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Shared and differing functional connectivity abnormalities of the default mode network in mild cognitive impairment and Alzheimer's disease

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Abstract

Alzheimer's disease (AD) and mild cognitive impairment (MCI) both show abnormal resting-state functional connectivity (rsFC) of the default mode network (DMN), but it is unclear to what extent these abnormalities are shared. To elucidate this, we performed a systematic review and meta-analysis of rsFC studies applying seed-based whole-brain analysis or independent component analysis to MCI or AD. We identified 31 eligible studies involving 960 MCI patients with cognitive decline and 20 studies involving 569 patients with AD dementia. MCI patients, compared to healthy controls, showed decreased rsFC within DMN (in bilateral medial prefrontal cortex/anterior cingulate cortex (mPFC/ACC), precuneus/posterior cingulate cortex (PCC), right superior and middle temporal gyri, and left angular gyrus) and increased rsFC between DMN and left inferior temporal gyrus. AD patients, compared to controls, showed decreased rsFC within DMN (in mPFC/ACC and precuneus/PCC) and between DMN and inferior occipital gyrus, and increased rsFC between DMN and right middle and inferior frontal gyri. Conjunction/disjunction analysis showed that MCI and AD shared decreased rsFC within DMN (in bilateral mPFC/ACC and precuneus/PCC). Compared to MCI, AD had decreased rsFC within DMN (in precuneus/PCC) and between DMN and left inferior occipital gyrus, and increased rsFC within DMN (in right superior and middle temporal gyri). Thus MCI and AD share a decrease in rsFC within regions of DMN likely underpinning episodic memory deficits and neuropsychiatric symptoms, but differ in DMN rsFC alterations likely related to impairments in other cognitive domains such as language, vision and execution. This may throw light on neuropathological mechanisms in these two stages of dementia.

Key words: Alzheimer's disease; mild cognitive impairment; default mode network; resting-state functional connectivity; meta-analysis.

1. Introduction

On the continuum of cognitive decline, mild cognitive impairment (MCI) is the symptomatic predementia stage, manifesting as objective cognitive decline but with no detectable impact on activities of daily living (Langa and Levine 2014). MCI patients progress to dementia at 10-15% per year, compared to 1-2% per year of the healthy elderly (Wee et al. 2012), and more than half within 5 years (Gauthier et al. 2006). Alzheimer's disease (AD) is the commonest dementia, characterized by progressive impairments in cognitive function (especially episodic memory) and neuropsychiatric symptoms (behavior symptoms) that affect daily life (McKhann et al. 2011). Patients with AD dementia have typically passed through the MCI stage before a full dementia diagnosis (Gauthier et al. 2006). Cognitive impairments in both AD and MCI involve multiple domains including episodic memory, executive function, attention, language, and visuospatial skills (McKhann et al. 2011). There is no curative treatment for AD dementia, but the hope is that it might be possible to slow or stop evolution at the MCI stage. However, the neuropathological substrates underlying cognitive decline at the different stages of dementia are not fully clear.

Normal cognitive function depends on the integrity of large-scale brain networks (Luo et al. 2022; You et al. 2022; Luo, Chen, et al. 2023; Luo, Li, et al. 2023). The default mode network (DMN) has received particular attention because of its early involvement in the AD continuum and its vital role in cognitive functions such as social cognition, semantic and episodic memory (Sperling et al. 2010; Smallwood et

al. 2021). Resting-state functional magnetic resonance imaging (rsfMRI), conveniently both non-invasive and task-free, has been widely used to demonstrate abnormalities of resting-state functional connectivity (rsFC) in both MCI and AD (Sperling et al. 2010; Wang et al. 2012). In MCI, decreased rsFC between angular gyrus and right precuneus correlated with poor episodic verbal learning and memory (Liang et al. 2012), increased rsFC between medial prefrontal cortex (mPFC) and parahippocampus/posterior hippocampus was related to impaired semantic memory (Gardini et al. 2015), and more severe global cognitive impairment was associated with increased rsFC in bilateral mPFC/anterior cingulate cortex (ACC), left angular gyrus, and right temporal pole (Wang et al. 2018). In AD, decreased rsFC between right temporoparietal cortices and left hippocampus correlated with lower Mini-Mental State Examination (MMSE) scores (Zhou et al. 2022), decreased rsFC between posterior cingulate cortex (PCC) and occipital regions correlated with impaired visuospatial function (Zhang et al. 2009), and DMN hypoconnectivity correlated with worse episodic memory (Weiler, Fukuda, et al. 2014).

