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# Intra-individual Variability in Attention-Switching Tasks Predicts Cognitive Performance in Alzheimer's Disease

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## Abstract

**Background:** Dementia is a growing concern worldwide with prevalence rates increasing exponentially – with the majority of these cases being individuals with Alzheimer's disease. Due to this high prevalence rate, identifying measures that can assist in detecting Alzheimer's disease early is crucial in decreasing the economic burden in LAMICS, such as South Africa. Intra-individual variability, a within-person measure, is showing promise as a measure of cognitive processing stability. **Method:** Our participants were healthy older adults (*n*=23), and those with possible or probable Alzheimer's (*n*=21). We used three measures of attentional control from the CANTAB: The attention-switching task conditions (Naming, Location, Switching), simple reaction-time, and choice reaction-time. Additionally, we had three screening measures: The CAMCOG-R, MMSE, and GDS. We used logistic regressions to assess the predictability of group membership and, multiple regressions to assess predictability of general cognitive performance. IIV-I was extracted for the measures of attentional control resulting in *iSDs*. **Results:** We found that in our logistic regressions model, the strongest predictor of group membership was the Location *iSDs* as it could predict above mean scores. For the multiple regressions model, the Location *iSDs* and simple reaction-time *iSDs* were the strongest predictors of general cognitive health but, could not predict above mean scores. **Discussion:** Differences in the predictability strength may have been due to varying cognitive demands of the conditions. Overall, the attention-switching measures of IIV, in particular Naming *iSDs* and Location *iSDs*, can, to an extent, predict both group membership and general cognitive performance in Alzheimer's.


**Keywords:** *Alzheimer's disease, Intra-individual variability, South Africa, group membership, cognitive demand, general cognitive performance*

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## Contents

Worldwide population trends indicate ageing populations and age-related diseases such as dementia are quickly developing into a global epidemic. Recent epidemiological figures estimate that around 50 million people worldwide currently live with dementia, and most of those cases – in the range of 50% to 70% – are individuals with Alzheimer's disease (Zhang et al., 2021). In addition, according to the 2015 World Alzheimer's Report, approximately 58% of global cases of dementia are found within lower- and middle-income countries (LAMICs; Fleming et al., 2020; Rizzi et al., 2014). These concerning figures are made even more troubling by the economic burden of Alzheimer's disease, which is exaggerated in LAMICs, where the burden of care falls largely on relatives as access to paid care is limited. Furthermore, the reliance on relatives in LAMICs is provided at great cost to carers, many of whom must reduce their hours of paid work to provide such care (Prince et al., 2015; Rasmussen & Langerman, 2019). Hence, research that attempts to reduce the burden of Alzheimer's within LAMICs, such as South Africa, contributes towards an important public health goal.

One line of inquiry explored by researchers to help alleviate the burden of age-related disease focuses on early detection and intervention. Studies with this focus report that early detection and intervention leads to delayed disease progression, reducing the long-term burden for caregivers and the economy through the associated cost reduction (Alzheimer's Association, 2019; Getsios et al., 2012; Rasmussen & Langerman, 2019). However, the progression and manifestation of Alzheimer's disease is heterogenous in nature, making it difficult to detect in the early stages, and so new methods of early detection are currently being investigated (Costa et al., 2019; Ryan et al., 2018). One method that is well-suited to the detection of pathological processes with heterogeneous trajectories, namely, intra-individual variability (IIV), focuses on within-patient change instead of the conventional emphasis on between-patient differences.

**Intra-individual Variability**

IIV is a marker of cognitive processing stability, and is thus defined as within-person fluctuation in measures of cognitive performance over time (Costa et al., 2019; Shin et al., 2013). There are two types of IIV measurement: Intra-individual variability *inconsistency* and intra-individual variability *dispersion*. IIV-dispersion is the measurement of variability across various cognitive tasks in a single session, whereas IIV-inconsistency is the measurement of variability within a single task on multiple occasions (Costa et al., 2019; Mumme et al., 2021). While both measures are used, there is a greater body of studies using IIV-inconsistency for predicting later cognitive decline (Kälin et al., 2014).

IIV, which increases with cognitive dysfunction, is a promising indicator of underlying neuropathology. For example, increased IIV is associated with information processing difficulties in patients with multiple sclerosis (Wojtowicz et al., 2012). Furthermore, in a study of 117 participants, consisting of healthy elderly individuals and individuals with mild cognitive impairment, it was found that those with mild cognitive impairment showed lower reaction-time speed and higher reaction-time IIV (Phillips et al., 2013). )

IIV may be a more effective method of indicating brain pathology than more commonly used measures of central tendency. Findings show that IIV is more sensitive in detecting neurocognitive dysfunction than the means of tests (Merritt et al., 2019). Thus, IIV may be a better way to differentiate between control and clinical groups than mean-level measures due to its sensitivity to underlying neuropathology (Wojtowicz et al., 2012). Through executive function tests, a study observed that there were no significant differences between mean-level performance scores in mild traumatic brain injury subjects and the controls, although a significant increase in IIV was identified in the clinical subjects and not in the controls (Sorg et al., 2021). An additional study found IIV to be a superior predictor of

group membership than performance accuracy measures in patients with mild cognitive impairment (Troyer et al., 2016). Thus, IIV may be well-suited to detecting pathological processes at the earliest disease stages where mean-level performance cannot. There are various methods of capturing IIV-inconsistency with reaction-time and accuracy-based IIV as two commonly used methods (Christ et al., 2018).

**Methods of Capturing Intra-individual Variability Inconsistency**

Reaction-time IIV and accuracy-based IIV are two types of IIV-inconsistency measures. Reaction-time IIV is based on reaction-time data, this being the response time of a participant during trials of tests that require the individual to respond to a stimulus. Reaction-time is measured by the time it takes an individual to respond to a stimulus or target (Phillips et al., 2013). Accuracy-based IIV looks at the participant's responses in the test trials and whether these responses are correct. The fluctuations in accuracy-based IIV is therefore based on correct and incorrect responses (Tarnanas et al., 2015). Reaction-time IIV is a commended measure as it remains sensitive after controlling for mean performance, whereas accuracy-based IIV has shown to reduce in sensitivity after mean performance is controlled for (Christ et al., 2018). In a study that compared reaction-time IIV and accuracy-based IIV as predictors of cognitive integrity, reaction-time IIV was found to be the more effective predictor (Christ et al., 2018). This is because the reaction-time measures were sensitive to between-group differences of the Alzheimer's group and control group, meaning it could successfully differentiate between the two groups, whereas two of the three accuracy-based measures could not significantly differentiate between the study's sample groups. This study highlighted the utility of IIV measures in predicting Alzheimer's disease.

**Intra-individual Variability as a Predictor for Alzheimer's Disease**

Due to the utility of reaction-time IIV measures in detecting underlying neuropathology and their relative sensitivity to early-stage disease processes, reaction-time

IIV may be a great fit for Alzheimer's research. Individuals in late-adulthood typically show higher reaction-time IIV than those in early- to middle-adulthood; however, individuals with Alzheimer's show an even greater increase in reaction-time IIV than those in late-adulthood (Haynes et al., 2017). Due to the increased reaction-time IIV in Alzheimer's patients, reaction-time IIV has been shown to discriminate between individuals with Alzheimer's and healthy controls (Christ et al., 2018; Hultsch et al., 2000).

