

Intraindividual Variability and Micro-structural White Matter Changes in Alzheimer's
Disease

Kara Engelbrecht
ENGGAR007

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of Master of Arts (Psychological Research).

ACSENT Laboratory
Department of Psychology
University of Cape Town
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Abstract

The costs associated with diagnosis, treatment and care of Alzheimer's disease (AD) patients places a significant financial and social strain on healthcare systems, patients and caregivers, especially in low-and middle-income countries (LAMICs). Traditional methods for diagnosing AD are time consuming and expensive, and treatments are often only effective in the early stages. These factors call for the development of alternative diagnostic methods.

One such method that has gained attention due to its neural overlaps with AD is the measurement of intraindividual variability (IIV; the within-person variation in performance over multiple trials of a single task). IIV researchers have highlighted the role of white matter in increased IIV, and micro-structural white matter changes have been implicated in the early stages of AD. The current study examined the relationship between IIV on simple and choice reaction time tasks and micro-structural white matter changes, as indexed by fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (DA) and radial diffusivity (DR) in a sample of 16 AD patients and 20 healthy older adults. Across the entire sample, increased IIV on both the simple and choice reaction time tasks was significantly correlated with lower FA in an area of the right hemisphere inferior longitudinal fasciculus (R-ILF). Increased IIV on the choice reaction time task was significantly correlated with lower DA in the same area. Finally, IIV on the choice reaction time task contributed significantly and uniquely to variance in DA in the same area. These results suggest that further longitudinal studies into the diagnostic utility of IIV for neurological disorders might be of value for clinicians, patients and caregivers.

Introduction

The 20th and 21st centuries have seen a worldwide increase in life expectancy and, concomitantly, an increasing incidence of age-related brain disorders, including dementia. Global estimates suggest that, in 2016, approximately 47 million people were living with dementia. This number is projected to increase to 131 million by 2050. According to the 2016 World Alzheimer's report, the annual global cost of dementia, including costs to government, primary caregivers and patients themselves, is US\$818 billion (Prince, Martin, Comas-Herrera, Knapp, Guerchet, & Karagiannidou, 2016).

Of particular concern for families, clinicians, and policymakers in low- and middle-income countries (LAMICs) are estimates suggesting that dementia prevalence in these regions is in fact higher, and increasing at a faster pace, than average global rates (De Jager, Joska, Hoffman, Borochowitz, & Combrinck, 2015; Prince et al., 2015). Consistent with these suggestions are estimates that, by 2050, approximately 71% of people living with dementia will be resident in developing-economy countries (Prince et al., 2013). These countries can least afford the costs associated with the disease, which include referral to a specialist, initial diagnosis and treatment, continued care, and, eventually, palliative care (Prince et al., 2016). In addition, the social and financial burden on caregivers for those with dementia is often greater in LAMICs, and lower income has been associated with increased caregiver burden among families (Andren & Elmstahl, 2007; De Jager et al., 2015; Thrush & Hyder, 2014). For example, one community-based study found that that 79% of patients attending a South African memory clinic were cared for by family members who received little to no formal support, and who, in at least some cases, had to leave their jobs to fulfil this role (Kalula et al., 2010).

Alzheimer's disease (AD) is the most common cause of dementia (Anstey, Cherbuin, & Herath, 2013). Importantly, some treatments for AD are only effective at the early stages

of the disease (Kälin et al., 2014). Hence, early detection of AD is an important area of research and clinical interest, and investigators across the neuroscientific disciplines have, over the past several years, focused intensive efforts on finding methods for detecting cognitive and functional changes that might signal prodromal AD (Snyder et al., 2014). One method of measurement that is increasingly applied in AD research, in part because it might contribute significantly to early detection of the neurodegenerative condition, is intraindividual variability (IIV). IIV may be a particularly useful tool for the early detection of risk for AD in LAMICs because it does not involve costly neuroimaging or comprehensive neuropsychological test battery administration.

IIV refers to within-person trial-to-trial variation in performance on a single task (Fiske & Rice, 1955a). Conventionally, studies investigating inter-individual differences in cognition assume that an individual's performance is stable over time, and that any variability that is not accounted for by practice effects and other such factors is best regarded as noise in the data. An increasingly persuasive counterargument, however, is that the amount by which an individual's performance varies is a function of lawful influences on behaviour, and is therefore relatively stable across time and across cognitive domains (Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000; MacDonald, Nyberg, & Bäckman, 2006; Ram, Conroy, Pincus, Hyde, & Molloy, 2012; Stamps, Briffa, & Biro, 2012).

Individual performance that varies over macro-timescales of months, years, and decades reflects developmental change, and is closely linked to the aging process. In contrast, individual variation in performance over micro-timescales of seconds, days, or weeks is unrelated to developmental change, and reflects dynamic within-person characteristics (Ram et al., 2012). Hence, it is the latter that is of interest to IIV researchers in psychology and the neurosciences, and that is the focus of this thesis.

IIV over micro-timescales is comprised of two separate components: time-structured and net IIV. *Time-structured IIV* refers to within-person variation that is somehow related to time-on-task-effects, such as fatigue and practice. It is therefore measured by examining patterns of change within a set of repeated measurements. Conversely, *net IIV* refers to within-person variation that is unrelated to time-on-task-effects. It is measured by statistics of central tendency and dispersion within a set of repeated measurements (Fiske & Rice, 1955). Net IIV (referred to as IIV from here onwards, as it is the type of micro-timescale IIV with which this thesis is primarily concerned) is therefore considered a relatively stable, trait-like quality, and a component of cognition that exerts a non-random influence on test scores (Hultsch et al., 2000; MacDonald et al., 2006).

Although IIV is stable within life stages, it increases as people move into older adulthood, and is negatively associated with cognitive performance in healthy adults (Christensen et al., 2005; Hultsch et al., 2000; Nesselroade & Salthouse, 2004). Furthermore, longitudinal studies of healthy older adults suggest that high IIV earlier in life can predict later cognitive decline. For instance, Lövdén, Li, Shing, and Lindenberger (2007) reported that higher IIV at baseline predicted cognitive decline in perceptual speed and ideational fluency up to 13 years later. Similarly, Bielak, Hultsch, Strauss, MacDonald, and Hunter (2010) reported that higher IIV at baseline was associated with a greater risk of non-dementia-related cognitive impairment 5 years later.

Furthermore, IIV can reliably distinguish between normal and pathological decline, and higher IIV has been associated with the clinical presence of AD compared to relatively lower IIV in healthy control groups (see, e.g., Gorus, De Raedt, Lambert, Lemper, & Mets, 2008; Hultsch et al., 2000). For instance, Kälin et al. (2014) showed that individuals with

mild cognitive impairment (MCI)¹ who later progressed to AD had higher IIV at baseline than those who did not progress. Similarly, Duchek et al. (2009) reported that IIV on two selective attention tasks was higher in apolipoprotein ϵ 4 (ApoE4) carriers, who are at a greater risk for AD, than in non-carriers, and was also positively correlated with cerebrospinal fluid biomarkers of AD. Recently, Christ, Thomas, and Combrinck (2018) found significantly higher IIV, on both time- and accuracy-based tasks, in South African older adults with mild-to-moderate AD than in matched healthy controls. These findings offer support for IIV as a sensitive marker of impending and long-term neurological change, and highlight the utility of using it as an early detector of AD.

Cognitive and Neural Correlates of Intraindividual Variability

A strong strand of research suggests that high IIV in performance on certain cognitive tasks is caused by lapses in executive control (Bellgrove, Hester, & Garavan, 2004; Braver, 2012; Stuss, Murphy, Binns, & Alexander, 2003; Unsworth, Redick, Lakey, & Young, 2010; Unsworth, 2015). Executive control recruits regions of the prefrontal cortex (PFC), as well as a wider network of brain regions, and is partially responsible for a variety of performance outcomes. For instance, executive control underlies performance on domain-specific executive functioning tasks (e.g., go/no-go tasks that test response inhibition) by maintaining goal-relevant information in either an anticipatory or reactive manner (Braver, 2012; Niendam et al., 2012; Unsworth et al., 2010).

Poor performance on tasks tapping into executive control has been related to poor attentional control (Kane & Engle, 2003; Unsworth et al., 2010). One paradigm used to study relations between executive and attentional control examines the association between

¹ Mild cognitive impairment represents a preclinical state of cognitive decline in older adults, and although not always indicative of imminent dementia, is often present in the prodromal stage of Alzheimer's disease.

performance on tasks tapping into executive control and the ex-Gaussian distribution parameters of reaction time (RT) tasks. RTs clustered toward the slower tail of the ex-Gaussian distribution tend to be more variable, reflecting fluctuations in attention, whereas RTs clustered toward the faster tail show less variability, and thus reflect better attentional control (De Jong, Berendsen, & Cools, 1999). One study using this paradigm used latent variable analysis to test whether performance on tasks requiring a high degree of executive control would relate to the distribution of slower RTs, faster RTs, or both. They found that performance on the executive control tasks were related to the distribution of slower RTs. Moreover, they found that performance on fluency tasks, requiring little executive control, was not related to either of the RT distributions (Unsworth et al., 2010).

In one study providing empirical support for the proposed link between IIV and executive control, West and colleagues (2002) found age-related increases in IIV on a task that required participants to press a button corresponding to a target digit (1, 2, 3, or 4), while ignoring a distractor letter (A, B, C, or D). In contrast, they found no age-related increase in IIV on a similar task that required minimal executive control (i.e., one in which no distractor letter was present). Similarly, Bellgrove et al. (2004) reported that IIV was a strong predictor of positive achievement in a sample of healthy young adults (18-36 years) performing a simple response inhibition task, and MacDonald, Hultsch, and Dixon (2003) found, in a sample of healthy older adults (54-89 years), that higher IIV was associated with poorer performance on an executive control task requiring retrieval of previously-learned information. Yet another study examined how IIV in performance on attentional control tasks was related to IIV in performance on a number of other domain-specific tasks in a sample of healthy young adults (18-35 years; Unsworth, 2015). The researchers reported that IIV on the attentional control tasks was related to IIV on working memory, fluid intelligence, and long-term memory tasks. Moreover, they found that IIV on the attentional control tasks was also

related to everyday attentional failures, and that these failures were linked to the participant's tendency to get distracted by internal thoughts, rather than by task-unrelated external stimuli. Taken together, these studies suggest that higher IIV might be reflective of an inability to maintain goal-directed information and focus, resulting in an increase in task-unrelated thoughts and associated lapses in attentional control.

Neuroimaging studies provide further evidence that lapses in executive control, and hence in task-related attentional processes, may be associated with higher IIV in cognitive performance (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008; Weissman, Roberts, Visscher, & Woldorff, 2006). Specifically, resting-state functional magnetic resonance imaging (fMRI) studies suggest that higher IIV may be associated with disconnections between the default mode network (DMN) and the task-related attentional network. The DMN is an interacting system of medial PFC, posterior cingulate, anterior temporal, and lateral parietal regions that are active in a highly correlated fashion, and in a distinct manner from other regions, when the scanned person is at rest. The task-related attentional network is a similar interacting system of PFC (dorsal, ventrolateral, and dorsomedial) and insular regions that are active (again in a highly correlated fashion, and in a distinct manner from other regions) during task performance. Kelly et al. (2008) argue that these two networks behave in a competitive manner. They based this argument on evidence from their fMRI study, which suggested that activity in the two was negatively correlated, with activation in one inhibiting activation in the other. Specifically, their participants performed a response inhibition task while being scanned, and data analyses indicated that smaller IIV on the task was associated with a strong negative correlation between activity in the two networks, whereas higher IIV was associated with a weak negative correlation.

A separate strand of neuroimaging research suggests that impaired functioning in frontal, prefrontal, and parietal regions underlying performance on focused attention,

sustained attention, and attentional control tasks is implicated in higher IIV on those tasks (Bunce et al., 2007; Jackson, Balota, Duchek, & Head, 2012; Stuss et al., 2003). One finding that has been consistent across a number of studies, sampling from a variety of populations and using a variety of imaging methods, is the association between measures of IIV and posterior cingulate functioning. Specifically, higher IIV has been associated with increased micro-structural white matter changes in the posterior cingulate and decreased posterior cingulate activation in samples of healthy younger and older adults (Grydeland, Walhovd, Tamnes, Westlye, & Fjell, 2013; Jackson et al., 2012; Yarkoni, Barch, Gray, Conturo, & Braver, 2009), as well as with decreased posterior cingulate volume in those diagnosed with early AD (Jackson et al., 2012). Importantly, the posterior cingulate has high structural and functional connectivity with networks involved in both internally and externally directed attention, and appears to play a pivotal role in executive control (Garrison et al., 2013; Leech & Sharp, 2013; Wen, Liu, Yao, & Ding, 2013).

Other studies have reported significant associations between frontal and parietal activity and higher IIV (MacDonald, Li, & Bäckman, 2009). For instance, two fMRI studies, both using samples of healthy male participants, found that higher IIV on an executive control task was associated with (a) decreased activation in the left pregenual anterior cingulate (Johnson et al., 2015), and (b) increased activation in right inferior parietal and thalamic regions, as well as in the right inferior frontal and bilateral middle frontal regions (Bellgrove et al., 2004). Similarly, studies using clinical samples with frontal lesions (Stuss et al., 2003) and frontal lobe dementia (Murtha, Cismaru, Waechter, & Chertkow, 2002) have found higher IIV on executive control and RT tasks in these individuals than in those with non-frontal lesions and AD, respectively.

A smaller set of neuroimaging studies, of wider scope, reports no significant associations between IIV and grey matter activity, but significant associations between IIV

and frontal, temporal, and parietal white matter tract volume, as well as inter- and intra-hemispheric corticocortical micro-structural white matter integrity (Moy et al., 2011; Ullen, Forsman, Blom, Karabanov, & Madison, 2008). Those studies, then, highlight the importance of studying white matter changes when attempting to understand the neural bases of higher IIV.

Indeed, there is now consistent and convincing evidence that disruptions in white matter integrity are related to higher IIV (Anstey et al., 2007; Bunce et al., 2007; Jackson et al., 2012; Moy et al., 2011; Stuss et al., 2003; Ullen et al., 2008). However, it is still unclear precisely which white matter changes are related to higher IIV. Some studies have focused on the relationship between IIV and micro-structural white matter changes (see, e.g., Grydeland et al., 2013; Lin et al., 2014; Moy et al., 2011), whereas others have focused on the relationship between IIV and macro-structural white matter changes, such as white matter hyperintensities (Bunce et al., 2007), lesions (Stuss et al., 2003), and volume (Jackson et al., 2012). Regardless of the type of white matter changes, these studies have emphasised the role of functional connectivity within the brain in stable task performance (Ullen et al., 2008; Walhovd & Fjell, 2007).

More specifically, these studies emphasize that the breakdown in white matter pathways, as a result of axonal degeneration and/or myelin thinning (as seen on, for instance, diffusion tensor magnetic resonance imaging (DTI)), leads to greater lapses in executive and attentional control and thus higher IIV (for two slightly different explanations of this view, see Jensen, 1992 and MacDonald et al., 2006). Within this general theoretical framework, decreased connectivity leads to difficulties in activating multiple brain areas in a coordinated way, thus explaining why higher IIV is seen especially on tasks that tap into executive functions (Bellgrove et al., 2004; Moy et al., 2011). Because there is evidence that sustained attention may rely in part on the functional connectivity of the brain (see, e.g., Morecraft,

Geula, & Mesulam, 1993), this theory is also consistent with the idea that lapses in attentional control result in higher IIV.

In further support of the proposed relationship between some index of white matter change and IIV, the U-shaped function of IIV across the lifespan mirrors the inverted U-shaped function of white matter volume throughout human development. That is, decreased white matter volume is associated with relatively high IIV in children due to brain immaturity, and in older adults due to age-related neurodegeneration (MacDonald et al., 2006). Consistent with this suggestion, Tamnes and colleagues (2012) found that age-related increases in white matter integrity were associated with lower IIV on an RT task in a sample of healthy children (8-19 years). Taken together with the empirical findings described above, there is strong evidence that white matter changes may underlie increased IIV, and that connections between and within brain regions supporting executive and attentional control may play a particularly important role.

A common clinical observation, supported by research findings, is that executive dysfunction, as well as impairments in focused and sustained attention, is present in early AD (Baudic et al., 2006; Faust & Balota, 1997; Parasuraman & Haxby, 1993; Rizzo, Anderson, Dawson, Myers, & Ball, 2000; Sgaramella et al., 2001). Furthermore, Rapp and Reischies (2005) showed that baseline performance on tasks assessing executive control and attention discriminated between those who went on to develop AD 4 years later and those who did not. The overlap between the cognitive correlates of IIV and AD, along with findings that IIV is relatively higher in AD, provide strong support for studying IIV in AD samples.

White Matter Markers of Alzheimer's Disease Pathology

A general consensus has emerged that there are both grey and white matter disruptions during the preclinical stages of AD (Braak, Heiko, Tredici, Schultz, & Braak, 2000; Douaud et al., 2013; Johnson et al., 2015; Zhang, Xu, Zhu, & Kantarci, 2014). Many

studies have found evidence for white matter disruptions during the prodromal stages of the disease (Braak & Braak, 1991; Johnson et al., 2010; Zhang et al., 2014). Douaud et al. (2013) found, at baseline, greater white matter damage in the body of the fornix and in the centrum semiovale (i.e., at the location where the superior longitudinal fasciculus and corticospinal tracts cross) in those who went on to develop AD 2 years later compared to those who did not. These findings have been replicated and extended in other studies examining both macro- and micro-structural white matter damage in those with aMCI who convert to AD within 3 years compared to healthy controls or to those with aMCI who do not convert to AD within 3 years. Specifically, these studies have found reduced white matter structural integrity in tracts connecting limbic regions, as well in limbic-temporal white matter connections, in those who convert compared to healthy controls (Hong et al., 2013; Lindemer et al., 2015; Sun et al., 2014) and to non-converters (Rémy, Vayssière, Saint-Aubert, Barbeau, & Pariente, 2015).

Similarly, studies examining white matter damage in those with mild-to-moderate AD have found significant white matter damage in numerous white matter tracts (e.g., those traversing limbic, parietal, and frontal regions, and those forming fronto-occipital-parietal and temporo-occipital connections), as well as regions of the corpus callosum and brainstem, compared to age-matched healthy controls (Agosta et al., 2011; Hong et al., 2013; Serra et al., 2010; Sun et al., 2014; Weiler et al., 2015). A recent review of the literature on diencephalic connections in AD, as imaged using DTI, emphasised the role of the fornix, which links the medial temporal lobes and diencephalon, in the AD pathological process (Acosta-Cabronero & Nestor, 2014). Similarly to grey matter damage, these studies suggest a diffuse pattern of white matter degeneration in AD, starting in limbic and deep brain regions, and extending into most of the major white matter tracts in the brain, with special emphasis on limbic connections.

Apart from the later degradation of cortical association fibres as a result of grey matter atrophy, there is evidence suggesting that the micro-structural white matter changes that occur early in AD do so independently of the effects of loss of grey matter and of vascular pathology (Agosta et al., 2011; Gold, Powell, Andersen, & Smith, 2010; Sachdev, Zhuang, Braidy, & Wen, 2013; Yoon et al., 2011). White matter changes similar to those seen in AD are present in the brains of patients with pre-clinical AD, and some of these changes differ from the gross white matter changes caused by vascular pathology (de la Monte, 1989). Numerous independent studies report that cognitively normal participants with high genetic risk for AD present with significant white matter changes, with no differences in grey matter volume, when compared to cognitively normal individuals with low genetic risk for AD (Gold et al., 2014; Heise, Filippini, Ebmeier, & Mackay, 2011; Molinuevo et al., 2014; Selnes et al., 2012).