Identifying the shared and differing patterns of DMN dysconnectivity in MCI and AD should help in understanding the underlying neuropathology. Few studies have directly compared DMN rsFC alterations in MCI and AD, and the findings have been varied (Gili et al. 2011; Wang et al. 2019). Previous meta-analyses of rsfMRI studies have revealed diverse abnormalities in MCI and AD patients compared to healthy controls (HC) (Jacobs et al. 2013; Lau et al. 2016; Badhwar et al. 2017; Pan et al. 2017; Wang et al. 2018; Eyler et al. 2019; Gu and Zhang 2019; Zhang et al. 2021; Yang et al. 2023) (Table S1), most consistently decreased local spontaneous activity and rsFC in precuneus/PCC in both MCI and AD. However, most meta-analyses have focused on MCI (Lau et al. 2016; Pan et al. 2017; Wang et al. 2018; Eyler et al. 2019;

Gu and Zhang 2019; Zhang et al. 2021); none have quantitatively compared DMN rsFC alterations between MCI and AD; and most have used meta-analysis methods excluding studies with null findings (Lau et al. 2016; Badhwar et al. 2017; Eyler et al. 2019; Gu and Zhang 2019; Zhang et al. 2021), which risks selection bias (Radua et al. 2012).

Therefore, to define shared and differing DMN rsFC alterations in MCI and AD, we conducted a quantitative and coordinate-based meta-analysis of published rsfMRI studies. We hypothesized that: 1) both patient groups would show shared decreases in rsFC in brain midline structures in DMN including precuneus/PCC and mPFC/ACC, more severe in AD than MCI; 2) patients with MCI and AD would show rsFC alterations differing in severity and/or distribution, reflecting their differing stages of dementia development.

2. Materials and Methods

2.1. Search strategy and selection criteria

The meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table S2). The protocol was registered on PROSPERO (CRD42023387809). We retrieved studies published up to 30 June 2023 in the PubMed, Web of Science, and Embase databases. Search terms included “mild cognitive impairment” or “MCI” or “Alzheimer's disease” or “Alzheimer disease” or “Alzheimer's” or “dementia of the Alzheimer’s type” or “Alzheimer’s dementia” plus “fMRI” or “functional magnetic resonance imaging” or “rsfMRI” or “functional connectivity” or “resting state functional connectivity” or “default mode network” or “DMN”. We manually searched the references cited by the

included studies and pertinent review articles. Studies were independently ascertained and checked by two co-authors (Y.X.W and L.Y). Any inconsistencies were discussed, and a consensus was reached.

Studies were included if they met the following criteria: 1) original MR studies using seed-based whole-brain analysis or independent component analysis (ICA) at the voxel level to compare DMN rsFC in patients with MCI or AD with HC; 2) seed-based rsFC studies used at least one seed region of interest (ROI) falling within DMN, as defined by a published whole brain network parcellation in 1000 healthy participants (Buckner et al. 2011; Yeo et al. 2011); 3) ICA studies obtained a network that largely overlapped with or fell within DMN, defined by the same parcellation; 4) the peak effect coordinates were reported in standard stereotaxic spaces (e.g. Montreal Neurological Institute or Talairach). To avoid selection bias, we did not exclude studies with null findings (i.e. those that did not survive statistical correction or showed no between-group differences in DMN rsFC), but assigned them conservatively a null effect size. We excluded seed-based whole-brain analysis or ICA studies if the peak coordinates of effects could not be retrieved even after attempting to contact the corresponding authors by email. Publications reporting on the same sample but with different seed ROIs or different analyses (i.e. seed-based *vs* ICA methods) were considered as separate datasets. Studies in which different subgroups of MCI or AD were each compared with either a single HC group or two corresponding HC groups were coded as distinct datasets. For longitudinal studies, only baseline data were included. Specifically, for a study that applied two models (model 1 and model 2) to control covariates (Pini et al. 2020), we extracted the results using model 2 since this included cognitive status as a covariate. For one study (Tuovinen et al. 2016), we extracted the results obtained by gray matter ICA

controlling for the coefficient of variation in each voxel, suggested as a strict approach to atrophy correction.

2.2. Meta-analysis

We conducted the meta-analysis using seed-based d mapping (SDM) software (version 5.15) (Radua et al. 2012). SDM uses the coordinates of peak effects and effect sizes of significant differences between patients and HC to recreate an effect-size brain map for each study (including both positive and negative results). The mean map was obtained by a random-effects analysis. Separate meta-analyses were conducted to identify DMN rsFC alterations in each patient group relative to HC and statistical significance was established by using standard randomization tests. We then performed a quantitative comparison between MCI and AD by calculating the difference in each voxel (Zhao et al. 2022). The meta-analyses were conducted with the default SDM threshold ($P < 0.005$ with peak $Z > 1$), recommended to ensure optimal balance between sensitivity and specificity, and an approximate equivalent to corrected $P < 0.05$ (Radua et al. 2012; Li et al. 2020). To minimize false-positive errors, we set the recommended extent threshold at 100 voxels (Tang et al. 2018). Using the probability maps obtained in the separate meta-analyses, we used the multimodal analysis in SDM to perform a conjunction/disjunction analysis investigating regions of shared/differing aberrant DMN rsFC relative to HC across both patient groups. To minimize false-positive errors, we determined the conjunction/disjunction threshold by computing the union of the P values for each patient group within each voxel, accounting for the noise in their estimation (Yao, Yang, et al. 2021); thus, a more stringent probability threshold was employed for

conjunction/disjunction analysis ($P < 0.0025$) than in the separate meta-analyses. Details of quality assessment, data extraction, method of meta-analyses**,** conjunction/disjunction analysis, jackknife, heterogeneity, publication bias analysis, and meta-regression are presented in Supplementary Methods.