One likely mechanism for higher IIV in Alzheimer's populations could be related to the relative integrity of the white matter structures of these individuals. White matter hyperintensities can indicate a higher risk of dementia, including Alzheimer's (Salvado et al., 2019). For instance, individuals who carry the APOE e-4 allele gene, known to increase the risk of developing Alzheimer's, and are deemed cognitively healthy, still show an increased risk of developing white matter hyperintensities than those who do not carry the gene (Rojas et al., 2018). Furthermore, IIV has been shown to be sensitive to white matter change. Studies have found that reaction-time IIV was able to predict white matter hyperintensities in magnetic resonance imaging scans, meaning that IIV can be used to identify healthy individuals at risk for developing Alzheimer's (Bunce et al., 2013; Jackson et al., 2012).

The findings of the literature reviewed thus far demonstrate that IIV is sensitive to underlying neuropathology and that there exists neuroanatomical overlap between the potential mechanisms of IIV and the neuropathology of Alzheimer's disease, which makes IIV well-suited to study the trajectory of cognitive change in Alzheimer's disease.

**Attention-switching Tasks**

Fluctuations in IIV on attention-switching tasks have been evaluated as an informative predictor for cognitive health. An attention-switching task is a reaction-time based measure of executive function and usually comprise of variations in conditions that

make up the task (Fray et al., 1996). These conditions usually comprise of an arrow stimulus in which the participants are asked, via a prompt, to respond to a certain property of the arrow. The prompts given to the participant change for each condition - for example, one condition may ask a participant to report on an arrow's location whilst ignoring the direction while another may ask for both location and direction of the arrow. The attention-switching task conditions usually comprise of congruent, neutral, and incongruent trials (Fray et al., 1996).

Attention-switching tasks are commonly used in ADHD research, where individuals with ADHD typically show more IIV in attention-switching performance, compared to individuals without ADHD (e.g., Luna-Rodriguez et al., 2018). However, attention-switching tasks may also have promise in Alzheimer's research, since executive control deficits tend to be present in the mildest stages of this disease (Kirova et al., 2015; Traykov et al., 2007). For instance, Tse et al. (2016) conducted a study on Alzheimer's patients to assess their performance on an attention-switching task compared to healthy controls. There were two conditions in this task, one which assessed prospective memory and one which assessed selective attention. The prospective memory task required participants to respond to an arrow when two colours were presented on the screen but, to not respond when only one colour was presented on the screen. The other condition of the task, which assessed selective attention, required participants to ignore the location of an arrow presented on a screen and only report the direction the arrow was pointing towards. The arrow was either congruent, as in pointing to the same direction of its location, incongruent, as in pointing to the opposite direction of its location, or neutral, where the arrow was in the centre of the screen. This study, which evaluated the task conditions separately, found that both task conditions were able to significantly predict group membership in Alzheimer's disease (Tse et al., 2010; 2016).

From the study cited above, it appears that assessing the different conditions of an attention-switching task separately may have some utility in Alzheimer's research. On this line of inquiry, a study by Traykov et al. (2007) noted that, in a sample of individuals with MCI and probable Alzheimer's, different attentions systems may deteriorate at differing rates – deficits were seen in selective attention, and inhibition, whereas sustained, and divided attention were relatively spared. This implies that studies assessing attention systems within the Alzheimer's and MCI population may benefit from using different tests to assess different types of attention, as the rate of deterioration of all attentional systems in these populations may not be parallel.

However, only one study has explored IIV in Alzheimer's patients using an attention-switching task (Duchek et al., 2009). There were two conditions in this task, the CV condition which asked participants to report whether the letter is a consonant or vowel, and the OE condition which asked participants to report whether the number was odd or even. However, these two conditions were evaluated as one task in the results (Duchek et al., 2009). The study reported that higher IIV in task-switching is seen in healthy older adults when compared to younger adults, and furthermore, that individuals in the early stages of Alzheimer's demonstrate more IIV in attention-switching when compared to healthy older adults. The increased IIV and increased errors in attention-switching was attributed by the authors to executive functioning deficits in Alzheimer's patients. Furthermore, increased IIV in task-switching was also able to identify individuals from the control group who were at risk of developing Alzheimer's through the use of cerebrospinal fluid biomarkers (Duchek et al., 2009). These findings demonstrate that IIV in an attention-switching task not only differentiated between healthy and pathological aging but, could also identify individuals at risk for developing Alzheimer's.

Lastly, it has been noted that a higher cognitive load on a task can influence the sensitivity of the task as an IIV measure, therefore an attention-switching task may be an effective IIV measure due to its higher cognitive load (Bielak et al., 2010). Tasks that require a higher cognitive load, such as an attention-switching task, have also been noted to result in poorer performance in a healthy older adult population due to the increased demand on executive control functioning (Eich et al., 2018). Interestingly, Allaire and Marsiske (2005) found that while high cognitive load does result in an initial poor performance, practice effects which arises from repeated trials in the same task, may lead to an increase in performance across trials in healthy controls. This increased in performance, from poor performance to better performance later on in the trials, results in an overall higher IIV for controls. This is supported by Christ et al. (2018) who found that a higher cognitive demand resulted in higher variability.

In conclusion, IIV-inconsistency is successful in identifying group membership, and has promising potential to predict the development of Alzheimer's disease. A gap in the literature has been identified, specifically with regards to evaluating the specific conditions of attention-switching tasks separately for IIV in Alzheimer's patients. Evidence suggests that, with the Alzheimer's population, in looking at attention-switching task as an IIV measure, there may be benefit in splitting up the task into its various conditions. There is a need for further literature on this topic to understand whether attention-switching, instead of the more commonly used reaction-time measures, can be used as a predictor of group membership in Alzheimer's. While reaction-time has been successful, it is necessary to explore additional measures of IIV to expand on this promising within-person measure.

## Rationale, Aims and Research Questions

IIV has been shown to be useful in research regarding cognitive functioning. Additionally, it appears well-suited to Alzheimer's research such as differentiating between clinical and healthy groups and predicting cognitive health. However, the majority of the studies have focused on reaction-time and thus, there is a need for further exploration of additional measures of IIV.

This study aimed to contribute towards the growing literature on IIV measurement by exploring the utility of an attention-switching task as a clinically useful measure of IIV. More specifically, this study aimed to explore the utility of the attention-switching conditions - Naming, Location, and Switching – as indicators of IIV. Thus, the study aimed to determine whether IIV in the attention-switching task conditions are an effective indicator of clinical group membership and general cognitive performance.

Therefore, due to the aforementioned aims the research questions are as follows: (1) Can IIV in each of the attention-switching conditions - Naming, Location, Switching - predict clinical group membership, i.e., can they differentiate between healthy adults and a clinical Alzheimer's group? (2) Are the attention-switching conditions of IIV – Naming, Location, Switching - stronger predictors of general cognitive performance than the more conventionally used simple and choice reaction-time measures of IIV?

## Method

### Design

This study formed part of a broader study which collected data until 2017. The broader study used a measurement-burst design, which incorporates both a longitudinal approach and cross-sectional comparisons (Christ et al., 2018). A measurement-burst design encompasses bursts of assessment in varying rates of succession over a short period of time – days/weeks- to capture short-term variability (Stawski et al., 2015). The measurement-burst

design of the broader study tested participants over three time-intervals (T1, T2, and T3). Within each interval (or burst), participants were tested 3 times over a 2-week period. Each burst took place 7.5 months apart: T1 took place immediately after recruitment, T2 at 7.5 months later, and T3 at 15 months after T1. The current study is a secondary analysis which used data from T1, and is thus of a cross-sectional variation, which is nested within a measurement-burst design.

