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ORIGINAL RESEARCH

White matter hyperintensities are associated with falls in older people with dementia

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Abstract

White Matter Hyperintensities (WMHs) are associated with impaired gait, balance and cognition and increased fall risk in cognitively healthy older people. However, few studies have examined such relationships in older people with dementia. Understanding the role of WMHs in falls may assist in developing effective fall prevention strategies. We investigated the relationship between baseline WMHs, cognitive and sensorimotor function and prospective falls in older people with dementia. Twenty-eight community-dwelling older people with mild-moderate dementia (MMSE 11–23; ACE-R < 83) underwent magnetic resonance imaging and assessment of sensorimotor and cognitive (global and processing speed) function at baseline. WMHs, were quantified using a fully automated segmentation toolbox, UBO Detector (https://cheba.unsw.edu.au/group/neuroimaging-pipeline). Falls were ascertained prospectively for 12-months using monthly calendars with the assistance of carers. The median age of the participants was 83 years (IQR 77–86); 36% were female; 21 (75%) fell during follow-up. Using Generalized Linear Models, larger volumes of total WMHs were found to be significantly associated with poorer global cognitive and sensorimotor function. Using modified Poisson regression, total, periventricular and deep WMHs were each associated with future falls while controlling for age, sex, intracranial volume and vascular risk. Each standard deviation increase in total and periventricular WMH volume resulted in a 33% (RR 1.33 95%CI 1.07–1.66) and 30% (RR 1.30 95%CI 1.06–1.60) increased risk of falling, respectively. When the deep WMH volume z-scores were dichotomized at the median, individuals with greater deep WMH volumes had an 81% (RR 1.81 95% CI 1.02–3.21) increased risk of falling. WMHs were associated with poorer sensorimotor and cognitive function in people with dementia and total, periventricular and deep WMHs were associated with falls. Further research is needed to confirm these preliminary findings and explore the impact of vascular risk reduction strategies on WMHs, functional performance and falls.

Keywords Dementia · Cognitive impairment · Accidental falls · White matter hyperintensities · Leukoaraiosis · Sensorimotor function

Introduction

Dementia and falls are common geriatric syndromes with global impact. Falls are more common in older people with dementia, and are more likely to lead to serious injury (e.g. hip fracture) and adverse consequences (e.g. placement in residential care and death) when compared to cognitively intact peers (Taylor et al. 2012; Harvey et al. 2016).

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Poor balance predicts falls in cognitively intact and impaired individuals (Taylor et al. 2014; Delbaere et al. 2010). The interrelationship between cognitive function, in particular executive function, and physical function and fall risk has also been demonstrated in cognitively intact and impaired older people (Taylor et al. 2017; Taylor et al. 2014; Martin et al. 2013; Mirelman et al. 2012). In recent years, the relationship between brain pathology, specifically white matter lesions and cognition, physical function and falls has also been investigated. White matter lesions are thought to result from chronic brain ischemia/small vessel disease and are commonly identified on magnetic resonance imaging (MRI) as white matter hyperintensities (WMHs) in older people (Prins and Scheltens 2015). WMHs have been associated with incident dementia, as well as gait impairment, postural instability and falls in cognitively healthy older people (Prins and Scheltens 2015; Zheng et al. 2012; Srikanth et al. 2009; Baezner et al. 2008).

Increased WMH volumes are commonly reported in individuals with Alzheimer's, vascular and Lewy body dementia and mixed dementia pathology is more common than clinically recognized (Prins and Scheltens 2015; van Uden et al. 2016; Sarro et al. 2017). However, less is known about the ongoing impact of WMHs on physical performance and falls and/or whether a threshold of brain pathology may be reached in relation to these outcomes in older people with dementia. Understanding how brain pathology influences physical and cognitive function and falls may help determine how best to assess and intervene (e.g. management of vascular risk such as hypertension and lipids) in this population, with the goal of preventing decline and falls.

