A Cross Sectional Study on The Relationship between Age, White Matter Lesion, Brain Atrophy and Cognitive Function

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Statement of Originality

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ABSTRACT

Scope: The present study was designed to examine the relationship between structural brain changes, involving macrostructural and microstructural white matter changes, brain atrophy and cognitive function.

Purpose: Cognitive deterioration is generally thought to be due to structural brain changes as part of the aging process. The present study sought to determine how age-related structural brain changes at the macrostructural and microstructural levels correlate with cognitive function among a cohort of reasonably healthy elderly. The study also explored the possible link between white matter damage and cognitive dysfunction, and examined whether this relationship was also influenced by age-associated loss of brain volume i.e. brain atrophy. Last but not least, the study examined the level of the usefulness of a global cognitive measure in comparison to specific neuropsychological subtests assessing executive function, working memory and episodic memory domains.

Methodology: The volumetric measures were utilised to account for brain macrostructural changes, while the Diffusion Tensor Imaging (DTI)-based measures were used to examine microstructural properties of white matter disruptions among seventy reasonably healthy elderly recruited from Hunter Medical Research Institute (HMRI) Volunteer Register and specialised neurovascular clinic. The Montreal Cognitive Assessment (MoCA) was used to assess global cognition and twelve neuropsychological subtests were administered to measure specific deficit associated with subtle cognitive dysfunction in white matter pathology. The Pearson correlation coefficient and hierarchical multiple regression were utilised for data analyses.
**Results:** The MoCA has captured variation associated with brain volumes and DTI-based changes, not fully accounted by specific cognitive tests administered in this study. Even after adjusting for age, FSIQ, and brain atrophy separately, the independent association between the MoCA and radial diffusivity remained stable. Interestingly, the MoCA is a brief, yet powerful tool that even accounts for global cognitive deficit for which white matter pathology and brain atrophy are not sensitive markers. White matter macrostructural and microstructural changes are associated with age-related cognitive dysfunction, characterised as subtle, varied, and diffuse in nature. Brain atrophy not only linked to age, but also influenced the association between global cognition and white matter pathology on the volumetric measure; and partially explained the relationship between white matter microstructural disruption and specific deficit in visual working memory and visual episodic memory. In addition, the hierarchical regression analysis revealed that the MoCA was the strongest predictor of radial diffusivity ($R^2 = .476, \rho < .01$) even after controlling for age ($R^2 = .392, \rho < .01$), and cerebral atrophy was not a significant predictor of radial diffusivity.

**Conclusions and Implications:** Age-related white matter macrostructural and microstructural changes are not benign, even among reasonably healthy elderly by which their future functioning may be compromised. The so-called ‘healthy’ elderly appear to be a more vulnerable population, as the nature of the dysfunction can be very subtle and diffuse. Early detection thus, serves as a main preventative measure for this population. Since our findings strongly point to the MoCA as a beneficial screening tool for cognitive dysfunction at the early stage of white matter disease, we therefore recommend this brief,
easily accessible tool for frontline clinicians to incorporate into their investigation protocol.
Overview

The relationship between structural brain changes, in particular, macrostructural and microstructural white matter changes, brain atrophy and cognitive function were examined in the present study. Part 1 will focus on a critical review of the literature leading to the objectives of the present study. Part 2 will present the study, written in a journal format and which has been submitted to a journal for peer review. To date, the Translational Neuroscience Journal has accepted the manuscript for review on the 10th February 2014 (see Appendix 1). The third and final part elaborates the outcomes and reflects upon the present study in a form of an Extended Discussion.

PART 1

Critical Literature Review

Introduction

Cognitive deterioration is prevalent with age, and even healthy elderly are not totally exempted from this natural course. However, individuals differ on their trajectories of the ageing process (DeCarli, 2003) and there is concern due to age-associated functional loss and increased risk for future pathology. The decline in health of neural tissue is thought to be due to structural brain changes and this adversely affects cognitive function (Breteler et al., 1994; Buckner, 2004; Raz et al., 2005). A key issue is the link between cognitive deficits with the aging brain and changes to the central nervous system. Advancement in the neuroimaging field contributes remarkably, allowing investigators to tap into the neural substrates of cognitive aging and further understand the relationship between age, brain and function.
Age-related white matter changes

There are diverse age-related neuroanatomical, neurophysiological, and neurochemical changes that remain incompletely understood as part of the aging process. Age-related white matter changes are prevalent among the elderly and there is concern due to its association with cognitive impairment and functional loss (Pantoni, 2010).

In view of this relationship, the cerebral white matter connects cortical and subcortical gray matter regions into coherent neural networks (Filley, 2012). Hence, they function as the network transmitters between areas of the brain that process information i.e. gray matter, enabling macroconnectivity within the brain (Filley, 2005, 2010). It is therefore understood that cerebral white matter plays a central role in interneuronal communication. When damage affects the normal myelin or axons as a result of aging, the neuronal signalling can still occur, but the speed of this process is greatly reduced. Given this, the integrity of the white matter tract is a crucial condition for normal functioning and an efficient neuronal network, in order to sustain effective cognitive functioning (Filley, 2012; Madden et al., 2012).

Previously, the cortical and subcortical gray matter nodes of these networks were frequently highlighted without much acknowledgement given to the white matter systems by which they are connected. Being treated as the ‘poor cousin’ in the past, it is now argued that myelinated tracts subserving information transfer via the macroconnectivity of white matter should be perceived in concert with the gray matter, by means of synaptic macroconnectivity (Filley, 2005, 2010).
With age, cerebral white matter accordingly presents age-related changes at the macrostructural and microstructural levels. The proliferation of white matter lesions (WMLs) is one of the areas that have recently prompted growing research interest. This is in part, due to growing radiologic findings on the incidence of hyperintense signals on T2 weighted imaging (MRI), which indicates macrostructural white matter changes within the aging brain. Etiologically considered as related to cerebral small vessel disease, evidence suggests that these hyperintense signals are regarded as important substrates for cognitive impairment (Pantoni, 2010; Goldberg & Ransom, 2003) and poor outcomes in the elderly (Inzitari et al., 2007).

This phenomenon is common in those with stroke (Kuller et al., 2004) and prevalence rate varies between 67% to 98% (Mantyla et al., 1999; Fu et al., 2005; Tang et al., 2004; Jimenez-Conde et al., 2010). Similarly, this finding is found among dementia patients (Bigler, Kerr, Victoroff, Tate, & Breitner, 2002) with estimated prevalence ranges from 28.9% to 100% (Aharon-Peretz, Cummings, & Hill, 1988; de Leeuw; Barkhof, & Scheltens, 2004; Targosz-Gajniak, Siuda, Ochudlo, & Opala, 2009). However, more concerning is that these hyperintensities not only affect the elderly with diseased states but are also associated with advancing age (Basile et al., 2006; de Leeuw et al., 2001; Henon, Godefroy, Lucas, Pruvo, & Leys, 1996; Jorgensen, Nakayama, Raaschou, & Olsen, 1995; Launer et al., 2005; Longstreth Jr. et al., 1996; Liao et al., 1997; Vermeer et al., 2003), and are not uncommon in asymptomatic-neurologically healthy older adults (Schmidt, Hayn, Fazekas, Kapeller, & Esterbauer, 1996). Prevalence rate in this population is relatively high reaching about 50% to 98% (Longstreth Jr. et al., 1996; Liao et a., 1996; de Leeuw et al.,
than age, it was linked to cerebral atrophy and other cerebrovascular risk factors (Xiong & Mok, 2011). Strong association was documented between hypertension and white matter damage (Liao et al. 1996), which potentially carries an increased risk of future stroke (Yamauchi et al., 2002; Wong et al., 2002).

Pathologically, these lesions were described as perivascular oligodendrocyte injury. The process was characterized by the initiation of demyelination, atrophic changes and often widening in perivascular spaces i.e. perivascular atrophic demyelination. These changes have had a long standing recognised association with arteriolar tortuosity and small penetrating artery arteriosclerosis, which was originally described by Binswanger in a pathological series (cited in Pantoni & Garcia, 1995).

Although previous findings suggest that overall volumes of WML among healthy elderly can be minimal and subtle (Boone et al., 1992; Kennedy & Raz, 2009), age- related microstructural damage is still apparent (Firbank, Minett, & O’Brien, 2003). Diffusion tensor imaging (DTI) is the most recent neuroimaging technique that further contributes to promising advancement in this field. This most current protocol has the ability to examine the integrity of white matter tracts beyond what can be appreciated by conventional Magnetic Resonance Imaging (MRI) (O’Sullivan et al., 2001; Van der Flier et al., 2002). The use of DTI techniques is sensitive to microstructural and biochemical changes of axons within the white matter. Such details are invisible to traditional T2- weighted imaging and this advancement therefore leads to additional insight into the pathophysiology of WML (Frisoni, Galluzzi,
The microstructural damage is characterised by poor organization of axonal fibres indicative of decline in white matter health (Pfefferbaum et al., 2000; Sullivan et al., 2001). The increasing precision to detect the location and integrity of specific tracts, therefore allows for better characterization of the efficiency of neural networks (Catani, 2006; Sullivan and Pfefferbaum, 2006).

Fundamentally, Diffusion Tensor Imaging (DTI) explains structural changes in tissue tracts by means of the water diffusion that allows us to infer fiber connection within the brain i.e. mapping the ‘brain wiring’. Given this, disruption in normal water flow can also be detected, yielding valuable information about the specificity of lesion locations (Basser & Pierpaoli, 1996).

This protocol thus, measures the mobility of water molecules responsible in shifting the magnitude and directional coherence of water molecule diffusion. The two main scalar metrics frequently used are mean diffusivity (MD) and fractional anisotropy (FA). The MD measures the magnitude of water diffusion, while the FA on the other hand, points to the direction of diffusion coherency (Basser & Pierpaoli, 1996). The MD and FA values thus, reflect the extent of microstructural changes in a negative direction i.e. as one value increases, the other value decreases with higher FA reflects greater efficiency in axonal organization and vice-versa (Le Bihan, 2003; Mori & Zhang, 2006).

In normal ageing, the MD tends to increase and FA decreases over time, suggestive of gradual microstructural decline in white matter coherency (Abe et al., 2002; Nusbaum et al., 2001; Pfefferbaum et al., 2000; Pfefferbaum & Sullivan, 2003; Rovaris et al., 2003; Salat et al., 2005; Wozniak & Lim, 2006).
More detailed measures in DTI are referred to as axial diffusivity (Ax) and radial diffusivity (RaD). The latter measures were less commonly found in previous research in comparison to FA and MD. However, existing evidence suggests that Ax is suggestive of axonal damage or loss (Budde, Xie, Cross, & Song, 2009; Song et al., 2003), while RaD is indicative of the extent of fibre myelination (Song, et al., 2005). This finding provide support that investigating Ax and RaD can be very informative in terms of understanding more precise microstructural values.

**Age-associated brain atrophy**

White matter lesions are also related to age-associated loss of brain volume- a relationship that parallels to losses on diverse parameters of cognitive performance among healthy elderly (Rabbitt & Mogapi, 2007). A longitudinal finding with 6-year follow-up suggests that the adverse effect of lesion progression on cognition could be explained by loss of brain volume that was linked to progressing lesion load (Schmidt et al., 2005). Other cross-sectional studies similarly found an association between WML volumes and global atrophy (Anders et al., 2009; Den Heijer et al., 2005; Mungas et al., 2002; De Leeuw, Barkhof, & Scheltens, 2004).

Generally, longitudinal findings demonstrated gross brain volume decreased between 0.2 to 0.5 per cent annually (Scahill et al., 2003; Ezekiel et al., 2004; Enzinger et al., 2005; Fotenos et al., 2005) which seemed to be higher than cross-sectional estimates (Scahill et al., 2003; Raz et al., 2005; Du et al., 2006). Being the most studied area according to Anders et al. (2009), hippocampus demonstrated annual atrophy rates ranging from 0.79 to 2.0 per
cent (Jack et al., 1998; Scahill et al., 2003; Ezekiel et al., 2004; Raz et al., 2005; Du et al., 2006; Barnes et al., 2009). Although atrophy rates in other parts of the brain are seldom studied (Anders et al., 2009), some important findings suggests that age-related atrophy differs across regions. With an average decline rate of between 0.9 to 1.5 per cent annually, the frontal lobes revealed the sharpest rate of atrophy (Pfefferbaum, Sullivan, Rosenbloom, Mathalon, & Lim, 1998; Raz et al., 2005; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003) and this frontal atrophy was associated with cognitive deficits mediated by frontal regions such as the executive functioning (e.g. Gunning-Dixon & Raz, 2003). The parietal lobes showed the second steepest decline in volume with an annual atrophy rate ranging from 0.34 to 0.90 per cent. In comparison, the occipital lobes revealed the least or non-significant age-related atrophy (Pfefferbaum et al., 1998; Raz, 2005; Resnick et al., 2003).

Moreover, it was also found that atrophy rates differ among subregions of each lobe. For instance, Rescnick et al. (2003) suggest evidence that within frontal and parietal cortex, more inferior subregions show the most remarkable rates of decline. Worse cognitive performances in specific domains are often found to be associated with smaller gray matter volumes in certain cerebral regions (Salat, Kaye, & Janowsky, 2002; Driscoll, Hamilton, Petropoulos, Yeo, Brooks, Baumgartner, Sutherland, 2003).

In the past, the gray matter cell loss i.e. cortical atrophy served as an explanation for decline in cognitive performance (Filley, 2012). Although this may still account for the deficits, accumulating microscopic evidence has found that a loss of brain white matter as a result of aging exceeds loss of cortical gray matter (e.g. Meier-Ruge et al., 1992; Double et al., 1996; Pakkenberg &
Gundersen, 1997; Tang et al., 1997; Turlejski & Djavadian, 2002). Discrepancy in these findings, may in part, reflect the mediating influence of white matter damage.

For instance, some studies included brain atrophy into predicting models and found the influence of white matter changes disappeared, while global and/or regional atrophy exerted greater effect upon cognitive impairment (Mungas et al., 2005; Mungas et al., 2002; Schmidt et al., 2005). Another study in community residents found that progression in age-related white matter changes predicted normal to mild cognitive impairment whereas global atrophy predicted a spectrum from mild cognitive impairment to dementia (Smith et al., 2008).

Overall, age-related cognitive dysfunction that does not meet the criteria for dementia is generally recognised, but the neurobiological basis for the mental alterations in healthy aging remains largely obscure. With findings suggesting that whole brain or cortical gray matter atrophy were related to severity of white matter changes (e.g. Mungas et al., 2005; Mungas et al., 2002; Schmidt et al., 2005), it is therefore relevant to include this measure as part of the overall investigation between age-related white matter changes and cognition. This also points to the relevance for investigation on how cognitive functions are associated with structural brain changes and the interplay between brain atrophy and white matter disruptions.

**Major cognitive domains: Executive function and Memory**

Growing neuroimaging evidence points to the decline in information-processing resources, such as working memory capacity, executive function,
attention regulation, and processing speed, as likely to occur in aging due to structural brain changes (Buckner, 2004; Raz et al., 2005).

Dysfunction in executive functioning is one of the most commonly documented age-related cognitive problems resulting from structural brain changes in both clinical and non-clinical samples (Buckner et al., 2004; Rabbitt et al., 2001). Structurally linked to the frontal brain area, executive function is a complex construct of cognitive processes. It involves a large range of higher order mental processes involved with individuals’ abilities to plan, organise, sustain attention, memorise, process information and self-regulate.

