Resting-State BOLD Variability in Alzheimer's Disease: A Marker of Cognitive Decline or Cerebrovascular Status?

by

Vanessa Scarapicchia
B.Sc., McGill University, 2015

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Supervisory Committee

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Abstract

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Background: Alzheimer's disease (AD) is a neurodegenerative disorder for which there is presently no cure. As a result, there is a critical need to improve upon early detection methods through the identification of ideally non-invasive biomarkers, such as functional magnetic resonance imaging (fMRI). Recently, novel approaches to the analysis of resting-state fMRI data have been developed that focus on the moment-to-moment variability in the blood oxygen level dependent (BOLD) signal. However, the findings on BOLD signal variability have thus far been equivocal, with some findings showing decreased BOLD variability with age and cognitive decline, and others suggesting that increased BOLD fluctuations may serve as a physiological signal reflecting underlying cerebrovascular challenges. Given the paucity of research in this area, the objective of the current study was to investigate BOLD variability as a novel early biomarker of AD and its associated psychophysiological correlates. **Method:** Neuroimaging and cognitive data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) 2 database from 19 participants with AD (mean age = 72.7 ± 6.5) and 19 similarly-aged controls (mean age = 74.7 ± 6.9). All analysis steps were performed using tools within the Functional MRI of the Brain Software Library (FSL). For each participant, a map of BOLD signal variability (SD_{BOLD}) was computed as the standard deviation of the BOLD timeseries at each voxel within both grey and white matter regions. Firstly, group comparisons were performed to examine global differences in resting state SD_{BOLD} in AD

versus healthy controls. Correlations were then examined between participant SD_{BOLD} maps and (1) ADNI-derived composite scores of memory and executive function and (2) neuroimaging markers of cerebrovascular status (total white matter hyperintensity [WMH] burden, as computed from FLAIR scans). **Results:** Between-group comparisons revealed significant ($p < 0.05$) increases in SD_{BOLD} in patients with AD relative to healthy controls in right-lateralized grey and white matter frontal regions, including the superior frontal and precentral gyri, and widespread regions of the corona radiata. Due to the novelty of the current study, secondary analyses investigating the association between SD_{BOLD} and psychophysiological correlates were examined with a more liberal threshold ($p < 0.1$). Results revealed that lower memory scores were associated with greater SD_{BOLD} in the medial temporal lobe and adjacent structures in the healthy control group. Conversely, higher total WMH burden was associated with greater SD_{BOLD} in highly localized grey and white matter regions in the healthy control group. No association between SD_{BOLD} and cognitive or cerebrovascular measures was identified in the AD group. **Conclusion**: The current study provides proof of concept that a novel resting state fMRI analysis technique that is non-invasive, easily accessible, and clinically compatible, can differentiate patients with AD from healthy controls. To further explore the potential of SD_{BOLD} as a biomarker of AD, additional studies in larger, longitudinal samples are needed to better understand the changes in SD_{BOLD} that characterize earlier stages of disease progression and their underlying psychophysiological correlates.

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Dedication

To my mom, Antoinette Cantelmi

Chapter 1: Resting State BOLD Variability as a Novel Biomarker for Alzheimer's Disease

Alzheimer's Disease

Each year, over seven million new cases of dementia are diagnosed worldwide, with number of persons living with the disease expected to nearly double every two decades to an estimated 65.7 million by the year 2030 (Sosa-Ortiz, Acosta-Castillo, & Prince, 2012). Alzheimer's disease (AD), the most common cause of dementia, accounts for approximately 60 to 80% of all diagnosed cases (Alzheimer's Association, 2017). Clinically, AD is a progressive, neurocognitive disorder characterized by impairments in memory, as well as numerous other cognitive domains, including language, executive functions, and visuospatial skills (Alzheimer's Association, 2016). In its later stages, AD often leads to complete dependence on caregivers for even the most basic tasks of everyday life, thereby severely compromising an individual's quality of life and capacity for independent living (Jin, 2015; Mayeux & Stern, 2012). In light of a rapidly aging global demographic, AD has quickly become one of the most salient health care challenges of the current century (Scheltens et al., 2016; Winblad et al., 2016).

Stemming from extensive research efforts, conceptualizations of AD as a clinicopathological syndrome have evolved considerably over the years. In 1984, the initial set of criteria for the diagnosis of AD was published by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984). According to these criteria, AD may be categorized into two primary clinical classes: (1) *Probable AD* and

(2) *Possible AD*. A diagnosis of *Probable AD* is indicated by low scores on standard neuropsychological tests; a progressive worsening of memory; deficits in two or more cognitive domains; impaired activities of daily living; and the exclusion of other possible neurodegenerative diseases. In contrast, a clinical diagnosis of *Possible AD* is synonymous with a dementia syndrome characterized by a single, gradually progressive cognitive deficit; aberrations in disease onset, presentation, and clinical course; and the absence of neurologic, psychiatric, or other systemic disorders sufficient to cause the dementia. A third category of *Definite AD* has also been described by this group, but is mostly limited to postmortem diagnosis through an individual's prior fulfillment of the criteria for Probable AD, with accompanying histopathological evidence obtained at autopsy (Khan, 2016; McKhann et al., 1984). Despite subsequent evolutions in the criteria used in the clinical diagnosis of AD, among which include those described in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5; American Psychiatric Association, 2013), the NINCDS-ADRDA criteria remains the most widely used in both clinical trials and clinical research, with an established diagnostic specificity of 81% and sensitivity of 70% (Khan, 2016; Knopman et al., 2001).

In terms of aetiology, emerging research has identified a number of both preventable and non-preventable risk factors associated with the development of AD. Recent reviews highlight the importance of vascular risk factors and related conditions, including diabetes, hypertension, obesity, and dyslipidemia (de Bruijn & Ikram, 2014; Mayeux & Stern, 2012; O'Brien & Markus, 2014). However, years of epidemiological research continue to suggest that the strongest risk factor for AD is age: indeed, while it is estimated that one out of every nine individuals beyond the age of 65 will develop AD,

this figure rises markedly to an estimate of nearly one out of three by age 85 (Alzheimer's Association, 2016). As the proportion of the population above age 65 continues to grow, so will the number of individuals living with AD (Alzheimer's Association, 2016). In Canada alone, the number of persons aged 65 or older is expected to reach nearly one in four within the next 15 years (Statistics Canada, 2014). In light of our rapidly aging population, AD is now an urgent public health concern, with an estimated cost of $293 billion per year to Canadian health care anticipated by the year 2040 (Alzheimer Society of Canada, 2015).

In December of 2013, the Group of Eight (G8) Industrialized Nations released a statement declaring dementia a global priority and urging a unanimous increase in research efforts to arrive at a cure or disease-modifying intervention by 2025 (Scheltens et al., 2016). Unfortunately, available treatment options for AD continue to be limited. Currently approved pharmacological therapies for AD fall into two major categories: (1) cholinesterase inhibitors and (2) NMDA receptor antagonists. These medications primarily target neurotransmitter systems involved in learning and memory to help control symptoms by regulating the level and activity of these transmitters in the synapse (National Institute on Aging, 2016). While some evidence from prospective studies of up to 3 years suggests that certain medications (e.g. memantine) may be effective in slowing the rate of cognitive decline in AD (e.g. Rountree et al., 2009; for a review, see: Wilkinson, 2012), these medications have not been shown to be effective in slowing or reversing the disease itself (Alzheimer's Association, 2016). Given that it is not currently possible to reverse neuronal degeneration, there is an urgent need to improve upon the

early identification of AD, so that neuroprotective treatments may be implemented as soon as they become available.

Increasingly, however, evidence has mounted in favor of the idea that relying on behavioral symptoms alone for the premortem identification of AD may result in delays in diagnosis and, therefore, treatment implementation (Sperling et al., 2011). For this reason, both the National Institute on Aging and Alzheimer's Association working groups (NIA-AA; McKhann et al., 2011) and the International Working Group (IWG; Dubois et al., 2014) have since published revisions to the NINCDS-ADRDA criteria to include pathological measures in the characterization and diagnosis of AD (McKhann et al., 2011; Sosa-Ortiz et al., 2012). Other changes include the reconceptualization of AD as existing on a *continuum* (Sosa-Ortiz et al., 2012), which encompasses a spectrum ranging from "preclinical AD", in which the disease is present though not yet clinically apparent, to a mild cognitive impairment (MCI) stage, and, ultimately, AD dementia (Berti et al., 2016; Sperling et al., 2011). Importantly, this preclinical stage is believed to be the period during which disease-modifying treatments will be most effective and is defined primarily by the presence of *biomarkers* (Berti et al., 2016; Sperling et al., 2011).

Biomarkers in AD

A biomarker is an objectively measurable biological indicator that can be used to assess the presence of disease or future disease risk (Colburn et al., 2001; Alzheimer’s Association, 2016). Biomarkers may also be used to monitor progression of disease, as well as to prioritize the selection of candidates for future trials of disease-modifying treatments (Berti et al., 2016; Pupi, Mosconi, Nobili, & Sorbi, 2005). The identification of biomarkers relies upon an understanding of the underlying neuropathology of AD.

AD Neuropathology

AD is characterized by three primary pathological hallmarks: (1) amyloid plaques, (2) neurofibrillary tangles and (3) progressive degeneration of neurons, which presents as brain atrophy. According to the original amyloid cascade hypothesis, alterations in amyloid beta processing in the cell are believed to lead to neuronal dysfunction and, ultimately, cell death (Ballard et al., 2011). Further, changes in tau, the major component of neurofibrillary proteins, are also hypothesized to be triggered by neurotoxic levels of amyloid beta (Ballard et al., 2011). However, as noted by Scheltens et al. (2016), while years of research have continued to support the core theory that accumulations of abnormal amyloid beta and tau are causally related to neurodegeneration in AD, there is evidence to suggest that the basic linear causality initially proposed by the amyloid cascade hypothesis cannot account for the full spectrum of the disease (e.g. Herrup, 2015). This is particularly true of late-onset cases of AD (Castello & Soriano, 2013). Indeed, though the precise mechanisms underlying AD pathology and its causes are not yet fully understood, increasingly, AD is viewed as a complex, widespread, and *multicausal* neurodegenerative disorder (Herrup, 2015; Scheltens et al. 2016).

In terms of disease presentation, one core characteristic of AD pathology is its progressive course: akin to a prion disorder, some evidence suggests that toxic conformations of amyloid beta and tau induce corruptive changes in normal peptides that ultimately results in a continuous propagation of the disease (Jucker & Walker, 2013; Scheltens et al., 2016). Of note is that this neural degeneration typically follows a stereotypical pattern; in the early stages of the disease, neuron loss figures most

prominently in the medial temporal lobe and adjacent structures, including the entorhinal cortex, parahippocampal gyrus, amygdala, and hippocampus (Bottino et al., 2002; Thompson et al., 2003). Following its early manifestation in the medial temporal lobes, this degeneration spreads to the parietal areas and, ultimately, the frontal and sensory cortical areas in the later stages of the disease (Braak & Braak, 1991; Delacourte et al., 1999; Korolev, 2014). The reason for this neuroanatomical trajectory remains unknown.

Although a diagnosis of AD can only be confirmed at autopsy (through visualization of the hallmarks of the disease), many lines of evidence suggest that the aforementioned pathophysiological changes may manifest several years prior to the onset of the cognitive and behavioral symptoms characteristic of AD. One of the earliest demonstrations of this idea was rooted in the work of Braak and Braak (1991) who examined 83 brains obtained at autopsy and found that neurofibrillary tangles may be present in the entorhinal cortex of individuals as young as 30 years of age. Based on these findings, Braak and Braak (1991) developed what was termed a neuropathological staging system of AD, which illustrates the progression of pathology in AD from latent prodromal stages to clinically manifest AD (Braak & Braak, 1991; Smith & Bondi, 2008).

In subsequent years, the seminal findings by Braak and Braak (1991) have been widely supported by a number of longitudinal studies suggesting that the pathological changes that typify the neurodegenerative process in AD may also be present up to a decade prior to the onset of cognitive symptoms (e.g. Bernard et al., 2014; Morris, 2005; Tondelli et al., 2012). In a series of influential studies, a "preclinical stage" was initially posited as one in which neuritic plaques are sufficiently present to warrant a pathological

diagnosis of AD, in the absence of the classic clinical manifestations of dementia (Morris, 2005). Contemporary definitions of preclinical AD have since broadened to also include the presence of genetic risk factors and abnormal cerebrospinal fluid (CSF) biomarkers, such as elevated T-tau and low amyloid beta$_{(1\text{-}42)}$ (Khan et al., 2016). In accordance with these findings, some groups have begun to distinguish between the pathophysiological processes underlying AD and the AD *syndrome*, characterized primarily by its clinical presentation (Dubois et al., 2010; Sperling et al., 2011). As noted by Khan (2016), emerging from this picture is therefore a hypothetical model of AD, in which a distinct pathological AD trajectory deviates from normal aging at a critical inflection point, with the clinical trajectory deviating only years later and accompanied by irremediable neurodegeneration (Figure 1).

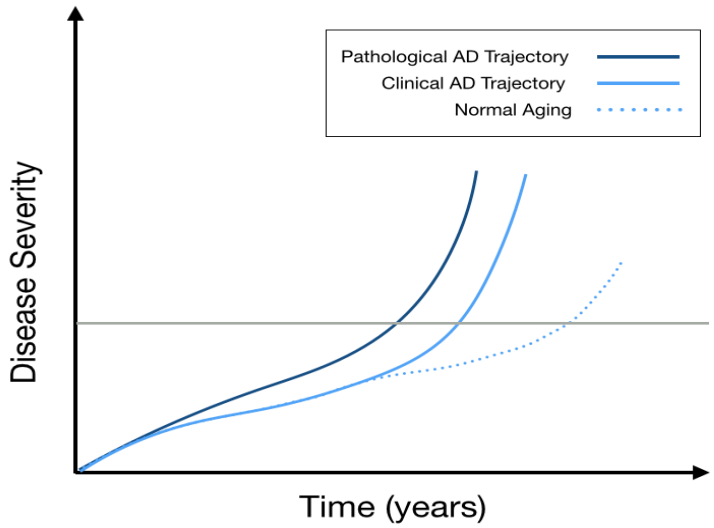

Figure 1. A hypothetical model of Alzheimer's disease proposed by Khan (2016). The model shows the independent trajectories of pathological AD (dark blue), clinical AD (light blue), and normal aging (dashed line) and their association with clinical impairment (illustrated as increasing disease severity). For individuals who ultimately develop AD, the pathological trajectory is posited to begin years prior to the clinically manifest AD syndrome. Figure adapted from Khan (2016).

