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Review article

White matter microstructural abnormalities in amnestic mild cognitive impairment: A meta-analysis of whole-brain and ROI-based studies

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ABSTRACT

Studies that examined white matter (WM) alterations in amnestic mild cognitive impairment (aMCI) abound. This timely meta-analysis aims to synthesize the results of these studies. Seventy-seven studies (total N_{aMCI} = 1844) were included. Fourteen region-of-interest-based (ROI-based) ($k \geq 8$; $N_{aMCI} \geq 284$ per ROI) and two activation likelihood estimation (ALE) meta-analyses (fractional anisotropy [FA]: $k = 15$; $N_{aMCI} = 463$; mean diffusivity [MD]: $k = 8$; $N_{aMCI} = 193$) were carried out. Among the many significant ROI-related findings, reliable FA and MD alterations in the fornix, uncinate fasciculus, and parahippocampal cingulum were observed in aMCI. Larger effects were observed in MD relative to FA. The ALE meta-analysis revealed a significant FA decrease among aMCI subjects in the posterior corona radiata. These results provide robust evidence of the presence of WM abnormalities in aMCI. Our findings also highlight the importance of carrying out both ROI-based and whole-brain-based research to obtain a complete picture of WM microstructural alterations associated with the condition..

1. Introduction

Mild cognitive impairment (MCI) was originally conceptualized to describe memory impairment that falls in between normal aging and dementia (Petersen et al., 1999). Subsequently, it was revised to encompass both memory and nonmemory cognitive impairments, thereby expanding the classification of MCI to include both amnestic (aMCI) and nonamnestic (naMCI) subtypes (Petersen, 2004). Since then, much attention has centered on the study of aMCI, even more so than naMCI (Tales et al., 2014). This might be due to the fact that aMCI was highly relevant to Alzheimer's disease (AD); patients with aMCI are at risk of developing AD, effectively rendering aMCI as a prodromal stage of AD (Gauthier et al., 2006; Petersen et al., 2014). Although it should be noted that aMCI may not be specific to an AD etiology, vascular and psychiatric conditions may also lead to an aMCI presentation (Petersen, 2004).

Neuroimaging methods have proliferated in recent years, and researchers have increasingly incorporated these methods into the study of aMCI, especially in identifying associated neural markers. With the burgeoning neuroimaging literature on aMCI, a need exists to synthesize these findings via meta-analyses. More importantly, in light of the controversial report of cluster-wise inference failure leading to unacceptable rates of false-positive findings in neuroimaging studies, meta-analyses have been suggested to be helpful in distinguishing between erroneous findings and consistent results (Eklund et al., 2016). A few meta-analyses on aMCI have been carried out across various neuroimaging modalities. For instance, one meta-analysis found significant gray matter atrophy in sub-cortical regions such as the amygdala, gyrus rectus, and anterior superior temporal sulcus in aMCI patients relative to controls (Schroeter et al., 2009). Resting state abnormalities in the posterior cingulate cortex, angular gyrus, parahippocampal gyrus, fusiform gyrus, supramarginal gyrus, and middle temporal gyri among aMCI participants relative to controls were also reported in another meta-analysis (Lau et al., 2016). However, a meta-analysis of the white matter microstructural abnormalities, observed via diffusion tensor imaging (DTI) measures, in aMCI patients has yet to be performed. The white matter microstructural involvement in aMCI cannot be understated. Changes in white matter microstructure have been widely theorized to be implicated in the development of AD and by extension its aMCI prodromal stage (Amlien and Fjell, 2014). Furthermore, memory impairments do not always occur as a result of neuronal loss; other pathophysiological processes such as the prion-like propagation of altered proteins or neuroinflammation, observable via white matter microstructural changes, can also contribute to memory impairments

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(Caso et al., 2016).

Nonetheless, two meta-analyses (Clerx et al., 2012; Sexton et al., 2011) have been carried out on the DTI outcomes in MCI (consisting of naMCI and aMCI). In these meta-analyses, researchers reported moderate to large effect sizes of decreased fractional anisotropy (FA) and increased mean diffusivity (MD) in several regions, among MCI subjects relative to controls. These earlier meta-analyses provide valuable insights into the white matter pathology underlying MCI. However, both meta-analyses have noted significant variability in their meta-analyzed results; one could speculate that the mixed MCI samples might have contributed to this heterogeneity. Specifically, both meta-analyses included studies with mixed groups of MCI (consisting of both aMCI and naMCI) subjects. The inclusion of such mixed MCI samples is problematic because aMCI and naMCI patients may differ tremendously in the nature of the cognitive impairment and this translates to differences in white matter pathology. Moreover, these meta-analyses looked mostly at large regions of the brain and did not include certain important white matter tracts, such as the fornix (Nowrangi and Rosenberg, 2015), which has been found to be implicated in aMCI and AD. Since then, many new DTI studies have examined these white matter tracts in the aMCI population. Lastly, coordinate-based meta-analytical methods were not used in these meta-analyses. Relative to region of interest (ROI)–based analyses, coordinate-based analyses are less susceptible to errors relating to the lack of spatial distinction (Laird et al., 2005a,b,c). Hence, there is a timely need to meta-analyze these white matter tract-related findings.

This study set out to reexamine the white matter microstructural pathology in aMCI. We synthesized results from both ROI- and whole-brain based studies and employed both ROI- and coordinate-based meta-analytical methods to examine FA and MD alterations in aMCI patients.

2. Methods

2.1. Data sources and study selection

The PubMed database was searched using the following keyword entry: (ADC [Title/Abstract] OR diffusion[Title/Abstract] OR DTI [Title/Abstract] OR diffusivity[Title/Abstract] OR “fractional anisotropy”[Title/Abstract] OR DKI[Title/Abstract]) AND (MCI[Title/Abstract] OR “mild cognitive impairment”[Title/Abstract]) AND (English[lang]). This keyword search was last carried out on 28 April 2017. The reference lists of relevant studies were also manually searched for additional studies.

Subsequently, studies that compared single domain and/or multiple domain aMCI subjects with appropriate controls, in a priori defined (via manual tracing, masking or tractography) ROIs, or used whole-brain methods such as tract-based spatial statistics (TBSS) or voxel-based analysis (VBA) on FA and MD were included. In order to maximize the number of included studies, the aMCI criteria were broadened to include studies that did not explicitly identify their MCI group as aMCI patients but had nevertheless adequately demonstrated equivalent memory impairments among all participants in their MCI group. These included studies that used the original Mayo Clinic’s MCI criteria (Petersen et al., 1999), National Institute on Aging-Alzheimer’s Association Workgroup’s MCI due to AD criteria (Albert et al., 2011), or Alzheimer's Disease Neuroimaging Initiative’s early and late MCI criteria (Aisen et al., 2011). Studies that included a mixed group of aMCI and naMCI subjects were excluded unless these MCI subtypes were analyzed separately. A detailed flow chart for the selection of studies is shown in Fig. 1.

2.2. Data extraction

Information, where available, regarding the participants (age, sex, education level and, Mini–Mental State Examination [MMSE] score), data acquisition (field strength, acquisition voxel size, number of directions and DTI measures), and analyses (whether free water elimination has been performed, ROI extracted, type of whole-brain analysis, and multiple correction methods) for each study were entered into a structured data abstraction form by the first and second authors. In cases where the age and MMSE scores that were reported in medians and ranges, means and standard deviations (SDs) were estimated using Hozo et al.’s (Hozo et al., 2005) formula before entering into the abstraction form.