Episodic Memory is another cognitive function widely investigated in previous studies in relation to age-related deterioration. It is a form of narrative memory that taps into one’s ability to store and retrieve a series of events (verbally or visually). Although some findings suggest early onset of cognitive deficit affecting episodic memory predicts future Alzheimer’s disease (Backman, Small, & Fratiglioni, 2001), other studies document that a similar condition is also prevalent among healthy elderly (Gunstad et al., 2006; Hultsch, Hertzog, & Dixon, 1990; Schaie, 1996).

While episodic memory implicates mental capacity to store and retrieve information, working memory function involves more complicated constructs. It requires intact ability in auditory and/or visual memory; verbal/visual sequential processing; attention and rote learning; and involves more sophisticated higher order abilities to plan, manipulate and transform the stimulus input before responding. The latter memory function therefore requires greater mental effort and poorer performance in this ability has been
associated with age (Borella, Carretti, & De Beni, 2008; Charlton, Barrick, Lawes, Markus, & Morris, 2010; Zahr et al., 2009).

**White matter pathology and cognitive function**

Many studies have addressed the direct association between cognitive impairment and WMLs either linking the occurrence of WMLs burden with global cognition, specific cognitive domain, or both. As an example, the incidence of WMLs in non-demented healthy elderly was associated with decreased cognitive performance measured by a wide variety of cognitive functions (Breteler, Van Amerongen, & Van Swieten, 1994; de Leeuw et al., 2001; Hickie et al., 1995; Longstreth et al., 1996; Van Swieten et al., 1996; Ylikoski et al., 1995). However, some findings were able to tap into specific cognitive deficits, associating healthy aging with particular decline in executive function and memory (Buckner, 2004; Rabbitt, Diggle, Smith, Holland, & McKinnon, 2001).

Previous studies also found evidence that WMLs affected processing speed more than they affected other cognitive functions (e.g. de Groot et al., 2000; Junque et al., 1990; Ylikoski et al., 1993). In relation to other markers for diffuse neurophysiological changes, global age-associated loss of brain volume i.e. global atrophy, were correlated with WMLs. This association was also linked to poorer performance in different types of cognitive functions, with more prominent decline demonstrated in slowing of information processing (McLullich et al., 2002; Rabbitt et al., 2006). Thus far, extensive evidence points to dysfunction in cognitive impairment, mainly involving global cognition (Breteler et al., 1994; de Groot et al., 2002; Jacobs et al., 2012;
Longstreth Jr. et al., 1996; van der Flier et al., 2005; Wright et al., 2008); executive function (Breteler et al., 1994; Kramer et al., 2007; Longstreth et al., 2005; Longstreth Jr. et al., 1996; Mok et al., 2004; Prins et al., 2005); attention and mental processing speed (Junque et al., 1990; Ylikoski et al., 1993).

Similarly, progressive cognitive decline was found in both community and stroke patients (Debette & Markus, 2010). Moreover, baseline periventricular white matter changes in longitudinal studies were not only linked to decline in mental processing speed (van den Heuvel et al., 2006) but also an increased risk of dementia (Prins et al., 2004; Vermeer et al., 2003); functional decline (Inzitari et al., 2007); and even death (Briley, Haroon, Sergent, & Thomas, 2000; Inzitari, Cadelo, Marranci, Pracucci, & Pantoni, 1997).

However, inconsistent results exist. For example, in a study of a community sample Vannorsdall et al. (2009) found increase in WML was related to reduced visual memory, fluency, and crystallised intelligence, but participants had improved in executive function following a 5-year interval. While some findings suggest an increase in WML burden was linked to decline in episodic memory (Breteler et al., 1994; Vannorsdall et al., 2009) and working memory function (Charlton et al., 2010; Vannorsdall et al., 2009), data supporting these links are relatively scanty. Therefore, although there is an emerging consensus that white matter lesions are associated with neuropsychological impairment (e.g. Gunning-Dixon and Raz 2000, 2003), the results are, however, partly conflicting, and makes the interpretation of published data more complex.
Problems with Assessment of Cognitive Function

The relationship between cognitive deficits and the aging brain has been investigated in the past and the classical methodology established the association between specific domains of cognitive deficit with focal brain lesions. To some degree, this approach can be problematic because some findings characterise the changes in the healthy aging brain as global, varied and diffuse rather than local and specific in nature (Rabbitt et al., 2007).

This question remains unclear and deserves attention because greater understanding of the pathogenesis of neural changes in the healthy aging brain will further enhance our ability to correctly identify a sensitive measure for early detection of cognitive impairment. Especially with healthy elderly, the pattern of cognitive decline may be very subtle making them a vulnerable population for future risk of ‘unexpected’ impairment. The effort to establish an adequate protocol for early screening may contribute to preventative measures of future disability and has important management implications including strategic intervention to reverse, limit or delay disease onset such as dementia.

On the other hand, neuropsychological tests used for investigating the link between white matter lesions and cognition are an equally a crucial research component as they contribute to varying methodology in previous studies. Discrepancies involve the selection of test in terms of sensitivity, as well as the way these tests are categorised. Some studies used a combination of global and specific cognitive tests e.g. Mini Mental State Exam (MMSE) to measure general cognition; Word List Learning to assess memory; Stroop test, Trail Making Test and Verbal Fluency to evaluate executive function (Breteler et al., 1994); some chose only a couple of tests e.g. Stroop test and Trail
Making Test to represent executive function (Jacobs et al., 2012), while other studies utilised an extensive neuropsychological battery for a comprehensive cognitive assessment (e.g. Vannorsdall et al., 2009; Voineskos et al., 2012).

On a few occasions, the same test was used to assess distinct cognitive domains. For example, the Backward Digit Span subtest (in addition to the Letter-Number Sequencing sub-tests) of the Wechsler Memory Scale III (Wechsler et al., 1998) was used to measure working memory (Charlton et al., 2010); the Backward Digit Span subtest from the WAIS III (Wechsler, 1997) was used to measure executive functioning (Kramer et al., 2007); and more recently, the Digit Span subtest (test version not reported) was used for the assessment of attention (Voineskos et al., 2012). Digit Span not only measures auditory short-term memory, verbal sequential processing, attention and rote learning; the backward and sequencing mode in that subtest also taps into working memory and to some extent, executive functioning. Thus, selections made by the previous studies are not incorrect, but rather show us that it is difficult to match each subtest with a particular cognitive function. This is especially true for executive functioning, as these mental processes tend to overlap.

In contrast to specific cognitive measures, the Mini-Mental State Examination (MMSE) has been frequently reported for the assessment on global cognitive performance in WML studies (van der Flier et al., 2005). However, the sensitivity and applicability of this tool for the healthy elderly is questionable. Nasreddine and colleagues (2005) in a validation study found that the majority of individuals meeting clinical criteria for Mild Cognitive Impairment (MCI) scored above 26 on the MMSE, which categorised them...
within the range of normal elderly individuals. However, The Montreal Cognitive Assessment (MoCA) detected 90% of MCI subjects as opposed to the MMSE, which merely uncovered 18% of MCI cases within the same sample (Nasreddine et al., 2005). It is therefore evident that the MoCA provides greater sensitivity in detecting subtle cognitive dysfunction in comparison to the MMSE. This may in turn, suggest that global cognitive burden associated with white matter damage in the previous studies could be underestimated. Thus, the MoCA is another brief cognitive screening tool recommended to assess global cognitive impairment, and seems to be more appropriate for this population of interest.

Another measure recommended as a sensitive instrument for white matter pathology is the Frontal Assessment Battery (FAB; Dubois et al., 2000), scores on which have been found to correlate with DTI measures of microstructural white matter involvement in patients with normal pressure hydrocephalus (Kanno et al., 2011). Another alternate tool is the Clock Drawing Test (CDT) where poor performance has been linked to periventricular white matter hyperintensities in dementia patients (Kim et al., 2009). Having said that, The MoCA (Nasreddine et al., 2005) outweighed the two instruments mentioned above as it combines advantages of both the FAB and CDT. The MoCA regarded as more comprehensive and convenient as it enables the testing of memory retrieval; and incorporates executive function and clock drawing tasks into a 30-point format (Filley, 2012). Another study conducted on elderly with leukoaraiosis using a 3.0-T DTI, used both MMSE and the MoCA to measure execution functioning. Upon conclusion, the MoCA was found to detect executive dysfunction in association to microstructural
white matter changes, whereas the MMSE showed normal cognition in the same sample (Griebe et al., 2011).

Moreover, the superiority of the MoCA over other global measures such as the MMSE has been documented in several studies, such as patients with subcortical dementia in Parkinson’s disease (Gill et al., 2008); Huntington’s disease (Videnovic et al., 2010); and small vessel disease (Wong et al., 2009). Although this tool seems more appropriate for assessing global cognitive function in relation to white matter pathology in healthy elderly, evidence is still lacking.

Problems with Assessment of WMLs

Part of the discrepancy in previous findings could stem from wide methodological differences and heterogeneity of the studies. Other than issues pertaining to neuropsychological assessment as mentioned above, methodological differences may include, but are not limited to, sample size, disparities in the level of sensitivities of the assessment of WML and imaging types (Pantoni, Poggesi and Inzitari, 2007; Xiong & Mok, 2011).

Because the occurrence of white matter changes in healthy elderly may be subtle in nature and vary minimally among this population (Boone et al., 1992; Kennedy & Raz, 2009), the choice of appropriate techniques and highly sensitive measures are crucial to adequately detect any changes. With the previous studies, the method of assessment and classification of WMLs varies between protocols with approximately half using visual ratings and the other half using volume measurement approaches.
Especially in earlier research, the visual rating scales were the most common approach used to quantify the extent and/or severity of WMLs in order to investigate the significance of relationship between white matter lesions and cognition. For instance, The Fazekas scale (Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987) assesses periventricular and subcortical WMH on a 4-point scale. The Scheltens scale (Scheltens et al., 1993) on the other hand, quantifies periventricular WMH on a 10-point scale and subcortical WMH on a 25-point scale.

Although such scales generate ordinal-level data at best and are complemented by variable inter- and intra-rater reliability, this approach however, is insensitive to subtle differences in WML profiles due to ambiguous terminology, and inconsistent analyses of lesion size and quantity, location and configuration (Bigler et al., 2002; Garrett et al., 2004; Pantoni & Gracia, 1995; Wardlaw, Ferguson, & Graham, 2004). When an automated volumetric estimate was compared with visual ratings of WMH, Van Straaten and colleagues (2006) found that brains calculated with the highest ratings of WMH severity revealed greater degree of variability in WMH load than those with lower ratings. The outcome is therefore problematic, given those with more severe WML burden are also more inclined to exhibit the worst cognitive function. Similarly, this suggests visual rating scales might obscure variability that is vital in tracing WMH-related cognitive impairment, specifically for individuals who are most likely to exhibit them (Vannorsdall et al., 2009).

More recently, volumetric approaches have become more prevalent as a means to quantify WMLs severity, computed as a proportion of total brain volume (e.g. Venkatraman et al., 2010; Paul et al., 2005; Van der Flier et al.,
2005). Nevertheless, while volumetric approaches are more sensitive when compared to prior techniques, there is substantial variability between procedures (Vannorsdall et al. 2009) and no validation has been generated against volumes derived from manual tracing (e.g. Van Straaten et al., 2006).

For instance, some studies assessed WML volumes with manual selection while some used semi-automated computerised techniques (Zijdenbos, Dawant, Margolin, & Palmer, 1994). Both techniques were rather time consuming, involving detailed selection of the hyperintense images on the T2-weighted MRI, which were then calculated as a total volume of WML. Although, the semi-automated computerised techniques utilised computer-based algorithms to detect the hyperintense areas, manual review still need to be performed in order to finalise the outcome (Payne et al., 2002). However, the latter techniques i.e. the semi-automated computerised techniques are more sensitive and demonstrated a more superior intra- and inter observer agreement in the quantification of WML as compared to the manual selection, and even better for visual rating techniques (Payne et al., 2002). Despite this fact, the visual rating scales seemed to be more widely applied by the previous studies, which imply that the incidence of WML burden assessed could be underrated. As such, the link between age-related cognitive deficit and WML burden are less apparent.

Similarly, while the usefulness of the data based on the quantification of total brain volume is acknowledged as they provide the estimate of WML burden at a global level, it also has resulted in discrepancies in terms of finding specific cognitive decline in different areas affected by WML. This therefore suggests that both visual rating scales and volumetric techniques are insensitive
to functional specificity of the affected cerebral white matter (Pantoni et al., 2007).

In contrast, Diffusion Tensor Imaging (DTI) has the most promise in providing more detailed views of white matter and this leads to a more accurate clinical- neuropathologic correlation. The increasing precision with which it detects the location and integrity of specific tracts, allows their participation in distributed neural networks to be better characterised, and a wide range of normal and abnormal states to be more comprehensively elaborated (Catani, 2006; Sullivan and Pfefferbaum, 2006). However, previous studies also used a different selection of diffusion measures and this methodological difference, again, contributes to inconsistent outcomes in the association between WML burden and cognition. For instance, a recent cross-sectional finding revealed that poorer global cognition was associated with reduced in FA and increased in diffusivity measures encapsulating the MD, Ax and RaD (Penke et al., 2010; van Norden et al., 2012). Studies investigating specific cognitive domains found decline in executive functioning to be linked with higher MD, RaD and Ax and lower FA values (Voineskos et al., 2012; Borghesani et al., 2013; Kennedy & Raz, 2009). Another study that only utilised global diffusion measures i.e. FA and MD, found the association between reduction in FA and proliferation of MD were linked to deficit in episodic and working memory (Kennedy & Raz, 2009; Zahr et al., 2009).

Thus far, earlier studies applying DTI-based measures in quantifying the extent of white matter disruption in relation to cognition, mainly utilised the general measure of diffusion i.e. FA and MD, whereas the use of more specific measures including the RaD and Ax were documented only in more recent
studies. On one hand, this trend could be inspired by the previous approaches that focus at WML burden at a global level with the use of volumetric measures. Alternatively, the four main DTI-based measures i.e. FA; MD; RaD and Ax are highly correlated to one another (Borghesani et al., 2013), with low level of FA tending to be negatively associated with higher values in MD, RaD and Ax. Thus, the selection of general measures might be considered as representative of other diffusion values.

However, in light of studies investigating age-related white matter microstructural damage, the selection measures restricted only to the FA and MD are possibly inadequate. This is because, measurement of MD reflects the extent of overall diffusivity regardless of its direction. Therefore, specific microstructural values provided separately by measuring RaD and Ax will be missed. Previous findings suggest that RaD is indicative of demyelination (Song et al., 2003; Song et al., 2005) and is prevalent with age and healthy elderly (Bennett, Madden, Vaidya, Howard, & Howard, 2010), whereas the measure on Ax is suggestive of axonal damage or degeneration (Budde, Xie, Cross, & Song, 2009; Song et al., 2003). The RaD measure thus, will be the most representative of the extent of microstructural damage experienced by elderly with WML burden among other diffusion metrics. Combining the RaD with FA would be most appropriate as the FA yield the property of anisotropic diffusion within a region of interest (ROI). Although the data on these measures are still limited, as a new advancement in measurement techniques within this field, existing data are insightful and pointing to a better direction. This then speaks for the importance of future research to improvise or improve the measurement techniques as part of overcoming other methodological issues.
Overall, white matter changes are common in elderly and cannot be regarded as incidental findings as higher lesion burden has been linked to future impairment and pathology. Early detection of cognitive dysfunction is crucial as it can be more sensitive to subtle changes, in comparison to physical symptoms that may only become apparent at more severe disease state. For this reason, the present study was designed to re-examine this relationship, with the use of volumetric and DTI-based measures (inclusive of FA, MD, RaD and Ax) that are thought to be more sensitive to subtle white matter pathology.

