetes mellitus or Alzheimer's disease) produced a small sample size for all three participant groups. Each group had fewer than 25 participants, with the PD and PDD groups having less than 13 participants, which may have impacted the power available to accurately draw conclusions based on results. A small sample size opens the possibility that results are due to chance (Type I error) and not actual differences between high or low insulin levels and neuropsychological performance in PD and PDD. Also, the criteria of no diagnosis of diabetes mellitus severely limited the sample of older adult participants given that prevalence rates of diabetes are increasing among the older adult population (Arvanitakis et al., 2006). In addition, there was little diversity in the participant sample. The participant sample consisted of only Caucasians, the majority of participants within the PDD group were men (90%), and all participants were in the mild to moderate stages of PD. These factors limited the ability to generalize findings to all older adults with PD or PDD.

While care was taken to develop a neuropsychological battery that was a comprehensive evaluation comprised of commonly used tests lasting approximately 1.5 hours, the length of testing may have been too long for some participants. Behavioral observations included fatigue near the end of the testing process, particularly within the PDD group. Fatigue may have

negatively skewed performance on the neuropsychological measures. Also, two of the three measures used to evaluate visuospatial ability were near the end of the neuropsychological battery. It is possible that performances on these measures were not accurate and could account for the lack of significant findings with respect to performance and insulin levels. Due to the high frequency with which visuospatial deficits are reported in PD and PDD (Robottom & Weiner, 2009; Stepkina et al., 2010), it was thought that significant correlations between insulin and visuospatial ability would have presented.

Furthermore, peripheral insulin levels from blood were used rather than insulin from within the central nervous system. High insulin levels correlate with the concentration of insulin receptors, with the highest concentration of insulin receptors found in the cerebral cortex, hippocampus, hypothalamus, olfactory bulb, and cerebellum (Cardoso et al., 2009; Rahman, 2011). Therefore, insulin gathered from blood rather than the central nervous system may have limited the accuracy of insulin levels. Due to the design of this study, collecting insulin levels from the central nervous system was not feasible and research using insulin levels from these sources is limited (Rahman, 2011). Future research using insulin from the cerebral spinal fluid may provide greater accuracy of insulin levels at different time points and may help to clarify the connection between insulin and performance on measures of executive functioning.

Future directions and conclusions

Future work should strive to include larger sample sizes and greater diversity that would more effectively represent older adults with PD and PDD. Including more women with PDD and individuals of minority status would allow results to be more effectively generalized to the broader population of those with the disease. In addition, using samples that include mild, moderate, and advanced stages of PDD would highlight whether executive functioning

performance continues to have significant associations to insulin levels or if different cognitive domains (e.g., memory, visuospatial ability, language, processing speed) are more strongly impacted as the disease progresses. Including participants with mild cognitive impairment (MCI) would also explore a category of PD patients that is under researched and highlight potential distinctions from those with normal cognition and those with PDD (Weintraub et al., 2011).

Future studies should also use different neuropsychological measures to evaluate various aspects of cognitive performance. Alternative measures evaluating memory, visuospatial ability, language, among other domains, may shed greater light on the connection between overall cognitive performance and insulin. Measures of executive functioning including the Delis-Kaplan Executive Function System (D-KEFS), Wisconsin Card Sorting Task, Tower of London (Leh et al., 2010), and Dementia Rating Scale-2 (Weintraub et al., 2011) are possible neuropsychological measures that could help determine if the significant connections between executive functioning and insulin are consistent across measures. Also, care should be taken to gather a comprehensive evaluation without over-taxing participants that may negatively skew results.

In addition, greater investigation into the connection between motor performance and insulin should be explored. Finally, due to the cross sectional nature of the data, causal conclusions cannot be formed. It is possible that a third process is acting on the population and may be revealed as the disease progresses. Longitudinal studies would be appropriate to see if higher insulin levels continue to predict poorer performance on measures of executive functioning in PD and PDD.

Despite limitations to the current study, the results expand literature, especially the relative lack of research examining the connection between insulin levels and cognitive

performance in those with PD or PDD. This study demonstrated a connection between insulin levels and executive functioning. However, more research is needed to establish the specific mechanisms for this connection and provide further evidence for insulin's role in cognitive changes for older adults with PD, PDD, and other neurodegenerative diseases.

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