Congruent with this modern conceptualization, and in light of the newly amended guidelines for the identification of AD, the NIA-AA has advocated for additional research on biomarker tests that, when considered along with core clinical criteria, may improve the specificity of an early AD diagnosis (Alzheimer's Association 2016; McKhann et al., 2011). However, to date, no single test has yet demonstrated the reliability suited for this purpose in routine clinical practice (Khan, 2016; Sperling et al., 2011). There remains a strong need for additional research to develop new methods that identify changes in the brain as they occur *in vivo*, prior to the onset of significant neuropathological changes and associated clinical symptoms.

Neuroimaging Biomarkers in AD

Currently established AD biomarkers are typically divided into two major classifications: markers of amyloid beta deposition and makers of neurodegeneration, the latter of which is typically characterized by the neuronal loss itself and the accompanying impairments in cellular functioning (Berti et al., 2016; Jack et al., 2013). An important issue surrounding biomarker identification, particularly in clinical populations, is that the investigative methods can be invasive. For instance, measuring amyloid beta or tau deposition often requires blood plasma or CSF extraction (e.g. Mattsson et al., 2009; van Oijen, Hofman, Soares, Koudstaal, & Breteler, 2006). Even an alternative method, such as ligand based studies using positron emission tomography, still require exposure to exogenous radioactive materials (e.g. Shin et al., 2010). Ideally, a biomarker suited to clinical populations such as AD would be (1) easily accessible, (2) non-invasive, and (3) able to detect changes at their earliest time points. In this regard, magnetic resonance imaging (MRI) has received increased attention as a promising biomarker tool, due to its

ability to non-invasively characterize changes in brain structure and function *in vivo* without the use of tracers or contrast agents (Ricker & Arenth, 2008).

Structural MRI

The physical principals of MRI are based on modern applications of nuclear magnetic resonance (NMR) theory (Brown, Cheng, Haacke, Thompson, & Venkatesan, 2014). Briefly, the 'nucleus' in MRI refers to the protons of hydrogen that are inherent in all human tissue. On the basis of NMR theory, certain atomic nuclei, such as hydrogen, possess an intrinsic magnetic moment, or *net spin.* This proton motion can be thought of as a loop of electric current circumventing the axis upon which the atom is spinning, and ultimately generating a small magnetic dipole moment (μ; Brown et al., 2014). When exposed to an external magnetic field (B_0), as occurs in the scanner environment, the magnetic moment vector of each hydrogen nucleus will tend to precess in a direction that is either parallel or antiparallel to the main magnetic field. Due an automatic recession to the more favorable (lower) energy state, more nuclei will tend to align parallel, rather than anti-parallel, to the direction of the magnetic field, thereby resulting in a stable longitudinal net magnetization vector (M_z; Weishaupt, Köchli, & Marincek, 2008). The angular frequency of precession for each nucleus is known as the *Larmor frequency* (ω_0) and is related to the strength of the magnetic field according to:

$$\omega_0 = \gamma B_0$$

B_0 is the strength of the magnetic field in tesla (T) and γ is a constant known as the gyromagnetic ratio, which has a value of approximately 42.6 MGz/T in water

In order to derive an image, energy is then introduced into this relatively stable system in the form of a radiofrequency (RF) pulse travelling at the same frequency as the Larmor frequency; this is referred to as the *resonance condition* (Weishaupt et al., 2008). Immediately after this excitation, the nuclei enter a state of phase coherence, in which the protons begin to precess in phase together, ultimately causing *excitation of the spin system*; some hydrogen protons that were in the low-energy state subsequently flip to the high-energy state, thereby reducing the net longitudinal magnetization in the z-plane and tipping the bulk magnetization vector to the xy-, or transverse, plane (M_{xy}; Weishaupt et al., 2008). The angle at which this bulk magnetization is tipped will vary depending on imaging parameters; Figure 2 illustrates this effect for a flip angle of 90^0.

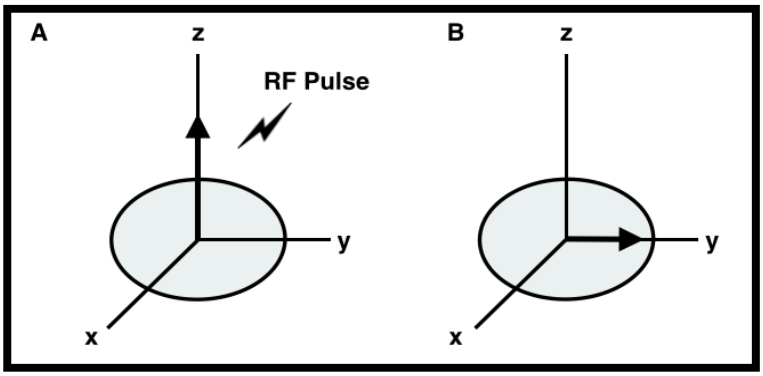

Figure 2**.** Application of an RF pulse causing the net magnetization vector (M_z) to rotate 90^0 from the longitudinal plane (Panel A) to the transverse plane (M_{xy}; Panel B). Adapted from Weishaupt et al. (2008).

Removal of the RF pulse subsequently results in a decay of this transverse magnetization and a restoration of magnetization in the longitudinal plane (M_z; parallel to B_0; Weishaupt et al., 2008), also known as T1 recovery or "spin-lattice" relaxation. Simultaneously, phase coherence among the nuclei is gradually lost, such that protons that were precessing synchronously now begin to fall out of phase with one another. This

difference in processional paths, or *spins*, results in a cancelling-out of the individual magnetization vectors and, thus, a decay of the transverse magnetization vector, also known as T2 or "spin-spin" relaxation; the shift in transverse magnetization caused by these two simultaneous yet independent processes ultimately gives rise to a voltage signal that is detected by the MRI's receiving coil (Weishaupt et al., 2008). In order to differentiate signals arising from different voxels, additional magnetic fields are created by a series of gradient coils located within the scanner. When superimposed on the main magnetic field, these *electromagnetic gradients* produce measurable distortions along the x-, y-, and z- axes. This allows for spatial encoding of the signal and, ultimately, a reconstruction of the MR image through Fourier transform (Weishaupt et al., 2008).

Based on these principles, different tissue types can be therefore differentiated by three intrinsic biological properties: proton density, T1-relaxation time, and T2-relaxation time (Weishaupt et al., 2008). Image contrasts will differ depending on which of these parameters is *weighted* in the MR sequence. The T1 relaxation time refers to the rate of recovery in the *longitudinal* plane: in T1-weighted images, tissues with a long T1 appear dark (e.g. CSF), whereas tissues with a short T1 appear bright (e.g. white matter; WM; Weishaupt et al., 2008). Conversely, the T2 relaxation time refers to the rate of decay in the *transverse* plane: in T2-weighted images, tissues with a long T2 appear bright (e.g. CSF, lesions), whereas tissues with a short T2 appear dark (e.g. WM; Weishaupt et al., 2008; Figure 3). The distinctive return to equilibrium of these nuclei in different tissues thus generates an MR contrast that is measured within small, three-dimensional imaging units called voxels. Collectively, thousands of voxels together comprise the high-resolution structural images that are characteristic of MRI (van Geuns et al., 1999).

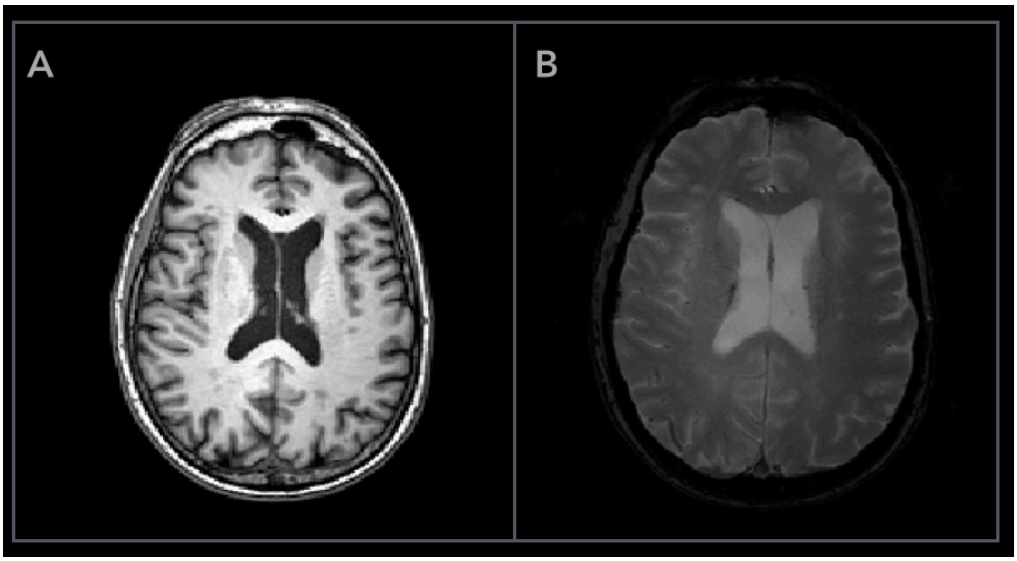

Figure 3. Axial scans illustrating the characteristics of two different MR-weighted images: T1 (Panel A) and T2 (Panel B).

Structural MRI in AD

In both research and clinical domains, structural brain MRI, particularly MRI-based measures of cortical atrophy, has become an important component in the diagnosis and assessment of disease progression in individuals with suspected AD (Frisoni, Fox, Jack, Scheltens, & Thompson, 2010). A review on the clinical utility of structural MRI in AD states that tissue loss in the hippocampus and entorhinal cortex is both a reliable measure of an individual's progression from MCI to AD, as well as a valid tool for differentiating brain changes in AD from other neurodegenerative disorders (Frisoni et al., 2010). Such structural changes may also reliably differentiate AD from the neurophysiological changes that typify the aging process: a systematic meta-analysis by Barnes et al. (2009) revealed annual hippocampal atrophy rates of 4.7% in patients with AD, relative to a 1.4% decline in age-matched healthy controls. Indeed, a more recent review of structural and functional changes in AD states that loss of volume in structures of the medial temporal lobe is one of the most characteristic findings in patients with

clinically manifest AD (Mueller, Keeser, Reiser, Teipel, & Meindl, 2012). Despite its remarkable specificity and reliability, in light of the previous discussion, the utility of structural MRI as a preclinical or early biomarker of AD may be limited by its inability to identify changes before significant neurodegeneration has already taken place. However, recent research in the field is beginning to elaborate on both structural and functional changes that occur *before* the onset of cognitive symptoms in AD (e.g. Burggren & Brown, 2014), with some suggesting that changes in brain function may actually precede changes in brain structure (Damoiseaux, 2012).

Functional MRI

Blood oxygen level dependent (BOLD) functional MRI (fMRI) is an MRI-based acquisition method that allows for the visualization of brain activity. The utility of fMRI as a functional neuroimaging tool is inherently linked to classic theory of neurovascular coupling initially proposed by Roy & Sherrington (1980): when a given brain region is involved in an activity or task, the neurons in that area become active and the need for oxygenated blood increases. Importantly, there is a discrepancy between the cerebral blood flow and volume and the metabolic rate of oxygen consymption, which results in a surplus of oxygenated hemoglobin in veins and capillaries (Kim & Bandettini, 2012).

To understand the mechanism by which MR signal intensity increases as a result of the surplus of oxygenated blood, it is important to further consider the properties of T2 relaxation. Specifically, T2 relaxation refers to the decay of transverse magnetization caused by a loss of coherence of the individual nuclei "spins", otherwise known as dephasing (Weishaupt et al., 2008). An important distinction is that this loss of coherence can occur in two separate ways: the first is the previously mentioned "spin-spin"

interaction, in which energy transfer between nuclei results in local changes in the magnetic field and occurs with the time constant T2 (Chavhan, Babyn, Thomas, Shroff, & Haacke, 2009). However, there is also a second, *reversible* dephasing effect that is due to time-independent inhomogeneities of the local magnetic field (Buxton, 2009; Chavhan et al., 2009; Weishaupt et al., 2008). This additional effect is denoted as T2*.

In BOLD fMRI, the local field inhomogeneities that are of interest are the result of differences in the magnetic susceptibility of oxygenated versus deoxygenated hemoglobin in the brain (Chavhan et al., 2009; Weishaupt et al., 2008). Deoxyhemoglobin is *paramagnetic*; as a result, it creates magnetic field gradients in the region surrounding the vessels, yielding the local field inhomogeneities described previously. This shortens the T2* which, in turn, reduces the MR signal (Buxton et al., 2009). In contrast, when oxygen binds to hemoglobin, *diamagnetic* oxyhemoglobin is produced, resulting in a shift in the magnetic susceptibility that varies according to the levels of blood oxygenation (Buxton et al., 2009; Weisskoff & Kiihne, 1992). Due to its magnetic properties, the excess of oxygenated blood during brain activation therefore acts as an endogenous contrast agent that generates a measurable marker of "activity" in T2*-weighted images, commonly referred to as the BOLD signal (Kim & Bandettini, 2012). Typically, fluctuations in the BOLD signal are measured through the acquisition of a timeseries of whole brain volumes collected every two to three seconds. This process results in a signal change over time that may be measured and analyzed to reveal patterns of brain activity. As with structural MRI, signal intensity is measured at each voxel within the brain. As a result, each individual voxel possesses a unique timeseries with an associated BOLD signal variance and mean (Figure 4).

