# Intra-Individual Variability and White Matter Changes in Alzheimer's Disease

Kara Engelbrecht (ENGKAR007)
Melinda Simon (SMNMEL001)

ACSENT Laboratory
Department of Psychology
University of Cape Town
2015

Supervisor: Dr Progress Njomboro
Co-Supervisor: Bjorn Christ
Word Count:
Abstract: [283]
Main Body: [9467]

**PLAGIARISM**
**DECLARATION**

1. I know that plagiarism is wrong. Plagiarism is to use another's work and pretend that it is one's own.

2. I have used the *American Psychological Association* convention for citation and referencing. Each contribution to, and quotation in, this essay/report/project from the work(s) of other people has been attributed, and has been cited and referenced.

3. This essay/report/project is my own work.

4. I have not allowed, and will not allow, anyone to copy my work with the intention of passing it off as his or her own work.

SIGNATURE: Kara Engelbrecht/ Melinda Simon

## Abstract

Intra-individual variability (IIV) refers to the within-person trial-to-trial variation in performance that occurs in a single task. Research has shown that it is a stable trait-like quality and is higher in cases of pathological aging, including Alzheimer's disease (AD). Although the neural and cognitive underpinnings of IIV have yet to be established, white matter changes are one of the proposed mechanisms thought to underlie lapses in executive functions and attention that are thought to give rise to higher IIV in neurological disease. This study investigated the correlation between simple and choice reaction time (RT) IIV and white matter changes as seen on CT and MRI scans in 13 participants with mild to moderate AD. IIV on the simple RT task correlated primarily with frontal white matter changes while IIV of on the choice RT tasks correlated primarily with parieto-occipital white matter changes, and also with overall white matter changes. These relationships remained significant after controlling for age. We discuss our findings in light of other studies that have found similar relationships, and propose that the association between IIV on the simple RT task and frontal white matter changes may reflect lapses in memory acquisition and focused attention.The association between IIV in the choice RT task and parieto-occipital white matter changes may reflect lapses in memory retrieval and visuospatial and focused attention. The association between IIV on the simple and choice RT task and overall, frontal and parieto-occipital white matter changes may reflect lapses in sustained attention which has been linked to executive control. These results support the hypothesis that white matter changes are a mechanism of IIV and suggest a unique role of frontal and parieto-occipital white matter regions in IIV in AD.


Keywords: *intra-individual variability, reaction time, white matter changes, Alzheimer's disease, attention, executive functioning, computerised tomography imaging*

Intra-Individual Variability and White Matter Changes in Alzheimer's Disease

The 20th and 21st Centuries have seen a worldwide increase in life expectancy. As people are living longer, the incidence of age-related brain disorders, including dementia, has also increased. Approximately 44 million people are living with dementia worldwide, 65% of whom have Alzheimer's disease (AD; Ferri et al., 2006). Aging research has consistently found that increasing age is the greatest risk factor for AD (De Jager, Joska, Hoffman, Borochowitz, & Combrinck, 2015). Importantly, some treatments for AD are only effective at the early stages of the disease (Kalin et al., 2014). Given these facts, early detection of AD has become increasingly important. One method of measurement that is increasingly applied in AD research, in-part because it contributes to the early detection of AD, is measuring intra-individual variability (IIV).

**Intra-Individual Variability as a Diagnostic Tool for Alzheimer's Disease**

IIV refers to the within-person trial-to-trial variation in performance on a single task (Fiske & Rice, 1955). Studies investigating *inter*-individual differences in cognition assume that an individual's performance is stable over time and any variability that is not accounted for by practice effects and other such factors is better seen as noise in the data (Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000). However, the amount by which an individual's performance varies is a function of lawful influences on behavior, and is therefore relatively stable across time and across cognitive domains. IIV can therefore be considered a stable trait-like quality and a component of cognition that exerts a non-random influence on test scores (Hultsch et al., 2000; MacDonald, Nyberg, & Backman, 2006).

AD has been associated with increased IIV (see e.g. Hultsch et al., 2000). Similarly, IIV increases in normal aging and has a negative association with cognitive performance (Nesselroade & Salthouse, 2004). High IIV has been shown to predict cognitive decline in perceptual speed and ideational fluency up to 13 years later in a sample of elderly participants (Lovden, Li, Shing, & Lindenberger, 2007). Furthermore, IIV can reliably distinguish between normal and pathological decline. For instance, in a study by Kalin et al. (2014) individuals with mild cognitive impairment, who later progressed to AD, had higher IIV than those who did not progress to AD. These findings offer support for IIV as a sensitive marker of impending and long-term change and highlight the utility of using IIV as an early detector of AD.

**Neural and Cognitive Correlates of Intra-Individual Variability**

The cognitive correlates of IIV are thought to reflect lapses in executive functions including attention and executive control (see MacDonald, Li, & Backman, 2009 for a

review). While lapses in executive functions including attention are linked to loss of white matter integrity and volume, the mechanisms have not been clearly established, nor are the neural correlates of IIV clear. An association has consistently been found between increased IIV and white matter integrity and volume in cognitively intact and impaired individuals (see MacDonald et al., 2009 for a review). Studies have shown that 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 increased IIV in children due to immaturity of the brain and in older adults due to degeneration in old age (MacDonald et al., 2006).

While there is no consensus as to the exact pattern of white matter changes that mediates increased IIV, there is some indication that white matter degeneration in the frontal lobes is the main influencing factor. In particular, white matter changes in the ventral and dorsolateral prefrontal cortex, superior frontal gyrus, and posterior cingulate are associated with higher IIV in AD (Jackson, Balota, Duchek, & Head, 2012). In healthy controls an association has also been found between increased IIV and white matter volume in frontal areas, however, such an association was not  not seen with other brain regions (Bunce et al., 2013). IIV increases in tests that rely on attention and other executive functions which are supported by frontal and parietal regions (Jackson et al., 2012; MacDonald et al., 2006).

Studies that emphasise diffuse white matter damage in IIV propose that damage to inter- and intra-hemispheric connections and cortico-cortical projections cause decreased functional connectivity. This decreased connectivity leads to difficulties in activating multiple brain areas in a coordinated way and this is why IIV increases in tasks that tap into executive functions (see e.g. Moy et al., 2011). A hypothesis relating to the role of diffuse white matter changes in IIV is in line with more recent neural network models of IIV that explain higher IIV as the breakdown in executive function (see e.g. Jackson et al., 2012). A breakdown in executive functions can result from macro-structural white matter changes, such as atrophy caused by ischemia. Such a breakdown can also result from microstructural changes and some have argued that IIV results from demyelination or myelin thinning that leads to inefficient action potential transmission (Jensen, 1992; MacDonald et al., 2006).

**Neural Correlates of Alzheimer's Disease**

Similarly to IIV, the neural correlates of AD are still being discovered. It is generally accepted that in the early, preclinical stages of AD neuronal changes occur in the enterorhinal cortex and hippocampus, and micro-structural white matter changes occur in the parahippocampus and the temporal lobes. At later disease stages, grey matter changes occur

in the cortical association areas of the frontal, parietal and temporal lobes and volumetric decreases of corresponding association fibres also occur (Braak & Braak, 1991; Johnson et al., 2010).

Apart from the degradation of cortical association fibres as a result of grey matter atrophy, there is evidence to suggest that micro-structural white matter changes occur early on in AD, independently of the effects of loss of grey matter, and vascular pathology (Sachdev, Zhuang, Braidy, & Wen, 2013). 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). Furthermore, animal studies have indicated that changes in myelin sheaths, oligodendrites and axons occur prior to the formation of the neurofibrillary tangles and amyloid-β plaques that are characteristic of AD pathology (Desai et al., 2009). It has been suggested that myelin changes in AD result from minor ischemic events, leading to a loss of oligodendrite cells and subsequent reductions in myelin integrity (Sjobeck, Haglund, & Englund, 2005). More importantly, disruptions in axonal transport tend to result in more axonal damage and trigger the production of amyloid- β peptides and the deposition of amyloid plaques (Stokin et al., 2005). Taken together, these studies suggest that micro-structural white matter changes not only occur early on in AD, but might be a causative factor in AD pathology.

Some studies have implicated white matter changes exclusively in frontal regions in AD (Choi, Lim, Monteiro, & Reisberg, 2005), while others have found evidence of more posterior or diffuse changes (Bozzalli et al., 2002; Medina et al., 2006; Stahl et al., 2007; Zhang et al., 2009). This difference in research outcomes could possibly reflect the differences in the methods used and the differences in disease severity across samples in the studies. For example, white matter changes have predominantly been found in more posterior regions in mild AD (Medina et al., 2006), with frontal changes being found in patients with more progressed AD (Bozzalli et al., 2002; Zhang et al., 2009). Nevertheless, one study found evidence for micro-structural white matter changes in frontal regions in early AD (Choi et al., 2005). It is therefore possible that early AD is characterised by both macro and micro-structural white matter changes, affecting frontal and more posterior brain regions.