The first interval of testing consisted of three test administrations: T1.1, T1.2, and T1.3. Multiple test sessions allowed for the capturing of IIV over different time-scales, i.e., within a day, across days, and across weeks.

**Participants**

The broader study consisted of two groups: Healthy adults ($n$ = 26) with no neurological history and clinical participants ($n$ = 26) with possible or probable Alzheimer's Disease. Clinical participants were recruited from Groote Schuur Hospital's Memory Clinic and the Geriatric Unit, in Cape Town. This process was monitored by neurologists from the hospital, who used the standard Clinical Diagnostic Criteria for Alzheimer's Disease (see **Appendix A**) to determine cases of possible or probable Alzheimer's Disease.

The healthy adult control participants were recruited from the Cape Metropolitan District, with the use of flyers, advertisements in retirement homes, local senior's clubs, and snowball sampling. Controls were matched to the patient group by three criteria: Socioeconomic status, age, and sex.

***Eligibility Criteria***

All participants, included in the broader study met the following eligibility criteria: (a) Older than 55 years of age; (b) English literacy – basic ability to read, write, and speak English; (c) access to medical health history (clinical participants only); and (d) availability

of a close relative or individual who could account for any recent changes in the participant's cognitive functioning.

### *Exclusion Criteria*

Participants in the broader study were excluded based on the following criteria: (a) Psychiatric illness – present or past; (b) Mini Mental State Exam (MMSE; Folstein et al., 1975) score below 12 at any of the 3 measurement-bursts (i.e., T1, T2, T3); (c) diagnosis of any medical condition that the research team deemed to have long-lasting effects – including, but not limited to, uncontrolled hypertension, HIV/AIDS, uncontrolled diabetes mellitus; (d) a score of greater than 15/30 on the Geriatric Depression Scale (GDS; Yesavage et al., 1982); (e) history of traumatic brain injury or cerebrovascular accidents within the last two years, or the presence of a major neurological disorder (for example, Parkinson's disease); and (f) current substance abuse i.e., drug or alcohol abuse or cigarette abuse of more than 20 cigarettes daily.

## Measures

### *Measures of Attentional Control*

The study used two subtests from the Cambridge Neuropsychological Test Automated Battery (*CANTAB*; Fray et al.,1996). Both tasks measured attentional control processes.

**Reaction-time.** There were two reaction-time subtests; the simple reaction-time task and the 5-choice reaction-time task. In the simple reaction-time task, a yellow dot appeared in the centre of the screen. The aim for the participant was to respond to this stimulus as quickly as possible. They responded by releasing a press pad and tapping on the dot on the screen. In the choice reaction-time there were now five locations where the yellow dot may appear. The same aim applied, the participant must release the press pad and touch the yellow dot. Once the participants had correctly completed 5 out of 6 attempts, they moved to the assessed phase. A correct attempt was when the participant touched the correct location of the yellow

dot and did not react too early or unusually late. The practice stage of both reaction-time tasks consisted of 10 trials and the assessed stage of both reaction-time tasks consisted of 30 trials. One block of trials for both the simple and choice reaction-time subtests of the reaction-time task took approximately five minutes to complete.

Both tasks that made up the reaction-time component on the CANTAB have shown to have high reliability. The simple reaction-time task has shown to have a test-retest reliability of .82 and the choice reaction-time task has shown to have a test-retest reliability of .73 (Cacciamani et al., 2018). Psychometric data on both reaction-time tasks is scarce. Both the simple and choice reaction-time tasks have been used in a South African context for assessing motor speed in children with Fetal Alcohol Spectrum Disorders (Chetty-Mhlanga et al., 2022).

**Attention-switching Task.** In the attention-switching task, the participants were presented with an arrow on the screen. This arrow could appear on the left or right side of the screen and could point either left or right. For each trial, the participant was prompted to respond to either the position of the arrow or the direction in which the arrow was pointing. These trials could be congruent (the arrow was pointing in the same direction as it was located) or incongruent (the arrow was pointing in the opposite direction to which it was located). There were seven stages to the attention-switching task; four practice stages containing 40 trials and three assessed stages of 160 trials. In total, the attention-switching task took approximately eight minutes to complete. The three assessed stages were the conditions that were used in this study. In the first condition, referred to as Naming, the arrow was presented in the centre of the screen and the participants were asked to respond in what direction the arrow was pointing. In the second condition, referred to as Location, the arrow was presented on either the left or right side of the screen and was pointing either left or right. In this condition the participants were asked to ignore the direction and only report on the

location of the arrow. In the third condition, referred to as Switching, the arrow could appear on the left or right of the screen and point in either direction. In this condition, the participants were asked to report on either the location or the direction of the arrow in different trials (Fray et al., 1996).

The attention-switching task has shown a three-month test-retest reliability of 0.75 (Karlsen et al., 2022). Further psychometric data on the CANTAB attention-switching task is scarce. The attention-switching task has been used to measure cognitive performance in a variety of populations. For example, it has been used to measure cognitive performance in young adult smokers, in individuals with clinical obesity, and in individuals who have suffered a traumatic brain injury (Meo et al., 2019; Bashir et al., 2017; Van Praag et al., 2021).

**Screening Measures**

Three screening measures were used in the broader study to measure general cognitive function and affect.

**The Geriatric Depression Scale (GDS).** The GDS (Yesavage et al., 1982) was used as a screening measure for depression in the broader study. This is a 30-item, self-report scale and a positive depression rating is a score above 15/30. The GDS has shown to have high reliability, with internal consistency of .903 and test-retest reliability of .94 (Massai et al., 2018). The GDS has been used in a South African context as a tool for measuring depression in older populations (Padayachey et al., 2017).

**The Cambridge Examination for Mental Disorders of the Elderly – Revised (CAMCOG-R).** The CAMCOG-R (Huppert et al., 1995) was used to measure general cognitive functioning in the healthy and clinical groups. This measure contains 67 items and measures an individual's performance across eight domains, namely, language, memory, abstract thinking, orientation, perception, attention, praxis and calculation. The CAMCOG-R

has shown to have high test-retest reliability, split half reliability of .83 and internal consistency of .81 (Pereiro et al., 2014). The CAMCOG-R has been used in the South African context as an indicator of general cognitive functioning in Alzheimer's patients (James et al., 2014).

**Mini-Mental State Examination (MMSE).** The MMSE (Folstein et al., 1975) was used as a screening measure for severe dementia. This measure is able to differentiate between individuals with cognitive impairment and healthy individuals (Folstein et al., 1975). The MMSE contains 19 items and tests five domains of cognitive functioning, namely; orientation, registration, attention and calculation, recall and language. The MMSE has shown to have an intraclass correlation coefficient of .94 (Hörnsten et al., 2021). This measure has been used as a screening measure for cognitive impairment in South African studies (Rademeyer & Joubert, 2016; Ramlall et al., 2013).

## Procedures

After the participants had been recruited to the study, verbal consent was obtained for participation. Following this, the study's Principal Investigator scheduled the screening sessions with the participants. The procedure of the study consisted of three phases, namely; the screening phase, the test phase and the neuroimaging phase. The current study did not make use of the data that was collected in the neuroimaging phase. The broader study obtained ethical consideration from the University of Cape Town Human Research Ethics Committee (see **Appendix C**)

### *Screening Phase*

In the beginning of the screening session, participants were required to read and sign an informed consent form (see **Appendix B**) if they wanted to participate in the study, which outlined that the process was voluntary, that the participants could withdraw their participation at any time, and that all identifying information would be treated with

confidentiality. All participant information was anonymised. As the current study made use of a secondary analysis, consent did not need to be obtained again as there was no interaction with the participants.