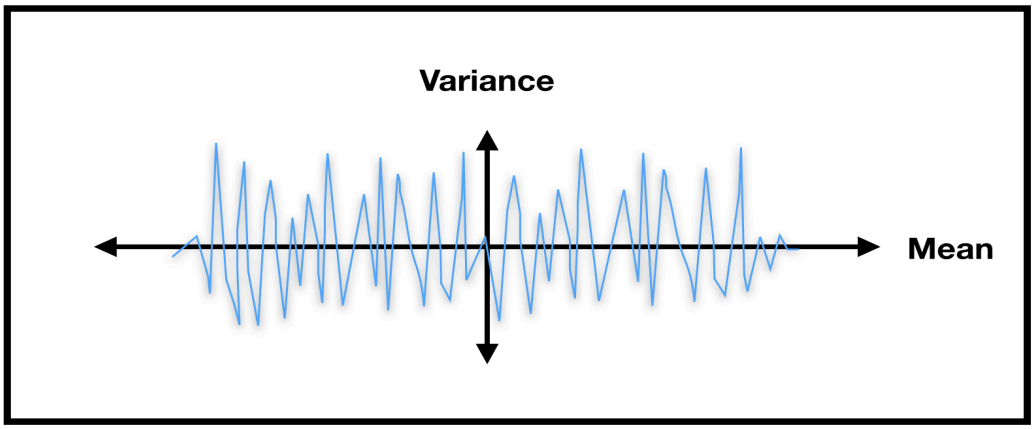

Figure 4. An fMRI timeseries showing signal change over time. Adapted from Garrett et al. (2010).

In traditional task-based fMRI studies, an individual is asked to respond to the presentation of stimuli while in the scanner in order to elicit changes in neural activation and measurable increases in oxygenated blood/BOLD signal in the regions that are involved in the task (Ricker & Arenth, 2008). There are, however, some limitations to the use of task-based fMRI studies in clinical populations, such as AD. As pointed out in a review by Mueller et al. (2012), task-based fMRI studies typically require high adherence to specific task paradigms that may not be appropriate for individuals in advanced stages of dementia. As such, enrolment in these studies is often limited to participants with mild-to-moderate stages of AD (Mueller et al., 2012), which can restrict the scope of research on fMRI biomarker development. A novel and increasingly popular fMRI approach known as resting-state fMRI (rsfMRI) may therefore serve as a promising alternative to traditional task-based studies in clinical populations, as it eliminates the cognitive burden of task performance and reduces the level of compliance required of the patient (Fox & Grecius, 2010; Mueller et al., 2012).

Resting State fMRI in AD

Unlike traditional task-based approaches, rsfMRI focuses on the examination of spontaneous network activity as it occurs in the brain at rest. In the context of rsfMRI studies, the term *at rest* is used to define the absence of an overt task or any external stimulus; typically, participants are instructed to lie in the scanner with their eyes closed or open or to fixate on a particular point on the screen (Fox & Greicius, 2010). Similar to task-based fMRI studies, resting fluctuations in the BOLD signal will occur that may be examined to reveal patterns of brain activity in different groups (Fox & Greicius, 2010). As articulated in a review by Fox and Grecius (2010), rsfMRI offers a number of unique advantages, including its aforementioned ability to allow for a broader sampling of clinical populations due to the minimal demands placed on the patient. This would allow for more translational research in disease populations, which may in turn improve the clinical applicability of fMRI. Another noted advantage of rsfMRI is its ability to eliminate task-related confounds, such as practice effects caused by repeated task administration; this may be an especially relevant advantage in longitudinal studies of disease progression (Fox & Greicius, 2010).

Resting-State Functional Connectivity Analysis

While there are a number of approaches to analyzing the spontaneous fluctuations that occur during the resting state, one of the most common approaches is referred to as functional connectivity analysis: this method consists of identifying temporally correlated low-frequency fluctuations in remote areas of the brain (Fox & Greicius, 2010; Vemuri, Jones, & Jack, 2012). The resulting large-scale networks of activity derived from this analysis are referred to as resting-state or intrinsic connectivity networks (Vemuri et al.,

2012). One of the most well studied networks is known as the default mode network (DMN): this network is has been shown to remain most active when the individual is in a state of wakeful rest or introspection and decrease its activity during tasks that demand attention to external stimuli (Fox & Greicius, 2010; Fransson, 2005, 2006; Greicius, Krasnow, Reiss, & Menon, 2003). Anatomically, the DMN in humans is divided into three primary subdivisions: (1) the ventral medial prefrontal cortex, (2) the dorsal medial prefrontal cortex, and (3) the posterior cingulate cortex and adjacent precuneus and lateral parietal cortices (Raichle, 2015). Each of these subdivisions is thought to be associated with a distinct behavioral function of the DMN, among which include emotional processing, self-referential mental activity, and recollection of past experiences (Raichle, 2015).

Resting-State Functional Connectivity in AD

In recent years, rsfMRI has become an increasingly popular method in AD biomarker research, with a number of findings pointing to consistent differences in DMN activation in AD versus healthy controls (Vemuri et al., 2012). A recent review by Hafkemeijer, van der Grond, & Rombouts (2012) on the DMN in aging and dementia revealed that the majority of studies show decreased activity in the DMN in AD versus normal aging, primarily in regions of the medial prefrontal cortex, posterior cingulate cortex, precuneus, anterior cingulate cortex, and the hippocampus (e.g. Greicius, Srivastava, Reiss, & Menon, 2004; Wang et al., 2007; Wang et al., 2006; Zhang et al., 2009; Zhou et al., 2010). However, some of these and other studies have also found regions of *increased* functional connectivity in the DMN of AD versus cognitively normal subjects, which many have attributed to compensatory processes (e.g.

Damoiseaux, Pratter, Miller, & Greicius, 2012; He et al., 2007; Wang et al., 2007; Zhang et al., 2009).

While most of the aforementioned studies were conducted in individuals with clinically manifest AD, further allusion to the potential of resting state changes as important early biomarkers of disease can also be found in studies examining individuals with mild cognitive impairment (MCI), as well as cognitively normal adults with amyloid deposition. Most recently, Lee et al. (2016) examined DMN connectivity in individuals at different stages of MCI recruited from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Their results revealed a progressive deterioration in DMN connectivity from early to late MCI, that which was most pronounced for early MCI individuals positive for amyloid deposition. Notably, other studies have also found evidence for both decreases and increases in functional connectivity within the DMN of clinically normal older adults with amyloid burden (e.g. Drzezga et al., 2011; Hedden et al., 2009; Mormino et al., 2011; Sheline et al., 2010).

Resting-State BOLD Variability Analysis

Until recently, the vast majority of resting state and task-based fMRI studies based their findings on patterns of *mean* brain activity. However, with new advances in fMRI data analysis techniques, some researchers are beginning to move beyond this traditional approach. As pioneers of this new movement, Garrett, Kovacevic, McIntosh, & Grady (2010) point out that mean-based fMRI methods are largely a consequence of longstanding statistical conventions that suggest that the mean is the most representative and, therefore, the most informative value in a given distribution. Based on this principle, many researchers perceive the mean value in a given timeseries as the true BOLD

"signal" among a distribution of "noise" (Garrett et al., 2010). As a result, any variability in this BOLD signal across a given fMRI timeseries is often discounted as noise, reflecting issues with the participant (e.g. excessive head motion), the equipment used to collect the data, or other physiological confounds such as pulse and respiration (Garrett et al., 2010), all of which is not of interest. However, as Garrett et al. (2010) note, there is substantial evidence to suggest that variability is a characteristic feature of the brain's natural state, with varying degrees of noise present at both cellular and behavioral levels of the nervous system that may actually be a critical component of the "signal" being transmitted across networks (Faisal, Selen, & Wolpert, 2008; Stein, Gossen, & Jones, 2005). Indeed, electroencephalography (EEG) studies also suggest that a greater complexity of physiological signals in the brain may even be related to more efficient neural networks that are better able to explore their "functional repertoire", as well as a greater flexibility and adaptability of these circuits (Garrett, Samanez-Larkin et al., 2013; McIntosh, Kovacevic, & Itier, 2008)

Given the lack of studies on signal variability in fMRI, Garret et al. (2010) questioned whether researchers might be capable of acquiring new and important information about the functional integrity of neural networks by examining, rather than discarding, the degree of signal variability of a BOLD timeseries. Since then, a handful of studies by this group and others have examined resting state BOLD variability with promising results (e.g. Burzynska, Wong, Voss, Cooke, Gothe et al., 2015; Burzynska, Wong, Voss, Cooke, McAuley et al., 2015; Garrett et al., 2010; Jahanian et al., 2014; Kielar et al., 2016; Makedonov, Black, & MacIntosh, 2013; Makedonov, Chen, Masellis, & MacIntosh, 2016; Nomi, Bolt, Ezie, Uddin, & Heller, 2017; Zoller et al., 2017).

However, the question remains: does this novel rsfMRI analysis technique have the potential to serve as a clinically compatible, non-invasive early biomarker of age-related neurodegenerative disorders and their physiological antecedents?

Resting-State BOLD Variability Analysis: A Potential Biomarker of AD?

BOLD Variability and Aging

Some of the earliest discussions on within-person variability of physiological signals and aging in the literature were focused on the concept of stochastic resonance in neurobiological systems. Stochastic resonance is a term used to refer to a phenomenon by which optimally increased levels of noise, such as random neural noise, results in an increase in the quality of signal transmission or detection (McDonnell & Abbott, 2009). Some have even suggested that the cognitive decline associated with aging may reflect reductions in neurotransmission (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006).

In light of these ideas, Garrett et al. (2010) examined whether the degree of variability in the BOLD signal could have predictive meaning in normal human aging, above that provided by mean-based spatial patterns. Specifically, they collected rsfMRI data during fixation blocks in a sample of young adults (mean age=25.79) and cognitively normal older adults (mean age=66.36) and examined patterns of both BOLD variability and mean activation. To examine signal variability in each participant and voxel, the standard deviation of each timeseries was calculated (SD_{BOLD}). Once they identified patterns of brain variability and activity that successfully differentiated younger and older adults, the authors performed a regression analysis to determine which measure could predict participant chronological age with greater accuracy (Grady & Garrett, 2014). The results of this study revealed three main findings. First, the SD_{BOLD} pattern

revealed activity in distinct subsets of brain regions that were not detected in the mean-based analysis, suggesting that SD_{BOLD} may reveal unique measures of brain activity not captured by other methods. Second, SD_{BOLD} multivariate patterns of brain activity were robustly related to chronological age, with a predictive ability that was over five times greater than that provided by the mean-based spatial patterns. Finally, they also found that, overall, patterns of SD_{BOLD} were generally *more* variable in younger versus older adults, which the authors suggest may be related to reductions in network complexity or synaptic and WM integrity that are typically seen in aging brains (Garrett et al., 2010). However, a bidirectional pattern of variability across regions was also observed: indeed, some areas actually exhibited *greater* signal variability with age, such as the superior frontal gyrus, inferior temporal gyrus, and the cerebellum. Based on the aforementioned stochastic resonance research, as well as the idea that young adult brains may represent an "optimal" neural system, the authors postulated that perhaps (1) the areas of increased variability could reflect a *compensatory process* that serves to counteract age-related cortical changes or (2) that such increased variability could simply reflect a dysfunctional neural process, whereby any directional deviation from "optimal" noise levels results in a less efficient system (Garrett et al., 2010; Garrett, Samanez-Larkin et al., 2013). In addition to a call for future work in this area to address these unanswered questions, the authors conclude that "moving beyond the mean" may allow for greater insight into age-related neural changes (Grady & Garrett, 2014).

In reflection of this, a very recent study by Nomi et al. (2017) sought to expand on the seminal work by Garrett et al. (2010) by examining changes in rsfMRI BOLD variability as they occur *across the lifespan,* ranging from early childhood to late

adulthood. Specifically, this group examined spontaneous BOLD signal variability in healthy participants ranging from ages 6 to 85, in order to identify regional changes characteristic of normative brain maturation. However, an important distinction between this study and Garrett et al. (2010)'s study is that, rather than directly examining the standard deviation (SD_{BOLD}) of the timeseries, the researchers utilized a within-subject measure known as the mean square successive difference (MSSD). The MSSD is essentially an estimate of voxelwise *variance*, however, rather than comparing each value to a single, fixed mean (as is done in traditional measures of variance when calculating the sum of squares), each time point is compared to the one preceding it (Garrett, Samanez-Larkin et al., 2013). To ensure translatability with prior work in this area, the authors computed average correlations between MSSD and SD for grey matter (GM) voxels and found strong correlations ($r \approx 0.7$). In congruence with the bidirectional findings by Garrett et al. (2010), the results of this study revealed that BOLD variability *decreased* across the lifespan in most regions of the brain, including subcortical, visual, and sensorimotor regions, as well as critical components of the default mode and central-executive networks. Notable exceptions to this global trend included the dorsal anterior insula and ventral temporal cortex, wherein BOLD signal variability was found to *increase* linearly with age. Remarking that the anterior insula constitutes a critical "hub" of the salience network that been demonstrated to participate in numerous cognitive processes (e.g. Menon & Uddin, 2010), the authors postulate that large differences in variability between functional network nodes and other brain systems may, in part, contribute to the sub-optimal functioning characteristic of early childhood and very late adulthood (Nomi et al., 2017).

BOLD Variability and Cognition

Though both the Nomi et al. (2017) and Garrett et al. (2010) studies were conducted in healthy samples, given the linear dependency between neurodegenerative disorders and increasing age, these findings strongly suggest that BOLD variability may also offer new insights into age-related cognitive decline. Notably, Garrett and colleagues (Garrett et al., 2011; Garrett, Kovacevic et al., 2013; Garrett, McIntosh, & Grady, 2014) went on to examine how patterns of SD_{BOLD} may be related to cognitive functioning in task-based fMRI studies. The results of these studies suggest that greater BOLD variability is associated with better performance on tasks of attention, perception, and perceptual matching (Garrett et al., 2011; Garrett et al., 2014) and that younger adults modulate BOLD variability more than older adults from fixation to task, that which is also associated with better task performance (Garrett, Kovacevic et al., 2013).