**Alzheimer's Disease, Intra-Individual Variability and Executive Dysfunction**

AD has been associated with increased executive dysfunction early on in the disease process (Baudic et al., 2006; Sgaramella et al., 2001). Those with AD have been shown to have difficulties with declarative memory recall (Golby et al., 2005). In addition to this,

impairments in visuospatial attention as well as focused and sustained attention have been found early on in the disease process, although difficulties in focused attention appear to be less severe in the early stages (Faust & Balota, 1997; Parasuraman & Haxby, 1993; Rizzo, Anderson, Dawson, Myers, & Ball, 2000). Interestingly, attentional lapses are thought to contribute to the memory problems seen in early AD (Parasuraman & Haxby, 1993). Importantly, all of these executive functions rely to some extent on posterior brain regions including parieto-occipital areas, which are known to degenerate early on in AD (Coull, Frith, Frackowiak, & Grasby, 1996; Kelly, Uddin, Biswal, Castellanos, & Milham, 2008; Lawrence, Ross, Hoffmann, Garavan, & Stein, 2003; Sakai et al., 1998; Sarter, Givens, & Bruno, 2001; Tuch et al., 2005). Sustained attention has also been shown to involve diffuse brain regions, while focused attention is thought to involve frontal regions as well (Kelly et al., 2008; Lawrence et al., 2003). Consistent with this idea are findings that damage to the fronto-parietal network, thought to underlie attentional processing, has been associated with lapses in attention control in AD (Neufang et al., 2011). Interestingly, IIV is higher in tasks which have a strong executive component (Jackson et al., 2012; MacDonald et al., 2006).

Although the findings discussed above highlight the possible utility of studying the relationship between IIV and white matter changes in AD, only one study to date has examined this relationship. This study found a significant positive correlation between loss of cerebral white matter volume in frontal and parietal areas and reaction time (RT) IIV in a sample of early-stage AD patients and in a healthy control group (Jackson et al., 2012). Taken together, the overlap in findings on the cognitive and neural correlates of both IIV and AD, as well as the possible diagnostic utility of IIV provide a strong case for studying the relationship between IIV and white matter changes in AD.

## Rationale for Research and Specific Aims

This study investigated the relationship between IIV and white matter changes in AD. Specifically, we investigated whether there is a positive correlation between IIV and white matter changes in AD. This study aimed to use computerised tomography (CT) scans to replicate Jackson et al.'s (2012) finding that RT IIV increases with decreased white matter volume, in a sample of AD patients with possible and probable AD. Although diffusion tensor magnetic resonance imaging (DT-MRI) as used by Jackson et al. (2012) is the most sensitive to micro-structural white matter changes, CT scanning is more readily available and cost-effective compared to DT-MRI. In addition, the scans for each of the participants were available from their patient files. The findings from this study add to the growing body of literature on the neural underpinnings of IIV, particularly in patients with AD. An

understanding of the neural underpinnings of IIV is a vital step towards the use of IIV in the detection of early cognitive and neurological changes in neurologically compromised patients.

## Methods

### Design and Setting

A correlational design was used to examine the relationship between white matter changes and IIV on RT tasks in a sample of patients diagnosed with possible or probable AD and in the early to moderate stages of the disease.

This study formed part of an ongoing broader study which tracks the progression of cognitive decline in AD over a one-year period. Data for the broader study is being obtained through the use of three sets of neuropsychological tests assessing memory, cognitive control, and motor functioning and collection of this data is on-going. Data for the current study consists of RT data from the cognitive control subtests of the broader study. The CT scans obtained from participants' medical records were used to determine white matter changes.

IIV was calculated at various time-scales in the current study. Specifically, IIV was calculated individually for the two administrations of the simple and choice RT tasks on each of the three days of testing (refered to as blocks). IIV was also calculated as an average of the two administrations of each task within each testing session and was also calculated as the average for all of the administrations of each task across all three of the testing sessions. This approach was used as IIV is still a growing area of research and it is unclear which time-scale is best to use when measuring IIV. Time-scales that are too small may only detect stable performance, while time-scales that are too large may miss more nuanced fluctuations in performance (Boker & Nesselroade, 2002). Another contentious issue in the IIV literature, is the minimum number of trials needed to find robust associations with neural correlates. Although each block in the current study only had 30 trials, significant correlations between frontal white matter changes and IIV on an RT task have been found using just 20 trials (Bunce et al., 2013).

### Participants

Participants for this study were recruited from Groote Schuur Hospital's (GSH) Memory Clinic, run by the University of Cape Town's Division of Geriatric Medicine and the Albertina and Walter Sisulu Institute of Ageing (part of UCT's Department of Medicine). The clinic assesses patients from Cape Town and the surrounding areas for memory impairment. Data collection was done either at GSH or in the participants' homes, depending on which option was the most convenient for the participant.

Participants had to meet the Diagnostic and Statistical Manual IV (DSM-IV) criteria for AD (see Appendix A). Potential participants were approached by one of the clinical staff at the Memory Clinic who provided them with the information about the study (see Appendix B). The sample ($n$ = 13) was drawn from a clinical population of patients diagnosed with AD falling within the mild to moderate range on the clinical dementia rating scale (CDR-scale; see Appendix C) and who met the DSM-IV diagnostic criteria for dementia of the Alzheimer's type. According to a power calculation performed using GPower (Faul, Erdfelder, Buchner, & Lang, 2009), 64 participants were needed in this study for adequate statistical power (.8) with a medium effect size (.3). This number of participants, however, was not feasible given the limited timeframe for the entire project.

**Inclusion criteria**. The inclusion criteria for the study included: (a) the availability of a patient's medical history, (b) an age of 55 years or older; (c) basic literacy with ability to speak, read and write; (d) English fluency; (e) a score of <80 on the Cambridge Examination for Mental Disorders of the Elderly - Revised (CAMCOG-R; Huppert, Brayne, Gill, Paykey, & Beardsall, 1995); (f) the availability of a close relative or informant to provide collateral information on cognitive changes.

**Exclusion criteria.** Potential participants with the following were excluded from taking part in the study: (a) uncontrolled hypertension, diabetes mellitus or other cardiovascular diseases; (b) diagnosis of HIV/AIDS; (c) psychiatric illness; (d) major neurological disorder or past stroke; (e) a history of alcohol or drug abuse or heavy smoking (>20 cigarettes per day); (f) a Geriatric Depression Scale (GDS; Yesavage, Brooks, Taylor, & Tinklenberg, 1993) score of more than 9/30. These criteria were chosen because of their known effect on cognitive performance in AD. Potential participants with a Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) score of less than 12 were also excluded. This was done to exclude participants with severe cognitive impairment.

**Measures**

**Screening measures.** The following measures were administered to screen for the effects of depression and cognitive impairment on IIV on the RT tasks.

***The Geriatric Depression Scale (GDS).*** The GDS is a valid measure of depressive symptoms in the elderly. It demonstrates high test-retest reliability and has been shown to be appropriate for South African participants (Dorsey, Rodriguez, & Brathwaite, 2001; Yesavage et al., 1993). The scale consists of 30 self-report items and; participants who scored below 9 points were excluded from this study.

***The Cambridge Examination for Mental Disorders of the Elderly - Revised (CAMCOG-R).*** The CAMCOG-R is part of the Cambridge Examination for Mental Disorders of the Elderly – Revised (CAMDEX-R) and tests several cognitive domains (Huppert, Brayne, Gill, Paykey, & Beardsall, 1995). It is commonly used as a screening tool for dementia and has demonstrated high test-retest and inter-rater reliability (O'Connor et al., 1989). We used a version of this measure that has been revised for use on a South African population (James, Grace, Thomas, & Combrinck, 2015).

***The Mini Mental State Examination (MMSE).*** The MMSE was used to measure the severity of cognitive impairment by testing several cognitive domains (Folstein et al., 1975). It consists of 19 items and was administered as part of the CAMCOG-R. The MMSE has been shown to have good inter-rater reliability, internal consistency and test-retest reliability and has also been used to diagnose early AD in South African populations (Folstein et al., 1975; Heckmann et al., 2004).

**Measures of reaction time.** The study used RT to determine IIV as RT is particularly sensitive to fluctuations in performance because it can be measured precisely using computerised measures of time. RT tasks are also less sensitive to practice effects and can be administered multiple times within one testing session. This allows for the examination of IIV within a single testing session (Allaire & Marsiske, 2005). In line with this idea, RT tasks have been used to determine IIV in the majority of studies investigating IIV (MacDonald et al., 2009).

The current study computed RT IIV by measuring performance variability on a simple and five-choice RT task on the attention-based Cambridge Neurospsychological Automated Test Battery (CANTAB) Reaction Time subtest (Fray, Robbins, & Sahakian, 1996).

The simple RT task involved participants monitoring the centre of a computer screen for the appearance of a yellow dot inside a white circle while holding down a press pad with the index finger of their dominant hand.. When the dot appeared they needed to release the press-pad and touch inside the white circle on the screen as quickly as possible. The choice RT task worked in a similar way, except participants were required to make a selection between five circles when indicating the appearance of the yellow dot.

Participants were given the opportunity to practise these tasks before testing began. Practise for the simple RT and choice RT tasks consisted of 10 trials. Participants only moved on to the testing phase after achieving 90% accuracy for the first practise phase or failing that, completing a second practise phase and moving onto the testing phase regardless of their accuracy. The testing phase for the simple RT and choice RT task consisted of 40 trials. The

CANTAB has been extensively reviewed and is the most widely published battery of computerised neuropsychological tests in the world (Égerházi, Berecz, Bartók, & Degrell, 2007). Furthermore, both the simple and choice RT tasks have high test-retest reliabilities with intraclass coefficients of .80 and .79, respectively (Lemay, Bédard, Rouleau, & Tremblay, 2004; Lowe & Rabbitt, 1998).