The screening session took place at either the participant's home or a private testing room at Groote Schuur Hospital. For the clinical participants, an individual close to the participant was present during the administration of the screening measures. The control participants were evaluated independently. The scores for each screening measure per participant were calculated to assess whether their scores did not fall into the exclusion criteria.

Individuals whose scores resulted in their exclusion from the study were debriefed and then dismissed. Individuals with a GDS score above 15 points were offered a note with information of their score that could be used for further medical consultation. Individuals who were excluded on the basis of a major neurocognitive impairment diagnosis were referred to the Memory Clinic, provided they were not existing patients.

***Test Phase***

As with the screening phase, the test phase occurred in either the participant's home or a private testing room at Groote Schuur Hospital. The test phase commenced within one month of the screening phase. Such as the screening phase, the control participants were tested individually, and the clinical participants had a friend or relative accompany them. There was a total of three testing intervals/measurement bursts in the broader study. The order of test administration within each session was different each time to prevent order effects. The current study only made use of the first measurement burst (T1).

We, the authors of the current study, received the relevant datasets from the Principal Investigator of the larger study for the secondary analysis. The attention-switching task data

was received in raw form; however, reaction-time data had been prepared prior by the broader study.

**Statistical Analyses**.

The analyses were conducted using SPSS (version 28) with an alpha level set at .05.

***Data Preparation***

The simple and choice reaction-time data had been previously prepared by the broader study (for more information, see Christ et al., 2018). Data preparation was thus only required for the attention-switching task conditions. The attention-switching task was divided into the Naming, Location, and Switching conditions. We included only correct responses and removed any incorrect responses to ensure only valid responses were used. Following on, outliers were identified and removed. That is, any drastic fluctuations, exceedingly fast (<150ms) or slow responses (3 SDs > group reaction-time mean in each testing block), were indicative of spurious performance, and removal prevented influence on mean reaction-time performance (Christ et al., 2018). Participants with an overall missingness of 40% or above were removed from the data set (Jakobson et al., 2017). For the remaining participants, a multiple imputations method making use of regressions, outlined by Lachaud and Renaud (2011), was used to replace the missing data.

***Extraction of Intra-individual Variability***

The IIV for simple and choice reaction-time had been previously extracted by the broader study (for more information, see Christ et al., 2018). The extraction process therefore only applied to that of the attention-switching task conditions.

We followed a method of extracting IIV based off the work by Hultsch et al. (2000, 2002, 2008). After preparing the data, we needed to detrend any systematic effects, such as group characteristics and time-on-task effects, in order to remove the effects of mean performance on our data. This was done through the use of a random intercept model that

was run on each attention-switching task condition – Naming, Location, and Switching. Following on, we captured the residuals from the random effects models and converted them into T-scores. Lastly, the intra-individual standard deviations (*iSDs*) were extracted by calculating the standard deviation across the T-scores calculated previously.

***Inferential Statistical Analyses***

The initial inferential statistics involved assessing between-group differences i.e., differences between the clinical group and control group. For assessing differences in age, education, sex, monthly household income, as well as the affective and cognitive characteristics (GDS, CAMCOG-R, MMSE), we created a series of independent samples *t*-tests for parametric data, Mann-U Whitney for non-parametric data, and chi-square for categorical data. Additionally, we assessed the between-group differences in the raw-score means and *iSDs* of our predictor variables.

**Research Question 1.** To assess the attention-switching task conditions as predictors of group membership, we built logistic regression models with group membership as the outcome variable and the attention-switching task conditions as the predictor. Control variables included in the models were the significant between-group differences identified. Predictor variables excluded from the logistic regression models were those that lacked significant between-group difference.

**Research Question 2.** Multiple regressions were used to assess if the attention-switching task conditions of IIV were stronger predictors of general cognitive performance, CAMCOG-R and MMSE, than simple and choice reaction-time measures of IIV. A correlation matrix assisted in the identification of control variables needed for inclusion. Furthermore, the bivariate correlations assisted in the identification of significant correlations between outcome variables and predictors – a lack of a significant correlation resulted in exclusion from the multiple regressions model.

# Results

## Sample Characteristics.

The two groups were healthy adults ($n$ = 23) and clinical participants ($n$ = 21) with possible or probable Alzheimer's Disease. The scale for monthly household income ranged from 1 to 5, education ranged from 4 to 17 years, and age ranged from 56 to 87 years old. The groups were matched on sex, and monthly household income; however, significant between-group differences in the demographic data were identified in age and education. There were significant differences in the affective and cognitive characteristics in the CAMCOG-R and MMSE (see **Table 1**).

**Table 1**

*Descriptive Statistics and Between Group Differences for the Clinical and Control Group: Sample Demographics, Affective, and Cognitive Characteristics*

| Variable | Group | | *t / x^2 / z* | *df* | *p* | ESE |
|---|---|---|---|---|---|---|
| | **Control** | **Clinical** | | | | |
| | (*n* = 23) | (*n* = 21) | | | | |
| Age (years) | 68.91 (6.68) | 73,48 (6.54) | -2.32 | 42 | .025* | -.70 |
| Education (years) | 4.78 (2.51) | 9,52 (2.29) | 3.23 | 42 | .002** | .97 |
| Sex (M:F) | 6:17 | 6:15 | .28 | 1 | .599 | -.08 |
| Household income (1:2:3:4:5) | 0:1:4:3:15 | 0:0:4:9:8 | 6.25 | 4 | .182 | .38 |
| GDS | 5.35 (3.20) | 6.29 (3.27) | -.951 | 42 | .342 | -.290 |
| CAMCOG-R | 91.42 (5.66) | 67.24 (11.56) | 9.21 | 42 | <.001*** | 2.78 |
| MMSE | 28.00 (1.59) | 21.00 (4.80) | -4.87 | | <.001*** | 0.73 |

*Note. For Age, Education, GDS, CAMCOG-R, and MMSE, the mean is presented with the standard deviation in parentheses. ESE, Effect Size Estimates (For t, Cohen's d, for chi square, Phi, and for Mann-Whitney, Cohen's r ). Household Income refers to the monthly household income: categroized on a scale of 1 = ZAR 500 - 999, 2= ZAR 1000-2499, 3= ZAR 2500-5499, 4= ZAR 5500-9999, 5= ZAR 10000+. Education refers to the highest level of education completed. GDS, Geriatric Depression Scale. CAMCOG-R, Cambridge Cognitive Examination for Mental Disorders of the Elderly-Revised. MMSE, Mini-Mental State Examination. *p<.05, **p<.01, ***p<.001. All p-values are two-tailed.*

**Primary Analyses.**

***Data Preparation.***

The attention-switching data was prepared via the identification and removal of incorrect responses and outliers - participants who had an overall missingness of 40% were removed from the data resulting in 23 participants in the control group and 21 participants in clinical group.

***Extraction of Intra-individual Variability***

We extracted IIV based off the work by Hultsch et al. (2000, 2002, 2008). Random intercept models for the Naming, Location, and Switching conditions were built to detrend any systematic effects. The random intercept models identified significant fixed effects of group, sex, session, and time for Naming; group, sex, session, test-order, and time for Location; and income and time for Switching (see **Appendix D**). We included the significant effects into a random slope model. In this model, the significant fixed effects were added as factorial variables. This adds both the main effects and the higher-order interactions between the variables. Thirdly, we captured the residuals from the random effects models and converted them into T-scores. Lastly, the intra-individual standard deviations were extracted by calculating the standard deviation across the T-scores.