WMH studies offer scope for increasing our understanding of fall risk in older people with dementia, but the studies conducted to date have had a number of limitations. First, only one study has ascertained falls prospectively and this study did not report data for total WMH and falls, i.e. only separate associations between deep and periventricular WMH burden and falls were reported (Horikawa et al. 2005). Second, the relationship between total WMH burden and physical function has been restricted to gait outcomes (Nadkarni et al. 2009; Bennett et al. 1992). Finally, all previous studies examining WMHs, physical function and falls in people with dementia have used visually rated WMH in their analyses; a methodology that has been purported to lack sensitivity and precision when compared to automated volumetric measurement (van Straaten et al. 2006; Prins and Scheltens 2015; Jiang et al. 2018).

This study used automated volumetric WMH measurements and investigated a) the relationship between total WMH volume and cognitive function and a comprehensive sensorimotor measure and b) the relationship between WMH volumes and falls ascertained prospectively over 1 year in older people with all-cause mild to moderate dementia.

Methods

Participants

The study sample ($n = 28$) was drawn from an observational study involving 177 older people with mild to moderate all-cause dementia who were recruited from routine health service settings, community services and advertisements in the local press. Inclusion criteria for the observational study were: aged 60 years or older, living in the community or low-level care ($n = 1$ in the MRI study), and having an identified and willing "person responsible" with at least 3.5 h of face-to-face contact per week. Mild to moderate dementia was defined as a Mini-Mental State Examination (MMSE) 11–23 inclusive, an Addenbrooke's Cognitive Examination – Revised (ACE-R) <83 (previous literature has demonstrated the ACE-R has good reliability and a cut-off of 82 has excellent specificity [1.0] and sensitivity [0.84] for dementia and the likelihood ratio of dementia is 100:1) (Mioshi et al. 2006) and/or where a specialist clinician had made a diagnosis of dementia/cognitive impairment. Exclusion criteria included recent stroke (within 18 months), progressive neurodegenerative disorders (excluding dementia), insufficient English to complete the assessments or known end stage illness. For the MRI study participants ($n = 28$) also needed to be eligible for and consent to MRI. The participants who underwent MRI (n = 28) did not significantly differ from those who did not with respect to age, education, number of medications, MMSE score or falls (0 vs 1+) during follow-up ($p > 0.05$). However, they were more likely to be male ($p = 0.020$) and had better sensorimotor performance ($p = 0.037$). The study was approved by the South-Eastern Sydney Human Research Ethics Committee and consent was obtained from all participants and their person responsible prior to assessment.

Assessment

Participants and their person responsible were initially assessed in their home environment obtaining demographic information, medical history (past or present) and current medications. Participants were categorized as having 'vascular risk' if they reported hypertension, heart problems, stroke and/or diabetes. The cognitive and sensorimotor assessments were also undertaken in the participants' homes.

Cognitive assessment

The Addenbrooke's Cognitive Examination – Revised (/100) was used to assess global cognitive function, it contains the MMSE and assesses multiple domains including attention, memory, verbal fluency, language and visuospatial ability

(Mioshi et al. 2006). Trail Making Test A was used to assess processing speed and requires the participant to connect 25 encircled numbers in numerical order with a pen/pencil as quickly as possible (Tombaugh 2004).

Sensorimotor assessment

Visual contrast sensitivity was assessed using the Melbourne Edge Test which presents 20 (circular 25 mm diameter) patches containing edges with reducing contrast with variable orientation (vertical, horizontal, 45° left, 45° right) as the identifying feature (Lord et al. 2003). The test uses a four-alternative forced choice response card. The lowest contrast patch edge orientation correctly identified provides a measure of contrast sensitivity in decibel units, where 1 dB = 10 $\log_{10}$ contrast. Simple hand reaction time (milliseconds [ms]) was measured using a visual stimulus and a finger-press response (score = average of 10 test trials) (Lord et al. 2003). Proprioception was measured using a lower limb matching task predominantly involving the knee and ankle joints, participants were seated with their eyes closed with a large acrylic protractor placed between their legs and asked to match their great toes to the same height. Errors in degrees of matching their great toes were recorded (score = average of five test trials) (Lord et al. 2003). Maximal isometric knee extension strength was measured in the dominant leg with a spring gauge in a seated position with the hip and knee flexed at 90° (best of three; kilograms) (Lord et al. 2003). Postural sway was assessed using a swaymeter that measured displacement of the body at waist level with participants standing on a foam mat (15 cm thick) with eyes open for 30s (Lord et al. 2003). Sway score (mm^2) was calculated using mediolateral × anteroposterior sway displacement. Weighted contributions from these five tests contribute to the final Physiological Profile Assessment (PPA) score, a measure of sensorimotor performance and estimate of overall fall risk (scoring: 0–1 = mild fall risk, 1–2 = moderate fall risk, 2–3 = marked fall risk) (Lord et al. 2003).