**White matter change severity scale.** The age-related white matter change **(**ARWMC) scale is a visual rating scale applicable to CT and MRI scans and was used to determine the severity and extent of white matter changes (Wahlund et al., 2001; see Appendix D). Specific brain regions in each hemisphere (frontal, temporal, parieto-occipital, basal ganglia and infratentorial) were graded from 0 to 3 based on the severity and extent of white matter changes. The scores for the regions were summed to give an overall score ranging from 0 to 30 that reflected the severity and extent of white matter changes in the whole brain (Wahlund et al., 2001).

**Procedure**

Participants were referred to the study from the Memory Clinic after they had been diagnosed with possible or probable AD in the mild to moderate disease stages and had met the other eligibility criteria. Once participants gave verbal consent we scheduled their screening session. Once participants understood and signed the consent form (see Appendix E) we administered the screening tests. Participants who failed to meet the eligibility criteria based on their performance on the screening tests were excluded from the study.

Testing took place in a quiet room in the Geriatric Unit at GHS, or in participant's homes when necessary. Participants were assessed individually with their relative or friend present. The data used for the current study was collected from three testing sessions over two weeks. Three groups of neuropsychological tests were administered as part of the broader study during each testing session (memory, cognitive control and motor functioning) and were counter-balanced to avoid order effects. For the current study, only the RT task data was used and each participant completed two simple and two choice RT tasks at each of the three testing sessions.

The CT scan data was reviewed throughout the duration of the research at GSH. We each graded the scans independently and came to a consensus for each grade we disagreed on.

**Ethical Considerations**

Informed consent was obtained by a consent form from all participants at the screening session. 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, 2014). However a relative or friend was also present during testing, ensuring that consent was informed and voluntary.

There were one screening and three testing sessions that required participants to travel to the Memory Clinic. The cognitive assessments that participants were required to complete were demanding and time-consuming. Participants were given regular breaks between tasks to lessen the burden and received R70 to cover their travelling expenses.

There were no direct benefits to participants taking part in this study. The risk to participants involved in this study was that answering questions about their declining cognitive status and performing tasks designed to be challenging may have made participants uncomfortable. Participants were informed of this possibility and that they were free to withdraw from the study should they feel uncomfortable. 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.

Ethical consent for the larger study has been obtained from the Human Research Ethics Committee (HREC) of the Faculty of Health Sciences of the University of Cape Town (HREC/REF: 167/2014). The currently study includes an imaging component and would therefore required an amendment to the protocol of the larger research project. The protocol amendment was approved by the HREC.

**Data Analysis**

**Outliers**. The mean and standard deviation for each of the six blocks for both simple and choice RT were calculated. The data was also examined for outliers based on the assumption that extremely fast or slow responses may correspond to errors such as a participant becoming distracted or releasing the button accidentally. The lower bound for legitimate responses was set at 150 ms and scores below this value were removed. This is based on the finding that it takes approximately 150 ms to process visual stimuli and decide on a response (Thorpe, Fize, & Marlot, 1996). Responses faster than 150 ms were likely to not involve a decision and were considered invalid. The upper bound was set at 3 standard deviations above the mean, determined on a participant-by-participant basis for each block. This definition of outliers has been used in other studies that examined RT and IIV (see e.g., Bielak, Hultsch, Strauss, Macdonald, & Hunter, 2010; Hultsch et al., 2000). The percentage of outliers is reflected in table 1.

Table 1

*Percentage of Outliers for all Participants in each Block of Simple and Choice Reaction Time Task (N=13)*

| | SRT | CRT |
|---|---|---|
| Block 1 | 2.10 | 0 |
| Block 2 | 1.41 | 1.19 |
| Block 3 | 1.58 | 1.43 |
| Block 4 | 2.39 | 1.19 |
| Block 5 | 1.08 | 1.67 |
| Block 6 | 2.09 | 1.43 |

*Note:* SRT = simple reaction time task; CRT = choice reaction time task; Values are percentages.

**Treatment of missing values.** Missing values due to removed outliers and invalid responses on the CANTAB task were replaced using the mean of the block of each participant, with the exception of one participant (RG001) whose missing scores were replaced with the mean of all participants in the block. RG001 had significantly more missing values than other participants and his mean value may not be representative of his performance. Nevertheless, his data was useable for four of the simple RT blocks and two of the choice RT blocks. Although other studies have used a regression method to replace missing values, it was not possible to use this method in the current study given the limited number of variables. The regression method uses the values of other variables to replace missing values but the current study only has two variables and these are not sufficient for this method (see e.g. Hultsch, MacDonald, & Dixon, 2002). Using the mean to replace missing values reduces variability, resulting in a conservative estimate of IIV. This reduces the chances of making a type 1 error.

Participants with too many missing values in a block were excluded from that particular block. The cut-off limit for the missing values for each block was set at 3 SD from the average number of missing values of all the participants in the block.

Using this approach, two participants, CD001 and RG001, had their data removed from several blocks. CD001's data was removed from block one of the simple RT task. RG001's data was removed from blocks two and five of the simple RT task, and blocks two, three, five and six of the choice RT task. The percentage of missing values in each block of the simple and choice RT tasks are given in table 2.

Table 2

*Percentage of Missing Values for all Participants in Each Block for Simple and Choice RT (N=13)*

| | SRT | CRT |
|---|---|---|
| Block 1 | 14.6 | 11.90 |
| Block 2 | 8.97 | 4.52 |
| Block 3 | 2.82 | 2.62 |
| Block 4 | 3.59 | 1.90 |
| Block 5 | 5.13 | 3.10 |
| Block 6 | 2.05 | 1.90 |

*Note:* SRT = simple reaction time task; CRT = choice reaction time task; Values are percentages.

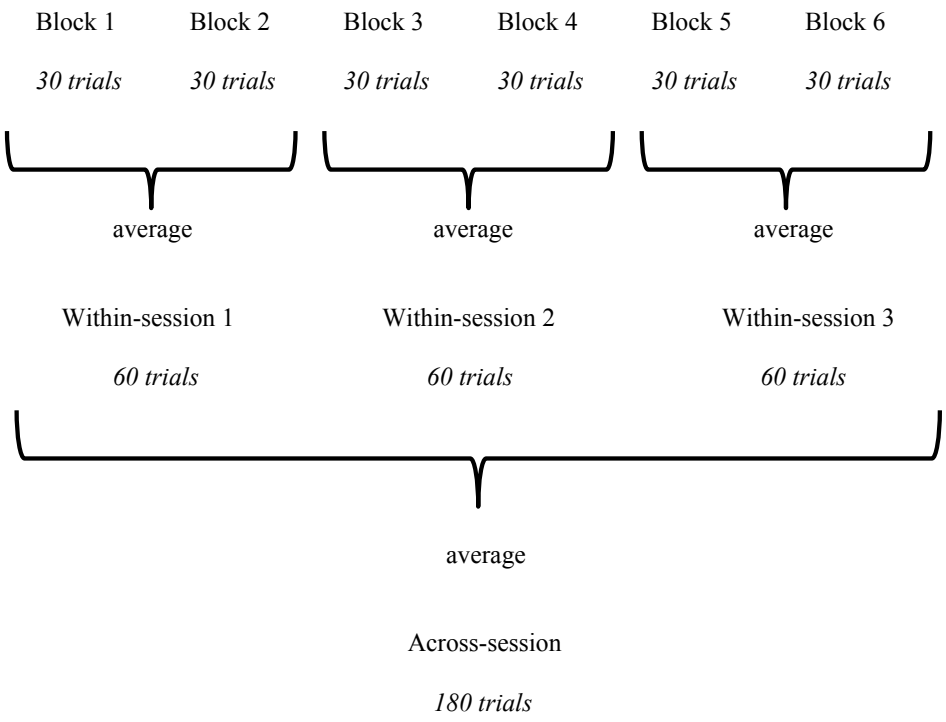
**Calculating the coefficient of variation (CoV).** Each participant completed two simple and two choice RT tasks at each of the three testing sessions. Each of these tasks consisted of 30 trials and are referred to as blocks in Figure 1 below. Each testing session consisted of two blocks of simple and two blocks of choice RT tasks for each participant. Each session was therefore made up of 60 trials. These are referred to as within-session one (referring to blocks one and two), within-session two (referring to blocks three and four) and within-session three (referring to blocks five and six) in Figure 1.

CoV was determined for each of the blocks and testing sessions, as well as across all three testing sessions. To calculate CoV for each block, the standard deviation of the RT latencies across the 30 trials of the block was divided by the mean of the RT latencies of those 30 trials for that block. This was done for all six blocks for each of the participants. To calculate CoV for each of the sessions, the average CoV of the blocks in each session was

calculated for each participant. That is, CoV for within-session one was calculated as the average between the CoV for blocks one and two , CoV for within-session two was calculated as the average between the CoV for blocks three and four and CoV for within-session three was calculated as the average between the CoV for blocks five and six for each participant. CoV across the three testing sessions was calculated as the average between the CoV for within-sessions one, two and three for each participant. This can be seen in figure 1. This method for determining COV at various timescales is suggested by Nesselroade and Salthouse (2004).

