# CONTRIBUTIONS TO COGNITIVE DYSFUNCTIONS IN NEURODEGENERATIVE DISEASE

A Dissertation

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by
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| | |
|---|---|
| Parkinson's disease | PD |
| Alzheimer's disease | AD |
| Alzheimer's disease and related dementias | ADRD |
| Mild Cognitive Impairment | MCI |
| Hydrogen Sulfide | $H_2S$ |
| Beta Amyloid | $A\beta$ |
| Magnetic Resonance Imaging | MRI |
| Fluid Attenuated Inversion Recovery | FLAIR |
| White Matter Hyperintensity | WMH |
| Diffusion Tensor Imaging | DTI |
| Fraction Anisotropy | FA |
| Radial Diffusivity | RD |
| Mean Diffusivity | MD |
| Axial Diffusivity | AxD |

## ABSTRACT

Parkinson's disease (PD) has been shown to preferentially affect males with increased incidence as well as more severe motor and cognitive symptoms compared to females. Conversely, Alzheimer's disease (AD) which has an array of etiologies, is characterized by late life learning and memory deficits, disorientation and other cognitive and behavioral impairments. Germane to the work presented here, recent evidence has shown vascular stress to be an important risk factor and contribute independently to AD pathogenesis. Thus, in this work I explored the contribution of sex on cognitive function between males and females with PD across domains of attention and working memory, executive function, language, visuospatial function, episodic memory and processing speed. I controlled for measures of disease stage and severity to identify the specific impact of sex on cognitive dysfunction associated with PD. Indeed, I find that males with PD performed significantly worse than females in measures of executive function, language, visuospatial memory, verbal episodic memory and processing speed. Given these findings and the involvement of the frontal lobe, I present a hypothesis of a sexually dimorphic disease mechanism that preferentially affects males in the prefrontal cortico-basal ganglia-thalamo-cortical loop, one of the five parallel loops known to be affected in PD as a result of dopamine signaling loss. Furthermore, I explored the contribution of vascular stress on AD cognitive dysfunction. I measured hydrogen sulfide ($H_2S$) and its metabolites (acid-labile (e.g., iron-sulfur clusters) and bound (e.g., per-, poly-) sulfides) which have been shown to regulate both vascular and neuronal homeostasis as our marker of vascular stress. I extend our previous work to show associations between elevated sulfides and magnetic resonance-based metrics of brain atrophy and white

matter integrity. Elevated bound sulfides were associated with decreased gray matter measures, while increased acid labile sulfides were associated with measures of decreased white matter integrity and increased ventricular volume. These findings are consistent with a ‘toxic’ sulfide model of ADRD with excess sulfides being a damaging byproduct of a compensatory mechanism aimed at producing antioxidant free sulfide in the face of AD pathophysiology.

# GENERAL INTRODUCTION

## *Parkinson's Disease*

Parkinson disease (PD) disproportionately affects individuals by sex with males 1.37-3.7 times more likely to develop PD compared to females (Gillies, Pienaar, Vohra, & Qamhawi, 2014). Males with PD experience more severe disease burden, including greater motor dysfunction and steeper rate of progression (Frentzel et al., 2017; Georgiev, Hamberg, Hariz, Forsgren, & Hariz, 2017; Lubomski, Louise Rushworth, Lee, Bertram, & Williams, 2014; Lyons, Hubble, Troster, Pahwa, & Koller, 1998). PD pathology is characterized by striatal dopamine deficiency caused by significant neuronal cell loss in the substantia nigra, as well as alpha synuclein aggregation(Halliday & McCann, 2010; Lees, Hardy, & Revesz, 2009). Major motor signs of PD typically occur after approximately 70% reduction of dopaminergic signaling in the basal ganglia (Bernheimer, Birkmayer, Hornykiewicz, Jellinger, & Seitelberger, 1973; Fearnley & Lees, 1991). While reduced dopaminergic activity in PD is well known to cause motor signs, it is also associated with cognitive dysfunction (Bayram, Kaplan, Shan, & Caldwell, 2020; Biundo, Weis, & Antonini, 2016; Chung et al., 2018; Cummings, 1993; Siepel et al., 2014). For example, cognitive switching deficits in PD are associated with dopaminergic dysfunction (Riggeal et al., 2007; Shook, Franz, Higginson, Wheelock, & Sigvardt, 2005; van Schouwenburg, Aarts, & Cools, 2010) in networks linking striatum to prefrontal cortex (Jokinen et al., 2013; Sawamoto et al., 2007).

Cognitive deficits in PD can occur at both early and late stages and contribute significantly to disease burden (Fang, Lv, Mao, Dong, & Liu, 2020). Reported prevalence of mild

cognitive impairment at baseline has ranged from 18-36% (Aarsland et al., 2009; Aarsland et al., 2010; Elgh et al., 2009; Foltynie, Brayne, Robbins, & Barker, 2004; Kandiah et al., 2009; Muslimovic, Post, Speelman, & Schmand, 2005; Santangelo et al., 2015) The risk of dementia increases as the disease progresses (Braak, Rub, & Del Tredici, 2006), is associated with disease severity (Riggeal et al., 2007; Wojtala et al., 2019), and longitudinal studies of PD have reported an approximate 80% prevalence of dementia in late stages of the disease (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003; Hely, Reid, Adena, Halliday, & Morris, 2008). Cumulative incidence of PD-MCI has been estimated at 9.9% after 1 year, 23.2% after 3 years, and 28.9% at 5-year follow-up (Pedersen, Larsen, Tysnes, & Alves, 2017). In addition, Kandiah and colleagues (Kandiah et al., 2009) found that 31% of newly diagnosed idiopathic PD subjects with cognitive decline had a 2.39 average decrease in score per year on the Mini Mental State Examination (MMSE). A baseline score of ≤ 26 on the Montreal Cognitive Assessment (MoCA) indicated a significantly increased risk of cognitive decline (Aarsland et al., 2021).

Male sex has been identified as a risk factor for motor dysfunction, cognitive decline (Pigott et al., 2015; Uc et al., 2009) and dementia in PD (Cereda et al., 2016). Cholerton and colleagues (Cholerton et al., 2018) showed that, compared to cognitive performance, male sex was a more powerful predictor of cognitive decline from no impairment to MCI, as well as from MCI to dementia. Furthermore, females showed lower prevalence of cognitive impairment and experienced cognitive decline more slowly compared to male PD counterparts (Cholerton et al., 2018). However, data on sex differences in cognitive

function in PD are mixed. For example, in a longitudinal study using the Parkinson disease Progression Markers Initiative (PPMI) database, an observational longitudinal clinical database containing imaging, biological, clinical and behavioral data (ppmi-info.org), no significant differences were found between males and females on the MoCA, nor were there differences in MoCA score change over time (Bayram, Banks, Shan, Kaplan, & Caldwell, 2020). Sex as a biological variable has been a largely overlooked element of diversity for several decades. In 2015 the National Institutes of Health initiated policy aimed to emphasize sex as a biological variable in biomedical research. Examining the role sex plays in PD is critical for our understanding of disease mechanism, onset, incidence, progression, and management (L. R. Miller et al., 2017).

*Sex Differences in Incidence, Prevalence, Presentation and Progression of PD*

There is compelling evidence indicating that males are more likely to be diagnosed with PD, with earlier disease onset and more severe motor signs. The mean age of onset has been reported to be approximately 2 years later for females than males (Alves et al., 2009; Haaxma et al., 2007). Lifetime risk for developing PD is estimated to be 2% for males and 1.3% for females (Elbaz et al., 2002). While reports on sex differences in incidence rates vary from 1.37 to 3.7 (Gillies et al., 2014), agreement upon the male bias remains consistent (Dorsey, Sherer, Okun, & Bloem, 2018). Incidence rates of parkinsonism and PD in the U.S. between the years 1976 and 2005 increased significantly, particularly for males aged 70 or older (Savica, Grossardt, Bower, Ahlskog, & Rocca, 2016). Despite the global age-standardized prevalence of PD increasing by 21.7% between 1990 and

2016, the male-to-female ratio of age-standardized prevalence of PD has remained relatively constant (1990 = 1.37, 2016 = 1.4) (Dorsey et al., 2018).

In regards to sex differences in motor phenotype, males with PD present with more severe motor dysfunction and disease burden compared to females as measured by the Unified Parkinson disease Rating Scale (UPDRS) and Hoehn and Yahr (H&Y) rating scale (Frentzel et al., 2017; Lubomski et al., 2014; Lyons et al., 1998). In a study of 630 PD participants (315 male, 315 female) males had significantly higher (worse) UPDRS-III (motor evaluation) scores than females. While Lyons and colleagues (Lyons et al., 1998) reported that among individuals with early stage PD (< 5 years) there were no significant associations between sex and severity of motor function, male sex was significantly associated with increased disease burden and worse motor scores on the UPDRS among individuals with later stage PD. A large study by Baba and colleagues (Baba, Putzke, Whaley, Wszolek, & Uitti, 2005) (818 males, 410 females), reported that males had significantly higher rigidity scores than females on the UPDRS. Similarly, a recent meta-analysis of both longitudinal data from 5946 PD participants and 17,719 participants from web-based online cohorts found that females had much slower disease progression than males measured by UPDRS and H&Y scale (Iwaki et al., 2021). Furthermore, freezing of gait is more common in males (C. Gao, Liu, Tan, & Chen, 2020) and is associated with more severe motor and cognitive dysfunction during late stage disease (Amboni, Barone, & Hausdorff, 2013; Lord et al., 2014; Pal et al., 2016; van der Heeden et al., 2016).

However, not all studies agree that that males have more severe disease than females (Frentzel et al., 2017; Lubomski et al., 2014; Lyons et al., 1998). For example, some studies have reported no differences between males and females in UPDRS total score or UPDRS-III (Baba et al., 2005; Farhadi et al., 2017; Haaxma et al., 2007; Reekes et al., 2020; Song, Gu, An, Chan, & Chinese Parkinson Study, 2014; Tremblay et al., 2020). In a study by Picillo and colleagues (Picillo et al., 2016) (31 males, 16 females), significantly higher UPDRS-III motor scores were reported for females compared to males at baseline but no significant differences at the 2- or 4-year follow-up were found. Similarly, one study found that females reached H&Y stage III (indicative of balance disturbance) before males after 5- and 10-year follow-up, but there were no significant differences between males and females in time to reach H&Y stage IV or V after 5-, 10-, and 15-year follow-up (Sato et al., 2006). A large study by Abraham and colleagues (Abraham et al., 2019) found no significant differences between males and females in disease progression until after the 20-year mark. However variability in motor performance is known to be high in PD (Keloth, Radcliffe, Raghav, Arjunan, & Kumar, 2020; Puyjarinet et al., 2019; Reed, 1998; Sheridan & Flowers, 1990; Torres, Cole, & Poizner, 2014; J. M. Wilson et al., 2020), which may contribute to differences across studies, especially in smaller samples.

Three major clinical subtypes have been described in PD: postural instability and gait disturbance (PIGD), tremor dominant (TD), and akinetic-rigid. Patients with PIGD were found to have greater motor and intellectual impairment compared to TD subjects (Aleksovski, Miljkovic, Bravi, & Antonini, 2018; Jankovic et al., 1990; Wojtala et al., 2019), as were akinetic-rigid subjects (Wojtala et al., 2019). Females were more likely than

males to develop tremor (L. Gao et al., 2015; Haaxma et al., 2007; Solla et al., 2012). The tremor dominant phenotype has been associated with more benign disease with slower disease progression (Haaxma et al., 2007) compared to freezing of gait. Haaxma and colleagues (Haaxma et al., 2007) found that, compared to individuals with bradykinesia, tremor dominant subjects had a 38% slower increase in UPDRS-III scores. Additionally, the severity of postural and gait dysfunction is associated with poorer cognitive function, including measures of working memory, verbal memory, language, and processing speed (Alves, Larsen, Emre, Wentzel-Larsen, & Aarsland, 2006; Kelly et al., 2015; Pal et al., 2016; Zuo et al., 2017). Cognitive decline was also greater in PD subjects with PIGD subtype compared tremor dominant phenotype (Burn et al., 2006; J. P. Taylor et al., 2008). Furthermore, PIGD and attention deficits were independently associated with increased rate of cognitive decline in non-demented individuals with PD (J. P. Taylor et al., 2008). Akinetic-rigid subjects have been shown to have greater deficits in executive functions, working memory, word fluency, attention, and visuospatial functions than tremor dominant patients (Wojtala et al., 2019). The link between cognitive dysfunction and gait disturbance has been attributed to more widespread brain pathology compared to the tremor dominant phenotype (Forsaa, Larsen, Wentzel-Larsen, Herlofson, & Alves, 2008; Heremans et al., 2013; Shine et al., 2013).

There is some evidence that males are more likely to develop bradykinesia (Georgiev et al., 2017) and freezing of gait (C. Gao et al., 2020), which is associated with dopamine depletion (Kim et al., 2018) and cognitive dysfunction (Heremans et al., 2013; Peterson, King, Cohen, & Horak, 2016) such as deficits in executive function (R. G. Cohen et al.,

2014) and visuospatial processing (Nantel, McDonald, Tan, & Bronte-Stewart, 2012). However, many studies report that PIGD is more common in females with PD (Baba et al., 2005; Georgiev et al., 2017; A. R. Johnson et al., 2016; Kovacs et al., 2016; Solla et al., 2012; Szewczyk-Krolikowski et al., 2014), and that PIGD symptoms were also more severe (Baba et al., 2005; Kovacs et al., 2016; Szewczyk-Krolikowski et al., 2014). Taken together, these findings suggest a complex and multifaceted relationship among cognitive dysfunction, gait disturbance and sex in PD. There continues to be accumulating evidence of a male bias in PD with males being more likely to be diagnosed with PD having more severe motor signs and disease progression as well as being more likely to show freezing of gate associated with cognitive dysfunction, while females are more likely to show the tremor dominant phenotype associated with milder disease.

These findings are consistent with increased cognitive dysfunction in males with PD, however not all findings agree, and data from PIGD, which is also associated with cognitive dysfunction, may indicate the opposite finding. One possible explanation that would account for these contradictory results is the existence of disease subgroups that interact with sex linked disease factors and confer different vulnerability to widespread versus local neurodegeneration.

A primary hypothesis to explain both decreased incidence and delayed onset in females is the known protective role of estrogen on the regulation of dopamine. Some evidence suggests that males have reduced dopaminergic activity compared to females. Estrogen is known to enrich the dopamine system and dopamine transporter (DAT) activity in the

striatum of PD patients is higher in women compared to men (Lee et al., 2015). This data confirms an earlier finding demonstrating a higher level of available DAT in women than in men with PD (Haaxma et al., 2007). Additionally, greater dopaminergic neurodegeneration and reduced DAT function has been observed in estrogen knockout animal models compared to controls (Picillo et al., 2017). However, sporadic PD typically presents postmenopausal and studies have found mixed findings on the relationship between age of menopause and onset of PD (Ragonese et al,, 2006; Cereda et al., 2013; Greene et al., 2014; Lv et al., 2017); therefore, work is needed to better understand the role sex plays in the pathogenesis and progression of PD.

*Sex Differences in Cognitive Dysfunction*

PD is known to affect a number of cognitive functions. Five domains have been implicated in the diagnosis of MCI in PD: 1) Attention and Working Memory, 2) Executive Function, 3) Language, 4) Episodic Memory, and 5) Visuospatial Function (Litvan et al., 2012). Furthermore, work from our lab and others underscores the importance of information processing speed in normal cognitive function (Salthouse, 1996) (Salthouse, 1996) and in PD (Cummings, 1993; Nguyen et al., 2017). Deficits in these 6 domains may present individually (single-domain) or concomitantly (multiple-domain) (Levin, Tomer, & Rey, 1992; Litvan et al., 2012) (Levin et al., 1992; Litvan et al., 2012). Recent work is shedding light on the influence of sex on PD-associated cognitive disturbance, and Aim 1 of this dissertation will explore the contribution of sex on cognitive performance across these six domains.

### *Alzheimer's Disease and Related Dementia*

Alzheimer's disease (AD) is the most common age-related neurodegenerative disease affecting one in ten elderly adults over the age of 65. AD is characterized by progressive cognitive deficits and brain atrophy (Backman, Jones, Berger, Laukka, & Small, 2004; Pini et al., 2016). AD is known to affect a number of cognitive domains including attention, executive function (Perry & Hodges, 1999), working memory (Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991), semantic memory and language (Verma & Howard, 2012), decline in episodic memory and difficulty acquiring new information are the most commonly identified cognitive deficits (Albert, 1996). Deficits in cognitive function may arise as soon as 5-6 years prior to dementia and 4-6 years prior to mild cognitive impairment (MCI) (R. S. Wilson, Leurgans, Boyle, & Bennett, 2011) with evidence suggesting that deficits in semantic and working memory may precede deficits in other domains (Amieva et al., 2008). However, other studies suggest that domains of episodic memory and visuospatial ability may arise sooner (Grober et al., 2008; D. K. Johnson, Storandt, Morris, & Galvin, 2009). Imaging studies have found that medial temporal lobe structure, which includes the hippocampus and subserves episodic memory, may be an early region affected by AD and AD pathology (Kesslak, Nalcioglu, & Cotman, 1991; Killiany et al., 1993). This decline in cognitive status is linked to specific brain pathology and a range of hypotheses have been suggested for the pathogenesis and progression of AD.

#### *Alzheimer's Disease and related hypotheses*

The prevailing hypothesis of AD is the amyloid cascade hypothesis, which describes the accumulation of extracellular beta amyloid (Aβ) plaques and intracellular phosphorylated tau (p-tau) neurofibrillary tangles, has been suggested as a primary mechanism of AD (though recently some work on this topic has been questioned https://www.science.org/content/article/potential-fabrication-research-images-threatens-key-theory-alzheimers-disease). The proposed cause of these aggregated Aβ plaques is the cleavage of amyloid precursor protein (APP) sequentially by β-secretase and γ-secretase enzymes producing shorter, toxic Aβ fragments (J. Wang, Gu, Masters, & Wang, 2017). The resulting fragments, $A\beta_{40}$ and $A\beta_{42}$, are insoluble (Perl, 2010; Walsh & Selkoe, 2007) with $A\beta_{42}$ being more hydrophobic and prone to aggregation. The aggregation of Aβ and subsequent plaque formation leads to microglial activation, cytokine release, reactive astrocytosis and inflammation (Eikelenboom, Zhan, van Gool, & Allsop, 1994; McGeer & McGeer, 1995; Rogers et al., 1996). Plaque formation induces synaptotoxic structural and biochemical changes in surrounding neurons causing neuron loss and cerebral atrophy (Braak & Braak, 1994; Terry et al., 1991).

A secondary theory deemed the “mitochondrial cascade hypothesis,” pioneered by Swerdlow and Kahn (2004) describes that mitochondrial dysfunction may reconcile mixed histopathological and physiological findings. The hypothesis contends that individuals have different basal rates of electron transport chain activity and therefore the rate of reactive oxygen species production and mitochondrial damage differs person to person. Oxidative mitochondrial damage sets off a cascade of increased amyloid production, induced cell death and cell cycle disruption leading tau phosphorylation and neurofibrillary

tangle development (Swerdlow & Khan, 2004). Subsequent studies have corroborated the fundamental role of mitochondrial dysfunction in the pathogenesis of AD with specific emphasis on the loss of mitochondrial structure and function (W. Wang, Zhao, Ma, Perry, & Zhu, 2020).

*Vascular contributions to AD*

An emerging hypothesis germane to this portion of the dissertation focuses on the role vascular health plays in AD risk and pathogenesis. Recent evidence suggests that cardiovascular and cerebrovascular pathology are important risk factors for AD and dementia and may accelerate early-stage AD progression (Santos et al., 2017). Furthermore, vascular pathologies have been shown to independently contribute to cognitive dysfunction and dementia (Esiri, Nagy, Smith, Barnetson, & Smith, 1999; Jellinger, 2010; Launer, 2007; Schneider, Arvanitakis, Bang, & Bennett, 2007; Schneider et al., 2003; Snowdon et al., 1997). The “vascular dysregulation hypothesis” proposes that vascular deficits intensify other common AD pathological contributors such as amyloid deposition, glial activation and metabolic dysfunction, creating a feedback cycle that synergistically advances both AD and vascular pathology (Govindpani et al., 2019). For example, chronic cerebral hypoperfusion has been linked to cognitive deficits (Safouris, Tsivgoulis, Sergentanis, & Psaltopoulou, 2015) and neurodegeneration (Broughton, Reutens, & Sobey, 2009).Cardiovascular risk factors such as hypertension, hyperlipidemia, atherosclerosis, diabetes and smoking all contribute to the pathogenesis of chronic cerebral hypoperfusion (Meyer, Rauch, Rauch, & Haque, 2000; Valerio Romanini et al., 2013) and may independently incur increased risk for AD. For example,

chronic hypertension causes endothelial dysfunction, arterial stiffness and atherosclerosis which may lead to cerebral hypoperfusion, ischemia and hypoxia (Katayama & Hasebe, 2013; C. Qiu, Winblad, & Fratiglioni, 2005). Moreover, chronic systolic hypertension has shown to increase AD risk by up to 25% (Lennon, Makkar, Crawford, & Sachdev, 2019). Importantly, midlife hypertension is also linked with ADRD risk (de Bruijn & Ikram, 2014; Iadecola, 2014) independently of other cardiovascular risk factors (Iadecola, 2014; C. Qiu et al., 2005). Similarly, high cholesterol has been shown to be associated with AD (Sjogren, Mielke, Gustafson, Zandi, & Skoog, 2006), and increased Aβ production (Martins et al., 2006; Sjogren et al., 2006; Troncone et al., 2016). A major identified risk factor for AD is the E4 allele of apolipoprotein (ApoE; (Poirier et al., 1993; Strittmatter et al., 1993), which is involved in the transport and metabolism of lipids (Martins et al., 2006) and carriers of ApoE4 are shown to have higher cholesterol levels (de Bruijn & Ikram, 2014).

Cerebral hypoperfusion may exacerbate AD pathology through increased Aβ aggregation and hyperphosphorylated tau (Pluta et al., 2016; L. Qiu et al., 2016). Evidence has suggested that there is a relationship between Aβ and vascular dysfunction with as many as 80% of AD patients showing some degree of cerebral amyloid angiopathy (CAA; (Biffi & Greenberg, 2011; Reijmer, van Veluw, & Greenberg, 2016)) characterized by acellular thickening of small and medium arterial walls (Vinters, 1987). Cerebral hypoperfusion may promote neurodegeneration through disrupted redox status including the production of reactive oxygen species, peroxides and proinflammatory cytokines (Zhao & Gong, 2015) and may trigger apoptosis (Broughton et al., 2009), and Thomas and colleagues

(1996) found that Aβ interacted with blood vessel endothelial cells to produce superoxide radicals resulting in disruptions to endothelial structure and function. This pathophysiology likely contributes to common signs of AD including brain atrophy, cortical thinning and white matter deterioration.

*Brain Atrophy in ADRD and Dementia*

A hallmark of AD pathology is diffuse brain atrophy, and the relationship between declining cognitive status and brain atrophy has been well described (Barnes et al., 2013; Kalaria, Akinyemi, & Ihara, 2012; Snyder et al., 2015). For example, accelerated ventricular enlargement and hippocampal atrophy have both been reported in mild cognitive impairment (MCI) and AD compared to normal ageing (Apostolova et al., 2012; Coupe, Manjon, Lanuza, & Catheline, 2019; Leung et al., 2013; Nestor et al., 2008). Furthermore, there is a link between vascular dysfunction and brain atrophy in ADRD. For example, several studies have demonstrated decreased brain volume in cohorts with cerebral small vessel disease (De Guio et al., 2020; Nitkunan, Lanfranconi, Charlton, Barrick, & Markus, 2011). A large postmortem evaluation revealed that 84% of AD patients had significant cerebrovascular lesions (Petrovitch et al., 2005), which have been shown to exacerbate AD pathology and cognitive impairment (Bennett, Wilson, Boyle, Buchman, & Schneider, 2012; Gorelick et al., 2011; Jellinger, 2007; Snowdon et al., 1997; Snyder et al., 2015; Strozyk et al., 2010; Toledo et al., 2013; Zekry et al., 2002).

White matter integrity is also reduced in AD. White matter disruption such as myelin and axonal loss and gliosis (Black, Gao, & Bilbao, 2009; Gouw et al., 2011), increase over

time resulting in progressive atrophy, and are exacerbated by vascular risk factors such as high blood pressure (van Dijk et al., 2004; R. Wang et al., 2015), ApoE4 status (R. Wang et al., 2015) and chronic cerebral hypoperfusion (Gurol, 2013). These changes have been attributed to cerebral small vessel disease ((Gouw et al., 2011; Xing et al., 2021) see also review and meta-analysis (Debette & Markus, 2010)) and blood brain barrier disruption resulting in the infiltration of inflammatory cells ((Takata, Nakagawa, Matsumoto, & Dohgu, 2021)). White matter integrity is reduced in both mild cognitive impairment and AD. Disruption to white matter integrity is also correlated with brain atrophy and cognitive trajectory (Chandra, Dervenoulas, Politis, & Alzheimer's Disease Neuroimaging, 2019; Coutu, Lindemer, Konukoglu, Salat, & Alzheimer's Disease Neuroimaging, 2017; Garnier-Crussard et al., 2022), including deficits in global and domain specific cognitive function (Arvanitakis et al., 2016; Bolandzadeh, Davis, Tam, Handy, & Liu-Ambrose, 2012; Kloppenborg, Nederkoorn, Geerlings, & van den Berg, 2014; Papp et al., 2014; Prins & Scheltens, 2015; van den Heuvel et al., 2006; Xing et al., 2021). Longitudinal studies have demonstrated that decreased white matter integrity predicts accelerated cognitive decline, MCI and dementia (Zeestraten et al., 2017) with increased risk for stroke and death (Debette & Markus, 2010; Kloppenborg et al., 2014; Prins & Scheltens, 2015; Verdelho et al., 2010).