One longitudinal study found, at baseline, significant reductions in white matter integrity in areas similar to those seen in AD in a cognitively normal sample who went on to develop aMCI 2 years later, compared to those who did not go on to develop aMCI. Of note here is that the analyses in that study detected no significant between-group differences in any grey matter structures at baseline (Zhuang et al., 2012). In a similarly-designed study, Rieckmann et al. (2016) examined the association between markers of AD risk at baseline and micro-structural white matter changes 2.6 years later in a sample of healthy older adults. They found that baseline measures of amyloid burden were associated with greater micro-structural white matter changes in the parahippocampul cingulum, and that some of these changes were independent of changes in hippocampal volume due to amyloid burden. The growing body of evidence for an independent role of white matter in AD neurodegeneration has provided the impetus for more thorough investigations of the types of white matter

changes (e.g., demyelination or axonal degeneration) that may be involved in the disease process.

Diffusion tensor imaging and micro-structural white matter changes. Diffusion-weighted MRI (DWI) was first described in the mid-1980s (see, e.g., Le Bihan et al., 2001). The basic principle behind DWI relates to the random movement of water molecules (viz., the *distribution of displacement*). This term describes the direction and distance of the movement of water molecules from a central point over a specific time period. Without any barriers, the distribution of displacement of water molecules over time is completely random. However, the presence of physical barriers (e.g., such as those found in organic tissue) affects the distribution of displacement such that it is no longer random. Measuring the distribution of displacement of the water molecules in and around organic tissue therefore provides information on the structure of the surrounding tissue. Using a combination of traditional MRI techniques and bipolar magnetic field gradient pulses, DWI is able to obtain a six-dimensional representation of the distribution of displacement within a single tissue voxel in the human body. This representation provides unique information about the location, density, and integrity of the surrounding tissue.

DTI is a variant of DWI. Originally developed to better measure the direction of water displacement within a tissue voxel, it has become one of the most common methods used to examine micro-structural white matter changes in both clinical and healthy populations (Alexander, Lee, Lazar, & Field, 2007; Bammer, 2003; Winklewski et al., 2018). Using a series of diffusion-weighted images, DTI yields three diffusivity parameters (λ_1 , λ_2 and λ_3) corresponding to parallel (λ_1) and perpendicular (λ_2 and λ_3) diffusivity. *Axial diffusivity* (DA) describes the overall displacement parallel to the axon, whereas *radial diffusivity* (DR) describes the overall displacement perpendicular to the axon. Because white matter is highly directional (*anisotropic*), one expects highly directional water diffusion along the direction of

the tissue fibre in healthy white matter. Hence, non-directional (*isotropic*) diffusion in white matter is indicative of a loss of structural integrity or density.

These measurement bases allow DTI to yield two main determinants of white matter integrity. *Fractional anisotropy* (FA) describes the total degree of water diffusion along the tissue fibre, and is represented as a scalar value between 0 (*isotropic*) and 1 (*anisotropic*). *Mean diffusivity* (MD), on the other hand, describes the average water diffusion within a tissue voxel in both directions, and represents the overall displacement of molecules and presence of obstacles to water diffusion.

Relatively high FA and lower MD values are associated with healthy white matter. FA values in healthy human white matter are usually > 0.2 , while MD values in healthy white matter vary depending on the tissue organisation within a particular voxel (Mori & Zhang, 2006). Although DTI parameters should always be interpreted with caution, many studies suggest they can indicate different kinds of changes in tissue micro-structure (Alexander et al., 2007; Soares, Marques, Alves, & Sousa, 2013). Relatively low FA values have consistently been found in a number of pathological processes known to affect the structural integrity of white matter. Due to its non-specific nature, though, the specific kind of micro-structural damage reflected by FA values has not yet been determined (Alexander et al., 2007). On the other hand, relatively higher MD in the absence of lowered FA often indicates a breakdown in myelin integrity or density (Alves et al., 2012). In addition, multiple animal studies have found relatively high DR values in experimentally induced demyelination, with little to no change in DA values (Song et al., 2002; Sun et al., 2006). Conversely, animal studies, as well as a collection of human studies, have found relatively low DA values to be associated with a greater degree of axonal damage (Gold, Johnson, Powell, & Smith, 2012; Sun et al., 2006). For a further explanation on DTI interpretations, see Alexander et al.

(2007). For a brief technical review on inferring the type of tissue changes associated with DA and DR, see Winklewski et al. (2018).

Micro-structural white matter changes in Alzheimer's disease. The exact mechanisms of micro-structural white matter changes in AD are still being investigated. Sjöbeck, Haglund, and Englund (2005) suggest that myelin changes during AD progression result from a series of minor ischemic events that lead to a loss of oligodendrocytes and subsequent reductions in myelin integrity. This theory stands in contrast to the retrogenesis theory of white matter degeneration in AD (Reisberg et al., 1999). The latter postulates that late-myelinating axons with a smaller axonal circumference are more susceptible to damage arising from a number of sources, including brain oxidation. Hence, the proposal is that these late-myelinating axons are the first to be affected in the AD degenerative process. For a review of this theory, see Alves et al. (2015).

Several longitudinal studies have used DTI to examine micro-structural white matter changes across AD progression (see Amlien & Fjell, 2014 and Sexton, Kalu, Filippini, Mackay, & Ebmeier, 2011 for two slightly different reviews). For example, Kitamura et al. (2013) reported finding significant decreases in FA and increases in DR, but no changes in MD or DA, over an 18-month period in a sample of participants with mild AD at baseline. Another longitudinal study replicated this finding, using a sample of patients diagnosed with very mild to mild AD (Acosta-Cabronero, Alley, Williams, Pengas, & Nestor, 2012). Conversely, other longitudinal studies have reported finding significant increases in MD, but no changes in FA, over a 12-month period in samples of participants with mild AD at baseline (Firbank et al., 2016; Nowrangi et al., 2013). These longitudinal studies are suggestive of both axonal breakdown and a loss of myelin integrity influencing longitudinal micro-structural white matter integrity loss in AD.

Regardless of the exact mechanism of white matter pathology, and whether it relates to loss of myelin integrity or axonal degeneration, there is evidence from animal and human neuropathological studies suggesting that a loss of micro-structural white matter integrity might be a causal factor in AD neuropathology (Desai et al., 2009; Stokin et al., 2005). One such study, using a mouse model of AD, found that disruptions in axonal transport tended to result in more axonal damage, distinct from that seen in the normal AD process, more than 1 year before the presence of any disease-related pathology. This early axonal damage was linked to disruptions in axonal transport, resulting in further axonal damage and triggering an increase in production of amyloid- β peptides and in subsequent amyloid deposition (Stokin et al., 2005). Importantly, the authors found similar early axonal damage to that seen in the mouse model in a human sample with early AD.

In support of the above, another animal study found evidence of myelin disruption in the hippocampus and entorhinal cortex of mice prior to the formation of the neurofibrillary tangles and amyloid- β plaques that are characteristic of AD pathology (Desai et al., 2009). The authors of that study suggested that the observed myelin disruption might occur as a result of damage to oligodendrocytes, which are known to play a role in the myelination process. They further speculate that this damage results in a loss of myelination, and a subsequent decrease in axonal transport, resulting in axonal damage and the cognitive deficits seen in early AD.

Taken together, these human and animal neuropathological studies suggest that micro-structural white matter changes occur early in AD and might be a causal factor in the neuropathology characteristic of that neurodegenerative disorder.

Distribution of micro-structural white matter integrity loss in Alzheimer's disease. Despite a growing body of evidence indicating early compromise of micro-structural white matter integrity in AD, it is unclear exactly which brain regions might be affected

consistently by those changes. In an attempt to provide some clarity around these issues, Sexton et al. (2011) conducted a meta-analysis of studies that used region of interest (ROI) analyses to examine white matter changes in AD and MCI. Their analysis consisted of 41 studies published between 1980 and February 2010, all of which compared an AD/MCI group to a group of matched healthy controls. They selected only studies that used manual tracing, masking, or tractography to examine pre-defined ROIs. Subsequent analyses included a total of 2026 participants: 617 AD patients, 494 MCI patients, and 915 controls. Their quantitative summary found that, in AD/MCI participants relative to controls, (a) FA was decreased in all brain regions except for internal capsule and parietal areas; (b) the largest effect sizes for FA were in the uncinate fasciculus, superior longitudinal fasciculus, and posterior sections of the cingulum; (c) medium effect sizes for FA were found in the genu and splenium of the corpus callosum, as well as anterior sections of the cingulum; and (d) MD was increased in all brain regions, with the largest effect sizes in the hippocampus as well as in other temporal and parietal areas.

Subsequent studies also using ROI analyses have replicated these findings. Specifically, damage to micro-structural white matter of AD patients has consistently been found in the hippocampus, fornix, cingulum, right inferior longitudinal fasciculus, and areas of the corpus callosum, when compared to patients with MCI or to healthy controls (Alves et al., 2012; Hong et al., 2013; Lee et al., 2015; Nowrangi et al., 2013; Tang et al., 2017; Tang, Qin, Zhu, & Miller, 2017; Zhang et al., 2014). In one ROI study suggesting that such white matter changes appear preclinically, researchers found increased micro-structural white matter damage in the left fornix and right inferior longitudinal fasciculus (R-ILF) in a group of healthy adults with cerebrospinal fluid biomarkers for AD, compared to a group of healthy adults with no such biomarkers (Gold et al., 2014).

Other studies using whole-brain analytic methods, rather than ROI analyses, to study white matter changes in AD have replicated the patterns of data described above. Specifically, these studies have found, in samples with AD, aMCI or MCI, but not in healthy controls, evidence for micro-structural white matter damage in the hippocampus, fornix, cingulum, inferior longitudinal fasciculus, and areas of the corpus callosum (Kim et al., 2015; Wang & Wang et al., 2015). Others using the same analytic method have found additional micro-structural white matter damage in the superior longitudinal fasciculus, anterior thalamic radiations, cortico-spinal tract, and the inferior fronto-occipital fasciculus in those with AD relative to healthy controls (Rémy et al., 2015; Teipel et al., 2014). In one whole-brain analysis study suggesting that white matter changes appear preclinically, researchers found such changes in the corona radiata, internal capsule, left fornix, superior longitudinal fasciculus, uncinate fasciculus, inferior fronto-occipital fasciculus and areas of the corpus callosum in those with preclinical AD compared to a control group with no AD biomarkers (Molinuevo et al., 2014).

In summary, although it is still unclear which white matter changes occur first in the AD process, and where they occur, the studies reviewed above suggest strongly that white matter changes may serve as a pre-clinical marker of AD.

Rationale, Aims, and Hypotheses

Taken together, the studies reviewed above provide convincing evidence for both a cognitive and neural overlap between IIV and AD. This evidence, along with consistent evidence that IIV is relatively higher in individuals with AD, and that higher IIV is often a marker of pathological cognitive decline in older adults, provides sufficient reason for using an AD population to further study the neural mechanisms underlying IIV.

Although the findings discussed above highlight the possible utility of studying the relationship between IIV and white matter changes in AD, only one published study has

examined this relationship. Jackson and colleagues (2012) used a conventional MRI ROI approach to study total cerebral white matter volume, as well as superior frontal gyrus, ventral and dorsolateral PFC, anterior and posterior cingulate, precuneus, and inferior parietal lobe volume, using the primary visual cortex as a control ROI. They found a significant positive correlation between loss of white matter volume in the superior frontal gyrus, posterior cingulate, precuneus, and ventral and dorsolateral PFC, and reaction time IIV (IIV_{RT}) in a sample of early-stage AD patients and healthy controls. They found no significant correlations between white matter volume in the anterior cingulate, inferior parietal lobule, or primary visual cortex and IIV_{RT} within either group. Furthermore, the correlation between total cerebral and regional white matter volume and IIV_{RT} was not significantly stronger in patients than in controls, even though IIV_{RT} was higher in patients than in controls. It is possible that the lack of the predicted stronger correlation between white matter volume and IIV_{RT} in patients was due to the specific sample of early-stage AD patients these researchers used. On average, those participants had relatively high education levels and socio-economic status, and thus may have had high enough cognitive reserve to compensate for potentially impairing effects of the observed organic changes on cognition (Tucker & Stern, 2011).

The current study aims to extend the findings of Jackson et al. (2012) by examining the relationship between IIV_{RT} and micro-structural white matter changes, as indexed by DTI, in a sample of older adults with mild-to-moderate AD and a group of age-matched healthy controls. It tested the hypothesis that IIV_{RT} contributes significantly and independently from age, sex, level of education, household income and mean RT latencies to micro-structural white matter changes in a group of AD patients and age-matched healthy controls.

Methods

Design and Setting

This study examined the association between white matter changes and IIV_{RT} in samples of (a) patients diagnosed with possible or probable AD, in the mild-to-moderate stages of the disease, and (b) demographically matched healthy controls. It forms part of a larger longitudinal research program that tracks the progression of cognitive decline in AD (Christ et al., 2018), using RT outcome data from that parent study's neuropsychological test battery. Furthermore, DTI data for each participant (which were used to index white matter changes) were obtained from an MRI scan that took place not more than 6 months after cognitive testing.

The study used a measurement-burst design (Fiske & Rice, 1955). Such a design consists of repeated assessments on the same task over multiple time-frames. Specifically, I obtained from each participant a measurement of IIV for each of two administrations of two different RT tasks (simple and choice) on each of 3 days of testing (see Figure 1). Each administration of each RT task consisted of 30 trials, although significant correlations between frontal white matter changes and IIV_{RT} have been found using as few as 20 trials per administration (Bunce et al., 2013). The six administrations of each of the RT tasks were used to calculate net IIV for both the simple and choice tasks, for each of the participants.

Previous studies investigating the relationship between white matter changes and IIV have only measured IIV in micro-time (i.e., minutes or hours; see, e.g., Jackson et al., 2012; Moy et al., 2011). Although there is evidence that the time-frame across which IIV is measured plays an important part in the measurement outcome (Ram & Gerstorf, 2009), no published study has assessed white matter changes and IIV in macro-time (e.g., days, weeks). A measurement-burst design consisting of multiple repeated assessments on the same task over multiple time-frames, and calculating net as opposed to time-structured IIV, means one

is better able to ensure that the variance being measured is a reflection of each individual's true variability, rather than a reflection of group and time-on-task effects such as learning or fatigue (Ram & Gerstorf, 2009).

All cognitive testing took place in a private room in the Geriatric Unit at Groote Schuur Hospital (GSH) in Cape Town, or in a quiet room in the participant's home, depending on what was more convenient for him/her. MRI scans were taken at the Cape University Body Imaging Centre (CUBIC), located at GSH.

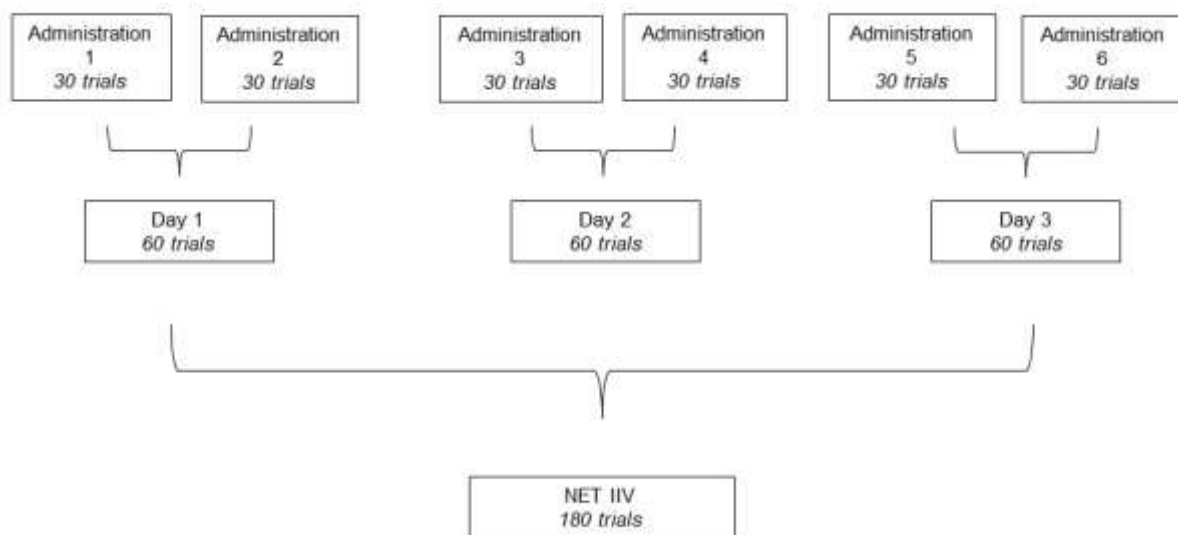


Figure 1. Measurement-burst design used to collect reaction time data on the simple and choice reaction time tasks.

Participants

Eligibility criteria. These were identical to those applied in the parent study.

Individuals were eligible for participation if they (a) had a readily available and accessible medical history; (b) were aged 55 years or older; (c) had basic English literacy (i.e., ability to speak, read, and write fluently in that language); and (d) could identify a close relative or informant who could provide collateral information (e.g., regarding cognitive changes in clinical participants).

Individuals were excluded from participating if they reported or if their medical records showed: (a) uncontrolled hypertension, diabetes mellitus, or another cardiovascular disease; (b) a diagnosis of HIV/AIDS; (c) a current diagnosis of a psychiatric illness; (d) a history of stroke or other major neurological disorder; (e) a history of alcohol or drug abuse or heavy smoking (> 20 cigarettes per day). Individuals with a score > 9/30 on the Geriatric Depression Scale (GDS; Yesavage, Brooks, Taylor, & Tinklenberg, 1993) were also excluded from participating. These criteria were applied because of their known effects on cognitive performance in AD (Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004; Bernardin, Maheut-Bosser, & Paille, 2014; Etkin, Gyurak, & O'Hara, 2013; Gorelick et al., 2011; Grant, Contoreggi, & London, 2000; Hagen et al., 2016; Jokinen et al., 2015; Makin, Turpin, Dennis, & Wardlaw, 2013; Rincon & Wright, 2013; Swan & Lessov-Schlaggar, 2007; van den Kommer, Tessa N et al., 2013; Wang & Blazer, 2015). Participants with a Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) score of less than 12 were also excluded. This criterion was applied to ensure that individuals with severe cognitive impairment would not be part of the sample.

AD patients. Clinical participants ($n = 29$) who met criteria for mild-to-moderate stage possible or probable AD were recruited into the parent study from the GSH Memory Clinic, which is administered by the University of Cape Town's Division of Geriatric

Medicine and the Albertina and Walter Sisulu Institute of Ageing in Africa. Patients with suspected age-related memory disorders are referred to the Memory Clinic from primary healthcare institutions in Cape Town and surrounding areas (Kalula et al., 2010). Potential clinical participants were approached by one of the Memory Clinic staff members, who provided them with information about the study (see Appendix A).

All clinical participants met the Diagnostic and Statistical Manual – Fourth Edition (DSM-IV; American Psychiatric Association, 2000) criteria for AD (see Appendix B). They also fell within the mild-to-moderate range on the Clinical Dementia Rating (CDR) scale (see Appendix C). Diagnosis was finalised by the team of health professionals working at the Memory Clinic. That team includes individuals from the fields of geriatric medicine, psychiatry, neurology, and neuropsychology.

Of the 29 clinical participants recruited into the study, data from 16 (12 women) formed part of the final statistical analyses. Of these 16 participants, 15 were diagnosed with possible or probable AD and one was diagnosed with mixed AD and vascular dementia.

