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Review

Effects of sustained cognitive activity on white matter microstructure and cognitive outcomes in healthy middle-aged adults: A systematic review

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ABSTRACT

Adults who remain cognitively active may be protected from age-associated changes in white matter (WM) and cognitive decline. To determine if cognitive activity is a precursor for WM plasticity, the available literature was systematically searched for Region of Interest (ROI) and whole-brain studies assessing the efficacy of cognitive training (CT) on WM microstructure using Diffusion Tensor Imaging (DTI) in healthy adults (> 40 years). Seven studies were identified and included in this review. Results suggest there are beneficial effects to WM microstructure after CT in frontal and medial brain regions, with some studies showing improved performance in cognitive outcomes. Benefits of CT were shown to be protective against age-related WM microstructure decline by either maintaining or improving WM after training. These results have implications for determining the capacity for training-dependent WM plasticity in older adults and whether CT can be utilised to prevent age-associated cognitive decline. Additional studies with standardised training and imaging protocols are needed to confirm these outcomes.

1. Introduction

Ageing is associated with a decline in memory and cognition, with longitudinal as well as cross-sectional research revealing significant decrements in specific cognitive domains such as processing speed, memory and reasoning ability with increasing age (MacDonald et al., 2003; Schaie and Willis, 2010; Shock et al., 1984; Singer et al., 2003; Singh-Manoux et al., 2012). Cognitive complaints are also often reported in the elderly, and are associated with reductions in daily functioning, ratings of quality of life (Montejo et al., 2012, 2011; Slavin et al., 2010), and increased risk of clinical cognitive disorders such as dementia (Jessen et al., 2010). Changes in brain structure have also been reported in older adults and may partially explain the poor cognitive and psychological outcomes with increasing age (Grady, 2012; Hedden and Gabrieli, 2004).

Recent advances in neuroimaging techniques have allowed researchers to better identify the specific changes to brain structure underpinning subsequent age-associated brain differences. For example, studies using a technique called Diffusion Tensor Imaging (DTI) have identified specific age-related changes to the microstructure of white matter (WM) tracts and how these changes may relate to cognitive function (Sullivan and Pfefferbaum, 2006; Yap et al., 2013). DTI utilises the motional properties of water molecules within and around neuroanatomical structures (such as axons, myelin etc), facilitating identification of specific changes to the microstructure of WM (Johansen-Berg and Behrens, 2014; Wozniak and Lim, 2006). For instance, the behaviour of water molecules around axons could indicate WM tract presence (fast diffusion along the long axis of the fibre, or the degree of *anisotropy*); myelin integrity (rate of diffusion perpendicular to the long axis of the fibre), and presence of non-WM tissue or breakdown of WM tissue cell barriers (degree of fast diffusion in multiple directions, or the degree of *isotropy*) (Basser, 1995; Chanraud et al., 2010; Soares et al., 2013). DTI allows the calculation of multiple scalar metrics indicative of WM presence and degree of tissue damage, including Fractional Anisotropy (FA), Mean Diffusivity (MD), Radial Diffusivity (RD) and Axial Diffusivity (AD) (Curran et al., 2016). An increase in MD is an indication of cellular tissue breakdown, as the increase in isotropic water movement is a marker for diminished restricted movement between aligned cell barriers (like those seen in WM) (Basser, 1995). In contrast, a decrease in FA is an indication of microstructural degeneration as there is reduced anisotropic movement along axon fibres (Beaulieu, 2011). Previous research has observed an increase in MD and a decrease in FA in damaged WM tissue, such as the injured tissue seen in cerebral ischemia (Sorensen et al., 1999), multiple sclerosis (Bammer et al., 2000; Cercignani et al., 2001; Ciccarelli et al., 2001) and Wallerian disease (Pierpaoli et al., 2001). RD and AD have

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also shown to be markers of neuronal damage. AD is a measure of water movement along the long axis of the fibre, and a reduction in AD has been shown to be a marker of axonal damage as seen in injured spinal cord tissue (Kim et al., 2006) and the optic nerve and tract (Sun et al., 2007, 2006) in mice. RD is a measure of water movement perpendicular to the long axis of the fibre and may reflect demyelination, with previous research showing increased RD in mice with chemically (Song et al., 2005) and physically induced myelin damage (Song et al., 2005, 2003). Subsequently, increases in MD and RD and decreases in FA and AD can be used as a maker of cellular tissue damage.

The development of DTI measures have allowed researchers to better understand if WM microstructure differs between age groups, and how these differences are related to differences in cognitive outcomes (Sullivan and Pfefferbaum, 2006; Yap et al., 2013). For example, a cross-sectional DTI study of 120 healthy participants aged 18–83 years demonstrated an association between older age, lower FA and higher MD in comparison to younger adults (Bendlin et al., 2010). This was observed in a large number of WM tracts including areas that connect medial (corona radiata, anterior thalamic radiation) to frontal regions, long association fibres that connect frontal and posterior portions of the brain (superior longitudinal fasciculus, interior fronto-occipital fasciculus) as well as commissural fibres that connect frontal areas (genu of the corpus callosum). When controlled for non-linear age-associated relationships, the association between age, FA and MD was preserved, revealing that those in later life (between 40 and 80 years) show poorer microstructure compared to the preceding age group, inferring decline may occur from mid-life onward (see figure 5 in Bendlin et al., 2010). Similar cross-sectional studies have demonstrated lower FA and higher MD in similar regions connecting medial to frontal areas (e.g., corticospinal tract: Gazes et al., 2016), frontal and posterior regions (uncinate fasciculus: Gazes et al., 2016; cingulum bundle: Bender and Raz, 2015; Gazes et al., 2016) and frontal portions of the corpus callosum (Bender and Raz, 2015; Malykhin et al., 2011; Sullivan and Pfefferbaum, 2006) in older compared to young adults. Similar to Bendlin et al., one study assessed both linear and non-linear age differences and observed FA was less in those in their late compared to early 20 s, while those in their 60 s to 80 s showed significantly higher MD compared to those in their 20 s to 50 s (Malykhin et al., 2011). These results are further corroborated by a large cross-sectional study utilising UK Biobank data (n = 3513), in which older adults (60 years) showed higher MD and lower FA compared to younger adults (45 years) (Cox et al., 2016). This pattern is also seen in adults aged 70 + years compared to adults in their 60 s, indicating MD continues to increase and FA continues to decrease into later life. Collectively, these results suggest a critical age-related factor driving decline in WM microstructure in tracts that subserve connections to frontal regions, and that these microstructural differences may appear from mid-life onward. To understand if the observed relationship between older age and worse WM microstructure was related to poorer cognitive outcomes, some of these studies also utilised cognitive testing. For example, Bendlin et al. (2010) observed that those with slower reaction times (as measured by the Trails A test) and poorer delayed visual memory recall score (as measured by the Brief Visuospatial Memory Test) showed higher MD compared to those who performed better on these tests. Lower FA was also significantly associated with slower reaction time, poorer delayed and total visual memory recall score and poorer performance in a measure of executive function (Trails B test). Similarly, a cross-sectional study assessing age-related differences in FA in a sample of 346 healthy participants (20–79 years), used Scaled Subprofile Modelling to identify if certain groups of WM tracts mediate the relationship between age and cognitive performance (Gazes et al., 2016). They first segmented DTI data to produce 18 major WM tracts, and the mean FA of these tracts were then used in Principle Component Analysis. The subsequent principle components were entered in a regression to determine what components (or combinations of tracts) best predict cognitive performance. These components were described as WM covariance patterns, in which combinations of tracts uniquely predict each measure of cognitive ability based on their mean FA. Next, a mediation analysis was conducted to identify if the separate WM covariance patterns mediated the relationship observed between older age and poorer cognitive ability. They demonstrated that these WM covariance patterns indirectly explained the relationship between older age and poorer performance in perceptual speed, episodic memory and fluid reasoning. These results suggest that age-related differences in cognitive ability are in part, characterised by differences in WM microstructure. These observations are further supported by other cross-sectional research assessing cognitive outcomes such as probabilistic reward learning (Samanez-Larkin et al., 2012), visual memory (Metzler-Baddeley et al., 2011; Voineskos et al., 2012), processing speed (Hedden et al., 2014; Salami et al., 2012) and executive function (Hedden et al., 2014; Voineskos et al., 2012). In particular, a pattern of lower FA (Hedden et al., 2014; Kerchner et al., 2012; Metzler-Baddeley et al., 2011; Salami et al., 2012; Samanez-Larkin et al., 2012; Voineskos et al., 2012) and higher MD (Salami et al., 2012) has been observed in older adults, and this relationship further explained poorer performance on cognitive tests.