Figure 1

*Time-Scale Measurements of Intra-Individual Variability and Calculation of CoV*




**Calculating correlation coefficients.** Bivariate correlations were performed between simple RT CoV at the block, within-session and across-session level and white matter changes overall and in frontal, parieto-occipital and basal ganglia regions using the Statistical Package for the Social Sciences SPSS (version 22). Partial correlations were performed using the same variables to control for the effects of age on the above relationships.

RT data is generally not normally distributed and tends to have a positive skew, however, RT data in the present study was approximately normally distributed after outliers

were removed (Gordon & Carson, 1990). Although the RT data was less normally distributed than that of white matter change data in the current study, it is generally agreed in in studies of this nature that the data is normal enough for the effective use of parametric tests (see e.g., Lachaud & Renaud, 2011).

**Covariates.** Previous research has included a range of covariates, such as education, depression and cardiovascular health, in their analyses (e.g. Jackson et al., 2012). Due to the small number of participants in this study only age was used as a covariate. Age was selected as a covariate given that it is the biggest risk factor for AD and is related to the two variables in the present study, namely white matter changes (for a review see Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009) and IIV (MacDonald, Hultsch, & Dixon, 2003). Mean level of performance was controlled for by using CoV as a measure of IIV, that is the standard deviation was divided by the mean in each block. Since IIV is taken to be a measure of performance separate from central tendency, it is important to calculate IIV in a way in which measures of central tendency, such as the mean are not represented in the score.

## Results

### Demographic Characteristics of Sample

Nine females and four males with a diagnosis of possible or probable AD in the mild to moderate stages took part in the study. The participants had a mean age of 72 years ($SD$ = 6.4) and a mean education level of ten years ($SD$ = 2.7) years, although education level was not available for one of the participants.

### White Matter Changes

**Inter-rater reliability**. Cohen's Kappa was calculated to determine the inter-rater agreement between the two independent raters for the CT and MRI scans. The level of agreement for CT scans was fair ($k$= .48, p<.001). The level of agreement for the MRI scans was substantial ($k$= .82, p<.001). The creators of the scale reported K=.48 for CT scans and K=.67 for MRI scans (Wahlund et al., 2001).

**Evidence of white matter changes.** White matter changes were found in frontal, parieto-occipital and basal ganglia regions. No white matter changes were found in temporal or infratentorial areas. These areas were therefore not included in the correlational analyses.

### Correlations Between the Simple Reaction Time Task Coefficient of Variation and White Matter Changes

Bivariate correlations were performed to determine the association between CoV of the simple RT task and white matter changes in various brain regions. Table 3 displays the results of the correlations between CoV of the simple RT task at various time-scales and

white matter changes in various brain region. The was a positive significant correlation between CoV of the simple RT task and white matter changes overall, as well as with frontal and parieto-occipital brain regions. These relationships were in the hypothesized direction and were in the moderate to strong range.

Table 3

*Bivariate Correlations Between CoV of the Simple Reaction Time Task at Various Timescales and White Matter Changes (N=13)*

| | Overall WMC | Frontal WMC | Parieto-occipital WMC | Basal ganglia WMC |
|---|---|---|---|---|
| Across-session CoV[a] | .50 | .70** | .24 | -.21 |
| Within-session 1 CoV[a] | .40 | .59* | .09 | -.09 |
| Within-session 2 CoV | .37 | .58* | .20 | -.29 |
| Within-session 3 CoV[b] | .42 | .64* | .19 | -.26 |
| Block 1 CoV[b] | .28 | .58* | .09 | -.39 |
| Block 2 CoV[b] | .33 | .47 | .06 | -.01 |
| Block 3 CoV | .15 | .57* | -.08 | -.43 |
| Block 4 CoV | .47 | .40 | .42 | -.06 |
| Block 5 CoV[b] | .08 | .47 | -.25 | -.20 |
| Block 6 CoV | .63* | .59* | 56* | -.17 |

*Note*: WMC = white matter changes; CoV = coefficient of variation; Statistics presented are Pearson correlation coefficients (*r*). All tests are 1-tailed.
[a]*n*=11; [b]*n*=12.
*p < .05. **p < .01.

Partial correlations were performed to determine the association between CoV of the simple RT task and white matter changes in various brain regions while controlling for age. Table 4 displays the results of the partial correlations between CoV on the simple RT task at various time-scales and white matter changes in various brain regions. For the most part, CoV of the simple RT task correlated positively and significantly with white matter changes overall as well as with frontal brain regions. These relationships were in the hypothesized direction and were in the moderate to strong range.

Table 4

*Partial Correlations Between CoV of the Simple Reaction Time Task at Various Timescales and White Matter Changes Controlling for Age (N=13)*

| | Overall WMC | Frontal WMC | Parieto-occipital WMC | Basal ganglia WMC |
|---|---|---|---|---|
| Across-session CoV[a] | .42 | .67* | .13 | -.22 |
| Within-session 1 CoV[a] | .48 | .66* | .13 | -.09 |
| Within-session 2 CoV | .23 | .51* | .04 | -.32 |
| Within-session 3 CoV[b] | .35 | .60* | .10 | -.27 |
| Block 1 CoV[b] | .40 | .69* | .17 | -.40 |
| Block 2 CoV[b] | .47 | .59* | .16 | -.01 |
| Block 3 CoV | .10 | .55* | -.16 | -.43 |
| Block 4 CoV | .31 | .26 | .28 | -.06 |
| Block 5 CoV[b] | .05 | .47 | -.30 | -.20 |
| Block 6 CoV | .55* | .52* | .48 | -.18 |

*Note*: WMC = white matter changes; CoV = coefficient of variation; Statistics presented are Pearson correlation coefficients (*r*). All tests are 1-tailed.

[a]*n*=11; [b]*n*=12.

*p < .05.**p < .01.

## Correlations Between the Choice Reaction Time Task Coefficient of Variation and White Matter Changes

Bivariate correlations were performed to determine the association between CoV of the choice RT task and white matter changes in various brain regions. Table 5 displays the results of the bivariate correlations between CoV of the choice RT task at various time-scales and white matter changes in various brain regions. For the most part, CoV of the choice RT task correlated positively and significantly with white matter changes overall as well as with

frontal and parieto-occipital brain regions. These relationships were in the moderate to strong range. The exception was the correlation between CoV of the choice RT task and white matter changes in the basal ganglia, which had a weak significant, negative relationship.

Table 5

*Bivariate Correlations Between CoV of the Choice Reaction Time Task at Various Timescales and White Mater Changes (N = 13)*

| | Overall WMC | Frontal WMC | Parieto-occipital WMC | Basal ganglia WMC |
|---|---|---|---|---|
| Across-session CoV[a] | .54* | .42 | .71** | -.38 |
| Within-Session 1 CoV[a] | .44 | .51* | .50* | -.51* |
| Within-Session 2 CoV[a] | .42 | .18 | .71** | -.31 |
| Within-Session 3 CoV[a] | .61* | .25 | .85** | -.10 |
| Block 1 CoV | .59* | 73** | .32 | -.30 |
| Block 2 CoV[a] | .02 | -.02 | .36 | -.50* |
| Block 3 CoV[a] | .48 | .54* | .26 | -.05 |
| Block 4 CoV | .35 | .16 | .68** | -.38 |
| Block 5 CoV[a] | .33 | .06 | .31 | .32 |
| Block 6 CoV[a] | .56* | .26 | .86** | -.28 |

*Note:* WMC = white matter changes; CoV = coefficient of variation; Statistics presented are Pearson correlation coefficients (*r*). All tests are 1-tailed.

[a]*n*= 12
*p<0.05. **p<0.01.

Partial correlations were performed to determine the association between CoV of the choice RT task and white matter changes in various brain regions while controlling for the effects of age. Table 6 displays the results of the correlations between CoV of the choice RT

task at various time-scales and white matter changes in various brain regions. CoV of the choice RT task correlated positively and significantly with white matter changes overall as well as with frontal and parieto-occipital brain regions. These relationships were in the hypothesized direction and were in the moderate to strong range. After controlling for age there was no longer a significant relationship between CoV of the choice RT task and white matter changes in basal ganglia brain regions.

Table 6

*Partial Correlations Between CoV of the Choice Reaction Time Task at Various Timescales and White Mater Changes N=13*

| | Overall WMC | Frontal WMC | Parieto-occipital WMC | Basal ganglia WMC |
|---|---|---|---|---|
| Across-session CoV[a] | .53* | .39 | .71** | -.36 |
| Within-Session 1 CoV[a] | .39 | .47 | .47 | -.49 |
| Within-Session 2 CoV[a] | .49 | .24 | .78** | -.33 |
| Within-Session 3 CoV[a] | .68* | .29 | .90** | -.11 |
| Block 1 CoV | .61* | .76** | .38 | -.25 |
| Block 2 CoV[a] | -.09 | -.15 | .30 | -.49 |
| Block 3 CoV[a] | .37 | .43 | .14 | .03 |
| Block 4 CoV | .39 | .19 | .72** | -.43 |
| Block 5 CoV[a] | .50 | .21 | .44 | .29 |
| Block 6 CoV[a] | .57* | .25 | .87** | -.27 |

*Note:* WMC = white matter changes; CoV = coefficient of variation; Statistics presented are Pearson correlation coefficients ($r$). All tests are 1-tailed.
[a]$n$= 12
*p<0.05. **p<0.01.