The Present Study

The present study is a small part of a larger research project by a PhD candidate (Jolly et al. in progress), which also involves other Honours students from the University of Newcastle. This project is also conducted in collaboration with The Centre for Translational Neuroscience and Mental Health Research and The Hunter Medical Research Institute (HMRI) in terms of research funding and professional inputs.

This study therefore, uses the same methodological approach utilised by Jolly et al. (in preparation) with the same sample of participants. As part of a wider methodological umbrella, the present study was tailored into a particular direction in order to investigate specific areas not addressed by other parts of the bigger study. The general aim of the present study was to investigate the relationship between structural brain changes and cognitive function, within relatively healthy elderly in a cross-sectional cohort. This study was conducted with seventy participants aged between 43 to 82 years.
As part of the study methodology, since the DTI can quantify microstructural changes and therefore is more sensitive to subtle white matter pathology, we utilised DTI-based measures (inclusive of FA, MD, RaD and Ax values) for this purpose. We also adapted the volumetric measures for white matter pathology in addition to DTI to compare for sensitivity. On the other hand, volumetric measures were also used in the assessment of age-related brain volume loss (accounting for the gray and white matter atrophy). This latter measure hence, served as a means to perceive structural brain changes from a wider perspective, in addition to white matter pathology. In terms of neuropsychological assessment, we selected The Montreal Cognitive Assessment (MoCA) and a general measure of full-scale IQ (FSIQ) from the Wechsler Abbreviated Scale of Intelligence (WASI) to assess global function and intellectual capacity. We further selected twelve specific cognitive tests, four of which were representative of executive function, working memory, and episodic memory domains.

In particular, we will be focusing on four main research questions. Firstly, we will determine how age-related structural brain changes at the macrostructural and microstructural levels correlates with cognitive function among reasonably healthy elderly. Secondly, we will further explore the possible link between white matter damage and cognition in healthy elderly, and examine whether this relationship is also influenced by age-associated loss of brain volume i.e. brain atrophy. Thirdly, we want to examine the usefulness of a global cognitive assessment as opposed to specific neuropsychological tests tapping into executive functioning, episodic and working memory.
Finally, we want to compare age, brain atrophy and the MoCA as predictors of WML.

Thus, on the basis of the previous literature, we expect that the structural brain changes at both the macrostructural and microstructural levels will be associated with age, by which brain atrophy and white matter pathology will increase with age and cognitive performance will decrease. With this, we hypothesised that (1) the FA value will decrease; and MD, RaD, Ax values, brain atrophy, WML load will increase with age, and performance on global and specific cognitive functions will decrease. Similarly, we hypothesised that (2) brain atrophy will be associated with age and influence the relationship between cognition and white matter pathology at least to some extent. Furthermore, assuming that cognitive impairment in healthy elderly can be very subtle, varied and diffuse in nature, we expect that (3) the global cognitive measure i.e. The MoCA will be more sensitive in detecting cognitive dysfunction in comparison to specific cognitive subtests tapping into executive function, working memory, and episodic memory domains.
PART 2

MANUSCRIPT

The Montreal Cognitive Assessment (MoCA) is associated with early stage age-related macrostructural and microstructural white matter changes and a strong predictor of radial diffusivity.

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Abstract

Cognitive deterioration is generally thought to be due to structural brain changes as part of the aging process. In this study, we examined the relationship between macrostructural and microstructural white matter changes, brain atrophy and cognitive function. The MoCA was used to determine the level of sensitivity of a global cognitive measure in comparison to specific neuropsychological tests tapping into working memory, episodic memory and executive functioning, in detecting subtle cognitive dysfunction in white matter pathology. The volumetric measures were utilised to account for brain macrostructural changes, while the Diffusion Tensor Imaging (DTI)-based measures were used to examine microstructural properties of white matter disruptions among seventy reasonably healthy elderly. Upon analyses, the MoCA has captured variation associated with brain volumes and DTI-based changes, not fully accounted by specific cognitive subtests administered in this study. Even after adjusting for age, FSIQ, and brain atrophy separately, the independent association between the MoCA and radial diffusivity remained stable. Furthermore, a hierarchical multiple regression analysis revealed that the MoCA was the strongest predictor of radial diffusivity ($R^2 = .476, p<.01$) even after controlling for age ($R^2 = .392, p<.01$), while cerebral atrophy was not a significant predictor. Interestingly, the MoCA is a brief, yet powerful tool that even accounts for global cognitive dysfunction for which white matter pathology and brain atrophy are not sensitive markers. In short, white matter macrostructural and microstructural changes are associated with cognitive aging, characterised as subtle, varied and diffuse in nature. The MoCA is a sensitive screening tool for cognitive dysfunction at the early stage of white matter disease. Thus, we highly recommend this brief, easily accessible tool for frontline clinicians to incorporate into their investigation protocol.

Key Words: white matter lesions, diffusion tensor, cognitive functioning, white matter changes, age-related loss of brain volumes, cognitive dysfunction
1. Introduction

Cognitive deterioration is prevalent with age, and even healthy elderly are not totally exempted from this natural course. There is concern due to age-associated functional loss and increased risk for future pathology. The relationship between cognitive deficits and changes to the ageing brain has been investigated in the past and thought to be due to structural brain changes. This decline in health of neural tissue adversely affects cognitive functions (Breteler et al., 1994; Buckner, 2004; Raz et al., 2005).

Advancement in the neuroimaging field contributes remarkably, allowing investigators to tap into the neural substrates of cognitive aging and further understand the relationship between age, brain and function. The incidence of hyperintense signals on T2 weighted imaging (MRI) is a common radiological finding, which indicates macrostructural white matter changes within the aging brain. Etiologically considered as related to cerebral small vessel disease, evidence suggests that these hyperintense signals are regarded as important substrates for cognitive impairment (Pantoni, 2010; Goldberg & Ransom, 2003) and poor outcomes in the elderly (Inzitari et al., 2007).

This phenomenon is common in those with stroke (Kuller et al., 2004) and prevalence rate varies between 67% to 98% (Mantyla et al., 1999; Fu et al., 2005; Tang et al., 2004; Jimenez-Conde et al., 2010). Similarly, this finding is found among dementia patients (Bigler, Kerr, Victoroff, Tate, & Breitner, 2002) with estimated prevalence ranges from 28.9% to 100% (Aharon-Peretz, Cummings, & Hill, 1988; de Leeuw; Barkhof, & Scheltens, 2004; Targosz-Gajniak, Siuda, Ochudlo, & Opala, 2009). However, these hyperintensities, not only affect the elderly with diseased states, they are also associated with
advancing age (Basile et al., 2006; de Leeuw et al., 2001; Henon, Godefroy, Lucas, Pruvo, & Leys, 1996; Jorgensen, Nakayama, Raaschou, & Olsen, 1995; Launer et al., 2005; Longstreth Jr. et al., 1996; Liao et al., 1997; Vermeer et al., 2003), and are not uncommon in asymptomatic- neurologically healthy older adults (Schmidt, Hayn, Fazekas, Kapeller, & Esterbauer, 1996). Prevalence rate in this population is relatively high reaching about 50% to 98% (Longstreth Jr. et al., 1996; Liao et a., 1996; de Leeuw et al., 2001; Wen, Sachdev, Li, Chen, & Anstey, 2009; Launer et al., 2005). Other than age, strong association between hypertension and white matter damage was found (Liao et al. 1996) which potentially carry an increased risk of future stroke (Yamauchi et al., 2002; Wong et al., 2002).

Moreover, cerebral white matter not only presents age-related macrostructural changes, the use of Diffusion Tensor Imaging (DTI) found that brain alteration also occurring at the microstructural level. Although previous findings suggest that overall volumes of white matter lesion (WML) among healthy elderly can be minimal and subtle (Boone et al., 1992; Kennedy & Raz, 2009), these age-related damage are still apparent (Firbank, Minett, & O’Brien, 2003). The microstructural damage is characterised by poor organization of axonal fibres indicative of decline in white matter health (Pfefferbaum et al., 2000; Sullivan et al., 2001).

Fundamentally, the DTI technique explains structural changes in tissue tracts by means of the water diffusion that allows us to infer fibers connection within the brain i.e. mapping the ‘brain wiring’. Given this, disruption in normal water flow can also be detected, yielding valuable information about the specificity of lesions location (Basser & Pierpaoli, 1996). This protocol allows
us to measure the mobility of water molecules responsible in shifting the magnitude and directional coherence of water molecule diffusion. The main two scalar metrics frequently used are mean diffusivity (MD) and fractional anisotropy (FA). The MD measures the magnitude of water diffusion, while the FA on the other hand, points to the direction of diffusion coherency (Basser & Pierpaoli, 1996). The MD and FA values thus reflect the extent of microstructural changes in a negative direction i.e. as one value increases, the other value decreases with higher FA reflecting greater efficiency in axonal organization and vice-versa (Le Bihan, 2003; Mori & Zhang, 2006).

In normal ageing, the MD tends to increase and FA decreases over time, suggestive of gradual microstructural decline in white matter coherency (Abe et al., 2002; Nusbaum et al., 2001; Pfefferbaum et al., 2000; Pfefferbaum & Sullivan, 2003; Rovaris et al., 2003; Salat et al., 2005; Wozniak & Lim, 2006). More precise microstructural values in DTI, which can be very informative, are referred to as axial diffusivity (Ax) and radial diffusivity (RaD). While less commonly found in previous findings in comparison to FA and MD, animal research has demonstrated that Ax is suggestive of axonal damage or loss (Budde, Xie, Cross, & Song, 2009; Song et al., 2003) and RaD is indicative of the extent of fibre myelination (Song, et al., 2005).

On the other hand, cerebral white matter changes are also related to age-associated loss of brain volume- a relationship that parallels the loss on diverse parameters of cognitive performance among healthy elderly (Rabbitt & Mogapi, 2007). A longitudinal finding with 6-year follow-up suggests that the adverse effect of lesion progression on cognition could be explained by loss of brain volume that was linked to progressing lesion load (Schmidt et al., 2005).
Other cross-sectional studies similarly found an association between WML load and global atrophy (Den Heijer et al., 2005; Mungas et al., 2002; De Leeuw, Barkhof, & Scheltens, 2004). Hence, cerebral white matter changes that are common in elderly are not benign, with more lesion burden associated with a host of poor clinical outcomes (Xiong & Mok, 2011).

In order to establish age-related cognitive changes, the classical methodology involving cognitive testing was done by establishing the association between specific domains of cognitive deficit with focal brain lesions. To some degree, this approach can be problematic because some characterise the changes in the healthy aging brain as global, varied and diffuse rather than local and specific in nature (Rabbitt et al., 2007). As an example, the incidence of white matter lesion in non-demented healthy elderly were associated with decrease in cognitive performance measuring a wide variety of cognitive functions (Breteler, Van Amerongen, & Van Swieten, 1994; de Leeuw et al., 2001; Hickie et al., 1995; Longstreth et al., 1996; Van Swieten et al., 1996; Ylikoski et al., 1995). However, inconsistent findings exist, with some evidence linking white matter lesion with specific cognitive deficits with particular dysfunction in executive function and memory (Buckner, 2004; Rabbitt, Diggle, Smith, Holland, & Mc Innes, 2001), and slowing of information processing speed (e.g. Groot et al., 2000; Junque et al., 1990; Ylikoski et al., 1993). In relation to other markers for diffuse neurophysiological changes, global age-associated loss of brain volume, i.e. global atrophy was also linked to poorer performance in different types of cognitive functions, with more prominent impairment demonstrated in slowing of information processing (McLullich et al., 2002; Rabbitt et al., 2006). It is
therefore unclear whether decrease performance in cognitive function among elderly exhibiting white matter changes, is global and diffuse or local and specific in nature.

This question deserves valid attention because greater understanding of the pathogenesis of neural changes in the healthy ageing brain will further enhance our ability to correctly identify a sensitive measure for early detection of cognitive impairment. Especially with neurologically asymptomatic elderly, the pattern of cognitive dysfunction may be very subtle making them a vulnerable population for future risks of ‘unexpected’ impairment. The effort to establish adequate protocol for early screening may contribute to preventative measure of future disability, and has important management implications including strategic intervention to reverse, limit or delay disease onset such as dementia.

Neuropsychological tests used for investigating the link between white matter pathology and cognition is an important research component as it contributes to wide methodological variance in previous studies. Discrepancies seemed to linger around the selection of test in terms of sensitivity, as well as the way these tests are categorised. While some used a combination of global and specific cognitive tests e.g. Mini Mental State Exam (MMSE) to measure general cognition; Word List Learning to assess memory; Stroop test, Trail Making Test and Verbal Fluency to evaluate executive function (Breteler et al., 1994); some chose only a couple of subtests e.g. Stroop test and Trail Making Test to represent executive function (Jacobs et al., 2012), while other studies utilised an extensive neuropsychological battery for a comprehensive cognitive assessment (e.g. Vannorsdall et al., 2009; Voineskos et al., 2012).
On a few occasions, the same test was used to assess distinct cognitive domains. For example, the Backward Digit Span subtest (in addition to the Letter-Number Sequencing sub-tests) of the Wechsler Memory Scale III (Wechsler et al., 1998) was used to measure working memory (Charlton et al., 2010); the Backward Digit Span subtest from the WAIS III (Wechsler, 1997) was used to measure executive functioning (Kramer et al., 2007); and more recently, the Digit Span subtest (test version not reported) was used for the assessment of attention (Voineskos et al., 2012). The fact that the Digit Span test not only measures auditory short-term memory, verbal sequential processing, attention and rote learning; the backward and sequencing mode in that subtest also taps into working memory and to some extent, executive functioning. Thus, selections made by the previous studies are not incorrect, but rather show us the fact that it is difficult to tailor each subtest for a particular cognitive function. This is especially true for executive functioning, as these mental processes tend to overlap, and some subtests are tapping into these cognitive sub-processes.

In contrast to specific cognitive measures, the Mini-Mental State Examination (MMSE) has been frequently reported for the assessment of global cognitive performance in WML studies (van der Flier et al., 2005). However, the sensitivity and applicability of this tool remains questionable. Nasreddine and colleagues (2005) in a validation study found that the majority of individuals meeting clinical criteria for Mild Cognitive Impairment (MCI) scored above 26 on the MMSE, which categorised them within the range of normal elderly individuals. In particular, the MoCA detected 90% of MCI subjects as opposed to the MMSE, which merely detected 18% of MCI cases
within the same sample (Nasreddine et al., 2005). It was therefore evident that the MoCA provides greater sensitivity and specificity in detecting subtle cognitive dysfunction in comparison to the MMSE (Nasreddine et al., 2005). This may in turn, suggest that global cognitive burden associated with white matter damage in the previous studies could be underestimated.

Moreover, the superiority of the MoCA over other global measures such as the MMSE has been documented in several studies, such as patients with subcortical dementia in Parkinson’s disease (Gill et al., 2008); Huntington’s disease (Videnovic et al., 2010); and small vessel disease (Wong et al., 2009). Although this tool seemed more appropriate for assessing global cognitive function in relation to white matter pathology in healthy elderly, evidence is still lacking.