Attrition that led to the loss of data from 13 participants is accounted for as follows:

- (a) 5 individuals were ineligible to continue after the screening phase (i.e., they did not meet the eligibility criteria described above);
- (b) 2 individuals (a 71-year old woman and a 78-year-old woman) were lost to follow-up after the second wave of testing;
- (c) 2 participants (an 87-year-old woman and a 78-year-old woman) did not complete the scan due to feelings of claustrophobia while in the scanner;
- (d) 1 participant (a 77-year-old man) did not consent to the scanning phase of the study;
- (e) 2 datasets (one from a 65-year old man, and the other from a 74-year-old man) were removed due to a high number of missing slices;

- (f) the dataset from a 79-year-old man was removed because the patient evinced extensive brain atrophy;

Healthy controls. I recruited control participants ($n = 35$) from various establishments in Cape Town and surrounding areas. Together with the parent study's principal investigator (PI), I searched for seniors' clubs, retirement centres, and doctor's offices in the areas surrounding GSH. We contacted doctor's secretaries and chairpeople of the identified establishments and provided them with details of the research study. We then followed necessary protocols for recruiting individuals from each establishment. These protocols involved setting up appointments via the chairpeople of the identified establishments and conducting informal information sessions during which we enquired whether individuals would participate in the research. Alternatively, they involved distributing flyers (see Appendix D) to the identified establishments and following up with individuals who contacted us expressing an interest in participating. I also recruited some of the healthy relatives who accompanied the clinical participants to their testing sessions.

Of the 35 control participants recruited into the study, data from 20 (14 women) formed part of the final statistical analyses. Attrition that led to the loss of data from 15 participants is accounted for as follows:

- (a) 7 individuals were ineligible to continue after the screening phase (i.e., they did not meet the eligibility criteria described below);
- (b) 2 participants withdrew from the study following the screening phase;
- (c) 1 participant, a 73-year-old woman, was lost to follow-up at the second wave of testing;
- (d) 1 participant, a 75-year-old-woman, withdrew from the study after the second wave of testing;

- (e) 2 participants were ineligible for the scanning phase of the study: an 88-year-old woman had had a pacemaker implanted, and a 73-year-old woman was unable to lie in the correct position for the duration of the scan
- (f) 2 participants (a 66-year old woman and a 76-year-old woman) did not consent to the scanning phase of the study.

Figure 2 provides a complete breakdown of participant attrition throughout each phase of the study.

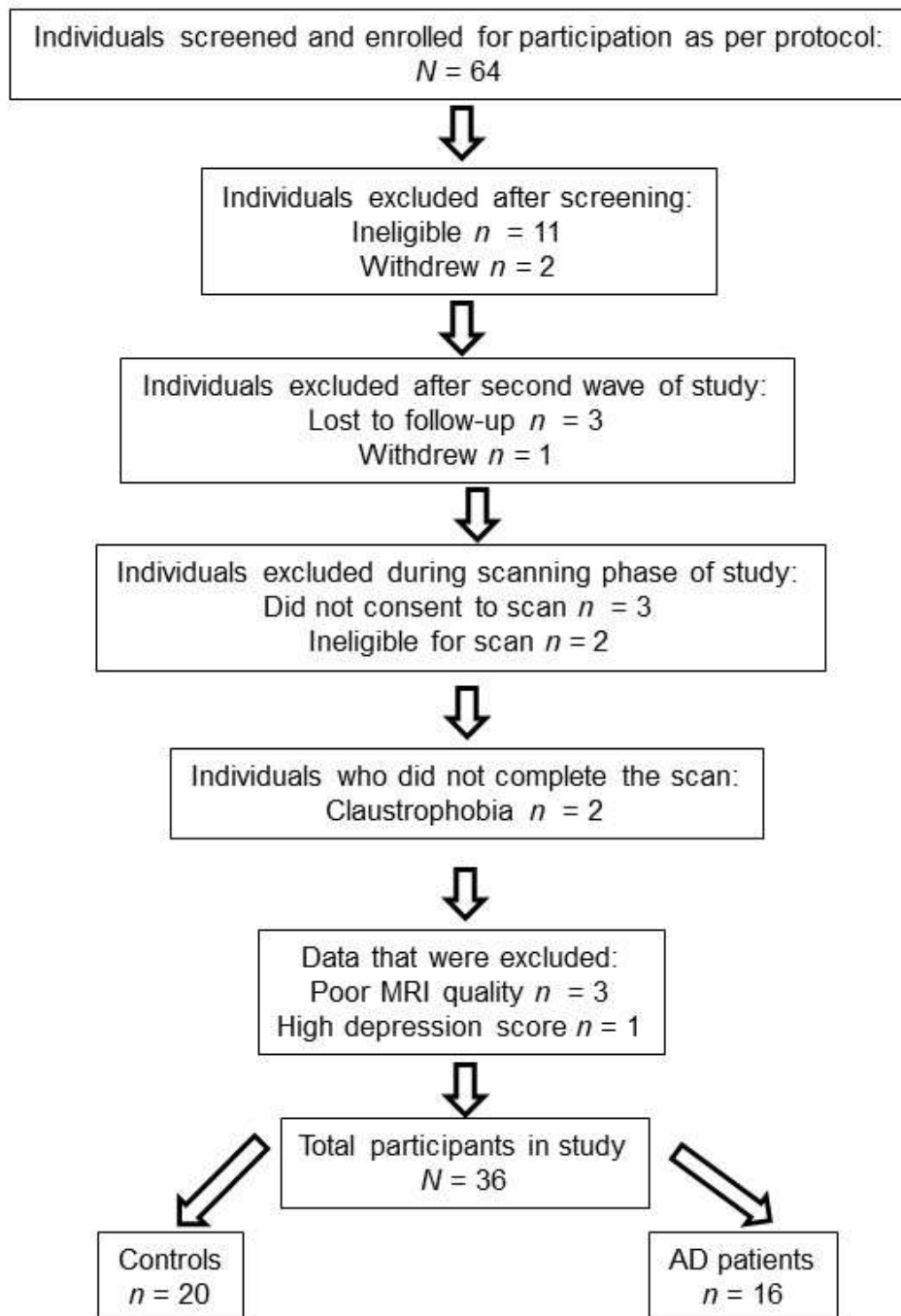


Figure 2. Diagram illustrating the number of participants (healthy controls and AD patients) enrolled in the study, as well as details relating to exclusion.

Measures

Screening measures. These measures helped ensure participants met the eligibility criteria described above.

Geriatric Depression Scale (GDS). This 30-item self-report instrument is a valid and reliable measure of depressive symptoms in the elderly (Yesavage et al., 1983). The GDS can accurately distinguish between those who are depressed and those who are not depressed, in both healthy individuals and those with dementia (Goodarzi, Mele, Roberts, & Holroyd-Leduc, 2017; Li et al., 2015). The GDS developers report that it has demonstrated good convergent validity, correlating at .84 with the Self-Rating Depression Scale (Zung, 1965) and at .80 with the Hamilton Rating Scale for Depression (Hamilton, 1960). The developers also report a median correlation of .56 between the 30 items on the scale and the corrected-item total score, an inter-item correlation of .36, and an alpha coefficient of .94 for overall internal consistency. Furthermore, they report good split-half reliability ($r = .94$) and good test-retest reliability ($r = .85$; Yesavage et al., 1983). The GDS has been used successfully in South African clinical practice and research studies (see, e.g., Dorsey, Rodriguez, & Brathwaite, 2002).

Cambridge Examination for Mental Disorders of the Elderly - Revised (CAMCOG-R). The CAMCOG-R, a multi-dimensional assessment of cognitive functioning, is part of the Cambridge Examination for Mental Disorders of the Elderly – Revised (CAMDEX-R; Huppert, Brayne, Gill, Paykel, & Beardsall, 1995). It is commonly used as a screening tool for dementia, and has demonstrated high test-retest and inter-rater reliability (O'Connor, Daniel W. et al., 1989). We used a version of this measure that has been adapted for use in South African populations, and that has been used successfully in previously published studies from our laboratory (Christ et al., 2018; James, Grace, Thomas, & Combrinck, 2015).

Mini-Mental State Examination (MMSE). This 19-item instrument (Folstein et al., 1975), one of the most commonly used dementia screening measures, is administered as part of the CAMCOG-R. In the current study, it was used to measure the severity of overall cognitive impairment. The MMSE has good inter-rater reliability, internal consistency, and test-retest reliability (Baek, Kim, Park, & Kim, 2016; Boban et al., 2012; Folstein et al., 1975; O'Connor et al., 1989). It has been used successfully in several previously published South African studies (Adam, Godlwana, & Maleka, 2016; Christ et al., 2018; James et al., 2015; Ramlall, Chipps, Pillay, & Bhigjee, 2013).

Reaction time measures. Reaction time (RT) is typically considered to be the time between the presentation of a stimulus and the beginning of the participant's response to that stimulus. RT tasks are particularly effective measures of IIV because, given that outcomes can be measured precisely (e.g., in milliseconds) using computer software, they are sensitive to even minor performance fluctuations. RT tasks are also less sensitive than accuracy-based tasks to practice effects, and so can be administered multiple times within one testing session. These characteristics allow for the examination of IIV_{RT} within a single testing session. Hence, RT tasks have been used to measure IIV in many previously published studies (Anstey et al., 2007; Fiske & Rice, 1955; Hultsch et al., 2000; Jackson et al., 2012; MacDonald et al., 2003; Moy et al., 2011; Nilsson, Thomas, O'Brien, & Gallagher, 2014).

I computed IIV_{RT} by measuring performance variability on the Simple Reaction Time (SRT) and Choice Reaction Time (CRT) subtests of the Cambridge Neuropsychological Test Automated Battery (CANTAB; Fray, Robbins, & Sahakian, 1996). These subtests were administered on a Windows 8.1 touchscreen device, with a 10.1" screen size, and carrying the CANTAB-minimum specifications (1 GHz processor, with 2 GB RAM and 1 GB free disc space). Two USB ports, as well as sound and display adapters compatible with Microsoft DirectX 9.0 or later, built-in speakers, and a press pad were also used.

The CANTAB is a widely published computerised neuropsychological test battery and has been reviewed extensively (Égerházi, Berecz, Bartók, & Degrell, 2007; Lowe & Rabbitt, 1998; Wild, Howieson, Webbe, Seelye, & Kaye, 2008; Zygouris & Tsolaki, 2015). Furthermore, the CANTAB SRT and CRT tasks have high test-retest reliabilities, with intraclass coefficients of .80 and .79, respectively (Lemay, Bédard, Rouleau, & Tremblay, 2004; Lowe & Rabbitt, 1998).

The SRT task requires participants to monitor, while holding down a press pad with the index finger of the dominant hand, the centre of a computer screen for the appearance of a yellow dot inside a white circle. When the dot appears, they must release the press pad and touch inside the white circle on the screen, with the index finger of the dominant hand, as quickly as possible. The stimulus was present on the screen for 250ms and participants had 5s to respond to the stimulus before the next trial started, with an inter-stimulus delay of between 750 and 2250ms. The CRT task works similarly in that the participants monitor the centre of a computer screen for the appearance of a yellow dot inside a white circle, except the yellow dot can appear in any one of five white circles and they are required to select between these five circles when signalling the appearance of the yellow dot. Figure 3 provides a visual depiction of the tasks.

Participants were allowed to practice each of these tasks for 10 trials before testing began. They were permitted to move on to the testing phase after achieving 90% accuracy for the first practice phase or, failing that, after completing a second practice phase. The test phase for both RT tasks consisted of 30 trials, and took approximately 5 minutes per administration.

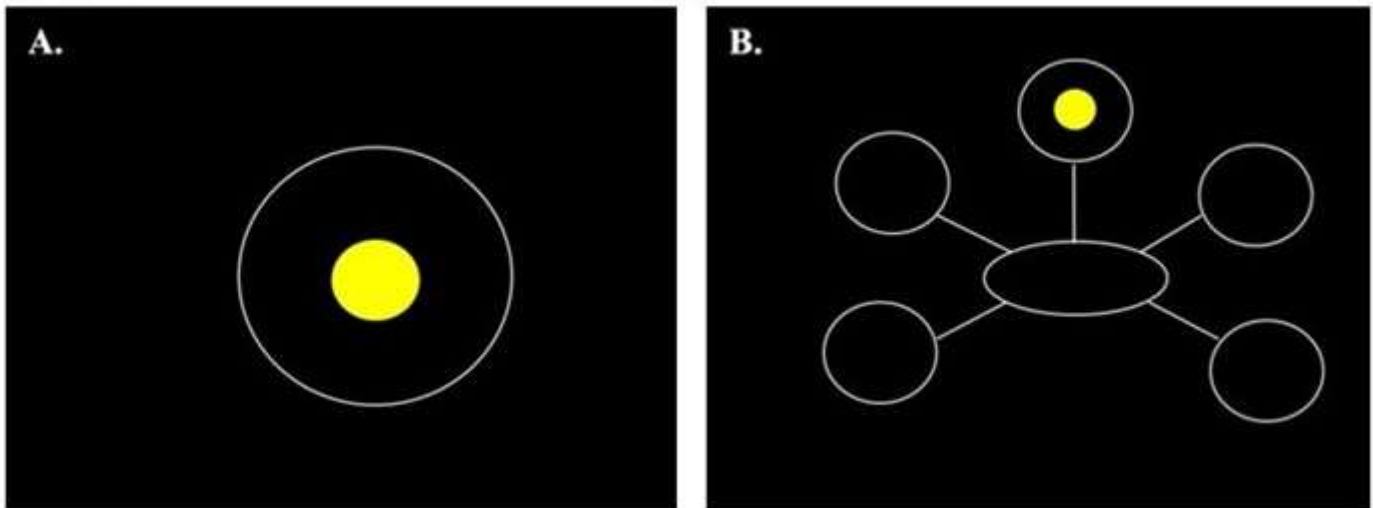


Figure 3A. Simple reaction time task of the Cambridge Neuropsychological Test Automated Battery.

Participants must release the press pad and touch inside the white circle as soon as the yellow dot appears.

Figure 3B. Choice reaction time task of the Cambridge Neuropsychological Test Automated Battery.

Participants must release the press pad and touch inside the upper-most white circle as soon as the yellow dot appears.

Diffusion tensor imaging acquisition. Each participant was imaged on a 3-Tesla Siemens Skyra MRI machine. Appendix E describes the parent study's MRI scanning protocol (total time = 45 min) from which the current DTI data were acquired. Two DTI acquisitions with alternating phase encoding directions (i.e., anterior–posterior and posterior–anterior (AP-PA)) and a T1-weighted high-resolution structural image were required to produce data relevant to the current study's aims.

Procedure

After an individual had given verbal consent for participation, either the parent study's PI, myself, or another graduate student scheduled the screening session.

Screening phase. After participants had signed the consent form (see Appendix F) and indicated they understood its contents, the PI of the parent study, myself, or another graduate student administered the screening tests. This administration occurred in a private examination room in the Geriatric Unit at GSH, or in a quiet room in the participant's home. Participants were assessed individually (although, in the case of clinical participants, a relative or friend remained present in the room). The test administrator calculated scores on each of the screening measures. These scores were then checked against the eligibility criteria by the PI of the parent study.

Individuals who did not meet the eligibility criteria described above were dismissed from the study after being given an appropriate explanation and debriefing. Those who were excluded from participation due to their GDS scores were given a note stating their score that they could give to their primary care physician. Those who were excluded from participation due to a DSM-IV diagnosis of major neurocognitive impairment were referred to the GSH Memory Clinic if they were not already patients there.

Individuals who met the eligibility criteria were scheduled for their first test session by the PI of the parent study, myself, or another graduate student.

Test phase. This phase was initiated within 30 days of screening. Individual face-to-face testing took place in a private room in the Geriatric Unit at GHS, or in the participant's home, depending on what was most convenient for him/her. For the clinical participants, a relative or friend remained present in the room for the testing session. The decision to allow a familiar person in the room during testing was made to avoid any unnecessary distress that could potentially impact on performance.

I collected IIV_{RT} data from three testing sessions. These sessions took place within a 2-week span, with seven days separating each test session (see Figure 4). During each of the three sessions, each participant completed two SRT and two CRT tasks. Each of these six tasks consisted of a 30-trial block (see Figure 1). Each session therefore comprised 60 trials. The order in which participants completed the RT tasks relative to the other tests they completed as part of the parent study was counter-balanced so as to avoid order effects. Participants always completed the SRT task before completing the CRT task, however.

Neuroimaging phase. All scans were conducted by a CUBIC MRI technician. Participants were asked during one of the three test sessions, or telephonically following the third such session, if they would agree to participate in this phase of the study. Those who verbally consented to undergo an MRI scan were asked to complete an MRI compatibility check-list either during the same telephone conversation or in person at the time of the scan (see Appendix G). Participants who were MRI compatible were booked for a scan on a date not more than 6 months after their third test session.

Upon arrival at the scanning centre, each participant was required to sign an MRI-specific consent form (see Appendix H) and to complete and sign a new MRI compatibility check-list. I explained each section of the consent form to them, and either I or an MRI technician answered any questions they had.

After signing the consent form, participants were taken into the scanning room and briefed on the coming procedure by an MRI technician. They were instructed that once inside the scanner they would need to keep their heads still. They were informed that the scanner would make a series of loud noises, and that during one of the sequences the bed would vibrate slightly. They were provided with a panic button and told that they should push it if they wanted the scan to stop immediately. Before lying down on the bed, participants were provided with noise-cancelling earplugs. Once participants were lying down, the MRI technician placed foam padding around their heads within the head coil. This helped reduce head movement during the scan. The bed then moved into the scanner. Once the door of the scanning room was closed, participants were informed that the scan was about to begin.

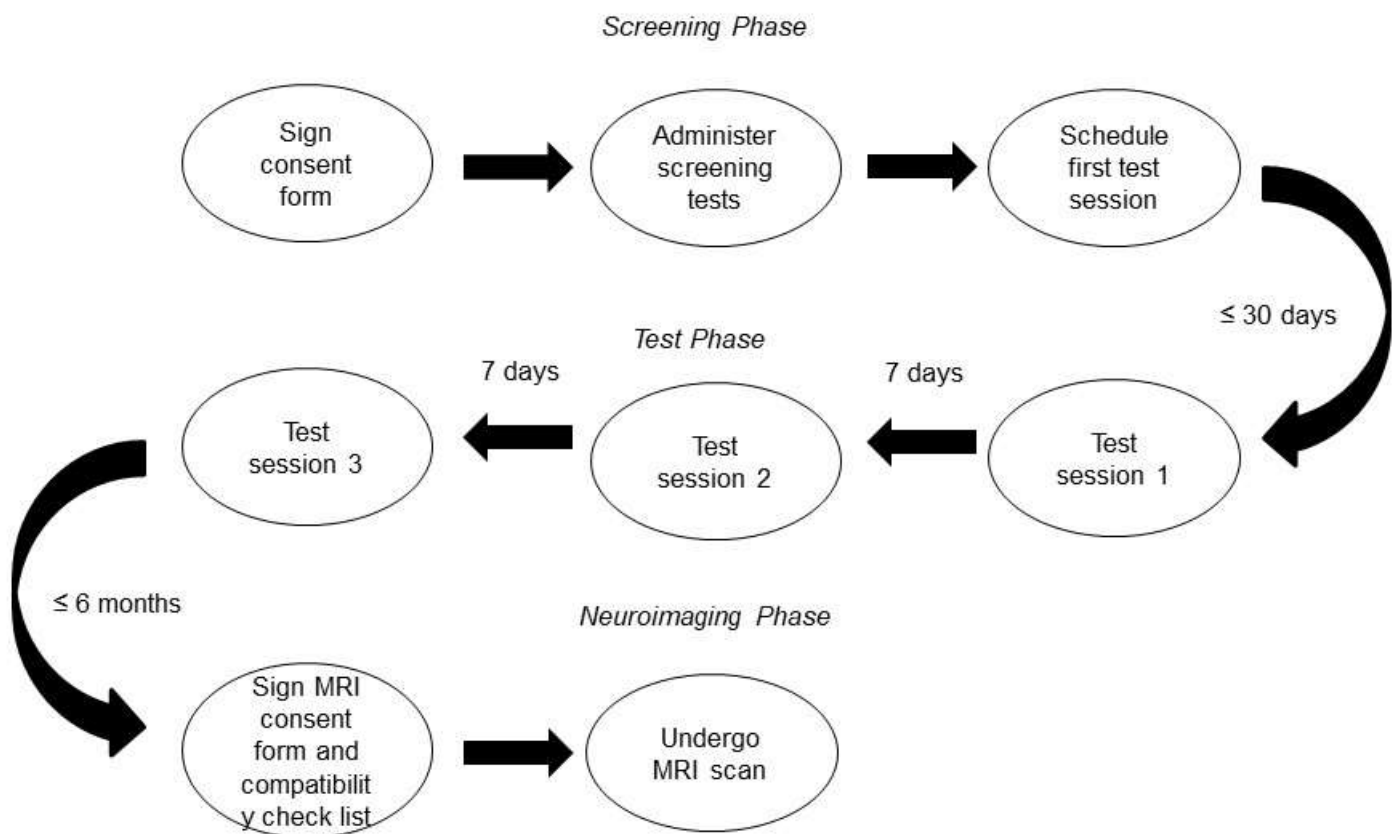


Figure 4. Timeline of the screening, test, and neuroimaging phase of the study.