Although cross-sectional research is informative for early investigation, it lacks the ability to account for intra-individual differences and is therefore problematic in ageing research (Lindenberger et al., 2011; Raz and Lindenberger, 2011). In particular, an association between variables (e.g. age, WM microstructure and cognitive ability) at one point in time between different individuals does not capture any within-person change over time and the presence of differences in this change between individuals. Longitudinal research measures change in the individual over a certain time frame, and therefore can identify within-person changes in WM, whether these changes are associated with a change in cognitive outcomes, and if the magnitude of change differs between individuals.

Evidently longitudinal research has demonstrated that WM deteriorates with increasing age in tracts connecting frontal regions. For example, a large-scale longitudinal study (n = 203) assessing change in WM microstructure over a 3.6-year period in adults aged 20–84 years, showed annual decreases in FA and increases in MD, with an average age of onset of 50 years (Sexton et al., 2014). Here, the largest age-associated effects were seen in frontal and parietal regions. Comparable longitudinal studies with middle aged to old (52–83 years, Hakun et al., 2015; Teipel et al., 2010) and the very old (81–103 years, Lövdén et al., 2014) corroborate these findings, with the same WM regions displaying age-dependent increases in FA and decreases in MD in tracts facilitating medial-fronto and fronto-occipital connections (Hakun et al., 2015; Lövdén et al., 2014; Teipel et al., 2010), long fibres connecting frontal to medial and posterior regions (Hakun et al., 2015; Teipel et al., 2010), and commissural fibres connecting the frontal lobes (Hakun et al., 2015; Teipel et al., 2010).

Longitudinal research has also shown that poorer cognitive outcomes may be a consequence of age-associated decline in WM microstructure. For example, in a study with a sample of older adults (81–103 years) who were tested at baseline and 2.3 years later further demonstrated that declines in FA and increases in MD are prospectively associated with an increase in perceptual speed (Lövdén et al., 2014). Similarly, in a study assessing WM microstructure and cognition in a sample of older adults at 73 years (n = 731) and then again at 76 years (n = 488), showed significant declines in FA which were also associated with a decline in fluid intelligence (as measured by tests assessing non-verbal reasoning and working memory) (Ritchie et al., 2015). Evidently, older adults show worse cognitive outcomes over time, and this is associated with deterioration in WM microstructure.

Despite evidence of age-related neurodegeneration in both cross-sectional and longitudinal studies, some researchers have argued that this process may be modifiable (La Rue, 2010; Schooler, 2007; Stern, 2013). Specifically, studies have observed older adults who have a history of greater cognitive activity, such as through higher educational

attainment (more years of education and higher levels of education) and/or through participation in cognitively engaging activities (such as social, leisure or occupational activities) have a lower risk of cognitive decline or dementia (Meng and DöArcy, 2012; Opdebeeck et al., 2016; Sharp and Gatz, 2011; Then et al., 2014; Valenzuela and Sachdev, 2006), and this relationship may be related to WM microstructure (Köhncke et al., 2016). In particular, Köhncke et al. observed older adults (> 80 years) who continued to engage in social activities showed preserved WM microstructure in the corticospinal tract and sustained performance in tests of perceptual speed over a three-year period. Although these findings are promising in providing evidence for interventions to reduce cognitive decline, they are largely observational and therefore it is difficult to ascertain causation (Bielak, 2009; Salthouse, 2006). Specifically, older adults who are already largely protected from cognitive decline due to genetic or other early environmental factors may be more likely to successfully participate in cognitively stimulating activities (Le Carret et al., 2003). This is in contrast to adults who may be more susceptible to age-related decrements in cognitive capacity and therefore already experiencing cognitive decline, who are then subsequently more likely to avoid or unsuccessfully participate in these activities (Aartsen et al., 2002; Mackinnon et al., 2003). Köhncke et al. in particular make this point about their data, in that those who continued to partake in social activities may do so due to already maintained white matter structure, and improved perceptual speed may mediate this relationship (see page 174).

To resolve this issue, purposeful, controlled and consistent cognitive activity must be introduced in a case control manner and the subsequent cognitive effects measured. One way in which to do this is through cognitive training (CT), which is the scheduled administration of cognitive domain specific games, puzzles or tasks. CT hasshown to have beneficial effects for working memory (Kelly et al., 2014; Kueider et al., 2012; Lampit et al., 2014), spatial memory (Kueider et al., 2012; Lampit et al., 2014), verbal and non-verbal memory (Lampit et al., 2014) as well as processing speed and reaction time (Kelly et al., 2014; Kueider et al., 2012; Lampit et al., 2014; Reijnders et al., 2013) among middle aged to older adults. These effects may particularly be the case for cognitive domains that are targeted by the CT program (Butler et al., 2018) with some research only observing small transfer effects to cognitive outcomes not associated with the CT games (Karbach and Verhaeghen, 2014; Lövdén et al., 2016) or no transfer to everyday function (Kelly et al., 2014; Reijnders et al., 2013).