MCI patients can be clinically classified into four subtypes: single-domain amnestic MCI (aMCI), multiple-domain aMCI, single-domain non-amnestic MCI (non-aMCI), and multiple-domain non-aMCI (Petersen et al. 2001). The number of included aMCI studies was allowed to conduct a subgroup meta-analysis. To evaluate potential methodology effects, we also conducted subgroup meta-analyses of seed-based studies, ICA studies, and studies with and without correction for gray matter volume (GMV) in both MCI and AD.

Based on the location of the significant clusters obtained from the meta-analysis, we classified them into the following seven resting-state networks for presentation and discussion (Buckner et al. 2011; Yeo et al. 2011): DMN, frontoparietal network (FPN), ventral attention network, dorsal attention network, affective network (AN; sometimes also known as limbic network), somatomotor network, and visual network (VN).

3. Results

3.1. Characteristics of included studies

Figure S1 shows the flowchart of literature search and eligibility assessment. There were two MCI studies (Yue et al. 2015; Zhang et al. 2019) and two AD studies (Whitwell et al. 2015; Wu et al. 2016) that met all the inclusion criteria for our meta-

analysis but for which the peak coordinates of effects could not be retrieved even after contacting the corresponding authors; these studies were excluded. We finally included 31 MCI studies (34 datasets) comprising 960 MCI patients (age 70.9 ± 7.6 years) and 1084 HC (age 68.0 ± 8.1 years) (Table S3) and 20 AD studies (24 datasets) comprising 569 AD patients (age 69.9 ± 9.1 years) and 661 HC (age 66.4 ± 8.5 years) (Table S4). Three studies did not report the percentage of females (Kenny et al. 2012; Balthazar et al. 2014; Cera et al. 2019), and for the rest, there were 489 (51.8%) female MCI patients and 588 (55.2%) corresponding female HC, and 287 (53.8%) female AD patients and 339 (54.0%) corresponding female HC. Demographic and methodological details of the included studies are given in the Supplementary Results and Tables S3-S6. Study quality assessments are given in Tables S7 and S8.

3.2. Altered DMN rsFC in MCI and AD

Relative to HC, patients with MCI showed decreased rsFC within DMN, in bilateral mPFC/ACC, bilateral precuneus/PCC, right superior and middle temporal gyri, left angular gyrus, and left middle temporal gyrus, and increased rsFC between DMN and left inferior temporal gyrus (belonging to AN) (Table 1, Figures 1A and 2A). Relative to HC, patients with AD showed decreased rsFC within DMN, in bilateral precuneus/PCC and bilateral mPFC/ACC, decreased rsFC between DMN and left inferior occipital gyrus (belonging to VN), and increased rsFC between DMN and right middle and inferior frontal gyri (belonging to FPN) (Table 1, Figures 1B and 2B). Conjunction/disjunction analysis revealed a shared decreased rsFC within DMN in bilateral mPFC/ACC and precuneus/PCC (Table 1 and Figure 1D) in both MCI and AD. Relative to MCI, AD showed decreased rsFC within DMN located in

precuneus/PCC and between DMN and left inferior occipital gyrus, and increased rsFC within DMN located in right superior and middle temporal gyri (Table 1, Figures 1C and 2C).