Due to the multitude of white matter tracts examined in the retrieved studies, only bilateral tracts with data reported (i.e., data from both the left and right tracts reported individually, or the bilateral tract reported as a whole) from at least eight studies were included in the meta-analysis. These ROI data were entered into the meta-analysis in the form of means and SDs of FA and MD values, as well as *P*-values for studies that did not report means and SDs. If non-exact *P*-values were reported, conservative estimates of $P = 0.049$, $P = 0.009$ and $P = 0.0009$ were assumed for $P \ll 0.05$, $P \ll .01$ and $P \ll .001$ respectively. In studies (Parente et al., 2008; Stahl et al., 2007) where only the medians and interquartile ranges were reported, the means and SDs were estimated using Wan et al. (2014) formula. For studies that divided their aMCI participants into subgroups (e.g. multiple domain vs. single domain or AD converters vs. nonconverters) and reported their results across these subgroups, the sample sizes, means and SDs from these subgroups were combined such that only one sample size and one set of means and SDs from all the aMCI subjects, regardless of subtypes, were obtained. In order to avoid double-counting of overlapping data from the same study cohort across multiple studies, if two or more studies reported on the same ROI from the same study cohort, then only the ROI data from the larger sampled study were extracted. Unlike the ROI data, the TBSS and VBA data did not overlap across studies

As for studies that reported TBSS and VBA data, the Montreal Neurological Institute (MNI) or Talairach coordinates of the significant foci were extracted. In studies where means and SDs of the ROIs or coordinates of the TBSS or VBA results were not reported (either in the full-text or supplementary materials), e-mails were sent to the authors of these studies to request the unreported data. If the initial e-mail was not replied to within two weeks, a second e-mail was subsequently sent. In total, attempts were made to contact the authors of 44 studies; however, we were only able to obtain the requested data from the authors of 14 such studies. As for the remaining ROI studies with incomplete information (means and SDs not reported in numeric format), their means and SDs were extracted from graphs (where available) via WebPlotDigitizer (Rohatgi, 2011) – a web-based application designed to facilitate data extraction from graphs.

2.3. Data synthesis

The standardized mean difference (SMD) between aMCI and control participants was calculated for every ROI in each study. Each ROI was studied as a bilateral whole. For studies that reported data from both lateralized ROIs individually instead of bilaterally as a whole, the means from the left and right tracts were averaged, and the SDs were combined using the formula $SD_{combined} = \sqrt{([SD_{left}{}^2 + SD_{right}{}^2 + 2r(SD_{left})(SD_{right})]/4)}$, where r is the left–right correlation. This method of combining the SDs was used because the FA or MD in the left and right tracts cannot be assumed to be independent. We chose to err on the side of producing conservative SMD estimates. Hence, an r value of 0.8 was used, and this value slightly overestimates the actual correlation between the left and right tracts in a dataset of an actual study included in this meta-analysis. Consequently, this resulted in SMDs computed via this procedure to be slightly smaller than the actual SMDs of the bilateral tracts. We pilot tested this method of combining the left and right tracts in the dataset and found that it generally produced more accurate SMD estimates in the bilateral tract, as compared to simply

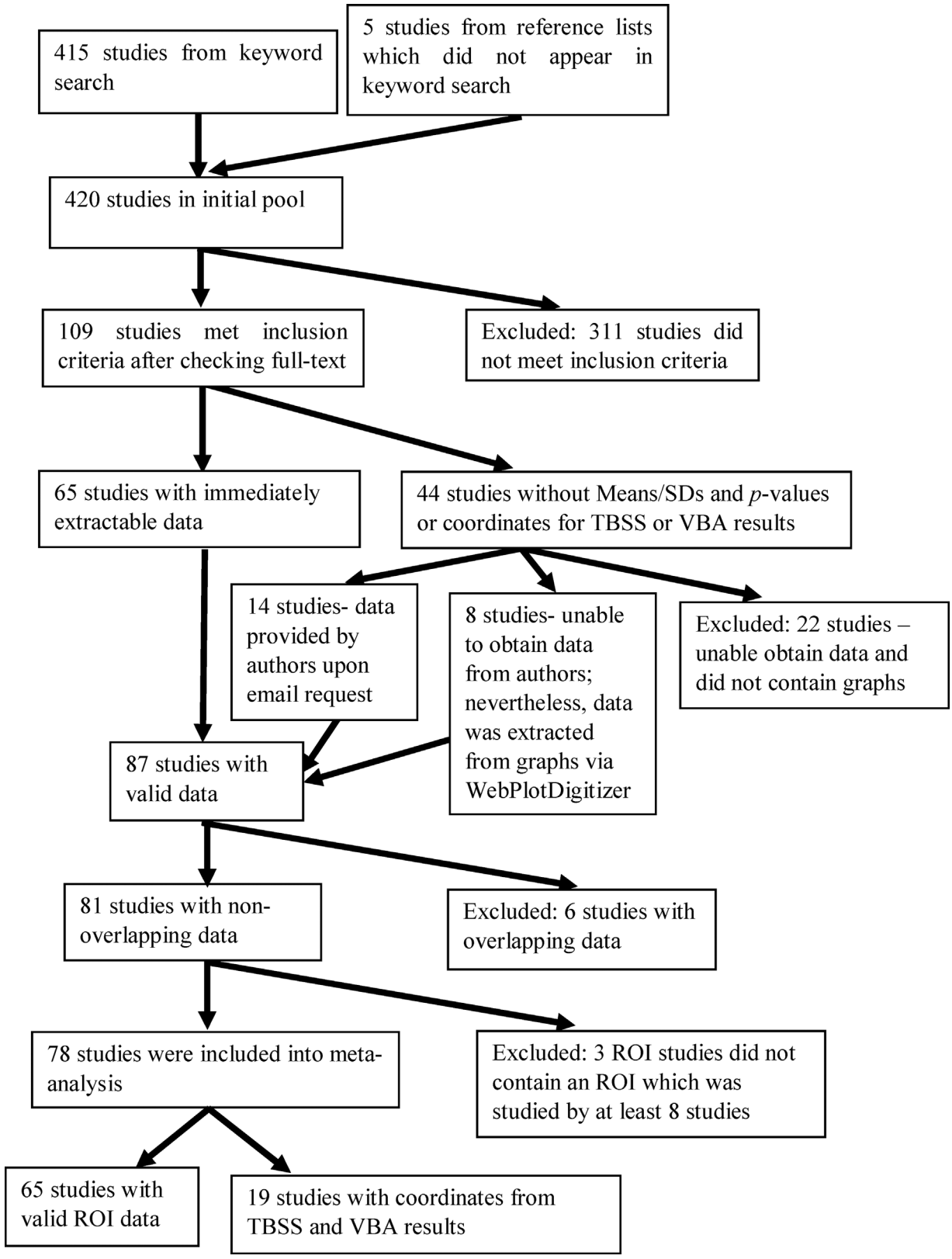

Fig. 1. Selection of studies.

averaging the effect sizes of the left and right tracts like in previous meta-analyses (Clerx et al., 2012; Sexton et al., 2011).

These SMDs were pooled and meta-analyzed using a random-effects model. A positive SMD would suggest that the FA or MD is greater in aMCI patients than in controls, and vice-versa. Heterogeneity was measured using the Q and I^2 statistics. A significant Q statistic suggests that the variability among the SMDs is larger than what is expected from subject sampling error alone. An I^2 value of 75% and above indicates a high degree of heterogeneity (Higgins et al., 2003). Trim and fill analysis (Duval and Tweedie, 2000) was conducted to assess

whether publication bias significantly influenced the aggregated SMDs. This analysis determines whether SMDs are missing. If so, the missing SMDs are imputed, and the aggregated SMD is recalculated. Follow-up leave-one-out analyses were carried out to assess the replicability and robustness of the results. These analyses were carried out using the metafor package (Viechtbauer, 2010) in R 3.4.0.

Two coordinate-based meta-analyses were carried out on FA and MD using the activation likelihood estimate (ALE) approach (Laird et al., 2005a,b,c; Laird et al., 2009) with GingerALE (Version 2.3.6; BrainMap, San Antonio, TX, USA). This approach models the reported coordinates as centers for 3-D Gaussian probability distributions (Turkeltaub et al., 2002) whose widths are based on empirical between-subject and between-template comparisons (Eickhoff et al., 2009), thus capturing the spatial uncertainty of the coordinates. For each study, an anatomical map was created by merging the probability distributions of all foci (Turkeltaub et al., 2012). Voxel-wise ALE scores were computed via the union of all anatomical maps, to quantify the anatomical convergence across studies in the brain. Therefore, the ALE approach assesses the above-chance clustering across studies rather than within studies (Eickhoff et al., 2009). To enable random-effects inference, ALE scores were compared to a null-distribution of random spatial association between studies (Eickhoff et al., 2012). Consequently, the *P*-value of ALE scores was obtained from the proportion of equal or higher values obtained under the null distribution.