Data Management and Statistical Analyses

Filtering SRT and CRT data. I examined data from the SRT and CRT tasks for outliers in order to remove from the final dataset responses that were either very slow or very fast. Very slow responses may have been the result of participants getting distracted, whereas very fast responses may have been the result of participants releasing the button accidentally or in premature anticipation of stimulus appearance. The upper limit for response times in each block was set at 3 *SDs* above the mean for that block, calculated separately for clinical and control groups. This limit is consistent with that set by other studies examining IIV_{RT} (see, e.g., Bielak et al., 2010; Hultsch et al., 2000). The lower limit for response times was set at 150 milliseconds. The decision around this criterion is based on evidence that it takes the average adult approximately 150 milliseconds to examine visual stimuli and decide on a response (Thorpe, Fize, & Marlot, 1996). Any responses occurring sooner than this cut-off were therefore excluded on the assumption that they did not involve any decision-making processes. There were 278 values that needed to be replaced, accounting for 1.96% of the RT dataset.

Values identified as outliers and missing values due to invalid responses were replaced using a multiple imputation technique. In SPSS (version 25.0), I selected the “Mersenne Twister” random number generator and fixed the starting point at 2 000 000. I then imputed the missing/outlier data points for each administration of both the SRT and CRT tasks for all participants. For each administration of each task, only the trials from that specific administration were used as predictors. I set SPSS to run five imputations, and manually calculated the average value across these five imputations for each of the missing/outlier data points. The average imputed value for each data point was then used to replace the missing value (Enders, 2017). This method was used instead of replacing

missing/outlier values with the mean value for each administration, as the latter method unavoidably reduces variability in the dataset.

Extracting intraindividual variability data. Net IIV differs theoretically from time-structured IIV in that it is believed to reflect a measure of variability that is independent of group and time-on-task effects (Ram & Gerstorf, 2009). To partial out these effects, two mixed-effects models were run using SPSS (version 25.0), with either SRT or CRT latency as the outcome variable. The participant's ID was entered as the subject variable in both models. The main effects of group status, age, sex, household income, and years of education were entered as one block to determine the influence of group effects on RT latency. The main effects of test order (one to three), trials (1-30), administrations (one to six), and interval (one to three) were entered as a single block to determine the influence of time-on-task effects on RT latency.

Calculating the intraindividual standard deviation (*iSD*). I determined net IIV by calculating the intraindividual standard deviation (*iSD*) over the 180 trials of both the SRT and CRT tasks for each of the participants. Measures of *iSD* are used by many IIV researchers as indices of stability, and are among the most commonly used methods for calculating net IIV (Bielak et al., 2010; Gorus et al., 2008; Grydland et al., 2013; Hulstsch et al., 2000; Moy et al., 2011; Ram & Gerstorf, 2009; Stuss et al., 2003; Tamnes et al., 2012; Walhovd & Fjell, 2007).

To obtain the *iSD* over all 180 trials, I first calculated the *SDs* for each of the six administrations of the SRT and CRT tasks. I then calculated the average *SD* for each day of testing. I did this by finding the mean of the *SDs* for both administrations of each task during test sessions one, two and three. As a final step, I calculated the average *SD* across the 3 days of testing by finding the mean of the *SDs* for test sessions one, two, and three for both RT tasks. This gave me an overall *iSD* score for each participant, for each task (see Figure 5). I

chose this method because it made the most theoretical sense when considering the nature of IIV, and how the data were structured in time.

DTI pre-processing. The DICOM images were converted to NiFTi format using the `dcm2nii` command in AFNI. All DTI data were first inspected visually for the presence of dropout slices and motion artifacts, which were removed from both AP and PA acquisitions. Pre-processing included motion, eddy current, and susceptibility (Andersson, Skare, & Ashburner, 2003) corrections using TORTOISE V.2.5.2 (Pierpaoli et al., 2010). Each subject's T1 image was converted to a T2-weight contrast image using the relative contrast of tissues methods (Taylor et al., 2015), which had a B0 contrast for the default setting in TORTOISE. The two DTI acquisitions were averaged and diffusion tensor parameters (FA, MD, DA and DR) were generated. Each subject's averaged B0 volume was co-registered to its T1 structural image using linear and nonlinear co-registration algorithms in AFNI. The same procedure was used for all registration steps. All T1 images were co-registered to a 1x1x1 mm³ MNI152 T1-weighted standard template. The FA, MD, DA, and DR images of each subject were warped using the same transformations. As a final step, co-registered FAs were averaged, and all FAs were again co-registered to this mean FA. These transformations were then applied to co-registered MD, DA, and DR images to further improve co-registration. A threshold of $FA > 0.2$ was set so as to only include white matter in the analysis (Mori & van Zijl, 2002).

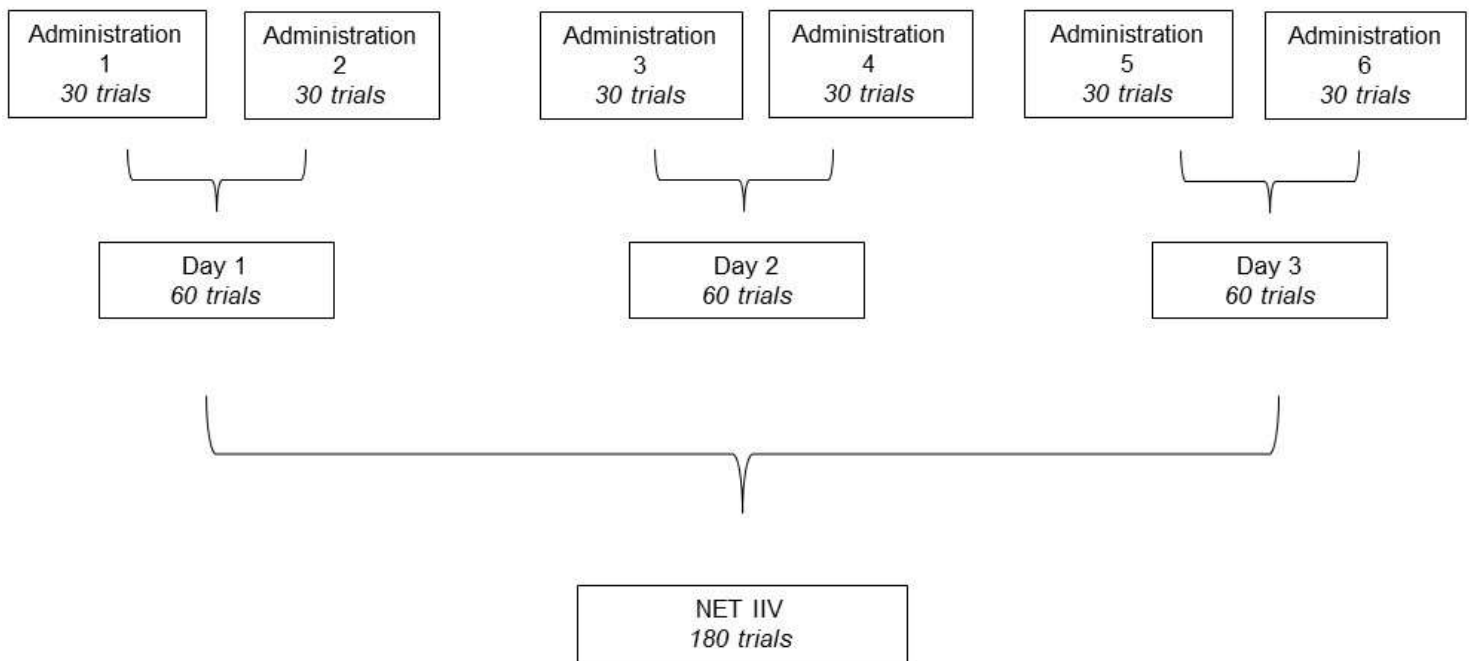


Figure 5. Calculating intraindividual standard deviation (*iSD*). *SDs* were calculated for each of the six 30-trial administrations of the simple and choice reaction time tasks. The average *SD* was calculated across each of the three test sessions for both tasks. Finally the average *SD* was calculated across the three test sessions to obtain an overall *iSD* score for both tasks.

Inferential statistical analyses. I conducted all of these analyses using SPSS (version 25.0) with α set at .05, unless otherwise stated.

Between-group differences. A series of independent sample t-tests investigated between-group differences in sample demographic characteristics (e.g., age, sex, highest level of education, household income) and cognitive performance (CAMCOG and MMSE scores, mean SRT and CRT values, and *iSD* SRT and CRT values).

To identify clusters of significant between-group differences in white matter FA and MD, I used FSL-randomise to perform voxelwise comparisons. Monte Carlo simulations (Forman et al., 1995) helped control for Type I error. AFNI's 3dFWHMx and 3dClustSim (v17.0.17) were used to calculate the minimum volume of clusters within each network mask for significance at voxelwise $p < .01$ and $< .05$ (Cox, 1996). I extracted the mean FA or MD,

as well as AD and RD, for all clusters with significant between-group differences in white matter FA and MD.

Bivariate correlations. A series of bivariate correlational analyses, using Pearson's coefficient, sought to identify predictor variables that would be used in subsequent regression modelling. Specifically, I correlated the mean DTI parameters (FA, MD, DA, DR) extracted from each cluster showing significant between-group differences with *iSD* for SRT and CRT, separately. I also considered correlations between those same clusters and participant demographic variables (viz., age, sex, highest level of education, household income).

Regression models. A series of hierarchical regression models examined the utility of RTIIV (i.e., *iSD* for either SRT or CRT) for predicting white matter integrity. The outcome variable in each model was one of the DTI white matter indices (i.e., FA, MD, DA, or DR) that had been observed, at the previous step of the analysis, to correlate significantly with either simple or choice RTIIV. Each model consisted of three blocks of predictors. The first block contained sample demographic variables that correlated at $p < .10$ with the DTI white matter indices identified by the bivariate correlational analyses. The second block contained either mean SRT or mean CRT, depending on whether SRT or CRT *iSD* was correlated at $p < .10$ with the outcome variable (i.e., the white matter index under consideration). The third block contained either SRT *iSD* or CRT *iSD*, again depending on whether SRT or CRT *iSD* was correlated at $p < .10$ with the outcome variable.

Ethical Considerations

Ethical approval. Ethical approval for the parent study was obtained from the Human Research Ethics Committee (HREC) of UCT's Faculty of Health Sciences (HREC/REF: 167/2014). See Appendix I for the original approval letter and subsequent updates.

Consent and confidentiality. As noted above, all participants were asked to read and sign an informed consent document at each of the screening sessions, and a similar document at the MRI scanning session. The first document briefly explained the purpose of the parent study, the study procedure, and the risks and benefits of participation. It also explained that participation was voluntary and that participants were free to withdraw from the study at any point. It stated that such withdrawal would not affect any existing or future GSH treatment. This document also provided the names and contact details of persons with whom participants could communicate should they have any questions or concerns about the study. In addition to the above information, the second document described the MRI procedure and outlined the potential risks of undergoing an MRI scan. Although AD patients are cognitively impaired, those in the mild-to-moderate stage of the disease are still able to make decisions (Kim, Caine, Currier, Leibovici, & Ryan, 2001). However, a relative or friend was also present during testing to ensure that consent was informed and voluntary.

To ensure patient confidentiality, participants' medical records were not removed from GSH and their names and medical histories were not discussed with anyone not involved in the study. To ensure confidentiality of the collected data, all computerised data were password protected. Data collected on the CANTAB device were kept inside a locked office, with password protection effected whenever the device was not in use. All hardcopy data were kept in a secure filing cabinet.

Potential risks and discomfort. There were no direct physical, psychological, or social risks associated with participation. There were, however, several potential sources of discomfort. For instance, participants were required to travel to GSH for at least the neuroimaging session, and perhaps for as many as three test sessions in addition to that. Furthermore, the cognitive assessments they were required to complete were demanding and time-consuming. Some participants may have felt uncomfortable answering questions about

their declining cognitive status and performing tasks designed to challenge that status. They were, however, given regular breaks and were reminded that they could take as many breaks as needed in order to lessen the burden of completing the test session.

Finally, the partially enclosed MRI scanning machine, as well as the loud noises the scanner makes, may have made some participants nervous. Participants were alerted to these aspects of the scan beforehand, and were assured that they could end the scan at any point should they feel too anxious to carry on. Participants were instructed verbally, as well as in the MRI consent form, to notify either the researcher or the MRI technician of any metal other than dental fillings they had in their bodies. Participants with certain metals that would be attracted to the magnetism of the MRI machine would have been excluded from the imaging component of the study. Participants were further reminded that they were free to withdraw from the study at any point if they felt uncomfortable and did not wish to participate further.

Potential benefits and compensation. Participants were compensated ZAR70 (at the time of the study, approximately US\$5.13) at each of the test sessions to compensate them for their travelling costs. They were also given a total of ZAR200 (at the time of the study, approximately US\$14.65) at the end of the neuroimaging phase to compensate them for their travelling costs and effort.

Results

Sample Characteristics

Analyses detected no significant between-group differences in age, sex distribution, or monthly household income distribution. On average, however, controls had completed significantly more years of formal education. They also achieved significantly higher CAMCOG-R and MMSE scores (see Table 1).

Preliminary Analyses: Between-group differences in predictor and outcome variables

Extraction of *iSDs*. The first (mixed-effects) model identified sex, test order, trials, and test administrations as fixed effects that contributed significantly to SRT latency. The second (mixed-effects) model identified group membership, sex, household income, test order, trials, and test administrations as fixed effects that contributed significantly to CRT latency.

I then ran two random coefficient models, one with SRT latency and the other with CRT latency as the outcome variable. All fixed effects identified by the two models above, as well as their higher-order interactions, were entered as predictors into each random coefficient model. Furthermore, both models included trials as a random slope. The standardised residuals from each of the random coefficient models were computed and then converted into T-scores. Using the compute variable function in SPSS, I entered the Z-scores as the target variable and then multiplied each score by 10 before adding 50 to the total score. This method, which is consistent with that used by Hulstsch et al. (2000), Hulstsch, MacDonald, and Dixon (2002) and Moy et al. (2011), helped partial out group and time-on-task effects, and thus ensured that *iSD* was calculated on true error variance.

Table 1

Descriptive Statistics and Between-group Differences: Sociodemographic variables and general cognitive functioning (N = 36)

Variable	Group		$t / \chi^2 / z$	p	ESE
	Controls ($n = 20$)	AD Patients ($n = 16$)			
Age (years)	69.70 (7.13)	73.25 (6.18)	1.57	.125	-0.52
Sex (M:F)	6:14	4:12	0.11	1.00	.739
Education (years)	11.95 (2.67)	9.00 (2.25)	-3.53	.001***	1.03
Income (1:2:3:4:5)	1:3:3:4:9	0:1:9:3:3	7.8	.01	.465
CAMCOG-R total score	92.45 (5.99)	67.94 (11.83)	-7.55	< .001***	1.61
MMSE total score	27.75 (1.86)	22.19 (4.20)	-4.93	< .001***	1.34

Note. For the variables *Age*, *Education*, *Income*, *CAMCOG total score*, and *MMSE score*, means are presented with standard deviations in parentheses. For the variable *Sex*, M = male and F = female. The variable *Income* refers to monthly household income; this was categorized on a 1-6 scale, where 1 = ZAR 500-999, 2 = ZAR 1000-2499, 3 = ZAR 2500-5499, 4 = ZAR 5500-9999 and 5 = ZAR 10000+. For each between-group comparison, degrees of freedom were 34, except *CAMCOG-R total score* (21.1) and *MMSE total score* (19.7). CAMCOG-R = Cambridge Cognitive Examination - Revised; MMSE = Mini-Mental State Examination; ESE = effect size estimate (for t , Cohen's d , for chi square, ϕ , and for Mann-Whitney, Cohen's r).

* $p < .05$. ** $p < .01$. *** $p < .001$.

Between-group differences in RT variables. Regarding IIV_{RT} values, analyses detected significant between-group differences on both the SRT and CRT tasks. In both cases, patients showed significantly more IIV in performance (see Table 2).

Regarding mean RT values, analyses detected a significant between-group difference on the CRT task, but not on the SRT task. In both cases, however, the average response time of controls was faster than that of patients.

Between-task differences in IIV_{RT} and mean RT. The descriptive statistics in Table 2 show that, in both controls and patients, IIV on the CRT task was higher than that on the SRT task. Independent-samples t-tests indicated that this difference was statistically significant for controls, $t(19) = 2.32$, $p = .01$, but not for patients, $t(15) = 0.65$, $p = .26$.

The descriptive statistics in that table also show that, in both controls and patients, mean RT latencies were slower on the CRT task than on the SRT task. Independent-samples t-tests indicated that this difference was statistically significant for patients, $t(30) = 2.09$, $p = .045$, and for controls, $t(38) = 2.92$, $p = .006$.

Table 2

Descriptive Statistics and Between-group Differences: Predictor variables (N = 36)

Variable	Group		<i>t</i>	<i>p</i>	95% CI	
	Controls (<i>n</i> = 20)	AD Patients (<i>n</i> = 16)			Lower	Upper
<i>iSD</i>						
SRT	8.36 (1.49)	10.30 (2.43)	2.95	.006**	0.61	3.28
CRT	8.88 (1.37)	10.63 (2.29)	2.85	.007**	0.51	3.00
Mean RT						
SRT	318.39 (35.11)	341.01 (58.03)	1.45	.157	-9.17	54.40
CRT	350.46 (34.31)	383.15 (56.05)	2.16	.038*	1.87	63.51

Note. Data presented are means, with standard deviations in parentheses. For each between-group comparison, degrees of freedom were 34. *iSD* = intraindividual standard deviation; Mean RT = Mean reaction time across 180 trials of task performance; SRT = Simple Reaction Time task; CRT = Choice Reaction Time task; 95% CI = confidence intervals at the 95% level. All *p*-values are two-tailed.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Voxelwise analyses. Regarding FA, initial voxelwise comparisons and post-hoc analyses detected two clusters where, on average, values were significantly lower in patients than in controls. These clusters corresponded to regions in (a) the R-ILF, and (b) the body of the corpus callosum (BCC; Figure 6). Further analysis detected no significant between-group differences in DA in these two regions, but significantly higher mean DR in patients than in controls in both. Table 3 gives the peak coordinates and size of each cluster, as well as the group mean FA, DA, and DR values.

Regarding MD, initial voxelwise group comparisons and post-hoc analyses detected one additional cluster where, on average, values were significantly higher in patients than in controls. That cluster corresponded to a region in the genu of the corpus callosum (GCC; Figure 7). Further analysis of that region detected significantly higher mean DR in patients than in controls, but no significant between-group differences in DA. Table 4 gives the peak coordinates, as well as the group mean MD, DA, and DR values.