## Discussion

We had hypothesized that increased IIV on the RT tasks would be associated with a greater extent of white matter changes. The results indicate that IIV on the simple RT task was associated most strongly with a greater extent of white matter changes in frontal regions. These associations were evident at the block, within-session and across-session levels. Higher IIV on the simple RT task was also associated with a greater extent of overall white matter changes, however these associations were only evident at the block level. Increased IIV on the choice RT task was associated most strongly with a greater extent of parieto-occipital white matter changes, with these associations also being seen at the block, within-session and across-session levels. Higher IIV on the choice RT task had smaller associations with overall white matter changes and white matter changes in frontal regions, with associations at the block and across-session levels only. These associations were evident even after controlling for age. This indicates that the observed relationships are specific to white matter changes in AD and are not influenced by normal age-related white matter changes (Gunning-Dixon et al., 2009).

The current study found a positive relationship between increased IIV on the simple RT task in block six and increased IIV on the choice RT task in blocks one and six, session three and at the across-session level and a greater extent of overall white matter changes. These findings were consistent with those of Wallhovd and Fjell (2007) who found a negative association between IIV and overall white matter volume. Although Wallhovd and Fjell (2007) used a different population of participants to the current study and performed a volumetric analysis of white matter, the task used relied on several of the same cognitive functions that the RT tasks of the current study did, making the findings comparable. The task used by Wallhovd and Fjell (2007) was similar to both RT tasks used in the current study because both involved responding to a visual stimulus, and therefore relied on focused and sustained attention. Nevertheless, the visual oddball task used by Wallhovd and Fjell (2007) was more similar to the choice RT task used in the current study because participants were required to respond to a target stimuli and ignore distractor stimuli and therefore involved a decisional component and relied on visuospatial attention. However, the task required selective attention to discriminate between distractor and target stimuli, which neither of the tasks in the current study did.

The current study found significant associations between increased RT IIV and a greater extent of overall white matter changes. It also found significant associations between increased IIV on the simple RT task and frontal white matter changes in blocks one, two,

three and six, within all three sessions and across-session. Lastly, it found significant associations between increased IIV on the choice RT task in block one and greater frontal white matter changes as well as increased IIV on the choice RT task in blocks four and six, within session two and across-session and greater parieto-occipital white matter changes. These findings are consistent with those of Jackson et al. (2012) who found significant negative correlations between increased IIV and overall white matter volume and white matter volume in frontal and parietal white matter regions in participants with early AD and in cognitively healthy controls.

The fact that Jackson et al. (2012) and the current study found these associations in AD suggests that overall as well as frontal and parieto-occipital white matter changes are involved in IIV in AD. Although Jackson et al. (2012) used different tasks to those used in the current study, the tasks in both studies relied on similar cognitive functions, including sustained, focused and visuospatial attention. Taken together these findings provide support for the idea that lapses in attention underlie IIV, specifically in AD.

The significant positive associations between increased IIV on the simple and choice RT tasks and greater overall, frontal and parieto-occipital white matter changes were partially consistent with findings by Bunce et al. (2007) who found significant negative associations between IIV and frontal white matter volume in cognitively healthy older individuals. Bunce et al. (2007) found no significant correlations between temporal, parietal, occipital, anterior and posterior horns and the periventricular bodies. There are three possible reasons for this difference in findings.

Firstly, the current study used a sample of mild to moderate AD participants, whereas Bunce et al. (2007) made use of cognitively intact older individuals. It is possible that loss of frontal white matter integrity in normal aging affects performance on choice reaction time (Gunning-Dixon et al., 2009). On the other hand it has been shown that AD involves changes of both frontal and more posterior white matter (Bozzalli et al., 2002). As such, the observed correlation in the current study could be a result of more diffuse white matter changes in AD compared to that of controls. It is also possible that these differences in results arise from the differences in the imaging techniques used. While the present study used CT scans, Bunce et al. (2007) used MRI scans which are more sensitive to detecting micro-structural white matter changes, while CT is limited to detecting macrostructural changes.

The other possible difference could lie in the tasks used in each of the studies. Bunce et al. (2007) made use of two choice RT tasks (as well as various other tasks) to measure IIV. Although Bunce et al. (2007) used a choice RT task, their task differed significantly from the

one used in the current study. The task used in the current study required visuospatial attention, which has been shown to rely on parietal regions (Tuch et al., 2005). The task used in Bunce et al.'s (2007) study did not require the same degree of visuospatial attention and this may be why no correlations between IIV and the brain regions supporting this cognitive function were found. The task used in Bunce et al.'s (2007) study was more similar to the simple RT task in the current study and the association between increased IIV and greater frontal white matter changes found by Bunce et al. (2007) is more similar to the pattern of associations with IIV on the simple RT task in the current study.

**The Role of Attention and Executive Control in Intra-Individual Variability**

The correlation between IIV on a task and white matter changes in an area was interpreted based on the assumption that the task relied on cognitive functions supported by that area and that white matter changes in this area would result in IIV. Based on this approach it is useful to identify the differences between the tasks when explaining differences in relationships with brain regions. This approach was used when interpreting the results of the current study.

The current study found that only choice RT IIV positively correlated with overall white matter changes, at the block level after controlling for age. This is possibly due to the more demanding nature of the choice reaction time task, compared to the simple RT task, requiring a greater degree of cognitive effort (Sarter et al., 2001). We found that increased IIV on the choice RT task was associated with significant parieto-occipital and frontal white matter changes, while increased IIV on the simple RT task was associated with significant white matter changes in frontal regions. Both simple and choice RT tasks rely on sustained attention. Sustained attention has been linked to executive control (Unsworth, Redick, Lakey, & Young, 2009). Moreover, problems in executive control have been suggested to underlie IIV (West, Murphy, Armilio, Craik, & Stuss, 2002). Importantly, diffuse brain regions including frontal and parietal areas are involved in sustained attention (Baddeley et al., 2001; Levinoff et al., 2005).

Some have found sustained attention to rely more on right frontal (Murtha, Cismaru, Waechter, & Chertkow, 2002) or right fronto-parietal regions (Coull et al., 1996). Others argue that sustained attention relies on a diffuse network of brain regions including frontal, parietal, occipital, thalamic, caudate and cerebellar regions (Lawrence et al., 2003). It has also been suggested that sustained attention relies on two separable neural and cognitive processes. The first of these is the bottom-up process involving the basal forebrain cholinergic system (Mirsky, Anthony, Duncan, Ahearn, & Kellam, 1991; Sarter et al., 2001).

This process is equivalent to what can be termed vigilance for incoming information. The other is a top-down process involving frontal and parietal regions (Sarter et al., 2001). This process is mediated by the basal forebrain cholinergic system and is involved in inhibiting attention to irrelevant stimuli (Sarter et al., 2001). This evidence suggests that sustained attention required to complete both simple and choice RT tasks may employ diffuse brain regions including frontal, parietal and occipital areas and their white matter connections.

The current study found a significant correlation between both simple and choice RT IIV and frontal and parietal-occipital white matter changes. Both simple and choice RT have been found to rely on focused attention (Baddeley, Baddeley, Bucks, & Wilcock, 2001; Levinoff, Saumier, & Chertkow, 2005). Focused attention is believed to rely on the synchronous activity between frontal and parietal brain regions (Kelly et al., 2008). Focused attention has also been thought to rely on superior temporal and inferior parietal and striatal regions (Mirsky et al., 1991). Taken together these findings are consistent with the idea that lapses in attention and executive control as a result of white matter changes underlie IIV.

**The Role of Executive Functions in Intra-Individual Variability**

A distinctive pattern of findings was evident in the current study: IIV on the simple RT task correlated with frontal white matter changes and the relationship, for the most part, got weaker over time; IIV on the choice RT task correlated to the parieto-occipital white matter changes and the relationship got stronger over time; and IIV on only some blocks of the simple and choice tasks correlated significantly with frontal and parieto-occipital white matter, respectively.

Evidence suggests that endogenous influences, such as the role of white matter changes, on IIV are best indexed over a relatively short period of time (MacDonald et al., 2003). For this reason, IIV at the block level is thought to give the most insight into the neural and cognitive mechanisms underlying IIV in the current study.

A possible explanation for the patterns of correlations found in the different blocks of the current study may lie in the underlying cognitive components of each task. The simple and choice RT tasks required a motor sequence to make a response. However, because the simple RT task was always administered first, it was during this task that the motor sequence was acquired, while the motor sequence was only retrieved in the choice RT task that followed. Acquiring and retrieving a motor sequence are different cognitive functions that rely on the frontal dorsolateral prefrontal cortex and pre-supplementary motor areas, and parietal precuneus and intraparietal sulcus, respectively (Sakai et al., 1998). Moreover, older individuals have been found to rely more on prefrontal areas during the acquisition of

episodic memories compared to younger individuals (Morcom, Good, Frackowiak, & Rugg, 2003). Although these, and other cognitive functions, rely on grey matter, white matter is integral for effective neural communication (Catani & Ffytche, 2005). Therefore it follows that fluctuations in performance on a cognitive task relying on a specific neural region is likely to be influenced by white matter changes in that area. The pattern of correlations at the block level indicate that the relationship between simple RT IIV and frontal white matter changes is strongest in the first blocks of each session when learning is most likely to take place. The significant correlation seen between choice RT IIV in the first block of the first session and frontal white matter changes offers support to the fact that the involvement of the frontal lobes is due to learning and not specific to the simple RT task.