Table 1. Results of meta-analyses of altered DMN rsFC in MCI and AD

Comparison	Effect network	MNI coordinates	SDM Z value	P value	Voxels
MCI vs HC (see Fig 1A): all the abnormalities in MCI					
MCI < HC					
Bilateral medial prefrontal cortex/anterior cingulate cortex	DMN	-2,50,6	-4.001	< 0.0001	3133
Bilateral precuneus/posterior cingulate gyrus	DMN	4,-52,28	-2.931	< 0.0001	2800
Right superior and middle temporal gyri	DMN	54,-6,-10	-2.284	0.0001	1212
Left angular gyrus	DMN	-40,-70,40	-2.081	0.0003	794
Left middle temporal gyrus	DMN	-60,-30,-10	-1.942	0.0006	207
MCI > HC					
Left inferior temporal gyrus	AN	-44,-22,-30	1.028	0.0001	199
AD vs HC (see Fig 1B): all the abnormalities in AD					
AD < HC					
Bilateral precuneus/posterior cingulate gyrus	DMN	4,-40,26	-3.897	< 0.0001	4180
Bilateral medial prefrontal cortex/anterior cingulate cortex	DMN	2,42,8	-3.266	< 0.0001	2738
Left inferior occipital gyrus	VN	-22,-94,-10	-1.984	0.0016	329
AD > HC					
Right middle and inferior frontal gyri	FPN	50,30,16	1.319	< 0.0001	1879
AD (vs HC) vs MCI (vs HC) (see Fig 1C): disjunction between the abnormalities in MCI and AD					
AD (vs HC) < MCI (vs HC)					
Left posterior cingulate gyrus	DMN	-4,-44,20	-2.718	< 0.0001	733
Left inferior occipital gyrus	VN	-22,-94,-8	-1.699	0.0008	302

Left precuneus	DMN	-6,-58,54	-1.588	0.0015	165
AD (vs HC) > MCI (vs HC)					
Right superior and middle temporal gyri	DMN	58,-4,-12	1.348	0.0002	724
AD (vs HC) vs MCI (vs HC) (see Fig 1D): conjunction between the abnormalities in MCI and AD					
Both (AD < HC) and (MCI < HC)					
Bilateral precuneus/posterior cingulate gyrus	DMN	4,-52,30	-	-	1934
Bilateral medial prefrontal cortex/anterior cingulate cortex	DMN	2,44,6	-	-	1608

Abbreviations: MCI, mild cognitive impairment; HC, healthy controls; AD, Alzheimer's disease; DMN, default mode network; VN, visual network; FPN, frontoparietal network; AN, affective network; rsFC, resting-state functional connectivity.

Figure 1. Results of meta-analyses of altered DMN rsFC in MCI and AD. (A) All the abnormalities in MCI: regions of decreased rsFC (blue) and increased rsFC (red) in MCI compared to HC. (B) All the abnormalities in AD: regions of decreased rsFC (green) and increased rsFC (violet) in AD compared to HC. (C) Disjunction between abnormalities in MCI and AD: regions of decreased rsFC (purple) and increased rsFC (yellow) in AD compared to MCI (D) Conjunction between abnormalities in MCI and AD: regions of shared decreased rsFC (brown) in both MCI and AD. Abbreviations: MCI, mild cognitive impairment; AD, Alzheimer's disease; versus; HC, healthy controls; DMN, default mode network; rsFC, resting-state functional connectivity.