Prior to the ALE computation, coordinates reported in the Talairach space were converted into MNI space. The resulting ALE image was thresholded using uncorrected $P \ll 0.001$ and a cluster-level inference threshold of $P \ll 0.05$ against a null-distribution generated by 5000 random permutation tests. If significant results were obtained from the ALE meta-analyses, the results were subsequently followed up with leave-one-out analyses.

3. Results

3.1. Study and sample characteristics

The characteristics of the aMCI and control samples of all included studies are presented in Table 1. Table 2 presents the DTI acquisition parameters and the types of data extracted for each study. The meta-analyses on the MMSE scores, age, education levels and gender distribution across all included studies suggested that these variables had differed significantly between aMCI and control participants. As expected, a large effect size was obtained on the MMSE score differences between aMCI and control participants (see Table 3). These results were also associated with significant heterogeneity.

3.2. ROI meta-analyses

At least eight studies reported valid FA data for the genu of the corpus callosum (gCC), splenium of the corpus callosum (sCC), fornix, uncinate fasciculus (UF), superior longitudinal fasciculus (SLF), inferior frontooccipital fasciculus (IFF), posterior cingulum (PC), and parahippocampal cingulum (PHC). As for MD, at least eight studies presented with valid data for the gCC, sCC, fornix, UF, PC, and PHC. Subsequently, meta-analyses were carried out on these FA and MD outcomes. Detailed leave-one-out analyses, forest plots, and funnel plots are presented in the supplementary materials.

Apart from the non-significant SMD of SLF-FA, all other meta-analyzed FA and MD outcomes were significant and associated with mostly medium effect sizes. The non-significant finding of SLF-FA could be attributed to the study of Fu et al. (2014). Leave-one-out analyses (see Supplementary Table (c)) showed that the exclusion of Fu et al.'s study, but not any others, resulted in a statistically significant pooled effect size (SMD = − 0.34; $P = 0.01$; 95% CI = − 0.61, −0.08). Relatedly, the forest plot of the SLF-FA (see Supplementary Fig. 1(g)) clearly showed that Fu et al.'s SMD (=2.27) was an outlier. Furthermore, the leave-one-out analyses also indicated that the exclusions of Cho et al. (2008) and Liao et al. (2010) from the SLF-FA and sCC-MD meta-analyses respectively resulted in large ($\gg > 33\%$) changes in the pooled SMD estimates (see Supplementary Tables 1(c) and 2(b)). The exclusion of any single study for all ROIs except SLF-FA did not render the pooled SMD estimates in their respective meta-analyses to be statistically non-significant.

Significant heterogeneity was found in the meta-analyzed FA outcomes in the gCC, sCC, SLF, IFF, PC, and PHC, as well as MD outcomes in the fornix and PC. The significant heterogeneity in the PHC-FA and fornix-MD results were mostly attributed to the study of Metzler-Baddeley et al. (2012a,b,c). Leave-one-out analyses revealed that the I^2 for fornix-MD decreased from 45.72 to a mere 0.01 after excluding Metzler-Baddeley et al.'s study (see Supplementary Table 2(c)). The I^2 for PHC-FA also decreased tremendously from 72.52 to 41.94 with the exclusion of the same study (see Supplementary Table 1(e)). In both cases, the Q statistics were no longer statistically significant after the exclusion. Furthermore, the forest plots for the fornix-MD and PHC-FA (see Supplementary Figs. 1(e) and 3(c)) also suggested this study to be an outlier.

Next, trim and fill analyses suggested some degree of publication bias in all meta-analyzed outcomes apart from FA in the gCC, IFF, and PC, and MD in the fornix and PC. Nevertheless, even after accounting for such bias via the imputed SMDs, most of these effect sizes were only slightly attenuated and all, except for SLF-FA, had remained statistically significant. Additionally, the direction of effect for FA in the SLF changed from decreased to increased FA in aMCI patients with the imputation of the missing studies. The detailed results for each of the ROI-based meta-analyses and their trim and fill adjusted results are presented in Table 4.

3.3. ALE meta-analysis

All extracted foci for FA and MD were of the aMCI ≪ control and aMCI ≫ > control contrasts respectively; no foci were found in which the FA was greater in aMCI or MD was greater in controls. The ALE meta-analysis for FA (15 studies; $N_{aMCI} = 463$, $N_{controls} = 599$) revealed decreased FA among aMCI relative to control subjects in the bilateral posterior corona radiata (see Table 5 and Fig. 2). No significant cluster emerged in the ALE meta-analysis for MD (8 studies; $N_{aMCI} = 193$, $N_{controls} = 210$).

Leave-one-out analyses suggested that these FA clusters are reliable (see Supplementary Table 3). The left and right posterior corona radiata clusters remained significant after the one-at-a-time exclusion of 12 and 13 studies respectively. In addition, a third cluster- hippocampal cingulum (MNI: 25, −6, −29) was obtained upon the one-at-a-time exclusion of five studies.

4. Discussion

The current meta-analyses sought to examine the white matter alterations in the aMCI population. We included 77 relevant studies and carried out ROI-based and ALE meta-analyses. Overall, the ROI-based meta-analyses revealed significant white matter abnormalities in numerous regions; in particular, these abnormalities were reliably and significantly observed in the fornix, UF, and PHC. On the other hand, ALE meta-analysis showed significant FA decreases in the bilateral posterior corona radiata among aMCI subjects relative to controls.

4.1. ROI-based meta-analyses

The ROI-based meta-analyses revealed significant differences between aMCI and controls in the FA and MD of all studied ROIs (after outliers were removed). These pooled results provide compelling evidence that several white matter tracts are implicated in aMCI patients. It should be noted that many of these findings were associated with

Table 1
Summary information of the subjects in each study included in the meta-analysis.

