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Toward Systems Neuroscience in Mild Cognitive Impairment and Alzheimer's Disease: A Meta-Analysis of 75 fMRI Studies

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Abstract: Most of the previous task functional magnetic resonance imaging (fMRI) studies found abnormalities in distributed brain regions in mild cognitive impairment (MCI) and Alzheimer's disease (AD), and few studies investigated the brain network dysfunction from the system level. In this meta-analysis, we aimed to examine brain network dysfunction in MCI and AD. We systematically searched task-based fMRI studies in MCI and AD published between January 1990 and January 2014. Activation likelihood estimation meta-analyses were conducted to compare the significant group differences in brain activation, the significant voxels were overlaid onto seven referenced neuronal cortical networks derived from the resting-state fMRI data of 1,000 healthy participants. Thirty-nine task-based fMRI studies (697 MCI patients and 628 healthy controls) were included in MCI-related meta-analysis while 36 task-based fMRI studies (421 AD patients and 512 healthy controls) were included in AD-related meta-analysis. The meta-analytic results revealed that MCI and AD showed abnormal regional brain activation as well as large-scale brain networks. MCI patients showed hypoactivation in default, fronto-parietal, and visual networks relative to healthy controls, whereas AD-related hypoactivation mainly

Additional Supporting Information may be found in the online version of this article.

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located in visual, default, and ventral attention networks relative to healthy controls. Both MCI-related and AD-related hyperactivation fell in frontoparietal, ventral attention, default, and somatomotor networks relative to healthy controls. MCI and AD presented different pathological while shared similar compensatory large-scale networks in fulfilling the cognitive tasks. These system-level findings are helpful to link the fundamental declines of cognitive tasks to brain networks in MCI and AD. *Hum Brain Mapp 36:1217–1232, 2015.*

Key words: mild cognitive impairment; Alzheimer's disease; default mode; neuronal network; fMRI

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease that is characterized by the presence of amyloid deposition, neurofibrillary tangles, and widespread functional disturbances in the brain [Terry et al., 1991; Touchon and Ritchie, 1999]. AD patients gradually lose capacity in memory, executive function, and other cognitive abilities and ultimately are unable to conduct activities of daily living [Husain and Garrett, 2005]. Mild cognitive impairment (MCI) is considered as a transitional stage between normal aging and AD [Petersen et al., 2001; Petersen et al., 1999]. Previous studies have reported that persons with MCI exhibited impairments in memory and many other cognitive functions [Arnaiz and Almkvist, 2003].

Three meta-analyses have explored the brain activation with task-based functional magnetic resonance imaging (fMRI) in MCI and AD. In the meta-analysis of Schwindt and Black [2009], they included 14 fMRI and positron emission tomography (PET) studies of episodic memory in AD; the results revealed that healthy elderly showed greater activity in medial temporal lobe and frontal pole in both encoding and retrieval processing while AD showed increased activation in ventral lateral prefrontal cortex, superior temporal gyrus, and a number of other regions. Including 16 fMRI studies and 144 foci totally, Browndyke et al. [2013] found MCI and AD patients showed decreased activation in medial temporal lobe while increased activation in default mode and prefrontal gyrus in comparison with healthy controls during memory encoding. Jacobs et al. [2013] investigated the brain activity in people at risk of AD, MCI, and AD in 53 fMRI studies totally; they found the medial parietal regions and subcortical areas were differentially affected with disease progression; they concluded that AD patients might present neural network disruptions before cognitive deficits.

With increasing fMRI studies in AD, some cortical regions were found to be activated in a variety of tasks, Dickerson and Sperling [2009] proposed that AD might be a disease with multiple dysfunctional large-scale neuronal networks instead of alterations in single brain regions. During associative memory task, MCI and AD patients were found to demonstrate memory network disruptions [Celone et al., 2006]. Default network activity exhibits high sensitivity and specificity in differentiating AD from healthy older adults [Greicius et al., 2004; Koch et al., 2012]. Dysfunctional activation of the default network was considered to play a critical role in understanding the cognitive decline observed in AD [Andrews-Hanna et al., 2007; Chhatwal and Sperling, 2012]. The aforementioned studies provided a new promising large-scale network approach to investigate the brain functional deficits in MCI and AD. Although resting-state fMRI studies have provided preliminary findings about the large-scale functional brain networks in MCI and AD, these insights have less been incorporated into task-based fMRI studies. The difficulty of application large-scale brain networks into task-fMRI studies is the appropriate and reliable brain network parcellation. Based on the resting-state fMRI data from 1,000 healthy participants and a data-driven clustering approach, researchers have derived seven cortical neuronal networks: the visual, somatomotor, dorsal attention, ventral attention, limbic, frontoparietal, and default mode networks [Yeo et al., 2011]. This group further explored the functional projections from the cerebellum and striatum to these seven networks and parcellated the cerebellum and striatum into seven networks according their functional connectivity findings [Buckner et al., 2011; Choi et al., 2012]. Cortese et al. [2012] applied the idea of the seven reference neuronal systems into an ADHD meta-analysis, and extended the previous findings that the dysfunctions in ADHD were not only involved in higher-level cognitive functions but also in sensorimotor and default networks.