Given these findings, as well as previous diffusion tensor imaging (DTI) studies linking cognitive performance to WM integrity in aging (Madden et al., 2012), another study of resting-state BOLD variability by Burzynska, Wong, Voss, Cooke, McAuley et al. (2015) sought to examine: (1) whether changes in BOLD variability are associated with cognitive abilities susceptible to age-related decline, such as reasoning, processing speed, and episodic memory and (2) whether these effects may be related to DTI measures of WM structural integrity.

The authors collected resting-state fMRI and DTI data from a group of healthy older participants 60 to 80 years of age. Task-related performance was assessed using previously collected laboratory measures of fluid intelligence, perceptual speed, episodic memory, and vocabulary. Similar to the Garret et al. (2010) study, measures of SD_{BOLD}

were obtained by calculating the standard deviation across the timeseries for each voxel. For the WM analysis, fractional anisotropy (FA) maps were computed, with greater FA reflecting greater WM integrity. Their results revealed that higher fluid intelligence and memory scores were linked to greater SD_{BOLD} in multiple regions including: the precuneus, the insula, temporal, parietal, and prefrontal regions, as well as the cingulate cortex. The authors postulated that the specific cognitive findings may be related to the greater cognitive flexibility required in tasks of fluid intelligence and memory. Further, it was also found that participants with greater SD_{BOLD} and cognitive scores had greater global WM integrity, above and beyond the effects of age (Burzynska, Wong, Voss, Cooke, McAuley et al., 2015). Based on these findings, the researchers argued that greater structural integrity of WM tracts allows for efficient communication in the brain, which in turn supports greater cognitive flexibility.

In a subsequent follow-up study, Burzynska, Wong, Voss, Cooke, Gothe et al., (2015) found that SD_{BOLD}, and its association with WM integrity, may also be preferentially related to factors known to support healthy cognitive aging, such as physical activity. Specifically, using the same methods as above, the association between resting state BOLD variability, global WM structural integrity, and both self-report and objective accelerometry measures of physical activity was examined in a sample of healthy older adults. The results of this study revealed that participants who engaged in more low-to-moderate physical activity tended to exhibit greater variability in spontaneous BOLD fluctuations in multiple GM regions, including the precuneus, hippocampus, and medial and lateral prefrontal cortices. Moreover, in accordance with the multivariate patterns observed their previous study, it was also found that participants

with greater SD_{BOLD} and higher physical activity scores had greater global WM integrity, that which the authors suggest may be due to the pro-myelination effects of physical activity on WM structural integrity (Burzynska, Wong, Voss, Cooke, Gothe et al., 2015). Relating their previous findings to the literature on aging as a whole, the authors further suggest that age-related changes in myelination could impair WM integrity, thereby compromising the efficiency and reliability of signal transmission in the brain, of which resting-state BOLD variability is a marker (Burzynska, Wong, Voss, Cooke, McAuley et al., 2015).

BOLD Variability and Cerebrovascular Status

As evidenced by the studies reviewed thus far, and reflected in Garrett et al. (2010)'s original conceptualization of SD_{BOLD}, variability in the rsfMRI BOLD signal has largely been interpreted as an index of cognitive function. More recently, however, an alternative hypothesis has emerged that centers on BOLD fluctuations as a vascular contrast. In particular, Makedonov et al. (2013, 2016) hypothesized that increased arterial stiffness caused by cerebrovascular dysfunction may result in greater pulsatility down vascular networks and small vessels in groups with white matter hyperintensities (WMH) on neuroimaging (an indicator of cerebral small vessel disease; CSVD). This may, in turn, be captured by *increased* temporal variance in WM in rsfMRI. In other words, BOLD variability in WM is hypothesized to serve as a non-neuronal, physiologically based signal related to an individual's cerebrovascular status (Makedonov et al., 2013, 2016). In their initial study, Makedonov et al. (2013) examined resting state BOLD data in a group of older adults with extensive WMH from confirmed CSVD versus healthy young and older adult controls. To quantify temporal WM BOLD variance, they used a

physiological noise metric calculated on a voxel-wise basis: specifically, they subtracted the variance in the signal attributed to thermal noise from the total variance at each voxel, resulting in a measure of BOLD variance due to physiological processes. Their results revealed that, while physiological noise was reduced in proximal regions of WMH relative to healthy WM, overall, physiological noise in normal WM regions of older adults with CSVD was *higher* compared to healthy elderly controls and positively correlated with WMH volume, which supported their initial hypothesis (Makedonov et al., 2013).

Given the close association between CSVD, cognitive decline, and neurodegenerative disorders (Cai et al., 2015), Makedonov et al. (2016) went on to examine whether measures of WM BOLD variance, which they refer to as physiological fluctuations in white matter (PFWM), may be used as an index of AD and neurodegenerative processes more generally. Specifically, they investigated whether (1) PFWM may be used to differentiate healthy aging, MCI, and AD and (2) whether PFWM may be associated with cognitive and physiological markers of AD pathology. To explore these ideas, composite scores of memory and executive function, as well as physiological measures of glucose metabolism, ventricular volume, and hippocampal volume were derived from the ADNI database. Indices of resting-state physiological fluctuations were isolated using a method similar to that described in Makedonov et al. (2013), however, in this study the mean physiological noise across all WM voxels was used to derive a PFWM summary score (Makedonov et al., 2016).

The results of this study revealed three main findings. First, in line with the hypotheses and the findings from Makedonov et al. (2013), PFWM were significantly

increased in AD compared with patients in the MCI and control groups. Second, PFWM were inversely correlated with the memory from the cognitive composite score data, suggesting that increased PFWM is associated with poorer memory performance across groups. Finally, in terms of physiological markers, it was found that PFWM were inversely correlated with regional GM glucose metabolism. Based on these findings, the authors postulate that between-cohort differences in PFWM may reflect underlying differences in cerebrovascular health that are not captured by existing biomarker data. However, to this end, a central limitation of this second study is that it did not directly examine participant WMH burden or other markers of vascular health, which leaves room for further consideration of this hypothesis. Nonetheless, these findings do provide an alternative perspective on previous studies that have implicated WM integrity as a conduit for changes in BOLD variability (e.g. Burzynska, Wong, Voss, Cooke, Gothe et al., 2015; Burzynska, Wong, Voss, Cooke, McAuley et al., 2015).

Rationale for Further Investigation of Resting-State BOLD Variability in AD

Alzheimer's disease is a neurodegenerative disorder for which there is presently no cure; this has rendered critical the need to develop ideally non-invasive biomarkers that may aid in the early implementation of disease-delaying treatments. In recent years, resting state BOLD variability has emerged as a novel analysis technique that may provide new insights into the functional pathology of neurodegenerative disorders. However, the findings on BOLD variability have thus far been equivocal, with some findings showing decreased BOLD variability with age and cognitive decline, and others suggesting that BOLD fluctuations may increase with the progression of AD and associated vascular pathologies. Importantly, despite the emergence of these two

seemingly divergent hypotheses in the literature, no existing studies to date have concurrently examined GM and WM SD_{BOLD}, cognition, and neurovascular burden in a single sample of AD patients.

Given the paucity of research in this area, further work is needed to more precisely parse out the relationship between GM and WM BOLD variance, and its association with both cognition and cerebrovascular status in a clinical population. Such investigations hold the promise of exploiting the potential for resting state BOLD variability, as a non-invasive, easily accessible, and clinically compatible tool for the early identification of AD and its neurophysiological correlates.

Chapter 2: BOLD Variability in Alzheimer's Disease: A Marker of Cognitive Decline or Cerebrovascular Status?

Introduction

Alzheimer's disease (AD) is a progressive, neurocognitive disorder characterized by impairments in memory, as well as other cognitive domains, including language, visuospatial skills, and executive functions (Alzheimer's Association, 2016). Although a number of factors have been associated with the development of AD, epidemiological evidence suggests that the strongest risk factor for AD is age. Nearly one out of every nine individuals beyond the age of 65 is expected to develop the disease; by age 85, this figure rises markedly to an estimate of nearly one out of three (Alzheimer's Association, 2016). In light of globally increasing life expectancies and a rapidly aging population, AD has become an urgent public health concern (Winblad et al., 2016).

At present, there are no curative treatments for AD (Scheltens et al., 2016). Available treatment options are limited and focus primarily on delaying the progression of symptoms (Alzheimer's Association, 2016; Wilkinson, 2012). In order to effectively delay disease progression with neuroprotective treatments, it is imperative to identify early biomarkers for AD. The ideal technique for biomarker identification would be non-invasive, easily repeatable, and widely available, as is magnetic resonance imaging (MRI). Although most MRI based biomarker research on AD to date has focused on structural changes in grey matter (GM; Cash, Rohrer, Ryan, Ourselin, & Fox, 2014), it is possible that changes in brain function may precede changes in brain structure. Blood oxygen level dependent (BOLD) functional MRI (fMRI) is a MRI based technique that

allows for non-invasive examination of brain function by measuring fluctuations in signal intensity over time that are a consequence of oxygenated blood supplying active neurons. Recently, resting-state fMRI (rsfMRI) has emerged as a promising clinical imaging method, as it eliminates the cognitive burden of task performance that is characteristic of task-based fMRI and thus reduces the level of compliance required of the patient (Fox & Grecius, 2010; Mueller et al., 2012).

Traditionally, the majority of fMRI investigations have based their findings on patterns of *mean* brain activity. This is based on the longstanding premise that the mean value across an fMRI timeseries represents the average, and therefore most representative, "signal" among a distribution of unwanted "noise" (Garrett et al., 2010). This stands in contrast to theories postulating that the brain is an intrinsically variable system, and that such variability may provide meaningful insights into its functional architecture (Deco, Jirsa, & McIntosh, 2011; Faisal et al., 2008; Stein et al., 2005). Stemming from these emerging conceptualizations, novel approaches to analyzing rsfMRI data have been developed that focus on the moment-to-moment variability in the BOLD signal (Garrett, Samanez-Larkin et al., 2013).

Recently, an increasing number of studies have focused on BOLD signal variability in normative aging. For instance, an early pioneering study by Garrett and colleagues (2010) examined the BOLD signal standard deviation (SD_{BOLD}) in a sample of healthy adults ranging in age from 20 to 85. The results revealed that, overall, patterns of resting-state SD_{BOLD} are generally more variable in younger versus older adults, which have been suggested to reflect reductions in synaptic complexity and integrity in older age (Garrett et al., 2010). In support of this framework, subsequent task-based studies by

the same group have found that greater BOLD signal variability is associated with younger age and superior cognitive task performance (Garrett et al., 2011; Garrett, Kovacevic et al., 2013; Grady & Garrett, 2014; Garrett et al., 2014). Moreover, related studies have found that a greater resting-state SD_{BOLD} may be associated with increased microstructural integrity of white matter (WM) pathways in healthy older adults (Burzynska, Wong, Voss, Cooke, Gothe et al., 2015; Burzynska, Wong, Voss, Cooke, McAuley et al., 2015). Of note, however, is that many of these and other studies have also found bidirectional effects. Specifically, regional *increases* in fMRI BOLD variance have been identified in older versus younger healthy adults (Garrett et al., 2010, 2011; Nomi et al., 2017), in stroke patients (Kielar et al., 2016) and in individuals with neurological disease (Petracca et al., 2017; Zoller et al., 2017). Although the source of increased regional BOLD fluctuations remains unclear in the context of earlier findings, it has been postulated to reflect sub-optimal functioning or compensatory mechanisms (Garrett et al., 2010; Nomi et al., 2017; Petracca et al., 2017).

Although previous findings have been mixed, the emerging consensus is that variability in the rsfMRI BOLD signal may serve as a neuronal index of cognitive function and, thus, age-related cognitive decline. Given the association between neurodegenerative disorders and older age, it is possible that BOLD variability may also offer new insights into age-related pathologies. While some recent rsfMRI studies have begun to examine other aspects of the temporal dynamics of spontaneous BOLD fluctuations in mild cognitive impairment (Han et al., 2011; Xi et al., 2012; Zhao et al., 2015) and AD (Liu et al., 2013; Liu et al., 2014), the utility of variance measures such as SD_{BOLD} as a biomarker of AD requires further investigation.

Recently, Makedonov and colleagues (2013) used a slightly different method than the previous investigations and found that BOLD fluctuations in WM regions are higher in older adults, and in normal appearing WM structures of older adults with cerebral small vessel disease (CVSD; Makedonov et al., 2013). They put forth the idea that increased arterial stiffness caused by cerebrovascular disease may result in greater pulsatility down vascular networks and small vessels, which may, in turn, have translated into the *increased* temporal variance observed in their study. This idea was supported by a subsequent study that found greater variation of spontaneous BOLD fluctuations in both GM and WM in hypertensive elderly patients (Jahanian et al., 2014). Together, these findings suggest that resting-state BOLD variance may serve as a physiological signal related to an individual's cerebrovascular status.

Most recently, Makedonov et al. (2016) examined resting state BOLD fluctuations in WM in individuals with AD. It was found that BOLD fluctuations were significantly *increased* in patients with AD relative to those with mild cognitive impairment and age-matched controls. Furthermore, the increased BOLD fluctuations were found to have a negative relationship with memory scores, thereby supporting a link between increased WM BOLD fluctuations and lower functionality. It has therefore been hypothesized that between-cohort differences in BOLD fluctuations may reflect underlying differences in cerebrovascular health that are not captured by existing AD biomarker data (Makedonov et al., 2016). However, given that this study limited its investigation to WM and did not directly examine participant WM vascular burden, further consideration is warranted.