Study	N (%Male)		Age ± SD		Years of education ± SD		MMSE ± SD	
	aMCI	controls	aMCI	controls	aMCI	controls	aMCI	Controls
Alves et al. (2013)	18 (50)	17 (18)	72.8 ± 6.5	71.2 ± 8.1	10.4 ± 3.5	7.1 ± 4.8	26.2 ± 3.4	28.4 ± 1.4
Bai et al. (2009a)	32 (50)	31 (52)	71.4 ± 5.0	70.4 ± 5.1	13.6 ± 3.3	14.4 ± 3.1	26.8 ± 1.5	28.3 ± 1.3
Bai et al. (2009b)	22 (50)	22 (50)	72.0 ± 4.4	40.2 ± 5.4	12.5 ± 3.1	14.1 ± 3.8	26.8 ± 1.7	28.4 ± 1.5
Benitez et al. (2014)	15 (40)	12 (42)	79.1 ± 7.2	77.5 ± 4.0	15.1 ± 3.7	16.1 ± 2.5	–	–
van Bruggen et al. (2012)	17	15	70.0 ± 5.0	66.0 ± 7.0	–	–	26.0 ± 1.7	–
Carter et al. (2014)	11 (82)	11 (27)	74.1 ± 6.4	69.6 ± 5.5	13.5 ± 4.1	13 ± 3.2	28.6 ± 1.3	29.6 ± 0.5
Chang et al. (2015)	24 (33)	36 (42)	71.8 ± 8.3	70.7 ± 6.0	12.1 ± 3.9	13.7 ± 3.0	27.2 ± 1.7	29.1 ± 1.0
Chen et al. (2009)	13 (31)	16 (50)	73.2 ± 9.3	69.0 ± 8.4	11.4 ± 4.3	10.5 ± 3.8		
Cho et al. (2008)	11 (45)	11 (55)	72.6 ± 7.3	70.6 ± 2.9	10.9 ± 4.4	9.6 ± 4.6	24.9 ± 2.4	28.7 ± 0.8
Choo et al. (2010)	19 (31)	18 (33)	71.6 ± 7.1	70.7 ± 5.2	7.5 ± 5.6	10.7 ± 3.3	35.5 ± 8.4	49.4 ± 8.3
Christiansen et al. (2016)	24 (54)	20 (50)	76.7 ± 7.5	74.0 ± 6.5	–	–	26.0 ± 1.7	
Chua et al. (2009)	55 (55)	153 (39)	80.0 ± 4.4	77.3 ± 4.4	11.8 ± 3.4	11.6 ± 3.2	27.4 ± 1.5	28.5 ± 1.1
Cui et al. (2012)	79 (63)	204 (42)	79.4 ± 4.7	77.7 ± 4.4	12.2 ± 3.8	11.9 ± 3.6	28.2 ± 1.4	28.9 ± 1.1
Defrancesco et al. (2014)	13 (31)	28 (43)	73.3 ± 6.7	72.2 ± 7.1	10.3 ± 4.5	9.5 ± 3.7	25.2 ± 1.7	28.6 ± 1.2
Delano-Wood et al. (2012)	11 (64)	20 (100)	77.9 ± 7.3	78.3 ± 6.3	15.9 ± 2.7	16.7 ± 2.1	–	–
Dimitra et al. (2013)	63 (37)	25 (48)	74.2 ± 3.6	65.3 ± 4.3	–	–	25.9 ± 1.2	28.0 ± 0.6
Eustache et al. (2016)	14 (50)	14 (43)	71.1 ± 4.7	70.9 ± 4.6	11.0 ± 2.9	11.9 ± 2.8	25.8 ± 1.5	28.4 ± 0.8
Fellgiebel et al. (2005)	17 (65)	21 (62)	67.5 ± 8.9	67.7 ± 8.5	–	–	25.3 ± 2.2	28.7 ± 1.1
Fellgiebel et al. (2004)	14 (36)	10 (70)	68.2 ± 9.2	62.0 ± 6.8	–	–	24.6 ± 2.7	28.6 ± 1.3
Fieremans et al. (2013)	12 (50)	15 (33)	79.1 ± 7.2	77.5 ± 4.0	15.1 ± 3.7	16.1 ± 2.5	–	–
Fu et al. (2014)	41 (49)	20 (50)	70.6 ± 6.3	71.0 ± 6.3	12.6 ± 2.0	13.9 ± 2.9	24.7 ± 1.1	29.7 ± 0.5
Fujie et al. (2008)	16 (25)	16 (25)	71.7 ± 7.1	70.9 ± 4.0	11.0 ± 2.2	11.8 ± 2.4	27.2 ± 2.3	29.2 ± 1.2
Gong et al. (2017)	18 (56)	18 (39)	75.0 ± 6.9	73.2 ± 5.5	5.0 ± 4.7	4.9 ± 4.5	23.1 ± 5.4	27.4 ± 2.4
Hong et al. (2015)	29 (34)	28 (32)	70.5 ± 5.2	70.6 ± 6.5	8.6 ± 4.4	8.8 ± 6.2	25.5 ± 2.8	28.7 ± 1.4
Ito et al. (2015)	36 (42)	21 (33)	78.6 ± 7.7	77.4 ± 8.5	–	–	–	–
Jhoo et al. (2010)	17 (29)	15 (33)	70.8 ± 7.0	70.8 ± 5.4	7.7 ± 5.5	10.5 ± 3.3	24.4 ± 3.7	28.4 ± 1.9
Kehoe et al. (2015)	18 (50)	22 (55)	68.8 ± 7.7	68.9 ± 6.5	14.5 ± 3.0	14.4 ± 3.2	27.2 ± 2.1	28.8 ± 1.0
Kiuchi et al. (2014)	43 (86)	41 (44)	75.2 ± 5.3	74.6 ± 6.4	11.6 ± 2.5	12.3 ± 2.1	26.3 ± 1.5	28.9 ± 0.6
Lee et al. (2012)	44 (45)	96 (34)	74.1 ± 7.7	74.1 ± 7.4	12.7 ± 5.8	12.0 ± 5.1	24.6 ± 4.0	27.9 ± 2.3
Li et al. (2013)	40 (48)	37 (49)	65.0 ± 7.3	62.9 ± 5.4	11.4 ± 2.8	11.2 ± 2.4	26.2 ± 1.6	28.3 ± 1.7
Li et al. (2014)	18 (61)	33 (48)	75.4 ± 6.5	72.3 ± 8.3	–	–	27.3 ± 1.8	28.8 ± 1.3
Li et al. (2016)	35 (71)	37 (27)	69.2 ± 8.6	65.1 ± 6.8	8.9 ± 4.3	9.9 ± 4.5	24.6 ± 3.8	27.5 ± 1.9
Liang et al. (2015)	24 (38)	29 (52)	65.4 ± 7.3	63.0 ± 5.4	11.7 ± 2.3	11.0 ± 2.5	26.1 ± 1.8	28.2 ± 1.8
Liao et al. (2010)	20 (50)	21 (48)	73.0 ± 4.0	73.6 ± 5.6	14.9 ± 1.9	13.1 ± 4.1	27.3 ± 1.7	28.2 ± 1.7
Lin et al. (2014)	8 (50)	15 (33)	73.8 ± 8.7	71.1 ± 6.9	10.4 ± 4.3	12.0 ± 3.6	28.5	29.0
Lin et al. (2017)	41 (49)	40 (55)	68.3 ± 6.7	65.4 ± 6.2	–		23.7 ± 4.9	28.6 ± 1.1
Liu et al. (2011)	27 (56)	19 (58)	75.0 ± 6.0	75.0 ± 6.0	8.0 ± 3.0	9.0 ± 3.0	26.0 ± 2.0	28.0 ± 1.0
Liu et al. (2013)	40 (43)	28 (39)	65.7 ± 7.2	63.5 ± 7.2	10.3 ± 4.3	10.5 ± 4.1		
Liu et al. (2016)	83 (54)	85 (52)	69.4 ± 7.5	68.4 ± 6.3	11.9 ± 3.2	12.1 ± 3.0	26.2 ± 2.6	28.3 ± 1.3
Liu et al. (2017)	32 (53)	23 (43)	70.8 ± 6.4	64.6 ± 9.1	8.2 ± 3.7	11.3 ± 3.3	24.1 ± 3.3	28.4 ± 1.5
Medina et al. (2006)	21 (14)	14 (71)	78.0 ± 5.6	77.3 ± 10.1	14.3 ± 3.3	15.1 ± 2.0	26.9 ± 2.1	29.3 ± 0.7
Metzler-Baddeley et al. (2012a)	25 (44)	20 (50)	76.8 ± 7.3	74.0 ± 6.5	14.0 ± 3.7	15.0 ± 2.8	–	–
Metzler-Baddeley et al. (2012b)	25 (44)	20 (50)	76.8 ± 7.3	74.0 ± 6.5	14.0 ± 3.7	15.0 ± 2.8	–	–
Mielke et al. (2009)	25 (72)	25 (44)	75.8 ± 5.3	74.3 ± 7.1	15.7 ± 3.0	16.2 ± 2.6	26.6 ± 2.1	28.8 ± 1.2
Nowrangi et al. (2013)	25 (72)	25 (44)	75.8 ± 5.3	74.3 ± 7.1	15.7 ± 3.0	16.2 ± 2.6	26.6 ± 2.1	28.8 ± 1.2
Oishi et al. (2012)	24	25	75.0 ± 5.2	74.0 ± 7.1	–	–	27.0 ± 2.1	29.0 ± 1.3
O'Dwyer et al. (2011)	14 (50)	61 (34)	68.0 ± 8.0	63.0 ± 7.0	13.0 ± 4.0	13.0 ± 4.0	27.9 ± 3.7	29.4 ± 1.0
Parente et al. (2008)	25 (68)	16 (75)	72.0 ± 9.3	68.0 ± 7.7			28.0 ± 1.2	29.4 ± 0.9
Pievani et al. (2010)	19 (53)	15 (40)	68.5 ± 7.9	69.8 ± 6.0	9.3 ± 4.2	12.3 ± 3.6	26.0 ± 1.2	28.8 ± 1.5
Pineda-Pardo et al. (2014)	37 (51)	52 (29)	74.2 ± 6.5	69.9 ± 4.5	–	–	27.4 ± 2.5	29.3 ± 0.9
Ray et al. (2006)	13 (69)	13 (54)	74.0 ± 6.0	75.0 ± 4.0	–	–	26.8 ± 2.6	28.6 ± 0.8
Rémy et al. (2015)	22 (45)	15 (47)	72.1 ± 4.9	70.5 ± 4.7	–	–	25.0 ± 2.1	28.4 ± 0.7
Rogalski et al. (2009)	14 (29)	14 (64)	76.8 ± 7.0	73.6 ± 6.7	16.5 ± 3.1	16 ± 2.4	26.9 ± 2.0	29.4 ± 0.8
Rose et al. (2006)	17 (59)	17 (59)	73.6 ± 9.0	73.6 ± 9.1	9.7 ± 3.1	11.3 ± 2.9	26.1 ± 2.2	28.2 ± 1.3
Scola et al. (2010)	19 (58)	20 (35)	68.2	65.2	–	–	–	–
Scott et al. (2017)	77 (62)	46 (50)	72.7 ± 7.3	72.9 ± 5.9	–	–	–	–
Selnes et al. (2017)	50 (52)	21 (24)	61.2	62.0	–	–	27.6	29.5
Serra et al. (2012)	16 (44)	13 (69)	72.9 ± 5.9	64.7 ± 9.2	11.3 ± 4.1	13.6 ± 3.3	25.0 ± 1.3	29.0 ± 2.2
Sexton et al. (2010)	8 (38)	8 (38)	77.1 ± 4.6	73.0 ± 7.5	–	–	28.1 ± 1.8	28.8 ± 1.0
Shim et al. (2008)	40 (48)	17 (47)	71.7 ± 6.6	68.8 ± 3.6	9.7 ± 4.6		24.9 ± 2.8	28.7 ± 1.1
Stahl et al. (2007)	16 (56)	19 (42)	68.9 ± 9.3	63.9 ± 10.3	–	–	26.7 ± 2.4	29.3 ± 1.6
Teipel et al. (2014)	37 (59)	32 (63)	70.2 ± 6.3	71 ± 5.4	12.2 ± 3.1	13 ± 3.3	25.7 ± 4.7	28.5 ± 1.2
Ukmar et al. (2008)	15 (27)	18 (56)	72.3 ± 10.5	59.5 ± 6.9	9.1 ± 4.1	14.6 ± 3.3	28.9 ± 0.8	29.9 ± 0.2
Wang et al. (2009)	10 (30)	10 (50)	72.2 ± 7.7	70.1 ± 7.7	14.0 ± 4.0	15.2 ± 4.1	26.4 ± 2.2	29.7 ± 0.5
Wang et al. (2012)	28 (57)	35 (29)	74.3 ± 5.8	71.6 ± 5.2	–	–	27.0 ± 1.9	28.9 ± 1.2
Wang et al. (2013)	12 (42)	12 (42)	73.8 ± 5.4	72.6 ± 5.3	–	–	25.0 ± 1.7	28.8 ± 1.8
Wang et al. (2017)	64 (56)	82 (52)	71.3 ± 6.2	69.2 ± 5.9	–	–	25.8 ± 2.8	28.2 ± 1.3
Weiler et al. (2017)	21 (71)	30 (33)	70.0 ± 9.0	70.0 ± 9.0	9.2 ± 5.5	9.2 ± 5.3	25.5 ± 2.4	28.3 ± 1.9
Wessa et al. (2016)	24 (79)	20 (55)	67.7 ± 4.3	66.7 ± 4.9	11.5 ± 3.3	12 ± 3.8	28.2 ± 1.2	29.0 ± 0.9
Wu et al. (2016)	17 (59)	13 (69)	61.1 ± 9.2	64.2 ± 7.8	8.9 ± 2.8	11.2 ± 3.9	27.2 ± 2.1	28.3 ± 1.7
Zhang et al. (2011)	26 (65)	18 (67)	69.4 ± 7.4	64.7 ± 8.8	11.5 ± 4.2	13.7 ± 4.9	22.2 ± 1.9	27.3 ± 1.0
Zhang et al. (2013)	31 (65)	66 (47)	73.1 ± 7.5	67.2 ± 10.0	–	–	27.5 ± 1.9	29.4 ± 1.0