Overall, white matter changes are common in elderly and cannot be regarded as incidental finding as higher lesion burden was linked to a multitude of future impairment and pathology. Early detection of cognitive dysfunction is crucial as it can be more sensitive to subtle changes, in comparison to physical symptoms that may only become apparent at more severe disease state. Although there is an emerging consensus between WML and cognition, the results are, partly conflicting that makes the interpretation of published data more complex. Part of the discrepancy could stem from wide methodological differences and heterogeneity of the studies. This may include but is not limited to sample size, disparities in the level of sensitivities and depth of the assessment of WML, imaging types, setting, and choice of cognitive tests (Pantoni, Poggesi, & Inzitari, 2007; Xiong & Mok, 2011).
For this reason, the present study was designed to re-examine this relationship, with the use of volumetric and DTI-based measures (inclusive of FA, MD, RaD and Ax) that are thought to be more sensitive to subtle white matter pathology. On the other hand, volumetric measures were also used in the assessment of gray and white matter brain atrophy, in addition to white matter pathology. This approach provide a more detailed assessment of white matter changes and the addition of volumetric measures served as a means to perceive structural brain changes from a more comprehensive picture, albeit not entirely.

Firstly, we sought to determine how age-related structural brain changes at the macrostructural and microstructural levels correlate with cognitive function among a cohort of reasonably healthy elderly. Secondly, we further explored the possible link between white matter damage with cognitive dysfunction and examined whether this relationship was also influenced by age-associated loss of brain volume i.e. brain atrophy. Thirdly, using the MoCA, we examined the level of sensitivity of a global cognitive measure as opposed to specific neuropsychological tests tapping into working memory, episodic memory and executive functioning. Finally, we want to compare age, brain atrophy and the MoCA as predictors of WML.

Thus, on the basis of the previous literature, we expected that the structural brain changes at both the macrostructural and microstructural levels will be associated with age, by which brain atrophy and white matter pathology will increase with age and cognitive performance will decrease. More specifically, we predicted that the FA value will decrease; and MD, RaD, Ax values, brain atrophy, WML load will increase with age, and performance on global and specific cognitive functions will decrease. Similarly, we expected
brain atrophy to be associated with age and influence the relationship between cognition and white matter pathology at least to some extent. Furthermore, assuming that cognitive dysfunction in healthy elderly can be very subtle, varied and diffuse in nature, we anticipated the global cognitive measure i.e. the MoCA will be more sensitive in detecting cognitive dysfunction in comparison to specific cognitive subtests tapping into executive function, working memory, and episodic memory domains.

2.0. Materials and Methods

2.1. Subjects

70 participants aged between 43 to 82 years participated for this study. 35 participants were neurologically healthy individuals recruited from Hunter Medical Research Institute (HMRI) Volunteer Register. Another 35 participants recruited from a neurovascular clinic – referred by two neurologists (CL, MP) were cerebrovascular patients who showed white matter abnormalities in their radiologic assessment. Out of 70 participants, three subjects were excluded. One male subject did not complete the MoCA test and later withdrew from the entire study. Another 2 subjects (a male and a female) scored 18 or below on the MoCA, which is indicative of probable dementia (Nasreddine et al., 2005). The final participants therefore consisted of 67 subjects (male: n= 35; female: n= 32) (see Table 1).

Ethics approval was granted by The Hunter New England (HNE) Human Research Ethics Committee (Ref: 10/03/17/5.04) and written informed consent for the study was obtained from all participants. This study is a small part of a larger project where the same participants underwent other types of
cognitive assessments including cognitive control and task switching, as well as assessment related to structural and functional neuroimaging studies. Another study has been published (e.g. Jolly et al., 2013) but those data are not included in this paper.

The cognitive assessment was administered in the Neuropsychology lab at the University of Newcastle, while the imaging acquisition was administered at the Radiology Department, John Hunter Hospital in two separate occasions. All participants underwent cognitive assessment protocol inclusive of other cognitive variables (not addressed by the present study) as part of the larger project. Because of the location and the cognitive assessment battery itself required more than two hours of involvement by the participants, the imaging acquisition was administered on a different occasion depending on the lab and participant’s availability. Some participants were able to make it within the same week, while some may had two to four weeks time interval. The author and a PhD student were involved in performing the cognitive assessment. The author then analysed all the results for the neuropsychological variables included in the present study. On the other hand, the PhD student completed training on the neuroimaging protocols and conducted all neuroimaging analyses.
Table 1: Mean (standard deviation) for age, Full scale IQ, Montreal Cognitive Assessment (MoCA), Cerebral atrophy, Leukoaraiosis severity (LA), Lesion percentage of white matter, mean fractional anisotrophy (FA), and radial diffusivity (RaD) of participants.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
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<tbody>
<tr>
<td>Age</td>
<td>66.70</td>
<td>9.35</td>
</tr>
<tr>
<td>FSIQ</td>
<td>112.30</td>
<td>14.46</td>
</tr>
<tr>
<td>MoCA</td>
<td>26.21</td>
<td>2.76</td>
</tr>
<tr>
<td>Cerebral Atrophy</td>
<td>0.737</td>
<td>0.047</td>
</tr>
<tr>
<td>LA (% of ICV)</td>
<td>0.481</td>
<td>0.779</td>
</tr>
<tr>
<td>Lesion % of white matter</td>
<td>0.016</td>
<td>0.026</td>
</tr>
<tr>
<td>FA</td>
<td>0.395</td>
<td>0.018</td>
</tr>
<tr>
<td>RaD</td>
<td>0.457</td>
<td>0.029</td>
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</tbody>
</table>

2.2. Cognitive Assessments

2.2.1. Global cognitive assessment

The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) was chosen as the instrument to measure global cognitive dysfunction (see Appendix D). Although it is brief, this tool covers major cognitive domains including short-term memory, visuospatial abilities, executive functioning, attention and working memory, language, and orientation to time and place. The test-retest reliability was 0.92, with good internal consistency i.e. Cronbach alpha on the standardised item of 0.83. Additionally, the MoCA possessed excellent positive and negative predictive values for Mild Cognitive Impairment (MCI) i.e. 89% and 91% respectively, and 89% and 100% respectively for mild AD (Nasreddine et al., 2005). This test can be administered in 10 minutes, with only one test page that comprises a total maximum score of 30. This test was administered to all participants.
2.2.2. Assessment of Intellectual Functioning: The Wechsler Abbreviated Scale of Intelligence™ (WASI™)

This abbreviated Intelligence test comprised of four subtests namely Vocabulary, Similarities, Block Design and Matrix Reasoning. The battery yielded Full-scale IQ (FSIQ), Verbal IQ (VIQ) and Performance IQ (PIQ). This test took approximately 30 to 40 minutes to be administered. For the purposes of this paper, we only used the measure of participants’ FSIQ as an estimate of their intellectual functioning.

2.2.3. Assessment of Working Memory

2.2.3.1. Digit Span (Wechsler Adult Intelligence Scale- WAIS®-IV)

In The Wechsler Adult Intelligence Scale- WAIS®-IV, we used the Digit Span subtests (forward, backward and sequencing modes) to measure working memory. As the name suggests, each subtype differs in terms of the order these numbers are to be verbally recalled by the participant. A sequence of numbers was read to the participant who then recalled the number either in forward, backward or ascending order based on the test subtype. Apart from the test score for each mode, the number i.e. length of longest correct recall on the last passed trial were used in the outcome measures, referred as the Longest Digit Span Forward; Longest Digit Span Backward and Longest Digit Span Sequence. The length of the correct recall scores for each mode will be used for further analyses.
2.2.3.2. Spatial Span (The Cambridge Neuropsychological Test Automated Battery- CANTAB)

The Spatial Span (SSP) subtest assesses participants’ ability to recall multiple units of spatial information. The test is also known as a computerized version of the Corsi Blocks task, where a pattern of white boxes was displayed on a touch screen. The test consists of a clinical mode and the reverse mode. For the clinical mode, some of the presented boxes then changed in colour, one by one, in a variable sequence. As the sequence ended, a tone sounded as a signal for the participant to touch each of the boxes coloured by the computer following the same order of the original display. The presentation of the reverse mode was similar but on this occasion, following the tone, participants were instructed to touch each of the boxes coloured by the computer in the reverse order from the order of its original presentation. In both modes, the number of displayed boxes in the sequence progressively increased starting from 2 boxes at the beginning up to 9 boxes on the final level. This test was administered to assess participants’ visual working memory capacity.

2.2.4. Assessment of Episodic Memory

2.2.4.1. Pattern Recognition Memory (The Cambridge Neuropsychological Test Automated Battery- CANTAB, 2004)

The Pattern Recognition Memory (PRM) subtest is characterised as a test of visual pattern recognition memory using a 2-choice forced discrimination paradigm, which is sensitive to dysfunction in medial temporal areas. Also using the computer-based touch screen, the participants were presented with series of 12 visuals patterns, one at a time. Participants were
required to choose between a pattern they had already seen and a new pattern. Every pattern was designed in a way that verbal association was difficult to be formed by the participant. This test comprised of the immediate and delayed modes, administered 20 minutes after the initial presentation.

2.2.4.2. Logical Memory subtest [Wechsler Memory Scale-IV (WMS-IV)]

The Logical Memory subtest from the Wechsler Memory Scale-IV measured the participants’ abilities on immediate and delayed recall (Logical Memory I, II) and delayed recognition (LM Recognition). The Anna Thompson story of Logical Memory I and II was used as it could be administered to all age groups. The story was read to the participants and they were required to recall the story immediately after the presentation, by which a word-for-word recall was encouraged. The delayed recall was administered 30 minutes later.

2.2.5. Assessment of Executive Function

2.2.5.1. Intra/Extradimensional Set Shift (IED) (The Cambridge Neuropsychological Test Automated Battery- CANTAB, 2004)

This subtest is a measure of rule acquisition and reversal. It therefore taps into individuals’ ability in visual discrimination and attentional set formation. It also measures the maintenance, shifting and flexibility of attention. This subtest produced various outcome measures, which were highly correlated to one another. We therefore selected the least correlated outcomes and these are the IED Stages completed and IED Total Errors Adjusted. The first measure reflects the total number of stages the subject completed.
successfully. Maximum number of stages is 9. The latter measure the participants’ efficiency in attempting the test. To note, whilst a subject may succeed in all 9 stages, a substantial number of errors may be made in doing so. Thus, participants failing at any stage of the test by definition will be less likely to make errors. Based on this, the CANTAB adjusted the score by 25 for each unattempted stage due to failure. Because participants must complete 50 trials to fail a stage, it is assumed that half of these i.e. 25 could be correct by chance alone.

2.2.5.2. Stockings of Cambridge (SOC) (The Cambridge Neuropsychological Test Automated Battery- CANTAB, 2004)

This subtest assesses spatial planning and spatial working memory, which reflect frontal lobe function. This test utilise a touch screen device in which the subject will be shown two displays containing three coloured balls. Participants will be instructed to use the balls in the lower display to copy the pattern shown in the upper display. As the tasks gets more challenging when the level increases, time and number of moves will provide a measure of participant’s planning ability. This subtest also produced various outcome measures, which were highly correlated to one another. We therefore selected the least correlated outcomes and these are the SOC Problems solved in minimum moves (SOC problems solved) and SOC mean moves for 4 and 5 moves (SOC mean moves). The first is a fundamental measure, by which it records the number of occasions the subject has successfully completed a test problem in the minimum possible number of moves i.e. overall planning accuracy. The latter measure shows the mean number of moves required by the
subject to solve the problem i.e. the solution can be reached in a minimum number of moves (4 or 5).

2.3. Assessment of White Matter Lesions (WMLs)

The protocols for assessing WMLs used for this study were published in a separate article inclusive of neuroimaging protocols and quantification of leukoaraiosis severity; radial diffusivity; and fractional anisotropy (see Jolly et al., 2013).

2.3.1. Quantification of brain atrophy

Brain atrophy measures were calculated using the output from FreeSurfer- a program that performs automated cortical segmentation of Structural MRIs. The total cerebral volumes in both the gray and white matter were extracted. This then calculated as a percentage of the intracranial volume, which then provide us with an estimation of cerebral atrophy.

2.4. Statistical Analyses

We conducted Pearson correlations coefficient to examine relationships between variables. All analyses were conducted with two-tailed \( \alpha = 0.05 \). Corrected analyses were conducted using Partial correlations. A hierarchical multiple regression analysis was conducted to compare for predictors of WML.
3.0. Results

3.1. The association between structural brain changes and age

Table 2: Correlation between Age and macrostructural and microstructural brain changes

<table>
<thead>
<tr>
<th>Volumetric measure</th>
<th>Age</th>
<th>DTI-based measure</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral atrophy</td>
<td>-.590; p=.000</td>
<td>FA</td>
<td>-.447; p=.000</td>
</tr>
<tr>
<td>Cortical atrophy</td>
<td>-.567; p=.000</td>
<td>RaD</td>
<td>.563; p=.000</td>
</tr>
<tr>
<td>White Matter atrophy</td>
<td>-.348; p=.004</td>
<td>MD</td>
<td>.567; p=.000</td>
</tr>
<tr>
<td>Subcortical gray matter atrophy</td>
<td>-.515; p=.000</td>
<td>Ax</td>
<td>.549; p=.000</td>
</tr>
<tr>
<td>Lesion % of white matter</td>
<td>.421; p=.000</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>% of ICV</td>
<td>.419; p=.000</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

As expected, there was strong association between age and all volumetric and DTI-based measures (see Table 2). All relationships were on the correct directions and these relationships remained significant even after controlling for global cognitive function (i.e. either FSIQ and the MoCA). This finding confirmed that structural brain changes at both the macrostructural and microstructural levels declined with age. In particular, the values were indicated by reduced in FA and increased in MD, RaD, and Ax as age increases. We also found that loss of brain volumes similarly increase with age, with more profound association revealed by gray matter atrophy in comparison to white matter atrophy. The values were indicated by reduction in brain volume size as age increases, thus demonstrated by negative correlations between the two.
3.2. Global cognitive function and brain measures

For global cognitive function (see Table 3), the FSIQ was weakly correlated with most DTI-based measures, but not significantly associated with any of the volumetric measures. However, all the significance association between FSIQ and DTI-based measures disappeared after we controlled for either the MoCA, brain atrophy or white matter diffusivity.

In contrast, the MoCA (see Table 4) strongly correlates with FSIQ and moderately with age, demonstrated moderate to strong correlations with almost all volumetric measures; and strongly associated with all DTI-based measures. Further analyses revealed that the MoCA was related to white matter measures even after controlling for either age or FSIQ. The association between the MoCA and other volumetric measures were eliminated after controlling for brain atrophy, suggesting loss of brain volumes mediated this relationship. Meanwhile, the MoCA showed a consistent pattern of association with all DTI-based measures after correcting for brain atrophy. We further controlled for diffusivity measures to establish the strength of its relationship with the MoCA. As expected, the association between the MoCA and all volumetric measures was not retained upon this correction, suggesting the link between the MoCA and white matter diffusivity was relatively strong. We also found that the relationship between the MoCA and brain atrophy was mediated by RaD; while the association between the MoCA and volumetric white matter measures were mediated both by brain atrophy and RaD.

For further analyses, the most representative measures were selected for global cognition, volumetric and DTI-based measures. The MoCA was
selected to represent global cognition due to its strong association with our brain measures. Of the volumetric measures, the cerebral atrophy showed the highest correlation with global cognitive function i.e. the MoCA, therefore was the most representative of all volumetric measures. Similarly, amongst other DTI-based measures, the RaD yielded the strongest correlation with global cognitive function. Based on this initial finding, the MoCA, cerebral atrophy and RaD were selected for the rest of our analyses.