Table 3

Fractional Anisotropy: Size and peak coordinates (in MNI standard space) of regions showing

Region (MNI peak coordinates)	Group		<i>t</i>	<i>p</i>	95% CI	
	Controls (<i>n</i> = 20)	AD Patients (<i>n</i> = 16)			Lower	Upper
R-ILF (44, -35, -6)						
FA	0.34 (0.01)	0.31 (0.01)	5.32	< .001***	0.32	0.34
DA	0.28 (0.03)	0.27 (0.03)	1.18	.245	0.27	0.29
DR	0.21 (0.03)	0.24 (0.03)	-2.68	.011*	0.21	0.23
BCC (4, -27, 18)						
FA	0.26 (0.03)	0.23 (0.02)	4.49	< .001***	0.24	0.25
DA	0.20 (0.05)	0.21 (0.04)	-1.16	.253	0.19	0.22
DR	0.27 (0.04)	0.31 (0.02)	-4.29	< .001**	0.28	0.30

Note. Data are group averages (*SD*) of the mean FA, DA, and DR in 8mm³ ROIs around the peak coordinates. For each between-group comparison, degrees of freedom were 34, except *BCC-FA* (32) and *BCC-DR* (28). MNI = Montreal Neurological Institute; R-ILF = right inferior longitudinal fasciculus; BCC = body of corpus callosum; FA = fractional anisotropy; DA = axial diffusivity; DR = radial diffusivity; CI = confidence intervals at the 95% level. All *p*-values are two-tailed.

p* < 0.05. *p* < 0.01. ****p* < 0.001

Table 4

Mean Diffusivity: Size and peak coordinates (in MNI standard space) of region showing significant between-group differences (N = 36)

Region (MNI peak coordinates)	Group		<i>t</i>	<i>p</i>	95% CI	
	Controls (<i>n</i> = 20)	AD (<i>n</i> = 16)			Lower	Upper
GCC (-5, 19, -1)						
MD	0.22 (0.03)	0.25 (0.03)	-2.95	.006**	-0.05	-0.01
DA	0.17 (0.06)	0.20 (0.05)	-1.51	.140	-0.06	0.01
DR	0.25 (0.03)	0.28 (0.03)	-2.78	.009**	-0.05	-0.01

Note. Data are group averages (*SD*) of the mean MD, DA, and DR in 8mm³ ROIs around the peak coordinates. For each between-group comparison, degrees of freedom were 34. MNI = Montreal Neurological Institute; GCC = genu of corpus callosum; DA = axial diffusivity; DR = radial diffusivity. 95% CI = confidence intervals at the 95% level. All *p*-values are two-tailed.

p* < 0.05. *p* < 0.01. ****p* < 0.001.

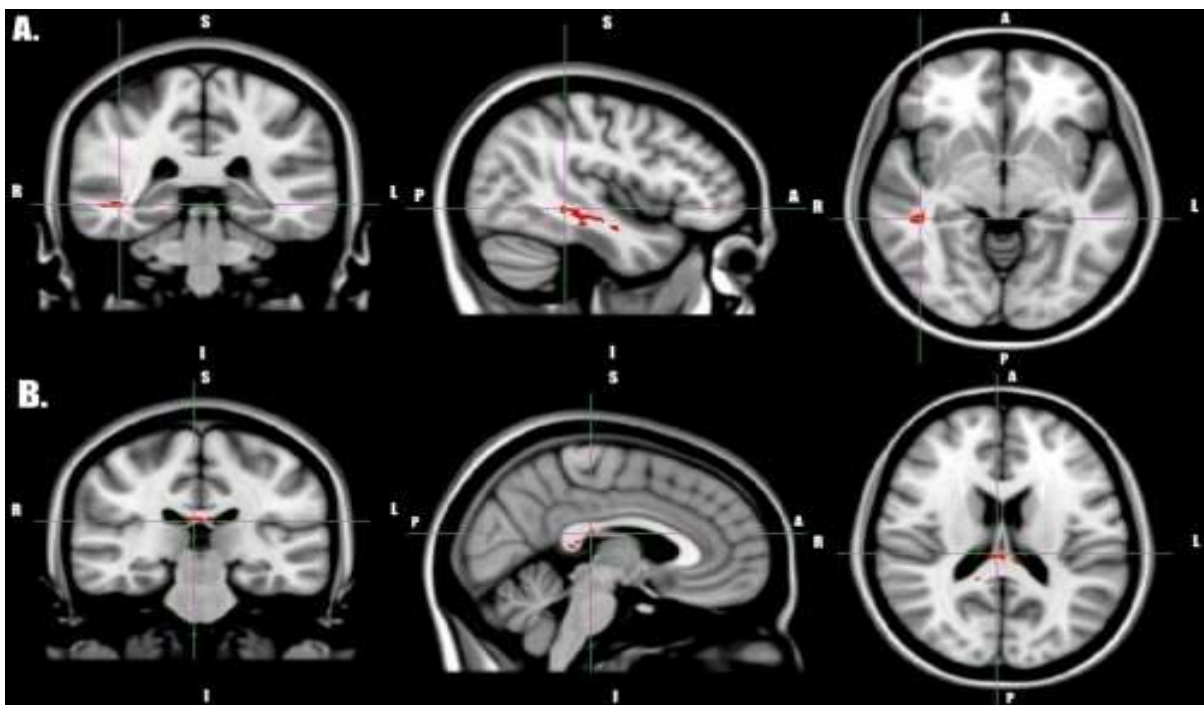


Figure 6. Fractional anisotropy (FA): Brain regions where mean values were significantly lower in AD patients ($n = 16$) than in matched healthy controls ($n = 20$). Panel A highlights an area in the right inferior longitudinal fasciculus, and Panel B highlights an area in the body of the corpus callosum. In both panels, cross-hairs indicate peak coordinates.



Figure 7. Mean diffusivity (MD): An area in the genu of the corpus callosum where mean value was significantly higher in AD patients ($n = 16$) than in matched healthy controls ($n = 20$). Cross-hairs indicate peak coordinates.

Main Analysis: Regression modelling

Bivariate correlations between cognitive predictors and white matter outcome variables. The first series of correlational analyses (see Table 5) investigated associations between IIV_{RT} (derived separately, as described earlier, for the SRT and CRT tasks) and FA (and corresponding DA and DR) values in the regions in which the voxelwise comparisons described above detected significant between-group differences. As the Table shows, the analysis detected significant associations between (a) FA in R-ILF and SRT *iSD*, (b) DA in R-ILF and SRT *iSD*, and (c) DA in R-ILF and CRT *iSD*.

The second series of correlational analyses (see Table 5) investigated associations between IIV_{RT} (the same variables as described above) and MD (and corresponding DA and DR) values in the regions in which the voxelwise comparisons described above detected significant between-group differences. As the Table shows, the analysis detected no significant correlations.

Bivariate correlations between sociodemographic variables and white matter outcome variables. This series of correlational analyses (see Table 6) sought to identify possible confounding factors that should be entered into subsequent regression models. Hence, they investigated associations between a set of sociodemographic variables (age, sex, monthly household income, number of years of education, and group membership) and the white matter index values identified as being significant by the previous set of bivariate correlations. In this instance, I set the α level at $< .10$ to decrease the probability of making a Type I error. As the Table shows, the analysis detected a significant association between FA in R-ILF and years of education ($r = .33, p = .051$). Hence, I added the latter sociodemographic variable to the subsequent regression models.

Table 5
Bivariate Correlations: Associations between measures of cognition (IIV_{RT}) and indices of white matter integrity in regions that showed significant between-group differences (N = 36)

Predictor	Region (MNI peak coordinates)	Outcome		
		Fractional Anisotropy		
		FA	DA	DR
SRT <i>iSD</i>	R-ILF (44, -35, -6)	-.33 (.047)	-.33 (.050)	.27 (.116)
	BCC (4, -27, 18)	-.04 (.816)	.13 (.461)	.05 (.786)
CRT <i>iSD</i>	R-ILF (44, -35, -6)	-.31 (.063)	-.43 (.008)	.22 (.190)
	BCC (4, -27, 18)	-.14 (.409)	.16 (.338)	.17 (.334)
		Mean Diffusivity		
		MD	DA	DR
SRT <i>iSD</i>	GCC (-5, 19, -1)	.01 (.965)	.13 (.461)	-.10 (.577)
CRT <i>iSD</i>	GCC (-5, 19, -1)	.04 (.817)	.09 (.618)	-.02 (.927)

Note. Data presented are Pearson product-moment correlation coefficients (*r* values), with associated *p* values in brackets. Statistically significant associations are marked in boldface font. SRT *iSD* = intraindividual *SD* on the Simple Reaction Time task; CRT *iSD* = intraindividual *SD* on the Choice Reaction Time task; FA = fractional anisotropy; MD = mean diffusivity; DA = axial diffusivity; DR = radial diffusivity.

Table 6
Bivariate Correlations: Associations between sociodemographic characteristics and indices of white matter integrity in regions that correlate significantly with IIV_{RT} (N = 36)

	Age	Sex	Income	Education
FA R-ILF	-.07 (.680)	-.03 (.874)	5.61 (.230)	.33 (.051)
DA R-ILF	.06 (.749)	-.00 (.988)	0.85 (.931)	-.01 (.959)

Note. Data presented are Pearson product-moment correlation coefficients (*r* values), with associated *p* values in brackets, except for the variable *Income* where the Kruskal-Wallis test statistic is presented, with associated *p* values in brackets. Statistically significant associations are marked in boldface font. FA = fractional anisotropy; DA = axial diffusivity; R-ILF = right inferior longitudinal fasciculus.

Hierarchical regression models. Given the results of the series of bivariate correlations, I ran three hierarchical regression models, all related to outcome variables associated with FA as an index of white matter integrity. For each model, the first prediction block included only the sociodemographic variable (education) that was significantly correlated with the relevant white matter index.

The first model sought to determine the degree to which SRT *iSD* predicted FA in R-ILF (see Table 7). As the Table shows, at the second step I added mean SRT latency to education, and at the third step I added SRT *iSD* to the other two predictors. Overall, this model accounted for 12% of the variance in FA in R-ILF. None of the predictors entered at any of the steps made a unique, significant contribution to that variance, however.

Table 7

Regression Model 1: Standardized regression coefficients for SRT iSD as a predictor of fractional anisotropy (FA) in the right inferior longitudinal fasciculus (R-ILF; N = 36)

Block / Predictor	<i>b</i>	<i>SE b</i>	β
Step 1			
Education	0.002	0.001	.33
Step 2			
Education	0.002	0.001	.32
Mean SRT latency	-2.89	0.00	-.07
Step 3			
Education	0.002	0.001	.26
Mean SRT latency	6.26	0.00	.15
SRT <i>iSD</i>	-0.003	0.002	-.37

Note. The predictor *Education* refers to the number of years of formal education completed successfully. SRT = Simple Reaction Time task; *iSD* = intraindividual *SD*.

Step 1: $\Delta R^2 = .11$; $\Delta F(1, 34) = 4.11$, $p = .051$.

Step 2: $\Delta R^2 = .01$; $\Delta F(1,33) = 0.18$, $p = .674$.

Step 3: $\Delta R^2 = .08$; $\Delta F(1,32) = 3.21$, $p = .083$.

Total adjusted R^2 for the model = .12.

The second model sought to determine the degree to which SRT *iSD* predicted DA in R-ILF (see Table 8). As the Table shows, the order in which predictors were added to this model was identical to that of the first model, described above. Overall, this model accounted for 3% of the variance in DA in R-ILF. Again, none of the predictors entered at any of the steps made a unique, significant contribution to that variance.

The third model sought to determine the degree to which CRT *iSD* predicted DA in R-ILF (see Table 9). As the Table shows, at the first block of predictors I included the demographic variable (number of years of completed education) that was significantly correlated with the white matter indices, at the second step I added mean CRT latency, and at the third step I added CRT *iSD*. Overall, this model accounted for 24% of the variance in DA in R-ILF. Both mean CRT latency and CRT *iSD* made significant independent contributions to that variance.

Table 8

Regression Model 2: Standardized regression coefficients for SRT iSD as a predictor of axial diffusivity (DA) related to fractional anisotropy (FA) in the right inferior longitudinal fasciculus (R-ILF; N = 36)

Block / Predictor	<i>b</i>	<i>SE b</i>	β
Step 1			
Education	-8.33	0.002	-.01
Step 2			
Education	0.00	0.002	-.03
Mean SRT latency	0.00	0.00	-.21
Step 3			
Education	-0.001	0.002	-.09
Mean SRT latency	1.26	0.00	-.00
SRT <i>iSD</i>	-0.004	0.003	-.35

Note. The predictor *Education* refers to the number of years of formal education completed successfully. SRT = Simple Reaction Time task; *iSD* = intraindividual *SD*.

Step 1: $\Delta R^2 = .00$; $\Delta F(1,34) = 0.003$, $p = .959$.

Step 2: $\Delta R^2 = .04$; $\Delta F(1,33) = 1.47$, $p = .233$.

Step 3: $\Delta R^2 = .07$; $\Delta F(1,32) = 2.62$, $p = .115$.

Total adjusted R^2 for the model = .12.

Table 9

Regression Model 3: Standardized regression coefficients for CRT iSD as a predictor of axial diffusivity (DA) related to fractional anisotropy (FA) in the right inferior longitudinal fasciculus (R-ILF; N = 36)

Block / Predictor	<i>b</i>	<i>SE b</i>	β
Step 1			
Education	-8.33	0.002	-.01
Step 2			
Education	0.00	0.002	-.05
Mean CRT			
latency	0.00	0.00	-.35*
Step 3			
Education	-0.001	0.001	-.12
Mean CRT			
latency	0.00	0.00	-.21
CRT <i>iSD</i>	-0.005	0.002	-.38*

Note. The predictor *Education* refers to the number of years of formal education completed successfully. CRT = Choice Reaction Time task; *iSD* = intraindividual *SD*.

Step 1: $\Delta R^2 = .00$; $\Delta F(1,34) = 0.003$, $p = .959$.

Step 2: $\Delta R^2 = .12$; $\Delta F(1,33) = 4.52$, $p = .041$.

Step 3: $\Delta R^2 = .12$; $\Delta F(1,32) = 4.80$, $p = .036$.

Total adjusted R^2 for the model = .24.

* $p < .05$.

Discussion

The current study sought to determine whether changes in white matter microstructure, as measured by diffusion tensor imaging (DTI), contribute to intraindividual variability (IIV) on reaction time (RT) tasks. To answer this question, I gathered data from patients with mild-to-moderate Alzheimer's disease (AD) and age-matched healthy controls.

Cognitive test results indicated that IIV on both the simple and choice RT tasks (SRT and CRT, respectively) was higher in patients than in controls. Moreover, controls (but not patients) had significantly higher IIV on the CRT than on the SRT task. Finally, both patients and controls had significantly longer mean RT latencies on the CRT than on the SRT task.

DTI results indicated that, relative to values in controls, patients had significantly decreased white matter integrity in an area of the R-ILF, as well as in the body and the genu of the corpus callosum (BCC and GCC, respectively).

Results from the study's main analysis indicated that a loss of micro-structural white matter integrity was significantly associated with increased IIV. Specifically, fractional anisotropy (FA) in an area of the R-ILF was significantly negatively correlated with intraindividual standard deviation (*iSD*) on the SRT task, while axial diffusivity (DA) in the same brain region was significantly negatively correlated with *iSD* on both the SRT and CRT tasks. Moreover, in the same brain region, higher IIV_{RT} on the CRT task predicted lower DA, a result that held over and above mean CRT latencies.

Group Differences in Mean RT Latencies and IIV_{RT}

The current results suggest that IIV_{RT} may be able to detect subtle cognitive changes that group-mean measures do not. For instance, in contrast to the absence of significant between-group differences in terms of mean RT latency on the SRT task, patients had significantly higher *iSDs* than controls on the same task. Hence, IIV_{RT} may be able to detect cognitive decline when the level of impairment is not severe enough to affect mean-level measures significantly.

In contrast to the current findings, previous studies have reported significantly longer mean RT latencies in patients than controls on SRT tasks (Anstey et al., 2007; Hultsch et al., 2000). One potential reason for these discrepant findings is that, whereas the current patient sample consisted of individuals with mild-to-moderate AD, Hultsch et al. (2000) reported on patients with mild dementia (either AD or vascular dementia) and Anstey et al. (2007) included a sample of older adults with mild cognitive disorders (diagnosed by consensus clinical judgement as having either mild cognitive impairment, age-associated memory impairment, age-associated cognitive decline, or mild neurocognitive disorder). Two recent

reviews have suggested that AD pathology begins in deep brain regions (especially limbic and temporal lobe grey and white matter) and eventually extends into most cerebral grey and white matter as the disease progresses (Acosta-Cabronero & Nestor, 2014; Wang & Yu et al., 2015). Hence, one might expect that this pattern would hold for patients in the current sample. On the other hand, the neural damage within the clinical samples in the Hultsch et al. (2000) and Anstey et al. (2007) studies is likely to have been less circumscribed given that their patients' diagnoses likely encompassed a wider range of primary cognitive deficits. Because performance on RT tasks is known to rely on a diffuse collection of brain regions (especially within the frontal, parietal, and occipital lobes) involved in sustained and focused attention (Baddeley, Baddeley, Bucks, & Wilcock, 2001; Levinoff, Saumier, & Chertkow, 2005), it is possible that between-study discrepancies in results could be accounted for by differences in the brain regions affected in each clinical sample. More specifically, it is possible that the current clinical group performed similarly to the control group on the SRT task because the brain mechanisms required for performance were relatively intact compared to those of the clinical groups used in the other two studies.

Although the current analyses detected no significant between-group difference in mean latency on the SRT task, similar to those of Hultsch et al. (2000) and Anstey et al. (2007), they did detect such differences on the CRT task (patients performed more poorly than controls). Performance on CRT tasks involves a decisional component that is not needed during performance on SRT tasks (Levinoff et al., 2005). Furthermore, stimulus processing during performance on a CRT task requires additional visuospatial attention compared to that on a SRT task, as participants need to visually monitor several places for the appearance of the target stimulus (Tuch et al., 2005). Hence, the currently observed data pattern might be accounted for by an increase in cognitive load, requiring recruitment of additional brain mechanisms, during performance on the CRT task. In other words, one might argue that

although participants in the current patient group had sufficient cognitive and neural capacity to perform at a similar level to controls on the SRT task, this capacity was depleted by the increased demands of the CRT task. The differences in findings between the current study and those of Hultsch et al. (2000) and Anstey et al. (2007) could therefore be due to a combination of differences in samples used, and the relatively increased cognitive load of CRT tasks compared to SRT tasks.

Regarding IIV_{RT} , the current findings are consistent with those of several others reporting higher values in patients than in controls. For example, Hultsch et al. (2000) found that, compared to patients with arthritis and healthy controls, those with mild dementia had higher IIV on both SRT and CRT tasks. They also reported that, in the dementia group but not in the other two groups, IIV on the SRT task was significantly smaller than that on the other cognitive tasks. Similarly, Gorus et al. (2008) found that, compared to patients with MCI and healthy controls, patients with AD had higher IIV_{RT} . They also reported, similar to Hultsch et al. (2000), that IIV increased with task complexity, and that this increase was greater in the AD group than in the other two groups. Taken together, the findings from these two studies suggest that (a) IIV is higher in tasks with a higher cognitive load, and (b) this difference may be more pronounced in those with more severe neurological impairment.

In those respects, the current findings differ somewhat to those of Hultsch et al. (2000) and Gorus et al. (2008). Here, controls but not patients had significantly higher IIV on the CRT task than on the SRT task. That is, in contrast to those previous studies, the current results suggest that IIV is higher in tasks with a higher cognitive load in neurologically intact individuals but not in neurologically impaired patients. This pattern of findings leads to the suggestion that IIV is *only* higher in tasks with a higher cognitive load when the brain mechanisms responsible for maintaining consistency in performance are intact. It is possible that when cognitive load increases, the demand on these mechanisms increases to a point

where they can no longer keep up, and consistency in performance drops. When these same brain mechanisms are damaged (as they might be, for example, in AD patients), the effect of cognitive load on IIV is decreased and a more uniform increase in IIV is seen across cognitive tasks as a consequence of that damage.

