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Associations between reaction time measures and white matter hyperintensities in very old age.

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Abstract

In old age, a relationship has been reported between intraindividual variability (IIV) in reaction time and white matter integrity as evidenced by white matter hyperintensities (WMH). However, it is unclear how far such associations are due to incipient neurodegenerative pathology in the samples investigated. The present study examined the relationship between IIV and WMH in older individuals (N=526) drawn from the Sydney Memory and Ageing Study. Using a complex reaction time (RT) task, greater IIV and mean-RT were related to a higher WMH burden in the frontal lobe. Critically, significant associations remained having taken future dementia into account suggesting that they were not explained by incipient dementia. Additionally, independent measures of executive function accounted for the association between RT metrics and WHM. The results are consistent with the view that frontally-supported cognitive processes are involved in IIV-WMH relations, and that RT measures are sensitive to compromise in white matter structures in non-demented older individuals.

Key words, white matter hyperintensities, reaction time, intraindividual variability, executive function, cognition.

1. Introduction

Intraindividual variability (IIV), or inconsistency (e.g., Hultsch, MacDonald, & Dixon, 2002), refers to within-person variation in cognitive performance over time, and is often measured by the trial-by-trial variation in reaction times (RT) for a given cognitive task. It is well established that ageing is accompanied by cognitive decline and slowing of processing speed (e.g., Salthouse, 2010). However, an accumulating body of research suggests older adults are also more variable than younger adults (e.g., Bielak, Cherbuin, Bunce, & Anstey, 2014), even when response speed is taken into account (Dykiert, Der, Starr, & Deary, 2012). One proposal holds that IIV is an early indicator of neurobiological disturbance (Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000; Hultsch, Strauss, Hunter, & MacDonald, 2008). In support of this, greater variability is evident in individuals with age-related disorders such as mild cognitive impairment and dementia (Christensen et al., 2005; Duchek et al., 2009; Gorus, De Raedt, Lambert, Lemper, & Mets, 2008; Hultsch et al., 2000; Strauss, Bielak, Bunce, Hunter, & Hultsch, 2007), Parkinson's disease (de Frias, Dixon, Fisher, & Camicioli, 2007) and also frontal lobe lesions (Stuss, Murphy, Binns, & Alexander, 2003).

Given the suggestion that IIV is an indicator of neurobiological disturbance, a number of magnetic resonance imaging (MRI) studies have investigated the link between variability and structural brain measures. In healthy ageing, associations have been shown between IIV and white matter hyperintensities (WMH: Bunce et al., 2010; Bunce et al., 2007), white matter volume (Jackson, Balota, Duchek, & Head, 2012; Lovden et al., 2013; Ullen, Forsman, Blom, Karabanov, & Madison, 2008; Walhovd & Fjell, 2007) and diffusion tensor imaging metrics (e.g., FA - fractional anisotropy) (Deary et al., 2006; Fjell, Westlye, Amlien, & Walhovd, 2011; Mella, de Ribaupierre, Eagleson, & de Ribaupierre, 2013; Moy et al., 2011). Generally,

these investigations show that greater behavioural variability is associated with poorer neuroanatomical integrity (i.e., increased WMH burden, reduced volume, and lower FA). There is also evidence that the frontal lobes are particularly implicated in IIV. For example, neuropathological studies suggest that IIV is elevated in persons with frontal lobe damage (Murtha, Cismaru, Waechter, & Chertkow, 2002; Stuss et al., 2003) while in healthy populations, associations have been identified between increased IIV and frontal WMH (Bunce et al., 2010; Bunce et al., 2007) and pre-frontal white matter volume (Jackson et al., 2012; Lovden et al., 2013).

Studies have also shown stronger associations between IIV and structural MRI measures in individuals with mild cognitive disorder compared to those with normal cognition (Anstey et al., 2007), although this pattern is not always seen (e.g., Jackson et al., 2012). Longitudinal research suggests that increases in IIV may precede cognitive decline (Bielak, Hultsch, Strauss, Macdonald, & Hunter, 2010; Cherbuin, Sachdev, & Anstey, 2010; Lovden, Li, Shing, & Lindenberger, 2007; MacDonald, Hultsch, & Dixon, 2003) and there is evidence that brain pathology starts to accumulate prior to the symptomatic stage of dementia (Jack et al., 2010). Although Alzheimer's disease is typically characterised by amyloid-beta plaques and neurofibrillary tangles, there is also evidence that white matter abnormalities have a role in Alzheimer's disease pathogenesis (Sachdev, Zhuang, Braidy, & Wen, 2013). Also, WMH have been associated with an increased risk of developing future Alzheimer's disease (Debette & Markus, 2010) and are considered the main pathology in vascular dementia (Gorelick et al., 2011; Pantoni, 2010). One possibility, therefore, is that studies that have identified a relationship between white matter integrity and variability do so because they include participants who are already on the path to, as yet, undetected dementia.