IIV during the learning phase of a task is not necessarily maladaptive (Allaire & Marsiske, 2005). The significant correlations between IIV and pathological white matter changes in the frontal lobes, however, indicate that there are problems in the learning process in AD. Specifically, in normal learning one would expect to see an attenuation of variability over time. This was not the case in the current study, as increased IIV is seen even after several practice trials were completed. As such, correlations between frontal white matter changes and simple RT IIV may specifically reflect impairments in learning in AD. In support of this idea, adaptive learning is most often associated with tasks that require strategic performance. IIV on tasks that do not require implementing strategies and do not have prominent practice effects, such as the RT tasks in the current study, is typically maladaptive (MacDonald et al., 2009).

The choice RT task requires retrieval of the same motor sequence to a greater extent than is needed during the simple RT. The choice RT tasks include several blocks that are not likely to involve learning. These blocks, blocks four and six, are the second administrations in the second and third sessions and each correlate significantly with parieto-occipital white matter changes. As previously stated, parietal regions are involved in the retrieval of motor sequences (Sakai et al., 1998). In support of this, retrieval failures underpinned by functional failures of the parietal lobes, specifically the supramarginal gyrus, have been implicated in IIV (Kelly et al., 2008; MacDonald et al., 2009).

The choice RT task differs from the simple RT task in other ways. The choice RT task involves an additional decisional component when making the motor response because the participant has to decide where to touch the screen based on visual input from the stimulus (Levinoff et al., 2005). Processing the stimulus also requires visuospatial attention because of the several potential places the stimulus can and does appear (Tuch et al., 2005). Visuospatial

attention is a complex process involving the orientation of attention to specific locations in the visual field, usually in response to the appearance of a visual stimulus. Visuospatial attention is supported by white matter in parietal regions and a functional impairment can result in increased IIV as a result of lapses in visuospatial attention specifically (Tuch et al., 2005). Importantly, visuospatial attention has been found to be impaired in AD and is thought to rely on posterior brain regions, including parietal regions (Faust & Balota, 1997; Rizzo et al., 2000; Tuch et al., 2005). Taken together, these studies provide support for the fact that choice RT IIV correlated significantly with parieto-occipital white matter changes due to the increased reliance of this task on memory retrieval and executive functions including decision making as well as visuospatial attention, both of which involve parietal brain regions.

The observed associations between higher RT IIV and a greater extent of frontal white matter changes are consistent with suggestions of a unique role of frontal white matter regions in IIV. It is suggested that frontal regions are associated with variation in performance related to the effects of learning. This is in line with the idea that increased IIV has been associated with white matter in frontal regions in cognitively normal samples (Bunce et al., 2007). It is suggested that increased IIV which persists past the learning phase of a task, especially those tasks that are not benefitted from changing cognitive strategies, is maladaptive. As such, the fact that IIV continues to be high on each new testing session indicates a maladaptive learning strategy associated with higher IIV in AD.

On the other hand, parieto-occipital regions are associated with variation in performance related to memory retrieval and visuospatial attention functioning, both of which are shown to be affected in AD and to rely on brain regions which are known to degenerate early in the disease (Faust & Balota, 1997). As correlations between parieto-occipital white matter changes and IIV are present in the non-learning blocks of choice RT, this is taken to suggest that the increased IIV here represents pathological variation in performance, perhaps specific to AD (MacDonald et al., 2009).

The correlation between overall white matter changes and IIV in the current study could either reflect impairments in more global cognitive functions, such as sustained attention, or may merely be as a result of the accumulation of the white matter changes in specific regions.

**Limitations and Recommendations**

The number of participants in the current study could have had an effect on the observed relationships. The small sample size could reduce the reliability of the results. As such, future studies should be done using a larger sample size.

Although the majority of participant's scans were obtained within six months of testing, this was not the case for all of the participants. It is possible that further white matter changes had occurred during this time.

The current study made use of CT scans in order to measure white matter changes. CT scans have relatively poor spatial resolution and are useful for detecting macro-, but not micro-structural white matter changes. White matter hypodensities on CT scans represent atrophy, which may or may not involve changes in myelin integrity. Although the present study cannot confirm a role for changes in myelin in IIV, we cannot rule such a relationship out. Similarly the results from the current study cannot rule out a role for general white matter disconnectivity in IIV. Therefore, although our results are consistent with the idea that lapses in executive functioning contribute to IIV, it cannot be determined whether these lapses result from white matter disconnectivity or micro-structural changes in white matter leading to increased neural noise. Nevertheless, the strong correlations found between white matter changes using a blunt tool such as CT scans, and IIV indicates the robustness of the relationship found.

The use of CT scans as opposed to more sensitive tools for detecting white and grey matter changes also meant that we were unable to see if the white matter changes were of independent of grey matter change in AD. As such the inferences made may not apply to the independent changes in white matter seen early on in AD.

Further studies making use of more sensitive imaging techniques such as DT-MRI are needed to explore the possible neural correlates between micro-structural white matter changes and IIV in AD. Such studies will be better able to shed light on whether IIV results from lapses in executive function due to white matter disconnectivity or lapses in executive function due to micro-structural white matter changes resulting in increased neural noise. In addition to this the use of more sensitive imaging tools will enable researchers to better determine whether IIV correlates significantly with the independent white matter changes seen early on in AD.

Replicating the current study with a control group will shed light on the possibility that parieto-occipital white matter changes are exclusively implicated in IIV in AD, and not in healthy older individuals.

Studies should also be done using different cognitive tasks in different populations in order to better understand the cognitive mechanisms of IIV and how these might be related to specific clinical populations.

Using a reaction time task that does not include a motor sequence will allow a more pure measure of reaction time to be determined. However, if the same task is used researchers should ensure that the participants have had enough practice and counterbalance the order of administering the simple and choice RT tasks.

**Conclusion**

The current study suggests that at the neural level frontal, parieto-occipital and overall white matter changes are involved in IIV in AD. At the cognitive level, we suggest that frontal white matter changes are correlated more with variation in learning during the simple RT task, whereas parieto-occipital white matter changes are correlated more with variability in executive functions such as memory retrieval and visuospatial attention during the choice RT task. Both frontal and parieto-occipital white matter changes are associated with variability in sustained and focused attention. Lastly, overall white matter changes and IIV on the choice RT task are associated and may reflect greater variability in sustained attention or may simply reflect the accumulation of all white matter changes present. The results support the idea that IIV results from lapses in executive functions and attention, including focused attention which has been linked to executive control. The current study has shown that white matter changes in frontal, parieto-occipital and overall brain regions may underlie IIV in AD. Furthermore the results of the current study provide support for the idea that lapses in executive functions and attention underlie increased IIV.

**Acknowledgements**

We would like to thank our supervisor, Dr Progress Njomboro and co-supervisor Mr Bjorn Christ for their much valued feedback, advice and guidance.

We give special thanks to Dr Marc Combrinck, Professor of Neurology at Groote Schuur, Hospital for his knowledgeable input in reading CT scans and for the time he took to assist us.

We would also like to thank Miss Aimee Dollman for her input and advice, it was much appreciated.

**References**

Allaire, J. C., & Marsiske, M. (2005). Intraindividual variability may not always indicate vulnerability in elders' cognitive performance. *Psychology and Aging, 20*(3), 390-415. doi:10.1037/0882-7974.20.3.390

Baddeley, A. D., Baddeley, H., Bucks, R., & Wilcock, G. (2001). Attentional control in Alzheimer's disease. *Brain, 124*(8), 1492-1508. doi:10.1093/brain/124.8.1492

Baudic, S., Dalla Barba, G., Thibaudet, M. C., Smagghe, A., Remy, P., & Traykov, L. (2006). Executive function deficits in early Alzheimer's disease and their relations with episodic memory. *Archives of Clinical Neuropsychology, 21*(1), 15-21. doi:10.1016/j.acn.2005.07.002

Bielak, A. A., Hultsch, D. F., Strauss, E., Macdonald, S. W., & Hunter, M. A. (2010). Intraindividual variability in reaction time predicts cognitive outcomes 5 years later. *Neuropsychology, 24*(6), 731-741. doi:10.1037/a0019802

Boker, S. M., & Nesselroade, J. R. (2002). A method for modeling the intrinsic dynamics of intraindividual variability: Recovering the parameters of simulated oscillators in multi-wave panel data. *Multivariate Behavioral Research, 37*(1), 127-160. doi:10.1207/S15327906MBR3701_06

Bozzalli, M., Falini, A., Franceschi, M., Cercignani, M., Zuffi, M., Scotti, G., . . . Filippi, M. (2002). White matter damage in Alzheimer's disease assessed in vivo using diffusion tensor magnetic resonance imaging. *Journal of Neurology, Neurosurgery and Psychiatry, 72*(6), 742-746. doi:10.1136/jnnp.72.6.742

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica, 82*(4), 239-259.