Further to ways in which methodological choices might have contributed to between-study discrepancies in findings, in the task used by Hultsch et al. (2000), but not in the current task, participants were presented with a warning stimulus prior to presentation of the target stimulus. It is possible that this warning stimulus had a greater effect on variability in the SRT task and that this effect was stronger in Hultsch et al.'s controls more than patients. Several studies have highlighted the role of a non-specific motor preparedness, as well as responding without fully analysing the stimulus, in producing the warning effect (Hackley & Valle-Inclán, 2003; Zeigler, Graham, & Hackley, 2001). In addition, the neural correlates of the warning effect in automated responses, such as an eye blink, are similar to those of purposeful responses such as that seen in RT performance (Zeigler et al., 2001). This suggests that the efficacy of the warning effect lies at least in part on priming automatic or reflexive responses. Accurate performance on CRT tasks such as the one used by Hultsch and colleagues requires relatively more reflective cognitive processing (including visual processing and motor responses) compared to performance on a similar SRT task. It is therefore possible that the introduction of a warning signal will disproportionately improve performance on SRT tasks compared to CRT tasks, possibly reducing variability on the SRT task to a greater extent. Furthermore, several studies into the neural and cognitive correlates of the warning effect have identified top-down attentional control networks and motor cortical areas as being involved in improving performance on warning trials (Boulinguez, Ballanger, Granjon, & Benraiss, 2009; Yoshida et al., 2013). These same attentional control networks appear to be compromised in dementia (Parasuraman & Haxby, 1993; Rapp &

Reischies, 2005; Rizzo et al., 2000). Hence, it is reasonable to speculate that dementia patients will not benefit as much as controls from a warning stimulus such as that used by Hultsch et al. (2000).

Another explanation for the observed between-study differences is the number of RT trials used in the three studies. The current study had 30 test trials following the 10 practice trials, whereas Hultsch and colleagues' study had 50 test trials following the 10 practice trials, and Gorus and colleagues' study had 28 or 56 test trials and used replacement stimuli for trials where errors were made. The higher number of test trials in the other two studies may have introduced a fatigue effect, and that effect might have been stronger in patients than in controls. Cognitive fatigue has been linked to executive attention (Holtzer, Shuman, Mahoney, Lipton, & Verghese, 2010), and executive dysfunction is present in dementia patients (Baudic et al., 2006; Sgaramella et al., 2001; Sudo, Amado, Alves, Laks, & Engelhardt, 2017). Moreover, a tendency toward mental fatigue has been reported in several neurological conditions, including AD (for a review, see Chaudhuri & Behan, 2000). Hence, it is reasonable to speculate that Hultsch et al.'s and Gorus et al.'s patients became more fatigued than their controls during performance, and that this fatigue was more pronounced during the tasks with higher cognitive load, thus explaining (at least partially) the observed between-group and between-task discrepancies in IIV.

Group Differences in Indices of White Matter Integrity

DTI measures the movement of water molecules in and around organic tissue. Because white matter tissue is organized in a highly directional fashion, we expect to see highly directional (anisotropic) diffusion of water molecules in healthy white matter. DTI yields two main determinants of white matter integrity: mean diffusivity (MD) and fractional anisotropy (FA). MD represents the mean diffusion of water molecules in and around organic tissue in all directions. As such, higher MD values are indicative of more overall diffusion,

and hence of less healthy white matter. FA, on the other hand, represents the degree of anisotropy along the tissue fibre. In other words, it gives information on how water molecules are diffusing parallel to the tissue fibre. In healthy white matter, we expect the diffusion of water molecules to be highly anisotropic. Consequently, lower FA values are usually associated with less healthy white matter (Alexander et al., 2007).

DTI measures water diffusion in all possible directions, as well as the correlations between directions. This information is used to construct a tensor matrix. Three eigenvectors, representing the principle directions of diffusion, are extracted from this matrix. The diffusion tensor of each tissue voxel is then comprised of the three eigenvalues associated with each eigenvector. The eigenvectors are termed λ_1 , λ_2 , and λ_3 , and correspond to overall parallel (λ_1) and perpendicular (λ_2 and λ_3) displacement along the tissue. Parallel displacement is commonly termed axial diffusivity (DA), whereas perpendicular displacement is commonly termed radial diffusivity (DR; Alexander et al., 2007). Lower DA is associated with axonal damage, whereas higher DR is associated with demyelination (Gold et al., 2012; Song et al., 2002; Sun et al., 2006).

Compromised white matter integrity in the corpus callosum. The current analyses suggested that FA was lower in the BCC, and MD was higher in the GCC, in AD patients than in healthy controls. These results support the idea that micro-structural white matter in the body and anterior parts of the corpus callosum is affected in mild-to-moderate AD. They are also consistent with those of several other studies reporting compromised micro-structural white matter integrity in the body and anterior parts of the corpus callosum of those with AD compared to healthy controls (see, e.g., Canu et al., 2013; Kim et al., 2015; Rémy et al., 2015; Tang & Qin et al., 2017; Teipel et al., 2014; Wang & Wang et al., 2015).

Regarding the GCC specifically, the current findings are consistent with previous investigations in showing higher MD values in this region in AD patients than in controls

(Alves et al., 2012; Chen et al., 2009; Rémy et al., 2015; Wang & Wang et al., 2015).

However, the present results differ from previous studies in that the current analyses did not detect a significant between-group difference for FA in the GCC (Canu et al., 2013; Kim, et al., 2015; Liu et al., 2011; although see Chen et al. (2009), who also did not find such between-group differences). Because FA in white matter represents the degree of water diffusion along the axon, it is possible that the current analyses did not detect a significant between-group difference in FA in the GCC because the water diffusion in the direction of the axon was not sufficiently disrupted in the current AD sample to result in significantly lowered FA values (Alexander et al., 2007).

The current analyses also detected significant between-group differences in DR, but not DA, in the same areas where group differences in FA and MD were found. Together, this pattern of results suggests that the observed between-group differences in the body and anterior parts of the corpus callosum might be a consequence of AD-related changes in myelin, as opposed to compromised axonal integrity. Previous studies have found between-group differences in DA in the corpus callosum of those with AD or CSF biomarkers for AD compared to healthy controls or those with no such biomarkers, indicating AD-related changes in axonal integrity (Agosta et al., 2011; Molinuevo et al., 2014). Perhaps the type of damage (loss of myelin integrity or axonal degeneration) is dependent at least in part on the stage of the disease. For example, studies examining micro-structural white matter integrity in the corpus callosum of those with mild-to-moderate AD compared to healthy controls have found significant between-group differences in DR, but not DA, in the body, genu, and splenium (Alves et al., 2012; Canu et al., 2013). On the other hand, studies examining the same thing in those with moderate AD compared to healthy controls have found significant between-group differences in DA in the body, and in both DA and DR in the rostrum, genu, and splenium of the corpus callosum (Agosta et al., 2011; Wang & Wang et al., 2015).

Compromised white matter integrity in the R-ILF. The current analyses detected significant between-group differences in the R-ILF, with patient FA and DR values significantly lower than those of controls. These findings support the notion that the ILF, at least in the right hemisphere, is affected early in the AD process.

Regarding FA, several studies have found significantly decreased values in the ILF bilaterally in patients with mild AD compared to those with aMCI/MCI or healthy controls (Li et al., 2018; Liu et al., 2011; Rémy et al., 2015; Teipel et al., 2014). Consistent with the current results, Lee et al. (2015) found significantly reduced FA in the R-ILF in those with mild AD compared to a group of healthy controls and those with MCI. Similarly, a longitudinal study following patients from the mild to moderate stages of AD also found that FA decreased in the R-ILF over the course of the disease progression (Kitamura et al., 2013).

Regarding DR, the current finding is consistent with results of other DTI studies of AD patients. For instance, Alves et al. (2012) and Stricker et al. (2009) found increased DR, but not DA, in an area of the ILF in patients with mild AD compared to healthy controls. Moreover, the longitudinal study referred to above (Kitamura et al., 2013) found that decreased FA in the R-ILF over the course of progression from mild to moderate AD was a consequence of changes in DR and not in DA. These findings differ somewhat from those of Agosta et al. (2011) and Pievani et al. (2010), both of whom found significantly decreased DA and DR in the ILF in patients with mild-to-moderate AD compared to healthy controls. Some of these differences in results could be due to the disease stage, with DR being affected early on in the disease process, and DA becoming affected later on.

It is also possible that some of these cross-study differences are related to differences in analytic techniques between the studies. Three main data analysis techniques are used in region-specific DTI investigations: ROI, voxel-based (VBA), and tract-based spatial statistics (TBSS). In the current study, VBA identified clusters of significant between-group

differences in white matter FA and MD. This method is similar to the TBSS methods used by Agosta et al. (2011), Alves et al. (2012), and Stricker et al. (2009) - both take into account all brain white matter, identifying only those regions where there are significant between-group differences for subsequent statistical analyses. Although these two methods reduce bias by not relying on a priori specified brain regions, their results may be biased because they exclude brain regions that do not meet the (admittedly somewhat arbitrary) statistical threshold of significance. On the other hand, ROI analyses such as that used by Kitamura et al. (2013) and Pievani et al. (2010) examine white matter in pre-defined white matter tracts, eliminating the possibility of finding between-group differences in non-specified tracts (Soares et al., 2013).

In addition to the above, whole-brain analysis techniques such as VBA and TBSS generate a series of coordinates where clusters of unhealthy white matter have been identified. These coordinates are then used to determine which white matter structures are affected. As such, the results of whole brain analysis techniques only tell us about the structural integrity of a small cluster of brain tissue within the identified white matter structure. On the other hand, ROI analysis is based on the a priori specification of white matter tracts using seeds and target regions of interest. The results of ROI analyses help determine whether or not the specified tracts are affected by measuring the mean DTI indices (including FA and MD) of the entire tract. Hence, studies reporting results based on ROI analysis typically include a larger area of affected white matter compared to studies using whole-brain analysis methods. As such, the differences in findings between the current study and those of previous studies could be due, at least in part, to differences in data analytic techniques.

Nonetheless, the involvement of the ILF is not surprising given this brain region has been implicated in a number of functions known to be affected in AD. For example, a recent

study highlighted the role of the ILF in semantic autobiographical memory (Hodgetts et al., 2017), a key component of the memory loss observed from the early stages of AD (Kirk & Berntsen, 2018). The ILF has also been implicated in the semantic language system (Panesar, Yeh, Jacquesson, Hula, & Fernandez-Miranda, 2018), visual memory (Shinoura et al., 2007), emotional memory, as well as spatial awareness and visual object location (Grilli, Woolverton, Crawford, & Glisky, 2018; Latini et al., 2017), all of which are affected in the early stages of AD (Adlam, Bozeat, Arnold, Watson, & Hodges, 2006; Giffard, Laisney, Desgranges, & Eustache, 2015; Guariglia, 2007; Joubert et al., 2010; Kessels, Feijen, & Postma, 2005; Mårdh, Nägga, & Samuelsson, 2013; Tchakoute, Sainani, & Henderson, 2017).

Interim summary. Overall, the current DTI data support the proposal that there are micro-structural white matter changes in the early and moderate stages of AD, and that these changes are primarily due to disruptions in myelin integrity. Moreover, the results suggest that specific major white matter tracts (viz., those found in the corpus callosum and the inferior longitudinal fasciculus) are more heavily involved in the AD process than others. There are, however, a number of discrepancies between the current findings and those of previous studies, highlighting the importance of further examination of the micro-structural white matter changes seen in AD. Specifically, in order to reconcile differences in findings relating to DA and DR, more studies are needed to examine the role of myelin versus axonal degeneration in the early stages of AD. In addition, more research is needed into the specific areas of micro-structural white matter changes in AD, and how these changes progress over the course of the disease.

Associations between Micro-structural White Matter Changes and IIV

The current results are consistent with those reported in several previous studies suggesting a statistically significant relationship between IIV and some measure of micro-

structural white matter integrity in healthy adults (see, e.g., Grydeland et al., 2013; Lin et al., 2014; Moy et al., 2011). One of the main findings emerging from the current analyses was an association between IIV_{RT} and DA (but not DR) in the R-ILF (i.e., higher IIV_{RT} on the CRT task was correlated with lower DA in the R-ILF). As mentioned previously, lower DA values have been linked to disruptions in axonal integrity, whereas higher DR values have been linked to disruptions in myelin integrity. Thus, the current finding of a negative association between DA in the R-ILF and IIV_{RT} suggests that, in the current sample, changes in IIV might be due to disruptions in the integrity of axonal structure rather than that of myelin.

Previous studies have found that age-related increases in IIV_{RT} were associated with decreased DR and DA in the main white matter fibre tracts. In their cross-sectional study of healthy adults aged between 22 and 88 years, Moy et al. (2011) found that an age-related increase in IIV was significantly associated with decreased FA and increased MD and DR in the main white matter tracts, but was not significantly associated with DA in any white matter tract. However, in their study of healthy adults aged between 20 and 83 years, Fjell, Westlye, Amlien, and Walhovd (2011) found that age mediated the relationship between IIV and DR in approximately 42% of the skeleton voxels, and that the same mediation was present for DA in 26% of the skeleton voxels.

These cross-study differences in results are suggestive of the fact that the nature of the relationship between IIV and micro-structural white matter changes depends, at least partially, on the population being studied. For example, although AD is associated with disruption of both myelin and axonal integrity, several studies have argued that axonal disruption is the primary mechanism of white matter change in the disorder (Amlien & Fjell, 2014; Huang, Friedland, & Auchus, 2007; Skillbäck, Zetterberg, Blennow, & Mattsson, 2013; Stokin et al., 2005). Hence, it is possible that the current observations of an association between DA and IIV, in the absence of any association between DR and IIV, arose because

this sample included individuals with AD, and that IIV increased in patients as a result of disruptions to axonal integrity that were present as part of the disease process. In further support of this interpretation, demyelination is the primary mechanism of white matter disruption in normal aging (Bartzokis, 2004), and the results reported by Moy et al. (2011) and Fjell et al. (2011) suggest that age-related increases in IIV are primarily associated with decreases in myelin integrity.

Considering the above, the currently observed pattern of data may be indicative of a marker of pathological white matter changes that are independent of the usual age-related white matter changes. More specifically, the current analyses detected associations between IIV and DA in the R-ILF, but no such associations in any other brain regions. Analyses also did not detect any associations between IIV and DR. The R-ILF has consistently been implicated in AD (see, e.g., Kitamura et al., 2013), and AD has consistently been associated with disruptions in axonal integrity (indexed by DA; see, e.g., Amlie & Fjell, 2014 and Skillbäck et al., 2013). Conversely, the ILF has not been implicated in the normal aging process, and white matter disruption during normal aging is thought to reflect a loss of myelin, as opposed to axonal integrity. Although tentative, and in need of further study, this suggestion lends support to the idea that IIV may be a useful tool in detecting neuropathology specific to patients with AD.

It is also possible that the current pattern of data may reflect characteristics of the tasks used in this study. Data from Tamnes et al. (2012) suggest that tasks demanding a higher cognitive load rely on different white matter mechanisms than tasks with relatively less onerous requirements. Using a speeded version of the flanker task², they found that FA

² This task requires participants to respond to the presence of a target arrow in the middle of a screen, bordered by two “flanker” arrows on either side. Participants must indicate whether the target arrow is pointing left or right. On congruent trials, the flanker arrows are both pointing in the same direction as the target arrow.

and DA were associated with IIV_{RT} on the congruent trials only, whereas MD and DR were associated with IIV_{RT} on both congruent and incongruent trials. This pattern of data suggests that better overall white matter integrity underlies more consistent performance, but that when a task requires more attentional control and more complex cognitive processing (i.e., when it is of a higher cognitive load), myelin integrity plays a more important role in performance consistency than axonal integrity does. Hence, it is possible that the current analyses detected an association between DA and IIV_{RT} in the absence of any associations between DR and IIV_{RT} due to the fact that the current RT tasks were of relatively low cognitive load and thus relied less heavily on myelin integrity.

Intraindividual variability and micro-structural white matter in Alzheimer's disease. The current results are partially consistent with those of a previous study examining associations between white matter volume loss and IIV_{RT} in a sample of early-stage AD patients and healthy controls (Jackson et al., 2012). Those authors found a significant negative correlation between IIV_{RT} and white matter volume in the superior frontal gyrus, posterior cingulate, precuneus, and ventral and dorsolateral PFC. The current study extends those findings to micro-structural white matter integrity in AD patients.

There are, however, a number of differences between the current findings and those of Jackson and colleagues. The latter found associations between IIV_{RT} and white matter integrity in several brain regions, whereas the current analyses detected a significant association between IIV_{RT} and white matter integrity in only one brain region. The most obvious way to account for these different findings relates to differences in analytic approach.

On incongruent trials, the flanker arrows are pointing in the opposite direction. During the speeded version of this task, participants are instructed to respond as quickly as possible. Hence, accurate and rapid performance (on the incongruent trials, especially) is thought to demand a higher cognitive load and to require additional cognitive processes (e.g., inhibition and top-down attentional control).

Jackson and colleagues used measures of regional white matter volume in several regions of interest, determined on the basis of brain regions known to be involved in the default-mode network (DMN), which has previously been implicated in IIV (Kelly et al., 2008). In contrast, in the current study I first performed voxelwise group comparisons to determine brain regions with significantly lower FA or significantly higher MD in patients compared to controls. Subsequent analyses then included only those areas where significant between-group differences had been detected. I followed this analytic plan for both practical and theoretical reasons. First, this method cut down significantly on imaging analysis time. Moreover, the aim of the present study was to determine whether IIV was associated with changes in micro-structural white matter and whether these micro-structural changes were indicative of pathological brain changes as they might appear in AD patients. Hence, it made theoretical sense to first identify brain areas where pathological changes were present, and to then assess relations between IIV and micro-structural white matter within these areas. The fact that my analyses did detect an association between IIV_{RT} and white matter integrity in one of these brain regions suggests that increased IIV in the current sample may indeed be related to pathological changes in white matter micro-structure.

A second possible reason for the differences between the current findings and those of Jackson et al. (2012) relates to the tasks used in each study. In their study, Jackson and colleagues obtained a measure of IIV_{RT} from three attentional control tasks, whereas in the current study I obtained a measure of IIV_{RT} from simple and choice RT tasks. As noted earlier, Tamnes et al. (2012) suggest that performance on tasks requiring more attentional control relies more heavily on white matter integrity. If this is the case, one would expect to find stronger associations between IIV and white matter integrity on such tasks than one would on tasks requiring less attentional control. The pattern of findings in the current study supports that speculation. To wit, although the current analyses detected significant

correlations between IIV (on both the SRT and CRT tasks) and measures of micro-structural white matter integrity, regression modelling showed that only IIV on the CRT task was able to predict changes in micro-structural white matter integrity. CRT tasks are more attentionally demanding than SRT tasks, and involve a degree of inhibition not needed in SRT tasks (Burle, Vidal, Tandonnet, & Hasbroucq, 2004; Tuch et al., 2005).

Functional neuroanatomy of the ILF. One of the major findings of the current analyses was that higher IIV_{RT} on the CRT task predicted lower DA in the R-ILF, over and above the effect of mean CRT latency. To better interpret this finding, it is important to look into the structural and functional role of the inferior longitudinal fasciculus.

The inferior longitudinal fasciculus is one of the major occipito-temporal connections, although its exact anatomy and functional role remain under investigation (Ashtari, 2012). For example, although several early studies indicated that the ILF has structural connections to occipital and temporal regions, two recent studies have differed in their conclusions regarding its hemispheric lateralization. In their analyses of DTI data from a sample of 24 healthy adults, as well a post-mortem examination of 15 brains, Latini et al. (2017) found that the right ILF had more structural connections to other brain regions than did the left ILF. Panesar et al. (2018) reported a directly contrasting result, however: They used deterministic generalised Q-Sampling Imaging on 30 healthy adults, and found comparatively more structural connections between the ILF in the left hemisphere and other brain regions. Similarly, studies have differed in their conclusions regarding the functional role of the ILF. Some have implicated it in the semantic language system and in facial recognition (Panesar et al., 2018), whereas others have highlighted its role in visual, emotional, and semantic autobiographical memory (Hodgetts et al., 2017; Latini et al., 2017; Shinoura et al., 2007).