***Research Question 1***

We assessed the between-group differences in the mean and *iSDs* of our predictor variables (see **Table 2**). There were no significant differences identified in both the Switching condition mean and *iSDs* subsequently it was excluded from the logistic regression analysis.

Two logistic regression models were then built to assess whether the attention-switching task could predict group membership (see **Table 3**). Each model used a different condition of the attention-switching task, those which showed significant between-group

differences, as the predictor variable. Thus, Model 1 used Naming, and Model 2 used the Location condition as the predictor variable. Each model entered the predictor variable at the first step, the significant between-group demographic variables identified above at the second step, and each predictor's mean-based score at the third step. The variables were entered into each model in this 3-step sequence so that we could determine if the attention-switching task conditions continued to make a unique contribution towards predicting group membership once the demographic control variables - added in the second step - and mean scores - added in the third step - were introduced.

Significant findings were discovered in Step 1 where both Naming [Model 1: $R^2$ = .44, $p < .001$] and Location [Model 2: $R^2 = .67$, $p < .001$] significantly predicted group membership. In Step 2, after controlling for significant between-group demographic variables, both Naming [Model 1: $R^2 = .76$, $p < .001$] and Location [Model 2: $R^2 = .74$, $p < .001$] remained significant predictors of group membership. Lastly, in Step 3, once the predictor mean was added, only Location [Model 2: $R^2 = .74$, $p < .001$] remained a significant predictor. Thus, Location *iSDs* predicted group membership above and beyond the effect of significant demographic factors and mean-level performance.

**Table 2**

*Descriptive Statistics and Between Group Differences for the Clinical and Control Group: predictor variables (N=44).*

| Variable | Group | | *df* | *t/z* | *p* | ESE |
|---|---|---|---|---|---|---|
| | **Control** ($n$ = 23) | **Clinical** ($n$ = 21) | | | | |
| **iSD** | | | | | | |
| Simple-RT | 7.76(1.26) | 10.18(3.38) | | -2.74 | .006** | -.42 |
| Choice-RT | 7.45(1.33) | 10.16(3.26) | | -3.15 | .002** | -.49 |
| Naming | 8.82(2.01) | 11.7(2.18) | 31 | -3.76 | <.001*** | -1.39 |
| Location | 6.76(1.69) | 12.49(4.04) | | -4.36 | <.001*** | -.7 |
| Switching | 9.83(1.42) | 10.13(1.18) | 34 | -0.66 | .513 | -.23 |
| **MEAN** | | | | | | |
| Simple-RT | 318.36(32.51) | 340.21(56.23) | 40 | -1.56 | .123 | -.49 |
| Choice-RT | 351.25(37.22) | 387.07(67.87) | 40 | -2.17 | .036* | -.67 |
| Naming | 681(102.89) | 872(156.13) | | -3.21 | .001** | -.56 |
| Location | 499.53(95.17) | 705.83(166.07) | | -3.83 | <.001*** | -.61 |
| Switching | 1016(160.47) | 1065(158) | 34 | -.89 | .378 | -.31 |

*Note. For Simple-RT, Choice-RT, Naming, Location, and Switching, the mean is presented with the standard deviation in parentheses. Simple-RT, simple reaction time. Choice-RT, choice reaction time. ESE, Effect Size Estimates (For t, Cohen's d, and for Mann-Whitney, Cohen's r ). *p<.05, **p<.01, ***p<.001. All p-values are two-tailed.*

**Table 3**

*Logistic Regression Models: Naming, and Location as Predictors of Group Membership*

| **Predictor** | **Group Membership Outcome Variable** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Model 1: Naming** | | | | | **Model 2: Location** | | | | |
| | ***B (SE)*** | ***p*** | ***Odds Ratio*** | **95% CI** | | ***B (SE)*** | ***p*** | ***Odds Ratio*** | **95% CI** | |
| | | | | **Lower** | **Upper** | | | | **Lower** | **Upper** |
| **STEP 1 (Predictor)** | | | | | | | | | | |
| Predictor | .74 (.28) | .008** | 2.09 | 1.22 | 3.60 | .79 (.25) | .002** | 2.21 | 1.34 | 3.63 |
| **STEP 2 ( + Control Variables)** | | | | | | | | | | |
| Predictor | 1.57 (.68) | .022* | 4.80 | 1.26 | 18.35 | .67 (.27) | .013* | 1.95 | 1.15 | 3.30 |
| Age | .29 (.16) | .075 | 1.34 | .97 | 1.85 | .12 (.10) | .211 | 1.13 | .94 | 1.37 |
| Education | -1.29 (.61) | .033* | .27 | .08 | .90 | -.41 (.24) | .088 | .66 | .41 | 1.06 |
| **STEP 3 ( + Mean Scores)** | | | | | | | | | | |
| Predictor | .97 (.69) | .156 | 2.65 | .69 | 10.17 | .73 (.32) | .023* | 2.08 | 1.11 | 3.92 |
| Age | .34 (.19) | .076 | 1.41 | .96 | 2.05 | .12 (.10) | .207 | 1.13 | .94 | 1.36 |
| Education | -1.21 (.59) | .041* | .30 | .09 | .95 | -.45 (.26) | .083 | .64 | .38 | 1.06 |
| Mean Scores | .01 (.01) | .148 | 1.01 | 1.00 | 1.03 | -.00 (.01) | .698 | 1.00 | .99 | 1.01 |

*Note. For each predictor, the unstandardized beta (B) is presented with the standard error (SE) in parentheses. CI, Confidence Interval.*p<.05, **p<.01, ***p<.001*

***Research Question 2***

As a preliminary step to the regression analyses, we analysed the correlations between the demographic and affective variables, and our measures of general cognitive performance. The significant correlations that were identified for CAMCOG-R were: Group ($r_{(42)}$ = .82, $p$ <.001), Geriatric-Depression Scale ($r_{(42)}$ = .33, $p$ = .027), and Education ($r_{(42)}$ = .56, $p$ < .001). The significant correlations that were identified for MMSE were: Group ($r_{(42)}$ = .82, $p$ < .001), Geriatric-Depression Scale ($r_{(42)}$ = .35, $p$ = .018), and Education ($r_{(42)}$ = .41, $p$ < .005). Furthermore, bivariate correlations were used to identify relationships between our predictor and outcome variables (see **Table 4**). The *iSDs* and mean of the Switching condition, for both MMSE and CAMCOG-R, were not significantly correlated and thus, excluded from the multiple regression models.

**Table 4**

*Bivariate Correlations Between the Predictor Variables and Outcome Variables*

| Predictor | Outcome Variable | |
|---|---|---|
| | **CAMCOG-R** | **MMSE** |
| **iSD** | | |
| Naming | -.53*** | -.46** |
| Location | -.79*** | -.77*** |
| Switching | .06 | .01 |
| Simple-RT | -.56*** | -.49*** |
| Choice-RT | -.55*** | -.45** |
| **MEAN** | | |
| Naming | -.63*** | -.49** |
| Location | -.79*** | .73*** |
| Switching | -.17 | -.03 |
| Simple-RT | -.33* | -.30 |
| Choice-RT | -.44** | -.39* |

*Note. Simple-RT, simple reaction time. Choice-RT, choice reaction time. CAMCOG-R, Cambridge Cognitive Examination for Mental Disorders of the Elderly-Revised. MMSE, Mini-Mental State Exam. *p<.05, **p<.01, ***p<.001*

Then, we created a series of multiple regression models to assess how well the conditions of the attention-switching task could predict general cognitive performance, and to compare how well they predicted relative to conventional tests of IIV, namely, choice reaction-time and simple reaction-time. Thus, there were a total of four models for each IIV predictor, i.e., Naming, Location, choice reaction-time, and simple reaction-time. There was a set of four models for each outcome variable, CAMCOG-R (see **Table 5**) and MMSE (see **Table 6**). Each set of four models were broken up into three steps: Step 1 contained only the predictor, Step 2 controlled for the demographic and affective variables identified above, and Step 3 added mean-based scores.