In order to provide further insights into the association between behavioural variability and white matter integrity in old age, the present study investigated older adults aged 70-90 years participating in the Sydney Memory and Ageing Study. Our first aim was to investigate the relationship between IIV and WMH in this older sample. Associations were assessed for total WMH and then separately for periventricular white matter (WM) and deep WM. The latter was divided further into frontal, parietal, temporal and occipital lobes. Based on previous findings, we expected to see a relationship particularly for frontal WMH. However, it was also of interest to assess whether associations between WMH and IIV extended beyond the frontal lobe. Additionally, we sought to establish whether similar associations were present in this older age group for measures of mean-RT and IIV obtained from the same cognitive task. Previous research in healthy younger persons in their 60s (e.g., Bunce et al., 2007), and older adults with neuropathology (e.g., Dixon et al., 2007), suggest that the measures dissociate. Associations with WMH were, therefore, investigated for both RT metrics.

Our second aim was to establish if the relationship between IIV and WMH was due to the inclusion of participants who were in the pre-clinical phase of neurodegenerative decline. As well-characterised dementia diagnoses were available for participants up to six years following the present analyses, we were able to control for this source of variance. It was anticipated that controlling for future dementia would attenuate the relationship between IIV and WMH. In these analyses, we also adjusted for a range of dementia risk factors including, vascular disease, vascular risk factors, depression and *APOE* e4 genotype.

Our final aim was to consider whether specific behavioural measures of cognitive function accounted for the association between IIV and WMH. It is thought that IIV reflects fluctuations in attentional or executive control (Bunce, MacDonald, & Hultsch, 2004; West, Murphy, Armilio, Craik, & Stuss, 2002) which is supported by evidence implicating frontal

white matter compromise in increased IIV. Of particular interest, therefore, was the explanatory power of frontally supported measures of executive function relative to measures supported by other neuroanatomical structures (e.g., memory supported by the temporal cortex). We anticipated that adjusting for executive control would attenuate the relationship between IIV and WMH whereas controlling for memory would not.

2. Materials and methods

2.1 Participants

Participants were drawn from Wave 1 of the Sydney Memory and Aging Study, a cohort of 1037 community dwelling adults aged 70-90 years (Sachdev et al., 2010). All participants were invited for an MRI scan, and those who agreed were screened for contraindications. MRI scans were obtained for 542 (52.3%) participants, however, six were excluded due to poor scan quality (e.g., because of head movement) or were missing relevant MRI protocols (e.g., FLAIR), and a further 10 participants did not have RT data. Therefore a final sample of 526 participants was included in the present analyses. This study was approved by the Human Research Ethics Committees of the University of New South Wales and the South Eastern Sydney and Illawarra Area Health Service.

2.2 Dementia assessment

Participants were excluded from the Sydney Memory and Aging Study cohort if dementia was evident at Wave 1. At 2-, 4- and 6-year follow-up, dementia diagnoses were made by the consensus of an expert panel of clinicians including old age psychiatrists, neuropsychiatrists and neuropsychologists. The diagnoses were based on DSM-IV criteria (APA, 2000), and all available clinical, neuropsychological and MRI data were used.

2.3 Clinical assessment

Participants underwent a brief physical examination and a face-to-face medical history interview, which involved self-report of previous diagnoses. Variables that could potentially influence the relationship between WMH and IIV were included in the current analysis. These included a history of cardiovascular disease (e.g., heart attack, angina, atrial fibrillation, cardiac arrhythmia, cardiomyopathy, heart valve disease, or aortic aneurysm), cerebrovascular disease (e.g., stroke or transient ischemic attack), diabetes, a diagnosis of high blood pressure, a diagnosis of high cholesterol, neurological disorders (e.g., Parkinson's disease, epilepsy, brain infection, brain abscess), depression, and Apolipoprotein E-*ε4* status. In addition to assessing relevant variables separately, a cardiovascular disease risk factor was also generated, based on the Framingham Stroke Study (D'Agostino et al., 2008).

2.4 Psychomotor tasks

Participants completed simple (SRT) and complex (CRT) reaction time tasks using a touch screen tablet computer with millisecond accuracy. Both tasks were included to allow consideration of whether task complexity influenced the results. For the SRT task, participants had to respond as quickly as possible to a yellow square appearing against a grey background (interstimulus interval 1, 2, or 4 s). A total of 36 test trials were administered across two assessments. For the CRT task, participants had to respond as quickly and as accurately as possible to two coloured squares that appeared vertically on the screen (interstimulus interval 3 s). Participants had to press the upper square if the colours were the same, or the lower square if the colours were different. Prior to testing, practice trials ensured that participants achieved four consecutive correct answers before they were allowed to continue. Following this, a total of 40 test trials were completed over two assessments.

2.4.1 Calculation of intraindividual standard deviations

Before calculating variability metrics, unusually fast RTs (<250 ms for SRT and <400 ms for CRT) were removed. RTs greater than 3 *SD*s above the age-group mean (<75, 75-79, 80-85 and ≥85 years) and error trials (*M*=0.9, *SD*=1.0) for the CRT task were also removed. These trials were then replaced using a regression imputation procedure (replaced trials = <1% for SRT, <4% for CRT). In line with previous studies (Hultsch et al., 2000; Hultsch et al., 2008), intraindividual standard deviations (ISD) were generated using a regression procedure that partialled out the effects of extraneous influences (age, time-on-task, and trial type) and their higher order interaction from the individual RTs. To obtain the most reliable estimates, ISD and mean-RT metrics were averaged across the two assessments.