*Hydrogen Sulfide and Its Metabolites in Vascular Dysfunction and Neuropathology*

Hydrogen sulfide and its metabolites are produced endogenously from cysteine by enzymes including cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) (Erickson, Maxwell, Su, Baumann, & Glode, 1990; Griffith, 1987; Stipanuk & Beck, 1982;

Swaroop et al., 1992). Hydrogen sulfide ($H_2S$) is an important gasotransmitter regulating both neuronal and vascular homeostasis (Vandiver & Snyder, 2012), H2S exerts both antioxidant and prooxidant effects (Olas, 2017). Sulfides exist in three pools: antioxidant *free* $H_2S$, *bound* (per- and poly-) sulfides, and *acid-labile* (e.g., iron-sulfur clusters) sulfides. In the vascular system, sulfides accomplish a wide range of inflammatory and immunoregulatory functions (Pan et al., 2017). Studies have demonstrated that hydrogen sulfide has vasodilatory actions with potent anti-inflammatory capabilities (Polhemus & Lefer, 2014). However, the role of $H_2S$ and its metabolites in disease pathophysiology is complex, with reports of both protective and damaging effects on the vasculature. Plasma sulfide levels are high in younger individuals, but decline with age (Y. H. Chen et al., 2005). Furthermore, plasma sulfides are protective in vascular disease (Kolluru, Shen, & Kevil, 2020), with decreased levels of bound, acid labile and total sulfides predicting cardiovascular disease risk (Rajpal et al., 2018).

Hydrogen sulfide has also been shown to be produced in the brain and its metabolites have been found in physiological functional concentration (Goodwin et al., 1989; Savage & Gould, 1990; Warenycia et al., 1989). In the nervous system free sulfide acts as a calcium-based neuromodulator (Yong, Choo, Tan, Low, & Bian, 2010). Furthermore, hydrogen sulfide may act as a neurotransmitter/second messenger following nerve excitation (Ishigami et al., 2009). It may also modulate NMDA receptors during long term potentiation which are thought to control synaptic plasticity mediating memory consolidation (Kimura, 2013). Studies have demonstrated that hydrogen sulfide is produced by cerebral microvessels, is protective against global and focal cerebral

ischemic injury (Gheibi et al., 2014; Yin et al., 2013), and preserves blood brain barrier integrity (Jiang et al., 2015; Y. Wang et al., 2014). Studies have also described that free sulfide preserves brain vasomotion (X. Y. Liu, Qian, & Wang, 2022).

Moreover, hydrogen sulfide has been shown to preserve cognitive performance in experimental models of dementia possibly by improving antioxidant status and attenuating oxidative stress (Giuliani et al., 2013; Kumar & Sandhir, 2018; Vandini et al., 2019) and inflammation (Fan et al., 2013) in vitro and in vivo. Conversely, $H_2S$ and its metabolites have been suggested to contribute to neurological stress and vascular dysfunction in Downs' syndrome (Kamoun, Belardinelli, Chabli, Lallouchi, & Chadefaux-Vekemans, 2003), schizophrenia (Ide et al., 2019) and stroke (Qu, Chen, Halliwell, Moore, & Wong, 2006), suggesting that "sulfide distress" contributes to cognitive dysfunction. In human AD our group recently discovered an increase in *total* plasma sulfides associated with increased acid-labile and bound sulfide species (E. Disbrow et al., 2021). Furthermore, total sulfides significantly mediated the relationship between measures of cerebrovascular disease and cognitive performance, indicating that sulfides may provide a valuable marker of the vascular contribution to ADRD. Here, I extend our previous work to test the hypothesis that plasma sulfides are associated with the brain atrophy and white matter deterioration characteristic of ADRD.

## EXPERIMENTS

*Specific Aims*

Ageing is characterized by progressive physiological deterioration and increased vulnerability to death and disease. While there are many risk factors for neurodegeneration, the ageing process has the greatest impact on disease and disease progression. Neurodegenerative diseases, specifically Parkinson's disease (PD) and Alzheimer's disease (AD), are observed primarily in older adults and are among the most common age-related diseases and causes of cognitive dysfunction. Parkinson's Disease (PD) is a progressive neurodegenerative disorder that is 1.5 times more common in males than females, and while motor progression tends to be more aggressive in males, little is known about the role sex plays in cognitive progression. The Movement Disorder Society Task Force set out 5 domains critical for the diagnosis of cognitive impairment in PD; however, our lab and others have shown that processing speed mediates cognitive dysfunction across these domains. Furthermore, Alzheimer's disease (AD) is characterized by a progressive decline in cognitive function, but recent evidence suggests that vascular stress is an important risk factor for AD and may accelerate early-stage progression and the "vascular stress hypothesis" is an emerging hypothesis of AD. What remains unknown is if markers of vascular dysfunction are associated with structural changes within the brain and cognitive dysfunction. **The central hypothesis of this dissertation is that sex and vascular disease play independent roles in cognitive deficits in Parkinson's disease and Alzheimer's disease respectively.**

Aim 1: Evaluate the contribution of sex in Parkinson's disease associated cognitive dysfunction.

Aim 1.1: Compare cognitive performance between males and females with PD in domains of attention and working memory, executive function, language, and processing speed.

Aim 1.2: Compare cognitive performance between males and females with PD in domains of verbal and visuospatial episodic memory and processing speed.

Aim 2: Evaluate the contribution of vascular dysregulation in Alzheimer's disease associated cognitive dysfunction and brain structural changes.

Chapter 1

# Sex specific cognitive dysfunction in Parkinson disease

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## INTRODUCTION

Parkinson Disease (PD) is a progressive neurodegenerative disorder traditionally characterized by motor signs (Hoehn & Yahr, 1967); however, cognitive dysfunction has been shown in patients even in the absence of Parkinson disease dementia (PDD), including impairments in executive function (Kudlicka, Clare, & Hindle, 2011; Litvan, Mohr, Williams, Gomez, & Chase, 1991; Muslimovic et al., 2005) , processing speed (E. A. Disbrow et al., 2014; Lanni et al., 2014; Zweig, Disbrow, & Javalkar, 2016), and spatial working memory (Caballol, Marti, & Tolosa, 2007; Emre, 2003b). In addition, PD is associated with increased risk for progressive cognitive decline from mild cognitive impairment (MCI) to dementia (Emre, 2003b). Prevalence estimates vary, but MCI affects nearly a fourth of PD patients, and dementia eventually affects over 80% of patients with 20-year survival (Pfeiffer, 2016).

PD is 1.5 times more common in males than females (Elbaz, Carcaillon, Kab, & Moisan, 2016). There is evidence that symptomatic PD onset is delayed in females (Haaxma et al., 2007; Twelves, Perkins, & Counsell, 2003), with females reporting fewer symptoms in the pre-clinical phase of PD. Females often develop a more benign PD tremor dominant (TD) phenotype (Haaxma et al., 2007) (67% compared to 48% in males) associated with less severe motor deterioration and localized basal ganglia degeneration as opposed to more wide-spread disease. In contrast, studies have shown that males more often present with a postural instability dominant phenotype involving postural instability and gait disturbances (PIGD), freezing of gait (56% male) and postural instability with falling (59% males) (Factor et al., 2011; Picillo et al., 2017). Interestingly,

the TD phenotype has been associated with less cognitive dysfunction (Alves et al., 2006; Burn et al., 2006), while PIGD is associated with greater deficits in executive function (Kelly et al., 2015; Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007; Zuo et al., 2017).

Sex differences across several cognitive domains have been described in healthy aging. Healthy aging males have been shown to out-perform females in tasks of visuospatial functioning; however, females performed significantly better in most other tasks of cognition (Lewin, Wolgers, & Herlitz, 2001; Loring-Meier & Halpern, 1999; McCarrey, An, Kitner-Triolo, Ferrucci, & Resnick, 2016). Furthermore, males had significantly steeper rates of decline across several cognitive domains, while females showed no greater decline across any measure (McCarrey et al., 2016). Sex differences in cognitive performance have been reported for brain-related diseases as well. For example, Weiss and colleagues (E. Weiss et al., 2003) found that, in patients with a range of psychiatric disorders, males outperformed females on tests assessing visuospatial ability while females performed better on tasks involving verbal acuity. This difference in affected cognitive domain was maintained across disease type (Lewin et al., 2001; Millet et al., 2009).

Cognitive decline in PD is associated with advanced age, disease progression, and male sex (Cereda et al., 2016; Elbaz et al., 2016); however, data on differences in cognitive impairment between males and females with PD is sparse. For example, Jankovic and Kapadia (Jankovic & Kapadia, 2001) found that males showed a steeper slope of decline

on all subscales of the UPDRS, including UPDRS I, which measures mentation, behavior and mood. This scale contains a single "mentation" question which requires the investigator to rate intellectual impairment on a scale of 0-4, with 1 = mild (Consistent forgetfulness with partial recollection of events and no other difficulties) and 4 = severe (Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all). Males declined more rapidly than females on the entire UPDRS I scale, though the slope of decline was less pronounced on UPDRS I than on UPDRS II (Activities of Daily living) or III (motor performance). However, other studies have found no differences in motor progression (Dahodwala, Pei, & Schmidt, 2016; Diamond, Markham, Hoehn, McDowell, & Muenter, 1990) and in early, untreated PD patients, females have shown poorer cognitive performance than males (Song et al., 2014).

Thus, there is a paucity of data describing sex differences in cognitive function, especially across specific cognitive domains. Therefore, we tested the hypothesis that there are sex differences in cognitive dysfunction in non-demented PD. We examined the domains of attention, working memory, verbal fluency, inhibition, switching and processing speed. Identifying sex differences in cognitive dysfunction may improve prediction, diagnosis, and early treatment of cognitive dysfunction in PD and has the potential to shed light on mechanisms of neuroprotection.

## METHODS

A total of 84 participants (38 female) with PD without dementia and 59 participants (27 female) without PD were recruited from movement disorder clinics, senior centers, support groups, and veteran's organizations. Information about the study was provided to potential participants in the form of group presentations and/or fliers, and interested individuals contacted the lab to volunteer. Self-reported sex was used to divide participants into male and female groups. Only male and female categorizations were reported. Participants were between the ages of 54 and 83 years. An inclusion criterion was PD previously diagnosed by a movement disorder neurologist with a positive history of pharmacological intervention with responses to levodopa and/or dopamine agonists (PD only). Other inclusion criteria were: native English speaking, and between the ages of 55 and 85. Exclusion criteria were traumatic head or spine injury, history of stroke, brain tumor, or drug abuse, and global cognitive impairment (Mini Mental State Exam score < 24). Additional variables, which were considered potential confounds, included: Geriatric Depression Scale (GDS), Epworth Sleepiness Scale (ESS), Premorbid IQ (NART-R), and dopamine equivalents. Participants with PD were administered the Unified Parkinson's Disease Rating Scale (UPDRS) to assess disease stage and symptom severity at the time of evaluation. All motor and cognitive testing was performed when participants with PD were at their best ON medication state, for example, after his/her morning dose. This study was approved by an institutional review board at University of California, Davis and Louisiana State University Health Sciences Center, Shreveport. All participants provided written informed consent. Data was collected between 5/10/2010 and 1/12/2017.

Demographic and disease state data, motor performance, as well as a battery of neuropsychological tests surveying a range of cognitive domains were collected from each participant. Cognitive domains tested included attention and working memory, executive function and processing speed. Each participant was tested in a private examination room by a trained psychological technician. Time of testing ranged from 2-4 hours and the tests were pseudorandomized across participants.

- *Mini-Mental State Examination* (MMSE) (Folstein, Folstein, & McHugh, 1975): This test is a commonly-used instrument to gauge global level of cognitive function in areas of orientation, registration, attention and calculation, recall, and language.
- *Epworth Sleepiness Scale* (ESS) (Johns, 1991): This test is a self-evaluation of daytime sleepiness used to gauge the propensity for sleep during eight daytime activities. Daytime sleepiness has been closely associated with PD, and has been shown to be associated with a steeper rate of cognitive decline than patients without daytime sleepiness (Tandberg, Larsen, & Karlsen, 1999).
- *North American Adult Reading Test, Revised* (NAART-R) (Blair & Spreen, 1989): This test is a measure used to predict premorbid intellectual function. As a measure of semantic memory, it is resistant to decline. The test requires examinees to pronounce irregularly spelled words.
- *Geriatric Depression Scale* (GDS) (Sheikh & Yesavage, 1986): This test is a self-reported measure of depression symptoms in elderly persons. It consists of 15 yes/no questions.

- Dopamine Equivalents were calculated according to Tomlinson and colleagues (Tomlinson et al., 2010).
- *The Unified Parkinson's Disease Rating Scale* (UPDRS) (Fahn & Elton, 1987): This test is a clinical scale used to determine the severity of Parkinson Disease. Areas surveyed include: 1) mentation, behavior and mood, 2) activities of daily living, and 3) motor performance. The UPDRS interview and clinical evaluation was administered by a nurse practitioner or a trained technician. Specific questions from the UPDRS were used to determine Tremor Dominant (TD) or Postural Instability/Gait Disturbances (PIGD) phenotypes (Stebbins et al., 2013).
- *Hoehn and Yahr scale* (H&Y) (Hoehn & Yahr, 1967): This scale is a measure of PD disease progression. A score of one through five is given with higher scores representing a more advanced disease stage.
- *WAIS-III Digit Span* (David Wechsler, 1997): This measure is divided into two separate tasks, digit span forward and digit span backwards. Digit span forward (DSF) requires the participant to verbally reproduce a given sequence of single-digit numbers. Digit span backward (DSB) requires the participant to retain and manipulate a given sequence but reproduce the sequence in reverse order. Both tasks use progressively longer sequences until the sequence can no longer be reproduced. Digit span forward is considered a test of simple auditory attention, and digit span backward is considered a test of auditory working memory.
- *The Delis-Kaplan Executive Function Scale (D-KEFS) Verbal Fluency (VF) Test* (D. C. Delis, Kramer, Kaplan, & Holdnack, 2004): This test measures verbal orthographic and semantic fluency through a series of three conditions: letter

fluency, category fluency, and category switching. The letter fluency trial consists of three trials where participants are asked to state as many words as possible beginning with a specific letter for one minute each. Category fluency consists of two trials where a category is provided and the participant states as many words within that category for one minute each. Finally, category switching is a single one-minute trial in which participants are required to switch between providing exemplars of two different categories. Total switching accuracy is the number of correct switches between categories.

- *The D-KEFS Color-Word Interference Test (CWI)* (D. C. Delis et al., 2004): This test includes four conditions: color naming, word reading, inhibition, and inhibition/switching. Color naming requires the participant to name the color of sequential blocks as quickly as possible. Word reading requires the participant to read color words printed in black text as quickly as possible. The inhibition task requires the participant to state the color of the ink in which a color word is printed, inhibiting the overlearned word reading response. Finally, the inhibition/switching task requires the participant to either state the ink color of the word, or if the word is located inside of a box, then the participant must switch and read the word instead of naming the ink color, thereby adding a cognitive flexibility element to the task.
- *The D-KEFS Trail Making Test (TMT)* (D. C. Delis et al., 2004): This test measures cognitive flexibility through a series of five conditions: visual scanning, number sequencing, letter sequencing, number-letter switching, and motor speed. In the scanning condition participants cross out targets in an array of distractors to

assess visual scanning difficulties that can impact performance on later conditions. The number and letter sequencing trials involve drawing lines to connect numbers then letters in order. These two conditions are included to ensure that sequencing abilities are intact prior to the switching condition in which participants must connect both letters and numbers in order but switching back and forth between the two categories (i.e., 1-A-2-B…) assessing cognitive flexibility. A final motor speed condition in which participants use a pencil to follow dashed lines is administered to assess general psychomotor slowing. This psychomotor slowing condition is subtracted from the switching condition (condition 4 minus 5) in order to isolate switching (cognitive flexibility).

- Symbol Digit Modalities Test (SDMT, Oral version) (Smith, 1982): This test is a measure of processing speed. The participant is presented with a decoded key containing corresponding symbols and numbers. The task is to correctly code as many symbols as possible in 90 seconds by verbally stating the number that goes with each symbol in order in a series of rows of randomly ordered symbols below the key.

Preliminary data on cognitive sex differences in PD were sparse, making it difficult to perform a meaningful sample size estimate. However, we were able to confirm adequate power for the current study using the SDMT data. We found that for 80% power with an alpha level of 5%, 32 subjects per group were required, which is in line with the reported results.

Data from all subjects who met inclusion and exclusion criteria were included in the analysis. Multivariant analysis of variance (MANOVA) was used to assess differences in demographic and descriptive variables across sex within disease category (healthy controls vs. PD). One-way ANOVA was used to assess differences between the sexes in PD subjects. All tests were two-tailed. To determine disease phenotype, calculations were performed based on Stebbins and colleagues using UPDRS scores (Stebbins et al., 2013), and chi-squared analysis was used to determine significant sex differences in the frequency of the phenotypes. Lastly, effect size for significantly different comparisons was calculated as Cohen's d.

To control for alpha inflation, we used MANOVA, which reduces family-wise error without assuming independence of the dependent variables (e.g. researchgate.net). Each MANOVA is considered single comparisons. In addition, justification for use of uncorrected alpha level = 0.05 comes from Ridker and colleagues(Ridker et al., 2008), who did not correct for multiple comparisons in a similar situation where the same basic question (in our case sex differences in cognition) was asked multiple times and all results pointed to the same conclusion.

## RESULTS

Multivariate ANOVA (MANOVA) revealed that there were no significant differences across sex in either control or PD groups for demographic variables including: age ($F(3,139) = 0.928$ $p = 0.429$), years of education ($F(3,139) = 0.647$, $p = 0.586$), MMSE score ($F(3,139) = 0.396$, $p = 0.756$), daytime sleepiness (ESS) ($F(3,139) = 2.179$, $p = 0.093$), or NART-R ($F(3,139) = 1.573$, $p = 0.199$). For the Geriatric Depression Scale (GDS) there were significant differences between control and PD groups; however, within disease category, there were no significant differences between sexes ($F(4,138) = 0.950$, $p = 0.331$; Table 1). In the control groups there were no significant sex differences on any cognitive outcomes.

In assessing motor performance across the PD groups, there were no differences by sex in dosage of dopamine equivalents ($F(1,76) = 0.260$, $p = 0.612$). Furthermore, there were no significant differences between sexes on any UPDRS subscale scores (Table 2), total score ($F(1,74) = 0.311$, $p = 0.579$) or H&Y scale score ($F(1,73) = 0.469$, $p = 0.496$), nor were there differences in disease duration ($F(1,68) = 1.744$, $p = 0.191$). Finally, the proportion of TD versus PIGD phonotypes did not significantly differ between the sexes, $X^2$ ($2$, $N = 75$) $= 0.010$, $p = 0.995$. Therefore, there were no significant differences in demographic variables, nor were there any significant differences between clinical presentation or disease severity across the sexes.

In tests of attention and memory there were no significant differences across sexes in PD the group for digit span forward ($F(1,83) = 0.106$, $p = 0.745$) or backward ($F(1,83) =$

1.202, p = 0.276) (Table 3). Executive functions were measured via the D-KEFS Verbal Fluency (VF), Color Word Interference (CWI), and Trail Making (TMT) tests. In the PD group, we found sex differences in VF category fluency (F (1,82) = 11.820, p < 0.001; Cohen's d=0.76), category switching (F (1,82) = 10.855, p < 0.001; Cohen's d=0.72), and category switching accuracy (F (1,82) = 6.026, p = 0.016; Cohen's d=0.54; Table 3). These data show that males with PD produced fewer words per category and fewer switches between categories compared to females. For CWI we found differences between sexes in the PD group on the inhibition measure (F (1,82) = 4.286, p = 0.042; Cohen's d=0.46) but not on the inhibition switching condition (F (1,82) = 0.801, p = 0.374; Table 4). Variability was high for inhibition switch. PD males took longer to complete the inhibition test than females. On the Trail Making Test, using condition 5 as a motor speed correction, we found a trend toward deficits in males switching ability (condition 4 minus 5; F (1,82) = 3.151, p = 0.080; Table 5). Finally, for speed of processing, there were significant differences between sexes in PD on the SDMT (F (1,86) = 4.824, p = 0.031; Cohen's d=0.48; Table 5). Males with PD completed fewer items on the SDMT in 90 seconds compared to females.

When comparing normed mean scores from disease and sex-based groups, a pattern emerged. In general, females and controls showed similar performance while males showed lower, usually below average scaled scores (Table 6). However, all scores tended to be in the normal range, within 1 SD of the mean. Groups in our study did not vary by age or years of education. The mean education level for all participants was

relatively high (approximately 16 years) and scaled scores from group means are consistently slightly above average for controls.

We calculated Cohen's d to evaluate effect size. We identified small (0.2-0.5) and medium (0.5-0.8) effect sizes(J. Cohen, 1988). The verbal fluency measures had the largest effect sizes (0.5-0.8), while SDMT (0.48), trail making (0.39), and inhibition (0.46) were small to medium. Interpreting these differences in the context of the tests themselves, we found that the difference in average letter fluency was approximately 3 responses, for category fluency was approximately 6 responses and for switch number was about 2 switches. Similarly, for SDMT the average difference in items completed across groups was approximately 6 items. The difference in average completion time for the inhibition task was about 10 seconds and trail making (condition 4-5) was about 20 seconds.

Table 1

| | N | Age (years) | Education (years) | MMSE | ESS | NART-R | GDS^ |
|---|---|---|---|---|---|---|---|
| Control (M) | 32 | 65.63 (5.84) | 16.53 (3.29) | 28.94 (1.01) | 7.25 (3.59) | 112.03 (9.28) | 2.75 (3.07) |
| Control (F) | 27 | 65.04 (6.93) | 16.59 (3.13) | 28.59 (1.39) | 6.33 (3.37) | 113.83 (5.44) | 2.82 (3.89) |
| PD (M) | 46 | 67.34 (6.45) | 15.83 (2.68) | 28.83 (1.25) | 8.46 (4.14) | 113.18 (7.77) | 6.15 (5.58) |
| PD (F) | 38 | 66.53 (5.97) | 16.50 (2.46) | 28.84 (1.31) | 8.63 (5.07) | 115.53 (6.36) | 4.76 (3.94) |

Table 1: Demographic Variables (^ = significant differences between control and PD groups, $p < 0.05$; no significant differences between sexes in control and PD groups)

Table 2

| | Dopamine Equivalent (mg) | H&Y (median) | UPDRS I | UPDRS II | UPDRS III | UPDRS IV | UPDRS Total |
|---|---|---|---|---|---|---|---|
| PD (M) | 591.05 (484.88) | 1.88 (0.84) | 2.44 (1.91) | 8.97 (5.38) | 20.08 (12.80) | 4.09 (2.95) | 36.22 (18.26) |
| PD (F) | 648.68 (499.56) | 2.02 (0.80) | 1.88 (1.64) | 9.34 (7.06) | 22.16 (13.43) | 5.44 (4.08) | 38.81 (22.29) |

Table 2: PD disease severity, dopamine equivalents and UPDRS scores in PD groups

Table 3

| | DSF | DSB | Letter Fluency | Category Fluency* | Category Switch* | Total Switch Accuracy* |
|---|---|---|---|---|---|---|
| Control (M) | 10.19 (2.47) | 7.41 (2.24) | 37.5 (11.04) | 39.5 (7.56) | 13.19 (3.29) | 11.47 (3.81) |
| Control (F) | 9.96 (2.08) | 6.56 (2.26) | 37.22 (9.48) | 42.26 (7.36) | 13.93 (2.97) | 11.96 (3.56) |
| PD (M) | 9.96 (2.32) | 6.50 (1.63) | 40.52 (13.08) | 35.72 (9.33) | 11.87 (2.79) | 10.37 (3.30) |
| PD (F) | 10.13 (1.71) | 7.00 (2.14) | 43.50 (12.18) | 42.06 (7.14) | 13.91 (2.86) | 12.21 (3.57) |

Table 3: WAIS-III digit span forward (DSF) and backward (DSB) and D'KEFS Verbal Fluency (VF) scores for category fluency, category switching, and total switching accuracy. (* = significant differences between sexes in PD group, $p < 0.05$).

Table 4

| | Color Naming | Word Naming | Inhibition* | Inhibition Switch |
|---|---|---|---|---|
| Control (M) | 32.14 (6.25) | 22.86 (4.42) | 61.11 (16.00) | 65.57 (15.07) |
| Control (F) | 29.73 (5.19) | 22.30 (2.85) | 60.86 (11.38) | 64.76 (12.46) |
| PD (M) | 35.25 (7.95) | 25.73 (6.07) | 73.82 (26.03) | 81.97 (29.00) |
| PD (F) | 33.26 (7.85) | 24.09 (4.99) | 63.65 (17.00) | 75.78 (34.44) |

Table 4: D'KEFS Color Word Interference (CWI) scores. (*= significant differences between sexes in PD group, $p < 0.05$)

Table 5

| | Condition 1# | Condition 2 | Condition 3* | Condition 4 | Condition 5 | 4 minus 5 | SDMT* |
|---|---|---|---|---|---|---|---|
| Control (M) | 26.90 (13.15) | 37.11 (15.02) | 35.13 (16.51) | 94.32 (38.99) | 26.40 (8.97) | 67.91 (38.34) | 51.21 (7.94) |
| Control (F) | 25.22 (6.95) | 34.71 (9.09) | 35.94 (11.74) | 83.12 (35.62) | 31.02 (11.71) | 52.11 (36.69) | 54.56 (8.14) |
| PD (M) | 34.89 (12.89) | 47.81 (19.18) | 51.71 (21.62) | 122.87 (56.33) | 46.03 (49.12) | 76.84 (51.43) | 42.28 (10.94) |
| PD (F) | 30.22 (8.65) | 44.84 (18.73) | 42.01 (15.38) | 103.37 (52.55) | 46.05 (26.07) | 57.32 (48.59) | 47.92 (12.58) |

Table 5: D'KEFS Trail Making Test (TMT) scores and SDMT scores. (# = trending differences between sexes in PD group; $p < 0.08$; * = significant differences between sexes in PD group, $p < 0.05$).