Despite the purported cognitive benefits, direct measures of brain function may provide more useful in revealing if adults are able to make neuro-adaptive changes in response to CT. For example, functional neuroimaging studies have observed functional changes in older adults following CT (Belleville et al., 2011, 2014; Cao et al., 2016a,b; De Marco et al., 2016; Erickson et al., 2007; Li et al., 2014; Luo et al., 2016; McDonough et al., 2015; Miotto et al., 2014; Mozolic et al., 2010; Nyberg et al., 2003; Pieramico et al., 2012). For example, alterations to specific resting-state brain networks in aged populations have been observed across varying lengths of CT interventions, including frontal-parietal networks such as the dorsal attention network after 6 months of CT (Pieramico et al., 2012), left fronto-parietal network after one year of training (Luo et al., 2016) and central executive network after three months (Cao et al., 2016a,b) and 6 weeks (Chapman et al., 2015) of training. Reductions in activation of temporal regions are also observed with increasing age (Cabeza et al., 2004; Daselaar et al., 2005; Dennis et al., 2008; Gutchess et al., 2005), and this pattern of deterioration has shown to be ameliorated by CT (Chapman et al., 2015; Lampit et al., 2015; Zheng et al., 2015). For example, increased blood flow to the left middle temporal gyrus after 12 weeks of gist reasoning training (Chapman et al., 2015) and to the left superior/middle temporal gyrus after 6 weeks of a combined exercise, counselling and cognitive training program (Zheng et al., 2015). The majority of these studies observed improvements in the CT group and poorer functional outcomes in the control group after the interventional period, suggesting CT may beneficially alter current functional processing in older adults. Improved connectivity and/or function observed in these studies after CT may be evidence of activity-dependent synaptogenesis, in which the strength of connections between neurons are enhanced through the persistent excitation and activation of pre-synaptic neurons (Nicholson and Geinisman, 2006; Zito and Svoboda, 2002). CT may therefore encourage the enhanced formation of synaptic connections purely through its ability to induce neuronal activity. In contrast, one study showed no change in the CT group with a decline in functional connectivity in the control group (Luo et al., 2016), demonstrating preservation of brain function after CT. This is akin to brain maintenance in ageing, which defines successful ageing as the ability to maintain brain function, structure and health (Nilsson and Lövdén, 2018; Nyberg et al., 2012). In this context, the activity induced by CT may provide a compensatory mechanism to prevent age-related functional decline, and therefore reinforce current functional processing. Older age has been shown to be associated with impairments in downstream signalling molecules (in particular calcium) at the synapse, which are crucial for the formation of synaptic connections (Thibault et al., 2001; Toescu and Verkhratsky, 2007; Toescu and Vreugdenhil, 2010). Animal research has shown that impairments in signalling molecules increase the activity-dependent threshold needed to enact downstream processes for synaptic connectivity or long-term potentiation in older rats compared to young (Matthews et al., 2009; Tombaugh et al., 2005). This suggests a much higher level of activity is required to maintain long-term synaptic processes in older adults. As such, CT may be providing a higher level of challenge, increasing neuronal activity past this threshold and maintaining current functional ability.

Despite the purported functional benefits of CT and the possible activity-dependent mechanisms, the functional data does not provide sufficient information to conclude long term synaptic processes are occurring. Specifically, a change in function may simply be an indication of short-term functional representations in response to the CT exercises (Lövdén et al., 2010a). As changes to brain function are reliant on underlying changes to brain structural architecture (Greicius et al., 2009; Hagmann et al., 2008; Skudlarski et al., 2008), measures such as DTI may provide additional clues as to how CT may beneficially modify or preserve WM microstructure in the long term, as a way to facilitate positive cognitive outcomes. The presence of microstructural changes in response to CT may also help reveal the potential for older individuals to prevent or reverse age associated functional deterioration. If successful, CT may be a viable strategy to improve cognition and subsequent outcomes, such as quality of life and well-being, in older adults.

By searching the extant literature, the aim of the current review is to determine:

1) If older adults are able to successfully alter WM microstructure through persistent and scheduled cognitive activity (as measured by CT).
2) If CT specific alterations to WM microstructure produce positive changes to cognitive outcomes.

2. Method

2.1. Search strategy

An electronic search was performed using the Cochrane, Scopus and Web of Science databases for any studies published before 4 May 2018. The following search terms were used: (“computer training” OR “computeri?ed training” OR “cognitive training” OR “brain training” OR “memory training” OR “brain exercise” OR “memory exercise” OR “video game*”) AND (“age associated cognitive decline” OR “old* adults” OR ag?ing OR “cognitive ag?ing” OR “healthy older adults”) AND (“diffusion tensor imaging” OR DTI OR “diffusion weighted imaging” OR DWI OR “fractional anisotropy” OR “mean diffusivity” OR “radial diffusivity” OR “axial diffusivity”). The reference lists from

studies obtained from this search were also manually screened for any other relevant studies.

2.2. Selection criteria

Studies were included if they met the following criteria: (a) original publication in a peer reviewed journal; (b) published in English; (c) interventional study design with either a passive, active or healthy younger group control; (d) use of a diffusion imaging technique pre and post intervention; (e) assessment of cognition pre and post intervention; (f) inclusion of at least one group with healthy participants at or above 40 years of age. Studies were not included if: (a) they were studies using supplementary interventions with CT (such as including transcranial magnetic stimulation or neurofeedback with CT); (b) if results from younger or clinical samples could not be separated from the results from healthy older adults; and (c) if they were reviews, descriptions of treatment approaches, protocols or book chapters.

2.3. Recorded variables and data extraction

The following data were extracted from each article: first author's name, year of publication, participant characteristics including sample size, age (mean, SD and range) and gender, type of control group, description of CT [including duration (in weeks), location (home or at study site) and dose (in hours)], MRI technique [including Tract-based spatial statistics (TBSS), Voxel-Based Analysis (VBA) or Region of Interest (ROI), MRI field strength, voxel size, neuroimaging outcome], type of cognitive tests and cognitive outcome. For studies using whole-brain techniques, such as TBSS or VBA, the reported peak coordinates in Montreal Neurological Institute (MNI) stereotactic space were extracted.