2.5 Other cognitive measures

A comprehensive neuropsychological test battery was administered by trained psychology graduates. For present purposes, two domain composite measures were generated using two separate principal component analyses in which a single factor was requested and the factor scores saved. The executive control domain encompassed the Trail Making Test-part B (Reitan & Wolfson, 1993), verbal fluency (Benton, 1967), and animal naming (Spreen & Benton, 1969), while a memory domain score was computed from the Rey Auditory Verbal Learning Test (total learning and short- and long-term delayed recall) (Rey, 1964), Benton Visual Retention Test-recognition (Benton, Sivan, & Spreen, 1996), and Logical Memory Story A Test-delayed recall (Wechsler, 1997).

2.6 MRI acquisition

Of the 526 participants included in our study, 277 were scanned using a Philips 3T Intera Quasar scanner (Philips Medical Systems) located at the Prince of Wales Medical Research Institute, Sydney. The remaining participants were scanned using a Philips 3T Achieva

Quasar Dual scanner, as the original machine was replaced in 2007 for reasons beyond the investigators' control. As subject recruitment was random, it is unlikely that any systematic sampling bias was introduced by this change. Identical acquisition parameters for the T1-weighted structural MRI scans were used for both scanners. These were: TR = 6.39 ms, TE = 2.9 ms, flip angle = 8°, matrix size = 256x256, FOV = 256x256x190, and slice thickness = 1 mm with no gap between; yielding 1x1x1 mm^3 isotropic voxels. Fluid Attenuated Inversion Recovery (FLAIR) was acquired with TR = 10000 ms, TE = 110 ms, TI = 2800 ms, matrix size = 512×512, slice thickness = 3.5 mm without gap, and in plane resolution = 0.488 × 0.488 mm. Participants who were scanned using the different scanners were compared on social, demographic and imaging parameters. There were no significant differences on sex, years of education, or age, and grey matter, white matter, cerebrospinal fluid, and total intracranial cavity volumes were not significantly different after controlling for age, education, and sex. We analysed the scans of five healthy participants who were scanned on both scanners within two months. No significant scanner related differences were found in their sulcus morphometry (Liu et al., 2010).

2.7 Quantification of white matter hyperintensities

WMHs were delineated from coronal plane 3D T1-weighted and FLAIR structural image scans using the methods described in detail previously (Wen & Sachdev, 2004; Wen, Sachdev, Li, Chen, & Anstey, 2009).

2.8. Missing data and statistical analyses

At the aggregate sample level, the EM algorithm in IBM SPSS version 21 was used to impute missing data (1.4%) for the cognitive test battery. Due to the potential for threshold effects and following a precedent elsewhere (Zheng et al., 2012), WMH volumes were expressed as

a percentage of total intracranial volume, and entered into the models as a categorical variable. Three groups were used; less than 50th percentile (reference group), 50-75th percentile, and greater than 75th percentile, which were calculated separately for total and regional WMH volumes. For the main analyses, the RT metrics (ISD and mean-RT) were regressed onto WMH in a series of regressions models. In Step 1, we adjusted for age, years of education and sex, and each WMH variable was added separately at Step 2. To explore whether associations between WMH and the RT measures varied with age, Age x WMH interaction terms were added at Step 3. The residuals (errors) of these regression analyses were assessed for normality of the distribution. Due to deviations from the assumption of normality, the RT measures were log transformed.

3. Results

Means and standard deviations for demographic data, cognitive variables, and WMH are presented in Table 1. Older age was associated with greater variability and mean-RT and an increased WMH burden. Years in education was negatively associated with mean-RT, while sex was related to SRT mean-RT and frontal WMH.

3.1 Response time metrics and WMH

In the first analysis, the reaction time measures were regressed onto WMH. Although SRT ISD was not associated with WMH in any region (see Table 2), entering frontal WMH increased the shared variance in CRT ISD explained by the model (ΔR^2=.012, F(2,520)=3.25, p=.040). Participants with the highest WMH burden (in the fourth quartile) had higher ISDs compared to participants in the reference group. For all other regions, the addition of WMH did not significantly add to the model (ps≥.092 when the dummy variables for WMH were added). A similar pattern of results was evident for mean-RT, with significant relationships

only evident for frontal WMH and mean-CRT (ΔR^2=.013, F(2,520)=3.82, p=.022). Participants in the high WMH group had slower responses than those in the reference group. We further examined whether the association between WMH and variability changed with age by adding Age x WMH interaction terms to the models. For all RT measures across all brain regions, none of these interactions attained significance.

3.2 Analyses contrasting mean-RT and intraindividual variability

As ISD and mean-RT were highly inter-correlated (r=.70) and similar results were obtained for these measures, further analyses were run with ISD and mean-RT entered into the models together. The aim here was to see whether the association between frontal WMH and CRT ISD remained when controlling for CRT mean-RT and vice versa. The results indicated that neither measure was uniquely associated with frontal WMH, as this association was non-significant for ISD when adjusting for mean-RT (high vs low frontal WMH, β=.035, p=.305), and for mean-RT when adjusting for ISD (high vs low frontal WMH, β=.040, p=.240).