Table 6

| | Control (M) | Control (F) | PD (M) | PD (F) |
|---|---|---|---|---|
| VF Letter Fluency | 11 | 10 | 12 | 12 |
| VF Category Fluency* | 12 | 13 | 10 | 13 |
| VF Category Switch* | 11 | 12 | 9 | 12 |
| VF Total Switch Accuracy* | 10 | 11 | 9 | 11 |
| CWI Color Naming | 10 | 11 | 9 | 10 |
| CWI Word Naming | 11 | 11 | 10 | 10 |
| CWI Inhibition* | 10 | 10 | 7 | 9 |
| CWI Inhibition Switch | 12 | 12 | 9 | 10 |
| TMT Condition 1# | 10 | 11 | 7 | 9 |
| TMT Condition 2 | 12 | 12 | 10 | 10 |
| TMT Condition 3* | 12 | 12 | 10 | 11 |
| TMT Condition 4 | 11 | 12 | 9 | 11 |
| TMT Condition 5 | 12 | 11 | 9 | 9 |
| SDMT* | above average | above average | below average | average |

Table 6: Scaled scores for all reported measures.

For SDMT, the mean score for subjects >55 is 47.3 items for the oral test (Sheridan et al., 2006)

(# = trending differences between sexes in PD group $p < 0.08$; * = significant differences between sexes in PD group, $p < 0.05$)

## DISCUSSION

Males with PD had poorer performance on cognitive measures of verbal fluency, inhibition and processing speed compared to females, a difference that was not observed in healthy controls and could not be accounted for by demographic or disease variables. Switching measures showed higher variability and differences across sex were not significant. Nor were there differences in measures of working memory or attention. Thus, males showed consistently poorer performance across multiple cognitive domains.

Sex differences in cognitive function in PD are consistent with previous work on cognitive decline to dementia. For example, Cereda and colleagues(Cereda et al., 2016) found that male gender was a risk factor for dementia in PD. Similarly, a study by Cholerton and colleagues (Cholerton et al., 2018) showed that male sex was a predictor of cognitive decline from no impairment to MCI as well as from MCI to PDD. Furthermore, males had a more rapid progression of cognitive decline in processing speed and working memory (Cholerton et al., 2018). We extend this work by showing baseline sex differences in multiple cognitive domains for people with PD with MMSE scores in the normal range. Interestingly, Gao and colleagues(L. Gao et al., 2015) reported that cognitive disturbances were more severe in Chinese females than males with PD. Females presented with significantly lower scores on the MOCA (males=23.8 vs. females=20.6) after adjustment for disease duration and years of education, and females had a significantly lower level of education (males= 11.3 vs. females=8.2 years) which may explain this discrepancy. In our data, both global cognitive function and years of education were similar among males and females with PD.

One factor that has been proposed to explain sex differences in cognitive aging is related to cognitive reserve. Cognitive reserve, or an individual's ability to compensate for increasing brain pathophysiology, has been shown to develop through a combination of experiences through life, such as educational and occupational attainment (Mortimer, Snowdon, & Markesbery, 2003; Richards & Sacker, 2003; Stern, 2012). Cognitive reserve has been shown to contribute to delayed detection of AD and other related dementias (G. E. Alexander et al., 1997; Hindle et al., 2015; Scarmeas & Stern, 2003; Stern, Alexander, Prohovnik, & Mayeux, 1992). It has been proposed that the increased incidences of dementia in females may be related to reduced cognitive reserve (Musicco, 2009). It is known that differences between males and females are associated with both biological factors, including chromosomal and hormonal differences, and sociocultural differences between groups such as: environmental (e.g. toxicant) exposures, occupation, and educational expectations and access (Mielke, Vemuri, & Rocca, 2014; Regitz-Zagrosek, 2012).

The fact that historically females received less educational access than males has been referred to as "the educational gender gap" (Todaro, 1977). While the gender gap has been largely overcome in education, an elderly cohort like ours could have been subject to gender disparities in educational access and attainment (K. L. Alexander & Eckland, 1974). However, in both control and PD groups we found no sex differences in predicted premorbid IQ or years of education. It is also universally maintained that there are no significant differences between males and females with respect to IQ (Lynn, 1999).

Furthermore, occupation and educational achievement have been most closely associated with IQ (Crawford & Allan, 1996). Here we demonstrate that in PD, males show consistently greater deficits in cognitive function than females even though the groups were matched for several variables that are associated with cognitive reserve. Thus, cognitive reserve is not likely to contribute significantly to the observed sex differences in cognitive performance.

Two PD phenotypes have been described based on motor signs: postural instability/gait disturbance (PIGD) dominant and tremor dominant (TD). PIGD is more common in men (Haaxma et al., 2007), and is associated with increased disease severity, including more profound balance and gait disturbance, bradykinesia and cognitive impairments compared to patients presenting with TD (Alves et al., 2006; Burn et al., 2006; Haaxma et al., 2007; Jankovic & Kapadia, 2001; Jankovic et al., 1990; Kelly et al., 2015; Williams-Gray et al., 2007; Zuo et al., 2017). In contrast, TD is more common in women and is associated with earlier age of onset, less cognitive impairment and slower overall progression of the disease (Burn et al., 2006; Jankovic & Kapadia, 2001; Jankovic et al., 1990).

Burn and colleagues (Burn et al., 2006) described a faster rate of cognitive decline in patients with PIGD motor subtype. Furthermore, Jankovic and Kapadia (Jankovic & Kapadia, 2001) found that PIGD was associated with a steeper annual rate of global decline compared to TD in areas of mentation, behavior and mood, activities of daily living, and motor performance. Recently, Kelly and colleagues (Kelly et al., 2015) found that deficits in global cognition, specifically executive function, memory, and phonemic

fluency, were associated with PIGD symptom severity. Moreover, they found that executive function deficits were associated with gait disturbance, freezing, and postural stability impairments(Kelly et al., 2015).

Our finding that men are more cognitively impaired than women appears in agreement with this phenotypic profile, assuming that PIGD is more common in men and is associated with greater cognitive decline. PD symptomatology reflects dopaminergic as well as more wide-spread Lewy body pathology, and males may be more vulnerable to the widespread pathology that affects gait and cognitive function associated with the PIGD phenotype (Zweig et al., 2016). In our sample, the proportion of TD/PIGD phenotype was similar in the male and female groups based on a subset of UPDRS items, indicating that phenotype likely does not account for the cognitive difference between males and females observed here. However, our sample size was likely too small (less than 20 per group in some cases) and underpowered to make a definitive statement on a sex x phenotype interaction.

Our data suggest that non-demented male patients with PD represent a disease subgroup that is more vulnerable to cognitive impairment. Furthermore, we found that sex is more strongly associated with cognitive performance than motor phenotype. Identification of disease subgroups is an important step in the understanding and treatment of the disease.

Chapter 2

# Sex Differences in Parkinson Disease Associated Episodic Memory and Processing Speed Deficits

Reekes T, Higginson CI, Sigvardt KA, King DS, Levine D, Wheelock VL, et al. (Under Review) Sex Differences in Deficits across Memory Subtypes in Parkinson Disease.

## INTRODUCTION

Parkinson Disease (PD) disproportionately affects individuals by sex; the incidence is 1.5 times higher in males than in females (Elbaz et al., 2016). There is evidence that disease onset is earlier in males (Haaxma et al., 2007; Klebe et al., 2013), and that disease severity is greater in males (Picillo et al., 2017; Solla et al., 2012; Szewczyk-Krolikowski et al., 2014). For example, Lubomski and colleagues (2013) found that males had significantly higher scores on the UPDRS motor evaluation after adjustment for age and disease duration, and males required higher doses of pharmacological intervention, relied more heavily on caretakers, and reported lower quality of life scores regarding activities of daily living, communication, and cognition. In contrast, females reported fewer symptoms than males, although they did show higher levels of complications from symptoms such as greater distress from depression (Scott, Borgman, Engler, Johnels, & Aquilonius, 2000). Male sex has been shown to be a predictor of cognitive decline (Cereda et al., 2016; Cholerton et al., 2018) and cognitively normal men with PD have been shown to progress at a steeper rate than females (Cholerton et al., 2018; Pigott et al., 2015) with an increased risk for dementia (Cereda et al., 2016). Conversely, females more often present with a tremor dominant phenotype, which is associated with less severe motor symptoms and cognitive difficulties (Haaxma et al., 2007; Twelves et al., 2003).

PD is known to affect an array of cognitive functions. Inhibition, switching, sequencing (Kudlicka et al., 2011; Litvan et al., 1991; Muslimovic et al., 2005; Shook et al., 2005), spatial working memory (Caballol et al., 2007; Emre, 2003a), processing speed (E. A. Disbrow et al., 2014; Hansch et al., 1982; Lanni et al., 2014; Nguyen et al., 2017;

Pal et al., 2016; Vriend et al., 2020; Zweig et al., 2016), and working and recognition memory (Dubois & Pillon, 1997; Higginson, Wheelock, Carroll, & Sigvardt, 2005) have all been implicated. Therefore, the Movement Disorder Task Force (Litvan et al., 2012) suggest five cognitive domains relevant to the evaluation of cognitive impairment in PD: attention and working memory, executive function, language, ~~episodic~~ memory (unspecified), and visuospatial function. Although deficits in all these domains have been reported in PD, and cognitive deficits are associated with motor symptom phenotypes that differentially impact males and females, the presence of cognitive sex differences has not been extensively studied. While there is accumulating evidence of sex differences in PD-associated cognitive dysfunction in domains such as executive function (Cholerton et al., 2018; A. F. Curtis, Masellis, Camicioli, Davidson, & Tierney, 2019; Reekes et al., 2020) and elements of visuospatial function (Bayram, Banks, et al., 2020; R. Liu et al., 2015; Locascio, Corkin, & Growdon, 2003; Riedel et al., 2008), there is scant or inconsistent data on sex differences in areas such as verbal and visuospatial episodic memory, and processing speed (Bayram, Banks, et al., 2020; Cholerton et al., 2018; Reekes et al., 2020).

Existing data on sex differences of verbal episodic memory in PD is limited to simple list learning tasks including the Hopkin's Verbal Learning Test-Revised (HVLT-R; (Bayram, Banks, et al., 2020; R. Liu et al., 2015), and the Auditory Verbal Learning Test-Long (AVLT; (K. Yang et al., 2018). Episodic memory of visuospatial material has yet to be evaluated. There is existing data showing sex differences in visuospatial processing that does not involve memory in PD though findings are mixed. Studies have shown that males performed significantly better on the Benton Judgement of Line Orientation test

(Bayram, Banks, et al., 2020; R. Liu et al., 2015). Males have also shown superior visuo-construction and spatial reasoning on a clock drawing task (Riedel et al., 2008). Interestingly, Locascio and colleagues (2003) found that while males performed better on the Money Road Map test, over time male performance declined at a faster rate than female performance. Others have found similar performance between males and females with PD on visuospatial functions. Amick et al., (2007) found no sex differences using a mental rotation test. Similarly, a recent meta-analysis found no difference in visuospatial ability by sex in PD (A. F. Curtis et al., 2019).

Complicating the comparison of cognitive dysfunction across sex is the fact that, in healthy control populations (including adult and aging adult populations), studies show that females outperform males on tasks of verbal memory, but not on spatial memory tasks (A. Herlitz & Yonker, 2002; Lundervold, Wollschlager, & Wehling, 2014; Sundararaman et al., 2016).

It is well-established that persons with PD perform significantly worse on measures of processing speed compared to healthy controls. However, reports of sex differences in processing speed in PD are mixed. Some studies have shown that females with PD outperform males on digit symbol substitution tasks such as the SDMT (Reekes et al., 2020) and coding (Cholerton et al., 2018). Recently, a report of data from the Parkinson's Progression Markers Initiative (PPMI) found that while females outperformed males on the SDMT, decline over time did not differ by sex (Bayram, Banks, et al., 2020). However, others reported no significant sex differences on the SDMT (R. Liu et al., 2015).

Thus, while there is accumulating evidence that cognitive dysfunction in PD disproportionately affects males (Cereda et al., 2016; R. Liu et al., 2015; Lubomski et al.,

2013; Reekes et al., 2020) reports of sex differences across various cognitive domains remain inconsistent and incomplete. Therefore, we evaluated sex-specific cognitive differences in verbal and visuospatial episodic memory as well as processing speed. Based on previous findings regarding male disease severity and normal cognitive function, we expected poorer male recall on verbal and visuospatial episodic memory tasks and poorer performance on measures of processing speed in PD. Extending previous work on cognitive sex differences to include cognitive domains thought to be associated with MCI in PD (Litvan et al., 2012) will improve our understanding of disease subgroups, which is critical for clinical intervention.

## METHODS

The sample consisted of 182 individuals with idiopathic PD [59 female, consistent with increased incidence in males (Dorsey et al., 2018)] who were recruited as potential candidates for deep brain stimulation (DBS) surgical intervention. All individuals with PD were diagnosed by a board-certified neurologist based on DSM-IV-TR criteria. Individuals included in the current analysis were between the ages of 50 and 82 years. Sex was determined by self-report and only those entered as male or female were included. Exclusion criteria were history of functional neurosurgical intervention, diagnosis of other neurological illness or any other medical illness that could impact cognitive function. Individuals receiving a diagnosis of dementia by DSM-IV criteria were excluded. This study was approved by an Institutional Review Board at University of California, Davis and was completed in accordance with the Helsinki Declaration.

Demographic information was collected from each individual, including: age, years of education, disease duration, and pertinent personal and family history. In addition to demographic information, a large battery of neuropsychological measures was administered to each individual as part of his/her pre-surgical assessment. This battery included tests of global cognitive function, attention and working memory, executive function, language, memory, visuospatial function, and processing speed. We focused on verbal and visuospatial episodic memory because results are spare or contradictory. There is pervious work evaluating sex differences in domains of attention and working memory (Bayram, Banks, et al., 2020; R. Liu et al., 2015; Reekes et al., 2020), executive function (Cholerton et al., 2018; A. F. Curtis et al., 2019; Reekes et al., 2020), language

(Auclair-Ouellet et al., 2021; Locascio et al., 2003; Reifegerste et al., 2020), and visuospatial function (Bayram, Banks, et al., 2020; A. F. Curtis et al., 2019; Riedel et al., 2008). All individuals were tested in his or her best “On” medication state.

Instruments

*Unified Parkinson’s Disease Rating Scale (UPDRS)*

The UPDRS (Fahn & Elton, 1987) is a clinical scale used to determine the severity of Parkinson Disease. Areas surveyed include: (I) mentation, behavior, and mood; (II) activities of daily living, (III) motor performance, and (IV) complications in therapy. Scores from UPDRS III (motor evaluation) questions 20 (Tremor at Rest), 21 (Action or Postural Tremor of Hands) and 22 (Rigidity) for dominant hand/limb were also compared across groups.

*California Verbal Learning Test (CVLT)*

The CVLT (Dean C Delis, Kramer, Kaplan, & Ober, 1987) measures the ability to retain an orally presented list of words belonging to four distinct semantic categories. Examinees are read the same 16-item word list 5 times and asked to spontaneously recall as many words as possible after each presentation. The total number of words recalled on the five learning trials is an index of immediate recall. After a second, interference list is presented and recall of it tested, free and cued recall of the first list is assessed. Long delay free recall (LDFR) is measured by asking examinees to spontaneously recall words from the first list after a filled 20-minute delay. This edition of the CVLT was the most recent edition published at the time of data collection.

*Wechsler Memory Scale 3rd edition (WMS-III)*

The WMS-III (D Wechsler, 1997b) is used to assess various elements of episodic memory. The WMS-III consists of multiple subtests including measures of immediate and delayed auditory and verbal memory used in combination to produce composite index scores. This edition of the WMS was the most recent edition published at the time of data collection.

- Auditory Memory

The Auditory Memory Index measures the ability to retain orally presented information. The subtests contributing to the index are immediate and delayed portions of Logical Memory and Verbal Paired Associates. The stimuli for Logical Memory are brief prose passages. Examinees are read two stories and asked to repeat the content from memory. Responses are scored for content which is given credit regardless of the order in which it is described. The stimuli for Verbal Paired Associates are a series of word pairs. Following presentation, examinees are presented a word from each pair and asked to recall the paired word. These subtests also involve the same stimuli as those from their immediate index counterparts; however, examinees are asked to recall the information after a filled 30-minute delay interval (Auditory Delayed Memory, composed of Logical Memory II & Verbal Paired Associates II).

- Visual Memory

The Visual Memory Index measures the ability to recall visually presented information immediately after presentation. The subtests contributing to the Visual Memory index are the immediate and delayed portions of Faces and Family Pictures. Faces I involves the

presentation of a set of pictures of faces one at a time immediately followed by presentation of pairs of face pictures with the examinee having to recognize which of the two faces was previously presented. In Family Pictures, examinees are shown illustrations of families engaging in various activities and asked to answer questions about the pictures immediately after presentation. These subtests also involve the same stimuli as those from their immediate index counterparts; however, examinees are asked to recall or recognize the information after a filled 30-minute delay interval (Visual Delayed Memory, composed of Faces II & Family Pictures II).

*Wechsler Adult Intelligence Scale 3rd edition*

The WAIS-III (D Wechsler, 1997a) is used to assess various elements of intelligence and cognitive ability. The WAIS-III consists of thirteen subtests of attention, visuospatial and construction skills and semantic memory used in combination to produce index scores as well as verbal, performance and full-scale intelligence quotients (IQ). This edition of the WAIS was the most recent edition published at the time of data collection.

- Processing Speed

The Processing Speed Index measures the ability to respond to sequential stimuli in constrained time. The subtests contributing to the Processing Speed index are Digit Symbol Coding and Symbol Search. Digit Symbol Coding requires individuals to decode a series of symbols using a continually presented key of symbols with corresponding numbers. Symbol Search requires individuals to view a simple figure and identify if that symbol is or is not contained within a short series of test figures. Each of these tests ask individuals to complete as many items as possible in 90 seconds.

## Statistical Analysis

One way analysis of variance (ANOVA) using sex as our dependent variable age was performed for demographic and disease descriptive variables. Three multivariate analysis of covariance (MANCOVA) using sex as our dependent variable and age and years of education as covariates was performed for each cognitive domain (verbal episodic memory, visuospatial episodic memory and processing speed) using SPSS (IBM v26). Each analysis was considered a single comparison reducing family-wise error by assuming independence of the dependent variables (Foster et al., 2018). Thus, we corrected for three comparisons and used an alpha of $p < 0.017$ (=0.05/3) as the cut off for significance. There is also precedent for using a less stringent alpha cut off when the nature of the multiple comparisons (sex differences in cognitive function) is the same across comparisons and points to a similar conclusion (e.g. (Ridker et al., 2008). Effect size (Cohen's *d*) was calculated using the formula described by Cohen (1988).

## RESULTS

### Group Differences

Demographic data is contained in Table 7 and disease descriptive data in Table 8. One-way ANOVA revealed no significant differences between sexes in people with PD for age ($F(1,165) = 0.076$, $p = 0.783$), full scale IQ ($F(1,157) = 1.105$, $p = 0.295$) or MMSE score ($F(1,165) = 0.318$, $p = 0.574$). There was a significant difference in years of education favoring males ($F(1,165) = 6.246$, $p = 0.013$), thus years of education was also used as a covariate in all analyses of cognitive measures. Nor were differences seen in disease descriptive variables such as illness duration ($F(1,60) = 0.023$, $p = 0.880$), Hoehn & Yahr Scale ($F(1,91) = 1.289$, $p = 0.259$), or UPDRS I ($F(1,107) = 0.183$, $p = 0.670$), II ($F(1,106) = 3.113$, $p = 0.081$) or III ($F(1,106) = 0.957$, $p = 0.330$); however, females described more complications of therapy indicated by higher UPDRS IV scores ($F(1,105) = 6.565$, $p = 0.012$). Moreover, no difference was seen for dominant hand/limb resting tremor ($F(1,93) = 0.222$, $p = 0.630$), action or postural hand tremor ($F(1,81) = 2.354$, $p = 0.129$) or rigidity ($F(1,94) = 0.213$, $p = 0.645$).

In the verbal episodic memory tasks, results from the CVLT (Table 9) showed significant differences by sex in immediate free recall ($F(3,151) = 19.310$, $p < 0.001$, Cohen's $d = 0.62$) and long delayed free recall ($F(3,151) = 10.072$, $p = 0.002$, Cohen's $d = 0.43$) with females outperforming males. However, we saw no differences between males and females after alpha correction on the WMS-III immediate verbal episodic memory tasks (Table 10) of Logical Memory I ($F(3,151) = 2.495$, $p = 0.116$) and Verbal Paired Associates I ($F(3,151) = 5.730$, $p = 0.018$), nor delayed verbal episodic memory tasks of

Logical Memory II ($F(3,151) = 4.036$, $p = 0.046$) or Verbal Paired Associates II ($F(3,151) = 1.695$, $p = 0.195$).

Results were variable on tasks of visuospatial ability (Table 11). Female performance was not significantly different from males on the immediate ($F(3,158) = 2.425$, $p = 0.121$) or delayed ($F(3,158) = 0.043$, $p = 0.835$) recall portion of the WMS-III Faces subtest, but females did outperform males on Family Pictures I $F(3,158) = 9.005$, $p = 0.003$, Cohen's $d = 0.44$) and Family Pictures II ($F(3,158) = 7.574$, $p = 0.007$, Cohen's $d = 0.41$).

Finally, for processing speed (Table 12), we found a trend in superior performance by females compared to males on Digit Symbol Coding ($F(3,140) = 5.499$, $p = 0.020$, Cohen's $d = 0.28$) but not on Symbol Search ($F(3,140) = 2.103$, $p = 0.149$).

| | N | Age (years) | Education (years)* | Full Scale IQ | MMSE |
|---|---|---|---|---|---|
| Male | 111 | 65.82 (7.78) | 15.07 (3.20) | 98.09 (14.55) | 26.77 (2.27) |
| Range | | 50 - 82 | 8 - 21 | 64 - 134 | 20 - 30 |
| Female | 56 | 65.46 (7.98) | 13.80 (2.88) | 95.66 (12.61) | 26.98 (2.48) |
| Range | | 50 - 82 | 6 - 21 | 70 - 122 | 20 - 30 |

Table 7: Demographic variables of age, years of education, IQ and global cognitive status. *Significant difference between sexes, $p < 0.05$.

| | Illness Duration (years) | UPDRS I | UPDRS II | UPDRS III | UPDRS IV* | Hoehn & Yahr (median) | UPDRS III Q20 | UPDRS III Q21 | UPDRS III Q22 |
|---|---|---|---|---|---|---|---|---|---|
| Male | 11.89 (5.57) | 3.04 (1.87) | 9.77 (6.14) | 10.84 (6.75) | 8.53 (4.11) | 2 | 0.34 (0.70) | 0.35 (0.72) | 0.72 (0.80) |
| Range | 1 - 28 | 0 - 8 | 0 - 29 | 0 - 27 | 0 - 18 | 0 - 3 | 0 - 3 | 0 - 3 | 0 - 3 |
| Female | 11.67 (6.02) | 3.21 (1.89) | 12.24 (7.85) | 12.30 (8.03) | 10.73 (4.09) | 2.5 | 0.26 (0.81) | 0.13 (0.55) | 0.65 (0.71) |
| Range | 1 - 30 | 0 - 8 | 0 - 33 | 0 - 37 | 0 - 17 | 0 - 3 | 0 - 3 | 0 - 3 | 0 - 2 |

Table 8: Disease descriptive variables of illness duration, UPDRS I-IV, Hoehn and Yahr scale and questions from UPDRS-III on tremor and rigidity, *$p < 0.05$.

| | Total Words 1-5* | LDFR* |
|---|---|---|
| Male | 37.81 (10.92) | 7.44 (3.84) |
| Female | 45.00 (11.65) | 9.06 (3.33) |
| Cohen's d | 0.62 | 0.43 |

Table 9: Significant difference between sexes (*p < 0.017) on the California Verbal Learning Test (CVLT) in total words produced through trials 1-5 and long delayed free recall. Values indicate mean number of correct responses with standard deviations in parentheses.

| | Logical Memory I | Logical Memory II | Verbal Paired Associates I | Verbal Paired Associates II |
|---|---|---|---|---|
| Male | 31.09 (13.13) | 16.40 (7.96) | 12.64 (8.44) | 4.59 (3.50) |
| Female | 32.83 (10.77) | 18.29 (8.18) | 15.00 (7.42) | 4.98 (2.41) |

Table 10: No statistical differences were seen between sex on immediate and delayed portions of the Wechsler Memory Scale (WMS-III) verbal memory subscales of Logical Memory and Verbal Paired Associates. Values indicate mean number of correct responses with standard deviations in parentheses.

| | Faces I | Faces II | Family Picture I* | Family Pictures II* |
|---|---|---|---|---|
| Male | 31.93 (5.08) | 32.74 (11.64) | 26.47 (11.11) | 26.20 (12.05) |
| Female | 33.15 (5.10) | 33.07 (4.97) | 31.58 (11.65) | 31.15 (11.89) |
| Cohen's d | | | 0.44 | 0.41 |

Table 11: Significant difference between sexes (*$p < 0.017$) on immediate and delayed portions of the Wechsler Memory Scale (WMS-III) visual memory Family Pictures subscale. Values indicate mean number of correct responses with standard deviations in parentheses.

| | Digit Symbol Coding[#] | Symbol Search |
|---|---|---|
| Male | 41.49 (18.23) | 19.48 (8.19) |
| Female | 46.92 (17.72) | 21.65 (9.38) |
| Cohen's d | 0.30 | |

Table 12: Significant difference between sexes ($^{\#}p < 0.026$) on the Wechsler Memory Scale (WMS-III) processing speed subscales. Values indicate mean number of correct responses with standard deviations in parentheses.