In light of its promise as a novel biomarker, there is a clear need for additional research to investigate rsfMRI BOLD variability in AD. To this end, the objectives of the current study were to (1) examine whole brain differences in SD_{BOLD} in a group of individuals with AD and healthy age-matched controls, (2) determine whether measures of BOLD variability correlate with measures of cognitive ability, and (3) investigate the relationship between BOLD variability and WM cerebrovascular dysfunction. Based on previous research, it was hypothesized that there would be (1) widespread differences in rsfMRI BOLD variance in patients with AD versus healthy controls, (2) a relationship between BOLD variability and participant clinical test performance, and, in light of the recent findings by Makedonov et al. (2016), (3) a positive association between BOLD variability and MRI-based measures of WM lesion burden.

Methods and Materials

ADNI database

All data for the present study were obtained from the Alzheimer's Disease Neuroimaging Initiative 2 (ADNI-2) database (http://adni.loni.usc.edu). The ADNI, led by principal investigator Michael W. Weiner, began in 2003 as a partnership between the National Institute on Aging, the National Institute on Biomedical Imaging and Engineering, the Food and Drug Administration, as well as other private and public nonprofit organizations. Since its launch, the primary goal of ADNI has been to develop more sensitive methods that may be able to detect AD at its earliest time point, in order to maximize the efficacy of future disease modifying or delaying interventions. Now in its fourth phase, the ADNI is focused on tracking the longitudinal progression of neuroimaging, laboratory, and neuropsychological AD biomarkers in participants from acquisition sites across Canada and the United States. For further information, please see (http://www.adni-info.org).

Participants

All participants were selected from the ADNI-2 database, as the ADNI-1 phase did not collect rsfMRI data. Data were obtained from the first available time point from 19 individuals with AD (mean age = 72.7 years, SD = 6.5; 12 females) and 19 healthy age-matched controls (mean age = 74.7, years, SD = 6.9; 11 females). No significant differences were found between groups in participant age, sex, or education level. Participant demographic information can be found in Table 1.

Diagnostic classification of AD participants was made by ADNI investigators according to diagnostic criteria for Probable AD established by the National Institute of

Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease Related Disorders Association (NINCDS-ADRA; McKhann et al., 1984). Participants in the AD cohort also exhibited abnormal memory function on the Logical Memory II subscale of the revised Wechsler Memory Scale (WMS II, ≤ 8 for 16 years education and above)**,** a Mini Mental State Exam (MMSE) between 20 and 26 (inclusive), and a Clinical Dementia Rating of 0.5 (very mild) or 1 (mild).

All control participants were free of memory complaints and deemed cognitively normal based on clinical assessments by the site physician showing an absence of significant impairment in cognitive functioning and performance of daily activities. Participants in the control cohort also exhibited normal memory function on the Logical Memory II subscale of the revised WMS (WMS II, ≥ 9 for 16 years of education and above)**,** a MMSE score between 24 and 30 (inclusive), and a Clinical Dementia Rating of 0. For more information on group classifications, including all additional eligibility criteria, please consult the ADNI-2 procedures manual (Alzheimer's Disease Neuroimaging Initiative, 2008).

All ADNI participants or their authorized representatives provided written informed consent approved by the Institutional Review Board at each acquisition site. For the purpose of the current study, secondary use of the data was approved by the Human Research Ethics Board at the University of Victoria (British Columbia, Canada).

Table 1. *Participant Demographics*

	AD	*CN*	*AD vs. CN*
Age	72.7 ± 6.5	74.7 ± 6.9	p = 0.365
Females	12	11	p = 0.740
Males	7	8	
Education (years)	16.2 ± 2.6	16.3 ± 2.3	p = 0.896

Image Acquisition

MRI data were downloaded with permission from the ADNI. All images were acquired on 3.0 Tesla Philips MRI scanners across 10 North American acquisitions sites according to the standardized ADNI protocol (Jack et al., 2008). Whole-brain anatomical MRI scans were acquired sagittally, with a T1-weighted MPRAGE sequence, with the following parameters: 1.2 mm slice thickness, a 256 x 256 x 170 acquisition matrix, an echo time of 3 ms, a repetition time (TR) of 7 ms, and a flip angle of 9°. Functional MRI scans were obtained during resting state; participants were instructed to lay quietly in the scanner with their eyes open. Resting state fMRI scans were obtained with a T2*-weighted echo-planar imaging sequence with the following parameters: 140 volumes, a 64 x 64 x 48 acquisition matrix (voxel size = $3.3mm^3$), an echo time of 30 ms, a TR of 3000 ms, and a flip angle of 80°.

The participant's T2-weighted fluid-attenuated inversion recovery (FLAIR) images were obtained for the purpose of lesion volume computation. The T2-weighted FLAIR images were obtained with a 5.0 mm slice thickness, an echo time of 90 ms, a TR of 9000 ms, and a flip angle of 90 °.

Data Analysis

Image Preprocessing. All analysis steps were performed using tools within the Functional MRI of the Brain Software Library (FSL) version 5.0 (Analysis Group, FMRIB, Oxford, UK, http://fsl.fmrib.ox.ac.uk; Smith et al., 2004). Non-brain tissue in the raw T1 images was removed using the automated Brain Extraction Tool (Smith, 2002), followed by manual verification and optimization for each subject. BOLD data preprocessing was performed in FSL's FEAT as follows: each functional image was motion corrected and registered to a high-resolution anatomical image that was nonlinearly registered to standard stereotaxic space using a 12 degrees of freedom transformation. Additionally, global signal regression (GSR) was performed to correct for sources of confounding physiological noise and to improve the detection of localized variation in the BOLD signal (Desjardins, Kiehl, & Liddle, 2001; Fox, Zhang, Snyder, & Raichle, 2009; Macey, Macey, Kumar, & Harper, 2004).

Statistical Comparisons. Individuals with AD were compared to age-matched controls in the group-level analysis. Grey matter and WM regions were identified with the Harvard-Oxford probabilistic cortical and subcortical structural atlases (Desikan et al., 2006), the MNI structural atlas (Collins et al., 1995; Mazziotta et al., 2001), and the Johns Hopkins University's diffusion-tensor-imaging-based WM atlases (Hua et al., 2008; Mori et al., 2005, 2008; Wakana et al., 2007). All results were examined at a $p < 0.05$ significance level, unless otherwise stated.

Resting-State BOLD Variability (SD_{BOLD}). Though different conceptualizations of brain signal variability exist, an increasingly popular approach in rsfMRI involves examining the distributional width of the neuroimaging timeseries by computing the

signal variance or standard deviation (SD_{BOLD}) across voxels (for a review, see Garrett, Samanez-Larkin et al., 2013). Following this framework, the current study derived a measure of BOLD variability by first obtaining the variance of the residual signal left over after noise correction at each voxel across the whole brain. The square root of the variance within each voxel was subsequently computed in order to arrive at a SD_{BOLD} map for each participant; this map effectively describes the standard deviation of the BOLD timeseries at each voxel within both GM and WM regions. All images generated from these steps were then merged into a single 4D file and smoothed with a Gaussian kernel (6 mm). To examine differences in resting state BOLD variability in AD patients versus healthy age-matched controls, between-group contrast comparisons of SD_{BOLD} were performed using randomise (Winkler, Ridgway, Webster, Smith, & Nichols, 2014) with threshold-free cluster enhancement and correction for multiple comparisons.

Relationship Between BOLD Variability and Cognitive Scores (Executive Function and Memory). Neuropsychological data were obtained according to the protocol outlined in the ADNI-2 procedures manual (Alzheimer's Disease Neuroimaging Initiative, 2008). The ADNI-2 database contains neuropsychological test scores for individual tests, as well as composite scores for the examination of memory and executive function. Deficits in both memory and executive function are core clinical characteristics of AD that have been shown to occur in the early stages of the disease (Baudic et al., 2006; Sperling et al., 2010). Moreover, the use of composite measures, as opposed to individual cognitive tests, has been suggested to increase measurement precision and further limit the challenges associated with multiple hypothesis testing (Crane et al., 2012; Gibbons et al., 2012). Thus, in order to determine whether differences in resting state BOLD variability were related to participant clinical scores, correlations

were examined between the participant's SD_{BOLD} maps, as described above, and composite clinical scores for (1) memory performance (ADNI-MEM) and (2) executive function (ADNI-EF). Both cognitive measures were derived from the ADNI neuropsychological test battery using item response theory (IRT) methods and validated in subsequent studies. Specifically, the ADNI-MEM score was derived from a single-factor confirmatory factor analysis model performed by Crane et al. (2012) using data from the Rey Auditory Verbal Learning Test (RAVLT), AD Assessment Schedule - Cognition (ADAS-Cog), MMSE, and the WMS Logical Memory subscale. The ADNI-EF score was derived by Gibbons et al. (2012) using a bi-factor confirmatory factor analysis model with data from the Wechsler Adult Intelligence Scale – Revised (WAIS-R) Digit Symbol Substitution, Digit Span Backwards, Trails A and B, Category Fluency, and Clock Drawing. Due to missing data, two participants from the AD and CN groups, respectively, were omitted from this analysis. Statistical computations were performed using randomise with threshold-free cluster enhancement and correction for multiple comparisons.

Relationship between BOLD Variability and Cerebrovascular Status (WM Lesion Volumes). To derive a measure of cerebrovascular status in accordance with the hypothesis put forth by Makedonov et al. (2013, 2016), we examined participant white matter hyperintensities (WMH) at the time of scanning to determine total WM lesion burden. Following data screening, four AD participants were omitted from this analysis due to FLAIR image motion artifact. Lesions were segmented by the lesion prediction algorithm (LPA; Schmidt, 2017), using FLAIR images only, as implemented in the LST toolbox version 2.0.15 (http://www.statistical-modelling.de/lst.html) for the Statistical Parametric Mapping (SPM) software. Briefly, the LPA is a binary classifier in the form

of a logistic regression model that was initially trained on the data of 53 multiple sclerosis patients with severe lesion patterns (Schmidt et al., 2012). Parameters of this model are used to segment lesions in new images by computing an estimate for the lesion probability within each voxel. In the current analysis, lesion volumes (ml) derived from each participant's probabilistic map were extracted to derive a total lesion volume for each subject. To account for variability in parenchymal volume across participants, total brain volumes for each participant were computed using FMRIB's Automated Segmentation Tool (FAST; Zhang, Brady, & Smith, 2001). Lesion volumes were subsequently converted to a value representing the fraction of total brain volume (TBV) occupied by WMHs in each participant. Correlations were then examined between these values and the participants' resting-state SD_{BOLD} maps. As in previous steps, statistical computations were performed using randomise with threshold-free cluster enhancement and correction for multiple comparisons.

Results

Differences in Resting State SD_{BOLD} in Patients with AD versus Healthy Controls

Between-group comparisons were performed to examine differences in resting-state SD_{BOLD} in patients with AD relative to healthy age-matched controls. The results of this analysis revealed significant differences in BOLD variability ($p < 0.05$, corrected for multiple comparisons) in right-hemispheric GM and WM regions (Table 2). Specifically, AD > CN contrasts showed a greater resting state SD_{BOLD} in the AD group, predominantly in the right superior frontal gyrus and adjacent frontal regions, including the right precentral gyrus and right putamen. Significant WM regions were similarly right-lateralized and included portions of the right superior longitudinal fasciculus (frontal and temporal components) and right superior and inferior corona radiata (Figure 5). No GM or WM regions were found to have increased SD_{BOLD} in healthy controls relative to AD patients.

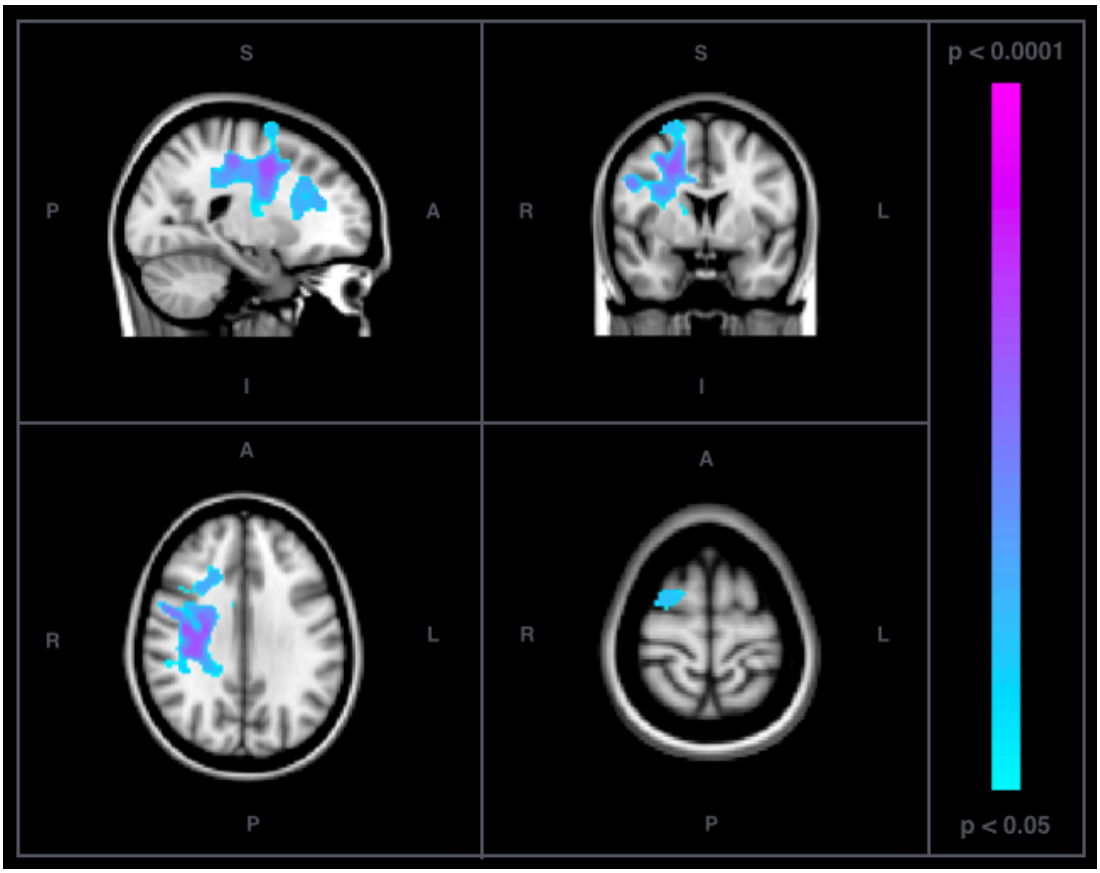

Figure 5. Results of between-group comparison of SD_{BOLD} in patients with AD versus healthy controls showing regions of increased signal variability in AD patients ($p < 0.05$, corrected for multiple comparisons) in both GM and WM. Images on overlaid on T1-weighted MNI152_T1_2mm standard template provided by the Functional MRI of the Brain's Software Library. The color bar shows the range of intensities across the regions of significance: colors in the violet range indicate a greater statistical robustness (smaller p-value threshold) of the observed results, whereas colors in the blue range indicate a lower statistical robustness (larger p-value threshold).