3.3 Analyses adjusting for future dementia and health variables

To investigate whether the association between frontal WMH and the RT measures was related to the inclusion of participants who were in the preclinical phase of dementia, the analyses were repeated controlling for future cognitive impairment and age, years in education and sex. Participants were coded as cases (n=51[1]) if they were given a dementia classification at any of the three follow-up assessments. When controlling for future dementia classification, the relationship between frontal WMH and CRT ISD (high vs low frontal WMH, β=.107, p=.017), and CRT mean-RT (high vs low frontal WMH, β=.109, p=.015)

[1] A further 132 participants did not complete the assessment at the 6-year follow-up, either because they were deceased (n=60) or declined (n=72). Analyses were repeated with these participants excluded to ensure we had not included any possible dementia cases in the non-demented group. All reported relationships remained statistically significant.

remained significant. Additionally, we controlled for dementia subtype: Probable or possible Alzheimer's disease, vascular dementia, mixed Alzheimer's and vascular dementia, or other (Parkinson's disease or dementia with Lewy bodies). This did not influence the initial results either. Thus, there was only a moderate attenuation of the β-values and corresponding significant levels, suggesting that incipient neurodegenerative disease was unlikely to be responsible for the significant variability-WMH associations. Next, to assess whether the relationship between RT-measures and WMH was explained by health variables, the models were repeated adjusting for each health factor in turn. None of these variables influenced the relationship between frontal WMH and the RT measures (high vs low WMH burden: ISD, β>.166, *p*s≤.021; mean-RT, β>.108, *p*s≤.017).

3.4 The influence of executive control

An important theoretical element of the present study was to assess whether independent measures of executive control explained relations between frontal WMH and variability. By contrast, we anticipated that controlling for memory performance would not attenuate the relationship as this aspect of cognition is primarily supported by temporal lobe structures. Therefore, models regressing CRT ISD on frontal WMH were rerun separately having adjusted for the respective cognitive measures. We used ΔR^2 before and after the addition of each cognitive measure to assess the degree of attenuation in variability-WMH associations (see Salthouse, 1992). Model 1a in Table 3 shows the beta values and ΔR^2 for the initial analyses (controlling for age, years in education and sex only), while Model 1b shows the same information when additionally controlling for executive control or memory. Adjusting for executive control attenuated the relationship between frontal WMH and CRT ISD by 58%. Such attenuation can be considered important (Salthouse, 1992). In contrast, controlling for memory did not attenuate the relationship between the frontal WMH and CRT ISD. Thus

the frontally-supported executive control measures exhibited greater explanatory power for the white matter-variability relationship than the measures primarily supported by other neuroanatomical structures. It was also important to establish the direction of influence of WMH-IIV-cognition associations. We therefore assessed the attenuation of the frontal WMH-cognition association (executive control or memory) having adjusted for CRT ISD (see Table 3, Models 2a and 2b). Of particular interest here was when executive control was taken into account, attenuation was lower (37%) and the WMH-executive control association remained statistically significant.

Lastly, as the MRI scanner was replaced midway through data collection, the main analyses were repeated controlling for scanner. This did not influence any of the findings.

4. Discussion

The present study produced a number of important findings. First, CRT variability and mean-RT were both related to frontal WMH. Second, there were no significant interactions between WMH and age, suggesting that the relationship between WMH and IIV did not vary with age in this older sample aged 70 years and above. Importantly, these significant associations remained after taking into account dementia up to six years following assessment and a range of health variables. Finally, adjusting for executive function attenuated the relationships between RT metrics and WHM, whereas controlling for memory did not. This latter finding is of some theoretical interest, as variability is thought to reflect fluctuations in attentional and executive control mechanisms.

The initial results indicated that IIV was associated with WMH in the frontal lobe. We particularly anticipated that IIV would be associated with frontal WMH, as previous imaging

(Bunce et al., 2010; Bunce et al., 2007; Jackson et al., 2012; Lovden et al., 2013) and neuropathological (Murtha et al., 2002; Stuss et al., 2003) studies suggest that there is a link between variability and frontal integrity. In the subsequent analyses, we anticipated that behavioural measures of executive control would account for the relationship between IIV and WMH, whereas measures such as memory would not. The results supported this expectation, as adjusting for executive control attenuated the association between WMH and variability, whereas taking memory performance into account had no effect on the initial findings. Conversely though, IIV attenuated the relationship between WMH and executive control to a lesser extent, and the association remained significant. In terms of direction of influence, this suggests that executive control mediated the WMH-IIV association, but that IIV failed to account for relations between WMH and executive control. Together, these findings are consistent with the view that variability measures are capturing attentional or executive control processes (Bunce et al., 2004; Bunce, Warr, & Cochrane, 1993; West et al., 2002). This possibility was further underlined by an effect of cognitive demand in which greater task demands inherent to the RT task (i.e., CRT compared to SRT) increased the sensitivity of IIV to differences in white matter integrity.