3. Results

3.1. Identified studies

The systematic search identified 169 articles, 25 of which were removed as they were duplicates and 115 were removed after screening the titles and abstracts. A total of 29 full-text articles were screened, and 22 subsequently excluded due to ineligibility. Studies were removed because they assessed WM using techniques other than diffusion imaging (such as voxel-based morphometry using T1 scans), only had data from a younger or a clinical sample or did not collect data both before and after the intervention. One study was excluded as data could not be extracted due to the use of an unconventional analysis technique based on graph theory (Kim et al., 2015). Another study was removed as the brain region assessed (hippocampus) is not a WM structure (Lövdén et al., 2012). Another study was excluded as the cognitive intervention included neurostimulation (Stephens and Berryhill, 2016). Two remaining studies were removed on the basis that they did not have an active or passive control group (Antonenko et al., 2016; Strenziok et al., 2014). For one study (Lampit et al., 2015) where participants were assessed at two time points (three weeks and 12 weeks), data from the 12-week time point was extracted. Another study used two types of CT programs (multi-domain or single-domain) (Cao et al., 2016a,b). Only data from the multi-domain CT was used. After screening, a total of seven studies remained and were included in subsequent analyses. A summary of the search and screening process can be found in Fig. 1.

3.2. Characteristics of included studies

The seven studies included in this review (Table 1) produced a total sample size of 280, of which 130 completed CT and 150 were controls. Mean age across samples ranged from 61.7 to 73.3 years for those who completed CT and 60.3 to 73.45 years for those who were controls. Females comprised 53.85% of those who completed CT and 54.66% of those who were controls. Three of the studies employed an active control group, three used passive controls, and one study had both a passive and active control group.

3.3. Whole-brain studies

Five studies performed whole-brain analysis, the majority of which used TBSS (Table 2). Of the four studies that conducted TBSS, three extracted peak voxels from clusters showing significant group-by-time interactions (Cao et al., 2016a,b; Lampit et al., 2015) or significant change form baseline to follow up (Nozawa et al., 2015), while one delineated regions based on the percentage voxels that showed significant differences from baseline to follow up between controls and those who completed CT (de Lange et al., 2017). Significant group and time effects after CT were observed in the following areas: the association fibres connecting frontal to temporal/parietal regions (superior longitudinal fasciculus, cingulum bundle in de Lange et al., 2017), projection fibres connecting mid brain to posterior (posterior corona radiata in Cao et al., 2016a,b) and commissural fibres connecting hemispheres (corpus callosum in de Lange et al., 2017). Of the studies that extracted peak coordinates, all were in the left hemisphere.

The direction of change in DTI measures for each study showed increased deterioration in control groups (Cao et al., 2016a,b; de Lange et al., 2017), in contrast to no change (Cao et al., 2016a,b) or decelerated deterioration (de Lange et al., 2017) in CT groups. One study did observe WM improvement in the control group compared to CT (Nozawa et al., 2015). Two studies did not find any significant voxels showing group-by-time differences (Chapman et al., 2015; Lampit et al., 2015).

3.4. ROI studies

Four studies used ROI techniques and are summarised in Table 3. Two regions were chosen based on data from preliminary analysis, specifically from whole-brain analysis (Cao et al., 2016a,b) and from a region showing longitudinal change in the entire sample (both CT and controls) (Engvig et al., 2012). The remaining regions were selected a priori and were theoretically driven (Chapman et al., 2015; Lövdén et al., 2010b). One study segmented ROIs both automatically and manually (Chapman et al., 2015).

Results from ROI studies are mixed. The two studies who chose ROIs based on preliminary analysis (Cao et al., 2016a,b and Engvig et al., 2012) observed no change in the CT group, while the control group showed WM deterioration (decrease in FA, increase in MD and increase in RD). The remaining two studies that delineated ROIs a priori (Chapman et al., 2015 and Lövdén et al., 2010b) observed an improvement in WM microstructure (increased FA and decreased MD) in the CT group, with no or less change in the control group.

3.5. Relationship between cognitive training dependent changes to WM and cognitive outcomes

Four studies further explored the effects of CT on WM by determining if the observed DTI changes in either the CT or control group were related to the observed improvements in cognitive tests (Table 4). Two studies used non-parametric Spearman's ρ to determine the relationship between the DTI values extracted from peak voxels showing group by time effects and change in cognitive test scores in the CT and control group separately (Cao et al., 2016a,b; Engvig et al., 2012). One study compared mean CT-related changes in microstructure with change in cognitive tests scores (specified as performance pre-test – post-test) using partial correlations (Lövdén et al., 2010b). The remaining study performed general linear modeling comparing observed FA and MD change and differences in cognitive test scores from pre-test to post-test (de Lang et al., 2017). Two studies showed significant

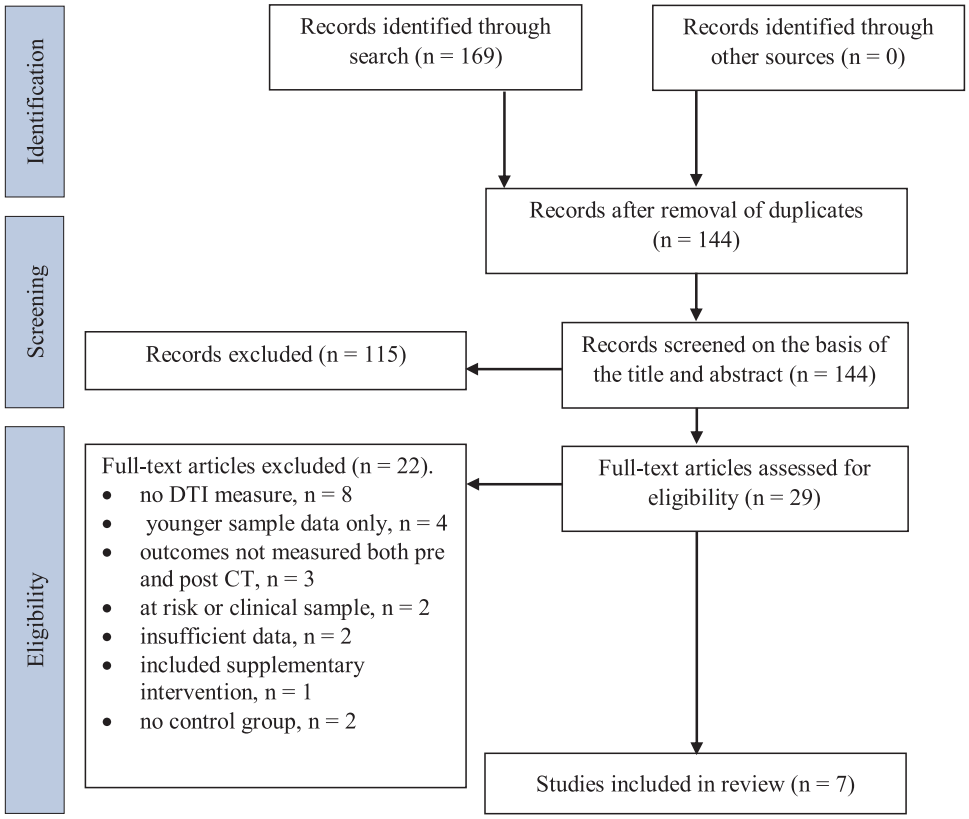

Fig. 1. Summary of study identification and selection.