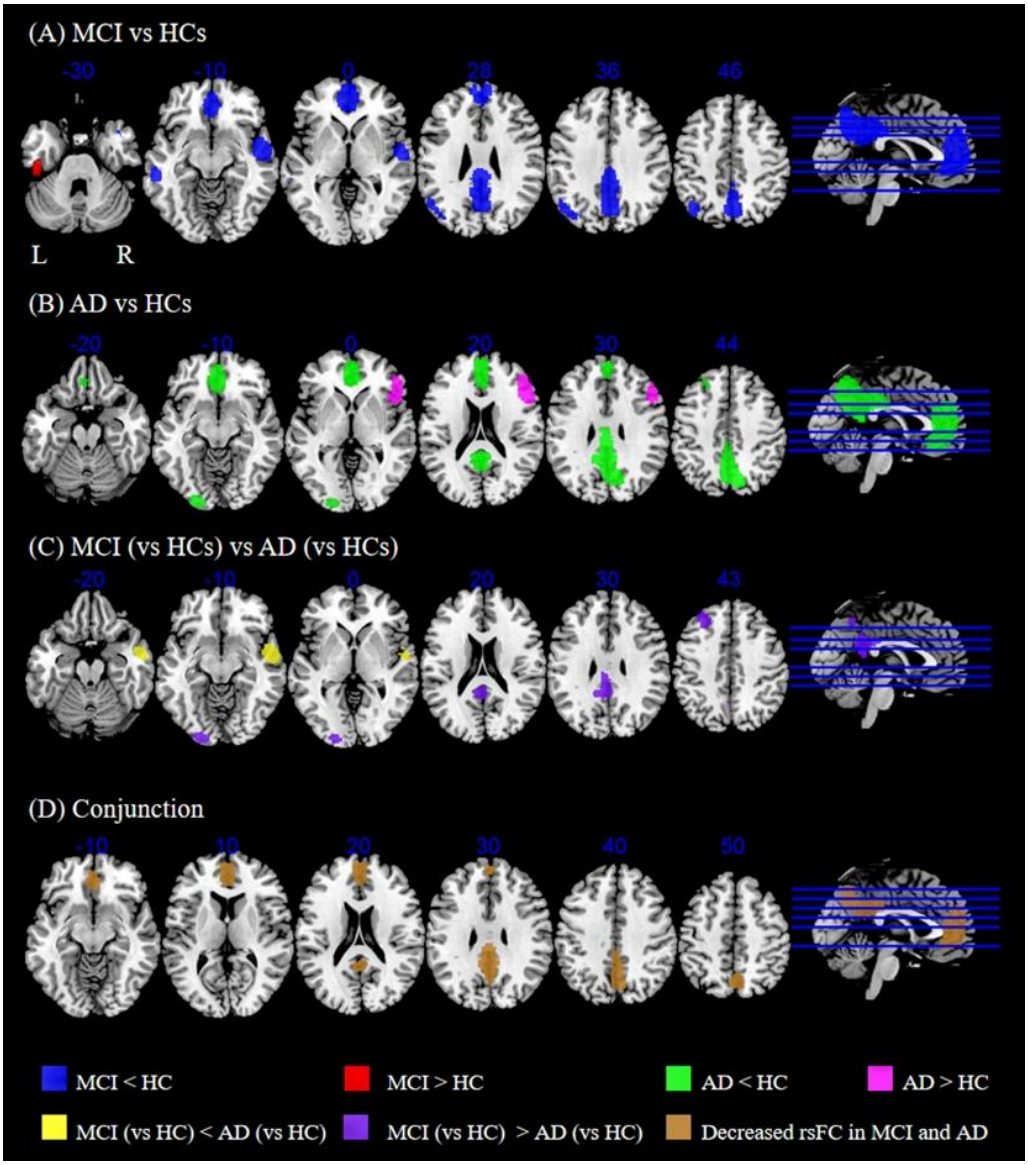
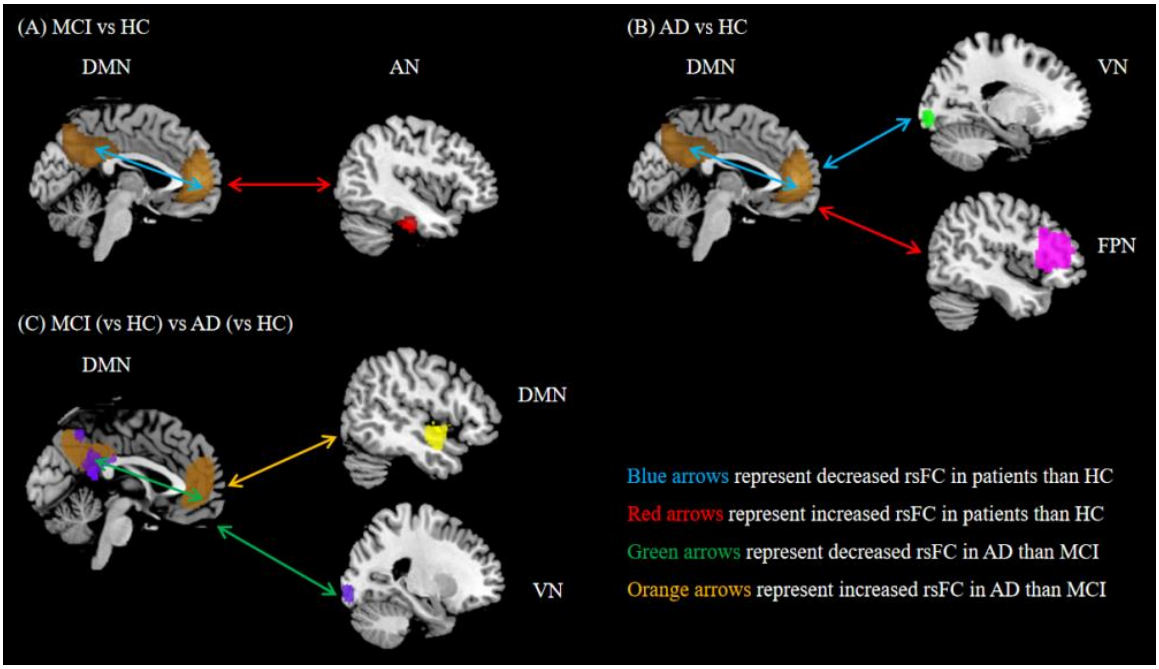


Figure 2. Summary of altered patterns of DMN rsFC in MCI and AD. See key for arrow color-coding; the network color-coding follows the image labels in Fig 1. (A) abnormalities in MCI compared to HC (as in Fig 1A). (B) abnormalities in AD compared to HC (as in Fig 1B). (C) comparison of abnormalities between MCI and AD, showing both disjunction (as in Fig 1C) and conjunction (as in Fig 1D). Abbreviations: rsFC, resting-state functional connectivity; MCI, mild cognitive impairment; AD, Alzheimer's disease; HC, healthy controls; DMN, default mode network; VN, visual network; FPN, frontoparietal network; AN, affective network.