Given the initial associations between the RT-measures and WMH, one key aspect of the study was to explore how far the findings were related to the inclusion of persons in the pre-clinical stage of dementia. However, unexpectedly, adjusting for future dementia did not alter those initial finding. Although there is a broad literature relating increased IIV to neurobiological disturbance, the present results suggest that the association between RT measures and WMH is likely to be related to normal age associated deterioration rather than neuropathological decline relating to dementia up to six years following assessment. It is also important to note that the relationship between the RT metrics and WMH was not influenced

when statistically adjusting for health measures including neurological conditions, depression, cardio- or cerebrovascular disease, cardiovascular risk factors, or *APOE* e4 status. We were particularly interested in the health variables as a large body of evidence suggests that WMH have a vascular aetiology (e.g., Jeerakathil et al., 2004; Wen & Sachdev, 2004; Young, Halliday, & Kril, 2008). Our findings suggest that the WMH-RT associations found here were related to ageing rather than other physical health comorbidities in the present sample. This is consistent with previous research in middle- and early old-aged adults (Bunce et al., 2010; Bunce et al., 2007) and extends the findings into extremely old age where the prevalence of these health concerns, including cardiovascular risk factors, is higher.

Overall, we obtained very similar results for both mean-RT and variability measures. Our final analyses, therefore, compared the relationship between WMH and the two measures. Previous work suggests a dissociation exists between these RT metrics, with white matter integrity being associated with variability but not mean-RT (Bunce et al., 2010; Bunce et al., 2007; Fjell et al., 2011; Mella et al., 2013; Walhovd & Fjell, 2007) and in older samples with neuropathology, variability is a stronger predictor of group membership than mean-RT (e.g., Dixon et al., 2007). In contrast to this work, we found comparable results when using measures of IIV and mean-RT, and neither measure was uniquely predictive of WMH. However, previous studies investigating the relationship between RT measures and WMH were conducted in younger participants than those in the present study. Therefore, it is possible that variability is a more sensitive measure of subtle white matter effects in early old age (e.g., adults in their 60s: Bunce et al., 2007) and that with increasing age, the degree of age-related change to brain parenchyma becomes more marked such that it affects both RT variability and mean performance.

The present study has a number of strengths including the use of state-of-the-art automated methods to delineate the WMHs and a large population-based sample allowing identification of small effects. Also, a comprehensive medical assessment allowed us to adjust for future dementia and various health conditions up to six years following the present assessment point. Despite these strengths, however, there are some limitations that we should acknowledge. First, it remains possible that despite comprehensive screening, the significant associations found reflected the inclusion of participants on the clinical path to dementia, but beyond the six year time frame measured in the present study. However, this is unlikely as we would expect to see a stronger relationship between IIV and WMH in those who had a shorter time to dementia diagnosis than those who were temporally more distant. Removing individuals who were within six years of dementia conversion should, therefore, have had a greater impact on the IIV-WMH association. Also, the RT task was relatively short, which precluded us from using distributional analysis which may have helped delineate whether WMH was related to intermittently slower RTs or a general slowing of responses. However, it has previously been shown that 20 trials are sufficient to provide a reliable indicator of frontal WMH (Bunce et al., 2013).

In summary, the present study suggests that variability and mean-RT were both related to frontal WMH. The results indicate that in old age, WMH burden increases and is associated with greater behavioural variability and slower responding. Controlling for dementia up to 6 years following the present assessment did not alter this effect, suggesting the findings were independent of neurodegenerative change leading to dementia over that period. Additionally, adjusting for behavioural measures of executive control attenuated the frontal WMH-IIV relationship. The results are consistent with the view that frontally-supported cognitive

processes are involved in IIV-WMH relations, and that measures of RT variability and speed are sensitive to compromise to those neural structures.

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6. References

Anstey, K. J., Mack, H. A., Christensen, H., Li, S. C., Reglade-Meslin, C., Maller, J., . . . Sachdev, P. (2007). Corpus callosum size, reaction time speed and variability in mild cognitive disorders and in a normative sample. *Neuropsychologia, 45*(8), 1911-1920. doi: 10.1016/j.neuropsychologia.2006.11.020

APA. (2000). *Diagnostic and statistical manual of mental disorders: DSM-IV-TR*. Washington, DC: American Psychiatric Association.

Benton, A. L. (1967). Problems of test construction in the field of aphasia. *Cortex, 3*(1), 33-58.

Benton, A. L., Sivan, A. B., & Spreen, O. (1996). *Der Benton Test (7th ed.)*. Bern: Huber.