associations between change in performance and the observed changes in WM after CT. Improved performance was associated with reductions in RD (Cao et al., 2016a,b; Engvig et al., 2012), MD and AD (Cao et al., 2016a,b) in the CT groups. Although Engvig et al. observed FA increases after CT were significantly associated with improved performance, X. Cao et al. did not observe the same relationship to FA change. Two studies also did not observe significant relationships between observed changes in DTI measures and memory performance (de Lange et al., 2017) or performance on working memory, episodic memory and perceptual speed (Lövdén et al., 2010b). No studies observed significant associations between DTI outcomes and performance on cognitive tests in the control groups.

4. Discussion

Ageing is associated with decrements to cognition, and changes to neural function and structure (Sullivan and Pfefferbaum, 2006; Yap et al., 2013). As a result, researchers have become increasingly motivated to determine if and how these changes could be prevented in older adults. The aim of the current review was to determine if: 1) white matter (WM) microstructure in middle-aged to older aged adults can undergo neuroplastic changes after persistent cognitive activity, and 2) if these changes translate into improved cognitive outcomes. To do this, the available literature was searched for studies using cognitive training (CT), and measures of WM microstructure in middle-aged to older adults (over 40 years). Results from these studies were extracted and summarised separately based on the MRI analysis technique used (whole-brain or Region of Interest, ROI). Results from the review suggest there are some beneficial effects to WM microstructure in middle-aged to older adults after persistent cognitive activity in brain regions shown to be negatively affected by increasing age.

From both whole-brain and ROI studies, CT appeared to influence WM regions that have been implicated in age-associated cognitive decline (Bender and Raz, 2015; Bendlin et al., 2010; Gazes et al., 2016; Hakun et al., 2015; Teipel et al., 2010). These WM regions included tracts that connected medial regions to posterior (posterior corona radiata) and frontal areas (cingulum, anterior thalamic radiation and corticospinal tract). One study (de Lange et al., 2017) observed a large area affected by CT that also included long association fibres connecting frontal to posterior regions (the superior longitudinal fasciculus) and between hemispheres (corpus callosum). Interestingly, one study observed microstructure improvements (decrease in FA) in the control group (Nozawa et al., 2015). This may be because the controls in this study completed crossword puzzles, which is still largely a cognitively stimulating activity (Pillai et al., 2011). ROI studies observed beneficial effects of CT on WM in similar regions, including areas that connected medial to posterior (posterior corona radiata; Cao et al., 2016a,b), medial to frontal areas (uncinate fasciculus, Chapman et al., 2015; anterior thalamic radiation, Engvig et al., 2012) and between hemispheres within the frontal lobe (segment 1 of the corpus callosum, Lövdén et al., 2010b). Improvements in WM microstructure in these areas after CT are important in light of previous research observing WM microstructure deterioration in similar regions in older adults compared to young (e.g. Bender and Raz, 2015; Bendlin et al., 2010; Gazes et al., 2016) and with increasing age (Hakun et al., 2015; Teipel et al., 2010). These regions include frontal portions of the corpus callosum (Bender and Raz, 2015; Bendlin et al., 2010; Hakun et al., 2015; Teipel et al., 2010), and fibres connecting medial to frontal regions such as the anterior thalamic radiation and uncinate fasciculus (Bendlin et al., 2010; Gazes et al., 2016).

Despite the observed CT-related benefits to WM in both whole-brain and ROI studies, the interpretation of this benefit varies. For the majority of studies observing significant effects (three), differences in microstructure appeared largely due to deterioration in the control groups and no change in the CT groups (Cao et al., 2016a,b; Engvig et al., 2012) or reduced deterioration in the CT group (de Lange et al., 2017). These results suggest that the brains of middle-aged to older adults are not able to undergo training-dependent alterations to WM,

Table 1
Characteristics of included studies.

Study		Characteristics			Control type	Intervention				
	N	Mean age (SD) in years	Age range in years	% female		Description	Duration (weeks)	Location		Total dose (hours)
								Research site	Home	
Cao et al. (2016)	CT: 17 Con: 14	CT: 71.1(3.2) Con: 69.1 (3.9)	56 - 75	CT: 23.5 Con: 35.7	Active (lectures on healthy living)	Memory (verbal, episodic and face-name association), reasoning (Tower of Hanoi, Raven's progressive matrices and numerical and verbal reasoning), problem solving/strategy, visuospatial ability (map reading), handicrafts and exercise tips (stretching)	12	2 supervised one-hour sessions per week in groups of 15.	None	24
Chapman et al. (2015)	CT: 18 Con: 19	CT: 61.8 (3.3) Con: 73.3 (3.6)	56 - 71	CT: 55.5 Con: 73.7	Passive (wait-list)	Gist reasoning: generate meanings and goals important to activities encountered in real life or their own internal thought processes, to train a habit of solving and approaching tasks at hand.	12	1 one-hour supervised session per week in groups of less than 5	2 one-hour sessions per week	36
de Lange et al. (2017)	CT: 44 Con: 67	CT: 73.3 (2.7) active con: 73.5 (2.9) Passive con; 73.4 (3.2)	NR	CT: 52.57 Con: 65.67	Active (answer questions about scientific lectures) and passive (no training)	Training in memory technique (Method of Loci) to memorise lists of words	10	Weekly supervised sessions	8 assigned with a minimum requirement of 4 assignments to be completed per week	NR
Engvig et al. (2012)	CT: 21 Con: 20	CT: 61.7 (9.4) Con: 60.3 (9.1)	42 - 77	CT: 52.4 Con: 55	Passive (instructions to continue normal activities in everyday life)	Serial verbal recollection using memory technique (Method of Loci)	8	1 one-hour supervised session per week in small groups	Homework exercises to be completed on 4 days per week	16.66
Lampit et al. (2015)	CT: 7 Con: 5	CT: 72.3 (NR) Con: 70.2 (NR)	NR	CT: 85.7 Con: 0	Active (answer questions about nature documentaries)	COGPACK program: memory, attention, speed, executive function and language exercises	12	3 one-hour supervised sessions per week in groups	None	36
Lövdén et al. (2010b)	CT: 12 Con: 13	CT: 68.9 (2.7) Con: 69.7 (3.5)	65 - 76	CT: 58.3 Con: 30.8	Passive (no training)	Continual practice of 3 working memory, 3 episodic memory, and 6 perceptual speed tasks.	24.7	101 1 one-hour supervised sessions in groups of 6	None	101
Nozawa et al. (2015)	CT: 11 Con: 12	CT: 68.24 (5.7) Con: 67.77 (4.7)	60 - 75	CT: 36.4 Con: 33.3	Active (crossword puzzles)	Reaction time task involving immediate and delayed response to visual stimuli	8	Three 20-minute supervised sessions per week	None	8

Note. CT = cognitive training group, Con = control group; NR = not reported.