## DISCUSSION

We evaluated sex differences in both verbal and visual episodic memory as well as processing speed in persons with Parkinson disease. We found that males with PD performed significantly worse on several tests of episodic memory involving verbal and visuospatial memory and processing speed despite no differences in disease descriptive data and controlling for age and greater years of education in males. Our findings are consistent with other reports showing superior performance in verbal episodic memory (R. Liu et al., 2015; K. Yang et al., 2018) and processing speed (Bayram, Banks, et al., 2020; Cholerton et al., 2018; Reekes et al., 2020) in females with PD. While we found no differences in measures of visuospatial recognition memory (Faces I and II), we extend previous work by reporting that males with PD performed significantly worse on tests of immediate and delayed visuospatial recall (Family Pictures I and II).

### *Episodic Memory*

On measures of verbal episodic memory, we found that females with PD demonstrated significantly stronger performance in word recall compared to males with PD. Research on healthy controls shows superior performance by females on episodic memory tasks including autobiographical memory using the Autobiographical Interview (Fuentes & Desrocher, 2013) and verbal memory such as word recall (Dixon et al., 2004; Agneta Herlitz & Rehnman, 2008) and word, sentence and prose recall (Asperholm, Nagar, Dekhtyar, & Herlitz, 2019; Asperholm, van Leuven, & Herlitz, 2020).

Our findings on visuospatial memory were mixed. We found a significant male deficit in the delayed Family Pictures subtest but not in the delayed Faces subtest. This discrepancy may be because Family Pictures is a free recall measure whereas Faces involves recognition memory, and recognition memory has been shown to be relatively preserved in PD (Whittington, Podd, & Kan, 2000). Differences in performance between the sexes on these two tasks could also be due to the potentially larger spatial memory component in Family Pictures compared to Faces. However, this discrepancy would predict better performance in men than women on Family Pictures, a pattern of performance opposite to the one observed here. In studies by Dulay and colleagues (2002) and Chapin and colleagues (2009), Family Picture performance was best predicted by performance on other measures of declarative memory such as logical memory, suggesting that Family Pictures could be encoded verbally, and thus have both a visual and a verbal memory component. Indeed, the stimuli used in Family Pictures illustrate stories. Therefore, our observed sex differences may reflect the generally superior verbal skills of females rather than reflecting a deficit in visual memory skills.

*Processing Speed*

Increased adult age is associated with a slowing of processing speed resulting in impaired temporal capacity (limited time) and degradation of quantity and/or quality of available information (simultaneity), which degrades executive and other cognitive functions (Cummings, 1993; Salthouse, 1996). In healthy aging, deficits in processing speed have been postulated to subserve cognitive decline across a wide range of domains (Salthouse, 1996). However, findings of sex differences in processing speed in PD

remain mixed with some studies reporting superior female performance (Bayram, Banks, et al., 2020; Cholerton et al., 2018; Reekes et al., 2020) while others report no differences between male and females with PD (M. L. Chen et al., 2021; R. Liu et al., 2015). Our lab has shown that deficits in processing speed mediate the relationship between age and executive dysfunction in persons with PD (Nguyen et al., 2017). Moreover, in individuals with PD, processing speed deficits have been associated with progression from PD mild cognitive impairment to Parkinson Disease Dementia (Cholerton et al., 2018). Therefore, sex differences in processing speed may be associated with sex specific deficits across a range of cognitive domains.

*Common Mechanism for Cognitive Deficits Across Domains?*

Basal ganglia degeneration, the hallmark pathophysiological change of PD, is known to disrupt five cortico-basal ganglia-thalamo-cortical loops (G. E. Alexander, DeLong, & Strick, 1986). Specifically, the associative loop has connections to frontal lobe, which has long been associated with cognitive changes in PD (Auning et al., 2014; Kudlicka et al., 2011; Paek, Murray, & Newman, 2020) and that dopamine deficiencies negatively affect attention, stimulus distinction, affective regulation, and motor abilities (Mehler-Wex, Riederer, & Gerlach, 2006; Nieoullon, 2002). Mattay (2002) also found that individuals with PD in a hypodopaminergic state had reduced efficiency of prefrontal cortical information processing. Later studies postulated that disruption to white matter connectivity and integrity was linked to cognitive dysfunction in PD and may serve as an early indicator of cognitive decline and PD disease progression (Linortner et al., 2020; Melzer et al., 2013; Rektor et al., 2018).

Interestingly, in addition to the hippocampus, memory has a strong frontal lobe component, subserving working memory as well as the encoding and retrieval of episodic memories (Fletcher & Henson, 2001). Frontal lobe dysfunction is common in PD (A. E. Taylor, Saint-Cyr, & Lang, 1986) and has been implicated in free recall and recognition of verbal memory in PD (Higginson et al., 2003a; Higginson et al., 2005). Prefrontal cortex is also involved in the processing (Chafee & Goldman-Rakic, 2000) and maintenance (Aysenil Belger et al., 1998; G. McCarthy et al., 1996) of visuospatial material in working memory. PD associated prefrontal cortex damage has been linked to visuospatial recognition memory deficits (Owen et al., 1993) as well as visuospatial working memory. Visuospatial working memory has been identified as a core feature of PD (Owen, 1997; Owen et al., 1993). Furthermore, processing speed is associated with frontal-subcortical circuits, as well as disruption to frontal lobe white matter integrity (Turken et al., 2008). Thus, findings of sex differences in hippocampal dependent episodic memory functions are largely consistent with superior healthy female performance on verbal-based tasks. However, our finding of deficits in male visuospatial episodic memory and processing speed commonly associated with hippocampal and frontal lobe function, and frontal lobe white matter, respectively, suggest that there may be sex specific mechanisms that impact frontal lobe deterioration in PD.

## LIMITATIONS TO THE STUDY

This study consisted of presurgical assessments for individuals with PD eligible for DBS surgery. Levodopa equivalent dose was not collected in this study, but several studies have found no sex differences in dose (Reekes et al., 2020; Solla et al., 2012) and or type of medication (Umeh et al., 2014). Furthermore, no control group was collected for this study; however, the differences between PD and control groups in cognitive function has been extensively reported. The cross-sectional design of this study is not as reliable or powerful as a longitudinal design. Effect sizes, however, were in the small to medium range presented by Cohen, and while modest, are consistent in direction with existing literature and provide a first look at sex differences in memory subtypes in individuals with PD. Moreover, this study used the first edition of the CVLT and the third edition of the WMS which were the most current at the time this data was collected. Due to these limitations, the results should be interpreted with care.

# Chapter 3

## Elevated Sulfides are associated with Cognitive Dysfunction and Brain Atrophy in Alzheimer's Disease and Related Dementias

Reekes TH, Ledbetter CR, Pardue S, Alexander JS, Stokes KY, Bhuiyan MAN, Patterson JC, Lofton KT, Kevil CG, Disbrow EA. (In Preparation) Elevated Sulfides are associated with Cognitive Dysfunction and Brain Atrophy in Alzheimer's Disease and Related Dementias.

## INTRODUCTION

Alzheimer's disease (AD) is characterized by progressive cognitive deficits (Bäckman et al., 2004), specifically in episodic memory (Albert, 1996) as well as progressive brain atrophy (Pini et al., 2016). However, the disease mechanism underlying these deficits is incompletely understood. The amyloid cascade hypothesis, which describes the accumulation of beta amyloid (Aβ) plaques and phosphorylated tau (p-tau) neurofibrillary tangles, has been suggested as a primary mechanism of AD (Barage & Sonawane, 2015; Hardy & Higgins, 1992; Karran, Mercken, & De Strooper, 2011). However, recent evidence suggests that vascular stress is also an important risk factor for AD and may accelerate progression from early to late-stage disease (Santos et al., 2017).

The "vascular dysregulation hypothesis" proposes that vascular deficits intensify other common AD pathological contributors such as amyloid deposition, glial activation and metabolic dysfunction, creating a feedback cycle that synergistically advances both AD and vascular pathology (Govindpani et al., 2019). For example, chronic cerebral hypoperfusion has been linked to cognitive deficits (Safouris et al., 2015) and neurodegeneration (Broughton et al., 2009).Cardiovascular risk factors such as hypertension, hyperlipidemia, atherosclerosis, diabetes and smoking all contribute to the pathogenesis of chronic cerebral hypoperfusion (Meyer et al., 2000; Valerio Romanini et al., 2013) and may independently incur increased risk for AD. Chronic hypertension causes endothelial dysfunction, arterial stiffness and atherosclerosis which may lead to cerebral hypoperfusion, ischemia and hypoxia (Katayama & Hasebe, 2013; C. Qiu et al., 2005). Moreover, chronic systolic hypertension has been shown to increase AD risk by

up to 25% (Lennon et al., 2019). Midlife hypertension is also linked with ADRD risk (de Bruijn & Ikram, 2014; Iadecola, 2014) independently of other cardiovascular risk factors (Iadecola, 2014; C. Qiu et al., 2005), and high cholesterol has been shown to be associated with AD (Sjogren et al., 2006), including increased Aβ production (Martins et al., 2006; Sjogren et al., 2006; Troncone et al., 2016). A major identified risk factor for AD is the E4 allele of apolipoprotein (ApoE; (Poirier et al., 1993; Strittmatter et al., 1993), which is involved in the transport and metabolism of lipids (Martins et al., 2006) and carriers of ApoE4 are reported to have higher cholesterol levels than non-carriers (de Bruijn & Ikram, 2014).

Cerebral hypoperfusion may exacerbate AD pathology through increased Aβ aggregation and hyperphosphorylated tau (Pluta et al., 2016; L. Qiu et al., 2016). Evidence has suggested that there is a relationship between Aβ and vascular dysfunction with as many as 80% of AD patients showing some degree of cerebral amyloid angiopathy (CAA; (Biffi & Greenberg, 2011; Reijmer et al., 2016)) characterized by acellular thickening of small and medium arterial walls (Vinters, 1987). Cerebral hypoperfusion may promote neurodegeneration through disrupted redox status including the production of reactive oxygen species, peroxides and proinflammatory cytokines (Zhao & Gong, 2015) and may trigger apoptosis (Broughton et al., 2009). Thomas and colleagues (1996) found that Aβ interacted with blood vessel endothelial cells to produce superoxide radicals resulting in disruptions to endothelial structure and function. This pathophysiology likely contributes to common signs of AD including brain atrophy, cortical thinning and white matter deterioration.

A hallmark of AD pathology is diffuse brain atrophy, and the relationship between declining cognitive status and brain atrophy has been well described (Barnes et al., 2013; Kalaria et al., 2012; Snyder et al., 2015). For example, accelerated ventricular enlargement and hippocampal atrophy have both been reported in mild cognitive impairment (MCI) and AD compared to normal ageing (Apostolova et al., 2012; Coupe et al., 2019; Leung et al., 2013; Nestor et al., 2008). Furthermore, there is a link between vascular dysfunction and brain atrophy in ADRD. Several studies have demonstrated decreased brain volume in cohorts with cerebral small vessel disease (De Guio et al., 2020; Nitkunan et al., 2011), and vascular pathologies can provoke dementia independent of AD pathologies (Esiri et al., 1999; Jellinger, 2010; Launer, 2007; Schneider et al., 2007; Schneider et al., 2003; Snowdon et al., 1997). A large postmortem evaluation revealed that 84% of AD patients had significant cerebrovascular lesions (Petrovitch et al., 2005), which have been shown to exacerbate AD pathology and cognitive impairment (Bennett et al., 2012; Gorelick et al., 2011; Jellinger, 2007; Snowdon et al., 1997; Snyder et al., 2015; Strozyk et al., 2010; Toledo et al., 2013; Zekry et al., 2002).

White matter integrity is also reduced in AD. White matter disruption such as myelin and axonal loss and gliosis (Black et al., 2009; Gouw et al., 2011), increase over time resulting in progressive atrophy, and are exacerbated by vascular risk factors such as high blood pressure (van Dijk et al., 2004; R. Wang et al., 2015), ApoE4 status (R. Wang et al., 2015) and chronic cerebral hypoperfusion (Gurol, 2013). These changes have been attributed

to cerebral small vessel disease (Gouw et al., 2011; Xing et al., 2021) see also review and meta-analysis: (Debette & Markus, 2010) and blood brain barrier disruption resulting in the infiltration of inflammatory cells (Takata et al., 2021). White matter integrity is abnormal in both mild cognitive impairment and AD, and these abnormalities have been observed in people with AD in the frontal lobe, hippocampus and posterior corpus callosum. Disruption to white matter integrity is also correlated with brain atrophy and cognitive trajectory (Chandra et al., 2019; Coutu et al., 2017; Garnier-Crussard et al., 2022), including deficits in global and domain specific cognitive function (Arvanitakis et al., 2016; Bolandzadeh et al., 2012; Kloppenborg et al., 2014; Papp et al., 2014; Prins & Scheltens, 2015; van den Heuvel et al., 2006; Xing et al., 2021). Longitudinal studies have demonstrated that decreased white matter integrity predicts accelerated cognitive decline, MCI and dementia (Zeestraten et al., 2017) with increased risk for stroke and death (Debette & Markus, 2010; Kloppenborg et al., 2014; Prins & Scheltens, 2015; Verdelho et al., 2010).

We recently reported that measures of microvascular disease and cognitive dysfunction were linked with redox-related disturbances in sulfide metabolism. Hydrogen sulfide ($H_2S$) is an important gasotransmitter regulating both neuronal and vascular homeostasis (Vandiver & Snyder, 2012), $H_2S$ exerts both antioxidant and prooxidant effects (Olas, 2017). Sulfides exist in three pools: antioxidant *free* $H_2S$, *bound* (per- and poly-) sulfides, and *acid-labile* (e.g., iron-sulfur clusters) sulfides. In the vascular system, sulfides accomplish a wide range of inflammatory and immunoregulatory functions (Pan et al., 2017). In the nervous system free sulfide acts as a calcium-based neuromodulator (Yong

et al., 2010). However, the role of $H_2S$ and its metabolites in disease pathophysiology is complex, with reports of both protective and damaging effects on the vasculature. Plasma sulfide levels are high in younger individuals, but decline with age (Y. H. Chen et al., 2005). Furthermore, plasma sulfides are protective in vascular disease (Kolluru et al., 2020), with decreased levels of bound, acid labile and total sulfides predicting cardiovascular disease risk (Rajpal et al., 2018). Studies have demonstrated that hydrogen sulfide is produced by cerebral microvessels, and we and others have also previously described that free sulfide preserves brain vasomotion (X. Y. Liu et al., 2022), is protective against global and focal cerebral ischemic injury (Gheibi et al., 2014; Yin et al., 2013), and is involved in blood brain barrier integrity (Jiang et al., 2015; Y. Wang et al., 2014).

Moreover, hydrogen sulfide has been shown to preserve cognitive performance in experimental models of dementia possibly by improving antioxidant status and attenuating oxidative stress (Giuliani et al., 2013; Kumar & Sandhir, 2018; Vandini et al., 2019) and inflammation (Fan et al., 2013) in vitro and in vivo. Conversely, $H_2S$ and its metabolites have been suggested to contribute to neurological stress and vascular dysfunction in Downs' syndrome (Kamoun et al., 2003), schizophrenia (Ide et al., 2019) and stroke (Qu et al., 2006), suggesting that "sulfide distress" contributes to cognitive dysfunction. In human AD we recently discovered an increase in total plasma sulfides associated with increased acid-labile and bound sulfide species (E. Disbrow et al., 2021). Furthermore, total sulfides significantly mediated the relationship between measures of cerebrovascular disease and cognitive performance, indicating that sulfides may provide

a valuable marker of the vascular contribution to ADRD. Here we extend our previous work to test the hypothesis that plasma sulfides are associated with the brain atrophy and white matter deterioration characteristic of ADRD.

## EXPERIMENTAL MODEL AND SUBJECT DETAILS

### Data Selection

Approval for this work (Study 00000059, PI: Disbrow) was obtained from the LSU Health Sciences Center Institutional Review Board and all participants gave informed consent prior to participation.

To investigate the association between hydrogen sulfide, neuroimaging metrics and/or cognitive performance in an aged population with and without Alzheimer's disease and related dementias (ADRD) the following study enrollment criteria were established: Age greater than 55 years, fluent English speaker, no history of severe head trauma, no medical disease other than ADRD known to affect cognitive function (such as Parkinson's disease, stroke, etc.), no history of substance/alcohol abuse, ability to understand the informed consent process and study procedures (or a legally authorized representative), not pregnant. Additional criteria for those undergoing MRI neuroimaging included: body stature able to fit comfortably in the MRI scanner, not claustrophobic, no metal objects that could not be removed, and no medical implants contraindicated for an MRI exam at 3T. Participants who met study criteria and enrolled gave informed consent and went on to complete the following study procedures: MRI of the brain, cognitive assessment including the Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog), and a blood based hydrogen sulfide analysis.

One-hundred and twenty-three participants completed the cognitive testing and blood draw, and 59 of those also completing the MRI exam. Participants were divided into two groups: ADRD and Control. ADRD classification was based on a prior clinical diagnosis or an Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog) score greater than or equal to 17 (Monllau et al., 2007).

Cognitive assessments

Cognitive function was assessed using The Alzheimer's disease Assessment Scale (ADAS-Cog) which is considered a gold standard in assessing the efficacy of treatments targeting Alzheimer's Disease and dementia (Rosen, Mohs, & Davis, 1984). The ADAS-Cog consists of 11 participant or observer-based tasks which assess cognitive domains of memory, language and praxis.

Hydrogen Sulfide Analysis

Whole blood was collected in lithium-heparin vacutainer tubes and processed within 15 minutes. Blood samples were spun at 1400 RCF for 4 minutes. Plasma was combined in a 5:1 ratio of plasma to stabilization buffer (degassed 100mM Tris–HCl buffer, pH 9.5, 0.1 mM DTPA (diethylene triamine pentaacetic acid), quickly frozen and stored in liquid nitrogen until analysis.

To calculate the levels of the individual sulfide pools, three measurements are required. First the free sulfide alone, which is present in all measurements, was measured by derivatization of hydrogen sulfide with excess MBB (monobromobimane) in pH 9.5 50 mM

Tris-HCl buffer containing 0.1 mM DTPA for 30 min in 1% $O_2$ at room temperature. The reaction was stopped by adding 200 mM sulfosalicylic acid and placing the sample on ice for 10 minutes. For the second measurement, a combination of the free and acid labile pools, the sample was incubated with 100 mM phosphate buffer (pH 2.6) with 0.1 mM DTPA, to release the acid labile sulfur in an enclosed system to contain volatilized $H_2S$. All reactions were performed in BD vacutainer tubes with rocking to facilitate $H_2S$ gas release. After removal of the liquid solution with a syringe equipped with a long needle, trapping buffer (100 mM Tris-HCl, pH 9.5, 0.1 mM DTPA) was added into the vacutainer tube and rocked for 30 min. Sulfide levels of these solutions were measured by derivatization of hydrogen sulfide as above for the free sulfide alone. Finally, the total sulfide measurement, which includes the free, acid labile and bound sulfide components, was processed as above, with the exception that 1mM tris(2-carboxyethyl)phosphine hydrochloride (TCEP), which releases the bound sulfide, was added to the 100 mM phosphate buffer (pH 2.6) with 0.1 mM DTPA. For all measurements, the fluorescent product sulfide-dibimane was then measured by RP-HPLC with fluorescence detector using an Eclipse XDB-C18 (4.6×250 mm) column and a gradient elution by 0.1% (v/v) trifluoroacetic acid (TFA) in acetonitrile and water at a flow of 0.6 ml/min.

The total sulfide and individual pools were calculated as follows. The total sulfide was obtained directly from the total sulfide measurement. The free sulfide was obtained directly from the free sulfide measurement. The bound sulfide was calculated by subtracting the combined free sulfide and acid labile sulfide measurement from the total sulfide measurement. Finally, the acid labile sulfide level was calculated by subtracting

the free sulfide measurement from the combined free sulfide and acid labile sulfide measurement.

MRI scan parameters

MRI of the brain was performed on a 3T Philips Ingenia MR scanner using a 32-channel headcoil. The exam lasted for approximately one hour and included acquisition of a high-resolution 3D, T1-weighted anatomical image, a 3D fluid-attenuated inversion recovery (FLAIR) image, and a diffusion weighted image. Acquisition parameters for the T1 were field of view (FOV) = 250 mm x 250 mm x 181 mm, acquisition matrix = 228 x 227, reconstruction matrix = 240 x 240, echo time (TE) = 3400 ms, repetition time (TR) = 7400 ms. Acquisition parameters for the FLAIR image were FOV = 270 mm x 270 mm x 168 mm, acquisition matrix = 228 x 227, reconstruction matrix = 240 x 240, echo time (TE) = 3400 ms, repetition time (TR) = 7400 ms. Acquisition parameters for the diffusion weighted images were FOV = 270 mm x 270 mm x 168 mm, acquisition matrix = 228 x 227, reconstruction matrix = 240 x 240, echo time (TE) = 3400 ms, repetition time (TR) = 7400 ms.

MRI data processing

Cortical Thickness and Volume Quantification

For volume and thickness measurements, T1-weighted images were subjected to automated cortical reconstruction implemented in version 7.2 of the FreeSurfer™ image analysis suite (surfer.nmr.mgh.harvard.edu). Images were then processed for motion correction, intensity normalization and acquisition artifacts. Images were transformed and

stripped of non-brain tissue for normalization into Talariach space for morphometric estimations. Data were visually inspected at key steps for errors preceding the analyses. Images underwent cortical surface parcellation and subcortical volume-based segmentation. Cortical thicknesses were calculated for regions of interest based on the Desikan-Killiany atlas (Desikan et al., 2006) and mean thicknesses for the medial aspect f the temporal lobe and the frontal lobe were also calculated based on this atlas. Regions defined as frontal and temporal lobe in this atlas were combined for lobe-based analysis. The segmentation pipeline provides volumetric estimates. Inferior lateral ventricle volume was used independently for analysis and total white matter volume produced by this pipeline was used for normalization of white matter hyperintensity (WMH) volumetric analysis.

After cortical parcellation, vertex-wise analysis of cortical thickness was performed. Subjects were separated into high and low sulfide groups based on the total level of blood hydrogen sulfide (cutoff of 1.64μM; Disbrow et al; 2021). Using FreeSurfer, subjects' T1 images were normalized to a standardized template brain. Group differences in cortical thickness were compared vertex by vertex and tested for significance between high and low sulfide groups. To reduce the number of false positives, multiple comparison correction was performed, generating clusters of reliably significant correlation. These clusters were then mapped onto the standardized template brain to provide a visual representation of differences in cortical thickness between high and low hydrogen sulfide groups (Figure 2).

FLAIR Lesion Volume

Quantitative WMH analysis was conducted using the lesion growth algorithm (Schmidt et al., 2021) an analysis pipeline in the Lesion Segmentation Tool (LST) open-source toolbox version 3.0.0 for SPM in MATLAB R2019a and SPM12. T1 and FLAIR images were co-registered and lesion maps were calculated based on a user-determined threshold (kappa, 0.3). WMH volume was normalized to total white matter volume, produced by FreeSurfer parcellation, for a percentage of FLAIR lesion for each subject.

DTI FA, RD, MD and AxD Quantification

Whole brain fractional anisotropy (FA) radial diffusivity (RD), mean diffusivity (MD) and axial diffusivity (AxD) analysis of DTI images was carried out using tract-based spatial statistics (TBSS) in the FMRIB software library (FSL v6.0, https://fsl.fmrib.ox.ac.uk/fsl). Briefly, a group mean FA skeleton is generated and represents common fiber bundles between subjects. To estimate a mean FA, each subject is projected on to the skeleton where voxelwise statistics are carried out and a mean FA is calculated. RD, MD, and AxD maps were aligned to the same FA skeleton for whole brain mean diffusion calculation. A more detailed description of TBSS is described by Smith et al., 2006.

Quantification and Statistical Analysis

All variables were evaluated across groups using one-way analysis of variance (MANOVA). Pearson correlation was used to evaluate the relationship between sulfide metabolites and cognitive and imaging outcome measures. Receiver-operating characteristic (ROC) curve analysis was performed to determine the discrimination

capabilities of individual sulfide pools. These analyses were performed using SPSS version 26. An experiment-wise Bonferroni correction was made for each imaging dataset. Alpha was adjusted based on the number of comparison in each analysis ($p = 0.05 / n$). Each dataset analysis was considered a single comparison thus reducing our overall family-wise error by assuming independence of the dependent variables (Foster et al., 2018).

## RESULTS

Group differences

All participants were evaluated for cognitive function and assigned to the ADRD (ADAS Cog >18, N=50) or control (N=82) groups. One-way ANOVA revealed that there were significant differences by group for demographic variables of age ($F(1, 131) = 7.581$, $p = 0.007$) and education ($F(1, 131) = 18.146$, $p < 0.001$; Table 13) . Subjects in the ADRD group had, on average, significantly greater age and fewer years of education. ADRD subjects had significantly lower performance on measures of global cognitive function (ADAS-cog; $F(1, 127) = 229.265$, $p < 0.001$). An experiment wise Bonferroni correction was applied for each analysis (corrected alpha, $p < 0.01$).

Sulfide analysis revealed that the ADRD group had significantly elevated total ($F(1, 122) = 38.307$, $p < 0.001$), bound ($F(1, 122) = 11.160$, $p = 0.001$) and acid labile sulfide ($F(1, 122) = 16.181$, $p < 0.001$) compared to controls. Free sulfide was not significantly different across groups ($F(1, 122) = 3.408$, $p = 0.067$) (Figure 1). For all subjects, poorer performance on the ADAS-Cog was associated with elevated total ($R^2 = 0.230$, $p < 0.001$), bound ($R^2 = 0.088$, $p = 0.001$), acid labile sulfide ($R^2 = 0.132$, $p < 0.001$). Cognitive performance was not associated with free sulfide ($R^2 = 0.0003$, $p = 0.858$) (Figure 6; corrected alpha, $p < 0.01$).