Bielak, A. A., Cherbuin, N., Bunce, D., & Anstey, K. J. (2014). Intraindividual Variability Is a Fundamental Phenomenon of Aging: Evidence From an 8-Year Longitudinal Study Across Young, Middle, and Older Adulthood. *Developmental Psychology, 50*(1), 143-151. doi: Doi 10.1037/A0032650

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

Bunce, D., Anstey, K. J., Cherbuin, N., Burns, R., Christensen, H., Wen, W., & Sachdev, P. S. (2010). Cognitive Deficits Are Associated with Frontal and Temporal Lobe White Matter Lesions in Middle-Aged Adults Living in the Community. *PLoS One, 5*(10). doi: 10.1371/journal.pone.0013567

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. M., 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

Bunce, D., MacDonald, S. W. S., & Hultsch, D. F. (2004). Inconsistency in serial choice decision and motor reaction times dissociate in younger and older adults. *Brain and Cognition, 56*(3), 320-327. doi: 10.1016/j.bandc.2004.08.006

Bunce, D., Warr, P. B., & Cochrane, T. (1993). Blocks in Choice Responding as a Function of Age and Physical-Fitness. *Psychol Aging, 8*(1), 26-33. doi: 10.1037/0882-7974.8.1.26

Cherbuin, N., Sachdev, P., & Anstey, K. J. (2010). Neuropsychological Predictors of Transition From Healthy Cognitive Aging to Mild Cognitive Impairment: The PATH Through Life Study. *American Journal of Geriatric Psychiatry, 18*(8), 723-733. doi: 10.1097/Jgp.0b013e3181cdecf1

Christensen, H., Dear, K. B. G., Anstey, K. J., Parslow, R. A., Sachdev, P., & Jorm, A. F. (2005). Within-occasion intraindividual variability and preclinical diagnostic status: Is intraindividual variability an indicator of mild cognitive impairment? *Neuropsychology, 19*(3), 309-317. doi: Doi 10.1037/0894-4105.19.3.309

D'Agostino, R. B., Sr., Vasan, R. S., Pencina, M. J., Wolf, P. A., Cobain, M., Massaro, J. M., & Kannel, W. B. (2008). General cardiovascular risk profile for use in primary care:

the Framingham Heart Study. *Circulation, 117*(6), 743-753. doi: 10.1161/CIRCULATIONAHA.107.699579

de Frias, C. M., Dixon, R. A., Fisher, N., & Camicioli, R. (2007). Intraindividual variability in neurocognitive speed: A comparison of Parkinson's disease and normal older adults. *Neuropsychologia, 45*(11), 2499-2507. doi: DOI 10.1016/j.neuropsychologia.2007.03.022

Deary, I. J., Bastin, M. E., Pattie, A., Clayden, J. D., Whalley, L. J., Starr, J. M., & Wardlaw, J. M. (2006). White matter integrity and cognition in childhood and old age. *Neurology, 66*(4), 505-512. doi: 10.1212/01.wnl.0000199954.81900.e2

Debette, S., & Markus, H. S. (2010). The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ, 341*, c3666. doi: 10.1136/bmj.c3666

Dixon, R. A., Lentz, T. L., Garrett, D. D., MacDonald, S. W. S., Strauss, E., & Hultsch, D. F. (2007). Neurocognitive markers of cognitive impairment: Exploring the roles of speed and inconsistency. *Neuropsychology, 21*(3), 381-399. doi: 10.1037/0894-4105.21.3.381

Duchek, J. M., Balota, D. A., Tse, C. S., Holtzman, D. M., Fagan, A. M., & Goate, A. M. (2009). The Utility of Intraindividual Variability in Selective Attention Tasks as an Early Marker for Alzheimer's Disease. *Neuropsychology, 23*(6), 746-758. doi: Doi 10.1037/A0016583

Dykiert, D., Der, G., Starr, J. M., & Deary, I. J. (2012). Age differences in intra-individual variability in simple and choice reaction time: systematic review and meta-analysis. *PLoS One, 7*(10), e45759. doi: 10.1371/journal.pone.0045759

Fjell, A. M., Westlye, L. T., Amlien, I. K., & Walhovd, K. B. (2011). Reduced White Matter Integrity Is Related to Cognitive Instability. *Journal of Neuroscience, 31*(49), 18060-18072. doi: 10.1523/Jneurosci.4735-11.2011

Gorelick, P. B., Scuteri, A., Black, S. E., Decarli, C., Greenberg, S. M., Iadecola, C., . . . Anesthesia. (2011). Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke, 42*(9), 2672-2713. doi: 10.1161/STR.0b013e3182299496

Gorus, E., De Raedt, R., Lambert, M., Lemper, J. C., & Mets, T. (2008). Reaction times and performance variability in normal aging, mild cognitive impairment, and Alzheimer's disease. *J Geriatr Psychiatry Neurol, 21*(3), 204-218. doi: 10.1177/0891988708320973

Hultsch, D. F., MacDonald, S. W., 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.

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

Hultsch, D. F., Strauss, E., Hunter, M. A., & MacDonald, S. W. S. (2008). Intraindividual variability, cognition and aging. In F. I. M. Craik & T. A. Salthouse (Eds.), *The handbook of aging and cognition* (3rd ed., pp. 491-556). New York: Psychology Press.