Table 2
Results from whole-brain studies.

Study	Strength	Voxel size (mm)	Type of analysis	DTI measure	Significant regions					Effects
					P-threshold	Brain area(s)	Peak coordinates (MNI)			Cluster size	
							x	y	z		
Cao et al. (2016)	3T	2x2x2	Voxel-wise two-way mixed effect ANOVA on TBSS skeleton	RD	P < .025 (corrected)[a]	Left posterior corona radiata	−18	−52	34	396	CT: NS (p = 0.43) Con: ↑ (p = 0.001)[b]
				FA MD AD	P < .05 (corrected)	NS					NS
Chapman et al. (2015)	3T	1.75x1.75x3	GLM on FA average at each time point	FA	NR	NS					NS
de Lange et al. (2017)	3T	1.96x1.96x2	Voxel-wise GLM on TBSS skeleton	FA	P < .05 (corrected)	Corpus callosum, corticospinal tract, cingulum bundle, temporal part of the superior longitudinal fasciculus and anterior thalamic radiation					CT ↓ < Con ↓ in 1.6% of voxels (p = 0.02)
				MD	P < .05 (corrected)						CT ↑ < Con ↑ in 8.7% of voxels (p = 0.02)
				RD	P < .05 (corrected)						CT ↑ < Con ↑ in 14.6% of voxels (p = 0.02)
				AD	P < .05 (corrected)						CT ↑ < Con ↑ in 6.8% of voxels (p = 0.02)
Nozawa et al. (2015)	3T	2x2x2	One sample t-test on TBSS skeleton	FA	P < .05 (corrected)	Left intraparietal sulcus/precuneus	−23	−59	37	1107	CT: NS
Lampit et al. (2015)	3T	2x2x2	Voxel-wise mixed repeated-measures ANOVA on TBSS skeleton	FA	NR	NS					NS (p = 0.80)
				MD	NR	NS					NS (p = 0.17)
				RD	NR	NS					NS (p = 0.24)
				AD	NR	NS					NS (p = 0.27)

Note. TBSS = Tract Based Spatial Statistics, GLM – General Linear Model, ANOVA = Analysis of Variance, DTI = Diffusion Tensor Imaging, FA = Fractional Anisotropy, MD = Mean Diffusivity, RD = Radial Diffusivity, AD = Axial Diffusivity, NS = not significant, NR = not reported, CT = cognitive training group, Con = control group.

[a] Initial threshold of p < 0.05 showed significant effects for a large cluster (2404 voxels). Threshold reduced to p < .025 to detect localised effects.

[b] Based on paired sample *t*-test for change from baseline to follow up in each group.

Table 3
Results from ROI studies.

Study	Justification for ROI	ROI	DTI Measure	Effects over time
Cao et al. (2016a,b)	Cluster showing significant group x time interaction effect on RD in whole-brain analysis	Left posterior corona radiata	FA	CT: NS (p = .224) Con: ↓ (p < .001)
			MD	CT: NS (p = 0.270) Con: ↑ (p = 0.010)
			AD	CT: NS (p = .055) Con: NS (p = 0.695)
Chapman et al. (2015)	WM tract that connects two regions showing monotonic blood flow increase from pCASL results	Left uncinate fasciculus	FA	CT > Baseline > Con (p = .003)[a] CT > Baseline > Con (p = .02)[b]
		Right uncinate fasciculus	FA	NS (p = 0.53)
Engvig et al. (2012)	Frontal region showing significant longitudinal change in MD across the entire sample	Left anterior thalamic radiation	FA	CT: NS (p = 0.17) Con: ↓ (p = 0.002)
			RD	CT: NS (p = 0.98) Con: ↑ (p = .001)
			AD	CT and Con: ↑ (p < .047)
Lövdén et al. (2010b)	Areas of the corpus callous that connect to frontal regions showing age associated decline in WM.	Segment 1 of the corpus callosum	FA	CT: ↑ (p = 0.010) Con: NS
			MD	CT: ↓ (p = 0.019) Con: NS
		Segment 2, 3, 4 and 5 of the corpus callosum	FA	NS

Note. ROI = Region of Interest, DTI = Diffusion Tensor Imaging, VWA = Voxel Wise Analysis, pCASL = pseudocontinuous arterial spin labelling, FA = Fractional Anisotropy, MD = Mean Diffusivity, RD = Radial Diffusivity, AD = Axial Diffusivity, N/A = not applicable, NS = not significant, CT = cognitive training group, Con = control group.
[a] Results from manual segmentation.
[b] Results from automatic segmentation.

but rather, that training may maintain current brain microstructure and deter decline seen with a lack of training (Nyberg et al., 2012).

This is in contrast to the two remaining studies (Chapman et al., 2015; Lövdén et al., 2010b)that observed improvement to WM microstructure following CT, with no change in the control groups. This contrasting interpretation to the other results, suggests middle-aged to older adults are able to experience training-dependent alterations to WM microstructure (Lövdén et al., 2013).