The following results are in relation to the CAMCOG-R model. In Step 1 significant findings were in, Naming [Model 1: $Adj.R^2$ = .26, $F_{(1, 31)}$= (12.28), $p$ =.001], Location [Model 2: $Adj.\ R^2$ =.61, $F_{(1, 37)}$= 61.17, $p$ <.001], simple reaction-time [Model 3: $Adj.\ R^2$ =.30, $F_{(1, 40)}$= 18.20, $p$ <.001], and choice reaction-time [Model 4: $Adj.R^2$ =.29, $F_{(1, 40)}$= 17.32, $p$ <.001]. These four all significantly predicted CAMCOG-R on their own. In Step 2, a significant result was identified in relation to our research question 2: Location [Model 2: $Adj.R^2$ = .83, $F_{(4, 34)}$= 45.79, $p$ <.001] and simple reaction-time [Model 3: $Adj.R^2$ =.76, $F_{(4, 37)}$= 34.18, $p$ <.001] remained the only significant predictors of the CAMCOG-R once the control variables were added into the model. In Step 3, none of the predictors remained significant above the effect of mean-level performance.

**Table 5**

*Mutliple Regression Models: Naming, Location, Simple-RT, and Choice-RT as Predictors of CAMCOG-R*

| **Predictor** | **CAMCOG-R Outcome Variable** | | | |
|---|---|---|---|---|
| | **Model 1** | **Model 2** | **Model 3** | **Model 4** |
| | Naming | Location | Simple-RT | Choice-RT |
| **STEP 1 (predictor)** | | | | |
| Predictor | -.53** | -.79*** | -.56*** | -.55*** |
| **STEP 2 (+ control variables)** | | | | |
| Predictor | -.11 | -.38*** | -.20* | -.18 |
| Group | -.75*** | -.42*** | -.59*** | -.58*** |
| GDS | -.15 | -.05 | -.12 | -.15 |
| Education | .10 | .28** | .25** | .26** |
| **STEP 3 (+ mean scores)** | | | | |
| Predictor | .00 | -.26 | -.25 | -.07 |
| Group | -.64*** | -.42*** | -.58*** | -.59*** |
| GDS | -.14 | -.03 | -.13 | -.14 |
| Education | .12 | .24** | .25** | .27** |
| Mean Scores | -.23 | -.17 | .05 | -.15 |

*Note. Data presented are standardized beta coefficients. Simple-RT, simple reaction time. Choice-RT, choice reaction time.*p<.05, **p<.01, ***p<.001*

The following results are in relation to the MMSE model. In Step 1, the significant predictors were, Naming [Model 1: *Adj.* $R^2$ =.18, $F_{(1, 31)}$= 8.09, $p$ =.008], Location [Model 2: *Adj.*$R^2$ =.58, $F_{(1, 37)}$= 52.82, $p$ <.001], simple reaction-time [Model 3: *Adj.*$R^2$ =.22, $F_{(1, 40)}$= 12.66, $p$ <.001], and choice-reaction time [Model 4: *Adj.*$R^2$ =.19, $F_{(1, 40)}$= 10.40, $p$ =.003]. In Step 2, interestingly the only significant predictor of MMSE, with the addition of control variables, was Location [Model 2: *Adj.*$R^2$ =.66, $F_{(4, 34)}$= 19.23, $p$ <.001]. Thus, the attention-switching Location *iSD* was the strongest IIV predictor of MMSE, and beyond the effects of significant demographic and affective variables. In Step 3, none of the predictors remained significant above the effect of mean-level performance.

**Table 6**

*Mutliple Regression Models: Naming, Location, Simple-RT, and Choice-RT as Predictors of MMSE*

| **Predictor** | **MMSE Outcome Variable** | | | |
|---|---|---|---|---|
| | **Model 1** | **Model 2** | **Model 3** | **Model 4** |
| | Naming | Location | Simple-RT | Choice-RT |
| **STEP 1 (predictor)** | | | | |
| Predictor | -.46** | -.77*** | -.49*** | -.45** |
| **STEP 2 (+ control variables)** | | | | |
| Predictor | -.11 | -.46** | -.17 | -.11 |
| Group | -.57** | -.34* | -.57*** | -.59*** |
| GDS | -.32* | -.06 | -.14 | -.16 |
| Education | -.09 | .15 | .13 | .13 |
| **STEP 3 (+ mean scores)** | | | | |
| Predictor | -.05 | -.38 | -.00 | .02 |
| Group | -.53* | -.34* | -.60*** | -.59*** |
| GDS | -.32* | -.04 | -.22 | -.15 |
| Education | -.08 | .12 | .18 | .14 |
| Mean Scores | -.12 | -.12 | .12 | -.18 |

*Note. Data presented are standardized beta coefficients. Simple-RT, simple reaction time. Choice-RT, choice reaction time.*p<.05, **p<.01, ***p<.001*

## Discussion

The current study aimed to investigate whether the Naming, Location, and Switching conditions of the attention-switching task were sensitive IIV measures in patients with Alzheimer's disease. Specifically, we investigated whether these measures could 1) predict both group membership and 2) general cognitive performance. The analyses explored three conditions of the attention-switching task and their utility as indicators of IIV. The data was collected by the Principal Investigator of the broader study. Our final groups consisted of 21 clinical participants and 23 healthy controls. The groups were matched on both monthly household income and sex, whereas there were significant between-group differences for years of education, age, and GDS. The measures of attentional control used in our study consisted of the CANTAB attention-switching task, simple reaction-time task, and choice reaction-time task. The screening measures in our study consisted of the GDS, CAMCOG-R, and MMSE.

### Research Question 1

Our first research question assessed whether the Naming, Location, and Switching conditions of the attention-switching task could predict group membership in Alzheimer's disease. A preliminary investigation found that IIV in Naming and Location was significantly higher for the clinical participants compared to the controls, whereas IIV in the Switching condition was not significantly different between our study groups and was thus, excluded from further analyses.

In the main analyses for research question 1, we found that both the Naming and Location condition of the attention-switching task could predict clinical group membership. That is, increases in IIV of both the Naming and Location condition increased the probability of belonging in the clinical group. Thus, the two conditions of the attention-switching task are able to differentiate between possible or probable Alzheimer's disease patients and

healthy individuals. Once the control variables were added, both the Naming and Location *iSDs* remained significant predictors of group membership. Thus, these variables continued to make a unique contribution towards predicting group membership even after controlling for the effect of other significant between-group variables. Lastly, once the mean scores for each condition were controlled for, we found that only the Location *iSDs* remained a significant predictor of clinical group membership.