Falls follow-up

Standardized, gold-standard fall ascertainment methods were used (Lamb et al. 2005). Monthly falls calendars and reply-paid envelopes were given to the participants and their carers to ensure accurate data collection prospectively over 12-months. The fall definition was, "In the past month, have you had any falls including a slip or a trip in which you lost your balance and landed on the floor or ground or lower level?" (Lamb et al. 2005). If a participant/carer failed to return the calendar, a telephone call was made to obtain the participant's falls data. Participants were categorized based on their fall reporting as non-fallers or fallers (1+).

Magnetic resonance imaging (MRI) data acquisition and processing

T1-weighted and T2-weighted fluid-attenuated inversion recovery (FLAIR) images were acquired from a Philips 3 T Achieva Quasar Dual scanner (Philips Medical Systems, Best, The Netherlands). The scanning parameters were set as follow: *T1-weighted*—Repetition time (TR) = 6.39 ms, echo time (TE) = 2.9 ms, flip angle = 8°, matrix size = 256 × 256, field of view (FOV) = 256 × 256 × 190, and slice thickness = 1 mm with no gap in between, yielding 1 × 1 × 1 mm^3 isotropic voxels. *T2-weighted FLAIR*—TR = 10,000 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.

T1 and FLAIR data were used to extract intracranial volume (ICV) and WMH volumes. Specifically, individual T1-weighted images were segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using SPM12. The sum of the probability of a voxel belonging to each tissue class was multiplied by the volume of a voxel in T1 images (i.e., 1 × 1 × 1 mm^3) to get the estimate of ICV. WMH volumes were calculated with a fully automated toolbox for extracting WMH, UBO Detector (https://cheba.unsw.edu.au/group/neuroimaging-pipeline) (Jiang et al. 2018). Briefly, individual FLAIR images were first registered to their corresponding T1 data. The T1 images were warped to Diffeomorphic Anatomical Registration Through Exponentiated Lie (DARTEL) space (Ashburner 2007), and the resultant field maps were then applied to the FLAIR images which have been registered to T1 space, to warp them to the same DARTEL space (Jiang et al. 2018). After non-brain tissue removal and the removal of inhomogeneity on FLAIR images in DARTEL space, a k-nearest neighbor (k-NN)-based algorithm was applied for the classification of WMH and non-WMH (Jiang et al. 2018). Periventricular WMH was defined as WMH voxels within 12 mm from a periventricular mask in DARTEL space, and the rest WMH voxels were regarded as deep WMH (Jiang et al. 2018). We found this distance threshold (12 mm) was optimal for segmenting periventricular and deep WMH in elderly cohorts similar to the current study (Jiang et al. 2018). All MRI processing was completed after the 12-month follow-up period by researchers/authors (WW and JJ) with access to basic demographic data (age and sex) only.

Statistical analysis

Data were analyzed using SPSS 25.0 for Windows (SPSS, Inc., Chicago, IL). Two participants were physically unable to perform the sway on foam test and were given a score of 3SD worse than the whole sample (n = 177) mean and

included in the analyses. TMT A was capped at 180 s ($n = 2$) based on population norms (Tombaugh 2004). Generalized Linear Models with robust estimates were used to examine the relationship between baseline total WMH volume (z-score) and baseline cognitive and sensorimotor function while controlling for age, sex and vascular risk (hypertension, heart problems, stroke and/or diabetes), as well as education for cognitive measures. Total WMH volume (z-score) was not linearly associated with Trail Making Test A scores, therefore total WMH volume (z-score) was dichotomized comparing participants falling in the worst quartile to the remainder of the cohort. Modified Poisson regression with robust estimates was used to examine the relationship between faller status (0 vs 1+) and total (z-score), periventricular (z-score) and deep (median split z-score) WMH volumes in unadjusted and adjusted models (age, sex, intracranial volume and vascular risk) (Zou 2004). The assumption of linearity of the logit was not met for Deep WMH z-scores, therefore this variable was dichotomized at the median. Due to the exploratory nature of these analyses, p-value corrections have not been applied and the p-value threshold for significance was set at $p < 0.05$.