A subset of participants (N=59, 29 ADRD) underwent MRI. Analysis of T1 anatomical images (Table 14) revealed that AD subjects showed significant cortical thinning compared to control subjects across the whole brain (mean thickness; $F(1, 58) = 64.611$,

$p < 0.001$) as well as in the medial aspect of temporal (Left: $F(1, 58) = 55.548$, $p < 0.001$; Right: $F(1, 58) = 52.316$, $p < 0.001$) and frontal lobe (Left: $F(1, 58) = 45.842$, $p < 0.001$; Right: $F(1, 58) = 42.171$, $p < 0.001$). ADRD subjects also showed increased atrophy compared to controls, including increased percent lateral ventricle volume ($F(1, 58) = 22.294$, $p < 0.001$) and decreased percent hippocampal volume ($F(1, 58) = 29.572$, $p < 0.001$). Lastly, significant group differences were identified for normalized fluid attenuated inversion recovery (FLAIR) lesion volume ($F(1, 58) = 12.928$, $p = 0.001$) with higher volumes in AD subjects (Table 15; corrected alpha, $p < 0.007$).

Of the 41 subjects (23 ADRD) that underwent diffusion weighted imaging (DWI), AD subjects showed significantly lower fractional anisotropy (FA) values ($F(1, 40) = 9.876$, $p = 0.008$) associated with loss of tissue or disruption of tissue organization (D. C. Alexander, Dyrby, Nilsson, & Zhang, 2019). ADRD subjects also had higher radial diffusivity (RD) ($F(1, 39) = 7.791$, $p = 0.008$) a measure of perpendicular water movement typically interpreted as myelin or cell membrane breakdown (Aung, Mar, & Benzinger, 2013), and a statistical trend (after correction for multiple comparisons) for mean diffusivity (MD) ($F(1, 39) = 6.110$, $p = 0.018$) which describes the turbulence of water within axonal fibers attributed to increased water content as a result of inflammation and edema (Ranzenberger & Snyder, 2022). Axial diffusion (AxD), which measures magnitude of diffusion parallel to axonal fibers, was not different across groups ($F(1, 39) = 3.444$, $p = 0.071$). The application of AxD to disease is incompletely understood (Wheeler-Kingshott & Cercignani, 2009). These data all indicating greater white matter microstructure disruption in ADRD (Table 15; corrected alpha, $p < 0.001$).

Measures of brain atrophy are associated with plasma sulfides

We evaluated the association between plasma sulfides and brain atrophy as measured using cortical thickness and ventricular volume (Schwarz et al., 2016). Total sulfide was significantly associated with whole brain mean cortical thickness ($R^2 = 0.269$, $p < 0.001$) as was bound sulfide ($R^2 = 0.156$, $p = 0.002$; Figure 2). Furthermore, total sulfide was associated with cortical thickness in the medial aspect of temporal lobe (Left: $R^2 = 0.206$, $p < 0.001$; Right: $R^2 = 0.261$, $p < 0.001$) and frontal lobe (Left: $R^2 = 0.197$, $p = 0.001$; Right: $R^2 = 0.199$, $p < 0.001$). Similarly, cortical thickness was associated with bound sulfide bilaterally specifically in the medial aspect of the temporal lobe (Left: $R^2 = 0.170$, $p = 0.001$; Right: $R^2 = 0.162$, $p = 0.002$) and frontal lobe (Left: $R^2 = 0.147$, $p = 0.003$; Right: $R^2 = 0.130$, $p = 0.006$) (Figure 3, corrected alpha, $p < 0.004$). Uncorrected statistical significance was found between decreased cortical thickness and increased total and bound sulfides for 30 and 29 of the 34 regions surveyed bilaterally. While acid labile was associated with some measures of thickness, the relationship was less consistent than the association with total and bound sulfide.

Moreover, volumetric analysis revealed relationships between plasma sulfide levels and tissue volumes in several brain regions. The percent inferior lateral ventricle volume was positively correlated with total sulfide ($R^2 = 0.256$, $p < 0.001$) and acid labile sulfide ($R^2 = 0.180$, $p = 0.001$). Percent hippocampal volume association with total sulfide was a trend ($R^2 = 0.100$, $p = 0.016$). We did not find a relationship between inferior lateral ventricular

volume and bound sulfide ($R^2$ = 0.061, p = 0.064) or percent hippocampal volume and bound sulfide ($R^2$ = 0.011, p = 0.443; Figure 7, corrected p<0.01).

Measures of white matter integrity are associated with microvascular disease and acid labile sulfide

We evaluated associations between plasma sulfides and quantitative white matter integrity measures. Increased FLAIR lesion volume was significantly associated with total sulfide ($R^2$ = 0.182, p = 0.001) and acid labile sulfide ($R^2$ = 0.130, p = 0.006), but not with bound or free sulfide pools (Figure 8). Diffusion images were used to calculate fractional anisotropy (FA), radial diffusivity (RD), mean diffusivity (MD) and axial diffusivity (AxD) to assess white matter microstructural integrity using TBSS. We found a statistical trend (corrected alpha, p < 0.006) between total sulfide FA and RD ($R^2$ = 0.089, p = 0.065; $R^2$ = 0.099, p = 0.054) respectively. Acid labile sulfide reached a statistical trend with diffusion measures of FA (inverse relationship; $R^2$ = 0.147, p = 0.016), RD ($R^2$ = 0.156, p = 0.014), and MD ($R^2$ = 0.130, p = 0.026) but not to AxD ($R^2$ = 0.088, p = 0.072). Whole brain diffusion metrics were not associated with free or bound sulfide (Figure 4; corrected alpha, p <0.01).

A receiver operator characteristic (ROC) curve analysis showed that acid labile, bound and total sulfide significantly discriminated between control and ADRD subjects (Figure 5). We found that discriminative capabilities bound (Area Under the Curve (AUC) = 0.627) and acid labile (AUC = 0.692) were modest, whereas total (AUC = 0.793) demonstrated

moderate discriminative ability. Free sulfide (AUC=0.559) was not a significant discriminator.

| | N | Sex | Race | Age* | Education* | ADAS-Cog* |
|---|---|---|---|---|---|---|
| Control | 82 | 62 F; 20 M | 28 AA; 54 C | 68.28 (8.81) | 15.80 (2.37) | 9.23 (4.04) |
| ADRD | 50 | 30 F; 20 M | 19 AA; 31 C | 72.26 (7.20) | 13.96 (2.57) | 30.41 (11.45) |

Table 13: Participant Demographic Variables by Group, count or mean (SD), *p<0.01

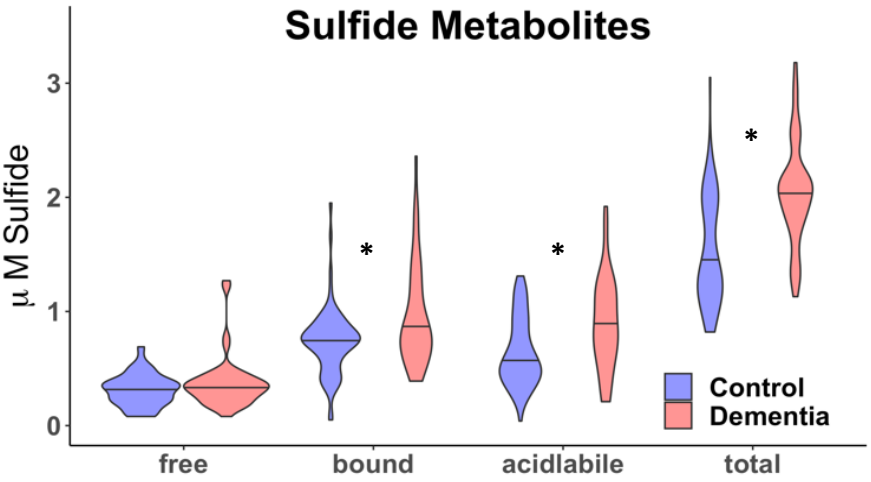
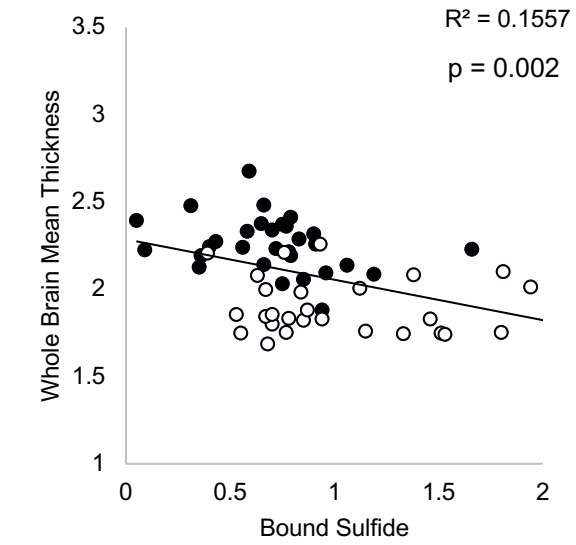



Figure 1: Violin plots for sulfide pools across groups. Horizontal bars = group mean, *p<0.01




○ ADRD ● Control

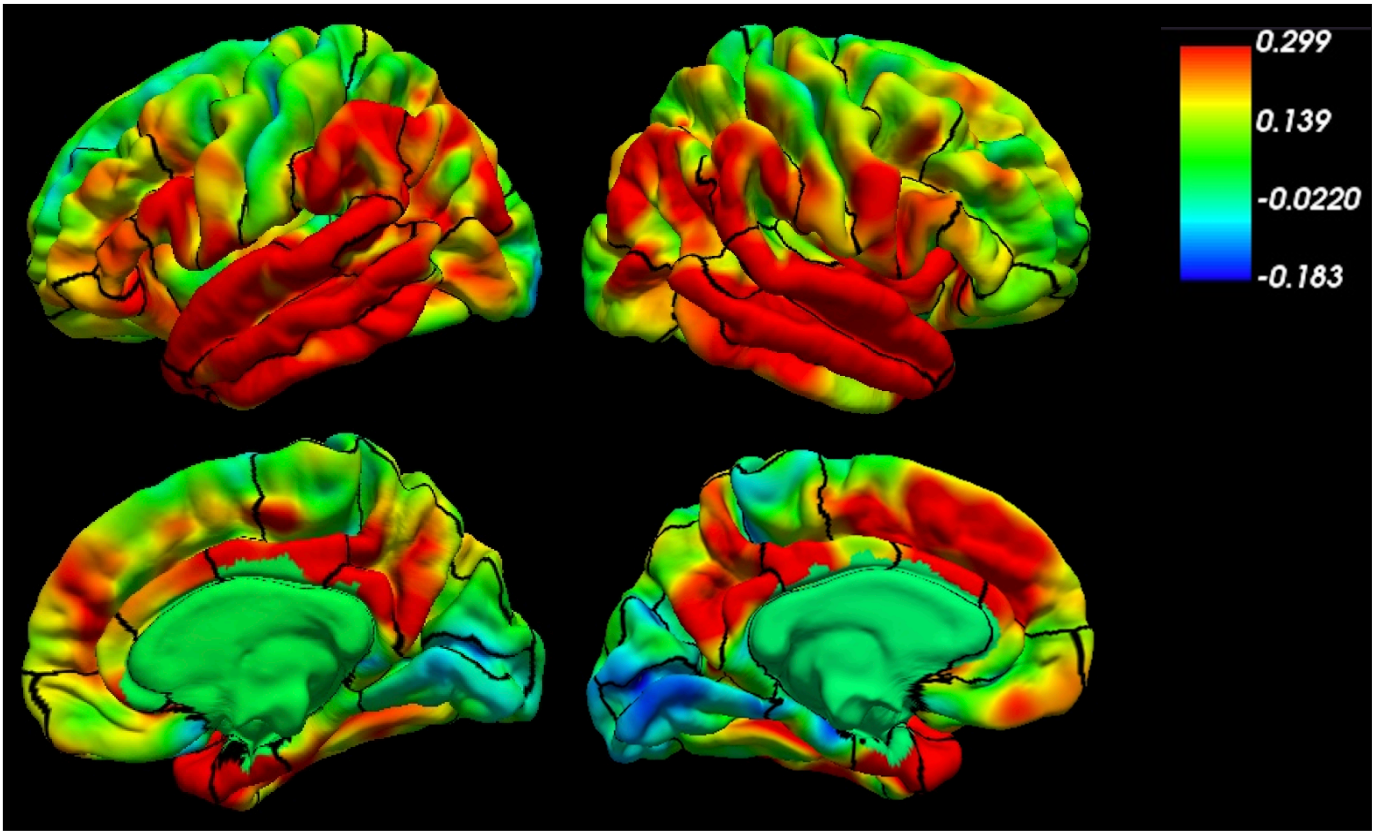



Figure 2: A) Association between whole brain thickness and bound sulfide. B) Comparison of cortical thickness between “high” and “low” sulfide groups. Groups were based on previous work showing a cutoff of 1.64μM total sulfides for discriminating between disease and control groups (Disbrow et al., 2021). Scale represents low sulfide group > high sulfide group mean group differences in cortical thickness (mm).

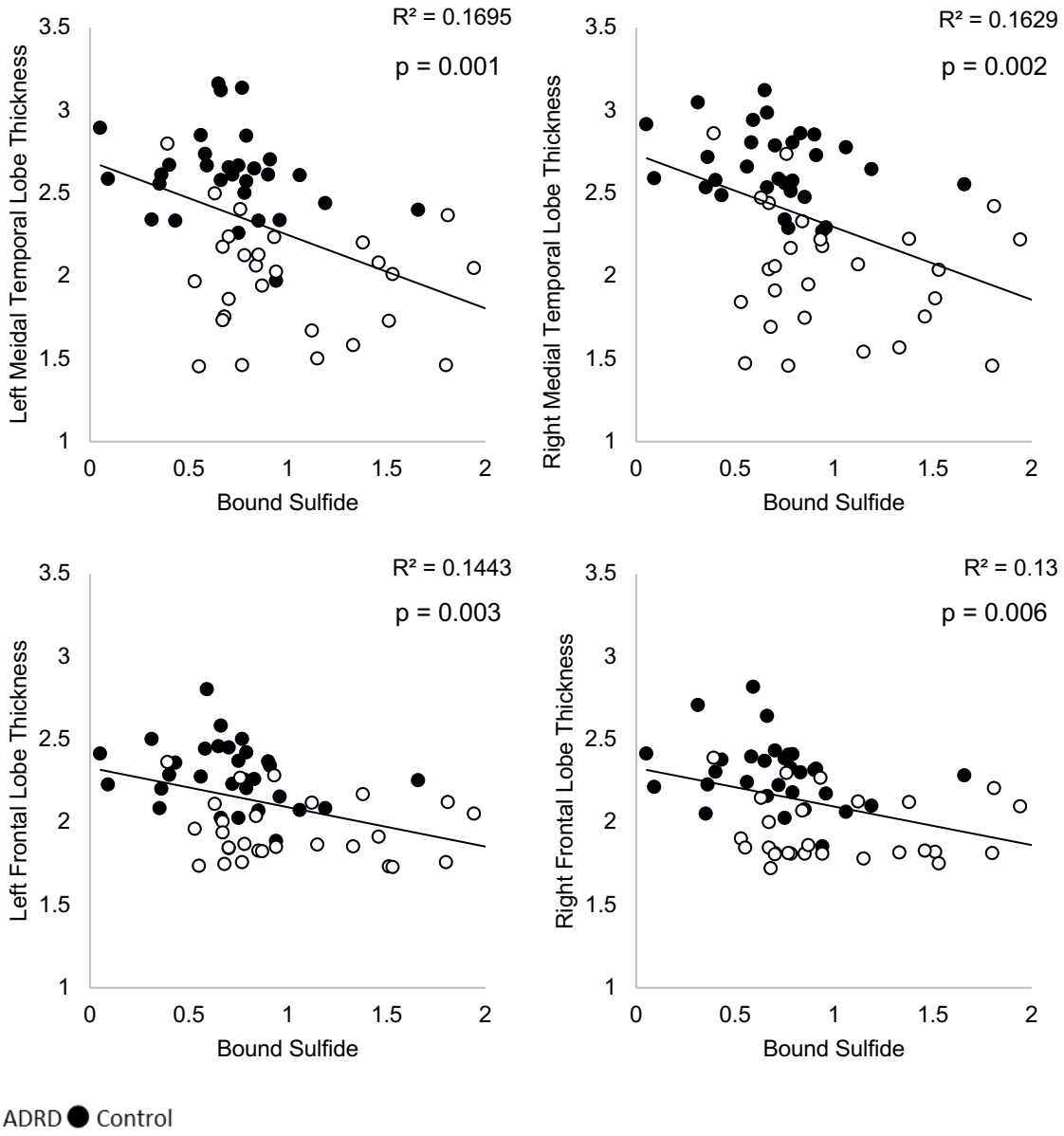



Figure 3: Bilateral medial temporal and frontal lobe are associated with elevated bound labile sulfide, $p < 0.001$, $p < 0.004$.

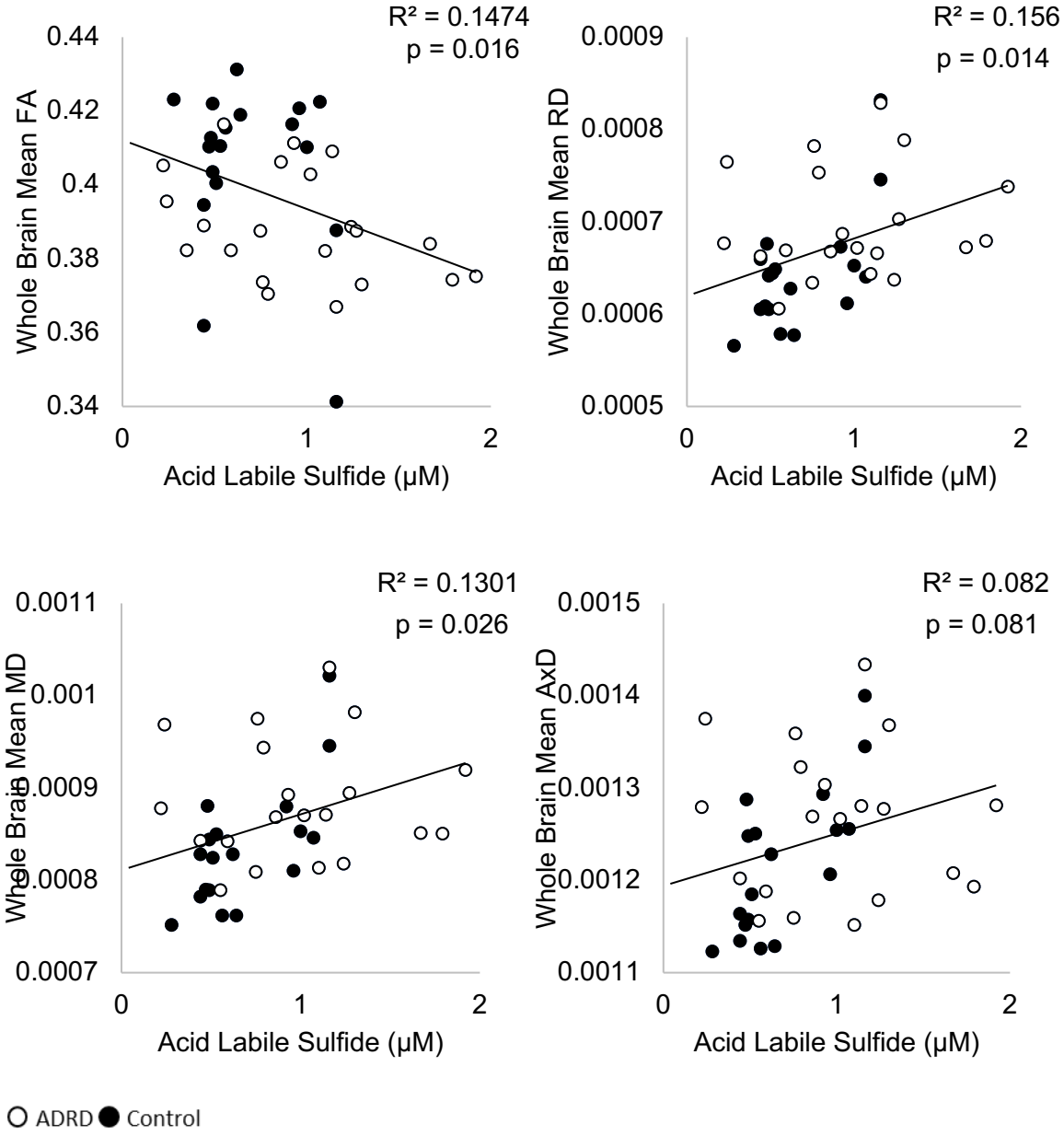



Figure 4: Whole Brain Mean FA, RD, MD and AxD are associated with elevated acid labile sulfide, $p < 0.001$.

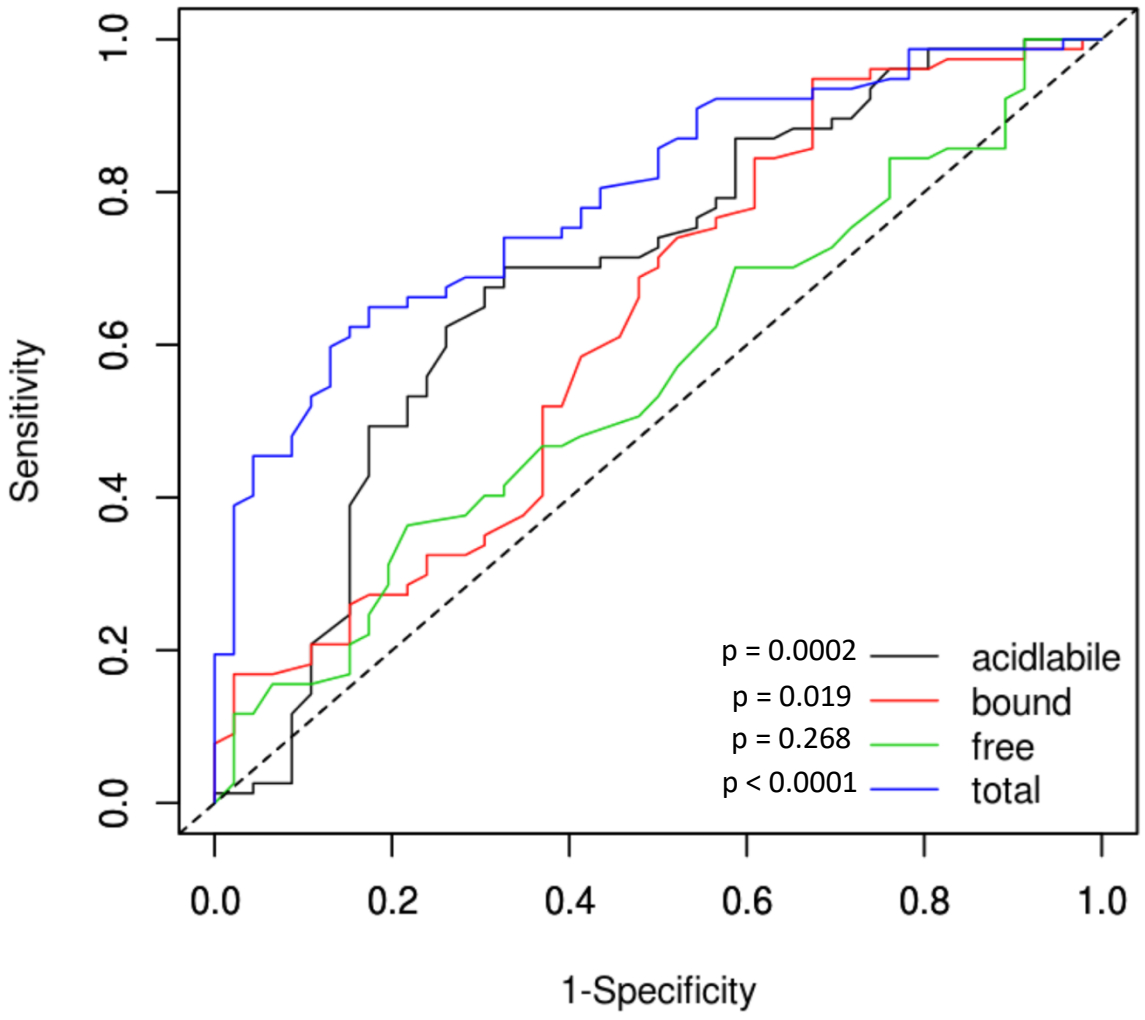



Figure 5: ROC curve analysis revealed that plasma hydrogen sulfide including some metabolites are significant discriminators of disease category.

| | Whole Brain Mean Thickness* | Left Temporal Lobe (medial aspect) Mean Thickness* | Right Temporal Lobe (medial aspect) Mean Thickness* | Left Frontal Lobe Mean Thickness* | Right Frontal Lobe Mean Thickness* | % Inferior Lateral Ventricle Volume* | % Hippocampal Volume* |
|---|---|---|---|---|---|---|---|
| Control | 2.26 (0.16) | 2.62 (0.26) | 2.66 (0.22) | 2.29 (0.19) | 2.30 (0.20) | 0.07% (0.04%) | 0.63% (0.12%) |
| ADRD | 1.92 (0.17) | 2.01 (0.35) | 2.06 (0.39) | 1.96 (0.18) | 1.96 (0.19) | 0.17% (0.11%) | 0.47% (0.12%) |

Table 14: Gray matter metrics (mean (SD)), *p<0.007.

| | % FLAIR Lesion Volume* | Whole Brain Mean FA* | Whole Brain Mean RD* | Whole Brain Mean MD | Whole Brain Mean AxD |
|---|---|---|---|---|---|
| Control | 0.57% (1.09%) | 0.41 (0.02) | 0.00122 (0.00008) | 0.00084 (0.00007) | 0.00064 (0.00006) |
| ADRD | 2.25% (2.30%) | 0.39 (0.01) | 0.00127 (0.00008) | 0.00089 (0.00006) | 0.00070 (0.00006) |

Table 15: White matter metrics (mean (SD)), *p<0.001.

