Neuropsychologia 96 (2017) 249–255

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

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

Becky I. Haynes[a], David Bunce[a,b,*], Nicole A. Kochan[b,c], Wei Wen[b,c], Henry Brodaty[b,d,e], Perminder S. Sachdev[b,c]

[a] School of Psychology, Faculty of Medicine and Health, University of Leeds, Leeds, UK
[b] Centre for Health Brain Ageing (CHeBA), School of Psychiatry, Faculty of Medicine, University of New South Wales, Sydney, Australia
[c] Neuropsychiatric Institute, Prince of Wales Hospital, Barker Street, Randwick, NSW 2031, Australia
[d] Dementia Collaborative Research Centre, School of Psychiatry, UNSW Medicine, The University of New South Wales, Sydney, NSW 2052, Australia
[e] Academic Department for Old Age Psychiatry, Prince of Wales Hospital, Avoca Street, Randwick, NSW 2031, Australia

ARTICLE INFO

Keywords:
White matter hyperintensities
Reaction time
Intraindividual variability
Executive function
Cognition

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.

1. Introduction

Intraindividual variability (IIV), or inconsistency (e.g., Hultsch et al., 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 et al., 2014), even when response speed is taken into account (Dykiert et al., 2012). One proposal holds that IIV is an early indicator of neurobiological disturbance (Hultsch et al., 2000, 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 et al., 2008; Hultsch et al., 2000; Strauss et al., 2007), Parkinson's disease (de Frias et al., 2007) and also frontal lobe lesions (Stuss et al., 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 et al., 2012; Lovden et al., 2013; Ullen et al., 2008; Walhovd and Fjell, 2007) and diffusion tensor imaging metrics (e.g., FA - fractional anisotropy) (Deary et al., 2006; Fjell et al., 2011; Mella et al., 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 et al., 2002; Stuss et al., 2003) while in healthy populations, associations have been identified between increased IIV and frontal WMH (Bunce et al., 2010, 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

* Corresponding author at: School of Psychology, Faculty of Medicine and Health, University of Leeds, LeedsLS2 9JT, UK.
E-mail address: d.bunce@leeds.ac.uk (D. Bunce).

http://dx.doi.org/10.1016/j.neuropsychologia.2017.01.021
Received 18 April 2016; Received in revised form 23 December 2016; Accepted 20 January 2017
Available online 21 January 2017
0028-3932/

cognitive decline (Bielak et al., 2010; Cherbuin et al., 2010; Lovden et al., 2007; MacDonald et al., 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 et al., 2013). Also, WMH have been associated with an increased risk of developing future Alzheimer's disease (Debette and 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 60 s (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 et al., 2004; West et al., 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, 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