A point biserial correlation was conducted to see if gender has any significant relationship with age, cerebral atrophy or the MoCA. It was found that there was no significant correlation between gender with either RaD ($r = .121, p > .05$), the MoCA ($r = -.069, p > .05$) or cerebral atrophy ($r = -.071, p > .05$). Therefore, gender was not included for further analyses.
Table 3: Correlation between FSIQ and all brain measures

<table>
<thead>
<tr>
<th>Brain Measures</th>
<th>FSIQ</th>
<th>Control for MoCA</th>
<th>Control for Atrophy</th>
<th>Control for RaD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volumetric measures:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral atrophy</td>
<td>ns (.173; p=.161)</td>
<td>ns (-.067; p=.594)</td>
<td>-</td>
<td>ns (.032; p=.798)</td>
</tr>
<tr>
<td>Cortical atrophy</td>
<td>ns (.117; p=.345)</td>
<td>ns (.040; p=.747)</td>
<td>-</td>
<td>ns (.007; p=.955)</td>
</tr>
<tr>
<td>White matter atrophy</td>
<td>ns (.223; p=.070)</td>
<td>ns (.005; p=.969)</td>
<td>-</td>
<td>ns (.112; p=.369)</td>
</tr>
<tr>
<td>Subcortical gray matter atrophy</td>
<td>ns (-.056; p=.650)</td>
<td>ns (-.198; p=.112)</td>
<td>-</td>
<td>ns (-.155; p=.513)</td>
</tr>
<tr>
<td>Lesion % of white matter</td>
<td>ns (-.140; p=.257)</td>
<td>ns (.090; p=.471)</td>
<td>ns (.022; p=.865)</td>
<td>ns (.039; p=.757)</td>
</tr>
<tr>
<td>% of ICV</td>
<td>ns (-.117; p=.344)</td>
<td>ns (-.114; p=.360)</td>
<td>ns (-.003; p=.981)</td>
<td>ns (.069; p=.584)</td>
</tr>
<tr>
<td><strong>DTI- based measures:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RaD</td>
<td>-.266; p=.029</td>
<td>ns (.024; p=.846)</td>
<td>ns (-.184; p=.149)</td>
<td>-</td>
</tr>
<tr>
<td>FA</td>
<td>.242; p=.049</td>
<td>ns (.037; p=.771)</td>
<td>ns (.145; p=.256)</td>
<td>ns (.010; p=.935)</td>
</tr>
<tr>
<td>MD</td>
<td>-.253; p=.039</td>
<td>ns (.031; p=.804)</td>
<td>ns (-.179; p=.160)</td>
<td>-</td>
</tr>
<tr>
<td>Ax</td>
<td>ns (.213; p=.083)</td>
<td>ns (.042; p=.735)</td>
<td>ns (-.159; p=.214)</td>
<td>-</td>
</tr>
</tbody>
</table>

*ns= non-significant correlation
Table 4: Correlation between The MoCA, FSIQ, Age, and all brain measures

<table>
<thead>
<tr>
<th></th>
<th>MoCA</th>
<th>Control for FSIQ</th>
<th>Control for Age</th>
<th>Control for Atrophy</th>
<th>Control for RaD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FSIQ</strong></td>
<td>.542; p=.000</td>
<td>-</td>
<td>.567; p=.000</td>
<td>.524; p=.000</td>
<td>.490; p=.000</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>-.332; p=.006</td>
<td>-.381; p=.002</td>
<td>-</td>
<td>ns (-.120; p=.338)</td>
<td>ns(-.053; p=.671)</td>
</tr>
<tr>
<td><strong>Brain Measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Volumetric measures:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral atrophy</td>
<td>.414; p=.000</td>
<td>.387; p=.001</td>
<td>.286; p=.020</td>
<td>-</td>
<td>ns (.175; p=.160)</td>
</tr>
<tr>
<td>Cortical atrophy</td>
<td>.277; p=.023</td>
<td>.255; p=.039</td>
<td>ns (.114; p=.364)</td>
<td>-</td>
<td>ns(.075; p=.548)</td>
</tr>
<tr>
<td>White matter atrophy</td>
<td>.405; p=.001</td>
<td>.347; p=.004</td>
<td>.327; p=.007</td>
<td>-</td>
<td>ns(.205; p=.099)</td>
</tr>
<tr>
<td>Subcortical gray matter atrophy</td>
<td>ns (.197; p=.111)</td>
<td>.271; p=.028</td>
<td>ns (.032; p=.801)</td>
<td>-</td>
<td>ns(.036; p=.776)</td>
</tr>
<tr>
<td>Lesion % of white matter</td>
<td>-.389; p=.001</td>
<td>-.375; p=.002</td>
<td>-.291; p=.018</td>
<td>ns (-.236; p=.057)</td>
<td>ns(-.084; p=.501)</td>
</tr>
<tr>
<td>% of ICV</td>
<td>-.381; p=.001</td>
<td>-.380; p=.002</td>
<td>-.282; p=.022</td>
<td>ns (-.235; p=.058)</td>
<td>ns(-.075; p=.551)</td>
</tr>
<tr>
<td><strong>DTI-based measures:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RaD</td>
<td>-.524; p=.000</td>
<td>-.468; p=.000</td>
<td>-.432; p=.000</td>
<td>-.388; p=.001</td>
<td>-</td>
</tr>
<tr>
<td>FA</td>
<td>.496; p=.000</td>
<td>.447; p=.000</td>
<td>.411; p=.001</td>
<td>.395; p=.001</td>
<td>ns(.038; p=.762)</td>
</tr>
<tr>
<td>MD</td>
<td>-.508; p=.000</td>
<td>-.456; p=.000</td>
<td>-.411; p=.001</td>
<td>-.367; p=.002</td>
<td>-</td>
</tr>
<tr>
<td>Ax</td>
<td>-.452; p=.000</td>
<td>-.410; p=.001</td>
<td>-.343; p=.005</td>
<td>-.298; p=.015</td>
<td>-</td>
</tr>
</tbody>
</table>
Descriptive statistics for specific cognitive domains consists of working memory; episodic memory; and executive functions are presented in Table 5. In global cognitive function, we found that the MoCA was accounting for variation associated with brain volumes and DTI-based changes (see Table 4). Interestingly, in addition to this finding, the MoCA also seemed to account for variance in global cognitive function not explained by any of our brain measures. To confirm this, we further analysed (1) the association between the MoCA and each cognitive subtest representing specific cognitive domains i.e. working memory; episodic memory and executive function, by controlling for age; brain volume measure (i.e. cerebral atrophy); and DTI-based measure (RaD) in a separate analyses (see Table 6). We also evaluated (2) the relationship between RaD and each specific cognitive subtest by correcting for age; cerebral atrophy; and the MoCA independently (see Table 7). Finally, we examined (3) the relationship between cerebral atrophy and each cognitive subtest by controlling for age, RaD and the MoCA impartially (see Table 8).

3.3. Global cognitive assessment vs. Specific cognitive subtests

The first part of these analyses shown that the MoCA was positively correlated with most cognitive subtests except for Pattern Recognition Memory (Immediate mode) (PRM I) in episodic memory domain; and IED (stages completed) from executive functioning domain (see Table 6). After we controlled for age; RaD; and cerebral atrophy, the MoCA remained correlated with most subtests from all three cognitive domains (episodic memory; working memory and executive functioning) with few exceptions. This is where, the RaD measure appeared to mediate MoCA’s performance and the longest recall digit span (sequence mode) i.e. verbal working memory and SOC
I i.e. executive function. On the other hand, age; RaD; and brain atrophy are likely to explain the association between MoCA’s performance and PRM II i.e. visual episodic memory; IED (errors) and SOC (mean moves) i.e. executive functions.

3.4. The relationship between white matter pathology and deficit in specific cognitive domains

The second part of the analyses examined the relationship between RaD and each cognitive subtest (see Table 7). We found that RaD was correlated with most verbal working memory subtests. Upon correcting for age, cerebral atrophy and the MoCA separately, we found the association between RaD and Longest recall digit span (backward and sequence modes) were influenced by age, cerebral atrophy and the MoCA. On the other hand, we found that cerebral atrophy and the MoCA had mediated the relationship between visual working memory subtest (SSP) and RaD. Moreover, in episodic memory domain, the RaD only correlates with PRM II i.e. visual delayed recall, and this relationship seemed to be influenced by cerebral atrophy and the MoCA. In executive function domain, RaD correlates with SOC (problems solved) and SOC (mean moves) i.e. overall planning, and further analyses revealed that age and the MoCA influenced this relationship but not cerebral atrophy.
Table 5: Mean (standard deviation) for working memory; episodic memory and executive function domains.

<table>
<thead>
<tr>
<th>Cognitive Measure</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Working Memory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longest Digit Span Backward</td>
<td>6.21</td>
<td>1.20</td>
</tr>
<tr>
<td>Longest Digit Span Forward</td>
<td>4.73</td>
<td>1.47</td>
</tr>
<tr>
<td>Longest Digit Span Sequence</td>
<td>6.01</td>
<td>1.21</td>
</tr>
<tr>
<td>Spatial Span Length (SSP- CANTAB)</td>
<td>5.21</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Episodic Memory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logical Memory I *(Immediate)</td>
<td>11.25</td>
<td>4.14</td>
</tr>
<tr>
<td>Logical Memory II *(Delayed)</td>
<td>9.09</td>
<td>3.89</td>
</tr>
<tr>
<td>PRM: Immediate recall (%)</td>
<td>90.30</td>
<td>8.90</td>
</tr>
<tr>
<td>PRM: Delayed recall (%)</td>
<td>79.98</td>
<td>12.14</td>
</tr>
<tr>
<td><strong>Executive Function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IED Stages completed</td>
<td>7.85</td>
<td>1.60</td>
</tr>
<tr>
<td>IED Total errors</td>
<td>41.64</td>
<td>37.28</td>
</tr>
<tr>
<td>SOC Problems solved</td>
<td>8.27</td>
<td>2.06</td>
</tr>
<tr>
<td>SOC Mean moves</td>
<td>12.54</td>
<td>2.38</td>
</tr>
</tbody>
</table>
Table 6: Correlation between the MoCA with other cognitive subtests

<table>
<thead>
<tr>
<th>Specific test</th>
<th>MoCA</th>
<th>Control for Age</th>
<th>Control for RaD</th>
<th>Control for Cerebral atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Working Memory:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longest recall DSforward</td>
<td>.243;p=.047</td>
<td>ns(.221;p=.075)</td>
<td>ns(.184;p=.139)</td>
<td>ns(.229;p=.064)</td>
</tr>
<tr>
<td>Longest recall DSbackward</td>
<td>.507;p=.000</td>
<td>.470;p=.000</td>
<td>.460;p=.000</td>
<td>.487;p=.000</td>
</tr>
<tr>
<td>Longest recall DSsequence</td>
<td>.312;p=.010</td>
<td>.265;p=.032</td>
<td>ns(.223;p=.072)</td>
<td>.280;p=.023</td>
</tr>
<tr>
<td>SSP (Span Length)</td>
<td>.408;p=.001</td>
<td>.352;p=.004</td>
<td>.277;p=.024</td>
<td>.309;p=.012</td>
</tr>
<tr>
<td><strong>Episodic Memory:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMI</td>
<td>.411;p=.001</td>
<td>.389;p=.001</td>
<td>.364;p=.002</td>
<td>.414;p=.001</td>
</tr>
<tr>
<td>LMII</td>
<td>.304;p=.012</td>
<td>.299;p=.015</td>
<td>.251;p=.042</td>
<td>.326;p=.008</td>
</tr>
<tr>
<td>PRM I</td>
<td>ns(.223;p=.070)</td>
<td>ns(.168;p=.178)</td>
<td>ns(.138;p=.270)</td>
<td>ns(.212;p=.087)</td>
</tr>
<tr>
<td>PRM II</td>
<td>.248;p=.043</td>
<td>ns(.237;p=.055)</td>
<td>ns(.126;p=.313)</td>
<td>ns(.184;p=.139)</td>
</tr>
<tr>
<td><strong>Executive Function:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IED Stages completed</td>
<td>ns(.227;p=.064)</td>
<td>ns(.193;p=.120)</td>
<td>ns(.159;p=.202)</td>
<td>ns(.235;p=.058)</td>
</tr>
<tr>
<td>IED Errors</td>
<td>-.241;p=.049</td>
<td>ns(-.191;p=.124)</td>
<td>ns(-.150;p=.229)</td>
<td>ns(-.231;p=.061)</td>
</tr>
<tr>
<td>SOC Problems Solved</td>
<td>.358;p=.003</td>
<td>.260;p=.035</td>
<td>ns(.214;p=.085)</td>
<td>.284;p=.021</td>
</tr>
<tr>
<td>SOC Mean moves</td>
<td>-.246;p=.045</td>
<td>ns(-.137;p=.272)</td>
<td>ns(-.096;p=.442)</td>
<td>ns(-.203;p=.102)</td>
</tr>
</tbody>
</table>

*ns = non-significant correlation
Table 7: Correlation between radial diffusivity and specific cognitive subtests

<table>
<thead>
<tr>
<th>Specific test</th>
<th>RaD</th>
<th>RaD Control for Age</th>
<th>RaD Control for Cerebral Atrophy</th>
<th>RaD Control for MoCA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Working Memory:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longest recall DSforward</td>
<td>ns (-.169; p=.171)</td>
<td>ns (-.131; p=.294)</td>
<td>ns (-.147; p=.238)</td>
<td>ns (-.051; p=.686)</td>
</tr>
<tr>
<td>Longest recall DSbackward</td>
<td>-241; p=.049</td>
<td>ns (-.142; p=.254)</td>
<td>ns (-.180; p=.148)</td>
<td>ns (.033; p=.793)</td>
</tr>
<tr>
<td>Longest recall DSsequence</td>
<td>-244; p=.049</td>
<td>ns (-.161; p=.198)</td>
<td>ns (-.200; p=.108)</td>
<td>ns (-.100; p=.426)</td>
</tr>
<tr>
<td>SSP (Span Length)</td>
<td>-.359; p=.003</td>
<td>-.263; p=.033</td>
<td>ns (-.212; p=.088)</td>
<td>ns (-.187; p=.133)</td>
</tr>
<tr>
<td><strong>Episodic Memory:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMI</td>
<td>ns (-.201; p=.103)</td>
<td>ns (-.145; p=.245)</td>
<td>ns (-.184; p=.139)</td>
<td>ns (-.019; p=.883)</td>
</tr>
<tr>
<td>LMII</td>
<td>ns (-.179; p=.147)</td>
<td>ns (-.171; p=.169)</td>
<td>ns (-.204; p=.101)</td>
<td>ns (-.025; p=.844)</td>
</tr>
<tr>
<td>PRM I</td>
<td>ns (-.207; p=.093)</td>
<td>ns (-.113; p=.368)</td>
<td>ns (-.200; p=.107)</td>
<td>ns (-.108; p=.387)</td>
</tr>
<tr>
<td>PRM II</td>
<td>-.276; p=.024</td>
<td>-.284; p=.021</td>
<td>ns (-.202; p=.105)</td>
<td>ns (-.177; p=.155)</td>
</tr>
<tr>
<td><strong>Executive Function:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IED Stages completed</td>
<td>ns (-.180; p=.145)</td>
<td>ns (-.123; p=.325)</td>
<td>ns (-.194; p=.118)</td>
<td>ns (-.073; p=.558)</td>
</tr>
<tr>
<td>IED Errors</td>
<td>ns (.222; p=.071)</td>
<td>ns (.140; p=.262)</td>
<td>ns (.218; p=.079)</td>
<td>ns (.116; p=.353)</td>
</tr>
<tr>
<td>SOC Problems solved</td>
<td>-.358; p=.003</td>
<td>ns (-.177; p=.156)</td>
<td>-.265; p=.035</td>
<td>ns (-.215; p=.083)</td>
</tr>
<tr>
<td>SOC Mean moves</td>
<td>.321; p=.008</td>
<td>ns (.140; p=.261)</td>
<td>.288; p=.019</td>
<td>ns (.233; p=.060)</td>
</tr>
</tbody>
</table>