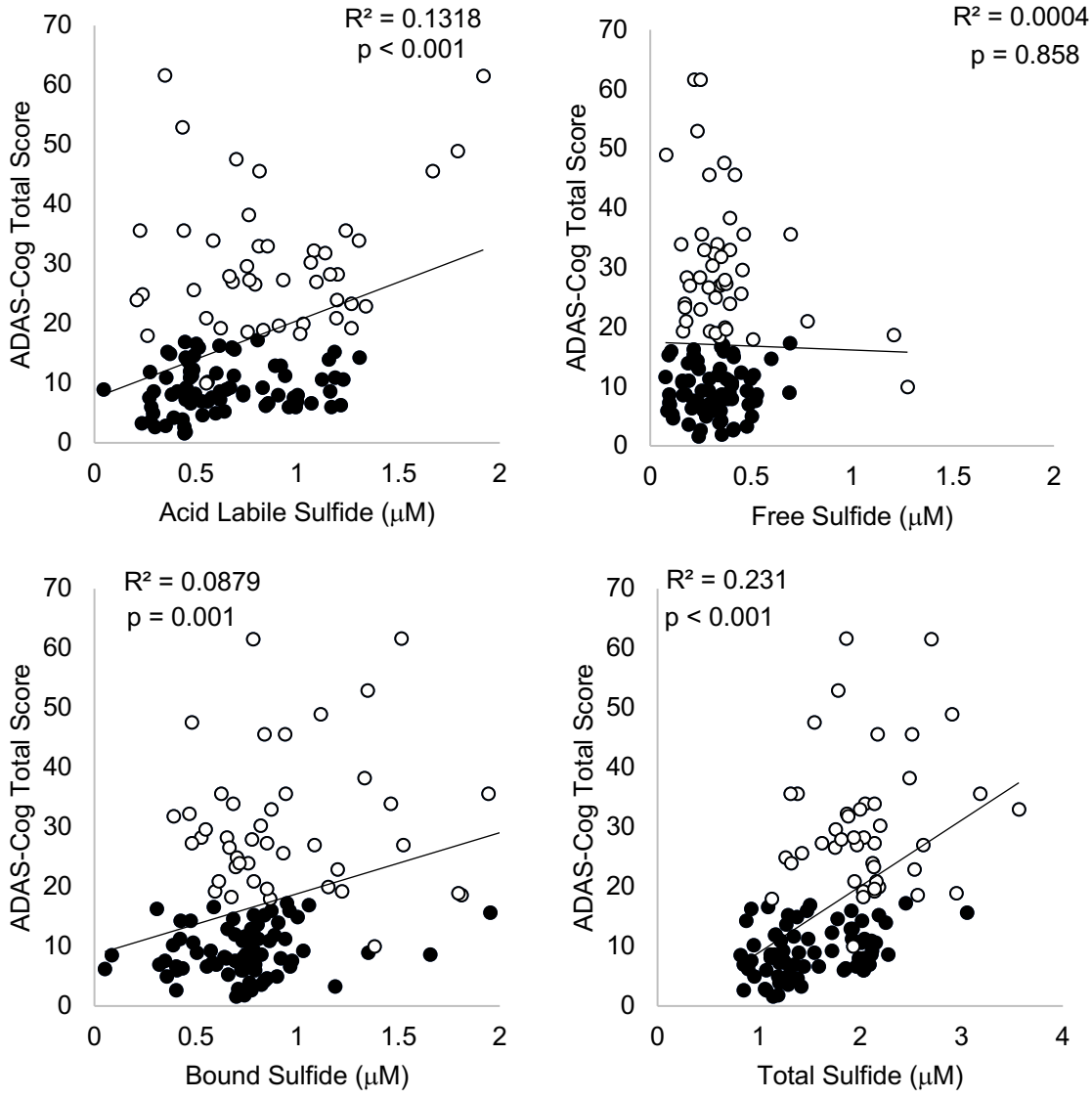



Figure 6: Elevated Sulfides are Associated with Decreased Cognitive Function. Results are similar to previous work (Disbrow et al., 2021).

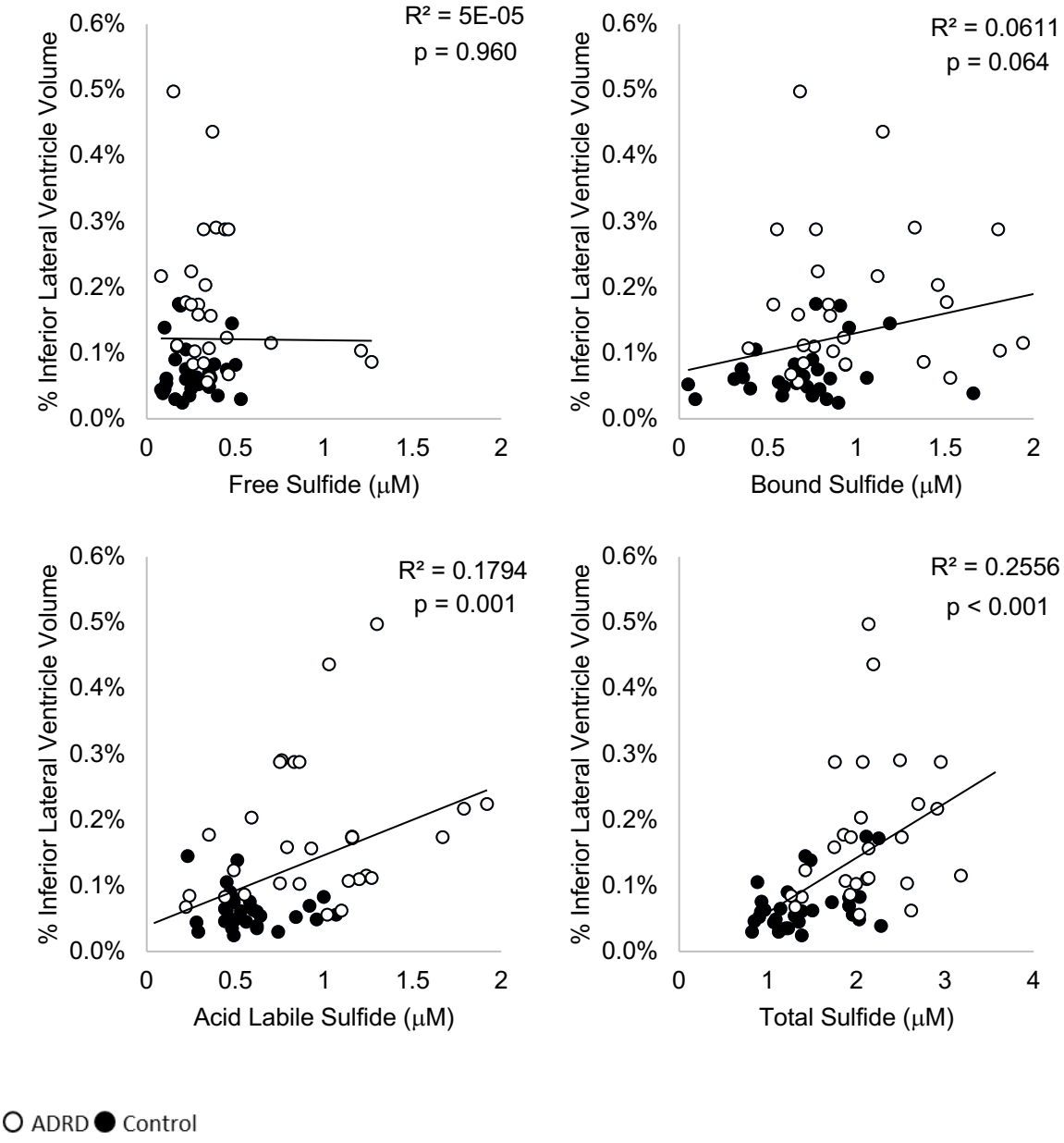



Figure 7: Elevated sulfides are associated with increased lateral ventricle volume and decreased hippocampal volume.

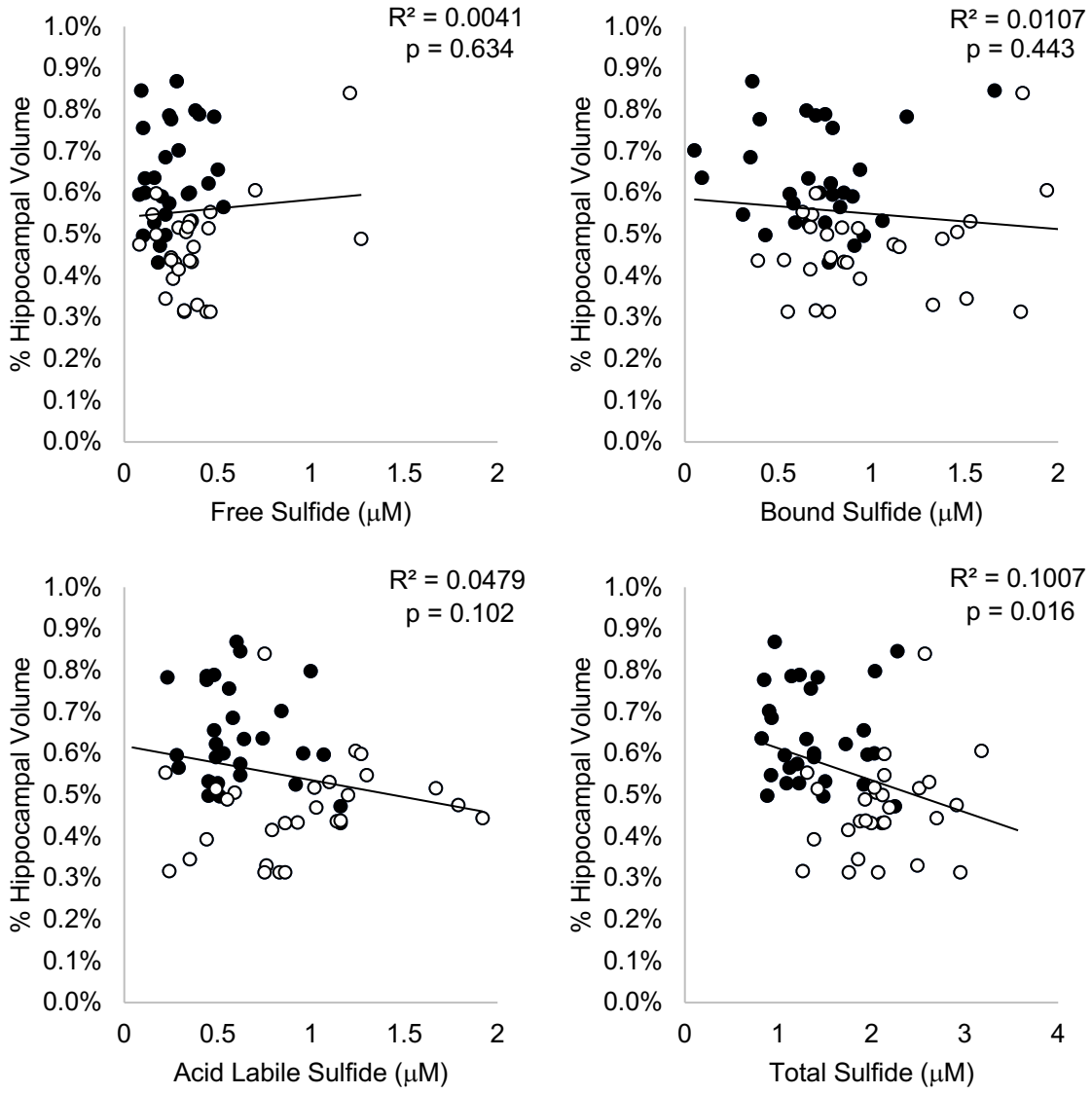



Figure 7 cont.: Elevated sulfides are associated with increased lateral ventricle volume and decreased hippocampal volume.

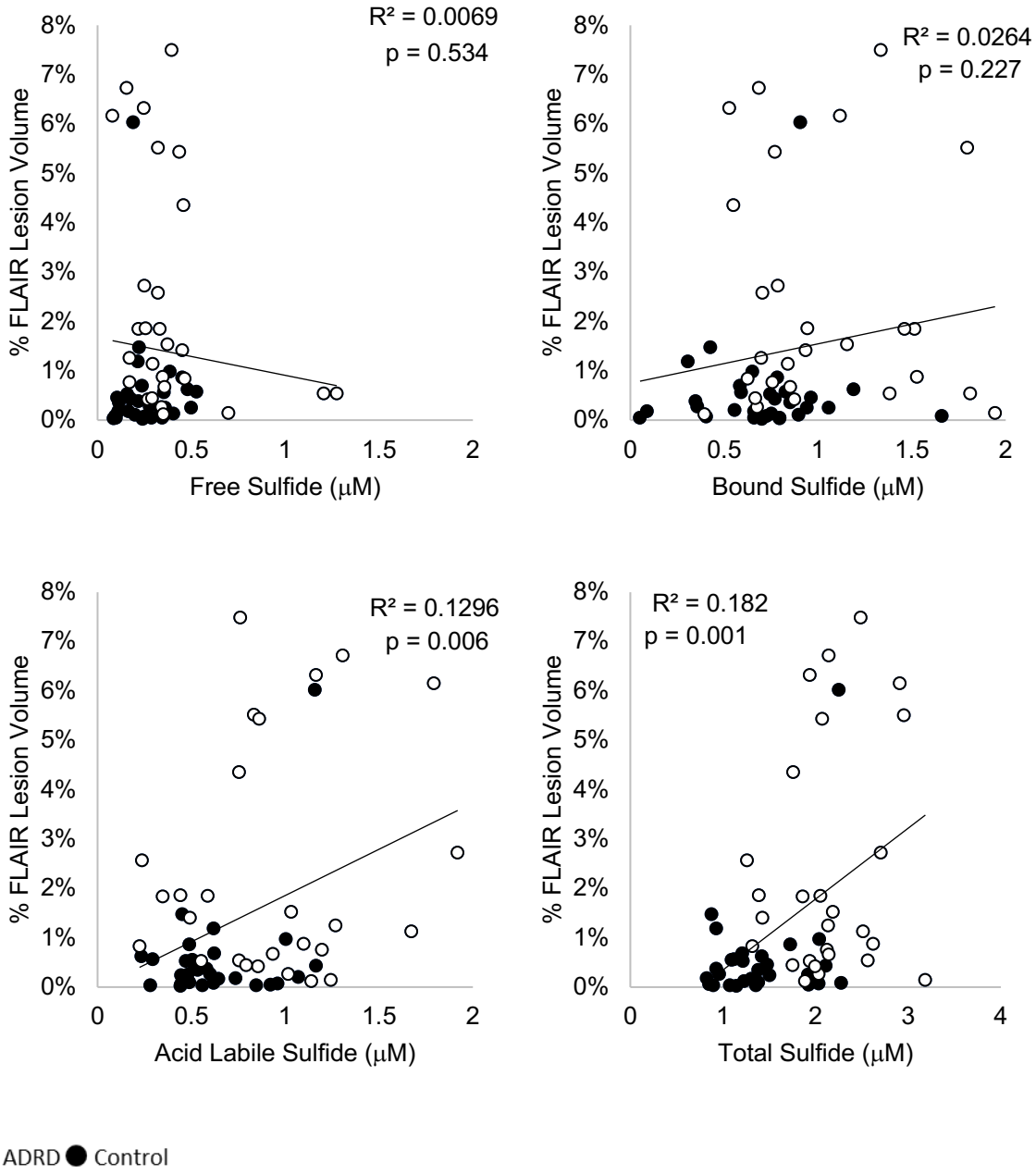



Figure 8: Elevated Acid Labile and Total Sulfide are Associated with Increased FLAIR Lesion Volume.

## DISCUSSION

In this study, we tested the hypothesis that elevated plasma sulfides are associated with cerebral atrophy and white matter integrity. These findings support a relationship between vascular disturbances and ADRD pathology. We showed that increased plasma bound sulfides, which play a role in endothelial barrier function, were associated with decreased cortical thickness across the entire cortex. We also demonstrate that elevated acid labile sulfides, often attributed to iron sulfur clusters, were also associated with atrophy, specifically increased volume of the inferior lateral ventricle and decreased hippocampal volumes. Moreover, increased acid labile sulfides were correlated with increased white matter hyperintensity volume and, to a lesser extent, decreased microstructural integrity. Our work indicates that plasma sulfides are potential biomarkers of the vascular contributions to cognitive impairments and dementia (VCID; (E. Disbrow et al., 2021).

### Cortical Thickness and Bound Sulfides

Both pre- and postmortem analysis show that loss of cortical thickness, which has been deemed a “disease signature” (Dickerson et al., 2009), is associated with AD (Noh et al., 2014; Querbes et al., 2009; Sabuncu et al., 2011). Reduced cortical thickness has also been linked to severity of dementia particularly in temporal and inferior parietal cortices, as well as posterior cingulate and precuneus gyri. Higher levels of cortical thinning were even observed in patients with mild AD compared to controls (Dickerson et al., 2009). Cortical thinning is a sign of diffuse atrophy reflecting neuronal and glial loss (Coleman & Flood, 1987; DeKosky, Scheff, & Styren, 1996; Dickerson et al., 2009; Scheff, DeKosky,

& Price, 1990), and may indicate pathologic accumulation of neurofibrillary tangles and amyloid plaques (Ossenkoppele et al., 2019). Interestingly, the vascular burden index has also been associated with cortical thinning (Tchistiakova, MacIntosh, & Alzheimer's Disease Neuroimaging, 2016). Ottoy and colleagues (2022) found that vascular burden contributed significantly to cortical thinning independent of Aβ. Previous studies also demonstrate that patients with cerebral amyloid angiopathy, a cerebrovascular disease affecting small and medium blood vessels of the brain, had significantly more cortical thinning compared to healthy controls (Subotic et al., 2021).

We found striking differences across groups in bound sulfides which were associated with cognitive function as well as cortical structure. Bound sulfides, such as poly- and persulfides, can include protein-sulfur adducts which are post-translational modifications of several proteins. Bound sulfides have both pro- and antioxidant effects through their actions as reductants and nucleophiles (Francoleon, Carrington, & Fukuto, 2011). We have reported that exposure of endothelial monolayer to persulfides disintegrated endothelial barrier with remodeling of claudin 5 and VE-cadherin and actin stress fiber contraction (Yuan et al., 2016). It has also been shown that the sulfide generating enzyme cystathionine γ-lyase (CSE), which is a major source of vascular sulfides (G. Yang et al., 2008), may be induced by vascular stress (Huang et al., 2015; Yuan et al., 2016). Stress induced CSE appears to represent at least one source of elevated sulfides, and lack of CSE in animal and cellular models showed improved barrier function over normal levels (Yuan et al., 2016). We found that when CSE was genetically eliminated, that *bound* sulfides were reduced, while free and acid labile sulfides were not affected. This finding

suggests that at the level of the microvasculature, elevations in bound sulfides produced by CSE could lead to loss of barrier function. Mechanistically, this may involve not only junctional retraction of claudin 5 and VE-cadherin, but also reduced expression of claudin 5 which would lead to a weaker overall barrier. Thus reduced cortical thickness volumes, which represents an important indices of brain atrophy, may be due to bound sulfide driven BBB dysfunction.

In the setting of Alzheimer's disease, bound sulfide associated loss of blood brain barrier may be one important process through which the brain becomes metabolically and functionally stressed leading to destructive remodeling and diminished cognitive processing. We and others have described how weakening the blood brain barrier in AD may initiate and drive progression of vascular dysfunction and inflammation which cause neuronal tissue pathophysiology characteristic of AD progression. For example, loss of BBB integrity often triggers excitotoxic calcium signaling and metabolic dysfunction (Rajeev et al., 2022) which accumulate destructive signatures of brain structure/function including amyloid plaques and phosphorylated-Tau tangles (Alzheimer's Association Calcium Hypothesis, 2017; Khachaturian, 1989, 1994).

*White Matter Integrity and Acid Labile Sulfides*

In addition to increases in bound plasma sulfide, we also found significant increases in acid labile sulfide which were correlated with cognitive dysfunction and increased white matter hyperintensity (WMH) burden. WMH in ageing and AD are indicators of chronic ischemia and cerebral small vessel disease (Prins & Scheltens, 2015). WMH burden is

elevated in both MCI and AD and is associated with common pathological changes seen in AD such as Aβ aggregation and neurofibrillary tangles (Brickman et al., 2008). WMH may lower the threshold for the manifestation of dementia with AD pathologies (Jack et al., 2018). Increased Aβ was associated with increased WMH burden in the parietal, temporal, occipital, and posterior corpus collosum regions (Garnier-Crussard et al., 2020). Evidence also suggests that WMH increase with age and hypertension (de Leeuw et al., 2001; Pantoni & Garcia, 1997), and the ApoE4 allele has been associated with greater WMH volume (Brickman et al., 2014). In a review by Jorgensen et al., (2018) vascular risk factors including hypertension, increased systolic and diastolic blood pressure, increased mean arterial pressure, increased pulse pressure and other cardiovascular factors imparted the greatest risk for WMH.

In addition, we found that increased acid labile sulfide was associated with decreased white matter integrity, indicated by decreased FA, and increased MD, RD, and AxD. Growing evidence describes a link between vascular risk factors and disturbed white matter microstructural integrity (Cox et al., 2019; Ingo et al., 2021; Xing et al., 2021). For example, decreased FA was associated with increased WMH volume and vascular risk factors such as ApoE4 status and hypertension (R. Wang et al., 2015) as well as aggregate vascular risk score (Cox et al., 2019). Moreover, Xing and colleagues. (2021) found that in patients with evidence of cerebral small vessel disease , decreased whole brain FA was a stronger predictor of cognitive impairment than tract specific or regional volumetric analysis. Similarly, decreased FA and increased RD, MD and AxD were significantly associated with WMH burden in a cohort of patients with subcortical ischemic

vascular disease (X. Liu et al., 2019). Finally, in a 5-year follow-up study of a cohort of patients with small vessel disease, decreased white matter integrity and increased WMH volume predicted the progression to dementia (Zeestraten et al., 2017).

Currently, there is very little known about how acid-labile sulfides affect the vasculature, but this sulfide pool is known to react with transition metals like iron in 'iron-sulfur clusters.' Iron-sulfur clusters are important for maintaining cellular homeostasis, reflecting their roles in enzyme action (including formation of oxidants), protein stability (J. L. Liu, Fan, Yang, Wang, & Guo, 2018), and mitochondrial electron transport chain complexes where increased generation of iron sulfur clusters may trigger the overproduction of reactive oxygen species within mitochondria, possibly inducing cell injury or death (Read, Bentley, Archer, & Dunham-Snary, 2021). Critically, increases in both plasma acid-labile sulfides and brain iron levels have been associated with development of white matter hyperintensities (Yan, Sun, Chen, Selim, & Lou, 2013) and poorer memory recall (Ding et al., 2009). Yan and colleagues (2013) found that iron deposition in the brain was independently linked to white matter hyperintensity (WMH) severity and suggest that iron may play a role in the pathogenesis of WMH. Interestingly, increased cerebral iron deposition in white matter as well as cortical and subcortical grey matter including the hippocampus has been implicated in AD and may be linked to Aβ deposition and hyperphosphorylated tau formation (B. Liu et al., 2011; Mandel, Amit, Bar-Am, & Youdim, 2007; Rao & Adlard, 2018). One possible role for elevated acid labile sulfides is increased generation of iron-sulfur clusters which intensify β-amyloid plaque progression, and ultimately cognitive decline in AD.

Limitations of the study

While we see that plasma sulfides are significantly elevated in ADRD, the degree to which this represents events that originate in neural tissue, or the vascular network is unclear. It is possible that both systems release sulfides which influence progression in ADRD. Although tempting to regard plasma sulfides exclusively as toxic species based on this and our previous report (E. Disbrow et al., 2021), it is as likely that some sulfide species are neuro-protective, and that generation of acid labile and bound sulfides is actually adaptive. Future studies which can evaluate the specific source, targets and processes through which sulfides are formed, act and are cleared may help to explain these roles and develop mechanism-based therapeutics for ADRD.

# GENERAL DISCUSSION

### *Cognitive impairment in Parkinson's disease*

In chapters 1 and 2 of this dissertation, I explored sex specific differences in PD cognitive dysfunction in the five domains described by the movement disorder task force for the diagnosis of cognitive impairment in PD (Litvan et al., 2012) including attention and working memory, executive function, language, visuospatial function and episodic memory. I also explored sex differences in PD associated processing speed dysfunction as our lab has shown that deficits in processing speed subserve other domains of cognitive function (Nguyen et al., 2017). My work expands our understanding of the contribution of sex on PD associated cognitive dysfunction across domains. My major findings include results consistent with existing literature describing no differences between males and females with PD in domains of attention and working memory. I am also the first to identify consistent sex differences with males performing significantly worse in executive function including set shifting and inhibition as well as the first to show sex that males with PD demonstrate significantly poorer semantic language production. Although the current literature describes superior visuospatial performance in males, I am the first to identify that males with PD perform significantly worse on a task of visuospatial memory. I also add to the knowledge base by expanding the neurocognitive evaluation of verbal episodic memory to include more thorough tasks including prose and word pair recall. Lastly, I add two idependent reports of sex differences in processing speed of which there is a paucity of data in the existing literature. The origin of these sex differences is unknown. However, since the basal ganglia degeneration, the hallmark pathophysiological change in PD, affects five basal ganglia thalamo-cortical loops, and

more specifically, the dorsolateral prefrontal loop is associated with cognitive changes in PD (Auning et al., 2014; Kudlicka et al., 2011; Paek et al., 2020) and neurodegeneration may be different in males and females (Yadav et al., 2016). My findings have led me to hypothesize a sexually dimorphic disease process based on known anatomical changes, specifically within the frontal lobe, for the observed male bias in PD associated cognitive dysfunction.