Results

Sample characteristics

The median age of the sample was 83 years and 36% were female (Table 1). Baseline characteristics of the sample are presented in Table 1. Twenty-one (75%) of the participants fell at least once during the one-year follow-up. The median total WMH volume of the faller and non-faller groups were 26.3 cm^3 (IQR 13.5–41.6) and 8.8 cm^3 (IQR 4.6–15.2) respectively. The mean ICV of the faller and non-faller groups were 1557.9 ± 189.3 cm^3 and 1507.9 ± 197.0 cm^3 respectively.

The relationship between WMHs and, cognitive and sensorimotor function

Total WMH volume was significantly associated with global cognitive function measured by the ACE-R and sensorimotor function measured by the PPA while controlling for age, sex and vascular risk, as well as education for the cognitive measures (Table 2). Each standard deviation increase in total WMH volume was associated with a five-point decrease in ACE-R score and 0.63 increase in Physiological Profile Assessment score.

WMHs and falls

Total, periventricular and deep WMH volumes were each significantly associated with faller status (0 vs 1+) in unadjusted and adjusted analyses controlling for age, sex, intracranial volume and vascular risk (Table 3). Each standard deviation increase in total WMH volume was associated with a 33% increased risk of falls in the adjusted analysis (Table 3).

Discussion

Total, periventricular and deep WMH volumes, quantified using automated methods, were each associated with an increase in falls in this population of older people with all-cause dementia. Total WMH volumes were also associated with poorer sensorimotor and cognitive function at baseline.

Intact cerebral networks are required for normal cognitive and sensorimotor function. WMHs can interrupt the integrity, structure and function of these important networks, affecting network strength, density and efficiency (Tuladhar et al. 2015). Our finding that increased total WMH volumes were associated with poorer sensorimotor performance is consistent with previous work in cognitively healthy older people (Prins and Scheltens 2015; Zheng et al. 2012; Srikanth et al. 2009; Baezner et al. 2008) and in particular, one study that found a significant relationship between the PPA scores and WMH volumes in a cognitively intact sample (Zheng et al. 2012). Our findings also build on those of other studies undertaken in older people with dementia that have reported: periventricular WMHs (grades 1 and 2) were associated with postural control (Horikawa et al. 2005); total WMH scores were correlated with stride length and gait disturbance (Bennett et al. 1992; Nadkarni et al. 2009); and various regional WMH burdens were associated with assorted postural control and mobility measures (Ogama et al. 2014). The above findings provide a consistent picture that increased WHM volumes (likely reflecting chronic ischemic brain changes/small vessel disease) are associated with impaired physical performance in older people both with and without dementia.

The literature examining the relationship between volumetric WMH volumes and cognition in older people with dementia is sparse and has produced inconsistent findings (Ramirez et al. 2014; Altamura et al. 2016; Wahlund et al. 1994; van der Vlies et al. 2013; Burton et al. 2006). In this study, increased total WMH volumes were significantly associated with poorer global cognitive performance, but not slower processing speed; the latter null finding being possibly due to low statistical power. Compared to the remainder of the sample, participants in the worst quartile of total WMH were 24 s slower on Trail Making Test A while controlling for confounders. However, this difference was not statistically significant. A recent meta-analysis of cross-sectional studies in

Table 1 Participant baseline characteristics

Characteristics, n (%), median (IQR) or mean ± SD	Total sample ($n = 28$)
Demographics	
Age, years	83 (77–86)
Female	10 (36)
Education, years	10 ± 3
Medical history	
Hypertension	14 (50)
Heart problems	8 (29)
Diabetes	5 (18)
Stroke	1 (4)
Medication use	
Total number	5 ± 3
Cognitive function	
Addenbrooke's Cognitive Examination-Revised	74 (63–82)
Attention and orientation	16.0 (13.3–17.0)
Memory	13.6 ± 5.1
Verbal fluency score	6.7 ± 2.6
Phonemic fluency, total correct enumerated	9.0 ± 4.7
Animal fluency, total correct enumerated	9.7 ± 3.9
Language	23.0 (18.3–24.0)
Visuospatial	14.0 (12.3–15.8)
Trail Making Test A, seconds	63 (49–96)
Sensorimotor function	
Physiological Profile Assessment Score	1.7 ± 1.4
Brain volumes from magnetic resonance imaging	
Total white matter hyperintensities, cm^3	17.9 (9.2–37.2) / 24.1 ± 18.8
Intracranial volume, cm^3	1520.4 ± 192.9