Despite both types of effects demonstrating a benefit for CT overall, it is compelling that some benefit was shown to be due to maintenance of brain microstructure, while other studies show a benefit due to changes in brain microstructure. In theory, CT provides a means for activity-dependent long-term potentiation (LTP) and synaptogenesis (formation and strengthening of synapses between adjacent neurons). When an action potential reaches the pre-synaptic neuron, it causes the release of signalling molecules that initiate downstream molecular processes that encourage and strengthen synaptic formation (Nicholson and Geinisman, 2006; Zito and Svoboda, 2002). Research has indicated this also applies to microstructural properties of WM. For example, in-vitro research has demonstrated the degree of myelination can be altered by either blocking or enhancing action potentials in cells using neurotoxins or electrical impulses (Demerens et al., 1996; Ishibashi et al., 2006; Stevens et al., 2002; Wake et al., 2011) and axon branching decreases in thalamocortical projections (Yamada et al., 2010) and in hippocampal tissue (Yasuda et al., 2011) after chemically disrupting excitation. A purported mechanism of this process may be through the actions of oligodendrocyte progenitors – specialised glial cells that regulate myelin and axonal growth in response to increased excitation (Barres and Raff, 1993; Gibson et al., 2014; Wake et al., 2011). These phenomena may have been captured in some of the reported studies, as the higher FA and lower MD observed after CT represents increased axon packing density and myelination (as these would increase axon diameter and compactness and therefore the degree of anisotropy between cellular membranes) (Alexander et al., 2010; Beaulieu, 2011; Takahashi et al., 2002). As research shows these alterations may be activity-dependent, the higher level of cognitive activity provided by CT may improve WM microstructure through activity-dependent myelination and axonal branching, and this is represented by the changed DTI metrics observed in the reported studies.

This does not explain the remaining and higher number of studies that observed unchanged or reduced decline of WM microstructure after CT. These results suggest that the increased activity provided by CT may regulate myelin content and axon density, rather than enhance it. These studies also observed deterioration of WM microstructure in the control groups, suggesting WM microstructural properties such as myelin content and axonal branching, are compromised over time and that CT may protect older adults from this decline. Animal and histology research corroborate this assumption, with the observation that marked myelin and axon loss are present in the brains of aged Rhesus monkeys compared to young (Bowley et al., 2010; Sandell and Peters, 2003) and in post-mortem samples of old human brain tissue compared to young tissue (Marner et al., 2003; Meier-Ruge et al., 1992). One reason for why these differences are seen in older brains may be because the observed myelin and axon loss are not being sufficiently replaced or repaired. For example, remyelination has shown to occur at a slower rate in aged rats compared to young (Shields et al., 1999; Sim et al., 2002). Despite this, some research has shown that rates of remyelination may be increased by learning and cognitive stimulation. For example, in a study that subjected some middle aged to old rats to an enriched environment (larger cage, free access to food and water, multiple forms of stimulation such as balls, tunnels and toys) and some to a standard environment (smaller cage with food and water only) over a four month period, they observed higher rates of remyelination in the rats that lived in the enriched environment (Yang et al., 2013). They specifically observed enhanced myelin fibres of smaller sizes with thinner sheaths, which has been shown to be a marker for remyelination of demyelinated fibres (Franklin and Ffrench-Constant, 2008; Franklin and Hinks, 1999). Results from this study provide a purported mechanism by which cognitive enrichment (such as from CT) may maintain WM in older adults – that CT may restore and repair important microstructural components lost with age.

Despite the theorised mechanisms underpinning the two CT-related microstructural patterns (change vs maintenance or myelination vs remyelination), it is difficult to ascertain if these two types of patterns

Table 4
Results from studies comparing DTI changes to cognitive outcomes.

Study	Brain Area	Cognitive Outcomes		DTI metric	Effect	
		Cognitive task	CT targeted outcome?		CT	Control
Cao et al. (2016)	Left posterior corona radiata	Colour Trails Test Trial 1 completion time	No	RD	↓RD and ↓ completion time (ρ = 0.627, p = 0.007)	NS (ρ = 0.143, p = 0.626)
				FA	NS (ρ=-0.272, p = 0.291)	NS (ρ = 0.015, p = 0.958)
				MD	↓MD and ↓ completion time (ρ = 0.588, p = 0.013)	NS (ρ = 0.305, p = 0.288)
				AD	↓AD and ↓ completion time (ρ = 0.505, p = 0.039)	NS (ρ = 0.486, p = 0.078)
Engvig et al. (2012)	Left anterior thalamic radiation	Correct recognition and location of words from word lists	Yes	FA	↑FA and ↑ correct answers (ρ = 0.496, p = 0.022)	NS (p > 0.42)
				RD	↓RD and ↑ correct answers (ρ=-0.547, p = 0.010)	NS (p > 0.42)
				AD	NS (ρ=-0.026, p = 0.910)	NS (p > 0.42)
Lövdén et al. (2010b)	Segment 1 of the Corpus callosum	Working memory, episodic memory and perceptual speed composite measures	Yes	FA	NS (p > 0.21)	NI
				MD	NS (p > 0.21)	NI
de Lange et al. (2017)	Corpus callosum, corticospinal tract, cingulum bundle, temporal part of the superior longitudinal fasciculus and anterior thalamic radiation	Recall of word lists	Yes	FA	NS (p = 0.06)	NI
				MD	NS (p = 0.14)	NI

Note. CT = cognitive training, DTI = Diffusion Tensor Imaging, RD = radial diffusivity, FA = fractional anisotropy, MD = mean diffusivity, AD = axial diffusivity, NS = not significant, NI = not investigated, ρ = Spearman's rho.

reliably delineate the different outcomes observed between studies. This is because the results from the studies are measured at the group level, while the possible neural mechanisms occur at the individual level. For example, in a study that suggests the CT group is showing CT-related myelination, there may be one participant that shows re-myelination after CT, or they may show myelination in one area of the brain and remyelination in another. Information about why this individual responded to CT in this particular way is lost at the group level. Theoretically, how the participant interacts with the training and what their baseline ability is or level of microstructural health, may predict their propensity to either change or maintenance (Lövdén et al., 2010a). For example, if an individual finds the training too difficult and therefore does not engage with the training, they are unlikely to receive any benefit. This is in comparison to an individual who finds the training to be at an adequate difficulty level and does receive a benefit to the training, which may potentially lead to microstructural changes. Similarly, an individual is unlikely to show increased myelination after training if his or her myelin health is initially already relatively intact, in comparison to someone who has poor myelin integrity beforehand and therefore a higher predisposition to CT-related myelination (assuming that their poor microstructural health does not prevent them from being able to engage with the training). The differences in the intrinsic potential for participants' brains to undergo microstructural changes therefore need to be considered. For example, participants who showed improvements in WM microstructure may have been healthier than participants who maintained WM microstructure. Previous research has shown that healthy lifestyle factors such as higher participation in physical activities and healthier diets (such as the Mediterranean diet or higher consumption of fruits and vegetables) show improved white matter structure (Sexton et al., 2016), increased cortical thickness (Staubo et al., 2017) and improved cognitive outcomes (Samieri et al., 2008) in older adults. Cardiovascular health may also be an important precursor for WM microstructural outcomes (Raz et al., 2007), with previous research observing significant associations between diagnosed hypertension and decreased FA in WM from the temporal and occipital regions after controlling for age (Kennedy and Raz, 2009) and a significant age-related decline in FA in WM in frontal regions (Burgmans et al., 2010). All studies extracted for this review described their sample as 'healthy' adults, volunteers or seniors, and excluded participants with major psychological or neurological conditions. Despite this, none collected data on health status or participation in healthy behaviours, which may have provided additional insight into potential factors affecting CT-related cognitive and microstructural outcomes. Unfortunately, of the studies extracted all contained relatively small sample sizes, reducing the potential variation seen in the general population that may explain differences in outcomes. By summating a small number of participants based on group means, there may be some showing improved, some deterioration and some maintenance after CT, and when averaged together, this is presented as no change. With a larger sample, a greater range of individual differences are accounted for and will therefore be more likely to reveal the true effects of CT on WM microstructure.