(*continued on next page*)

Table 1 (*continued*)

Study	N (%Male)		Age ± SD		Years of education ± SD		MMSE ± SD	
	aMCI	controls	aMCI	controls	aMCI	controls	aMCI	Controls
Zhuang et al. (2010)	96 (59)	252 (42)	79.6 ± 4.7	77.9 ± 4.5	12.3 ± 3.8	11.9 ± 3.6	28.1 ± 1.5	28.8 ± 1.1
Zhuang et al. (2012)	76 (66)	206 (43)	80.6 ± 5.0	79.2 ± 4.4	12.5 ± 4.2	12.1 ± 3.7	28.2 ± 1.5	29.2 ± 1.1
Zhuang et al. (2013)	66 (64)	155 (15)	80.9 ± 5.0	79.1 ± 4.4	13.0 ± 4.4	12.0 ± 3.7	–	–
Zimny et al. (2012)	23 (30)	15 (40)	66.0 ± 9.4	69.0 ± 7.9	–	–	27.4 ± 2.4	29.8 ± 0.4
Zimny et al. (2015)	55	15	66.2 ± 9.4	69.0 ± 7.9	–	–	27.1 ± 2.2	29.1 ± 0.4

MMSE = Mini-mental status examination.

significant heterogeneity. For instance, although the largest effect size was noted in the FA of IFF, this effect was also associated a very high level of heterogeneity. Heterogeneity in the ROI results could be attributed to many factors. Firstly, with regards to the participants, there may be heterogeneous presentations of nonmemory-related cognitive impairment in aMCI patients, given that the different subtypes of aMCI (single-domain vs. multiple-domain) were pooled together. Relatedly, previous research has found differences in white matter alterations between different subtypes of aMCI (Haller et al., 2013; Li et al., 2013; Liu et al., 2017). Furthermore, variability within aMCI may also be attributed to the presence or absence of AD-related pathology as assessed via AD-related markers such as the ε4 allele of the Apolipoprotein E gene and/or beta amyloid deposition. For instance, one study has reported amyloid-related differences in white matter diffusivity of the corpus callosum and longitudinal fasciculus among participants with aMCI (Lim et al., 2014). Apart from participants-related factors, differences in the preprocessing of DTI data may also influence the results. For instance, it has been shown that the use of different smoothing kernel sizes in the voxel-based morphometric analyses of DTI data among patients and controls would lead to different results(Jones et al., 2005). Another methodological issue that may contribute to the heterogeneous results relates to whether cerebrospinal-fluid (CSF) contamination have been corrected for using free water correction (Pasternak et al., 2009). This contamination, if uncorrected for, will lead to both type I and II errors in the group differences between MCI and controls, especially in the fornix (Berlot et al., 2014). Metzler-Baddeley et al. (2012a,b,c) further demonstrated that spurious age-related differences in the diffusivity metrics of the fornix could be observed if free water elimination was not performed. This may be a significant concern considering that the age of the participants in both the aMCI and control groups were not evenly matched among the included studies. Given that only a small number of studies have explicitly reported performing free water elimination, it is possible that differences in the diffusivity metrics between aMCI and controls, at least in the fornix, have been over-estimated in the literature

It may be more meaningful to look at the white matter alterations that were more consistently observed across studies instead of the statistical significance of the SMDs. These consistently observed alterations include decreased FA in the fornix and UF as well as increased MD in the gCC, sCC, UF, and PHC. The stability of these white matter alterations across studies suggests that these are perhaps more specific to memory impairments that are supposedly present in aMCI regardless of subtype. More importantly, it was found that both FA and MD outcomes in the UF, fornix, and PHC were significantly and reliably (after excluding outliers) implicated in aMCI. Nevertheless, one should exercise caution in interpreting the findings relating to the fornix, especially in light of the CSF contamination issue described above. Notwithstanding this issue, these findings provide robust impetus for future aMCI classification studies to include fornix, UF, and PHC in their classification models.