Bunce, D., Anstey, K. J., Christensen, H., Dear, K., Wen, W., & Sachdev, P. (2007). White matter hyperintensities and within-person variability in community-dwelling adults aged 60–64 years. *Neuropsychologia, 45*(9), 2009-2015. doi:10.1016/j.neuropsychologia.2007.02.006

Bunce, D., Bielak, A. A., Cherbuin, N., Batterham, P. J., Wen, W., Sachdev, P., & Anstey, K. J. (2013). Utility of intraindividual reaction time variability to predict white matter hyperintensities: a potential assessment tool for clinical contexts? *Journal of the International Neuropsychological Society, 19*(9), 971-976. doi:10.1017/S1355617713000830

Catani, M., & Ffytche, D. H. (2005). The rises and falls of disconnection syndromes. *Brain, 128*(10), 2224-2239. doi:10.1093/brain/awh622

Choi, S. J., Lim, K. O., Monteiro, I., & Reisberg, B. (2005). Diffusion tensor imaging of frontal white matter microstructure in early Alzheimer's disease: a preliminary study. *Journal of Geriatric Psychiatry and Neurology, 18*(1), 12-19. doi:10.1177/0891988704271763

Coull, J., Frith, C., Frackowiak, R. S. J., & Grasby, P. (1996). A fronto-parietal network for rapid visual information processing: a PET study of sustained attention and working memory. *Neuropsychologia, 34*(11), 1085-1095. doi:10.1016/0028-3932(96)00029-2

De Jager, C. A., Joska, J. A., Hoffman, M., Borochowitz, K. E., & Combrinck, M. I. (2015). Dementia in rural South Africa: A pressing need for epidemiological studies. *South African Medical Journal, 105*(3), 189-190. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22404854

De la Monte, S. M. (1989). Quantitation of cerebral atrophy in preclinical and end-stage alzheimer's disease. *Annals of Neurology, 25*(5), 450-459. doi:10.1002/ana.410250506

Desai, M. K., Sudol, K. L., Janelsins, M. C., Mastrangelo, M. A., Frazer, M. E., & Bowers, W. J. (2009). Triple-transgenic Alzheimer's disease mice exhibit region-specific abnormalities in brain myelination patterns prior to appearance of amyloid and tau pathology. *Glia, 57*(1), 54-65. doi:10.1002/glia.20734

Dorsey, S. M., Rodriguez, H. D., & Brathwaite, D. (2001). Are things really so different? A research finding of satisfaction, illness and depression in rural South African elderly. *The ABNF Journal, 13*(2), 41-44. doi:1046-7041

Égerházi, A., Berecz, R., Bartók, E., & Degrell, I. (2007). Automated Neuropsychological Test Battery (CANTAB) in mild cognitive impairment and in Alzheimer's disease. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 31*(3), 746-751. doi:10.1016/j.pnpbp.2007.01.011

Faul, F., Erdfelder, E., Buchner, A., & Lang, A. G. (2009). Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behavior Research Methods, 41*(4), 1149-1160. doi:10.3758/BRM.41.4.1149

Faust, M. E., & Balota, D. A. (1997). Inhibition of return and visuospatial attention in healthy older adults and individuals with dementia of the Alzheimer type. *Neuropsychology, 11*(1), 13-29. doi:10.1037/0894-4105.11.1.13

Ferri, C. P., Prince, M., Brayne, C., Brodaty, H., Fratiglioni, L., Ganguli, M., . . . Huang, Y. (2006). Global prevalence of dementia: A Delphi consensus study. *The Lancet, 366*(9503), 2112-2117. doi:10.1016/S0140-6736(05)67889-0

Fiske, D. W., & Rice, L. (1955). Intra-individual response variability. *Psychological Bulletin, 52*(3), 217-250. doi:10.1037/h0045276

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*(3), 189-198. doi:10.1016/0022-3956(75)90026-6

Fray, P. J., Robbins, T. W., & Sahakian, B. J. (1996). Neuorpsychiatyric applications of CANTAB. *International Journal of Geriatric Psychiatry*. doi:10.1002/(SICI)1099-1166(199604)11:4<329::AID-GPS453>3.0.CO;2-6

Golby, A., Silverberg, G., Race, E., Gabrieli, S., O'Shea, J., Knierim, K., . . . Gabrieli, J. (2005). Memory encoding in Alzheimer's disease: An fMRI study of explicit and implicit memory. *Brain, 128*(4), 773-787. doi:10.1093/brain/awh400

Gordon, B., & Carson, K. (1990). The basis for choice reaction time slowing in Alzheimer's disease. *Brain and Cognition, 13*(2), 148-166. doi:10.1016/0278-2626(90)90047-R

Gunning-Dixon, F. M., Brickman, A. M., Cheng, J. C., & Alexopoulos, G. S. (2009). Ageing of cerebral white matter: a review of MRI findings. *International Journal of Geriatric Psychiatry, 24*(2), 109-117. doi:10.1002/gps.2087

Heckmann, J. M., Low, W. C., de Villiers, C., Rutherfoord, S., Vorster, A., Rao, H., . . . Kalaria, R. N. (2004). Novel presenilin 1 mutation with profound neurofibrillary pathology in an indigenous Southern African family with early-onset Alzheimer's disease. *Brain, 127*(1), 133-142. doi:10.1093/brain/awh009

Hultsch, D. F., MacDonald, S. W., & Dixon, R. A. (2002). Variability in reaction time performance of younger and older adults. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 57*(2), 101-115. doi:*10.1093/geronb/57.2.P101*

Hultsch, D. F., MacDonald, S. W. S., Hunter, M. A., Levy-Bencheton, J., & Strauss, E. (2000). Intraindividual variability in cognitive performance in older adults: Comparison of adults with mild dementia, adults with arthritis, and healthy adults. *Neuropsychology, 14*(4), 588-598. doi:10.1037//0894-4105.14.4.588

Huppert, F. A., Brayne, C., Gill, C., Paykey, E. S., & Beardsall, L. (1995). CAMCOG-A concise neuropsychological test to assist dementia diagnosis: Socio-demographic determinants in an elderly population sample. *British Journal of Clinical Psychology, 34*(4), 529-541. doi:10.1111/j.2044-8260.1995.tb01487.x

Jackson, J. D., Balota, D. A., Duchek, J. M., & Head, D. (2012). White matter integrity and reaction time intraindividual variability in healthy aging and early-stage Alzheimer

disease. *Neuropsychologia, 50*(3), 357-366. doi:10.1016/j.neuropsychologia.2011.11.024

James, K. A., Grace, L. K., Thomas, K. G., & Combrinck, M. I. (2015). Associations between CAMCOG-R subscale performance and formal education attainment in South African older adults. *International Psychogeriatrics, 27*(02), 251-260. doi:10.1017/S1041610214002233

Jensen, A. R. (1992). The importance of intraindividual variation in reaction time. *Personality and Individual Differences, 13*(8), 869-881. doi:10.1016/0191-8869(92)90004-9

Johnson, D. K., Barrow, W., Anderson, R., Harsha, A., Honea, R., Brooks, W. M., & Burns, J. M. (2010). Diagnostic utility of cerebral white matter integrity in early Alzheimer's disease. *International Journal of Neuroscience, 120*(8), 544-550. doi:10.3109/00207454.2010.494788

Kalin, A. M., Pfluger, M., Gietl, A. F., Riese, F., Jancke, L., Nitsch, R. M., & Hock, C. (2014). Intraindividual variability across cognitive tasks as a potential marker for prodromal Alzheimer's disease. *Frontiers in Aging Neuroscience, 6* (147). doi:10.3389/fnagi.2014.00147

Kelly, A. M., Uddin, L. Q., Biswal, B. B., Castellanos, F. X., & Milham, M. P. (2008). Competition between functional brain networks mediates behavioral variability. *Neuroimage, 39*(1), 527-537. doi:10.1016/j.neuroimage.2007.08.008

Kim, S. Y., Caine, E. D., Currier, G. W., Leibovici, A., & Ryan, J. M. (2014). Assessing the competence of persons with Alzheimer’s disease in providing informed consent for participation in research. *American Journal of Psychiatry, 158*(5), 712-717. doi:10.1176/appi.ajp.158.5.712

Lachaud, C. M., & Renaud, O. (2011). A tutorial for analyzing human reaction times: How to filter data, manage missing values, and choose a statistical model. *Applied Psycholinguistics, 32*(02), 389-416. doi:10.1017/S0142716410000457

Lawrence, N. S., Ross, T. J., Hoffmann, R., Garavan, H., & Stein, E. (2003). Multiple neuronal networks mediate sustained attention. *Cognitive Neuroscience, Journal of, 15*(7), 1028-1038. doi:10.1162/089892903770007416

Lemay, S., Bédard, M. A., Rouleau, I., & Tremblay, P. L. (2004). Practice effect and test-retest reliability of attentional and executive tests in middle-aged to elderly subjects. *The Clinical Neuropsychologist, 18*(2), 284-302. doi:10.1080/13854040490501718

Levinoff, E. J., Saumier, D., & Chertkow, H. (2005). Focused attention deficits in patients with Alzheimer's disease and mild cognitive impairment. *Brain and Cognition, 57*(2), 127-130. doi:10.1016/j.bandc.2004.08.058

Lovden, M., Li, S. C., Shing, Y. L., & Lindenberger, U. (2007). Within-person trial-to-trial variability precedes and predicts cognitive decline in old and very old age: longitudinal data from the Berlin Aging Study. *Neuropsychologia, 45*(12), 2827-2838. doi:10.1016/j.neuropsychologia.2007.05.005

Lowe, C., & Rabbitt, P. (1998). Test re-test reliability of the CANTAB and ISPOCD neuropsychological batteries: Theoretical and practical issues. *Neuropsychologia, 36*(9), 915-923. doi:10.1016/S0028-3932(98)00036-0

MacDonald, S. W., Hultsch, D. F., & Dixon, R. A. (2003). Performance variability is related to change in cognition: evidence from the Victoria Longitudinal Study. *Psychology and Aging, 18*(3), 510-523. doi:10.1037/0882-7974.18.3.510