Because IIV is higher on tasks tapping into attentional control, and on tasks with a higher cognitive load, one might expect associations between white matter integrity in the

ILF and IIV_{RT} if that brain region played an important role in attentional control or higher-order cognitive functioning. However, several studies examining the neural correlates of attentional control have found frontal and parietal (rather than occipital and temporal) regions to be associated with attentional control (Berry, Sarter, & Lustig, 2017; Wang et al., 2010). Similarly, resting state fMRI studies suggest the ILF is not a part of the task-related attentional network (Kelly et al., 2008).

Several studies have, however, found an association between the structural integrity of the ILF and various aspects of visual processing, such as spatial awareness, objection location, and attentional shifts during visual perceptual processing (see e.g., Latini et al., 2017; Shinoura et al., 2007; Shinoura et al., 2009). Of note here, then, is that performance on the RT tasks used in the current study relies in part on these visual processes. On both the SRT and CRT tasks, participants had to visually monitor the screen for the presence of the target stimulus (e.g., on the CRT task, participants had to identify the correct position of the target stimulus from amongst five possible locations, and had to shift their attention to the correct location in order to respond accurately). It is therefore possible that the current analyses detected an association between micro-structural white matter integrity in an area of the R-ILF and IIV on the RT tasks because of the role the ILF plays in visual processing.

The above suggestion is supported by the fact that white matter integrity in the R-ILF predicted IIV on the CRT, but not the SRT. Because performance on the CRT task relies to a greater extent on these visual processes, one would expect to see a more robust relationship between white matter integrity in an area underlying these processes and IIV on that task. This proposal is consistent with findings from a prior study that examined the relationship between IIV on a CRT task and micro-structural white matter integrity in a group of healthy young adults. Tuch et al. (2005) found that IIV was significantly associated with the integrity of various white matter pathways supporting visuospatial attention, but was not associated

with integrity of white matter pathways supporting motor functions or with integrity of the corpus callosum.

Limitations and Directions for Future Research

The following limitations must be borne in mind when evaluating this study's findings. First, the current results might have been confounded by the presence of unmeasured vascular pathology in the sample. Although eligibility criteria specified that individuals with a known history of stroke and other neurological disorders that impact on white matter integrity would be excluded from participation, the clinical group included patients diagnosed with mixed dementia (i.e., concurrent Alzheimer's and vascular dementia). Furthermore, age-related vascular changes are common in those with Alzheimer's disease (frequently at sub-clinical levels) as well as in healthy older individuals (Gorelick et al., 2011; Rincon & Wright, 2013). Hence, it is not clear whether the observed associations between IIV_{RT} and micro-structural white matter integrity are strictly related to the white matter changes seen in AD and normal aging, or whether a loss of white matter integrity as a result of vascular pathology played a role.

A second general limitation relates to the nature of the cognitive measures and the way in which they were used. Both the SRT and CRT tasks have a relatively low cognitive load compared to the executive function and attention control tasks used by other researchers (e.g., Jackson et al., 2012; Tamnes et al., 2012), and they were administered multiple times over several test sessions. These characteristics of the tasks and the procedure could have resulted in boredom and a lack of task engagement, especially in higher-functioning participants. Previous studies suggest that a lack of task engagement results in slower RT latencies and artificially increased IIV (Garrett, MacDonald, & Craik, 2012; Pan, Shell, & Schleifer, 1994; Wang, Ding, & Kluger, 2014). Moreover, the SRT task was always

administered before the CRT task. Hence, lack of task engagement and fatigue effects might have had disproportionate effects on mean RT latencies, as well as IIV_{RT} , for the CRT task.

A third general limitation relates to sample size. Although several published studies in this field have used samples smaller than the current one (see, e.g., Kim et al., 2015; Lin et al., 2014; Rémy et al., 2015), the current N of 36 means one has to be cautious in making strong inferences on the basis of, or generalizing substantially from, the current results. A related limitation is that, because analyses combined data from the clinical and control groups in order to increase statistical power, it was not possible to engage in meaningful examination of between-group differences in the magnitude of association between micro-structural white matter integrity and intraindividual variability. Hence, the current analyses do not allow comment on whether the observed associations between IIV and micro-structural white matter integrity are driven more strongly by the clinical group or by the control group, or whether each contributed relatively equally.

In addition to the above limitations, the use of DTI, and interpretation of DTI-based data, requires some critical thought. Although advances have been made in the use of this imaging method for measuring disruptions in white matter integrity, several authors still advise caution when interpreting axonal and myelin integrity on the basis of such measures (see, e.g., Alexander et al., 2007; Soares et al., 2013). There are multiple reasons this caution is warranted. First, the presence of crossing white matter tissue fibres in numerous brain regions makes it difficult to accurately determine whether disruptions are due to axonal or to myelin degeneration (Assaf & Pasternak, 2008; Hagmann et al., 2006; Mori & Zhang, 2006; Winklewski et al., 2018). Second, both myelin and axonal degeneration are present in several different diseases, and the mechanisms of degeneration are varied. For example, several studies have highlighted the importance of interactions between myelinated and unmyelinated axons, and axonal disruption has been shown to occur secondarily to disruptions in myelin

integrity (Beirowski, Babetto, & Wrabetz, 2016; Klingseisen & Lyons, 2018; Nguyen et al., 2009; Popko, 2010). On the other hand, one study (a mouse model of myelin-related disease) showed that demyelination does not necessarily lead to axonal degeneration (Smith, Cooksey, & Duncan, 2013). Hence, caution is warranted in concluding that the observed associations between IIV_{RT} and micro-structural white matter integrity are due purely to disruptions in axonal integrity, as it is possible that disruptions in axonal integrity in the current sample are related to or caused by disruptions in myelin integrity.

A further limitation relates to the increased possibility of Type II error when using voxelwise between-group comparisons. In other words, it is possible that some brain regions with decreased white matter integrity in patients were not detected as they did not survive the statistical cluster thresholds of $p < .01$ and $p < .05$.

To address these limitations, and to thereby allow firmer conclusions regarding associations between IIV and micro-structural white matter integrity, future studies should:

(a) include separate clinical and control groups, taking care to exclude participants with vascular pathology. Although Jackson et al. (2012) attempted this strategy in their study, they also used a relatively small sample of AD patients ($n = 33$), and may therefore have missed significant between-group differences in their analyses;

(b) use longitudinal studies of both AD patients and healthy controls to further examine the exact associations between IIV_{RT} and micro-structural white matter integrity, in terms of both axonal and myelin disruption;

(c) use more engaging tasks and ensure that these tasks are counter-balanced in their presentation; and

(d) ensure their investigations are adequately powered by including larger numbers of participants.

In addition to the above recommendations, it would be interesting to see whether the observed associations between IIV_{RT} and micro-structural white matter integrity remain when IIV is measured over a single time-frame of minutes or hours. I calculated IIV in the current study using RT measures obtained over six administrations spanning three test sessions. IIV measured in macro-time compared to that measured over a single time-frame of minutes or hours (micro-time) provides a more reliable measure of variability (Ram & Gerstorf, 2009). IIV measured in micro-time, however, is more easily obtained and thus might be a more fruitful avenue in investigating the clinical utility of IIV. To date, there is only one published study examining associations between IIV_{RT} in micro-time and white matter integrity in a sample of AD patients and matched healthy controls. That study found no significant between-group differences in terms of this association (Jackson et al., 2012). As mentioned previously, however, those authors used a small sample and examined white matter volume as opposed to micro-structural white matter integrity.

Summary and Conclusion

Despite several methodological limitations, the current study provides evidence for an association between intraindividual variability in reaction time and micro-structural white matter integrity in older adults, including those with mild-to-moderate Alzheimer's disease. The major findings were that there were significant associations between intraindividual variability on both reaction time tasks (simple and choice reaction time) and measures of micro-structural white matter integrity. Furthermore, higher intraindividual variability on the choice reaction time task predicted decreased micro-structural white matter integrity in the right inferior longitudinal fasciculus over and above mean choice reaction time latency. These results suggest that further investigation into these associations (e.g., longitudinal designs focusing specifically on whether intraindividual variability in cognitive performance can predict pathological changes in white matter) might be a fruitful avenue for future

research. Such studies will shed light on the possible diagnostic utility of intraindividual variability measures for detecting pathological brain changes during the early stages of age-related degenerative diseases, when treatments and interventions are most likely to be effective.

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Appendix A
Participant Information Sheet

PARTICIPANT INFORMATION LEAFLET

TITLE OF THE RESEARCH PROJECT: Intraindividual Variability in the Progression of Alzheimer's disease: A longitudinal trajectory of cognitive decline

PROTOCOL NUMBER: HREC/REF: 167/2014

PRINCIPAL INVESTIGATOR: Mr. Bjorn U. Christ

ADDRESS: Department of Psychology, PD Hahn Psychology Building, University Avenue,
University of Cape Town, Rondebosch, Cape Town, 7701

CONTACT NUMBER: +27 72 0710 346

I am inviting you to participate in a research project that looks at how memory and other mental functions change with time. Please take some time to read the information presented in this information leaflet, because it explains the details of this project so that you can understand what this project is about. If you have any questions about this project, or if you want more information, please feel free to ask me (or your doctor at the memory clinic). It is very important that if you decide to participate in this study that you understand what this study is about and that all of your questions are answered before you participate.

Your participation is entirely voluntary - this means that you don't have to participate if you don't want to - and you are free to decline to participate. If you say no, and don't want to participate, then this will not affect you negatively in any way whatsoever. It will not affect any future medical treatment you may need, and it won't affect your treatment that you currently receive. If you decide that you do not want to take part in the study anymore, even though you said that you did want to, you are welcome to stop participating. You can stop participating in this study at any stage of the study, and you do not have to give a reason for stopping. If you do stop, it will not affect your future medical treatment.

This study has been approved by the Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town. This means that all the parts of this study, for example its design, procedures, and the materials and equipment that are used for the research, have been evaluated by an administrative authority and found to be respectful of the feelings and rights of its research participants. Furthermore, the study will be conducted according to the ethical guidelines and principles of the International Declaration of Helsinki, the South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research. These guidelines will ensure that this study upholds a range of research practices that are accepted all over the world to be fair and respectful towards participants.

The project is being run by the Applied Cognitive Sciences and Experimental Neuropsychology Testing (ACSENT) laboratory and the Divisions of Neurology and Geriatric Medicine in the Department of Medicine at the University of Cape Town. This means the project is supported and supervised by experienced and qualified researchers within the Psychology Department and the Department of Medicine at the University of Cape Town. Furthermore, I aim to recruit a total of 90 people to take part in the study. This will happen over a period of 18 months.

What is this research study all about?

Some people develop memory problems as they get older. Many elderly people have mild memory difficulties. However, in a few, the problem may be more severe. I am interested in finding out more about how the difficulties with memory and other higher brain functions change over time. In order to do so, I should like to investigate the course of these changes using a small number of methods. These include questions you would need to answer about yourself and tests of memory and other higher brain functions.

I am interested in testing people both with memory difficulties and those without, so that we can compare the two groups. In this way I might be able to better understand the progression of change in brain function associated with memory impairment. My research findings may aid in the early detection and treatment of these conditions and help improve the design of drug intervention trials associated with these conditions in the future.

Procedures

If you agree to take part in the study you will be required to partake in a short telephonic interview about your medical history. This is done to ensure you meet all the conditions required to enter the study. You will then be invited to visit our clinic on three separate days over a two week period. At these visits to our clinic I shall:

- (1) interview your relative/friend (someone who knows you well) to find out whether he/she thinks you have any memory difficulties.
- (2) ask you to complete a short questionnaire about your mental and emotional functioning.
- (3) perform tests of your memory and other higher mental functions. These will be conducted in a quiet, relaxed atmosphere. I expect that these tests will be about an hour's duration. However, there will be opportunities to rest in-between tests.

The questionnaires and the tests will be administered during the first visit, however for the subsequent two visits you will only be required to complete the tests. After the three baseline visits I would like to re-assess your memory and other higher functions again after six months and twelve months, respectively, provided you continue to consent to participation in the study.

If I find that you or your relative/friend has a significant memory problem that is interfering with your daily living activities, we shall refer you to a Memory Clinic. Your permission will always be sought first.

What will your responsibilities be?

You will be required to attend the study visit at the appropriate time and to participate as fully as you can with the tests and questionnaires. You should answer the questions as fully and honestly as you can. If there are any questions that you cannot, or do not wish to answer, you should tell us so.

Will you benefit from taking part in this study?

You will receive little direct benefit from the study. However, you will undergo a range of cognitive tests. As previously indicated, we shall, with your permission, refer you to the appropriate medical services if any treatable abnormalities are found.

Are there any risks in your taking part in this research?

You may feel uncomfortable about answering some of the questions about yourself or your friend/relative. Some people don't like talking, or knowing about, problems related to memory or thinking. You should feel free to mention your feelings or concerns to any member of the study team.

If you do not agree to take part, what alternatives do you have?

You are free not to participate in the study or to refuse parts of the study.

Who will have access to your medical records?

The information collected about you will be treated as confidential and protected. If it is used in a publication or thesis, your identity will remain anonymous. Only the direct study team will have full access to the information. If we need to refer you to a clinic for treatment, we will provide them with the relevant information needed to treat your condition.

Will you be paid to take part in this study and are there any costs involved?

You will not be paid to take part in the study but your transport costs will be covered for the study visit. You will be reimbursed for the sum of R50-00 at each visit to the research site. There will be no costs involved for you, if you do take part.

Is there anything else that you should know or do?

- You should inform your family practitioner or usual doctor that you are taking part in a research study.
- You can contact me on 072 0710 346 if you have any further queries or encounter any problems.

- You can contact the Research Ethics Committee of the Health Sciences Faculty of the University of Cape Town 021-4066338 if you have any concerns or complaints that have not been adequately addressed by your study doctor.
- You will receive a copy of this information for your own records.

Appendix B

DSM-IV diagnostic criteria for dementia of the Alzheimer's type

Diagnostic and Statistical Manual of Mental Disorders, 4th ed., American Psychiatric Association, 1994; p142.

- A. The development of multiple cognitive deficits manifest by both
- (1) memory impairment AND
 - (2) one (or more) of the following cognitive disturbances:
 - (a) aphasia (language disturbance)
 - (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
 - (c) agnosia (failure to recognize objects despite intact sensory function)
 - (d) disturbance in executive functioning (i.e. planning, organization, sequencing, abstracting).
- B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

The deficits do not occur exclusively during the course of a delirium.

Appendix C
Clinical Dementia Rating (CDR)

Ref: Hughes CP *et al. British Journal of Psychiatry* 1982; 140: 566-572

	Impairment Level and CDR Score (0, 0.5, 1, 2, 3)				
	None	Questionable	Mild	Moderate	Severe
	0	0.5	1	2	3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	No pretense of independent function outside home Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Appendix D

Study Flyer

Memory Study!

Participate in research on memory

Are you over 55 years old?

Would you like to be part of a research project in Cape Town that studies how memory and other brain functions change with time?

We are looking for people who may be experiencing memory difficulties (such as forgetting names of people, places, where you have put things, etc.).

The Research

We are interested in finding out more about how difficulties with memory and other higher brain functions change as people get older.

The information may in the future aid earlier detection and improved management of memory problems.

This study has been approved by the UCT/GSH Research Ethics Committee

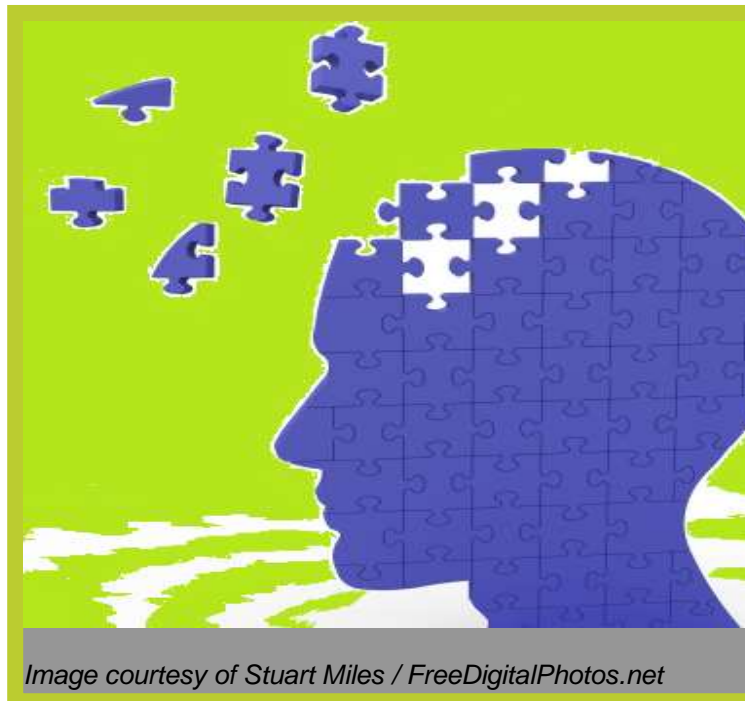


Image courtesy of Stuart Miles / FreeDigitalPhotos.net

Benefits

- You will be contributing to important research in the field of memory and aging
- You will be compensated for your travel costs
- A report will be sent to your GP on request

Would you like to take part in an important research project on memory?

The Procedure

- The study will take place over 12 months.
- You will visit us on a few occasions over the 12-month span.
- Each visit will require you to complete a small number of tests and questionnaires
- Each visit will range between 60 and 90 minutes.
- You will be compensated for your travel costs.
- Although we do not provide medication we shall advise your GP or refer you to a clinic if necessary.

Please Note: All participation is voluntary and participants may withdraw at any stage. Confidentiality of all data is ensured



Image courtesy of ratch0013 / FreeDigitalPhotos.net

**FOR ADDITIONAL INFORMATION
OR TO SCHEDULE A PRE-
SCREENING APPOINTMENT
PLEASE CONTACT:**

Bjorn Christ

Cell: project number

Email: project email

Appendix E

MRI Scanning Protocol

Scanning protocol – WMC and IIV in AD

The time of each acquisition is called TA (total acquisition)

Localizer (TA: 0:54)

T1 high resolution structural

imaging: MEMPRAGE_1mm_iso_iPATx3 (TA: 5:21) (5:21 means 5 mins and 21 sec)

Resting state:

Field map:gre_field_mapping (TA: 1:10)

Resting state acquisition: ep2d_Resting (TA: 6:08)

Diffusion tensor imaging in AP direction: BME_DTI_30gr_4b0_2mm_ISO_52sl_AP
(TA: 6:14)

Diffusion tensor imaging in PA

direction: BME_DTI_30gr_4b0_2mm_ISO_52sl_PA (TA: 6:14)

FLAIR for fluid attenuation using tirm: t2_tirm_tra_dark-fluid (TA: 4:32)

3D Susceptibility weighted imaging (SWI3D): t2_swi3d_tra_p2_1.5mm (TA: 4:54)

Proton Density weighted sequence.

Appendix F

Informed Consent Form

TITLE OF THE RESEARCH PROJECT: Intraindividual Variability in the Progression of Alzheimer's disease: A longitudinal trajectory of cognitive decline

PROTOCOL NUMBER: HREC/REF: 167/2014

PRINCIPAL INVESTIGATOR: Mr. Bjorn U. Christ

ADDRESS: Department of Psychology, PD Hahn Psychology Building, University Avenue,
University of Cape Town, Rondebosch, Cape Town, 7701

CONTACT NUMBER: +27 72 0710 346

I am inviting you to participate in a research project. Please take some time to read the information presented here. It explains the details of the project. If there are any aspects of the project you do not understand, please do not hesitate to ask the study staff or doctor. It is important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Your participation in the study is entirely voluntary and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. It will not affect any future medical treatment you may need. You are also free to withdraw from the study at any point, even if you did initially agree to take part. You do not have to give a reason for withdrawing.