*ns= non-significant correlation
Table 8: Correlation between cerebral atrophy and specific cognitive subtests

<table>
<thead>
<tr>
<th>Specific test</th>
<th>Cerebral Atrophy</th>
<th>Atrophy Control for Age</th>
<th>Atrophy Control for RaD</th>
<th>Atrophy Control for MoCA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Working Memory:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longest recall DSforward</td>
<td>ns (.085; p=.496)</td>
<td>ns (.025; p=.841)</td>
<td>ns (-.011; p=.930)</td>
<td>ns (-.018; p=.885)</td>
</tr>
<tr>
<td>Longest recall DSbackward</td>
<td>ns (.169; p=.172)</td>
<td>ns (.046; p=.714)</td>
<td>ns (.044; p=.727)</td>
<td>ns (-.052; p=.677)</td>
</tr>
<tr>
<td>Longest recall DSsequence</td>
<td>ns (.144; p=.246)</td>
<td>ns (.031; p=.808)</td>
<td>ns (.011; p=.932)</td>
<td>ns (.017; p=.893)</td>
</tr>
<tr>
<td>SSP (Span Length)</td>
<td>.351; p=.004</td>
<td>.249; p=.044</td>
<td>ns (.196; p=.115)</td>
<td>ns (.219; p=.077)</td>
</tr>
<tr>
<td><strong>Episodic Memory:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMI</td>
<td>ns (.087; p=.485)</td>
<td>ns (.001; p=.996)</td>
<td>ns (-.030; p=.811)</td>
<td>ns (-.101; p=.422)</td>
</tr>
<tr>
<td>LMII</td>
<td>ns (.017; p=.890)</td>
<td>ns (-.028; p=.825)</td>
<td>ns (-.100; p=.425)</td>
<td>ns (-.125; p=.317)</td>
</tr>
<tr>
<td>PRM I</td>
<td>ns (.073; p=.556)</td>
<td>ns (-.061; p=.629)</td>
<td>ns (-.050; p=.687)</td>
<td>ns (-.021; p=.864)</td>
</tr>
<tr>
<td>PRM II</td>
<td>ns (.202; p=.102)</td>
<td>ns (.196; p=.115)</td>
<td>ns (.061; p=.627)</td>
<td>ns (.112; p=.370)</td>
</tr>
<tr>
<td><strong>Executive Function:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IED Stages completed</td>
<td>ns (.033; p=.790)</td>
<td>ns (-.062; p=.618)</td>
<td>ns (-.081; p=.518)</td>
<td>ns (-.069; p=.584)</td>
</tr>
<tr>
<td>IED Errors</td>
<td>ns (-.075; p=.548)</td>
<td>ns (.049; p=.693)</td>
<td>ns (.060; p=.635)</td>
<td>ns (.028; p=.821)</td>
</tr>
<tr>
<td>SOC Problems solved</td>
<td>.262; p=.032</td>
<td>ns (.036; p=.776)</td>
<td>ns (.082; p=.515)</td>
<td>ns (.134; p=.285)</td>
</tr>
<tr>
<td>SOC Mean moves</td>
<td>ns(-.152; p=.219)</td>
<td>ns (.097; p=.440)</td>
<td>ns (.033; p=.795)</td>
<td>ns (-.057; p=.649)</td>
</tr>
</tbody>
</table>

*ns= non-significant correlation
3.5. The relationship between cerebral atrophy and specific cognitive dysfunction

The final part of the correlational analyses further evaluated the relationship between cerebral atrophy and each cognitive subtest (See Table 8). Our finding indicated that cerebral atrophy merely correlates with SSP subtest from the working memory domain, but this association was partially shared with RaD and the MoCA. Cerebral atrophy was not correlated with any of episodic memory subtests, and merely correlated to SOC (problem solved) from the executive function domain. Upon controlling for age, RaD and the MoCA, our finding revealed that the association between cerebral atrophy and this subtest was mediated by age, RaD and the MoCA.

3.6. Predicting radial diffusivity from age, cerebral atrophy and the MoCA

A three models of hierarchical multiple regression was conducted with radial diffusivity (RaD) as the dependent variable. Age was included in the first model to control for age factor. The cerebral atrophy was entered in the second model and the MoCA in the third model (See Table 9).

On the first model, the outcome revealed that age contributed significantly to the regression model accounted for 31.7% of the variation in radial diffusivity (p<.001). Adding cerebral atrophy into the second model further explained an additional 7.5% of the variation in radial diffusivity, which increased the predictive capacity of the model from 31.7% to 39.2% in a statistically significant way (p<.01). Finally, when the MoCA was introduced on the third model, the predictive capacity of the overall model raised
significantly from 39.2% to 47.6%, explaining another 8.4% of the variance in radial diffusivity (p<.01).

When all three independent variables were included in the last stage of the regression model, interestingly, cerebral atrophy was not a significant predictor of RaD. On the other hand, the MoCA stood up as the strongest predictor of RaD (p<.01) even after controlling for age.

**Table 9: Hierarchical regression analysis for variables predicting radial diffusivity**

<table>
<thead>
<tr>
<th>Model</th>
<th>( \beta )</th>
<th>( R )</th>
<th>( R^2 )</th>
<th>( R^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>.563</td>
<td>.317</td>
<td>.317</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>.563***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>.626</td>
<td>.392</td>
<td>.075</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>.362**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA</td>
<td>-.340**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>.690</td>
<td>.476</td>
<td>.084</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>.319**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA</td>
<td>-.232 (ns)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MoCA</td>
<td>-.322**</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: \( N=67, \) *p<.05, **p<.01, ***p<.001, ns= non-significant, CA= cerebral atrophy, DV= radial diffusivity

**4.0. Discussion**

The principal finding of this study is that the MoCA has captured variation associated with brain volumes and DTI-based changes not fully accounted for by specific cognitive tests administered in this study. Even after adjusting for age, FSIQ, and brain atrophy separately, the independent
association between the MoCA and radial diffusivity remained stable. The sensitivity of the MoCA to detect age-related early white matter changes was further strengthened when we found that the MoCA was the strongest predictor of RaD, even after controlling for age. Cerebral atrophy on the other hand, was not a significant predictor.

Interestingly, the MoCA is a brief yet powerful tool that even accounted for global cognitive deficit beyond our brain measures. Hence, we not only found the MoCA to be highly sensitive to subtle cognitive dysfunction in white matter pathology, our findings also suggest that it could be sensitive to other age-related neurophysiological changes for which macrostructural and microstructural white matter pathology and brain atrophy are not sensitive markers.

To the best of our knowledge, this is the first study to demonstrate the value of the MoCA from this perspective by combining more detailed brain measures in relation to white matter pathology i.e. the microstructural properties of DTI such as RaD. While the need for early detection of age-related white matter changes become apparent, our finding support the reliability of the MoCA as a valuable screening tool for this purpose. This is in line with previous studies documenting the usefulness of the MoCA for early detection of cognitive decline such as in cases of Mild Cognitive Impairment (MCI) and Alzheimer’s Disease (AD).

To summarise, consistent with previous findings, we found that structural brain changes declined with age at both the macrostructural and microstructural levels. In particular, our volumetric measures indicated higher white matter lesions load and loss of brain volume with age, suggestive of
macrostructural changes. Additionally, we also found that the gray matter atrophy exhibited stronger association with age than the white matter volume loss. On the other hand, our DTI-based measures reflected the microstructural changes by which the efficiency of axonal organisation appeared to be compromised by age, indicated by an increase in RaD and a reduction in FA values.

As expected, white matter pathology was strongly associated with global cognitive dysfunction, but minimally detected within specific cognitive domains involving working memory, episodic memory and executive functioning. As the MoCA captured greater cognitive deficit at the global level, this provided support to our initial prediction that cognitive dysfunction in healthy elderly could be subtle, varied and diffuse in nature. In addition, we also found that brain atrophy partially explained the relationship between white matter pathology and episodic and working memory, but not for executive function. Consistent with previous studies, this finding implies that loss of brain volume influenced the relationship between white matter pathology and cognition, at least to some extent. Age in contrast, was found to influence the association between white matter pathology and working memory and executive function, but not episodic memory.

Overall, although we did not expect the MoCA to detect cognitive dysfunction beyond our brain measures, this link is not surprising. This is because white matter macrostructural and microstructural changes certainly cannot account for the entire age-related neurophysiological changes that take place within the brain impacting cognitive performance among the elderly. However, it would be interesting for future work to further utilise the MoCA
and look into other type(s) of neurophysiological variables that might explore the ‘unexplained variance’ we found with the MoCA.

The use of DTI-based measures in addition to our volumetric properties is one of the strength of the present study. Most studies have applied conventional MRI techniques to assess white matter lesions, hence only macrostructural properties have been examined. We brought the present study a few steps further by applying DTI-based measures. The DTI techniques can quantify microstructural changes and are therefore more sensitive to subtle white matter pathology. Thus far, earlier studies applying DTI-based measures in quantifying the extent of white matter disruption in relation to cognition, mainly utilised the general measure of diffusion i.e. FA and MD. Because the four main measures i.e. FA; MD; RaD and Ax are highly correlated to one another and therefore prone to overlap, selection of general measures might be considered as representative of other diffusion values. However, in light of studies investigating age-related white matter microstructural damage, the selection measures restricted only to the FA and MD are possibly inadequate. This is because, the MD measure represents the extent of overall diffusivity level regardless of its direction and therefore, more informative microstructural values provided separately by RaD and Ax can be masked. Previous findings suggest that RaD is indicative of demyelination (Song et al., 2003; Song et al., 2005) and is prevalent with increasing age and healthy elderly (Bennett, Madden, Vaidya, Howard, & Howard, 2010), whereas the measure on Ax is suggestive of axonal damage or degeneration (Budde, Xie, Cross, & Song, 2009; Song et al., 2003). The RaD measure thus, will be the most representative of the extent of microstructural damage experienced by the elderly with WML
burden among other diffusion metrics. Very recently, the used of more specific DTI- measures are emerging (e.g. Borghesani et al., 2013; Davis et al., 2009) but remained limited. This study therefore, provides additional support for this selection measures. Additionally, since we also added volumetric properties in our measures, the present study not only accounts for white matter microstructural disruptions, but it also perceived structural brain changes from a bigger picture.

On the other hand, there are a few limitations to this present study. Firstly, this is a cross-sectional study; therefore our outcome measures are limited to one observation by which progressing changes cannot be determined. Secondly, the sample size is relatively small and participants were recruited from a specialized neurology clinic and volunteer database. These participants mainly comprised individuals from middle to higher socio-economic status and their existing levels of intellectual and overall functioning were relatively higher compared to elderly who came from lower socio-economic status in the wider population. Hence, generalization of this finding may not be appropriate. Consequently, this suggests the need for the study to be further corroborated with community-based studies involving more participants and a more representative sample. To note, a follow-up study on this cohort is in progress, which then will provide us with longitudinal data in the near future.

4.1. Clinical implication

It is vital to emphasise that age-related white matter macrostructural and microstructural changes are not benign, even among reasonably healthy elderly by which their future functioning may be compromised. The so-called
'healthy' elderly appear to be a more vulnerable population, as the nature of the dysfunction can be very subtle and diffuse. Early detection thus, serves as a main preventative measure for this population. Since our findings strongly point to the MoCA as a reliable screening tool for cognitive dysfunction at the early stage of white matter disease, we therefore recommend this brief, easily accessible tool for frontline clinicians to incorporate into their investigation protocol.

4.2. Acknowledgements

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4.3. Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
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associated with white matter hyperintensities in elderly subjects.


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Wong, A., Xiong, Y. Y., Kwan, P. W., Chan, A. Y., Lam, W. W., Wang, K....


PART 3

Extended Discussion

In general, this study examined the relationship between structural brain changes and cognitive function among a cohort of reasonably healthy elderly. It is acknowledged that there are diverse age-related neuroanatomical, neurophysiological and neurochemical changes that take place in the aging brain, which remain incompletely understood. The incidence of hyperintense signal on T2-weighted imaging (MRI) is becoming more prevalent in radiological findings, even among healthy elderly. This suggests decline in white matter health and there is concern about age-associated functional loss and future risk of pathology. This study thus, focused on the cerebral white matter changes at both the macrostructural and microstructural levels and loss of white and gray matter brain volumes within the aging brain; and examined the association between these measures and cognitive function.

*Age-associated macrostructural and microstructural white matter changes*

Following this investigation, it was found that cerebral white matter changes occur with age at both the macrostructural and microstructural levels. Macrostructurally, age-associated white matter changes were shown by increased in white matter lesion loads and reduction in global brain volume. This association was strongly linked with age, reflecting global decline in white matter health. This finding supports previous studies, which relate white matter lesions with age-associated loss of brain volume (Rabbitt & Mogapi, 2007). On the other hand, it was found that the gray matter atrophy exhibited stronger
association with age although the white matter atrophy also showed a similar trend. While not directly investigated by the present study, this finding contradicts previous reports that claimed loss of brain white matter exceeded loss of gray matter in relation to age (e.g. Meier-Ruge et al., 1992; Double et al., 1996; Pakkenberg and Gundersen, 1997).

Microstructurally, the integrity of white matter tracts was compromised by age, which reflects less efficient axonal organisation. Consistent with previous studies, the FA value showed negative association with age, suggesting greater isotropy that is less directionally restricted as one ages. Specific DTI-based measures revealed the RaD value was positively linked with age, indicating a lesser degree of fibre myelination and poorer white matter health. The Ax value also showed an increase with age, reflecting axonal damage pointing to decline in white matter health. The increase in MD value therefore provides a general indicator of deterioration in white matter health as a result of age. As expected, all findings with the use of volumetric and DTI-based brain measures were consistent with the previous studies. The first hypothesis that predicted the FA value will decrease; and MD, RaD and Ax values along with brain atrophy and WML load will increase with age is therefore confirmed.

**Global cognitive dysfunction**

Interestingly, in relation to age-associated cognitive deficit, the MoCA has captured variation associated with brain volumes and DTI-based changes, not fully accounted by specific cognitive tests administered in this study. Even
after adjusting for age, FSIQ, and brain atrophy separately, the independent association between the MoCA and radial diffusivity remained stable.

On the volumetric measures, the MoCA was positively linked to loss of brain volume, with reduced brain volume size associated with poorer performance on the MoCA, while higher white matter lesion load was negatively correlated with the MoCA score. Cerebral atrophy and radial diffusivity however, were found to mediate the association between white matter lesion volume and poor performance on the MoCA. Thus, the specific microstructural measure i.e. RaD appears to be more sensitive in detecting subtle white matter pathology as shown by the independent association between radial diffusivity and global cognitive dysfunction i.e. poorer performance on the MoCA. This finding therefore suggests that the pattern of global cognitive function was not associated in the same way on the volumetric and DTI-based measures.