Next, in all ROIs but fornix, we observed larger differences between aMCI patients and controls in MD relative to FA. Additionally, these differences in MD were also less heterogeneous than those of FA. Sexton et al. (2011) had obtained similar findings in their meta-analysis and suggested that MD, which measures the absolute level of diffusion, is a more reliable marker of neurodegeneration relative to FA. FA measures the ratio of anisotropic and isotropic diffusion. Hence, while equivalent increases in anisotropic and isotropic diffusivities in the context of AD-related neurodegeneration would correspondingly increase MD or the absolute size of the diffusion ellipsoid, the shape of this ellipsoid or FA would remain unchanged (Acosta-Cabronero et al., 2010). This dissociation between FA and MD is illustrated in one of the studies (Fu et al., 2014) included in the current meta-analysis. The authors of this study reported higher FA among aMCI participants relative to controls in most of the studied ROIs, such as the SLF, which was associated with an atypically large positive effect size in the current study, in contrast to the negative effect sizes computed from most of the studies included for the SLF-FA meta-analysis. Nevertheless, their MD related findings were perhaps more consistent with the present findings; they found decreases in MD, though not statistically significant, among aMCI relative to controls in all of the studied ROIs including the SLF. It is plausible that while the ratio of anisotropic and isotropic diffusion was high among aMCI participants in this study, the overall white matter diffusion or MD among these aMCI participants remain low or at least similar to controls. Perhaps, to obtain a complete picture on the nature of the altered white matter diffusion in aMCI, it important to look at FA and MD together with axial and radial diffusivities. The latter two provide essential information relating to the shape of the diffusion ellipsoid (Acosta-Cabronero et al., 2010). Unfortunately, there were a lot fewer studies, relative to those that studied FA and/or MD, in our initial pool that had looked at both axial and radial diffusivities in aMCI to provide an informed conclusion on this matter. Future research should aim to study all four DTI metrics simultaneously so as to obtain a more comprehensive picture of the white matter abnormalities in aMCI.

Although many of these findings were subjected to some publication biases, in most cases the adjusted findings were not very different from the unadjusted findings, suggesting that publication biases did not have a major influence on the results in general. Relatedly, publication biases were also observed within studies. For instance in some studies, although DTI outcomes were explicitly reported to be extracted from several white matter tracts via DTI atlases, and only a fraction of these white matter tracts (usually the ones with significant findings) was eventually reported.

4.2. ALE meta-analysis

Our ALE meta-analysis revealed a significant FA decrease in the bilateral posterior corona radiata among aMCI patients relative to controls. The corona radiata is a bundle of projection fibers connecting the cortices of the brain with the brainstem via the internal capsule. Decreased FA in the corona radiata has been reported in a coordinate-based meta-analysis comparing AD patients to controls (Yin et al., 2015). Furthermore, semantic and episodic memory were found to correlate with the FA of a white matter cluster that includes the posterior corona radiata, in a sample consisting of AD, aMCI, and healthy control participants (Serra et al., 2010). Taken together, robust evidence from whole-brain studies shows that the FA of the corona radiata is implicated in memory impairments.

Table 2
Summary information of imaging data in each study included in the meta-analysis.

Study	DTI Acquisition parameters			FE	Whole Brain Analyses			ROI data extracted
	Strength (T)	Voxel size (mm)	directions		Type	No. of foci	Threshold	
Alves et al. (2013)	1.5	0.23 × 0.23 × 5.0	25	No	TBSS	FA: 3	$p \ll 0.05$; TFCE & FWE	FA: UF, FN, IFO
Bai et al. (2009a)	1.5	0.95 × 1.25 × 2	25	No	VBA	FA: 8		
Bai et al. (2009b)	1.5	1.88 × 1.88 × 4	25	No				FA: gCC, PC, SLF, IFO
Benitez et al. (2014)	3	2.7 × 2.7 × 2.7	30	No				FA: SLF
van Bruggen et al. (2012)	1.5	2.5 × 2.5 × 2.5	6	No				FA: FN
Carter et al. (2014)	3	1.88 × 1.88 × 2.1	42	No	TBSS	FA: 2	$p \ll 0.05$; TFCE & FWE	FA: UF,SLF, IFO
Chang et al. (2015)	3	2.5 × 2.5 × 2.5	102	No				FA: PC
Chen et al. (2009)	1.5	1.88 × 1.88 × 5	25	No				FA: gCC, sCC; MD: gCC, sCC
Cho et al. (2008)	1.5	2 × 2 × 4	25	No				FA: gCC, sCC, PC, SLF; MD: gCC, sCC, PC
Choo et al. (2010)	3	1.88 × 1.88 × 3.5	25	No				FA: PHC, PC
Christiansen et al. (2016)	3	2.4 × 2.4 × 2.4	30	Yes				FA: FN
Chua et al. (2009)	3	1.95 × 1.95 × 3.50	6	No				MD: gCC, sCC
Cui et al. (2012)	3	1 × 1 × 2.5	32	No				FA: gCC, sCC, PC, SLF, IFO
Defrancesco et al. (2014)	1.2	1.8 × 1.8 × 3.0	6	No	VBA	MD: 2	$p \ll 0.001$ unc, $k \geq 100$	
Delano-Wood et al. (2012)	1.5	1.88 × 1.88 × 3.8	42	No				FA: sCC, PC
Dimitra et al. (2013)	1.5	2 × 2 × 3	15	No				FA: gCC, sCC, PC, SLF; MD: gCC, sCC, PC
Eustache et al. (2016)	3	2 × 2 × 2	32	No	VBA	MD: 3	$p \ll 0.001$; TFCE	
Fellgiebel et al. (2005)	1.5	1.8 × 1.8 × 5	6	No				FA: PC; MD: PC
Fellgiebel et al. (2004)	1.5	5.0 thickness	6	No				FA: gCC, sCC; MD: gCC, sCC,
Fieremans et al. (2013)	3	2.7 × 2.7 × 2.7	30	No	TBSS	FA: 2; MD: 1	$p \ll 0.05$; TFCE & FWE	FA: gCC, sCC; MD: gCC, sCC
Fu et al. (2014)	3	1 × 1 × 2	15	No				FA: gCC, sCC, SLF, IFO; MD: gCC, sCC
Fujie et al. (2008)	3	1.72 × 1.72 × 3	12	No				FA: UF
Gong et al. (2017)	3	2 × 2 × 3	32	No	VBA	FA: 1; MD: 1	$p \ll 0.01$, monte carlo simulation, cluster $p \ll 0.05$	
Hong et al. (2015)	1.5	2 × 2 × 4	25	No				FA: PC; MD: PC
Ito et al. (2015)	3	0.86 × 0.86 × 1.6	6	No				FA: PHC, PC; MD: PHC, PC
Jhoo et al. (2010)	3	1.88 × 1.88 × 3.5	25	No				FA: PHC
Kehoe et al. (2015)	3	2.3 × 2.3 × 2.3	61	Yes				FA: FN; MD: FN
Kiuchi et al. (2014)	1.5	2.0 × 2.0 × 2.0	6	No	VBA	FA: 6; MD: 20		
Lee et al. (2012)	1.5	1.7 × 1.7 × 5	6	No				FA: FN
Li et al. (2013)	3	2 × 2 × 2	30	No				FA: gCC, sCC, FN, SLF; MD: gCC, sCC, FN
Li et al. (2014)		2 × 2 × 4		No				FA: UF, FN; MD: UF, FN
Li et al. (2016)	3	2.0 × 2.0 × 2.0	30	No	TBSS	FA: 1; MD: 1	$p \ll 0.05$; TFCE & FWE, $k \gg > 100$	
Liang et al. (2015)	3	2.0 × 2.0 × 2.0	30	No				FA: UF, SLF, IFO
Liao et al. (2010)	3	1.8 × 1.8 × 3.0	64	No				FA: gCC, sCC, PHC, PC; MD: gCC, sCC, PHC, PC
Lin et al. (2014)	3	2.5 × 2.5 × 2.5	102	No				FA: PC
Lin et al. (2017)	3	2 × 2 × 2	64	No	TBSS	MD: 3	$p \ll 0.05$; TFCE & FWE	MD: PHC, PC
Liu et al. (2011)	1.5	1.72 × 1.72 × 5	30	No				FA: gCC, sCC, FN, PHC, SLF
Liu et al. (2013)	3	2 × 2 × 2	32	No	TBSS	FA: 5	$p \ll 0.05$; TFCE & FWE	
Liu et al. (2016)	3	2.0 × 2.0 × 2.0	30	No				FA: gCC, UF, FN; MD: gCC,UF, FN
Liu et al. (2017)	3	2 × 2 × 5	12	No				FA: SLF
Medina et al. (2006)	1.5	1.88 × 1.88 × 6	6	No	VBA	FA: 12	cluster multiple comparison correlation, $p \ll 0.01$; $k \geq 7$	
Metzler-Baddeley et al. (2012a,b,c)	3	2.4 × 2.4 × 2.4	30	Yes				FA: PHC, PC; MD: PC
Metzler-Baddeley et al. (2012a,b,c)	3	2.4 × 2.4 × 2.4	30	Yes				FA: UF; MD: UF, FN
Mielke et al. (2009)	3	2.2 × 2.2 × 2.2	32	No				FA: sCC, FN, PC
Nowrangi et al. (2013)	3	2.2 × 2.2 × 2.2	32	No				FA: sCC, FN, PC; MD: sCC, FN, PC
Oishi et al. (2012)	3	2.2 × 2.2 × 2.2	30	No				FA: FN
O'Dwyer et al. (2011)	3	2 × 2 × 2	15	No				FA: UF, PHC, SLF; MD: UF, PHC
Parente et al. (2008)	1.5	1.8 × 1.8 × 5	6	No				FA: sCC, PC, SLF
Pievani et al. (2010)	1.5	1.88 × 1.88 × 2.5	12	No				FA: UF, FN, SLF, IFO; MD: UF, FN
Pineda-Pardo et al. (2014)	1.5	2.4 × 2.4 × 2.4	25	No	VBA	FA: 10	$p \ll 0.001$; unc, $k \gg > 20$	
Ray et al. (2006)	1.5	0.86 × 0.86 × 1.5	3	No				MD: PC, PHC
Rémy et al. (2015)	3	2.0 × 2.0 × 2.0	32	No	TBSS	FA: 5	$p \ll 0.05$; TFCE & FWE	FA: UF, FN, PHC; MD: FN, PHC
Rogalski et al. (2009)	1.5	1.95 × 1.95 × 3	24	No				FA: PHC; MD: PHC