Higher scores are better for Addenbrooke's Cognitive Examination-Revised (/100) and its domains (Attention and orientation /18; Memory /26; Verbal fluency score /14; Language /26; Visuospatial /16) and lower scores are better for Trail Making Test A and the Physiological Profile Assessment

cognitively healthy older people reported a significant association between WMHs and all cognitive domains (except language) with small but consistent effect sizes (Kloppenborg et al. 2014). Future research could similarly, and more systematically and comprehensively, examine the relationship between WMH volumes and cognitive performance by neuropsychological domain in older people with dementia (Ramirez et al. 2014; van der Vlies et al. 2013; Altamura et al. 2016).

Total, periventricular and deep WMH volumes were all associated with prospectively measured falls in the current sample. This finding builds on that of Horikawa and colleagues who reported a significant relationship between grade 2 periventricular WMHs and falls in participants with dementia, (Horikawa et al. 2005), as well as studies that have found total WMH burden is associated with falls in cognitively healthy older people (Zheng et al. 2012; Srikanth et al. 2009). The relationship between WMH and falls has previously been demonstrated to be independent of sensorimotor function and processing speed in cognitively healthy older people (Zheng et al. 2012; Srikanth et al. 2009). This suggests that the relationship between WMHs and falls is not simply caused by the effect of these cerebral network disruptions on cognitive and sensorimotor function. Future research could further examine this causal pathway to get a better understanding of how WMH affect daily life function and mobility in larger samples of older people with dementia.

In the few studies that have measured total WMH volumes in participants with dementia, the results have been quite varied (range 9–38 cm^3 in participants with Alzheimer's disease; 45–146 cm^3 in participants with vascular dementia; 5–25 cm^3 in dementia with Lewy bodies cohorts) (Hirono et al. 2000; van der Vlies et al. 2013; Altamura et al. 2016; van Uden et al. 2016; Sarro et al. 2017; Burton et al. 2006). The WMH volumes in the current sample (mean 24 cm^3 [median 18 cm^3]) were within the previously reported WMH range for participants with Alzheimer's disease and dementia with Lewy bodies, lower than the volumes reported for vascular dementia and higher

Table 2 Cross-sectional relationship between total white matter hyperintensities (WMH; z-score) and cognitive and sensorimotor function using linear Generalized Linear Models

	Unadjusted B	95%CI	*p*-value
Global cognitive function: Addenbrookes' Cognitive Examination - Revised[a]			
Total WMH	−5.28	−9.00 – −1.58	0.005
Processing speed: Trail Making Test A[a]			
Total WMH: worst quartile	24.30	−0.86 – 49.45	0.058
Sensorimotor function: Physiological Profile Assessment Score[b]			
Total WMH	0.63	0.10–1.15	0.020

[a] Controlling for age, sex, education and vascular risk

[b] Controlling for age, sex and vascular risk

than WMH volumes reported in studies of cognitively healthy older people (range for cognitively healthy 2–13 cm^3) (Zheng et al. 2012; Srikanth et al. 2009; Kloppenborg et al. 2014). Older age is unlikely to fully explain the increased WMH volumes in our sample with dementia when compared to cognitively healthy samples, with the larger volumes likely representing vascular changes associated with their neurodegenerative disease. With respect to the apparent WMH volume difference when the current sample is compared to cohorts with vascular dementia, our selection criteria may have precluded inclusion of some individuals with vascular dementia, in that, we excluded people with recent (<18 months) stroke. Therefore, based on the volumetric WMH data, the current sample may more closely represent individuals with Alzheimer's disease, dementia with Lewy bodies, and/or mixed dementia, with fewer participants with marked vascular dementia.