Table 2. *Brain regions showing increased SD_{BOLD} in patients with AD relative to healthy controls ($p < 0.05$, corrected for multiple comparisons). Coordinates are shown in Montreal Neurological Institute (MNI) standard stereotaxic space.*

Brain Region	Laterality	MNI Coordinates		
		x	**y**	**z**
Grey Matter				
Superior frontal gyrus	R	24	0	68
Precentral gyrus	R	56	4	32
Putamen	R	32	-8	0
White Matter				
Superior longitudinal fasciculus	R	36	-22	28
Posterior corona radiata	R	24	-32	36
Superior corona radiata	R	24	-6	38
Anterior corona radiata	R	20	24	24
Forceps minor	R	20	38	16
External capsule	R	30	-8	12

Relationship Between Resting State SD_{BOLD} and Cognitive Scores

ADNI-MEM. When a conventional significance threshold ($p < 0.05$) was employed, no significant relationship was found between ADNI-MEM scores and SD_{BOLD} in AD patients or healthy controls. However, given the novelty and exploratory nature of this research, relationships were also explored using a more liberal threshold ($p < 0.1$, corrected for multiple comparisons). In doing so, an association was identified in the healthy control group, showing a negative relationship between SD_{BOLD} and ADNI-MEM scores in both GM and WM regions (Table 3). Specifically, lower ADNI-MEM scores were associated with greater SD_{BOLD} in the healthy control group in the medial temporal lobe (MTL) and adjacent structures, including the right hippocampus and right

amygdala, extending to the parahippocampal gyri bilaterally, as well as in the left superior longitudinal fasciculus and right inferior longitudinal fasciculus (Figure 6).

ADNI-EF. No significant relationship was found between ADNI-EF scores and SD_{BOLD} in AD patients or healthy controls using conventional and liberal thresholds.

Table 3. *Brain regions showing a negative association between SD_{BOLD} and ADNI-MEM scores in the healthy control group ($p < 0.1$, corrected for multiple comparisons). Coordinates are shown in Montreal Neurological Institute (MNI) standard stereotaxic space.*

Brain Region	Laterality	MNI Coordinates		
		x	**y**	**z**
Grey Matter				
Amygdala	R	20	0	-22
Hippocampus	R	22	-14	-24
Parahippocampal gyrus	R	22	4	-20
Parahippocampal gyrus	L	-16	-38	-14
Cerebellum	R	10	-50	-30
Cerebellum	L	-8	-50	-30
Temporal pole	L	-40	6	-24
Superior temporal gyrus	L	-64	-42	10
Planum temporale	L	-58	-12	4
Frontal orbital cortex	L	-28	8	-22
Heschl's gyrus	L	-52	-14	6
Insular cortex	L	-40	-2	-8
Precuneus cortex	L	-14	-52	4
Thalamus	L	-12	-6	6
Lingual gyrus	L	-14	-52	2
White Matter				
Inferior longitudinal fasciculus	R	44	4	-28
Fornix/stria terminalis	L	-28	-20	-10
Superior longitudinal fasciculus	L	-42	-12	30
Superior corona radiata	L	-20	-16	34
Internal capsule (posterior limb)	L	-24	-22	8

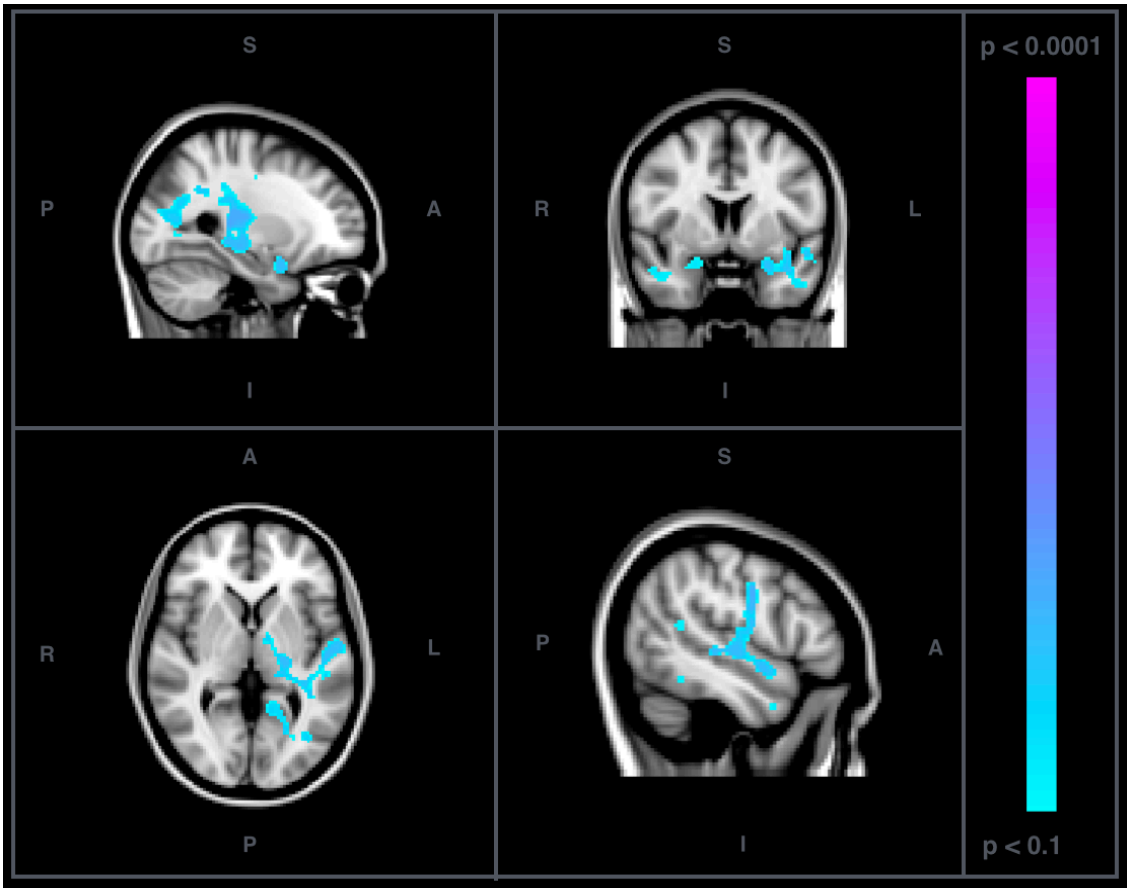

Figure 6. Images showing GM and WM regions where SD_{BOLD} is negatively associated with ADNI-MEM scores in healthy controls ($p < 0.1$, corrected for multiple comparisons). Images on overlaid on T1-weighted MNI152_T1_2mm standard template provided by the Functional MRI of the Brain's Software Library. The color bar shows the range of intensities across the regions of significance: colors in the violet range indicate a greater statistical robustness (smaller p-value threshold) of the observed results, whereas colors in the blue range indicate a lower statistical robustness (larger p-value threshold).

Relationship Between Resting State SD_{BOLD} and Participant WMH Volume

White matter hyperintensity volumes for each participant were derived from probabilistic maps generated by the LST lesion prediction algorithm described previously; Figure 7 shows the probabilistic lesion volume maps for a prototypical AD and healthy control participant. To account for total brain volume, lesion volumes were subsequently converted to a value representing the fraction of TBV occupied by WMH in each participant. On average, AD patients had higher total WM lesion burden (mean fraction of TBV = 0.011 ± 0.007) than age-matched controls (mean fraction of TBV = 0.007 ± 0.007). No significant relationship was found between total WMH burden and SD_{BOLD} in either group. However, using a more liberal threshold ($p < 0.1$, corrected for multiple comparisons) a relationship was identified in the healthy control group, showing a positive association between WHM lesion burden and SD_{BOLD} in highly localized GM and WM regions (Table 4). Specifically, higher WMH lesion burden was associated with greater SD_{BOLD} in temporal, frontoparietal, and orbitofrontal regions, and most prominently in the right parahippocampal gyrus (Figure 8).

Table 4. *Brain regions showing a positive association between SD_{BOLD} and white matter hyperintensity burden in the healthy control group ($p < 0.1$, corrected for multiple comparisons). Coordinates are shown in Montreal Neurological Institute (MNI) standard stereotaxic space*

Brain Region	Laterality	MNI Coordinates		
		x	**y**	**z**
Grey Matter				
Parahippocampal gyrus	R	26	-32	-14
Central opercular cortex	R	46	-14	12
Heschl's gyrus	R	44	-14	8
Orbitofrontal cortex	L	-32	20	-26
White matter				
Posterior corona radiata	L	-28	-54	24

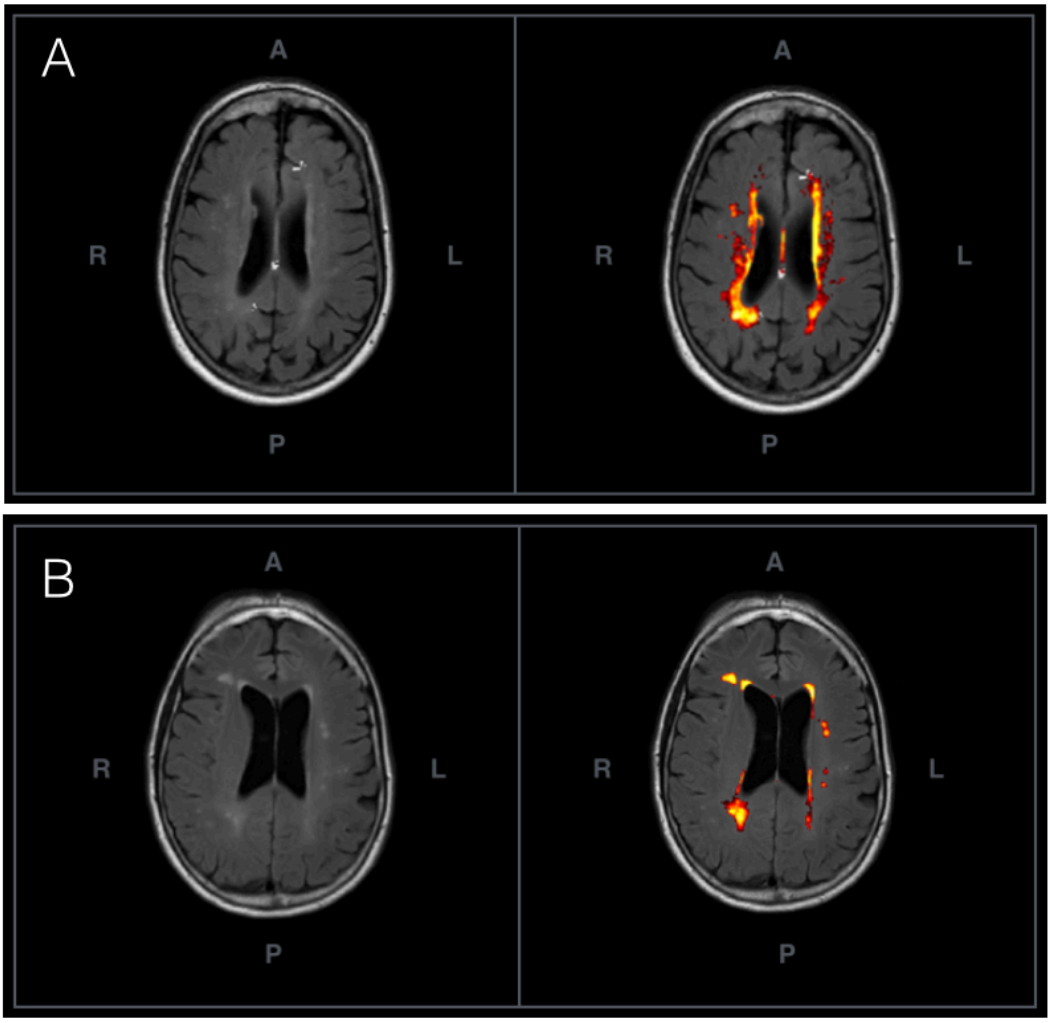

Figure 7. Panel A: An axial T2-FLAIR image of a prototypical patient from the AD group (left) and associated probabilistic lesion volume map (right) generated by the LST-PLA. Panel B: An axial T2-FLAIR image of a prototypical patient from the healthy control group (left) and associated probabilistic lesion volume map (right) generated by the LST-PLA. Prototypical AD and healthy control participants were selected based on the proximity of their WM lesion burdens to their respective group means.