*Attention and Working Memory*

Attention and working memory are fundamental cognitive processes in receiving and making sense of incoming information (Awh, Vogel, & Oh, 2006). Theoretically, attention overlaps with the constructs of consciousness and short-term memory, capturing the content of current thought. Working memory takes these contents a step further by performing mental operations on the material. The evidence for sex differences in attention in healthy people is mixed. Studies have shown superior female performance primarily in visual orienting attention from a sample of 38 healthy males and 35 females (G. Liu, Hu, Fan, & Wang, 2013) whereas males outperformed females on an attentional task requiring a visuospatial component, such as the forward Corsi Block-tapping test (Piccardi et al., 2019). However, my work is in agreement with others who found that males and females performed similarly on digit span forward, a verbal attention task (Piccardi et al., 2019; Reekes et al., 2020). While both tests require participants to reproduce the stimuli in a specific sequence there may be inherent sex differences between stimulus type with a male advantage in visually presented stimuli.

Several studies have reported no significant differences between healthy males and females in working memory on verbal versions of the n-back test (Lejbak, Crossley, & Vrbancic, 2011; Li, Luo, & Gong, 2010; Schmidt et al., 2009). A study of young adults (18 male, 18 female) found that while males and females performed similarly on the verbal version of the n-back test, males outperformed females on spatial and common object n-back tasks (Lejbak et al., 2011). Consistent with other reports, I found no sex differences in healthy individuals in auditory working memory using the digit span backward task (Piccardi et al., 2019; Reekes et al., 2020) or Letter-Number Sequencing (G. Liu et al., 2013). In order to better understand sex differences in disease subgroups, it would be advantageous for future studies to incorporate visual based tests of working memory such as the spatial working memory task from the Wechsler Memory scale which is known to involve more diffuse neuroanatomical representations to evaluate if there are sex differences in all subtypes of working memory.

Attention deficits have been described in individuals with PD with and without dementia (Brown & Marsden, 1988; Cools, Rogers, Barker, & Robbins, 2010; Downes et al., 1989), though my work and that of others do not agree (Ma et al., 2018; K. M. Miller, Price, Okun, Montijo, & Bowers, 2009; Reekes et al., 2020; Zokaei, Burnett Heyes, Gorgoraptis, Budhdeo, & Husain, 2015). In the evaluation of sex differences in cognitive function, I found that sex did not play a role in performance on the digit span forward task in PD (Reekes et al., 2020). Nor did sex impact working memory in PD groups as measured by the digit span backward tasks (Reekes et al., 2020) or letter-number sequencing (G. Liu et al., 2013). Similarly, in a 4-year longitudinal study using the PPMI database, no sex

differences were found in letter-number sequencing (Bayram, Banks, et al., 2020) in PD. My work provides strong evidence for similar performance between males and females with and without PD using well-established measures of attention and working memory which provides support that our observed differences in other domains were not a result of confounding gross cognitive deficits or other impairments. Interestingly, while attention and working memory have traditionally been ascribed to prefrontal cortex function recent neuroimaging studies have described diffuse anatomical representations including frontal and parietal regions for attention and working memory tasks (Constantinidis & Klingberg, 2016; C. E. Curtis & D'Esposito, 2003; Eriksson, Vogel, Lansner, Bergstrom, & Nyberg, 2015). Furthermore, for visual based attention and working memory tasks, representation in posterior visual areas have been identified (Paneri & Gregoriou, 2017). Taken together, the data in the literature and my current findings are in line with our hypothesis for a sexually dimorphic disease phenotype that preferentially affects the frontal lobe.

*Executive Function*

Executive functions are a broad set of mental processes required to control behavior toward goal-oriented problem solving (Barkley, 2012) and are attributed to frontal lobe function (Linortner et al., 2020; Otero & Barker, 2014; Rae et al., 2012; Theilmann et al., 2013). They can be considered supraordinate to other elements of cognition due to their ubiquity in cognitive tasks and their importance in allocating cognitive resources. Examples of executive function include memory retrieval, task preparation, selection, initiation, planning and prioritizing, shifting/switching cognitive set (i.e., cognitive flexibility), inhibition, and cognitive control. Executive functions are differentially

associated with frontal lobe activity (Miyake et al., 2000) and top-down signaling from the prefrontal cortex to subcortical regions during memory retrieval (Tomita, Ohbayashi, Nakahara, Hasegawa, & Miyashita, 1999), task preparation (MacDonald, Cohen, Stenger, & Carter, 2000) and selection (Pouget, Murthy, & Stuphorn, 2017; Wagner, Maril, Bjork, & Schacter, 2001), set shifting (Bissonette, Powell, & Roesch, 2013) and other tasks of cognitive control (Badre, 2008; E. K. Miller, 2000). Using high-resolution diffusion tensor imaging in healthy populations, Shen and colleagues (2020) found that interhemispheric frontal connections, a fronto-parietal subnetwork, and fronto-striatal connections between right dorsolateral prefrontal cortex and right caudate were strongly associated with performance on tests of executive function.

Thus far, no evidence clearly indicates sex differences in healthy populations in executive function (Gaillard, Fehring, & Rossell, 2021), although males tend to be more impulsive and less sensitive to negative outcomes than females (Grissom & Reyes, 2019). For example, a meta-analysis identified no sex differences in executive behavioral control for tasks including Stroop color word interference, Go/No-go, the Stop task, and Continuous Performance Test; however, sex differences in motivational responses were identified, with males demonstrating more punishment and reward sensitivity, risk-taking behavior, and sensation seeking (Cross, Copping, & Campbell, 2011). I identified no differences between males and females in tasks of set switching and inhibition using the Delis -Kaplan Executive Function System (D-KEFS) subtests of Trail Making Test, Verbal Fluency, and color-word Inhibition in healthy controls as in previous work (Gaillard et al., 2021; Reekes et al., 2020).

A primary symptom of PD is loss of executive control and my work found significant sex differences in a measure of inhibition using the color-word inhibition task from the D-KEFS (Reekes et al., 2020). Here, I extend previous work (Cholerton et al., 2018) by also describing impairments in male performance on cognitive switching tasks in D-KEFS Trail Making Test conditions 4 minus 5 (Reekes et al., 2020) (number letter sequencing with correction for motor speed), although using Stroop-based measure of inhibition and switching I saw no sex differences between males and females with PD (Reekes et al., 2020) likely due to task complexity. The task requires the combination of both inhibition and set shifting which contributed to increased errors and task completion time as well as increased variance. In verbal based executive function tasks, I found that females produced significantly more words for conditions of category switching and showed higher switching accuracy on the D-KEFS verbal fluency task (Reekes et al., 2020). The effect size for verbal category switching and verbal switching accuracy were large (Cohen's d = 0.5-0.8), while tests of other executive functions (switching and inhibition) produced medium effect sizes (Cohen's d = 0.2-0.5) (Reekes et al., 2020). Furthermore, a recent meta-analysis of 22 studies with sex-segregated executive function data in PD subjects revealed that while both males and females showed deficits compared to healthy controls, female PD vs. control comparison produced a smaller effect size (Hedges' g = 0.382) than male PD vs. control (Hedges' g = 0.575) (A. F. Curtis et al., 2019). Sex differences in PD associated executive function are common, with deficits showing a strong male bias. Future work should investigate if sex differences in executive functions such as cognitive control relate to motor phenotype which are known to be more severe in males.

My work presents the most comprehensive analysis of sex differences in PD associated executive dysfunction to date and given previous work on frontal lobe involvement in executive function, provides further evidence of sex specific disease pathology of the frontal lobe.

*Language*

Language is the principal mode of human communication consisting of words used in a structured and conventional way (Fromkin, Rodman, & Hyams, 2013). Verbal fluency is an index of expressive (versus receptive) language often measured by asking individuals to state as many words as possible within one minute that either begin with a specific letter (i.e., letter or orthographic fluency) or belong to a specific category (i.e., category or semantic fluency). Letter fluency may be considered an element of executive function because of its large problem-solving component and activation of the prefrontal cortex. A large meta-analysis of 134 studies of verbal fluency showed that while age and education were associated with variance in performance, verbal fluency did not vary by sex in healthy adults (Barry, Bates, & Labouvie, 2008). A longitudinal study examined verbal fluency over time and while a superior female performance was observed, decline was not significantly different for males and females over time (Capitani, Laiacona, & Basso, 1998).

People with PD may experience problems with speech (Levin et al., 1992), word-finding (anomia) (Matison, Mayeux, Rosen, & Fahn, 1982), confrontation naming (dysnomia) (Bayles & Tomoeda, 1983; Pagonabarraga & Kulisevsky, 2012), sentence

comprehension and construction as well as more global progressive aphasia. Individuals with PD have been shown to perform significantly worse than controls in letter or category fluency (Dadgar, Khatoonabadi, & Bakhtiyari, 2013; I. Obeso, Casabona, Bringas, Alvarez, & Jahanshahi, 2012). A study of 68 males and 36 females with PD from the Movement Disorder Unit of the Neurology Department at Massachusetts General Hospital indicated that males had significantly poorer performance than females on a task of letter fluency, and performance in males was shown to decline earlier and faster compared to females in both letter and category fluency (Locascio et al., 2003). Males with PD have also shown deficits in producing action verbs using the action fluency test (Auclair-Ouellet et al., 2021). Moreover, using a test originally described by Ullman and colleagues (Ullman et al., 1997), males with PDdemonstrated significant deficits in producing regular past-tense verbs compared to females with PD (Reifegerste et al., 2020). Females with PD also demonstrated similar performance to healthy control subjects (Reifegerste et al., 2020). However, other studies disagree. One study found no evidence of sex differences in letter or category fluency (I. Obeso et al., 2012), and a longitudinal study using the PPMI database showed that a sample of 89 males and 33 females scored similarly on letter and category fluency tests (Bayram, Banks, et al., 2020). In my study, however, I found that males produced significantly fewer words in a task of category fluency (Reekes et al., 2020). While language deficits are common in PD, future studies should assess sex differences in disease specific deficits beyond speech production including word finding and sentence comprehension and construction. Interestingly, Weiss and colleagues (E. M. Weiss et al., 2006) found that processing speed in males, which is of particular interest to our lab and this dissertation, was associated with verbal fluency

performance in PD and may represent a role for frontal lobe dysfunction in the observed male deficit in language performance.

*Visuospatial Function*

Visuospatial function is an element of perception that uses vision or imagery in tasks involving the relative location of objects. Healthy males perform significantly better than females on most visuospatial tasks including visuospatial episodic memory (Lewin et al., 2001; McCarrey et al., 2016), working memory (Loring-Meier & Halpern, 1999; Voyer, Voyer, & Saint-Aubin, 2017) and processing (Clements et al., 2006). However, while at baseline healthy males outperform females on visuospatial tasks, males demonstrate a steeper rate of decline compared to females in visuospatial ability (McCarrey et al., 2016). As in healthy adults, in PD, males scored significantly higher in visuospatial orientation on the Benton Judgement of Line Orientation test (Bayram, Banks, et al., 2020; R. Liu et al., 2015). Males with PD have also been shown to score better on the Clock Drawing Test, a test of visuo-construction and spatial reasoning, compared to females with PD (Riedel et al., 2008). While males with PD performed significantly better on the Money Road Map test (a left-right discrimination task requiring an egocentric mental rotation in space) compared to females with PD, male performance declined significantly faster over time compared to females (Locascio et al., 2003). In contrast, sex differences in visuospatial processing were not observed in PD subjects using a mental rotation task (Amick, Schendan, Ganis, & Cronin-Golomb, 2006). Similarly, a recent meta-analysis of 10 studies of PD subjects containing sex-segregated visuospatial data (A. F. Curtis et al., 2019) found that males and females perform similarly in visuospatial abilities. However,

my data demonstrates for the first time that males perform significantly worse in tasks of visuospatial episodic memory as measured by the Wechsler Memory Scale (WMS-III) immediate and delayed Family Pictures task, but not Faces likely due to differences in task requirements (Reekes et al., Under Review). Faces is more dependent on recognition memory which has been shown to be conserved in PD (Whittington et al., 2000), whereas Family Pictures has verbal and visuospatial components and performance on this task may be more closely associated with deficits in verbal memory (Chapin et al., 2009; Dulay et al., 2002). My data suggests that there may be task specific sex differences in PD associated visuospatial dysfunction with females performing worse on tasks of visuospatial orientation and males performing worse on tasks of visuospatial memory. Future studies evaluating sex differences in PD cognitive dysfunction should assess performance across domain subtypes.

*Episodic Memory*

Episodic memory is a type of long-term memory involving events rather than semantic knowledge and is commonly associated with dementia and PD-associated cognitive deficits (Broeders et al., 2013). Evidence from healthy individuals shows that females consistently outperform males in tests of verbal episodic memory, while males demonstrate stronger performance on tests of visuospatial episodic memory using added and moved inkblot tests, face recognition, Rey memory, object recognition and recall (Lewin et al., 2001) and the Benton Visual Retention Test (McCarrey et al., 2016). In addition, previous reports indicate that for both verbal and visuospatial episodic memory,

small to medium effect sizes are seen between healthy males and females (Lewin et al., 2001; McCarrey et al., 2016).

Relatively consistent sex differences in episodic memory have been described in PD. Females performed significantly higher on the Hopkin's Verbal Learning Test-Revised (HVLT-R) (Bayram, Banks, et al., 2020; R. Liu et al., 2015). In my study, females also outperformed males for words remembered from learning trials, as well as delayed free recall on the California Verbal Learning Test (Reekes et al., Under Review). Each of these are list-learning tasks requiring examinees to memorize a set list of words from four categories. However, I also found variable results in performance on the delayed auditory memory tasks from the Wechsler Memory Scale-Third edition (WMS-III), including Verbal Paired Associates (recall of word pairs) and Logical Memory subtests (recall of prose passages) where after alpha correction, no difference was seen in delayed verbal memory tasks (Reekes et al., Under Review). In general, these findings of verbal episodic memory impairment in males compared to females with PD are consistent with significant sex differences in PD associated memory dysfunction, with stronger effects in word recall versus paired word or prose recall. However, given my variable findings in more complex tasks of verbal episodic memory such as prose recall, future studies should evaluate the role of disease stage and progression as my study evaluated sex differences in non-demented individuals eligible for deep brain stimulation surgery who were thus relatively stable in both cognitive impairment and motor disease.

*Processing Speed*

Processing speed is the ability to recognize, react and begin to respond to sequential stimuli. In normal aging, processing speed has been postulated to subserve cognitive decline across domains, accounting for the variance in performance on a range of cognitive tasks (Salthouse, 1996). Increased adult age is associated with a decline in processing speed which results in a decrease of the number of cognitive operations able to be performed in time available (limited time) and degradation of quantity and/or quality of available information (simultaneity), which degrades executive and other cognitive functions (Cummings, 1993; Salthouse, 1996). Sex differences in tests of processing speed have been described in healthy controls. For example, existing studies show a wide age range of healthy females outperform males in processing speed tasks (Camarata & Woodcock, 2006; Keith, Reynolds, Patel, & Ridley, 2008; R. Liu et al., 2015; Roivainen, Suokas, & Saari, 2021), however my study did not find the same results (Reekes et al., 2020). My findings of no differences between healthy controls in processing speed may be the result of the increased age of the study population. It has been reported that females outperform males in processing speed at mid-life; however, this difference diminishes with age and decline of processing speed may be more accelerate in females (Nooyens et al., 2022).

Poorer performance on measures of processing speed has been well described in PD compared to healthy controls (C. Lee, Grossman, Morris, Stern, & Hurtig, 2003; Nguyen et al., 2017; Sanes, 1985; Sisco, Slonena, Okun, Bowers, & Price, 2016; Zimmermann, Sprengelmeyer, Fimm, & Wallesch, 1992) and recent work on PD associated cognitive dysfunction demonstrated that deficits in processing speed mediate the relationship

between age and executive dysfunction, specifically inhibitory control in PD (Nguyen et al., 2017).

Data from the PPMI database shows that females outperformed males with PD on the SDMT at baseline; however, no difference was seen in decline over time by sex (Bayram, Banks, et al., 2020). Furthermore, myself and others have shown that females with PD out-perform males with PD on the SDMT (Reekes et al., 2020) as well as a coding task (Cholerton et al., 2018) despite no differences in demographic or disease severity data. In both control and PD groups, effect sizes between males and females were small in measures of processing speed. In contrast, Liu and colleagues (R. Liu et al., 2015) found no significant sex differences in SDMT performance in PD. However, anxiety score in females was significantly higher, and anxiety has been associated with poorer processing speed in older adults (Beaudreau & O'Hara, 2009) potentially explaining the discrepancy in findings across studies. Thus, while males with PD tend to perform worse on measures of processing speed, this finding may be associated with preexisting sex differences observed in healthy controls, but future studies should evaluate processing speed along with other domains and employ imaging to identify and/or control for comorbid factors such as white matter disease to assess the contribution of sex differences in processing speed on deficits across domains. Thus, the role of processing speed in cognitive dysfunction across domains in PD, and a possible link to sex differences in cognitive dysfunction, are potentially important targets for future research on sex as a biological variable in PD.

*The Role of the Frontal Lobe in Cognitive Dysfunction*

My work and others indicate that males with PD consistently show deficits in cognitive domains including executive function such as switching and inhibition, language production, visuospatial memory, verbal episodic memory, and processing speed versus females with PD. One common factor across these multidomain deficits is a role for the frontal lobe, and here I propose a hypothesis based on underlying anatomy known to be affected in PD.

On tests of executive function (which is specific to frontal lobe), females show significantly stronger performance than males with PD. Furthermore, recent work demonstrates that executive dysfunction in PD is associated with changes to frontal lobe structural connectivity (Linortner et al., 2020; Rae et al., 2012; Theilmann et al., 2013), functional connectivity (Boon et al., 2019; E. A. Disbrow et al., 2022), and effective connectivity (Wu et al., 2011). Thus, a sex specific disease process may be preferentially affecting males thereby leading to my observed sex differences in set shifting and inhibition.

While findings regarding language are mixed, they suggest that males have more difficulty with speech production and that this is often associated with frontal lobe regions including the left inferior frontal gyrus, which contains Broca's area, as well as the precentral gyrus, both of which have known involvement in speech motor control (Behroozmand et al., 2015; Hickok & Poeppel, 2004; Jancke, Liem, & Merillat, 2021). Frontal lobe damage has also been associated with fluency (Robinson, Shallice, Bozzali, & Cipolotti, 2012) and areas including the dorsolateral prefrontal cortex and inferior frontal cortex have been

implicated in fluency performance in PD (Jaywant, Musto, Neargarder, Stavitsky Gilbert, & Cronin-Golomb, 2014). It is possible that my observed sex differences may be a result of motor loop degeneration which is known to be more severely disrupted in males with PD thus affecting speech motor control.

The dorsolateral prefrontal cortex is involved in visuospatial processing (Chafee & Goldman-Rakic, 2000) as well as maintenance of visuospatial working memory (A. Belger et al., 1998; C. McCarthy, Kissen, Yadley, Wood, & Lambert, 2006). The dorsal stream of visual processing and dorsolateral prefrontal cortex are associated with spatial perception and visually guided actions (Tres & Brucki, 2014) and are associated with visuospatial impairments in PD (Antal, Bandini, Keri, & Bodis-Wollner, 1998). Moreover, PD related damage to prefrontal cortex has been linked to deficits in visuospatial recognition memory as well as visuospatial working memory which has been described as a core feature of PD (Owen et al., 1993; Owen, Iddon, Hodges, Summers, & Robbins, 1997). The current literature assesses visuospatial function using tasks of orientation and processing with consistent findings of superior male performance consistent with findings in healthy controls. However, my use of a task of visuospatial memory that included both recognition and visuospatial recall, revealed for the first time that males with PD demonstrate significantly greater recall deficits compared to females which suggests that frontal cortex changes may also contribute to sex differences in specific aspects of visuospatial function.

The frontal lobe is also associated with episodic memory. Functional imaging studies have shown frontal lobe involvement in encoding and retrieval of verbal episodic memory (Fletcher & Henson, 2001). PD associated prefrontal cortex dysfunction has been implicated in both verbal free recall and recognition (Higginson et al., 2003b; Higginson et al., 2005) and synchronization between prefrontal cortex, hippocampus, and other regions plays a role in encoding and retrieval of visually presented objects (Fell & Axmacher, 2011). I found medium effect sizes in PD individuals with females significantly outperforming males for measures of verbal episodic memory which is consistent with my hypothesized role of the frontal lobe in sex specific PD associated cognitive dysfunction. Interestingly, deficits in episodic memory are correlated to deficits in executive function and processing speed, which have large representations in frontal lobe and are known to be affected in PD and may subserve my observed sex differences in episodic memory (T. Lee et al., 2012).

Finally, processing speed is associated with frontal-subcortical circuits (Borghesani et al., 2013; Lu et al., 2013) and disruption to these regions are well described in PD (Cummings, 1993; Linortner et al., 2020; Price et al., 2016). Previous work indicates that impaired white matter connectivity is associated with deficits in processing speed in healthy elderly adults, and white matter integrity in the frontal lobe mediated the relationship between age and cognitive processing speed (Borghesani et al., 2013; Kerchner et al., 2012; Lu et al., 2013; Melzer et al., 2013). Given our lab and others work demonstrating the mediating role of processing speed in PD associated cognitive dysfunction, pathological processes that differ by sex and disrupt frontal lobe may

preferentially affect processing speed which subserves other cognitive domains thus contributing to observed sex differences.

Sex differences have not been observed in attention and working memory. While early studies indicate that attention and working memory are linked to frontal lobe (Wilkins, Shallice, & McCarthy, 1987), recent imaging studies suggest that attention and working memory have a more distributed neuroanatomical representation (Lara & Wallis, 2015; Paneri & Gregoriou, 2017). Moreover, visuospatial function results were mixed, with males demonstrating significantly stronger performance on tasks of orientation (Bayram, Banks, et al., 2020; R. Liu et al., 2015) visuo-construction and spatial reasoning (Riedel et al., 2008) which have representations in parietal lobe (Kerkhoff & Zoelch, 1998; Pisella, 2017). For language, verbal fluency is associated with the frontal lobe, while Broca's and Wernike's areas are traditionally thought to subserve speech production and comprehension respectively, and recent work illustrates the widespread neuroanatomical representations of language (Dikker, Assaneo, Gwilliams, Wang, & Kosem, 2020). For example, the basal ganglia is known to play a role in language comprehension and production in PD (Cardona et al., 2013; Copland, 2003; Macoir et al., 2013; Skeel et al., 2001), and males showed significant deficits in regular verb production, but irregular verb production was similar across sex. While irregular verbs are thought to be memorized via declarative memory, deficits in regular verbal production have been attributed to procedural memory circuits of the left basal ganglia, and greater disruption of the basal ganglia has been shown in males compared to females in PD (Tremblay et al., 2020).

Thus, it may be that functions with more distributed neuroanatomical representations are less vulnerable to frontal lobe sex associated PD pathophysiology.

In summary, my work, in combination with others, indicates that males with PD consistently show deficits in cognitive domains including executive function, verbal fluency, specific visuospatial functions including visuospatial episodic memory, verbal episodic memory, and processing speed and that deficits across these domains seem to be reflective of frontal lobe dysfunction (Table 16). Reduced dopaminergic activity in fronto-striatal networks has been associated with cognitive slowing in PD (Bruck, Aalto, Nurmi, Bergman, & Rinne, 2005; Jokinen et al., 2013), and is consistent with anatomical work by Alexander and colleagues (Alexander et al., 1986) who described parallel basal ganglia thalamocortical circuits subserving a variety of functions (Figure 9). Pathological changes in basal ganglia as a result of dopaminergic denervation include altered neuronal firing rates (J. A. Obeso et al., 2008), increased neuronal oscillation and synchronization (Galvan, Devergnas, & Wichmann, 2015), and introduction of noise into the system disrupts the flow and processing of information (Gale, Amirnovin, Williams, Flaherty, & Eskandar, 2008). This increased noise may disrupt the receptive field, thus broadening the neuroanatomical representation within the frontal lobe leading to reduced spatial specificity in thalamocortical connectivity. This phenomenon of reduced spatial specificity in receptive fields of basal ganglia connectivity has been described as a potential mechanism of PD associated motor dysfunction (McGregor & Nelson, 2019). My findings in combination with others suggest potential sex specific mechanisms that impact frontal lobe function, with males representing a disease subgroup more susceptible to cognitive

disturbance. Given evidence of the underlying anatomy known to be affected in PD, I present a hypothesis of a sexually dimorphic PD phenotype preferentially affecting frontal lobe dysfunction in males.

| Domain | Sex Difference in PD | Frontal Lobe Component |
|---|---|---|
| **Attention** | None | Small |
| **Working Memory** | None | Small |
| **Executive Function** | Males Worse | Large |
| **Verbal Fluency** | Males Worse | Large |
| **Visuospatial Function** | Task Dependent | Task Dependent |
| **Episodic Memory** | Males Worse | Moderate |
| **Processing Speed** | Males Worse | Moderate |

Table 16: Summary of sex differences across domains from my studies and existing literature and frontal lobe involvement

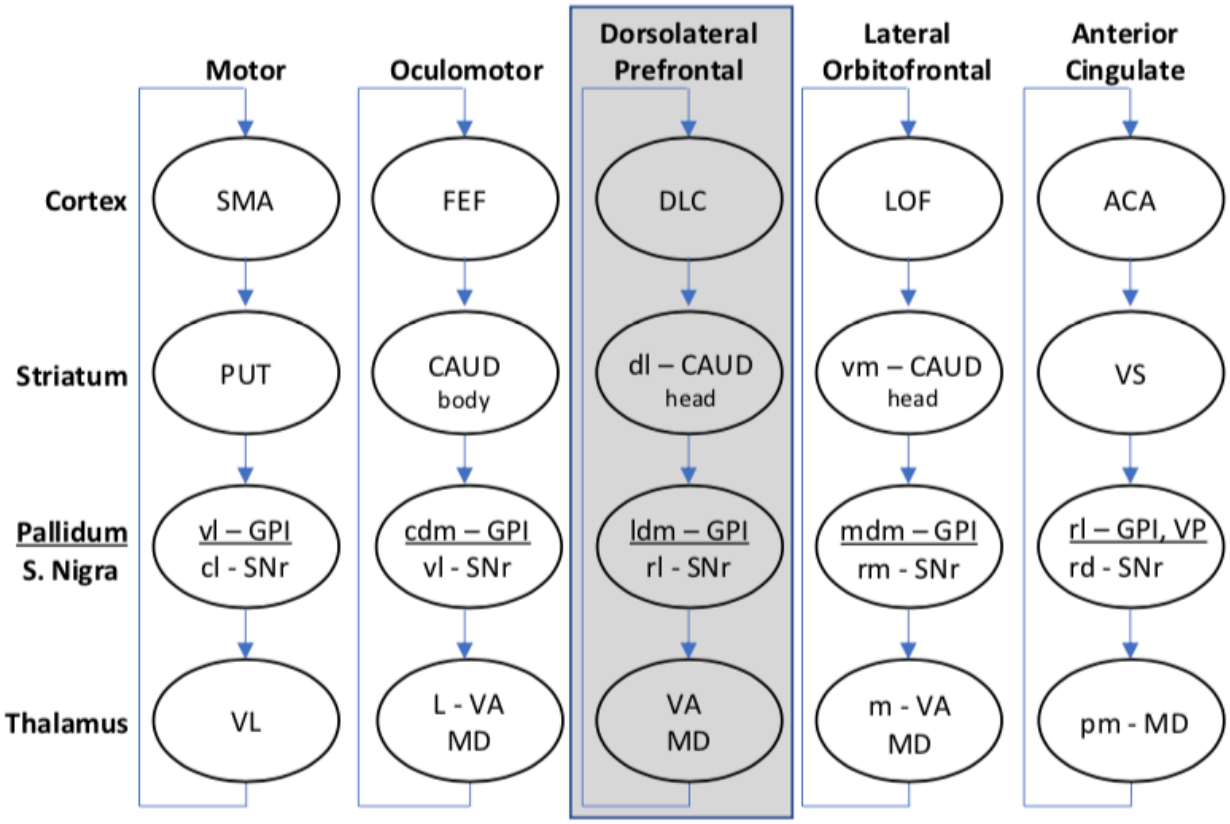



**Figure 9.** Parallel basal ganglia thalamo-cortical loops include specific regions of cerebral cortex, basal ganglia and thalamus (adapted from (Alexander et al., 1986)). Grey box indicates the circuit subserving cognitive function that may play a role in cognitive sex differences in PD. ACA, anterior cingulate area; CAUD, caudate; DLC, dorsolateral prefrontal cortex; FEF frontal eye fields; GPI globus pallidus internus; LOF, lateral orbitofrontal cortex; MD, medial dorsal nucleus of the thalamus; PUT, putamen; SMA, supplementary motor area; SNr, substantia nigra pars reticulata; VA, ventral anterior nucleus of the thalamus; Vl, ventral lateral nucleus of the thalamus; VA, ventral striatum; cl, caudolateral; dl, dorsolateral; pm, posteromedial; rd, rostrodorsal; rl, rostrolateral; rm, rostromedial; vm, ventromedial; vl, ventrolateral.