(*continued on next page*)

Table 2 (*continued*)

Study	DTI Acquisition parameters			FE	Whole Brain Analyses			ROI data extracted
	Strength (T)	Voxel size (mm)	directions		Type	No. of foci	Threshold	
Rose et al. (2006)	1.5	1.8 × 1.8 × 2.5		No	VBA	FA: 6; MD: 6	$p \ll 0.001$; multiple comparison correction, $k \geq 20$	
Scola et al. (2010)	1.5	1.95 × 1.95 × 6		No				FA: gCC, sCC; MD: gCC, sCC
Scott et al. (2017)		2.7 × 2.7 × 2.7		No				FA: gCC, sCC, UF, FN, SLF, IFO; MD: gCC, sCC, UF, FN
Selnes et al. (2017)	1.5	1 × 1.2 × 1.2 and 1 × 1.33 × 1.33	12	No				FA: PHC, PC; MD: PHC, PC
Serra et al. (2012)	3	2.3 × 2.3 × 2.3	61	No				FA: UF
Sexton et al. (2010)		2.3 × 2.3 × 2.8	51	No				MD: FN
Shim et al. (2008)	1.5	2.0 × 2.0 × 5.0	25	No				FA: gCC, sCC; MD: gCC, sCC
Stahl et al. (2007)	1.5	1.8 × 1.8 × 3.6		No				FA: gCC, sCC; MD: gCC, sCC
Teipel et al. (2014)	3	2.2 × 2.2 × 3		No	VBA	FA: 6	ICA 5 components	
Ukmar et al. (2008)	1.5	2.0 thickness	32	No				FA: gCC, sCC,
Wang et al. (2009)	1.5	0.945 × 0.945 × 2	16	No				FA: gCC, sCC
Wang et al. (2012)	1.5	1.88 × 1.88 × 3	12	No				FA: PHC; MD: PHC
Wang et al. (2013)	3	2 × 2 × 5	25	No				FA: sCC; MD: sCC
Wang et al. (2017)	3	2 × 2 × 2	30	No				MD: UF
Weiler et al. (2017)	3	2.0 × 2.0 × 5.0	32	No				FA: PHC; MD: PHC
Wessa et al. (2016)	3	2 × 2 × 2	40	No	TBSS	FA: 2	$p \ll 0.05$; TFCE & FWE	
Wu et al. (2016)	3	3.33 × 3.33 × 3	15	No				FA: UF, IFO
Zhang et al. (2011)	1.5	2 × 2 × 2.5		No				MD: PC
Zhang et al. (2013)	4	2 × 2 × 3	6	No				FA: gCC, sCC, UF, FN, PHC, PC, SLF, IFO
Zhuang et al. (2010)	3	1 × 1 × 2.5	32	No	TBSS	FA: 35	$p \ll 0.05$; TFCE & FWE	
Zhuang et al. (2012)	3	1 × 1 × 2.5	32	No				FA: FN
Zhuang et al. (2013)	3	1 × 1 × 2.5	32	No				MD: FN, UF
Zimny et al. (2012)	1.5	1.88 × 1.88 × 5	25	No				FA: gCC, sCC, SLF, IFO
Zimny et al. (2015)	1.5	1.88 × 1.88 × 5	25	No				FA: PC

FE = Free Water Elimination; ROI = regions of interest; TBSS = tract-based spatial statistics; VBA = voxel-based analysis; FA = fractional anisotropy; MD = mean diffusivity; TFCE = threshold-free cluster enhancement; FWE = family-wise error; ICA = independent component analysis; unc = uncorrected; k = cluster size (no. of voxels); gCC = Genu of corpus callosum; sCC = Splenium of corpus callosum; UF = Uncinate fasciculus; FN = Fornix; PHC = Parahippocampal cingulum; PC = Posterior cingulum; SLF = Superior longitudinal fasciculus; IFF = Inferior frontooccipital fasciculus.

However, our findings relating to the whole-brain MD differences between aMCI and controls were less conclusive. Unlike FA, no significant cluster had emerged in the whole-brain MD meta-analysis. It is likely that the null finding was due to the very limited number of whole-brain MD studies included in the meta-analysis. Given the strong MD-related findings reported in the above ROI-based meta-analysis, one could expect potentially significant and meaningful clusters to emerge when more whole-brain MD studies are included. Future meta-analyses may consider repeating such an analysis as soon as a sizable number of whole-brain MD studies have been accumulated.

Interestingly, very little research has been done on such white matter abnormalities among ROI studies in the MCI population. In fact, only one study (Thillainadesan et al., 2012) in our initial pool of studies had examined the corona radiata ROI. In this study, a significant MD increase in the bilateral corona radiata among aMCI participants relative to controls was observed. The fact that these corona radiata findings emerged mostly from whole-brain analyses and that this region was hardly ever studied among ROI researchers, highlights the value of whole-brain approaches and a major limitation of hypothesis-driven ROI approaches. The a priori selection of certain ROI may unnecessarily narrow the search in the brain for aMCI-related white matter abnormalities; important brain regions such as the corona radiata were excluded in the process. Nevertheless, the robust whole-brain finding relating to the posterior corona radiata reported here could provide a strong impetus for future ROI-based research to study this region.

It is noteworthy that the ALE meta-analysis did not reveal any significant differences in the FA or MD of limbic regions such as the ones studied in the ROI meta-analyses. We suspect that such null findings may simply be related to the small number of whole brain studies included. Relatedly, the leave-one-out analyses did, in fact, reveal decreased FA in the hippocampal cingulum among aMCI participants upon the exclusion of five studies. Given the small pool of studies, these five studies may have a considerable influence in determining the results in the hippocampal cingulum region. It is plausible that if the whole brain meta-analysis were carried out with a larger pool of studies, significant differences in FA or even MD of the white matter in the limbic region would be observed.

The lack of convergence between the ROI and whole-brain meta-analyses does not necessarily invalidate their respective findings. Notwithstanding the limited number of whole brain studies, the lack of convergence between ROI and whole-brain results have been widely documented and such difference may be attributed to the unique

Table 3
Meta-analyses on the demographic differences between aMCI and controls.

	N_{aMCI}	$N_{control}$	k	Estimate[a]	SE	95% CI	*Q*	I^2
MMSE	1816	2105	57	−1.35***	0.08	−1.51, −1.19	191.13***	73.88
Education	1180	1509	46	−0.16**	0.05	−0.26, −0.06	65.60*	28.51
Age	1844	2106	67	0.30***	0.05	0.21, 0.39	116.75***	45.17
Gender distribution	1844	2106	67	0.06*	0.02	0.01, 0.10	139.12***	54.89

N = sample size; k = number of studies; SE = standard error; CI = confidence intervals; MMSE = Mini–Mental State Examination. [a]Standardized mean difference for MMSE, education and age, φ for gender distribution. *$p \ll .05$; **$p \ll .01$; ***$p \ll .001$.