Jack, C. R., Jr., Knopman, D. S., Jagust, W. J., Shaw, L. M., Aisen, P. S., Weiner, M. W., . . . Trojanowski, J. Q. (2010). Hypothetical model of dynamic biomarkers of the

Alzheimer's pathological cascade. *Lancet Neurol, 9*(1), 119-128. doi: 10.1016/S1474-4422(09)70299-6

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

Jeerakathil, T., Wolf, P. A., Beiser, A., Massaro, J., Seshadri, S., D'Agostino, R. B., & DeCarli, C. (2004). Stroke risk profile predicts white matter hyperintensity volume - The Framingham Study. *Stroke, 35*(8), 1857-1861. doi: 10.1161/01.Str.0000135226.53499.85

Liu, T., Wen, W., Zhu, W., Trollor, J., Reppermund, S., Crawford, J., . . . Sachdev, P. (2010). The effects of age and sex on cortical sulci in the elderly. *Neuroimage, 51*(1), 19-27. doi: 10.1016/j.neuroimage.2010.02.016

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

Lovden, M., Schmiedek, F., Kennedy, K. M., Rodrigue, K. M., Lindenberger, U., & Raz, N. (2013). Does variability in cognitive performance correlate with frontal brain volume? *Neuroimage, 64*, 209-215. doi: 10.1016/j.neuroimage.2012.09.039

MacDonald, S. W. S., Hultsch, D. F., & Dixon, R. A. (2003). Performance variability is related to change in cognition: Evidence from the victoria longitudinal study. *Psychol Aging, 18*(3), 510-523. doi: Doi 10.1037/0882-7974.18.3.510

Mella, N., de Ribaupierre, S., Eagleson, R., & de Ribaupierre, A. (2013). Cognitive Intraindividual Variability and White Matter Integrity in Aging. *Scientific World Journal*. doi: 10.1155/2013/350623

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*(3), 360-372. doi: 10.1017/S1355617701020173

Pantoni, L. (2010). Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurology, 9*(7), 689-701. doi: Doi 10.1016/S1474-4422(10)70104-6

Reitan, R. M., & Wolfson, D. (1993). *The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation (2nd edn).* Tuscon: Neuropsychology Press.

Rey, A. (1964). *L'Examen Clinique en Psychologie* Paris: Press Universitaire de France.

Sachdev, P. S., Brodaty, H., Reppermund, S., Kochan, N. A., Trollor, J. N., Draper, B., . . . Team, M. A. S. (2010). The Sydney Memory and Ageing Study (MAS): methodology and baseline medical and neuropsychiatric characteristics of an elderly epidemiological non-demented cohort of Australians aged 70-90 years. *International Psychogeriatrics, 22*(8), 1248-1264. doi: Doi 10.1017/S1041610210001067

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

Salthouse, T. A. (1992). *Mechanisms of Age-cognition Relations in Adulthood*. Hillsdale, N.J: L. Erlbaum Associates.

Salthouse, T. A. (2010). Selective review of cognitive aging. *J Int Neuropsychol Soc, 16*(5), 754-760. doi: 10.1017/S1355617710000706

Spreen, O., & Benton, A. L. (1969). *Neurosensory Centre Comprehensive Examination for Aphasia Manual (NCCEA)*. Victoria: University of Victoria.

Strauss, E., Bielak, A. A., Bunce, D., Hunter, M. A., & Hultsch, D. F. (2007). Within-person variability in response speed as an indicator of cognitive impairment in older adults. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 14*(6), 608-630. doi: 10.1080/13825580600932419

Stuss, D. T., Murphy, K. J., Binns, M. A., & Alexander, M. P. (2003). Staying on the job: the frontal lobes control individual performance variability. *Brain, 126*, 2363-2380. doi: 10.1093/Brain/Awg237

Ullen, F., Forsman, L., Blom, O., Karabanov, A., & Madison, G. (2008). Intelligence and variability in a simple timing task share neural substrates in the prefrontal white matter. *Journal of Neuroscience, 28*(16), 4238-4243. doi: 10.1523/Jneurosci.0825-08.2008

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

Wechsler, D. (1997). *Wechsler Memory Scale. Third edition manual*. San Antonio: The Psycholgical Corporation.

Wen, W., & Sachdev, P. S. (2004). Extent and distribution of white matter hyperintensities in stroke patients: the Sydney Stroke Study. *Stroke, 35*(12), 2813-2819. doi: 10.1161/01.STR.0000147034.25760.3d

Wen, W., Sachdev, P. S., Li, J. J., Chen, X., & Anstey, K. J. (2009). White matter hyperintensities in the forties: their prevalence and topography in an epidemiological sample aged 44-48. *Human Brain Mapping, 30*(4), 1155-1167. doi: 10.1002/hbm.20586

West, R., Murphy, K. J., Armilio, M. L., Craik, F. I. M., & Stuss, D. T. (2002). Lapses of intention and performance variability reveal age-related increases in fluctuations of executive control. *Brain and Cognition, 49*(3), 402-419. doi: 10.1006/brcg.2001.1507

Young, V. G., Halliday, G. M., & Kril, J. J. (2008). Neuropathologic correlates of white matter hyperintensities. *Neurology, 71*(11), 804-811. doi: 10.1212/01.wnl.0000319691.50117.54

Zheng, J. J., Lord, S. R., Close, J. C., Sachdev, P. S., Wen, W., Brodaty, H., & Delbaere, K. (2012). Brain white matter hyperintensities, executive dysfunction, instability, and falls in older people: a prospective cohort study. *J Gerontol A Biol Sci Med Sci, 67*(10), 1085-1091. doi: 10.1093/gerona/gls063