Differences in methodology may also provide some insight into the discrepant results. For example, the studies observing change after CT made comparisons to a passive 'no training' group, potentially inflating the effect in the CT group. This is in contrast to studies comparing CT-related effects to an active no training group, who were engaging in some form of mental activity. Utilising an active control group would better differentiate between CT-specific effects and general cognitive effects. Interestingly, the studies observing changes in microstructure after CT also had some of the highest dosage of training of all the studies (36 and 101 h of training), suggesting CT-related changes may be dependent on the intensity of training. Previous research has detailed differences in cognitive test scores depending on the dosage and schedule of training, with a larger dose (Schwaighofer et al., 2015) and a more distributed training schedule (Penner et al., 2012) benefiting

cognitive outcomes. Subsequently if there were larger doses of training over longer periods of time, stronger microstructural effects may have been observed. Future research with more intensive training periods need to be conducted to verify this.

Four of the studies conducted further analysis to determine if any CT-related changes in WM microstructure were also associated with changes to cognitive outcomes. Two observed significant and two observed non-significant associations between changes in WM microstructure and improvements in particular measures of cognition in the CT group. Of the studies that did show significant associations, improvements in processing speed with an improvement in WM microstructure were observed (decreases in RD and MD) in the left posterior corona radiata (Cao et al., 2016a,b), and an improvement in word list recall with an improvement in WM microstructure (increases in FA and decreases in RD) in the left anterior thalamic radiation (Engvig et al., 2012). The effect on processing speed is in line with observational studies that have shown that impaired WM microstructure and older age is associated with poorer performance of measures of processing speed (Gazes et al., 2016; Hedden and Gabrieli, 2004; Lövdén et al., 2014; Salami et al., 2012). The reduction in RD and MD may be an indication of improved myelin content of the tissue (Song et al., 2003, 2005). By insulating neuronal tissue, myelin supports the fast conduction of a nerve impulse (Felts et al., 1997; Waxman, 1980) and may theoretically provide an explanation for an improvement in processing speed in older adults (Bartzokis et al., 2010; Penke et al., 2010).

The remaining study that observed associations between WM microstructure and cognitive outcomes, observed changes in the anterior thalamic radiation and improved performance in word recall. The authors attributed their findings to the role of the anterior thalamic radiation in declarative memory – an aspect of the training program, which involved using a memory technique (Method of Loci) to remember a series of words (Engvig et al., 2012). Interestingly, one of the other extracted studies (de Lange et al., 2017) that used a similar CT program involving the Method of Loci did not observe a relationship between improvements in WM microstructure and improvements in word recall from baseline to follow up in an area comprising of the anterior thalamic radiation. This area also included voxels within the corpus callosum, corticospinal tract, cingulum bundle and superior longitudinal fasciculus, suggesting changes to these regions were not related in word recall performance. Similarly, another study did not observe any changes to performance in working and episodic memory cognitive tests and changes to WM microstructure in the corpus callosum (Lövdén et al., 2010b). Interestingly, Cao et al. (2016a,b) observed that a decrease in AD was associated with improved performance in processing speed in the CT group. This is in the unexpected direction as decreased AD has previously shown to indicate deterioration of WM microstructure (Kim et al., 2006; Sun et al., 2007, 2006). Previous research has demonstrated higher AD in older adults compared to younger adults (Cox et al., 2016; Malykhin et al., 2011; Michielse et al., 2010) and with increasing age (Sexton et al., 2014), indicating ageing may actually be associated with an 'improvement' in AD. Other studies however, have shown there are different age-associated AD patterns depending on the type of WM tract. For example, AD has shown to be higher in commissural fibres in older adults compared to younger (Bennett et al., 2010) and with increasing age (Bender and Raz, 2015), while age-associated decreases in AD have been shown in association fibres (Bender and Raz, 2015), projection fibres (Bender and Raz, 2015; Bennett et al., 2010) and subcortical regions (Bennett et al., 2010). Ultimately, changes in WM microstructure (as measured by AD) may not be clear in the context of ageing, with more studies needing to be conducted to better differentiate these effects, and to determine whether training-dependent WM changes lead to subsequent measurable behavioural outcomes in this age cohort.

Differences in particular WM fibre structures in certain regions may also confound the interpretability of the outcomes from DTI (Alexander et al., 2001; Vos et al., 2011). DTI was chosen as an outcome as it is the most commonly used in-vivo technique to measure microstructural changes in WM (Assaf and Pasternak, 2008). Despite this, there are still issues relating to the accuracy and interpretability of DTI as a measure of WM microstructure (see Jones et al., 2013). In particular, results can be imprecise when more than two distinct fibre structures (based on thickness, orientation and curvature) are present in the one voxel, such as in the case of crossing, bending or fanning fibres (Alexander et al., 2001; Vos et al., 2011). Consequently, FA may be lower in particular regions containing these kinds of fibres, even if the individual fibres are relatively anisotropic (or would normally be high in FA). This could be problematic as potential differences may not be obvious in certain brain regions containing these complex tissues structure. More sophisticated diffusion techniques are being developed in order to address these known issues (Tournier et al., 2011), and if adopted in future research will provide more detailed information on the effects of training on WM microstructure.

5. Conclusion

In summary, this review provides evidence that persistent cognitive activity may benefit WM microstructure in middle aged to older adults. This benefit was mostly seen as a form of brain maintenance, where CT appeared to preserve brain structure rather than change it. Additional studies using whole-brain techniques, with active control groups, larger sample sizes with varied training schedules, doses and CT programs would provide valuable information about what specific WM regions are affected in a dose-dependent manner and what aspects of the CT program may benefit microstructural outcomes. Results from these studies would help determine if CT is an effective intervention that encourages training-dependent plasticity in older adults and whether CT can be utilised as a way to reduce age-associated cognitive decline.

Declarations of interest

None.

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