The challenge for future research lies in determining whether better management of vascular risk factors, and therefore prevention of WMHs development and progression, could contribute to falls prevention interventions. Potentially, management of vascular risk (e.g. smoking cessation and lipid lowering and antihypertensive therapy in individuals with these risk factors) is required from middle-age, before onset of detectable disease processes. Alternatively, treatment may need to be individualized depending on age and how various risks affect WMH development and progression e.g. antihypertensive medication in midlife and lipid lowering medications in later life (Dickie et al. 2016).

Our study has several strengths. We used established gold standard fall ascertainment methods (monthly diaries, telephone calls and carer assistance) and well-validated measures of cognitive and sensorimotor function. Furthermore, the MRI analysis was automated and analyzed independently and blind of physical, cognitive and fall outcomes. There are also some limitations that need considering. Firstly, the sample size was small, which reduces statistical power and can increase Type II errors, which can bias the results toward rejecting a false null hypothesis. Secondly, only a small number of participants agreed to and were eligible for MRI, which may have biased our findings, in that, the sample is less likely to represent the whole population, which is further influenced by the fact that the MRI study sample had more men and better sensorimotor performance which hypothetically could reduce fall incidence—but, in analysis comparing participants with and without MRI, there was no significant difference in the number of fallers. Finally, we used a pragmatic approach to recruiting participants with dementia (MMSE<24, ACE-R < 83 and/or specialist diagnosis) and the sample included participants with a variety of dementia types e.g. Alzheimer's disease, vascular dementia and mixed dementia. Therefore, although the

Table 3 White matter hyperintensities (WMHs; z-score) relationship with faller status (0 vs 1+) using modified Poisson regression

	Unadjusted		Adjusted [a]	
	RR (95%CI)	*p*-value	RR (95%CI)	*p*-value
Falls (0 vs 1+)[b]				
Total WMHs	1.24 (1.05–1.47)	0.011	1.33 (1.07–1.66)	0.012
Periventricular WMHs	1.27 (1.06–1.52)	0.010	1.30 (1.06–1.60)	0.014
Deep WMHs[c]	1.63 (1.01–2.62)	0.046	1.81 (1.02–3.21)	0.044

[a] Adjusted for age, sex, intracranial volume and vascular risk (vascular risk = hypertension, stroke, heart problems and/or diabetes)

[b] Total, periventricular and deep WMHs relationship with falls were examined in separate models

[c] Deep WMHs = dummy variable, median split

inclusion criteria screening tool scores indicate the presence of dementia, they do not provide a definitive diagnosis. Further, we are unable to determine if there were differential effects depending on dementia sub-group. However, recent literature has highlighted inaccuracies in clinical diagnoses of dementia suggesting that pathologies often overlap and are heterogeneous within individuals, which consequently reduces the utility and value of clinical diagnoses for participant selection (Prins and Scheltens 2015; Sarro et al. 2017). Also, while WMH volume is increased in Alzheimer's, vascular and Lewy body dementia compared to controls, the pathogenesis and pathophysiology of WMHs by dementia sub-group is not fully understood (McAleese et al. 2016; Prins and Scheltens 2015). However, there has been some suggestion that WMHs pathogenesis may differ according to dementia type and/or genetic predisposition e.g. small vessel disease versus hyperphosphorylated tau- and/or amyloid-related axonal loss (Prins and Scheltens 2015; McAleese et al. 2016). These differences may also affect WMHs relationship with cognitive and physical performance and falls and needs further investigation in larger samples. Nevertheless, in samples without dementia, WMH volume has been demonstrated to be associated with falls which may indicate that the pathophysiology of WMHs plays an insignificant role in this relationship. Alternatively, in these healthy samples, there may be a predominance of vascular related WMHs.

In conclusion, WMHs are associated with cognitive and sensorimotor function and falls in older people with dementia. Further research is needed to confirm these findings and to determine whether managing vascular risk, and therefore the evolution and progression of WMHs, can prevent falls in this population.

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Compliance with ethical standards

Conflict of interest The Physiological Profile Assessment (FallScreen) is commercially available through Neuroscience Research Australia (NeuRA). Professor Henry Brodaty holds a position on the advisory board for Nutricia.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individuals, and their person responsible, included in the study.

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