Table 1: Mean (SD) values for demographic variables, response time metrics and white matter hyperintensity volumes, and bivariate intercorrelations

		Correlation with demographic variables		
		Age	Education	Sex
	Mean (SD)	78.38 (4.61)	11.83 (3.62)	54.4†
Cognitive variables				
SRT ISD	5.95 (4.50)	.054	-.048	.036
CRT ISD	6.85 (2.89)	.240**	-.079	.017
SRT mean-RT	614.15 (188.93)	.188**	-.203**	.134**
CRT mean-RT	947.31 (198.91)	.250**	-.149**	.067
Executive control	0.00 (1.00)	-.261**	.281**	.009
Memory	0.00 (1.00)	-.306**	.134**	.251**
White matter hyperintensities				
Total	13.90 (14.22)	.133**	-.026	.079
Periventricular	6.48 (4.29)	.179**	-.014	.063
Deep	6.93 (10.43)	.110*	-.033	.081
Frontal	2.13 (3.87)	.086*	-.045	.105*
Parietal	3.87 (5.93)	.122**	-.026	.068
Temporal	0.30 (0.88)	.040	-.042	.081
Occipital	0.60 (0.49)	.122**	.044	-.073

Notes: Executive control/memory (z-scores); ISD=intraindividual standard deviation; RT=reaction time (ms); White matter hyperintensities (ml); Deep white matter = frontal + parietal + temporal + occipital; † percentage female, for the bivariate correlations sex was coded female=1, male=0. *p<.05; **p<.01.

Table 2: Response time metrics regressed on white matter hyperintensities.

		SRT ISD		CRT ISD		SRT mean-RT		CRT mean-RT	
		β	*p*	B	*p*	β	*p*	β	*p*
Step 1									
Age group		.051	.243	.237	<.001	.177	<.001	.244	<.001
Years in education		-.040	.366	-.069	.112	-.176	<.001	-.131	.002
Sex		.027	.544	-.003	.949	.095	.027	.035	.415
Step 2									
Total WM	< 50th percentile				Reference				
	50-74th percentile	-.024	.608	.012	.795	.036	.428	.040	.373
	≥75th percentile	-.019	.688	.077	.095	.039	.391	.096	.036
Periventricular WM	< 50th percentile				Reference				
	50-74th percentile	.023	.656	.013	.780	.054	.230	.062	.163
	≥75th percentile	-.034	.475	.105	.021	.018	.697	.080	.053
Deep WM	< 50th percentile				Reference				
	50-74th percentile	-.037	.424	.022	.629	.026	.556	.056	.209
	≥75th percentile	-.014	.762	.084	.067	.049	.279	.124	.006
Frontal WM	< 50th percentile				Reference				
	50-74th percentile	.029	.528	.065	.114	.014	.754	.085	.057
	≥75th percentile	.020	.679	.113	.014	.042	.360	.115	.011
Parietal WM	< 50th percentile				Reference				
	50-74th percentile	-.061	.188	-.007	.884	.029	.515	.043	.336
	≥75th percentile	-.024	.617	.092	.045	.031	.491	.111	.015
Temporal WM	< 50th percentile				Reference				
	50-74th percentile	.004	.940	.020	.657	.059	.188	.031	.492
	≥75th percentile	-.031	.501	.063	.167	-.006	.899	.068	.130
Occipital WM	< 50th percentile				Reference				
	50-74th percentile	-.027	.563	-.008	.858	-.009	.844	-.003	.939
	≥75th percentile	-.032	.495	.054	.230	.005	.919	.023	.606

Notes: SRT=simple reaction time; CRT=complex reaction time; ISD= intraindividual standard deviation; RT= reaction time; WMH=white matter hyperintensities. All models controlled for age, years in education and sex.

Table 3: The extent to which executive function or memory accounted for the association between frontal white matter hyperintensies and CRT ISD.

		Model 1a		Model 1b			Model 2a		Model 2b		
Cognitive composite		β	ΔR^2	β	ΔR^2	%	β	ΔR^2	β	ΔR^2	%
Executive control											
	Frontal WMH		.012*		.005	58%		.019**		.012*	37%
	50-74th percentile	.065		.050			-.051		-.034		
	≥75th percentile	.113*		.070			-.149**		-.119**		
Memory											
	Frontal WMH		.012*		.012*	0%		.001		.001	0%
	50-74th percentile	.065		.070			.035		.044		
	≥75th percentile	.113*		.114*			.009		.024		

Notes: Model 1a = WMH-ISD; Model 1b=WMH-ISD adjusting for cognitive composite (executive control or memory); Model 2a= WMH-Cognitive composite; Model 2b=WMH-Cognitive composite adjusting for ISD; % = percentage difference in ΔR^2 between Models 1a/2a and 1b/2b; CRT=complex reaction time; ISD= intraindividual standard deviation; WMH=white matter hyperintensities. All models adjusted for age, years in education and sex. *p<.05, **p<.01