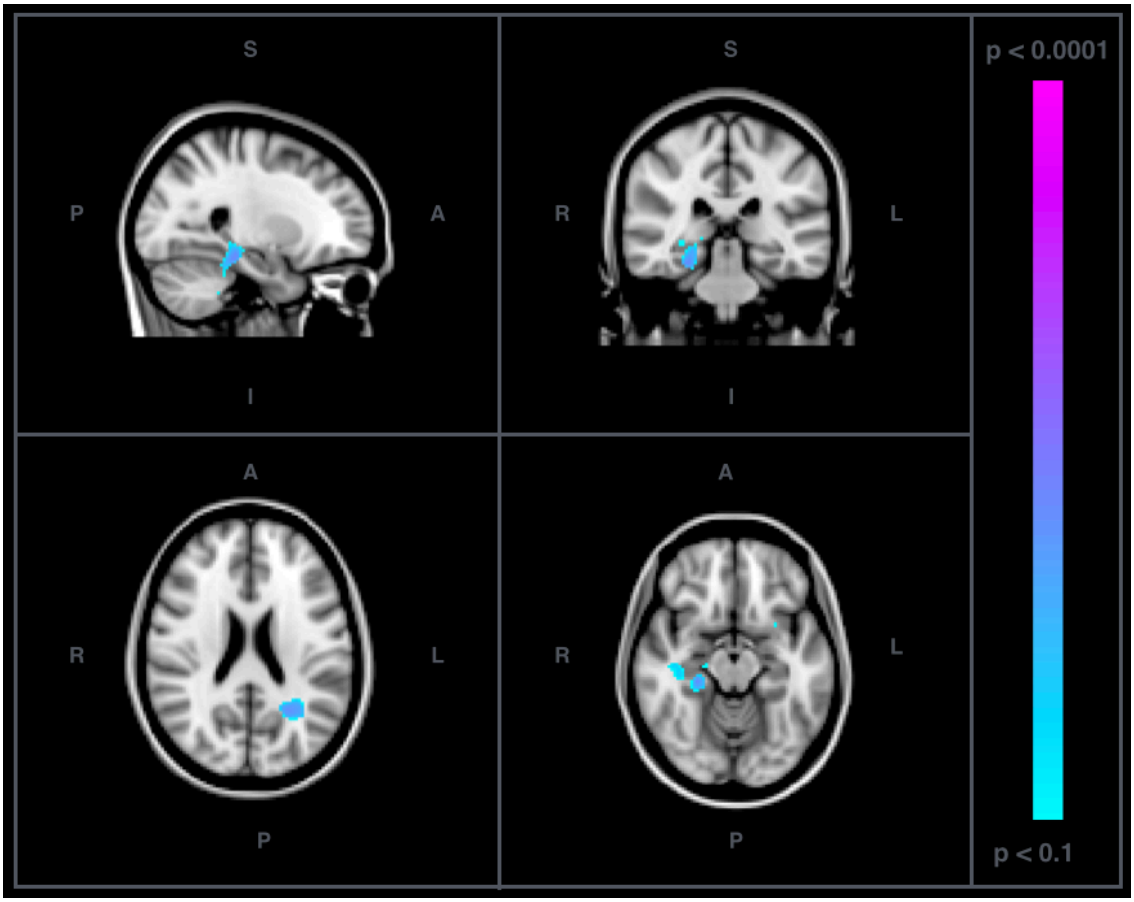

Figure 8. Images showing GM and WM regions where SD_{BOLD} is positively associated with WMH burden in the healthy control group ($p < 0.1$, corrected for multiple comparisons). Images on overlaid on T1-weighted MNI152_T1_2mm standard template provided by the Functional MRI of the Brain's Software Library. The color bar shows the range of intensities across the regions of significance: colors in the violet range indicate a greater statistical robustness (smaller p-value threshold) of the observed results, whereas colors in the blue range indicate a lower statistical robustness (larger p-value threshold).

Discussion

Alzheimer's disease is a neurodegenerative disorder for which there is no cure. As a result, there is an emphasis on improving early detection methods through the identification of ideally non-invasive biomarkers, such as MRI. In recent years, resting-state BOLD variability has emerged as a novel fMRI analysis technique that holds potential for new insights into the functional pathologies of aging and their associated underlying physiological correlates. Until recently, the majority of investigations of resting-state SD_{BOLD} have been focused on healthy populations and normative cognitive changes over the lifespan. To date, few studies have examined BOLD fluctuations in clinical populations with varying results (e.g. Huang et al., 2016; Jahanian et al., 2014; Kielar et al., 2016; Makedonov et al., 2013, 2016; Petracca et al., 2017; Zoller et al., 2017). However, given that this technique has been thought to provide an index of cognitive health, its utility as a biomarker for AD requires further investigation. The objective of the current study was to examine resting state SD_{BOLD} and its relation to psychophysiological variables in a sample of AD patients and healthy matched controls from the ADNI-2 database.

Resting State SD_{BOLD} in Patients with AD Compared to Healthy Controls

The first goal of the current study was to characterize differences in resting-state BOLD variability in AD relative to normative aging. In light of previous studies reporting a robust association between regional BOLD variability and age-related cognitive decline (Garrett et al., 2010; 2011; Garrett, Kovacevic et al., 2013), we hypothesized that there would be widespread differences in resting-state BOLD variability in patients with AD relative to healthy older adults. In line with our hypothesis, we observed significant

increases in SD_{BOLD} in patients with AD in a number of GM and WM frontal regions, including portions of the superior frontal and precentral gyri, the superior longitudinal fasciculus, and widespread regions of the corona radiata (Table 2). Notably, both GM and WM regions with increased BOLD variability in AD were right lateralized (Figure 5). No brain regions were found to have increased SD_{BOLD} in healthy aging relative to AD.

The finding of increased BOLD variability in AD conflicts with earlier studies of SD_{BOLD} in normative aging, wherein greater BOLD variability has been posited to serve as a neural marker of optimal brain function (Grady & Garrett, 2014). Given the neurodegeneration inherent in AD, it is plausible to expect BOLD variability, when conceptualized as a neuronal signal of functional integrity, to be reduced in this population. However, studies have also revealed regions of *increased* BOLD variability in older age (Garrett et al., 2010; 2011; Nomi et al., 2017), in stroke patients (Kielar et al., 2016) and in individuals with neurological disease (Petracca et al., 2017; Zoller et al., 2017), thereby alluding to a greater nuance in the association between BOLD variability and functional integrity. Notably, Makedonov et al. (2016), found that resting state BOLD fluctuations in WM were significantly increased in patients with AD relative to both participants with MCI and healthy controls. Moreover, in accordance with the present findings, many of the regions where increased BOLD variability has been identified in older or clinical populations have included portions of the frontal cortex (Petracca et al., 2017; Zoller et al., 2017), and particularly the superior frontal gyri (Garrett et al., 2010; Kielar et al., 2016). Interestingly, this localization to frontal regions is also reflected in mean-BOLD fMRI studies of aging, wherein prefrontal over-activation in older relative to younger adults has been postulated to reflect the additional

recruitment of executive resources in support of memory maintenance (Reuter-Lorenz & Park, 2010).

It is also notable that the right-hemispheric lateralization observed in the current study is also congruent with the existing BOLD fMRI compensatory literature: as summarized by Gauthier et al. (2013), one of the most common findings in aging is a decreased lateralization of the BOLD response, characterized primarily by a *decrease* in left frontal BOLD responses but an *increase* in the right frontal BOLD response (for a review, see: Reuter-Lorenz & Park, 2010).

Given the present finding of increased signal variability in patients with AD relative to healthy controls, an important question remains: what might be the underlying psychophysiological correlates driving the increased signal variability in AD?

SD_{BOLD} and its Association With Cognitive Function

Central to the aforementioned compensation hypothesis, and reflected in previous findings of BOLD variability (e.g. Grady & Garrett, 2014), is the notion that SD_{BOLD} may serve as a neuronal index of cognitive function. Therefore, the second objective of the current study was to determine whether measures of BOLD variability might be associated with measures of memory and executive function (ADNI-MEM and ADNI-EF). Contrary to our hypothesis, we did not find a significant relationship between SD_{BOLD} and clinical test performance in patients with AD or healthy age-matched controls. Due to the preliminary nature of the present investigation, results were also examined with a more liberal threshold ($p < 0.1$). In doing so, an association was identified in the healthy control group, revealing a negative relationship between SD_{BOLD} and composite memory scores. Specifically, lower memory scores were associated with

greater SD_{BOLD} in the healthy control group in the medial temporal lobe and adjacent structures (Table 3). No association was found between composite memory scores and SD_{BOLD} in the AD group. Moreover, no association was identified between composite scores of executive function and SD_{BOLD} in AD patients or healthy controls.

Though tentative interpretation is required, the trend towards a negative relationship identified in the healthy control group appears at odds with previous rsfMRI BOLD variability studies on healthy aging populations that have found that higher fluid intelligence and memory scores were linked to greater SD_{BOLD} in diffuse cortical regions (Burzynska, Wong, Voss, Cooke, McAuley et al., 2015). Interestingly, a study that examined patients with AD found that greater WM BOLD fluctuations were associated with *lower* composite scores of memory function in patients with AD from the ADNI database (Makedonov et al., 2016).

A number of factors may have contributed to the inconsistent association between BOLD variability and cognition observed in the present study. Notably, when Makedonov et al. (2016) included diagnostic status, glucose metabolism, and both head and global nuisance signal regressors in a final omnibus model, composite memory scores were no longer found to be significantly associated with WM BOLD fluctuations. The authors postulate that WM BOLD fluctuations may therefore provide novel information about diagnostic status that is not captured by existing biomarkers, including cognition (Makedonov et al., 2016). Thus, it is possible that the trend-level association between SD_{BOLD} and memory observed in the control group merely reflects a corollary association between BOLD variability and another factor associated with memory

composite scores in normative aging, that is otherwise disrupted by the diffuse pathophysiological changes in AD.

However, it is also notable that many of the GM regions in which we found BOLD variability to be negatively associated (at trend-level) with composite memory scores in healthy controls included critical structures of the MTL known to subserve memory function, including the amygdala, hippocampus and parahippocampal gyri (Cohen & Eichenbaum, 1993; Scoville & Milner, 1957; Squire, Stark, & Clark, 2004). In early AD, memory disturbances are often the primary and most salient clinical concern (Sperling et al., 2010). Moreover, in these early stages of the disease process, neuron loss figures most prominently in these MTL structures (Bottino et al., 2002). In addition to structural changes, up-regulatory functional changes are also known to occur in MTL memory circuits in patients with AD and in persons with mild cognitive impairment (Dickerson & Sperling, 2008; Faraco, Puente, Brown, Terry, & Miller, 2013). Thus, the present findings suggest that resting state SD_{BOLD} may provide a novel method of characterizing changes in functional integrity in these regions.

In order to further elucidate the association between SD_{BOLD} in behaviourally relevant regions of the MTLs and its association with pathological aging, there is a need for additional longitudinal studies examining SD_{BOLD} and its association with specific measures of memory and cognition.

SD_{BOLD} and its Association With Cerebrovascular Health

Although cerebrovascular factors have previously been hypothesized to underlie BOLD fluctuation patterns in AD (Makedonov et al., 2016), this relationship had not been examined until the present study. Specifically, the third objective of the current

study was to examine the association between GM and WM BOLD variability and neuroimaging markers of WM cerebrovascular burden. In light of the assertions by Makedonov et al. (2016, 2013), we hypothesized that there would be a positive association between resting-state BOLD variability and MRI-based measures of WM lesion load. When conventional thresholds were used, we did not find a significant association between total WMH burden and SD_{BOLD} in patients with AD or healthy controls. However, as in the previous analysis, we also chose to examine more liberal thresholds in order to further explore any potential directionality in the data. In doing so, an association was again identified in the healthy control group, showing a positive association between WMH lesion burden and SD_{BOLD}. Specifically, participants with a higher WM lesion burden had greater SD_{BOLD} in a set of highly localized brain regions, among which most prominently included the right parahippocampal gyrus and right temporal cortex (Figure 8).

Though tentative, the present results are in line with the initial findings by Makedonov et al. (2013), who discovered that WM rsfMRI BOLD fluctuations were increased in the normal appearing WM of patients with cerebral small vessel disease and positively correlated with WMH volume. This increased BOLD temporal variance has been suggested to reflect greater pulsatility down vascular networks and small vessels as a result of cerebrovascular compliance factors (Makedonov et al., 2013, 2016). Other studies have also lent support to this vascular interpretation in both clinical and healthy aging participants (Jahanian et al., 2014; Kannurpatti & Bismal, 2008; Kannurpatti, Motes, Rypma, & Biswal, 2011).

Though the current results do not appear to support an association between resting-state BOLD variability and WMH lesion burden in AD, further considerations are warranted. Specifically, due to strict exclusion criteria necessitating a group of patients with AD without significant vascular comorbidity, the WHM lesion burden in ADNI appears relatively low (Ramirez et al., 2016), which may have contributed to underpowered effects. However, despite low WMH burden levels, there is evidence to suggest that they are nontrivial. For instance, Carmichael et al. (2010) found that WMH volumes at baseline predicted 1-year global cognitive decline in a sample of over 800 participants from the ADNI database. This again echoes the need to re-examine the neurophysiological correlates of SD_{BOLD} from a longitudinal perspective.

Moreover, although the current study detected a trending relationship between vascular burden and BOLD signal variability in healthy controls, but not in patients with AD, the association between vascular risk factors and AD dementia is one that is well established (Cai et al., 2015; O'Brien & Markus, 2014). Indeed, vascular risk factors have been found to be significant risk factors for AD-specific neuropathology, including neuritic plaques and neurofibrillary tangles (O'Brien & Markus, 2014; Petrovitch et al., 2000). Interestingly, and in accordance with the results of the present study, a meta-analysis by Debette & Markus (2010) also found that WMHs tended to be associated with an increased risk of dementia and AD in healthy populations, but *not* in patients who already exhibit cognitive impairment. In light of this evidence, examination of SD_{BOLD} as a non-invasive biomarker for underlying cerebrovascular risk factors in aging is one that directly contributes to the ultimate goal of improving the early identification of AD. For these reasons, further exploration of the link between rsfMRI SD_{BOLD} and vascular

factors are needed, particularly in prodromal aging groups and with multimodal measures that may more comprehensively capture underlying cerebrovascular risk.

Study Limitations

A primary limitation of the current study relates to the diverse conceptualizations of fMRI BOLD variability, which have varied considerably across studies, making it challenging to systematically compare findings. Specifically, several different variations of 'BOLD variability' measures have been described (e.g. amplitude, variance, standard deviation, mean squared successive difference; for a review, see Garrett, Samanez-Larkin et al., 2013), with considerable range in the methodology used to derive them. As argued by Garrett, Samanez-Larkin et al. (2013), a significant barrier to adopting this novel imaging method on a larger scale lies in the lack of signal variability estimation tools in major neuroimaging software packages. Though some efforts have been made by this group to systematize the analysis of signal variability, implementation of BOLD variability as a novel imaging biomarker for AD will require increased efforts towards methodological standardization.