### *Cognitive impairments in ADRD*

In Chapter 3 of this dissertation, I tested the hypothesis that vascular dysfunction contributes to cognitive impairments and cerebral atrophy in ADRD. These findings support a relationship between vascular disturbances and ADRD pathology.

In this study, I found that ADRD subjects showed significantly poorer performance on the ADAS-cog, a measure of global cognitive function with an emphasis on episodic memory. Moreover, in agreement with previous work from our group (E. Disbrow et al., 2021), I found that these cognitive deficits were significantly associated with measures of total sulfide as well as bound and acid labile sulfides, indicative of vascular stress. My work extends these findings by exploring characteristic measures of brain atrophy and their association to cognitive and vascular dysfunction. I found that ADRD subjects showed greater evidence of diffuse cerebral atrophy with decreased whole brain cortical thickness, decreased frontal and medial temporal lobe thickness, increased inferior lateral ventricle volume and decreased hippocampal volume. I also demonstrated that white matter disruption was significantly greater in ADRD subjects with increased FLAIR lesion volume, decreased fractional anisotropy, and increased radial and mean diffusivity. In agreement with others, I showed that cognitive deficits were significantly associated to measures of cerebral atrophy including mean cortical thickness across the entire surface of the cortex (Dickerson et al., 2009) as well as increased inferior lateral ventricle size (Apostolova et al., 2012), a marker consistent with temporal horn atrophy, and decreased hippocampal volume (Mu & Gage, 2011). I also found that decreased cognitive function was associated with white matter damage including increased white matter hyperintensity volume (Prins & Scheltens, 2015), and white matter microstructure disruption (Xing et al.,

2021). Extending previous work from our group, I assessed vascular dysregulation through plasma levels of hydrogen sulfide and its metabolites to assess the vascular contribution to patterns of atrophy associated with ADRD and cognitive impairments. I showed that increased plasma bound sulfides, which play a role in endothelial barrier function, were associated with decreased cortical thickness across the entire cortex. I also demonstrate that elevated acid labile sulfides, often attributed to iron sulfur clusters, were associated with atrophy, specifically increased volume of the inferior lateral ventricle and decreased hippocampal volumes. Moreover, increased acid labile sulfides were correlated with increased white matter hyperintensity volume and decreased microstructural integrity.

*Cortical Thickness and Bound Sulfides*

Both pre- and postmortem analysis show that loss of cortical thickness is associated with AD (Noh et al., 2014; Querbes et al., 2009; Sabuncu et al., 2011), and has been deemed a “disease signature” (Dickerson et al., 2009). Reduced cortical thickness has also been linked to severity of dementia particularly in temporal and inferior parietal cortices, as well as posterior cingulate and precuneus gyri. Higher levels of cortical thinning were even observed in patients with mild AD compared to controls (Dickerson et al., 2009). Cortical thinning is a sign of diffuse atrophy reflecting neuronal and glial loss (Coleman & Flood, 1987; DeKosky et al., 1996; Dickerson et al., 2009; Scheff et al., 1990), and may indicate pathologic accumulation of neurofibrillary tangles and amyloid plaques (Ossenkoppele et al., 2019). Interestingly, the vascular burden index has also been associated with cortical thinning (Tchistiakova et al., 2016). Ottoy et al. (2022) found that vascular burden

contributed significantly to cortical thinning independent of Aβ. In addition, previous studies demonstrated that patients with cerebral amyloid angiopathy, a cerebrovascular disease affecting small and medium blood vessels of the brain, had significantly more cortical thinning compared to healthy controls (Subotic et al., 2021), suggesting a link between AD associated changes in cortical structure and vascular dysfunction.

Bound sulfides, such as poly- and persulfides, can include protein-sulfur adducts which are post-translational modifications of several proteins. Bound sulfides have both pro and antioxidant effects through their actions as reductants and nucleophiles (Francoleon et al., 2011). In my study I found that elevated bound sulfides were associated with cognitive impairment as well as diminished cortical structure. Work from our group reported that exposure of endothelial monolayer to persulfides disintegrated endothelial barrier with remodeling of claudin 5 and VE-cadherin and actin stress fiber contraction (Yuan et al., 2016). Other studies have shown that the primary sulfide generating enzyme in the vasculature (G. Yang et al., 2008), cystathionine γ-lyase (CSE), may be induced by vascular stress (Huang et al., 2015; Yuan et al., 2016). Stress induced CSE appears to represent at least one source of elevated sulfides, and lack of CSE in animal and cellular models showed improved barrier function over normal levels (E. Disbrow et al., 2021; Yuan et al., 2016). It was also shown that when CSE was genetically eliminated, that *bound* sulfides were reduced, while free and acid labile sulfides were not affected. This finding suggests that at the level of the microvasculature, elevations in bound sulfides produced by CSE could lead to loss of barrier function. Studies have described how weakening the blood brain barrier in AD may contribute to and drive progression of

vascular dysfunction and inflammation which, in turn, cause the neuronal tissue pathophysiology characteristic of AD progression (Hachinski et al., 2019). For example, loss of blood brain barrier integrity can trigger excitotoxic calcium signaling and metabolic dysfunction (Rajeev et al., 2022) which accumulate signatures of destruction of brain structure/function (Alzheimer's Association Calcium Hypothesis, 2017; Khachaturian, 1989, 1994). Thus reduced cortical thickness volumes, which represent important indices of brain atrophy, may be due to bound sulfide driven blood brain barrier dysfunction.

*White Matter Integrity and Acid Labile Sulfides*

In addition to increases in bound plasma sulfide, I also found significant increases in acid labile sulfide which were correlated with cognitive dysfunction and increased white matter hyperintensity (WMH) burden. WMH in ageing and AD are indicators of chronic ischemia and cerebral small vessel disease (Prins & Scheltens, 2015). Evidence also suggests that WMH volume increases with age and hypertension (de Leeuw et al., 2001; Pantoni & Garcia, 1997), and the ApoE4 allele has been associated with greater WMH volume (Brickman et al., 2014). In a review by Jorgensen et al., (2018) vascular risk factors including hypertension, increased systolic and diastolic blood pressure, increased mean arterial pressure, increased pulse pressure and other cardiovascular factors were identified as imparting the greatest risk for WMH. WMH burden is elevated in both MCI and AD and is associated with common pathological changes seen in AD such as Aβ aggregation and neurofibrillary tangles (Brickman et al., 2008). Interestingly, WMH may lower the threshold for the manifestation of dementia with AD pathologies (Jack et al., 2018). Furthermore, increased Aβ was associated with increased WMH burden in the

parietal, temporal, occipital, and posterior corpus collosum regions (Garnier-Crussard et al., 2020), suggesting a feedback loop between tissue and vascular changes.

In addition, my work showed for the first time that increased acid labile sulfide was associated with decreased white matter integrity, indicated by decreased FA, and increased MD, RD, and AxD. Growing evidence describes a link between vascular risk factors and disturbed white matter microstructural integrity (Cox et al., 2019; Ingo et al., 2021; Xing et al., 2021). For example, decreased FA was associated with increased WMH volume and vascular risk factors such as ApoE4 status and hypertension (R. Wang et al., 2015) as well as aggregate vascular risk score (Cox et al., 2019). Moreover, Xing et al. (2021) found that in patients with evidence of cerebral small vessel disease, decreased whole brain FA was a stronger predictor of cognitive impairment than tract specific or regional volumetric analysis. Similarly, decreased FA and increased RD, MD and AxD were significantly associated with WMH burden in a cohort of patients with subcortical ischemic vascular disease (X. Liu et al., 2019). Finally, in a 5-year follow-up study of a cohort of patients with small vessel disease, decreased white matter integrity and increased WMH volume predicted the progression to dementia (Zeestraten et al., 2017). My work represents a possible role for acid labile sulfide as a link between vascular dysfunction and deterioration of white matter integrity.

Currently, there is very little known about how acid-labile sulfides affect the vasculature, but this sulfide pool is known to react with transition metals like iron in ‘iron-sulfur clusters.’ Iron-sulfur clusters are important for maintaining cellular homeostasis, reflecting their

roles in enzyme action (including formation of oxidants), protein stability (J. L. Liu et al., 2018), and mitochondrial electron transport chain complexes where increased generation of iron sulfur clusters may trigger the overproduction of reactive oxygen species within mitochondria leading to cell injury or death (Read et al., 2021). In addition to my findings for plasma acid labile sulfides, others have shown brain iron levels to be associated with development of white matter hyperintensities (Yan et al., 2013) and poorer memory recall (Ding et al., 2009). Yan and colleagues (2013) found that iron deposition in the brain was independently linked to white matter hyperintensity (WMH) severity, and suggest that iron may play a role in the pathogenesis of WMH. Interestingly, increased cerebral iron deposition in white matter as well as cortical and subcortical grey matter including the hippocampus has been implicated in AD and may be linked to Aβ deposition and hyperphosphorylated tau formation (B. Liu et al., 2011; Mandel et al., 2007; Rao & Adlard, 2018). Thus, ne possible role for elevated acid labile sulfides in AD is increased generation of iron-sulfur clusters which intensify β-amyloid plaque progression, and ultimately cognitive decline in the disease.

I observe here that ADRD subjects demonstrate significantly higher levels of bound and acid labile sulfides compared to control subjects. Interestingly, I did not find a significant difference in plasma free sulfide, the pool most associated with antioxidant and protective properties. My working hypothesis to explain these findings is that elevated sulfides are the result of a compensatory mechanism aimed at producing free sulfides that consequently results in increased bound and acid labile species, an overaccumulation of both of which can become damaging.

Previous data from our group in combination with my own show that there may be an age-related increase in bound sulfide (Kolluru et al., 2020). I show here that increased bound sulfide is associated with decreased cortical thickness across the entire surface of the cortex with specific regions of interest being the medial temporal lobe which includes entorhinal and parahippocampal areas that are classically associated with memory deficits in ADRD, as well as frontal and parietal areas. It is possible that the increase of bound sulfide is associated with cortical thickness because of the higher vascular density in grey matter. Vascular stress is an emerging risk factor for AD; therefore, given the association between bound sulfides and barrier function described by our group, elevated bound sulfides may be a marker of vascular stress that both increases risk and results from AD pathology. Furthermore, I found that increased acid labile is associated with white matter integrity, specifically increased white matter hyperintensity volume, decreased fractional anisotropy and increased radial and mean diffusivity. These data support a hypothesis that acid labile interacts with iron in the form of iron sulfur clusters and may be involved in mitochondrial dysfunction through increased reactive oxygen species generation. The white matter represents a high neuronal structural content and thus is more sensitive to mitochondrial dysfunction. Future work should assess whether elevated acid labile sulfide is a result or a cause of mitochondrial dysfunction that leads to a destructive feedback loop contributing to a cascading AD pathology.

Taken together, the findings of chapter 3 of this dissertation suggest that elevated sulfides are associated with poor memory function, brain atrophy and cerebral microvascular

disease which support my working hypothesis that free sulfide may be oxidatively metabolized or consumed as part of a compensatory response to AD related pathophysiology and progression. I propose that the oxidation of free sulfide results in increased acid labile and bound sulfides (per- and polysulfides) as injurious byproducts. Future studies will investigate this hypothesis further to evaluate the specific source, targets and processes through which hydrogen sulfide and its metabolites are formed, used and are cleared, hopefully leading to mechanism-based therapeutics for ADRD.

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I am currently a PhD candidate in the department of Pharmacology, Toxicology, and Neuroscience at Louisiana State University Health in Shreveport. I work under the advisement of Dr. Elizabeth Disbrow. Our research focuses on cognitive dysfunction in age related neurodegenerative disease, in particular Alzheimer disease and Parkinson disease and uses clinical measures such as neuropsychological testing and neuroimaging to develop clinically based hypotheses. Our most recent work focuses on the role of cerebral microvascular disease and its impact on brain structure and cognitive function.

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Departmental Honors

## Accomplishments

- Ike Muslow Predoctoral Fellowship- $30,000 annual award
- Featured by the Washington Post in a piece on sex differences in

Parkinson's Disease
- 1st place poster presentation (clinical) - I.D.E.A.S. Day- LSU Health Shreveport
- 1st place poster presentation-Graduate Student Research Day-LSU Health Shreveport
- Departmental Honors, Biology- Hampden-Sydney
  College Dean's List- Hampden-Sydney College
- Presidential Scholarship- Hampden-Sydney College

## Skills

- IRB compliance and protocol management
- Statistical analysis (SPSS)
- Imaging analysis:
  - FreeSurfer (recon-all, TRACULA, PETsurfer, CONN)
  - SPM (Lesion Segmentation Tool)
- Neuropsychological Testing (WMS-IV, WAIS-IV, ADAS-Cog, etc.)

## Selected Mentorship

**Science and Medicine Academic Research Training (SMART) Program**
*Sponsor: Biomedical Research Foundation*
Molly McNulty (June 2020-May 2021)
Project Title: Processing Speed Subserves Executive Function in Parkinson Disease
Awards Received:
NWLA Mendelevian Society Annual Research Symposium - 1st Place
Louisiana Science and Engineering Fair – 2nd in category
Louisiana State Junior Science and Humanities Symposium – top 5 overall, National Qualifier

**Medical Student Research Program (MSRP)**
*Sponsor: LSU Health School of Medicine*
Benjamin Becnel (May 2019-October 2019)
Project Title: Theory of Cognitive Aging in Dementia Awards Received:
Research and Industry Day – 1st place
Olivia Feltner (May 2019-October 2019)
Project Title: Sex specific differences in cognitive decline in Parkinson's disease
Awards Received:

Research and Industry Day - 2nd place

**Undergraduate Research Apprenticeship Program (UGRAP)**

Sponsor: Office of Diversity Affairs

Hailey Phillips

Project Title: The Role of Sex in Parkinson's Disease Associated Executive Dysfunction Awards Received:

Summer Research Symposium – 2nd place

**Jumpstart Summer Enrichment Program (JSEP)**

*Sponsor: Office of Diversity Affairs*

Angle Ntenyi

Project Title: Impact of Depression in Parkinsonian Cognitive Dysfunction

**Cardiovascular Undergraduate Research Initiative for Underrepresented Students (CURIOUS)**

*Sponsor: National Institutes of Health*

*Brianna Callicoatte*

Project Title: Vascular Contributions to Processing Speed Deficits in Alzheimer's and Parkinson's Disease

Awards Received:

CURIOUS Poster Session – 2nd place, national conference qualifier

## Teaching Experience

**Bio 497 Medical Seminar** *Fall 2021*

*Louisiana State University, Shreveport*

Responsible for familiarizing students with research methods and discoveries being made in modern biomedical research

**Advanced Statistics 227** *Fall 2020/Fall 2021/Fall2022*

*LSU Health Shreveport*

Responsible for developing and instructing application lectures for two-way and repeated measures ANOVA

**Patient-Oriented Problem-Solving (POPS)** *Spring 2019- present*

*LSU Health Shreveport*

Responsible for facilitating medical student small group sessions on pharmacology-based case reports

**Biology Laboratory Teaching Assistant** *Fall 2015/Fall 2016*

*Hampden-Sydney College*

Responsible for assisting in lectures, and developing and editing the laboratory notebook, as well as providing individual assistance to students in understanding basic concepts such as project design, laboratory practices, and experimentation

## Contributions to Science

1. **Sex Differences in Cognitive Dysfunction in PD**

We have studied sex specific differences in cognitive dysfunction. Our findings suggest that males have more significant cognitive impairment than females.

**Published Manuscripts:**

Reekes, T.H., Higginson, C.I., Ledbetter, C.R. *et al.* Sex specific cognitive differences in Parkinson disease. *npj Parkinsons Dis.* **6,** 7 (2020). https://doi.org/10.1038/s41531-020-0109-1

**Published Abstracts:**

Reekes, T., et al. 2021 "Sex Differences in Deficits across Memory Subtypes in Parkinson Disease" presented at Society for Neuroscience annual meeting, SfN Global Connectome

Reekes, T., et al., 2019 "Sex Specific Cognitive Differences in Parkinson's Disease" presented at Society for Neuroscience annual meeting, Chicago, IL

Reekes, T., et al., 2019 "Sex/Gender Differences in Cognitive Dysfunction in Parkinson's Disease" presented at Graduate Student Research Day, LSU Health Shreveport, Shreveport, LA

Feltner, C.O., Reekes, T., et al. 2018 **"**Sex Specific Differences in Cognitive Decline in Parkinson's Disease" presented at Medical Student Research Program poster presentation, LSU Health Shreveport, Shreveport LA

Barras, A., Reekes, T., et al. 2020 Sex Differences in the Cognitive Estimation Test in Parkinson's disease presented at Research and Industry Day poster presentation, LSU Health-Shreveport, Shreveport, LA

Parvatanen, T., Reekes T., et al. 2020 "Sex Differences in Verbal Learning in Parkinson Disease" presented at Research and Industry Day, LSU Health Shreveport, Shreveport, LA

**2. Brain Imaging in Parkinson Disease**

We have identified anatomical and connectivity differences in PD compared to healthy controls. In addition, these differences are related to cognitive dysfunction in processing speed and executive dysfunction.

**Published Abstracts:**

Reekes, T., Ledbetter, C., PhD, Larmeu, L., MS, et al., 2021 "Basal ganglia amyloid beta accumulation and cognitive dysfunction in Parkinson disease" presented at LSU Health Graduate Student Research Day

Cale, J., Reekes, T., et al., 2021 "Effects of Parkinson's Disease on Motor and Cognitive Task-Switching Networks" presented at Organization for Human Brain Mapping Annual Meeting, Virtual

Ledbetter, C., PhD, Larmeu, L., MS, Reekes, T., et al., 2021 "Basal ganglia amyloid beta accumulation and cognitive dysfunction in Parkinson disease" presented at Society for Nuclear Medicine Annual Meeting, Virtual

Leach, K., Reekes, T., et al. 2020 "An Analysis of Brain White Matter Integrity and Processing Speed in ADRD" presented at Research and Industry Day poster presentation, LSU Health-Shreveport, Shreveport, LA

Haacker, C., Reekes, T., et al. 2020 "Association of Temporal Processing Speed Performance and White Matter Connectivity" presented at Research and Industry Day, LSU Health-Shreveport, Shreveport LA

Nelson, M.E., Reekes, T., et al. 2020 "Brain Atrophy, Microvascular Disease, and Cognitive Function in ADRD" presented at Research and Industry Day poster presentation, LSU Health-Shreveport, Shreveport LA

**3. Biomarkers of Cognitive Dysfunction and Alzheimer's Disease**

I am part of a team examining plasma hydrogen sulfide and its metabolites as biomarkers of the vascular contribution to dementia. Our finding is that H2S mediates the relationship between cerebral microvascular disease and memory dysfunction.

**Published Manuscripts:**

Disbrow, E., Stokes, K. Y., Ledbetter, C., Patterson, J., Kelley, R., Pardue, S., Reekes, T., … & Kevil, C. G. (2021). Plasma hydrogen sulfide: A

biomarker of Alzheimer's disease and related dementias. *Alzheimer's & Dementia*.

**4. Healthcare Disparities**

I am part of a team studying care disparities, race and literacy. In our community poverty, lack of education and access to healthcare impact over 30% or our population. We are identifying barriers to care and evaluating potential interventions to alleviate these disparities.

**Published Manuscripts:**

Yetman, M., Blancher, A., Reekes, T., Establishing a Health & Wellness Intervention Program for Head Start Teachers & Staff. *International Journal of Health, Wellness and Society,* in press (2020). https://doi.org/10.18848/2156-8960/CGP/v11i01/23-34 Pereira, C., LaRoche, A., Arredondo, B., Pugh, E.,
Disbrow, E., Reekes, T. H., ... & Sawyer, R. J. (2021). Evaluating racial disparities in healthcare system utilization and caregiver burden among older adults with
dementia. *The Clinical Neuropsychologist*, 1-14.
Blancher, A., Yetman, M., Reekes, T., Racial Disparities among the Physical and Mental Health of Head Start Staff. *Head Start Dialog: The Research-to-Practice Journal for the Early Childhood Field,* in press (2022).

**Published Abstracts:**

Pereira, C., Disbrow, E., Reekes, T., LaRoche, A., Arredondo, B., Sawyer, R. Evaluating racial disparities in healthcare system utilization among older adults with dementia. Poster to be presented at the International Neuropsychological Society Annual Conference; From Autism to Alzheimer's: New Perspectives in Neuropsychology; Feb 3-6, 2021, San Diego, CA

**5. Prenatal Alcohol Exposure**

We have identified deficits in motor learning in mice exposed to alcohol during prenatal development. This work suggests select brain regions may be more vulnerable to alcohol exposure.

**Published Manuscripts:**

Clabough, E., Ingersoll, J., Reekes, T., Gleichsner, A., & Ryan, A. (2021). Acute Ethanol Exposure during Synaptogenesis Rapidly Alters Medium Spiny Neuron

Morphology and Synaptic Protein Expression in the Dorsal Striatum. *International Journal of Molecular Sciences*, *23*(1), 290.
Reekes TH*, Vinyard III HT*, Echols W* *et al.* Moderate chronic fetal alcohol exposure causes a motor learning deficit in adult outbred Swiss-Webster mice. *F1000Research* 2016, **5**:1896

## Other Service

**LSUHS Chancellor Search Committee** *Spring 2022-current*
*LSU Health, Shreveport, Louisiana*
School of Graduate Studies student representative on the Search committee for the Chancellor of LSU Health Shreveport.

**School of Graduate Studies Special Projects Coordinator** *Summer 2022-current LSU Health, Shreveport, Louisiana*
Develop fundraising strategies for student development through alumni engagement on campus events.

**School of Graduate Studies Social Chair** *Summer 2021-current LSU Health, Shreveport, Louisiana*
Plan and execute monthly student engagement activities and fundraising events.

**SfN Student Representative** *Spring 2021-current LSU Health, Shreveport, Louisiana*
Assist with planning of SfN events and outreach, communicate with students and promote engagement

LSU Health Sciences Center
SHREVEPORT

*School of Graduate Studies*
*Louisiana State University Health Sciences Center*
*Shreveport, Louisiana 71130*

# DISSERTATION / THESIS DEFENSE FINAL EXAMINATION REPORT

Candidate: Tyler Reekes

Department: Pharmacology, Toxicology & Neuroscience

Degree: Doctor of Philosophy

Examination Date: November 8, 2022

Major Field: Pharmacology

Minor Field: Neuroscience

Dissertation Title: Contributions to cognitive dysfunctions in neurodegenerative disease

The undersigned members of the Graduate Faculty have examined the candidate and accept his/her Dissertation/Thesis.

| EXAMINING COMMITTEE | | |
|---|---|---|
| **Type Name** | **Signature** | **Department** |
| Elizabeth Disbrow, Ph.D. | Advisor | Pharmacology, Toxicology & Neuroscience |
| Nicholas Goeders, Ph.D. | | Pharmacology, Toxicology & Neuroscience |
| Xiaohong Lu, Ph.D. | | Pharmacology, Toxicology & Neuroscience |
| Yunfeng Zhao, Ph.D. | | Pharmacology, Toxicology & Neuroscience |
| Karen Stokes, Ph.D. | | Molecular & Cellular Physiology |
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APPROVALS:

Department Head — Date: 11/08/22

Dean of the Graduate School — Date: 11/8/22