3.3. Subgroup meta-analyses

In the subgroup meta-analysis of 21 aMCI studies (23 datasets), clusters of bilateral mPFC/ACC, bilateral PCC/precuneus, and left angular gyrus remained unchanged compared to the pooled meta-analysis; however, bilateral temporal regions did not show significant between-group difference (Table S9).The subgroup results of seed-based and ICA studies in MCI and AD (Tables S10 and S11) were broadly consistent with the pooled meta-analysis results. In the subgroup meta-analysis of 12 MCI studies with correction for GMV (14 datasets), results were largely consistent with the pooled results; by contrast the subgroup meta-analysis of 19 MCI studies without correction for GMV (20 datasets) only detected decreased within-DMN rsFC in bilateral mPFC/ACC and PCC/precuneus (Table S12). The subgroup meta-analysis of 10 AD studies with correction for GMV (12 datasets) only detected decreased within-DMN rsFC in bilateral mPFC/ACC and PCC/precuneus, by contrast the subgroup

meta-analysis results in 10 AD studies without correction for GMV (12 datasets) were similar to the pooled results (Table S13).

3.4. Additional analyses

For the pooled results, jackknife sensitivity analyses revealed all results to be replicable and reliable. For MCI, results in bilateral mPFC/ACC, bilateral precuneus/PCC, right superior and middle temporal gyri, and left angular gyrus remained significant in all combinations of datasets, while the rest remained significant in all but 2 combinations (Table S14). For AD, results in left inferior occipital gyrus remained significant in all but 4 combinations, the results of right middle and inferior frontal gyri remained significant in all but 2 combinations, and the rest remained significant in all combinations (Table S15). The results of the jackknife sensitivity analyses for the subgroup analyses are given in Tables S16-S20.

No inter-study heterogeneity was found in the MCI group; for AD, none of the clusters showed significant inter-study heterogeneity except right middle and inferior frontal gyri ($P < 0.0001$). There was no publication bias for MCI vs HC (Figure S2), and the only clusters for AD vs HC showing significant publication bias were right middle and inferior frontal gyri ($P = 0.017$) (Figure S3). In neither MCI nor AD were mean age, percentage of females or MMSE score significantly associated with altered DMN rsFC.

4. Discussion

In this coordinate-based meta-analysis, MCI and AD shared a decreased rsFC within DMN, localised in bilateral mPFC/ACC and precuneus/PCC (Table 1 and Fig 1D); furthermore, in left precuneus/PCC this decreased rsFC was worse in AD than MCI (Table 1 and Fig 1C). This suggests (but of course does not prove) a common mechanism in the neurodegeneration process. However, MCI and AD also differ in the patterns of decreased rsFC involving DMN (Table 1 and Figs 1C & 2C): in superior and middle temporal gyri in MCI, and between DMN and inferior occipital gyrus in AD. We discuss the possible implications below.

4.1. Shared decreased midline DMN rsFC in both MCI and AD (Table 1 and Fig 1D).

Bilateral precuneus/PCC and mPFC/ACC are key hubs of the DMN showing decreased rsFC in both MCI and AD. The precuneus and PCC are densely connected with the temporal lobes and deeply involved in cognitive processes, especially episodic memory (Sperling et al. 2010). Impaired episodic memory is the hallmark of AD (Dubois et al. 2010) and the commonest cognitive deficit in MCI (Knopman and Petersen 2014). Studies in AD report associations between decreased precuneus/PCC connectivity and impaired episodic memory (measured by the Rey Auditory Verbal Learning Test) (Weiler, Teixeira, et al. 2014), and between decreased PCC connectivity to other DMN regions, including mPFC, temporal lobes and inferior parietal lobule, and impairments in global cognition (measured by MMSE) and in memory (measured by enhanced cued recall and semantic fluency) (Celebi et al. 2016). In MCI, meta-analysis of task-related neuroimaging studies found aberrant

activity during episodic encoding and retrieval in precuneus, PCC, prefrontal cortex, angular gyrus and medial temporal lobe (Wang et al. 2016), while impaired episodic memory was correlated with decreased rsFC between precuneus and medial temporal lobe, and decreased effective connectivity from PCC to medial temporal lobe (Yang et al. 2017; Yao, Chen, et al. 2021). These findings support the idea that decreased rsFC in posterior DMN regions is causally important in episodic memory disturbance in both MCI and AD. Consistent with evidence that DMN connectivity is a continuum from healthy elderly through MCI to most impaired in AD (Petrella et al. 2011), our meta-analysis found lower DMN rsFC in left precuneus/PCC in AD than MCI (Table 1 and Fig 1C).