Results from the logistic regressions indicate that the attention-switching conditions can, to differing extents, predict group membership in Alzheimer's disease. This excludes the Switching condition, which this study postulates may be due to the demand on executive control required in the Switching condition. We believe that the Switching condition may have been too cognitively demanding for both the clinical and control groups. This would support the findings of Christ et al. (2018), who demonstrated that higher processing demands yields higher variability in both healthy older adults and those with cognitive impairment. Additionally, our study also supports findings by Allaire and Marsiske (2005), that increased performance on a cognitively demanding task, due to practice effects, can increase the IIV in healthy individuals. For the Switching condition, the high cognitive demands may have led to the healthy controls beginning with a low performance, but increasing in performance, due to practice effects, over the trials thus, resulting in overall increased *iSDs*. This is in contrast to the tasks that required relatively less processing demand, namely, Naming and Location, which significantly predicted group membership beyond the effect of control variables. The Location condition stood-out as the most resilient predictor of the three conditions, as it was the only predictor to remain significant after controlling for mean-performance. We postulate that Location outperformed Naming due it being a less cognitively demanding task – this was evident by Location having the lowest mean value of the *iSDs* for the control group thus, implying that they struggled the least with

this task. Given that Naming may have had a greater cognitive load than Location, there may have been greater practice effects. Therefore, leading to greater IIV in the control group, and decreased its ability to differentiate between the two groups.

Lastly, overall, our study supported the findings of Duchek et al. (2009) that attention-switching IIV was able to significantly predict group membership in Alzheimer's disease - supported by our study in both the Naming and Location condition. Therefore, our findings from our first research question are in line with previous research on the topic of attention-switching in Alzheimer's disease patients.

**Research Question 2**

The second research question explored whether the attention-switching conditions of IIV were stronger predictors of general cognitive performance than simple and choice reaction-time measures of IIV. The two outcomes for measuring general cognitive performance were the MMSE and CAMCOG-R. Bivariate correlations were used to identify relationships between our predictor and outcome variables. The significant correlations for both outcome variables were identified in Naming, Location, simple reaction-time, and choice reaction-time. The *iSDs* of the Switching condition, for both MMSE and CAMCOG-R, were not significantly correlated and, thus, excluded from the multiple regression models.

The main findings for research question 2 were that, as sole predictors in Step 1, the Naming and Location condition, as well as the simple reaction-time and choice reaction-time significantly predicted both MMSE and CAMCOG-R. However, notably, the strongest predictor in Step 1 for both outcome variables was the Location condition – this was evident by its high standardized beta score in comparison with the other predictor variables. The second strongest predictor in Step 1 was the simple reaction-time. Once the control variables were added into the models, the CAMCOG-R had two significant predictors – Location and simple reaction-time – with Location being the strongest predictor and simple reaction-time

being second strongest. However, the only significant predictor of the MMSE with the addition of the control variables, was the Location condition. Lastly, in Step 3, none of the predictors remained significant above the effect of mean-level performance.

The results of the multiple regression models provide further evidence of the utility of the Location condition in the attention-switching task as an indicator of IIV, since it was the strongest predictor for both MMSE and CAMCOG-R. The second strongest predictor was that of simple reaction-time; however, this variable was a weaker predictor for MMSE after controlling for covariates.

To the best of our knowledge, we are the only study to have investigated the IIVs of the attention-switching task conditions as predictors of general cognitive performance. Importantly, however, our results demonstrate the benefit of splitting up the attention-switching task into its relevant conditions. It was noted that, of the two significant conditions, Naming was a weaker predictor of general cognitive performance than Location – as is evident by their standardized beta coefficients. As discussed previously, Naming's likely higher cognitive demand may have influenced its strength as a predictor of general cognitive performance. Furthermore, Location was a stronger predictor than simple and choice reaction-time of general cognitive performance. We follow the same train of thought mentioned prior that Location may have had a lower cognitive demand than simple and choice reaction-time as evident by Location having the lowest mean value of the *iSDs* of these three predictors. For the simple and choice reaction-time, practice effects may have led to a greater increase in performance across trials, and thus higher *iSDs*. Overall, the simple and choice reaction-time would have thus, had a weaker predictability power of general cognitive performance compared to the Location condition.

Our study is in line with the findings of Allaire and Marsiske (2005) who found that IIV may differ across tasks that require different cognitive demands. Our study observed that

different performance demands on the participants, for instance, attending to a location, orientating to a direction, or switching between task requirements, may have affected its sensitivity as an IIV measure. This idea is supported by Traykov et al. (2007) who identified differing deterioration of attention systems in those with MCI and Alzheimer's, thus, advocating for the division of attention tasks into components that tap into different attentional demands.

While we are the only study to have divided up the attention-switching conditions, we can compare our results to that of other studies who have explored attention-switching as a predictor of general cognitive impairment. Our results agree with Duchek et al. (2009) who demonstrated that attention-switching IIV has the ability to predict general cognitive health. As sole predictors, both the Naming and Location *iSDs* were significant, thus, attention-switching tasks do have predictive power in general cognitive performance. Furthermore, Luna-Rodriguez et al. (2018) found that greater IIV in attention-switching measures were indicative of executive functioning deficits– our study supports this finding by demonstrating the efficacy of attention-switching IIV measures in predicting general cognitive performance.

**Limitations**

There were three limitations identified in our study, namely: a lack of previous attention-switching IIV literature, a small sample size, and no previous psychometric data on the individual attention-switching conditions.

To our knowledge, there is a lack of research on the topic of attention-switching measures of IIV in an Alzheimer's population. This posed a challenge to our research. Previous research can often help guide future research on their interpretations of their findings – due to our study being the first of its kind to assess the individual attention-switching conditions, we could not directly compare our findings with other researcher's. This means that our research should be taken at face value as there is a lack of further

evidence to confirm or refute our findings. This makes it difficult to fully comprehend the implications of our findings when it cannot fit into a broader research scope. However, our study does hold value in that it is largely the first of its kind.

A second limitation in our study is that we have a relatively small sample size. Due to it being a secondary analysis design in nature, we were not able to conduct a power analysis nor had much influence over our sample size. Furthermore, due to missingness in our data that consisted of inaccurate responses and outliers, we had to remove participants from our already small dataset. This left us with sample size of 44, consisting of 21 clinical participants and 23 healthy controls. A previous study which assessed the applicability of a selective attention IIV measure in Alzheimer's disease consisted of 291 clinical participants and 35 healthy controls (Duchek et al., 2009). Additionally, in a study which looked at attention tasks in an Alzheimer's population, however not for the purpose of an IIV measure, used 352 participants (Tse et al., 2010). From these two previous studies in a similar scope of research to ours, it can be inferred that our sample size was smaller than conventional. However, we were still able to answer all aspects of our research questions with the available participants. We recommend that future research into this topic use a larger sample size in order to more accurately reflect the broader Alzheimer's population therefore increasing the generalisability of the study.

Lastly, we believe that a limitation of our study is that, to the best of our knowledge, it is the first of its kind. No previous study has split up the CANTAB attention-switching task into its three conditions, Naming, Location, and Switching, for analysis. This means that there is no psychometric data on the reliability and validity of these individual conditions. Furthermore, the psychometric data on the CANTAB attention-switching task, as a whole, is scarce. This may have influenced the validity of our results. That being said, we do know that the CANTAB attention-switching task has shown a three-month test-retest reliability of .75

(Karlsen et al., 2022). This reliability would have been calculated by using all three conditions. We recommend to future researchers, given the successfulness of the Location condition specifically as an IIV measure in Alzheimer's disease, to conduct psychometric evaluations on these individual conditions so that they can have more utility in research.