Another potential limitation of the current study is that only WMH burden was examined as a proxy for cerebrovascular status across groups. While WMHs are believed to be an indicator of cerebral small vessel disease (Mok & Kim, 2015) and cerebral arterial stiffness has found to be correlated with WHM lesion volume (Kidwell et al., 2001), they remain nonspecific proxy measures. Future work should include more direct measures of cerebrovascular reactivity, such as cardiac-sampled BOLD data (Makedonov et al., 2013), to re-examine the hypothesis that BOLD variability in neurodegenerative disease may reflect underlying cerebrovascular factors. Moreover, due to the strict

exclusion criteria and, thus, the relatively low WMH lesion burden in the ADNI sample, future studies should examine more ecologically valid patient samples of AD with mixed vascular pathologies (Ramirez et al., 2016).

Finally, the sample size of the current study is small and limited to a single time point. To acquire a better understanding of BOLD variability and its association with AD pathology over time, future studies should examine larger samples at multiple time points of disease progression.

Conclusion

Increasingly, AD has become an urgent public health concern, rendering critical the need to improve upon its early identification, so that disease-delaying treatments may be implemented as soon as they become available. In support of this goal, the current study examined a novel approach to the analysis of rsfMRI data. Though, traditionally, fMRI investigations have based findings on patterns of mean brain activity, moment-to-moment variability in the BOLD signal may provide new information on disorders of aging and their associated clinical correlates (Garrett, Samanez-Larkin et al., 2013). The current study found increased SD_{BOLD} in patients with AD relative to healthy controls, with trends suggesting an association between SD_{BOLD} and both memory performance and WMH lesion burden in the control group. To further examine the clinical utility of this novel imaging parameter, future work should focus on longitudinal studies of SD_{BOLD} and its association with more comprehensive clinical and cerebrovascular data in both AD and prodromal aging.

Chapter 3: BOLD Variability in Alzheimer's disease: Implications and Directions for Future Study

The current body of work investigated the clinical utility of a novel resting state functional magnetic resonance imaging (rsfMRI) analysis technique as a biomarker for Alzheimer's disease (AD) and its associated psychophysiological correlates. Based on the main finding that SD_{BOLD} is increased in AD relative to healthy aging, the present study suggests that blood oxygen level dependent (BOLD) variability analysis may provide new avenues of examining the neural mechanisms underlying AD.

There are, however, a number of limitations associated with the current investigation, a few of which relate to methodological issues in this novel area of study. As mentioned previously, a major barrier to advancements in the study of fMRI BOLD variability, and particularly in its application as a biomarker in clinical populations, concerns the lack of methodological standardization in this area of research. Relatedly, conceptualizations of BOLD variability have also varied substantially across groups: for instance, some have conceptualized variability in the BOLD signal as a neuronal signal that provides novel information on the functional integrity of the brain (e.g. Burzynska, Wong, Voss, Cooke, Gothe et al., 2015; Burzynska, Wong, Voss, Cooke, McAuley et al., 2015; Garrett, Samanez-Larkin et al., 2013; Grady & Garrett, 2014), whereas others have posited that BOLD fluctuations may serve as a physiological signal reflecting underlying cerebrovascular challenges (e.g. Jahanian et al., 2014; Kannurpatti & Biswal, 2008; Kannurpatti et al., 2011; Makedonov et al., 2013, 2016).

To this end, a central objective of the present study was to further parse out the underlying variables that may account for differences in BOLD variability in AD versus healthy controls (i.e. cognitive or cerebrovascular). However, interpreting signal increases in BOLD fMRI in both healthy and pathological aging populations remains the subject of significant controversy. As noted by Grady (2012), findings of 'decreased' brain activity in older adults relative to younger adults have traditionally been viewed in the literature as an indicator of cognitive deficits, whereas 'increased' brain activity is often interpreted as a compensatory mechanism. However, given the lack of congruence between increased activation and improved performance, some have also suggested that age-related increases in brain activity may simply reflect less efficient neural processing or a lack of response specificity (Grady 2008, 2012). Extending these concerns to the present study, similar challenges also apply to the interpretation of increased SD_{BOLD} in AD relative to healthy aging.

Another important methodological limitation of the present area of study concerns the issue of participant motion and its contribution to measures of $SD_{BOLD.}$ Indeed, the effect of motion has been suggested to exert a significant effect on task-based measures of BOLD variability (Turner et al., 2015). This is a particularly salient issue in more severe cases of AD, wherein patients may be less able to avoid head motion while in the scanner (Sperling, 2011). Encouragingly, this concern is minimal in the current study, given that all participants moved within one voxel size (< 4mm), and motion correction was implemented to correct for artefact. Furthermore, a recent investigation has shown that subject-level motion artefact correction, such as global signal regression, is a highly effective method for removing artifactual variance in resting-state data and may reduce

motion-related group differences by up to two orders of magnitude (Power et al., 2014). In line with the goal of optimizing methodological standardization, additional work is still needed to identify the effect of various motion correction strategies on measures of SD_{BOLD} in clinical populations.

A final consideration for the present study, mentioned briefly in previous sections, concerns the unimodal measure used to characterize cerebrovascular status across participants. Stemming from the findings of Makedonov et al. (2013, 2016), the present study examined white matter hyperintensity (WMH) burden as a proxy for cerebrovascular status across groups. While evidence supports the use of WHM burden as a clinically significant marker of cerebrovascular outcomes (Chutinet & Rost, 2014; Debette & Markus, 2010), the current investigation cannot wholly reject the hypothesis that group differences in BOLD variability may be related to underlying cerebrovascular risk factors in AD. As noted by Makedonov et al. (2016), other unexplored pathophysiological changes in AD including cerebral amyloid angiopathy (Weller, Boche, & Nicoll, 2009), tortuous arterioles in white matter (Brown, Moody, Thore, Anstrom, & Challa, 2009), and altered cerebrovascular pulsatility (Rivera-Rivera et al., 2017) may also have contributed to the differences observed at the group-level. As such, further exploration of this hypothesis is warranted.

In addition to study-specific limitations, there are also a number of limitations associated with the use of the Alzheimer's disease neuroimaging initiative (ADNI) database more broadly. In particular, one central limitation concerns the criteria used in the diagnosis of AD in the ADNI-2 protocol. At present, participants in the AD group are required to meet the 1984 National Institute of Neurological and Communicative

Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria (NINCDS-ADRDA; McKhann et al., 1984), in which *Probable AD* is characterized primarily by behavioral measures (i.e. a deficit in two or more cognitive domains, a progressive course of decline, and supporting evidence of a dementia syndrome based on neuropsychological tests). While the NINCDS-ADRDA criteria remain widely used in both research and clinical domains (Khan et al., 2016), recent years have seen significant revisions to both the diagnosis and conceptualization of AD as a clinicopathological syndrome. Notably, both the National Institute on Aging and Alzheimer's Association working groups (NIA-AA; McKhann et al., 2011) and the International Working Group (IWG; Dubois et al., 2014) have since published revisions to the NINCDS-ADRDA criteria to include pathological measures in the characterization and diagnosis of AD (Sosa-Ortiz et al., 2012). As part of these revisions, AD has been re-conceptualized as existing on a *continuum* (Sosa-Ortiz et al., 2012), rather than as a static diagnostic entity, with a particular emphasis on the use of biomarkers in the identification of underlying AD pathology (Berti et al., 2016; Dubois et al., 2014; Scheltens et al., 2016; Sperling et al., 2011). Incorporating these updated diagnostic criteria in future investigations will therefore be critical, as this would not only aid in the specificity of an AD-group classification, but would also support future advances in clinical diagnosis and improved translatability of research findings.

Similar considerations also apply to the strict exclusion criteria in ADNI: at present, all participants in the database are required to be free of other neurological disorders, major psychiatric comorbidities, and significant vascular concerns (Hachinski Ischemic Scale Score ≤ 4). As argued by Ramirez et al. (2016), while such criteria is in

some ways a strength, in that it allows for a "pure" sample of AD pathology, omitting populations with comorbidities, and particularly those of vascular origin, also poses the risk of reducing the applicability of findings to "real-world" AD with mixed presentations. To this end, additional studies of SD_{BOLD} in more ecologically valid samples of AD are necessary to further investigate these concerns.

Another issue related to the ADNI sample pertains to the lack of stratification of disease stage within the AD group. Ideally, a biomarker suited to clinical AD would be able to detect changes at their earliest time point, *prior* to the onset of significant neurodegeneration. While the present study collected data from the initial (screening) time point for each individual, there is still likely to be significant variability in the stage of disease progression for each participant at their respective baselines. Although the ADNI-2 database includes individuals with late-mild cognitive impairment (MCI) as a means of approximating this critical early time-point, there are challenges associated with the study of MCI as an early form of AD (Mayo, Mazerolle, Ritchie, Fisk, & Gawryluk, 2017). Most notably of which includes evidence that a significant portion of individuals with MCI remain cognitively stable, without conversion to AD (Manly et al., 2008). Specifically, approximately 8-15% of individuals with MCI progress to AD (Petersen, 2009), but the vast majority of individuals diagnosed with MCI do not develop AD. Moreover, the significant clinical diversity of MCI as a diagnostic group (Libon et al., 2010) further poses the risk of diluting the investigation of psycho-physiological biomarkers underlying AD-specific pathology (Mayo et al., 2017). Thus, despite the limitations associated with the lack of disease stratification within the AD group, the

present investigation limited its focus to participants with clinically manifest AD relative to healthy aging.

Based on the presented limitations, there are a number of avenues open for future investigation. In particular, there is a clear need for longitudinal explorations of SD_{BOLD} in larger sample sizes, in order to acquire a better understanding of BOLD variability and its association with AD pathology over time. Ideally, such future studies should retrospectively investigate prodromal aging groups with conversion to AD in order to further characterize changes in SD_{BOLD} as they occur in the *earliest* stages of disease. Further, given that the ultimate goal of such investigations would be to identify a clinical biomarker of AD, such studies would ideally (1) employ updated diagnostic criteria for AD (with corroborating pathological evidence of disease) and (2) broaden the inclusion criteria to include AD with mixed vascular pathologies. This would not only allow for improved specificity of an AD-group classification, but would also increase the ecological validity of findings to individuals diagnosed with AD in '"real-world" clinical settings (Ramirez et al., 2016).

Moreover, as mentioned previously, though the present study provides preliminary evidence for an association between SD_{BOLD} and neuroimaging markers of cerebrovascular status in healthy aging, further consideration of this hypothesis is warranted. In particular, there is a need to re-examine this association with multimodal measures that may more comprehensively capture underlying cerebrovascular risk. To this end, future investigations should include more direct measures of cerebrovascular reactivity, such as cardiac-sampled BOLD data (Makedonov et al., 2013), transcranial Doppler pulsatility measures of arterial stiffness (Ghorbani, Ahmadi, & Shemshaki,

2015; Kidwell et al., 2001), or diffusion tensor imaging parameters of white matter microstructural integrity (Croall et al., 2017). Similar considerations also apply to measures of cognition: while the present study examined summary measures of memory and executive function, future studies should examine more *specific* measures of cognition in order to acquire a better understanding of the association between voxelwise SD_{BOLD} and functional integrity in behaviourally relevant regions of the brain.

More broadly, further studies examining rsfMRI BOLD variability in clinical populations may also aid in advancing our interpretation of the existing BOLD fMRI literature. Indeed, while mean- and variability-based measures of brain activity are essentially orthogonal parameters which have been suggested to reflect different aspects of brain function (Garrett et al., 2010, 2011), they are not completely dissociable: as noted by Garrett, Samanez-Larkin et al. (2013), many functional connectivity measures are automatically scaled for variance in their calculations, including the commonly used Pearson's correlation coefficient (r_{xy}), in which the within-region signal variability is accounted for in the denominator:

$$r_{xy} = \frac{\sum(x - \bar{x})(y - \bar{y})}{SD_x SD_y}$$

As discussed in previous chapters, a number of existing studies have reported consistent alterations in functional connectivity networks in patients with AD relative to healthy controls (e.g. Damoiseaux et al., 2012; Greicius et al., 2004; He et al., 2007; Wang et al., 2007; Wang et al., 2006; Zhang et al., 2009; Zhou et al., 2010). Thus, it is possible that such findings may, in part, be driven by increased BOLD variability in this patient group,

as shown in the present study. Along these lines, some groups have suggested an association between voxelwise BOLD variability measures and both resting state and task-related BOLD fMRI response amplitudes (e.g. Huang et al., 2016; Kannurpatti, Rypma, & Biswal, 2012; Mayhew et al., 2016). While some early efforts have been made to explore the relationship between resting-state networks and SD_{BOLD} in clinical populations (e.g. Petracca et al., 2017; Zoller et al., 2017), future work is needed to inform the use of SD_{BOLD}, both as a biomarker of pathological aging, and as a useful adjunct to existing fMRI studies on aging and AD.

In sum, the present thesis provides proof of concept that a novel rsfMRI analysis technique (SD_{BOLD}) that is non-invasive, easily accessible, and clinically compatible, can differentiate patients with AD from healthy controls. To further explore the potential of SD_{BOLD} as a biomarker of AD, additional studies in larger, longitudinal samples are needed to better understand the changes in SD_{BOLD} that characterize the various stages of disease progression and their underlying psychophysiological correlates. Elucidation of BOLD signal fluctuations in pathological aging will not only open the door to novel ways of characterizing the functional integrity of the brain, but may also help to inform our knowledge of the ever expanding literature on AD and its associated neural hallmarks. Ultimately, the goal of this work is to improve upon the early identification of AD, so that neuroprotective measures can be put in place at the earliest possible time point, thereby reducing the devastating effects of this disease on future generations.

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