On the other hand, the link between macrostructural changes and global cognitive function was not only mediated by radial diffusivity but also dependent upon cerebral atrophy. This confirmed the second hypothesis that predicted brain atrophy was not only linked to age, but also influenced the association between cognition and white matter pathology at least to some extent, which points to macrostructural changes. None of the previous studies have shown this association, particularly using the MoCA as a measure of global cognitive function as many studies used the MMSE, and none of the studies examined white matter pathology with the use of volumetric and DTI-based measures concurrently. While the independent relationship at the microstructural level suggests greater sensitivity of DTI-based measures in
detecting white matter damage, the mediating role of brain atrophy at the macrostructural level implies that differential changes in white matter macrostructural and microstructural health may be distinct to some extent, hence providing new insights into age-associated cerebral white matter disruptions.

**Domain-specific cognitive deficit**

On specific cognitive domain, the white matter microstructural disruption was associated with deficit in working memory performance on both verbal and visual tasks. On the verbal working memory tasks, higher radial diffusivity was linked to poorer cognitive performance, but this relationship was also mediated by age and cerebral atrophy. Performance on the visual working memory task however, was independent of age but influenced by cerebral atrophy. Although age and cerebral atrophy are strongly correlated to one another, this finding was able to show a differential influence of age on working memory. It was found that age influenced verbal abilities more so than visual abilities in working memory, while cerebral brain changes influenced both. Since the macrostructural measure was found as less sensitive to subtle white matter damage, it was not surprising that cerebral atrophy only correlates with visual working memory, but this association was eliminated after controlling for age, RaD and the MoCA.

In executive functioning, the volumetric measure i.e. cerebral atrophy demonstrated association with planning abilities, but this relationship was not retained after controlling for age, RaD and the MoCA. On the other hand, higher level of radial of diffusivity was also linked to poor planning abilities,
however this relationship similarly influenced by age, but not cerebral atrophy. Hence, macrostructural and microstructural white matter disruptions were associated with poorer planning abilities, but not on rule acquisition and reversal abilities. Since no significant relationship was found between radial diffusivity and IED tasks i.e. rule acquisition and reversal abilities, this may imply that subtle white matter damage is more sensitive to planning abilities rather than cognitive flexibility. However, this outcome is contrary to the previous findings (e.g. Borghesani et al., 2013) that report radial diffusivity was linked to cognitive flexibility. Nevertheless, because the present study was comprised of a cohort of intellectually high functioning participants (mean FSIQ of 112), this could also suggest that higher functioning individuals possess more superior cognitive flexibility, therefore these abilities remain intact with subtle white matter damage.

In the episodic memory domain, the volumetric measure was not linked to any of the memory measures. Similarly, verbal episodic memory was not associated with white matter microstructural damage, but visual episodic memory i.e. Pattern Recognition Memory (PRM) delayed tasks was linked to radial diffusivity. Interestingly, this link was independent of age, but influenced by cerebral atrophy. The association between white matter pathology and poor performance in this subtest was consistent with previous study reporting the use of similar subtest (van Dijk et al., 2004), but inconsistent with research that suggests deficit in episodic memory is associated with age (Gunstad et al., 2006; Hultsch, Hertzog, & Dixon, 1990; Schaie, 1996). The present study on the contrary, found the influence of age on working memory and executive function but not episodic memory. In the previous studies, early onset of
episodic memory dysfunction was found as a predictor for future Alzheimer’s disease (Backman, Small, & Fratiglioni, 2001). This may reflect that the trajectory of memory decline varies depending on disease state.

Overall, it was found that brain atrophy not only influenced the association between global cognition and white matter pathology, but to some extent, on specific cognitive domains. Again, this provides another support for the second hypothesis that predicted brain atrophy was not only linked to age, but also influenced the association between cognition and white matter changes. Nevertheless, none of specific cognitive functions in the present study revealed an independent relationship with microstructural white matter damage and even less association was found at the macrostructural level. The relationships were either influenced by age or cerebral atrophy.

However, in partial support of previous studies reporting white matter damage associated with deficit in working memory and executive functioning (e.g. Charlton et al., 2010; Vernooij et al., 2009), the present study further indicated a differential pattern of dysfunction within each domain which involves other cognitive sub-processes in working memory (i.e. verbal and visual) and executive functioning (i.e. planning and cognitive flexibility), as well as the mediating roles of age and cerebral atrophy. It therefore adds new insights on cognitive variance associated with specific patterns of cognitive deficit and the mediating roles in cognition.

This also confirmed our expectation that white matter pathology was strongly associated with deficit in global cognitive function, but minimally detected within specific cognitive domains involving working memory, episodic memory and executive functioning. As the MoCA captured greater
cognitive dysfunction at the global level, this provided support for the initial prediction that cognitive dysfunction in healthy elderly is relatively subtle, varied and diffuse in nature. This may imply that the characteristics of cognitive deficit among reasonably healthy elderly are much more diffused than specific and localised, therefore an independent link between a particular cognitive domains with white matter pathology is not apparent, as opposed to strong association witnessed at the global level. Based on this finding, it is assumed that since these subtests are measuring specific functions, a person can have white matter damage and have general dysfunction, but at the same time have intact ability in a specific function. As a result, measures that assess general cognitive functioning i.e. the MoCA will be more sensitive than subtests that merely assess specific functions. On the other hand, it would be interesting for future study to utilise neuropsychological tests that covered cognitive range used in the MoCA and examine whether the outcome of these neuropsychological tests are comparable to the MoCA.

In addition, although we did not expect the MoCA to detect cognitive dysfunction beyond our brain measures, this link is not surprising. This is because white matter macrostructural and microstructural changes certainly cannot account for the entire age-related neurophysiological changes that take place within the brain- impacting cognitive performance among the elderly. However, it would be interesting for future work to further utilise the MoCA and investigate other type(s) of neurophysiological variables that might explore the ‘unexplained variance’ we found with the MoCA.
The MoCA as the strongest predictor of RaD

Since the overall correlational findings indicated strong association between the MoCA and RaD, the present study further evaluated the data in light of multivariate models, using hierarchical regression to strengthen this outcome. This was done with interest to compare the predictive capacity of age, cerebral atrophy and the MoCA on radial diffusivity (RaD).

Most interestingly, the sensitivity of the MoCA to detect early stage of age-related white matter changes was supported when we found that the MoCA was the strongest predictor of RaD, even after controlling for age. Cerebral atrophy on the other hand was not a significant predictor. This outcome therefore suggests that the MoCA is the most important predictor of RaD, among other variables examined by the present study.

While the need for early detection of age-related white matter changes become apparent, our finding provide support on the reliability of the MoCA as a valuable screening tool for this purpose. This is in line with previous studies documenting the usefulness of the MoCA for early detection of cognitive dysfunction in other pathology such as Mild Cognitive Impairment (MCI) and Alzheimer’s Disease (AD).

Encouragingly, the present study discovered the value of the MoCA as a brief, yet powerful tool that even account for global cognitive dysfunction beyond the existing brain measures used by this study. Hence, not only the finding revealed that the MoCA was a strong predictor of RaD and sensitive to subtle cognitive dysfunction in white matter pathology, it also suggests that it could be sensitive to other age-related neurophysiological changes for which macrostructural and microstructural white matter pathology and brain atrophy
are not sensitive markers. To the best of our knowledge, this is the first study to demonstrate this outcome while combining the volumetric and DTI-based measures.

**Strengths and limitations of the present study**

The use of DTI-based measures in addition to our volumetric properties is one of the strengths of the present study. Most studies have applied conventional MRI techniques to assess white matter lesion, hence only macrostructural properties have been examined. We brought the present study a few steps further by applying DTI-based measures in conjunction to volumetric measures.

The DTI techniques can quantify microstructural changes and are therefore more sensitive to subtle white matter pathology. Thus far, earlier studies applying DTI-based measures in quantifying the extent of white matter disruption in relation to cognition, mainly utilised the general measure of diffusion i.e. FA and MD which are possibly inadequate. Very recently, the used of more specific DTI-measures have been emerging (e.g. Borghesani et al., 2013; Davis et al., 2009) but remain limited. As expected, a more detailed microstructural property of white matter changes such as RaD was more sensitive in detecting subtle white matter pathology. This study therefore, provides additional support for this selection of measure i.e. RaD. Moreover, the present study also incorporated volumetric properties for the brain measures. Therefore, this study not only accounts for white matter microstructural disruptions, but it also perceived structural brain changes from
a global level and explored the mediating role of brain atrophy in cognitive dysfunction.

However, the volumetric and DTI-based properties used to examine this relationship were limited to global brain measures. Some of the previous studies investigated the association between white matter pathology and cognition with the use of a more specific measure. On the macrostructural level, some studies measured white matter lesions based on lesion locations e.g. periventricular vs. subcortical; and regional-based e.g. frontal, temporal, parietal and occipital lobes. More recent studies that have utilised DTI-based measures examined specific white matter tracts e.g. anterior vs. posterior tracts. For instance, findings suggest that periventricular white matter is associated more with cognition than deep white matter changes (Xiong & Mok, 2011). Meanwhile, tract-specific findings indicated decreased in FA value and increased in RaD in anterior tracts were associated to poorer executive function; and posterior tracts was linked to visual memory (Davis et al., 2009). Since the microstructural DTI-based properties were found as more sensitive to subtle white matter damage, future work may further expand the present study by examining the white matter tracts. Investigation of the integrity of specific white matter tracts may reveal the link between poor white matter health, on a particular route with deficit in specific cognitive function.

There are several other important limitations to this present study. Firstly, this is a cross-sectional study; therefore the outcome measures are limited to one observation and so progressive changes cannot be determined. Secondly, the sample size is relatively small and participants were recruited from a specialized neurology clinic and volunteer database. Due to this
recruitment type, this cohort mainly comprised participants from middle to higher socio-economic status and their existing levels of intellectual and overall functioning were relatively high compared to those elderly from lower socio-economic status. Hence, generalization of this finding may not be appropriate. Consequently, this suggests the need for the study to be further corroborated with community-based studies involving more participants and a more representative sample. To note, a follow-up study on this cohort is in progress (Jolly et al.), which then will provide us with longitudinal data in the future.

Likewise, because the present cohort consists of high average participants with mean FSIQ of 112, it is also possible that their intellectual capacity serves as a protective factor on cognitive function, despite white matter disruptions. This assumption was based on the Brain Reserve Capacity Theory (Satz, 1993) that described the occurrence of brain lesions remains sub-threshold, when greater brain reserve capacity provides a barrier to the manifestation of cognitive impairment. However, this is merely a hypothetical construct, and because global cognitive dysfunction was still evident with the present sample, it is difficult to determine if a more representative sample would have produced a different outcome.

Moreover, the influence of education level cannot be determined by the present study, which is a drawback as individual differences such as education level have been linked to cognitive performance by previous studies involving healthy elderly (Knopman et al., 2001) and white matter changes (Knopman et al., 2001; Liao et al., 1997; Oosterman, Sergeant, Weinstein, & Scherder, 2004). The previous literature similarly suggests, years of education were linked to better cognitive functioning (Ardila, Ostrosky-Solis, Rosselli, &
Gomez, 2000; Backman et al., 2004; Meguro et al., 2001) and predicts less cognitive deterioration over time (Habib, Nyberg, & Nilsson, 2007).

The third limitation of the present study is also related to sampling issues. Although this cohort is considered as reasonably healthy elderly, approximately 40 per cent of the participants reported incidence of cardiovascular risks factors with three participants having experienced mild stroke. This to some extent may affect the results. In addition, the demographic information was obtained via face-to-face verbal interview of a semi-structured questionnaire. Accuracy of the reported cardiovascular incidence and/or risks may be underestimated or overrated as there was no clinical report to confirm the self-reported data. This gap can be expected since cardiovascular risks factors such as hypertension and hypercholesterolemia, especially for milder symptoms, may remain undetected if the participant is unaware of the existing condition. Moreover, the semi-structured interview also produced subjective answers, which makes analyses of quantitative data more complicated. Because the present study did not control for this variable in any of the analyses, therefore any confounding effect of cardiovascular risks factor is unknown.

Although getting a cohort of representative sample for this population can be challenging, future work to improve the present study may include combining the participants’ medical report, accounting for relevant information such as cardiovascular risks factor in addition to self-report questionnaire. With regards to demographic data, construction of a structured demographic questionnaire inclusive of education level and socio-economic status can be useful in order to obtain a more feasible data for analyses.
Contributions of the Current Research and Clinical implications

Based on the findings of the present study, the relationship between age-related white matter changes and global cognitive deficit has gained more support. It is vital to emphasise that the perceived changes both at the macrostructural and microstructural levels are not benign even among reasonably healthy elderly, by which their future functioning may be compromised. The so-called ‘healthy’ elderly appear to be a more vulnerable population, as the nature of the dysfunction can be very subtle and diffuse.

Although the present study demonstrated that deterioration in white matter health was associated with poorer cognitive function at the global level, some evidence albeit limited, points to domain-specific deficit involving working memory, executive functioning and to a lesser extent episodic memory. Deterioration in executive functioning and memory among healthy elderly has been reported in the previous studies (Buckner, 2004; Rabbitt, Diggle, Smith, Holland, & Mc Innes, 2001), and functional decline is one of the health concerns for this population. This may include future impairment in daily functioning, by which previous studies reported the association between executive functioning and instrumental activities of daily living (IADL) in community-dwelling elderly (Cahn-Weiner, Boyle, & Malloy, 2002; Tomaszewski Farias et al., 2009). In line with the present finding, increase in white matter lesion burden was linked to poor planning abilities. This function is not merely pertinent to day-to-day survival, but more importantly involves the execution of a more demanding task such as decision-making. Executive dysfunction may also affect the individual behaviourally, which can lead to impulsivity due to impairment in response inhibition and poor emotional
Moreover, intact executive functioning was shown to predict better independence among elderly (Grigsby, Kaye, Baxter, Shetterly, & Hamman, 1998). Independence is a valuable characteristic of healthy aging, not only due to physical health but also for psychological health. Independence promotes a sense of self-control, which in turn may improve health behaviours such as adoption of healthy lifestyle and adherence to medical treatment. Likewise, previous studies also reported that elderly with poorer memory performance found to face greater difficulties to comply with medication regime or other course of treatment (Insel, Morrow, Brewer, & Figueredo, 2006; Stilley, Beder, Dunbar-Jacob, Sereika, & Ryan, 2010). Therefore, deterioration in cognitive function as a sequence of age-related brain changes, not only affects individuals’ intellectual capacities but also predict poor clinical and functional outcomes.

Another concern related to age-associated white matter changes is the future risk of pathology. Many studies documented that white matter changes were associated with increased risk of future stroke (Fu et al., 2005; Vermeer et al., 2003; Buyck et al., 2009; Bokura et al., 2006) and death (Bokura et al., 2006; Oksala et al., 2009; Inzitari et al., 1997). Early detection thus, serves as a main preventative measure for this population. Findings of the present study strongly points to the MoCA as a reliable screening tool for cognitive dysfunction at the early stage of white matter disease. This, brief, easily accessible tool is therefore recommended for frontline clinicians to incorporate into their investigation protocol.

Additionally, this also speaks to the importance for future healthcare
planning involving aged care facilities. Previous studies also found the link between age-associated white matter changes and physical deterioration such as gait disturbance and falls risks (e.g. Guttmann et al., 2000; Rosano, Brach, Longstreth Jr., & Newman, 2006; Maki, 1997); and urinary incontinence (e.g. Kuo & Lipsitz, 2004; Kuchel et al., 2009; Sonohara et al., 2008; Poggesi et al., 2008). Psychologically, the incidence of white matter changes has been associated with late onset of depression (e.g. Taylor et al., 2003; Lesser, Hill-Gutierrez, Miller, & Boone, 1993; Nebes et al., 2002; Teodorczuk, et al., 2007; Godin et al., 2008). Incorporation of multidisciplinary services comprising healthcare professionals such as psychiatrist, clinical psychologists, physiotherapist and occupational therapists will add benefit for a more comprehensive approach in the assessment and intervention program for this vulnerable population.