Table 4
Results of the ROI-based meta-analyses.

	N_{aMCI}	$N_{control}$	k	SMD	SE	95% CI	Q	I^2
Fractional Anisotropy								
Genu of corpus callosum	656	696	20	−0.36***	0.09	−0.53, −0.19	35.63*	49.09
Splenium of corpus callosum	649	687	23	−0.38***	0.09	−0.56, −0.20	47.39**	55.06
TAF adjusted			25	−0.32**	0.10	−0.51, −0.13	58.88***	61.23
Fornix	588	767	17	−0.54***	0.06	−0.67, −0.42	20.33	11.87
TAF adjusted			19	−0.50***	0.07	−0.64, −0.36	28.69	31.19
Uncinate fasciculus	391	440	14	−0.37***	0.09	−0.54, −0.20	18.66	22.94
TAF adjusted			17	−0.26*	0.11	−0.47, −0.04	33.84	55.70
Superior longitudinal fasciculus	554	632	17	−0.23	0.20	−0.62, 0.17	101.63***	89.30
TAF adjusted			22	0.09	0.21	−0.31, 0.50	163.09***	91.39
Inferior frontooccipital fasciculus	362	458	11	−0.86**	0.27	−1.38, −0.33	84.71***	90.56
Posterior cingulum	588	645	19	−0.38*	0.15	−0.68, −0.08	86.08***	82.26
Parahippocampal cingulum	324	356	13	−0.46**	0.16	−0.78, −0.15	41.37***	72.52
TAF adjusted			16	−0.31*	0.16	−0.62, −0.00	56.27***	75.40
Mean Diffusivity								
Genu of corpus callosum	514	505	15	0.49***	0.09	0.32, 0.66	20.92	32.92
TAF adjusted			18	0.39***	0.11	0.18, 0.60	37.96**	60.12
Splenium of corpus callosum	468	457	16	0.40***	0.07	0.25, 0.54	17.05	6.48
TAF adjusted			17	0.37***	0.08	0.22, 0.52	19.72	12.24
Fornix	401	461	11	0.42***	0.10	0.21, 0.62	19.47*	45.72
TAF adjusted			13	0.34**	0.12	0.11, 0.57	26.58**	57.96
Uncinate fasciculus	366	497	8	0.49***	0.07	0.35, 0.64	5.20	≪0.01
TAF adjusted			10	0.45***	0.07	0.32, 0.59	10.34	≪0.01
Posterior cingulum	356	264	12	0.43**	0.17	0.11, 0.76	40.59***	72.84
Parahippocampal cingulum	284	291	11	0.51***	0.11	0.29, 0.73	16.92	34.69
TAF adjusted			12	0.45***	0.12	0.21, 0.70	21.97*	48.09

N = sample size; k = number of studies; SMD = standardized mean-difference, SE = standard error; CI = confidence intervals; TAF = Trim and Fill; TAF adjusted results are provided only if studies were imputed in the analysis. *$p \ll .05$; **$p \ll .01$; ***$p \ll .001$.

Table 5
Results of the ALE meta-analysis (15 studies; N_{aMCI} = 463, $N_{controls}$ = 599).

Brain region	Coordinates (MNI)			Volume (mm^3)	Extrema value
	X	Y	Z		
Right posterior corona radiata	21	−45	38	696	0.016
Left posterior corona radiata	−27	−53	23	640	0.016

limitations of each method (Douaud et al., 2006; Giuliani et al., 2005; Good et al., 2002; Szycik et al., 2009). Although the ROI method lacks spatial precision and is limited by its hypothesis-driven nature, the normalization procedure used in whole-brain studies attenuates group differences and rests on the debatable assumption that the brains of aMCI subjects and healthy controls can be forced into a common standard space (Giuliani et al., 2005; Laird et al., 2005a,b,c). As such, these different findings emphasize the complementarity of both methods and the need for both to be carried out to obtain a complete picture.

4.3. Implications

The validation of these neuroimaging markers in aMCI patients would go a long way in refining the implementation of AD diagnoses. Although neuroimaging tests are currently not recommended for routine AD-related diagnostic assessments, neuroimaging markers are nevertheless essential in indicating the presence of AD pathophysiological processes and ruling out dementia that is due to AD (McKhann et al., 2011). In showing that these white matter alterations do occur reliably at the prodromal stage of AD (i.e., aMCI), these alterations can be exploited as sensitive markers to track the progress of AD-related pathophysiology. Just as hippocampal and medial temporal lobe atrophy has been widely implemented as a biomarker for AD (Albert et al., 2011; McKhann et al., 2011), these white matter alterations could be used alongside such brain structural data to assist AD diagnoses. Furthermore, considering that a certain temporal order of observable neuroimaging markers exists in AD (Villain et al., 2010), an examination of these white matter alterations together with the other biomarkers of AD would provide additional information relating to the staging of AD.

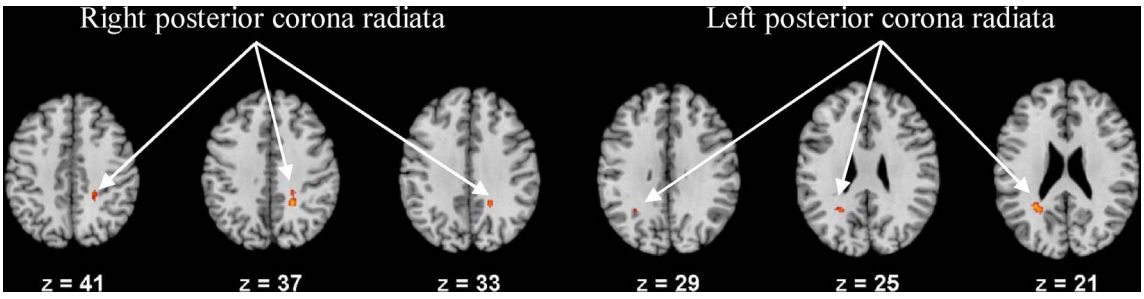

Fig. 2. Reduced FA in aMCI relative to controls in the bilateral posterior corona radiata (in red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.4. Limitations

The significant meta-analyzed estimates relating to age, education and gender distribution differences between aMCI and control participants indicate that both groups were not evenly matched on these levels. As such it is plausible that these variables may exert an extraneous influence on the DTI outcomes in both the ROI and ALE meta-analyses. Furthermore, the high level of heterogeneity observed in the MMSE scores between aMCI patients and controls suggests that heterogeneous standards were used in implementing the aMCI criteria across studies, consequently resulting in unwanted confounding influences on the DTI outcomes. Studies that used more stringent aMCI criteria will naturally obtain larger MMSE score differences and correspondingly larger effects on their FA and MD outcomes. The heterogeneous implementation of the MCI criteria remains an unresolved issue in the field and requires future work among clinicians and researchers to reach a consensus on a ubiquitous set of standards (Petersen et al., 2014). Finally, the fact that only whole-brain studies with significant findings could be included in the ALE meta-analysis may render its meta-analytic results highly susceptible to publication bias. The nonsignificant results from many whole-brain studies were unaccounted for as a result. Hence, a need exists for future ROI-based meta-analyses (when a sizable pool of ROI studies on the corona radiata have been accumulated) to replicate the findings of the current ALE meta-analysis and to examine the influence of publication bias.

4.5. Conclusions

This timely meta-analytical study sought to synthesize more than a decade of research on the white matter alterations in aMCI patients. The ROI-based meta-analyses revealed significant and moderate-to-large FA decreases and MD increases in many ROIs among aMCI patients relative to controls. However, many of these findings were associated with significant heterogeneity. Nevertheless, reliable FA and MD alterations were observed in the fornix, UF, and PC. Additionally, the ALE meta-analysis revealed a significant FA decrease among aMCI subjects in the bilateral posterior corona radiata. The differences in the findings of both types of meta-analyses highlight the importance of carrying out both ROI-based and whole-brain-based research to obtain a complete picture. These findings present important implications for the direction of future aMCI research and AD diagnoses.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2017.10.026.

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