**Conclusion**

In conclusion, we found that attention-switching measures of intra-individual variability, more specifically Naming and Location *iSDs*, were significant predictors of group membership with Location *iSDs* as the strongest predictor. For general cognitive performance, significant findings were identified in the simple reaction-time and Location *iSDs* for CAMCOG-R – with Location as the strongest predictor. For the MMSE outcome, the Location *iSDs* remained the most promising predictor. Overall, the results of our study indicate attention-switching measures of IIV, in particular Location *iSDs*, may have great utility in differentiating between possible or probable Alzheimer's disease patients and healthy individual, as well as in predicting general cognitive performance.

The implications of these findings are that we have contributed towards the growing literature on IIV measurement by exploring the utility of the attention-switching task conditions as clinically useful measures of IIV. The Location *iSDs* outperformed mean scores in predicting group membership, which advocates for its use in future IIV research. Furthermore, in the CAMCOG-R, the Location *iSDs* outperformed simple and choice reaction-time– this is of interest in future studies as these are the most commonly used measures of IIV that currently exist in the literature. Our research highlights the potential benefits of exploring the conditions of attention-switching tasks instead of evaluating them in their entirety.

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# Appendix A
## Clinical Diagnostic Criteria

**Mild Cognitive Impairment (MCI)**

Petersen RC *et al. Neurology 2001*; 56: 1133-42

1. Memory complaint, preferably corroborated by an informant.

2. Objective memory impairment.

3. Normal general cognitive functioning.

4. Intact activities of daily living.

5. Not demented.

**Dementia: definition (DSM IV)**

i) A deterioration from a known or estimated prior level of intellectual function;

ii) Sufficiently severe to interfere broadly with the conduct of the patient's customary affairs of life;

iii) Not isolated to a single narrow category of intellectual performance;

iv) Independent of level of consciousness;

v) Deterioration supported by historical evidence, and

vi) Documented by either bedside mental status testing or, ideally, more detailed neuropsychological examination using tests that are quantifiable, reproducible and for which normative data are available.

**NINCDS / ADRDA (Alzheimer's Disease)**

McKhann G *et al. Neurology* 1984; 34: 939-944

0. Negative

1. Possible

   i) Presence of a dementia syndrome, in absence of other neurological, psychiatric or systemic disorders capable of causing dementia, but with atypical features, such as variations in the onset, presentation or clinical course of the illness.

   ii) Presence of a second systemic disease or brain disorder sufficient to produce dementia, but not considered to be the cause of the dementia.

   iii) Single, gradually progressive, severe cognitive deficit (eg. worsening amnestic syndrome), in the absence of another identifiable cause.

2. Probable

   i) Dementia, established by history & clinical examination, and documented with, or confirmed by, cognitive or neuropsychological tests e.g. MMSE (<23), CAMCOG (<80).

   ii) Deficits in 2 or more areas of cognition.

   iii) Progressive worsening of memory and other cognitive functions.

   iv) No disturbance of consciousness.

   v) Age of onset > 40; usually > 65.

   vi) Absence of systemic disorders or other brain diseases [or psychiatric disorders] that could in themselves account

3. Definite

   i) Probable AD on clinical criteria.

ii) Histopathological evidence (biopsy, autopsy).

- Supportive evidence for the diagnosis of Probable AD:
  - i) Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);
  - ii) impaired activities of daily living and altered patterns of behaviour;
  - iii) family history of similar disorders,
  - iv) laboratory results of:
    - a) normal lumbar puncture as evaluated by standard techniques;
    - b) normal pattern or non-specific change in EEG, such as increased slow wave activity, and
    - c) evidence of cerebral atrophy on CT with progression documented by serial observation.

- Clinical features consistent with the diagnosis of Probable AD:
  - i) Plateaus in the course of progression of the illness;
  - ii) Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional or physical outbursts, sexual disorders and weight loss;
  - iii) Other neurological abnormalities in some patients, especially those with more advanced disease, including motor signs such as increased motor tone, myoclonus or a gait disorder;
  - iv) Seizures in advanced disease;
  - v) CT normal for age.

- Features that make the diagnosis of Probable AD uncertain or unlikely include:
  i) Sudden apoplectic onset;

  ii) Focal neurological signs such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness;

  iii) Seizures or gait disturbances at the onset or very early in the course of the illness.

**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

## Informed Consent Form

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

PROTOCOL NUMBER: HREC/REF: 167/2014

PRINCIPAL INVESTIGATOR: Mr. Bjorn U. Christ

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

CONTACT NUMBER: +27 72 0710 346

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

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

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

What is this research study all about?

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

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

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

Procedures

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

(4) interview your relative/friend (someone who knows you well) to find out whether he/she thinks you have any memory difficulties.

(5) ask you to complete a short questionnaire about your mental and emotional functioning.

(6) perform tests of your memory and other higher mental functions. These will be conducted in a quiet, relaxed atmosphere. I expect that these tests will be about an hour's duration. However, there will be opportunities to rest in-between tests.

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

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

What will your responsibilities be?

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

Will you benefit from taking part in this study?

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

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

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

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

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

Who will have access to your medical records?

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

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

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

Is there anything else that you should know or do?

□□□You should inform your family practitioner or usual doctor that you are taking part in a research study.

□□□You can contact me on 079 334 4404 if you have any further queries or encounter any problems.

□□□You can contact the Research Ethics Committee of the Health Sciences Faculty of the University of Cape Town 021-4066338 if you have any concerns or complaints that have not been adequately addressed by your study doctor.

□□□You will receive a copy of this information and consent form for your own records.

Declaration by participant and/or friend/relative/guardian

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

I declare that:

□□□I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.

□□□I have had a chance to ask questions and all my questions have been adequately answered.

□□□I understand that taking part in this study is voluntary and I have not been pressurised to take part.

□□□I may choose to leave the study at any time and will not be penalised or prejudiced in any way.

□□□I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

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

..... .....

Signature of participant Signature of witness

.....
.....

Signature of relative/friend/guardian Signature of witness

Declaration by investigator

I (name) ..... declare that:

□□□I explained the information in this document to .....

□□□I encouraged him/her to ask questions and took adequate time to answer them.

□□□I am satisfied that he/she adequately understands all aspects of the research, as discussed above

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

..... .....

Signature of investigator Signature of witness

# Appendix C

## Ethical Approval Letter

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

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

**03 June 2014**

**HREC/REF: 167/2014**

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

Dear Dr Thomas

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

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

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

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

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

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

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

**Please quote the HREC REF in all your correspondence.**

Yours sincerely

**PROFESSOR M BLOCKMAN**
**CHAIRPERSON, HSF HUMAN ETHICS**

**Hrec/ref:167/2014**

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

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

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

**Hrec/ref:167/2014**

# Appendix D

## Fixed Effects from Random Intercept Models

**Appedix D**

*Fixed Effects from Random Intercept Models (N=44).*

| Variable | Naming | | Location | | Switching | |
|---|---|---|---|---|---|---|
| | *F* | *p* | *F* | *p* | *F* | *p* |
| Age | 1.19 | .285 | .48 | .492 | 1.71 | .200 |
| Sex | 6.55 | .016* | 12.38 | .001** | 2.15 | .152 |
| Group | 22.87 | <.001*** | 21.41 | <.001*** | 3.01 | .092 |
| Education | .89 | .353 | .56 | .460 | .635 | .413 |
| Income | 1.02 | .417 | 1.25 | .306 | 4.52 | .005** |
| Trial | --- | --- | --- | --- | --- | --- |
| Time | --- | --- | --- | --- | --- | --- |
| Session | 10.73 | .001** | 31.93 | <.001*** | .149 | .699 |
| Test-order | .25 | .779 | 6.1 | .002** | 1.76 | .173 |

*Note. *p<.05, **p<.01, ***p<.001. All p-values are two-tailed.*