Areas for Future Research

For future research, replications of the study considering areas for methodological improvement as mentioned in the earlier section would be useful. Since to our knowledge, this is the first study to demonstrate the value of the MoCA as a highly sensitive tool to subtle cognitive deficit in relation to macrostructural and microstructural white matter changes, replication of the result will be beneficial.

Moreover, future researchers could also consider investigating the relationship between macrostructural and microstructural white matter changes with other important variables contributing to future clinical and functional outcomes. This may include the assessment of daily functioning and mental
health e.g. depression in order to determine how this association corresponds to the clinical and neuropsychological profile of healthy elderly.

Overall, this work has long-term implication for reducing and/or reversing the adverse consequence of white matter damage on cognitive functioning, reducing the risk of future pathology such as dementia and stroke, and preserving functional independence and maintenance of the quality of life among elderly.
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APPENDICES

Appendix A

Translational Neuroscience journal
http://www.springer.com/medicine/neurology/journal/13380

10th of February 2014

RE: Confirmation of manuscript status

To whom it may concern

This is to confirm that we have received the manuscript written by Syarifah Azizah, Todd A.D. Jolly, Karen Drysdale and Irini Karayanidou, and entitled “Montreal Cognitive Assessment (MoCA) is linked to white matter changes” for our consideration. The manuscript is currently under review (no. TN-D-14-00008).

Sincerely,

Goran Simic MD, PhD

Translational Neuroscience

Editor-in-Chief and Managing Editor
Appendix B

Details on WML measurement/ MRI protocol

Assessment of White Matter Lesions (WMLs)

The protocols for assessing WMLs used for this study were published in a separate article inclusive of neuroimaging protocols and quantification of leukoaraiosis severity; radial diffusivity; and fractional anisotropy (see Jolly et al., 2013).

Neuroimaging Protocols

All participants underwent a 3T Siemens Verio scanner using a 32 channel head coil. T1-weighted images were acquired in the sagittal plan using ultrafast gradient echo 3D sequence (MPRAGE) with 1 mm isotropic voxel resolution (repetition time = 1500 ms; echo time = 2.57 ms; inversion time = 900 ms; flip angle = 9°; slice thickness = 1 mm with no gap; TA = 3 min 29 s). A 3D Fluid Attenuated Inversion Recovery (FLAIR) sequence with 1 mm isotropic voxels was acquired in the sagittal plane using a phase encoding acceleration factor of 2 (TR = 5000 ms; TE = 395 ms; TI = 1800 ms; 160 slices with slice thickness = 1 mm, TA = 5 min 52 s). Diffusion weighted images (DWI) were acquired in axial plane using a twice refocussed spin echo sequence with a phase encoding acceleration factor of 3 (128 × 128 matrix; TR = 11200 ms; TE = 111 ms; 55 slices with a slice thickness = 2.2 mm; TA = 13 min 6 s). Diffusion was measured in 64 non collinear directions with a b-value of 3000 mm2/s along with one non diffusion weighted (b = 0) image.

According to DeLano et al. (2000), this high b-value provides enhanced
contrast to noise and decreased T2 shine through effect at a relative cost on signal to noise ratio (SNR). Higher SNR’s achieved at acquiring image at 3T however, compensates for the inferior SNR at high b-value DWI.

**Quantification of Leukoaraiosis Severity, Radial Diffusivity and Fractional Anisotropy**

Leukoaraiosis Severity (LA) was calculated using Fluid Attenuated Inversion Recovery (FLAIR). Manual segmentation was performed on the white matter hyperintense areas appearing in the FLAIR images to determined severity, and saved as regions of Interest (ROI). The total volume of LA was expressed as a percentage of intracranial volume (% of ICV). White matter fractional anisotrophy (FA) and radial diffusivity (RaD) measures were calculated from diffusion-weighted images using the software package FSL. A white matter mask based on the T1 structural image, and a second mask-extracted from performing probabilistic whole brain tractography using the software package MRtrix (Tournier et al., 2012) was used to differentiate white matter from the rest of the brain tissue. We used a threshold of 0.02% on the tractography-based mask to ensure gray matter partial volume effects did not affect the measures of FA and RaD (Jolly et al., 2013).
Appendix C

Demographics and Health Status Questionnaire

Participant Number: ________________

Firstly, I will need to ask you a few questions about you and your health status. These questions relate to your personal and family medical history, your habits and behaviours. If at any stage you have any questions or problems with any part of this questionnaire, please interrupt me. Your responses will remain confidential. You are free to withdraw your responses at any time.

________________________________________________________________________________

1. Can I ask your age? ______________ And your date of birth? __________________________

2. Are you Right Handed? Yes/ No

   What hand do you use for:

   Writing?

   Scissors?

   Knife (without fork)?

   Broom (upper hand)?

3. Do you have any ongoing medical condition or health problem? (Please specify)

   Prompts:

   When did this first occur?

   Did you see a doctor about it?

   (If yes) Did the doctor tell you what he or she thought was wrong?

   Were you ever given any medication?

4. Have you ever had a diagnosis of mental illness, such as depression, anxiety or Schizophrenia? (Please specify)

   Prompts:

   When did this first occur?

   Did you see a doctor or psychologist about it?

   (If yes) Did the doctor or psychologist tell you what he or she thought was wrong?

   Were you ever given any medication?

5. Have you ever suffered from any neurological disorder (eg epilepsy or stroke)?

   Prompts:

   When did this first occur?
Demographics and Health Status Questionnaire cont.

Did you see a doctor or neurologist about it?

(If yes) Did the doctor or neurologist tell you what he or she thought was wrong?

Were you ever given any medication?

6. Do you smoke tobacco, like for example cigarettes, cigars?

If Yes, How many per day?

7. Do you consider yourself dependent on any prescription drugs?

If Yes, Which ones?

8. Have you ever had any serious injury to your head, surgery to your head, or been unconscious (Please specify)?

Prompts:

When did this occur?

Did you see a doctor about it?

(If yes) Did the doctor tell you what he or she thought was wrong?

Were you ever given any medication?

9. Is there any possibility that you have metal in your body either through surgery or injury?

10. Do you suffer from claustrophobia?

11. In general, how would you rate your health?

    Excellent    Very Good    Good    Fair    Poor

12. Compared to a year ago, how would you rate your health in general now?

    Much better    Somewhat better    Same    Somewhat worse    Much worse

13. Do you have any problems with your eyes or your hearing? (Please specify).

14. On average, how often do you consume alcohol? ____________________________.

Prompts:

What do you normally drink? White wine

How much do you usually drink on these occasions? Standard drinks =

__________________________.
Demographics and Health Status Questionnaire cont.

15. What is the highest level of education that you have completed or are currently completing?

Prompts:

When did you complete this level of education?

(If Uni) In what area did you complete your degree?

16. What is your current living status?

married/de facto ( ) alone ( ) family ( ) divorced ( ) widowed ( )

17. What is your current employment status?

In what industry are or were you employed?

In what capacity are or were you employed?

(If retired) When did you retire?

18. Physical activity:

How much physical activity do you engage in during an average week? ____ ____ hours.
Appendix D

The Montreal Cognitive Assessment (MoCA)

**MONTREAL COGNITIVE ASSESSMENT (MOCA)**
Version 7.1 Original Version

**NAME:**

**EDUCATION:**

**SEX:**

**DATE OF BIRTH:**

**DATE:**

**POINTS**

**VISUOSPATIAL / EXECUTIVE**

- **Copy cube:**
- **Draw clock:** (ten past eleven) (3 points)

**NAMING**

**MEMORY**

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 1 minute.

**ATTENTION**

Read list of digits (1 digit/sec.). Subject has to repeat them in the forward order. Subject has to repeat them in the backward order.

**LANGUAGE**

Fluency / Name maximum number of words in one minute that begin with the letter F.

**ABSTRACTION**

Similarity between e.g. banana - orange = fruit.

**DELAYED RECALL**

Has to recall words.

**ORIENTATION**

- **Date**
- **Month**
- **Year**
- **Place**
- **City**

© Z.Nasreddine MD www.mocatest.org Normal ≥26/30

Add 1 point if ≤12 yr old.
### Appendix E

#### Cognitive Subtests

<table>
<thead>
<tr>
<th>Test classification</th>
<th>Test Name</th>
<th>Purpose</th>
<th>Test Description</th>
<th>Outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>WASI</td>
<td>Block Design (BD)</td>
<td>Measure the ability to analyze and synthesize abstract visual stimuli.</td>
<td>While viewing a constructed model or a picture in the Stimulus Book, the examinee uses red and white blocks to re-create the design within a specified time limit</td>
<td></td>
</tr>
<tr>
<td>WASI</td>
<td>Vocabulary (Voc)</td>
<td>Assesses examinee’s word knowledge and verbal concept formation.</td>
<td>3 Picture items</td>
<td>28 verbal items</td>
</tr>
<tr>
<td>WASI</td>
<td>Matrix Reasoning (MR)</td>
<td>The subtest taps fluid intelligence, broad visual intelligence, classification and spatial ability, knowledge of part–whole relationships, simultaneous processing, and perceptual organization.</td>
<td>Examinee views an incomplete matrix or series and selects the response option that completes the matrix or series.</td>
<td></td>
</tr>
<tr>
<td>WASI</td>
<td>Similarities (Sim)</td>
<td>Measure verbal concept formation and reasoning</td>
<td>Picture items (Items 1–3), the examinee selects the option that shares a common</td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>Subtest</td>
<td>Description</td>
<td>Note</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>---------------------</td>
<td>--------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>WAIS-IV</td>
<td>Digit Span (DS)</td>
<td>Measure of Working Memory</td>
<td>digit span, digit span forward, digit span backward, digit span sequencing</td>
<td></td>
</tr>
<tr>
<td>WMS</td>
<td>Logical Memory</td>
<td>Verbal episodic memory</td>
<td>logical memory ages 16-69, recognition (yes/no) 0-30 points, age 65-90, recognition (yes/no) 0-23</td>
<td></td>
</tr>
</tbody>
</table>

- characteristic with the target objects.
- verbal items (Items 4–24), the examinee is presented two words that represent common objects or concepts and describes how they are similar.
- unchanged
- Joe Garcia–city changed due to clinician feedback (e.g., San Francisco)
Age (65–90)

- Ruth and Paul Story–new short story more age-appropriate, less language demand is repeated.
- Anna Thompson unchanged

**CANTAB_Visual memory test**

<table>
<thead>
<tr>
<th>Pattern Recognition Memory (PRM)</th>
<th>Tests visual recognition memory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Test of visual pattern recognition memory in a 2-choice forced discrimination paradigm</td>
</tr>
<tr>
<td></td>
<td>• Sensitive to dysfunction in <strong>medial temporal areas</strong> but</td>
</tr>
</tbody>
</table>

**Scores**

- Immediate Memory – scaled score
- Delayed Memory – scaled score
- Delayed Recognition – cumulative percentage

**Contrast Scores**

- Immediate Versus Delayed Recognition Versus Delayed

<table>
<thead>
<tr>
<th>Number</th>
<th>% of correct trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>latency (speed of participant’s response)</td>
<td></td>
</tr>
</tbody>
</table>

**Modes:**

1. Immediate
<table>
<thead>
<tr>
<th>CANTAB_ Executive Function</th>
<th>Intra/ Extradimensional Set Shift (IED)</th>
<th>Measure:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANTAB_ Screening</td>
<td>Big Little Circle (BLC)</td>
<td>Test comprehension, learning &amp; reversal</td>
</tr>
<tr>
<td>Screening</td>
<td></td>
<td>• Meant to prepare subject for IED test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Administered prior to IED test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Delayed (20mins later)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ Latency (speed of response)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ % correct circle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ Errors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ numbers of trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ stages completed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted scores:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Participant failing at any stage of the test had less opportunity to</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*This test is a computerised analogue of The Wisconsin Card Sorting Test (WCST).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Sensitive to changes to the fronto-striatal areas of the brain.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Simple stimuli</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Measures:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• visual discrimination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• attentional set shifting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• rule acquisition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• rule reversal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• maintenance, shifting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• attentional flexibility</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stopped</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stimuli consists of</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measures:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• visual discrimination</td>
</tr>
<tr>
<td>• attentional set shifting</td>
</tr>
<tr>
<td>• rule acquisition</td>
</tr>
<tr>
<td>• rule reversal</td>
</tr>
<tr>
<td>• maintenance, shifting</td>
</tr>
<tr>
<td>• attentional flexibility</td>
</tr>
<tr>
<td>• Stopped</td>
</tr>
<tr>
<td>• Stimuli consists of</td>
</tr>
</tbody>
</table>

*Simple stimuli*
<table>
<thead>
<tr>
<th><strong>WHITE MATTER LESION, BRAIN ATROPHY AND COGNITION</strong></th>
</tr>
</thead>
</table>

| (colour-filled shape/white line); *Compound stimuli* (white lines overlying colour-filled shapes). |
| Criterion of learning at each stage: |
| • 6 consecutive correct responses will allow further progression through the test. (The 9th block ends the test). |
| • Failure to reach this criterion after 50 trials will terminate the test. |
| • Feedback teaches the participant which stimulus is correct, and after six correct responses, the stimuli and/or rules change. These shifts are initially intra-dimensional (e.g., colour-filled shapes remain the only |
| make errors. |
| • The adjusted errors calculated to compensate this. |
| • Calculated by adding 25 for each stage NOT ATTEMPTED due to failure. |
| • Why 25? Since the subjects must complete 50 trials to fail a stage and half of these could be correct by chance alone. |
| • Added score of 35 to participants who did not complete?
<table>
<thead>
<tr>
<th>CANTAB Executive Function</th>
<th>Stockings of Cambridge (SOC)</th>
<th>Planning ability indicated by:</th>
<th>3 outcome measures:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working Memory Planning</td>
<td></td>
<td>• Time taken to complete the pattern</td>
<td>➢ # and % of correct trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• The number of moves</td>
<td>➢ Latency (speed of participant’s response).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Measures included in analyses:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>SOC Problem Solved in Minimum Moves</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>*Fundamental measure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>*Provide a succinct expression of <em>overall planning accuracy</em>.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>*Provide minimum # of moves to successfully completed a test</td>
</tr>
<tr>
<td>CANTAB_ Executive Function</td>
<td>Spatial Span (SSP)</td>
<td>Test working memory capacity</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------</td>
<td>-----------------------------</td>
<td></td>
</tr>
<tr>
<td>Working Memory Planning</td>
<td></td>
<td>➢ A computerized version of the Corsi Blocks task.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ A <strong>visuospatial analogue</strong> of the Digit Span test.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ Provide a measure of <strong>frontal lobe functioning</strong>.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ Sequence mode and Reverse mode (Level 2- Level 9).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ If all 3 sequences at any level were completed unsuccessfully, the test will terminate.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ The sequence &amp; colour used change from sequence to sequence to minimize interference.</td>
<td></td>
</tr>
</tbody>
</table>

*Scored out of a possible 12 problems

Consists of 6 outcome measures:

- Span length (the longest sequence successfully recalled)
- Errors
- Number of attempts
- Latency.