MacDonald, S. W., Li, S. C., & Backman, L. (2009). Neural underpinnings of within-person variability in cognitive functioning. *Psychology and Aging, 24*(4), 792-808. doi:10.1037/a0017798

MacDonald, S. W., Nyberg, L., & Backman, L. (2006). Intra-individual variability in behavior: links to brain structure, neurotransmission and neuronal activity. *Trends in Neurosciences, 29*(8), 474-480. doi:10.1016/j.tins.2006.06.011

Medina, D., Urresta, F., Gabrieli, J. D., Moseley, M., Fleischman, D., Bennett, D. A., . . . Stebbins, G. T. (2006). White matter changes in mild cognitive impairment and AD: A diffusion tensor imaging study. *Neurobiology of Aging, 27*(5), 663-672. doi:10.1016/j.neurobiolaging.2005.03.026

Mirsky, A. F., Anthony, B. J., Duncan, C. C., Ahearn, M. B., & Kellam, S. G. (1991). Analysis of the elements of attention: A neuropsychological approach. *Neuropsychology Review, 2*(2), 109-145. doi:1040-7308/91/0600-0109

Morcom, A. M., Good, C. D., Frackowiak, R. S., & Rugg, M. D. (2003). Age effects on the neural correlates of successful memory encoding. *Brain, 126*(1), 213-229. doi:10.1093/brain/awg020

Moy, G., Millet, P., Haller, S., Baudois, S., de Bilbao, F., Weber, K., . . . Delaloye, C. (2011). Magnetic resonance imaging determinants of intraindividual variability in the elderly: combined analysis of grey and white matter. *Neuroscience, 186*, 88-93. doi:10.1016/j.neuroscience.2011.04.028

Murtha, S., Cismaru, R., Waechter, R., & Chertkow, H. (2002). Increased variability accompanies frontal lobe damage in dementia. *Journal of the International Neuropsychological Society, 8*(03), 360-372. doi:10.1017/S1355617702813170

Nesselroade, J. R., & Salthouse, T. A. (2004). Methodological and theroretical implications of intraindividual variability in perceptual-motor performance. *Journal of Gerontology: Psychological Sciences, 59*(2), 49-55. doi:*10.1093/geronb/59.2.P49*

Neufang, S., Akhrif, A., Riedl, V., Förstl, H., Kurz, A., Zimmer, C., . . . Wohlschläger, A. M. (2011). Disconnection of frontal and parietal areas contributes to impaired attention in very early Alzheimer's disease. *Journal of Alzheimer's Disease, 25*(2), 309-321. doi:10.3233/JAD-2011-102154

O'Connor, D. W., Pollitt, P., Hyde, J., Fellows, J., Miller, N., Brook, C., . . . Roth, M. (1989). The prevalence of dementia as measured by the Cambridge Mental Disorders of the Elderly Examination. *Acta Psychiatrica Scandinavica, 79*(2), 190-198. doi:10.1111/j.1600-0447.1989.tb08587.x

Parasuraman, R., & Haxby, J. V. (1993). Attention and brain function in Alzheimer's disease: A review. *Neuropsychology, 7*(3), 242-272. doi:10.1037/0894-4105.7.3.242

Rizzo, M., Anderson, S., Dawson, J., Myers, R., & Ball, K. (2000). Visual attention impairments in Alzheimer's disease. *Neurology, 54*(10), 1954-1959. doi:10.1212/ WNL.54.10.1954

Sachdev, P. S., Zhuang, L., Braidy, N., & Wen, W. (2013). Is Alzheimer's a disease of the white matter? *Current Opinion in Psychiatry, 26*(3), 244-251. doi:10.1097/YCO.0b013e32835ed6e8

Sakai, K., Hikosaka, O., Miyauchi, S., Takino, R., Sasaki, Y., & Pütz, B. (1998). Transition of brain activation from frontal to parietal areas in visuomotor sequence learning. *The Journal of Neuroscience, 18*(5), 1827-1840. doi:270-6474/98/181827

Sarter, M., Givens, B., & Bruno, J. P. (2001). The cognitive neuroscience of sustained attention: Where top-down meets bottom-up. *Brain research reviews, 35*(2), 146-160. doi:10.1016/S0165-0173(01)00044-3

Sgaramella, T., Borgo, F., Mondini, S., Pasini, M., Toso, V., & Semenza, C. (2001). Executive deficits appearing in the initial stage of Alzheimer's disease. *Brain and Cognition, 46*(1), 264-268. doi:10.1016/S0278-2626(01)80080-4

Sjobeck, M., Haglund, M., & Englund, E. (2005). Decreasing myelin density reflected increasing white matter pathology in Alzheimer's disease - a neuropathological study. *International Journal of Geriatric Psychiatry, 20*(10), 919-926. doi:10.1002/gps.1384

Stahl, R., Dietrich, O., Teipel, S. J., Hampel, H., Reiser, M. F., & Schoenberg, S. O. (2007). White matter damage in Alzheimer disease and mild cognitive impairment: Assessment with diffusion-tensor MR Imaging and parallel imaging techniques *Radiology, 243*(2), 483-492. doi:10.1148/radiol.2432051714

Stokin, G. B., Lillo, C., Falzone, T. L., Brusch, R. G., Rockenstein, E., Mount, S. L., . . . Williams, D. S. (2005). Axonopathy and transport deficits early in the pathogenesis of Alzheimer's disease. *Science, 307*(5713), 1282-1288. doi: 10.1126/science.1105681

Thorpe, S., Fize, D., & Marlot, C. (1996). Speed of processing in the human visual system. *Nature, 381*(6582), 520-522. doi:10.1038/381520a0

Tuch, D. S., Salat, D. H., Wisco, J. J., Zaleta, A. K., Hevelone, N. D., & Rosas, H. D. (2005). Choice reaction time performance correlates with diffusion anisotropy in white matter pathways supporting visuospatial attention. *Proceedings of the National Academy of Sciences of the United States of America, 102*(34), 12212-12217. doi:10.1073/pnas.0407259102

Unsworth, N., Redick, T. S., Lakey, C. E., & Young, D. L. (2010). Lapses in sustained attention and their relation to executive control and fluid abilities: An individual differences investigation. *Intelligence, 38(*1), 111-122. doi:10.1016/j.intell.2009.08.002

Wahlund, L., Barkhof, F., Fazekas, F., Bronge, L., Augustin, M., Sjögren, M., . . . Pantoni, L. (2001). A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke, 32*(6), 1318-1322. doi:10.1161/01.STR.32.6.1318

Walhovd, K. B., & Fjell, A. M. (2007). White matter volume predicts reaction time instability. *Neuropsychologia, 45*(10), 2277-2284. doi:10.1016/j.neuropsychologia.2007.02.022

West, R. (2001). The transient nature of executive control processes in younger and older adults. E*uropean Journal of Cognitive Psychology*, *13*(1-2), 91-105. doi: 10.1080/09541440042000232

Yesavage, J. A., Brooks, J., Taylor, J., & Tinklenberg, J. (1993). Development of aphasia, apraxia, and agnosia and decline in Alzheimer's disease. *The American journal of psychiatry, 150*(5), 742-747.

Zhang, Y., Schuff, N., Du, A.-T., Rosen, H. J., Kramer, J. H., Gorno-Tempini, M. L., . . . Weiner, M. W. (2009). White matter damage in frontotemporal dementia and Alzheimer's disease measured by diffusion MRI. *Brain, 132*(9), 2579-2592. doi:10.1093/brain/awp071

# Appendix A

## 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.

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

# Appendix B

## 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 a 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 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** **0** | **Questionable** **0.5** | **Mild** **1** | **Moderate** **2** | **Severe** **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<br><br>Appears well enough to taken to functions outside a family home | No pretense of independent function outside home<br><br>Appears too ill to be 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

## The ARWMC Rating Scale for MRI and CT

**The ARWMC Rating Scale for MRI and CT**

| | |
|---|---|
| White matter lesions | |
| 0 | No lesions (including symmetrical, well-defined caps or bands) |
| 1 | Focal lesions |
| 2 | Beginning confluence of lesions |
| 3 | Diffuse involvement of the entire region, with or without the involvement of U fibres |
| Basal ganglia lesions | |
| 0 | No lesions |
| 1 | 1 focal lesion (>5 mm) |
| 2 | >1 focal lesion |
| 3 | Confluent lesions |

White matter changes on MRI were defined as bright lesions >5 mm on T2, PD, or FLAIR images. Lesions on CT were defined as hypodense areas of >5 mm; left and right hemispheres were rated separately. The following brain areas were used for rating: frontal, parieto-occipital, temporal, infratentorial/cerebellum, and basal ganglia (striatum, globus palli- dus, thalamus, internal/external capsule, and insula).

# Appendix E

## PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

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

**PROTOCOL NUMBER:**

**PRINCIPAL INVESTIGATOR:** Mr Bjorn U. Christ

**SECONDARY INVESTIGATORS:** Ms Kara Engelbrecht and Ms Melinda Simon

**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:

(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 2 hours 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, which includes your Groote Schuur Hospital medical history (e.g. the records of the Geriatric Unit and the Memory Clinic), 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*) ……..……2015

..... .....

**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*) ……..…….. 2015

..... .....

**Signature of investigator** **Signature of witness**