The mPFC is involved in self-referential processes, regulation of emotion and motivation (Xu et al. 2019; Smallwood et al. 2021), modulated by ACC (Yamasaki et al. 2002), and implicated in cognitive functions including decision-making and motivation (Chang et al. 2020). In AD, decreased connectivity within mPFC and ACC has been linked to hyperactivity syndrome (Chang et al. 2020; Lee et al. 2020). Other studies in MCI and AD have associated decreased connectivity and reduced ACC activation with apathy (Joo et al. 2017; Buyukgok et al. 2020). A recent review found that in both MCI and AD, hypoactivation and decreased connectivity in mPFC/ACC and precuneus/PCC were associated with impaired self-referential processes, manifesting as anosognosia, the pathological unawareness or denial of a neurologic deficit (Mondragon et al. 2019); interaction with self-referential processes is vital in forming episodic memory (Chen et al. 2021).

4.2. DMN rsFC alterations in MCI (Table 1 and Figs 1C & 2C)

In MCI we found decreased DMN rsFC in left angular gyrus, left middle temporal gyrus, and right superior and middle temporal gyri, all DMN regions linked with episodic memory and language (Liu et al. 2021). In MCI decreased rsFC between right middle temporal gyrus and right hippocampus has been reported to worsen over time, and correlate with progressive impaired episodic memory (Li et al. 2018). In a task-based fMRI study, MCI patients showed hypoactivation of left middle temporal gyrus implicated in lexical-semantic retrieval, manifesting as subclinically impaired written word identification (Vandenbulcke et al. 2007). In addition, several fMRI studies in MCI found that mnemonic strategy training can increase rsFC between left middle temporal gyrus and right orbitofrontal cortex, as well as increase activation in superior and middle temporal gyri and angular gyrus, and attributed these effects to the recruitment of semantic processing to enhance new learning/memory (Hampstead et al. 2011; Simon et al. 2018; Simon et al. 2020). Another MCI study found improved dynamic FC in superior temporal gyrus accompanying improved episodic memory after mindfulness practice (Fam et al. 2020). Therefore, the reduced connectivity we identified in these regions may be a neural mechanism of MCI in impaired episodic memory and semantic cognition.

MCI patients showed increased rsFC between DMN and left inferior temporal gyrus, as also reported in a recent meta-analysis (Eyler et al. 2019). The inferior temporal gyrus is a non-DMN brain region affected in MCI, implicated in semantic language processing with neural interconnections with parahippocampal gyrus (Scheff et al. 2011). A neuroimaging study identified increased brain activity in left inferior temporal gyrus in MCI patients, which correlated positively with MMSE score (Zhou et al. 2020); another study suggested that greater functional activation in left inferior

temporal gyrus in MCI patients than controls during language tasks may serve as a compensatory process of brain function in MCI (Lenzi et al. 2011). We speculate that increased rsFC between DMN and left inferior temporal gyrus in MCI may reflect compensatory recruitment of cognitive resources to maintain cognitive function, especially in the language domain.

Among clinical subtypes of MCI, aMCI carries the highest risk of developing into AD (Petersen et al. 2001). In the aMCI subgroup meta-analysis, we still found decreased within-DMN rsFC in bilateral mPFC/ACC, bilateral PCC/precuneus and left angular gyrus, but did not find rsFC alterations in bilateral temporal regions, which might be partly due to the predominant manifestation of aMCI being memory deficits that are tightly related to dysfunction in DMN.

4.3. DMN rsFC alterations in AD (Table 1 and Figs 1C & 2C)

In AD we found decreased rsFC between DMN and inferior occipital gyrus, a region of VN typically affected later in AD (Weiler, Fukuda, et al. 2014). Visuospatial symptoms such as object agnosia and impaired face recognition have been associated with reduced rsFC and hypoactivation within VN (Thiyagesh et al. 2009; Balachandar et al. 2017). Poorer visuospatial function in AD was also correlated with disrupted network properties in DMN and VN areas, mainly in precuneus and occipital lobes (Tijms et al. 2014). Decreased connectivity between DMN and VN has been identified as a potential contributor to visuospatial dysfunction (Zhang et al. 2009; Chung et al. 2016).

In AD we found increased rsFC between DMN and right middle and inferior frontal gyri, which belong to FPN, also called the central executive network (CEN)

(Melrose et al. 2018). This requires further verification since inter-study heterogeneity and publication bias were detected. Nevertheless, there is evidence that increased rsFC between DMN and FPN may play a role in executive dysfunction in AD. Our clusters in right middle and inferior frontal gyri overlap with right dorsolateral prefrontal cortex (DLPFC); in AD, increased rsFC between DLPFC and mPFC is related to worse executive function (Vipin et al. 2018); also, inhibitory repetitive transcranial magnetic stimulation over right DLPFC improves recognition and memory function, probably by inhibiting pathological hyperactivity and hyperconnectivity (Turriziani et al. 2019; Zhou et al. 2020).