This study has been approved by the Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town. It will be conducted according to the ethical guidelines and principles of the International Declaration of Helsinki, the South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

This trial is being run by the Applied Cognitive Sciences and Experimental Neuropsychology Testing (ACSENT) laboratory and the Divisions of Neurology and Geriatric Medicine in the Department of Medicine at the University of Cape Town. I aim to recruit a total of 90 participants over a period of 18 months.

What is this research study all about?

Some people develop memory problems as they get older. Many elderly people have mild memory difficulties. However, in a few, the problem may be more severe. I am interested in finding out more about how the difficulties with memory and other higher brain functions change over time. In order to do so, I should like to investigate the course of these changes using a small number of methods. These include questions you would need to answer about yourself and tests of memory and other higher brain functions.

I am interested in testing people both with memory difficulties and those without, so that we can compare the two groups. In this way I might be able to better understand the progression of change in

brain function associated with memory impairment. My research findings may aid in the early detection and treatment of these conditions and help improve the design of drug intervention trials associated with these conditions in the future.

Procedures

If you agree to take part in the study you will be required to partake in a short telephonic interview about your medical history. This is done to ensure you meet all the conditions required to enter the study. You will then be invited to visit our clinic on three separate days over a two week period. At these visits to our clinic I shall:

- (4) interview your relative/friend (someone who knows you well) to find out whether he/she thinks you have any memory difficulties.
- (5) ask you to complete a short questionnaire about your mental and emotional functioning.
- (6) perform tests of your memory and other higher mental functions. These will be conducted in a quiet, relaxed atmosphere. I expect that these tests will be about an hour's duration. However, there will be opportunities to rest in-between tests.

The questionnaires and the tests will be administered during the first visit, however for the subsequent two visits you will only be required to complete the tests. After the three baseline visits I would like to re-assess your memory and other higher functions again after six months and twelve months, respectively, provided you continue to consent to participation in the study.

If I find that you or your relative/friend has a significant memory problem that is interfering with your daily living activities, we shall refer you to a Memory Clinic. Your permission will always be sought first.

What will your responsibilities be?

You will be required to attend the study visit at the appropriate time and to participate as fully as you can with the tests and questionnaires. You should answer the questions as fully and honestly as you can. If there are any questions that you cannot, or do not wish to answer, you should tell us so.

Will you benefit from taking part in this study?

You will receive little direct benefit from the study. However, you will undergo a range of cognitive tests. As previously indicated, we shall, with your permission, refer you to the appropriate medical services if any treatable abnormalities are found.

Are there any risks in your taking part in this research?

You may feel uncomfortable about answering some of the questions about yourself or your friend/relative. Some people don't like talking, or knowing about, problems related to memory or thinking. You should feel free to mention your feelings or concerns to any member of the study team.

If you do not agree to take part, what alternatives do you have?

You are free not to participate in the study or to refuse parts of the study.

Who will have access to your medical records?

The information collected about you will be treated as confidential and protected. If it is used in a publication or thesis, your identity will remain anonymous. Only the direct study team will have full access to the information. If we need to refer you to a clinic for treatment, we will provide them with the relevant information needed to treat your condition.

Will you be paid to take part in this study and are there any costs involved?

You will not be paid to take part in the study but your transport costs will be covered for the study visit. You will be reimbursed for the sum of R50-00 at each visit to the research site. There will be no costs involved for you, if you do take part.

Is there anything else that you should know or do?

- You should inform your family practitioner or usual doctor that you are taking part in a research study.
- You can contact me on 079 334 4404 if you have any further queries or encounter any problems.
- You can contact the Research Ethics Committee of the Health Sciences Faculty of the University of Cape Town 021-4066338 if you have any concerns or complaints that have not been adequately addressed by your study doctor.
- You will receive a copy of this information and consent form for your own records.

Declaration by participant and/or friend/relative/guardian

By signing below, I, hereby agree to take part in the research study entitled: "Intraindividual Variability in the Progression of Alzheimer's disease: A longitudinal trajectory of cognitive decline"

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) on (*date*)2017

.....
Signature of participant

.....
Signature of witness

.....
Signature of relative/friend/guardian

.....
Signature of witness

Declaration by investigator

I (*name*) declare that:

- I explained the information in this document to
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above

Signed at (*place*) on (*date*) 2017

.....
Signature of investigator

.....
Signature of witness

Appendix G
MRI Checklist



Cape Universities Brain Imaging Centre (CUBIC)

MRI Volunteer Screening Form

Volunteer Information:

Name	Contact number
Date of Birth	Project name
Weight	Principle investigator

The following information is very important to ensure your safety and to prevent any interference during the MR procedure.

Please answer the following questions (mark with an X):

	Yes	No	Don't Know
Pacemaker			
Aneurism clips			
Artificial heart valve			
Vena cava filter			
Prosthesis (e.g. eye, breast etc)			
Shrapnel in eye or body			
Neurostimulator			
Cochlear implant (ear) or hearing aid			
? Diabetic			
? Renal impairment			

? Asthma			
? Allergies			
? Any other implants (e.g. screws, plates, joint replacements)			
? Pregnant			
? Previous MRI investigation with intravenous contrast			
Is there any other device implanted or are there any other ailments that you think that we should be aware of?			

I hereby acknowledge that the potential risks of the examination have been explained to me and that during the course of the investigation it may be necessary for the intravenous injection of a contrast agent.

Attention: It is the policy of this institution not to discuss results of the MR investigation with the patients for ethical reasons. All enquiries in this regard should be directed to the referring physician.

Signature:

Date:

Cape Universities Brain Imaging Centre

Fisan Building, Faculty of Health Sciences, University of Stellenbosch, Tygerberg, 7505

Tel: 27-21-938-9646 Fax: 27-21-938-9728 www.sun.ac.za/cubic

Appendix H

MRI Consent Form

TITLE OF THE RESEARCH PROJECT: Intraindividual Variability in the Progression of Alzheimer's disease: A longitudinal trajectory of cognitive decline

PROTOCOL NUMBER: 167/2014

PRINCIPAL INVESTIGATOR: Mr. Bjorn U. Christ
SECONDARY INVESTIGATOR: Ms. Kara Engelbrecht

ADDRESS: Department of Psychology, PD Hahn Psychology Building, University Avenue, University of Cape Town, Rondebosch, Cape Town, 7701

CONTACT NUMBER: +27 72 0710 346

I am inviting you to receive a magnetic resonance imaging scan (MRI) as part of a research project. Please take some time to read the information presented here. It explains the details of the MRI scanning procedure. **PLEASE NOTE:** For specific details of the project please refer to your **INFORMATION LEAFLET**. This consent form will only describe the details of the MRI scan.

If there are any aspects of the project you do not understand, please do not hesitate to ask the study staff or doctor. It is important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Your participation in the study is entirely voluntary and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. It will not affect any future medical treatment you may need. You are also free to withdraw from the study at any point, even if you did initially agree to take part. You do not have to give a reason for withdrawing.

This study has been approved by the Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town. It will be conducted according to the ethical guidelines and principles of the International Declaration of Helsinki, the South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

This trial is being run by the Applied Cognitive Sciences and Experimental Neuropsychology Testing (ACSENT) laboratory and the Divisions of Neurology and Geriatric Medicine in the Department of Medicine at the University of Cape Town. I aim to recruit a total of 90 participants over a period of 18 months.

What is a magnetic resonance imaging (MRI) scan?

Magnetic resonance imaging is a procedure used to scan the body without X-rays. The MRI device utilizes a very strong magnet. This magnet sends out powerful magnetic fields during the examination. The magnetic fields allow us to pick up signals arising from the brain which are then measured and captured by a computer. The computer then turns the signals from the brain into pictures of the brain. The scan is completely painless and, to our knowledge, damaging long-term effects from the procedure have not been detected.

What does the scan involve?

The MRI machine consists of an enclosed tube or tunnel with a narrow bed placed inside, where you will lie for the duration of the scan. The scan will take approximately 40 minutes. During the scan, while you lie on the narrow bed, you will hear loud thudding noises. It is very important that you lie completely still because even slight movements will blur the image.

Procedures

If you agree to undergo an MRI you will be required to complete a short MRI safety questionnaire. This is done to assess your risk prior to the scan and to ensure your safety during the MRI procedure. Once you have completed the questionnaire the MRI technician will explain the full MRI procedure to you in preparation for your scan.

You will not be required to perform any additional tasks while you are in the MRI scanner.

Are there any risks in your taking part in this research?

The MRI scanning procedure requires that you be confined in a small partially enclosed space. Some individuals find this to be uncomfortable and may become nervous. During the scan you may also hear loud thudding noises. We will however attempt to reduce the noise through our noise reduction facilities.

In addition, the magnetism of the machine attracts certain metals; therefore, people with these metals within their bodies (such as pacemakers, infusion pumps, aneurysm clips, metal prostheses, joints, rods, or plates) will be excluded from the scanning component of the study. The “metal” in dental fillings is less responsive to magnetism and is therefore allowed.

The MRI technician will ask you if you have any metals within your body. **You will be expected to notify the investigator conducting the study of any metal in your body, other than dental fillings.** There are no other known side effects resulting from exposure to the MRI scan.

Because this is a research procedure, there may be risks that are currently unforeseeable. In the studies performed so far, there have been no significant risks reported in animals or humans for similar exposures.

If you do not agree to take part, what alternatives do you have?

You are free not to participate in the study or to refuse parts of the study.

Who will have access to your medical records?

The information collected about you – which includes your Groote Schuur Hospital medical history (e.g. the records of the Geriatric Unit and the Memory Clinic), cognitive test performance, and MRI data – will be treated as confidential and protected. If it is used in a publication or thesis, your identity will remain anonymous. Only the direct study team will

have full access to the information. If we need to refer you to a clinic for treatment, we will provide them with the relevant information needed to treat your condition.

Will you be paid to take part in this study and are there any costs involved?

You will not be paid to take part in the study but your transport costs will be covered for the study visit. You will be reimbursed for the sum of R200-00 at each visit to the research site. There will be no costs involved for you, if you do take part.

Is there anything else that you should know or do?

- You should inform your family practitioner or usual doctor that you are taking part in a research study.
- You can contact me on +27 72 0710 346 if you have any further queries or encounter any problems.
- You can contact the Research Ethics Committee of the Health Sciences Faculty of the University of Cape Town 021-4066338 if you have any concerns or complaints that have not been adequately addressed by your study doctor.
- You will receive a copy of this information and consent form for your own records.

PLEASE FIND THE DECLARATION ON THE FOLLOWING PAGE

Declaration by participant and/or friend/relative/guardian

By signing below, I, hereby agree to take part in the research study entitled: “Intraindividual Variability in the Progression of Alzheimer’s disease: A longitudinal trajectory of cognitive decline”

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) on (*date*)2016

.....
Signature of participant

.....
Signature of witness

.....
Signature of relative/friend/guardian

.....
Signature of witness

Declaration by investigator

I (*name*) declare that:

- I explained the information in this document to
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above

Signed at (*place*) on (*date*) 2016

.....
Signature of investigator

.....
Signature of witness

Appendix I

Ethics Approval Forms



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492 • Facsimile [021] 406 6411
Email: Sumayah.ariel@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

03 June 2014

HREC/REF: 167/2014

Dr K Thomas
Psychology
Room no:2.17
PD Hahn Building
Upper Campus -UCT

Dear Dr Thomas

Project Title: INTRAINDIVIDUAL VARIABILITY IN THE PROGRESSION OF ALZHEIMER'S DISEASE: A LONGITUDINAL TRAJECTORY OF COGNITIVE DECLINE-(Doctorate-Bjorn Christ)

Thank you for your letter dated 02 June 2014, addressing the issues raised by the Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above mentioned study.

Approval is granted for one year until the 30 June 2015.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

We acknowledge that the following student:- Bjorn Christ is also involved in this project.

Please note that the on-going ethical conduct of the study remains **the** responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

signature removed to avoid exposure online

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Hrec/ref:167/2014

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Ethics Approval Update and Amendment

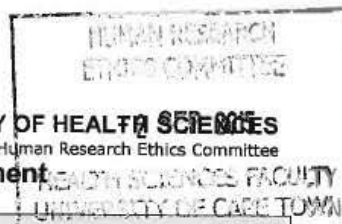


UNIVERSITY OF CAPE TOWN
UNIBESITHI YITHA AFRIKANYANZIYOZI YI VANDERBEEK

FACULTY OF HEALTH SCIENCES

Human Research Ethics Committee

Form FHS006: Protocol Amendment



HREC office use only (FWA00001637; IRB00001938)			
<input checked="" type="checkbox"/> Approved	<input checked="" type="checkbox"/> Type of review Expedited	<input type="checkbox"/> Full committee	
This serves as notification that all changes and documentation described below are approved.			
Signature Chairperson of the HREC	signature removed	Date	14/2/2015

Note: All amendments should include a Synopsis justifying the changes for the amendment (please see notice dated 23 April 2012)

Principal Investigator to complete the following:

The HREC also believe that the addition of MRI scanning is a major amendment

1. Protocol information

Date form submitted	
HREC REF Number	167/2014
Protocol title	Intraindividual Variability in the Progression of Alzheimer's disease: A longitudinal trajectory of recovery
Protocol number (if applicable)	
Principal Investigator	Associate Professor Kevin G. F. Thomas
Department / Office Internal Mail Address	Department of Psychology, Private Bag, Rondebosch 7700
1.1 Is this a major or a minor amendment? (see FHS006hlp) Major (tick box) Minor (tick box)	<input type="checkbox"/> Major <input checked="" type="checkbox"/> Minor
1.2 Does this protocol receive US Federal funding?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
1.3 If the amendment is a major amendment <u>and</u> receives US Federal Funding, does the amendment require full committee approval?	<input type="checkbox"/> Yes <input type="checkbox"/> No

2. List of Proposed Amendments with Revised Version Numbers and Dates

<p>Please itemise on the page below, all amendments with revised version numbers and dates, which need approval. This page will be detached, signed and returned to the PI as notification of approval. Please add extra pages if necessary.</p>
<p>Protocol Amendment 1 (September 3, 2015)</p> <p>This amendment describes the addition of a Magnetic Resonance Imaging (MRI) procedure to the study protocol. Each participant will undergo a structural MRI scan, using a diffusion tensor imaging (DTI) sequence, at either the first or second research visit. The DTI data will allow us to measure cerebral white matter integrity, and to correlate the degree of that structural integrity with cognitive performance.</p> <p>As part of the amendment, we submit the following documents related to the MRI scanning procedure:</p> <p>(a) an MRI-specific consent form; and, (b) a MRI-specific safety checklist.</p>



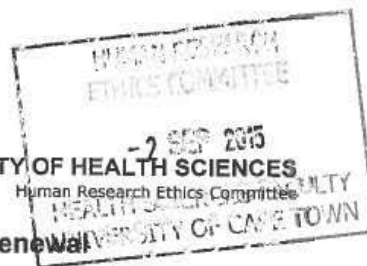
FACULTY OF HEALTH SCIENCES

Human Research Ethics Committee

HEALTH SCIENCES FACULTY

UNIVERSITY OF CAPE TOWN

FHS016: Annual Progress Report / Renewal



HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
<input checked="" type="checkbox"/> Approved	Annual progress report	Approved until/next renewal date	30.6.2016
<input type="checkbox"/> Not approved	See attached comments		
Signature Chairperson of the HREC	signature removed	Date Signed	2/12/2015
Comments to PI from the HREC			

Principal Investigator to complete the following:

1. Protocol information

Date form submitted			
HREC REF Number	167/2014	Current Ethics Approval was granted until	30 June 2015
Protocol title	Intraindividual Variability in the Progression of Alzheimer's disease: A longitudinal trajectory of recovery		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Associate Professor Kevin G. F. Thomas		
Department / Office Internal Mail Address	Department of Psychology, UCT, 7700		
1.1 Does this protocol receive US Federal funding?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	

Ethics Approval Update



FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)
This serves as notification of annual approval, including any documentation described below.

<input checked="" type="checkbox"/> Approved	Annual progress report	Approved until/next renewal date	30/4/19
<input type="checkbox"/> Not approved	See attached comments		
Signature Chairperson of the HREC	signature removed to avoid exposure online	Date Signed	29/4/2018
Comments to PI from the HREC <i>Please see separate HREC letter as well. Thank you</i>			

Principal investigator to complete the following:

1. Protocol Information

Date form submitted	18/04/2018
HREC REF Number	187/2014
Current Ethics Approval was granted until	30 June 2016
Protocol title	Intraindividual Variability in the Progression of Alzheimer's disease: A longitudinal trajectory of recovery
Protocol number (if applicable)	
Are there any sub-studies linked to this study?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
If yes, could you please provide the HREC Refs for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.	
Principal Investigator	Associate Professor Kevin G. F. Thomas
Department / Office Internal Mail Address	Department of Psychology, UCT, 7700
HUMAN RESEARCH ETHICS COMMITTEE 17 APR 2018 HEALTH SCIENCES FACULTY UNIVERSITY OF CAPE TOWN	
1.1 Does this protocol receive US Federal funding?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	<input type="checkbox"/> Yes <input type="checkbox"/> No

1-3 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
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2. List of documentation for approval

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3. Protocol status (tick ✓)

<input type="checkbox"/>	Open to enrolment
<input checked="" type="checkbox"/>	Closed to enrolment (tick ✓)
<input type="checkbox"/>	Research-related activities are ongoing
<input type="checkbox"/>	Research-related activities are complete, long-term follow-up only
<input checked="" type="checkbox"/>	Research-related activities are complete, data analysis only
<input type="checkbox"/>	Main study is complete but sub-study research-related activities are ongoing
<input type="checkbox"/>	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	52
Number of participants enrolled since last HREC Progress report (continuing review)	9
Additional number of participants still required	0

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	5
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6. Cumulative summary of participants

Total number of participants who provided consent	60
Number of participants determined to be ineligible (i.e. after screening)	8
Number of participants currently active on the study	0
Number of participants completed study (without events leading to withdrawal)	52 – Wave 1
	50 – Wave 2
	42 – Wave 3
Number of participants withdrawn at participants' request (i.e. changed their mind)	2
Number of participants withdrawn by PI due to toxicity or adverse events	0
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	0

Number of participants lost to follow-up (please comment below on reasons for loss of follow-up)	10
Two participants were deemed ineligible by study criteria after screening for Wave 2. A further eight participants were lost to follow-up at Wave 3: five withdrew, two were unreachable, and one participant moved to a different city.	
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	0

7. Progress of study

Please describe the overall progress and indicate the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:

Since the last annual report we have successfully recruited 9 additional research participants, concluding recruitment of the study, and we successfully completed the MRI scanning protocol and all three waves of data collection. The study is currently in the data analysis phase.

We would however like to bring to the committee's attention that an annual progress report was not submitted in 2016 or 2017 and that we would like to report these missed deadlines as incidents of non-compliance. The report of non-compliance due to these missed deadlines is outlined in the attached letter.

8. Protocol violations and exceptions (tick ✓ all that apply)

No prior violations or exceptions have occurred since the original approval

Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved

Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

No prior amendments have been made since the original approval

Prior amendments have been reported since the last review and have already been approved

New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS008). Specific changes in the amended protocol and consent/assent forms must be bolded, italicised or tracked and all changes must include a rationale.

10. Adverse events

20 September 2013

Page 3 of 8

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

FHS016

10.1 Please provide below or attach a narrative summary of serious adverse events and/or unanticipated problems, since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.

No adverse events were experienced.

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?

Yes No Not applicable

If yes, please describe:

Participants who were found to score unusually high on our depression scale were given a note to forward to their GP explaining their performance and outlining psychiatric services the GP could recommend them to.

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. MCC, FDA)?

Yes No Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?

Yes No Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.

Agency Name	Report attached	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not applicable
	DSMB report attached	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?

Yes No

If yes, please explain:

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:

Increased

Decreased



FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

<input checked="" type="checkbox"/>	Shown no change
If there has been a change, please explain:	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.

13. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)

Yes No

If yes, please explain and if necessary attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form (FHS013):

14. Signature

My signature certifies that the above is complete and correct.

Signature of PI	signature removed to avoid exposure online	Date	April 11, 2018
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