Brain abnormalities differ with age at onset in many neurodegenerative diseases (Frisoni et al. 2007; Ai et al. 2023). Late onset AD tends to present the typical phenotype of progressive amnestic problems, while early onset AD is more likely to present atypically with visuospatial, executive, or language dysfunction (van der Flier et al. 2011). This is reflected in some neuroimaging findings. Structural MRI studies typically report medial temporal lobe atrophy in late onset AD, while early onset AD can be hippocampal-sparing but with GM loss in PCC, precuneus, and temporoparietal areas (van der Flier et al. 2011). A functional MRI study found lower within-DMN rsFC in precuneus/PCC in early than late onset AD (Adriaanse et al. 2014); another reported increased DLPFC rsFC in late onset AD, but decreased DLPFC rsFC in early onset AD (Gour et al. 2014). The differences between late and early onset AD may account for the significant heterogeneity for right DLPFC identified in our pooled findings. However, only a few studies included (3 out of 20) reported the age at onset for AD patients (Kenny et al. 2012; Adriaanse et al. 2014; Gour et al. 2014), precluding relevant subgroup meta-analysis.

4.4. Potential effects of GMV on rsFC (Tables S12 & S13)

The relationships between brain structure and function are complex. Although rsFC disruption may precede GM atrophy, the latter may also have a long-term effect on brain disconnection (Gili et al. 2011), both factors interacting to impair cognitive performance (Xie et al. 2015). For MCI, subgroup meta-analysis of studies without correction for GMV revealed only decreased within-DMN rsFC in bilateral mPFC/ACC and PCC/precuneus, and missed the altered rsFC in lateral temporal gyri found in studies with GMV correction and in the pooled studies. By contrast, for AD, subgroup meta-analysis of studies corrected for GMV revealed rsFC differences only in bilateral mPFC/ACC and PCC/precuneus, results in the subgroup meta-analysis of AD studies without correction for GMV being similar to the pooled findings; for AD, then, alterations involving left inferior occipital gyrus and right DLPFC might be attributable to GM atrophy. GMV correction in future rsFC studies will be helpful in resolving these issues.

4.5.Limitations

First, since we only included cross-sectional studies, we could not establish any imaging features specific for AD conversion from MCI; this will need large longitudinal studies of MCI individuals who may or may not progress to AD. Second, although we performed a subgroup meta-analysis of aMCI, the limited information available precluded subgroup analyses in each clinical subtype of MCI, as well as analyses in early *vs* late onset AD. Further studies with more clinically homogeneous patients with MCI and AD will help here. Third, the small number of studies using the same neuropsychological tests precluded meta-regression analysis of the relationship

between DMN rsFC alterations and behavioral symptoms or cognitive impairments. Fourth, because disrupted DMN rsFC is also reported in other psychiatric disorders, such as schizophrenia (Li et al. 2019) and posttraumatic stress disorder (Bao et al. 2021), transdiagnostic studies will be needed to explore possible disease specificities. Fifth, there is indirect evidence in AD from task-related fMRI (right superior temporal hyperactivity during semantic tasks) and structural MRI (correlation between naming performance and temporal cortical thickness) of compensatory mechanisms for language deficits (Nelissen et al. 2007; Nelissen et al. 2011; Leyton et al. 2017): we did not find any increased rsFC in relevant regions that might support this. However, the neuropathological and compensatory mechanisms underlying language deficits in AD warrant further exploration using multimodal brain MRI methods. Lastly, there was publication bias and heterogeneity in AD studies that showed increased rsFC between DMN and right middle and inferior frontal gyri, which mandates caution in interpreting our meta-analysis findings, and needs to be evaluated by original studies and explored by further meta-analysis as more studies become eligible.

5. **Conclusion**

Our coordinate-based meta-analysis identified shared decreased DMN rsFC in bilateral mPFC/ACC and precuneus/PCC in both MCI and AD patients, suggesting shared neural correlates for episodic memory disturbance and neuropsychiatric symptoms. Moreover, decreased DMN rsFC in left precuneus/PCC was more severe in AD than MCI, perhaps reflecting the different degrees of disruption at the predementia and dementia stages. For MCI patients, altered rsFC between DMN and bilateral temporal regions and left angular gyrus reflected possible neuropathological

and compensatory mechanisms for memory and language cognition, respectively. Patients with AD exhibited decreased rsFC between DMN and inferior occipital gyrus and increased rsFC between DMN and right middle and inferior frontal gyri, indicating possible neurobiological mechanisms underlying visuospatial and executive dysfunction. Together, these findings demonstrate shared and different altered DMN rsFC patterns in MCI and AD patients, providing novel insights for understanding the shared and differing neural correlates of cognitive dysfunction at the stages of predementia and dementia.

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Author contributions

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Declaration of Competing Interest

All authors declare no biomedical financial interests or potential conflicts of interest.

Availability of data and materials

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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