The seven neuronal networks functional parcellation can be integrated into an activation likelihood estimation (ALE) task-based meta-analysis to seek a feasible solution to determine network variation in MCI and AD and to understand their progresses in brain pathological aging at a system level. To date, although three meta-analyses have been conducted to explore the fMRI findings in MCI and AD [Browndyke et al., 2013; Jacobs et al., 2013; Schwindt and Black, 2009], however, limited by the analytic strategies, no study has been conducted to systematically incorporate the brain functional parcellation into MCI and AD. In this study, we aimed to conduct a comprehensive review of the extant task-based fMRI studies of MCI and AD from a systems neuroscience perspective and attempt to reveal neuronal dysfunction of large-scale brain circuits in pathological aging progresses.

METHODS

Literature Search

To identify pertinent articles, an online search of the PubMed, EBSCOHost (PsycINFO, PsycARTICLES), ISI Web of Knowledge, and NeuroSynth databases were performed for articles published between January 1990 and January 2014. "In press" articles were also included. Because we intended to make two main comparisons (MCI patients vs. healthy controls, AD patients vs. healthy controls, respectively), we conducted literature searches separately for these two meta-analyses.

The search terms related to MCI were "mild cognitive impairment, MCI, age-associated memory impairment, cognitive decline, cognitive impairment no dementia, preclinical, subclinical, prodromal, prediagnostic, prediagnostic, presymptomatic, presymptomatic, early stages, early symptoms, early diagnosis, and early detection." The search terms related to AD were "Alzheimer's disease, Alzheimer disease, Alzheimer's, Alzheimer, or AD, and dementia."

The search terms related to fMRI were "functional magnetic resonance imaging, functional MRI, fMRI, imaging, neuroimaging, magnetic resonance imaging, MRI, functional imaging." Search terms regarding MCI and AD were combined with different fMRI-related terms. We conducted an additional literature search using the reference lists of the included studies and several relevant review articles [Browndyke et al., 2013; Chhatwal and Sperling, 2012; He et al., 2009; Jacobs et al., 2013; Schwindt and Black, 2009; Woodard and Sugarman, 2012] to identify as many potential studies as possible. To provide additional evidence in functional activity and neuronal networks, we also searched resting-state fMRI studies in MCI and AD, details could be found in Supporting Information.

Study Selection

Inclusion criteria

For fMRI studies, two separate group comparisons were made in this meta-analysis. For the MCI-related meta-analysis, studies must include both a group of MCI patients [Petersen 2004; Petersen et al., 2001; Petersen et al., 1999; Winblad et al., 2004] and a group of healthy controls. For the AD-related meta-analysis, studies should include a clinical sample of AD patients (diagnosed according to the NINCDS-ADRDA, DSM-IV, or ICD-10 criteria) and a group of healthy controls. Furthermore, for task-based fMRI meta-analyses, the studies must focus on a certain cognitive task and reported three-dimensional (3D) Talairach or Montreal Neurologic Institute (MNI) coordinates of between-group comparisons. For resting-state fMRI meta-analyses, the studies should include a resting-state fMRI scan and reported 3D Talairach or MNI coordinates of between-group comparisons.

Exclusion criteria

Studies were excluded if they: (1) used any other neuroimaging methods such as PET, single photon emission computed tomography (SPECT), and other non-fMRI procedures because we only included fMRI studies to exclude the variability across different neuroimaging findings; (2) reported only within-group contrasts; (3) conducted a priori regions of interest (ROI) analysis; (4) assessed the effect of medication and took the fMRI results as outcomes while without reporting fMRI data at baseline. Moreover, two studies were excluded because they provided only the coordinates of neural deactivation [Gould et al., 2006; Rombouts et al., 2005].

Data Extraction

Two of the authors (HJL and XHH) determined whether the studies identified by our literature search should be included. Additionally, these authors independently extracted the demographic information, 3D coordinates, tasks, and contrasts of the included studies.

Deactivation coordinates were excluded during the data extraction procedure because they may have reflected different signal changes as activation coordinates (Ginger ALE forum, http://www.brainmap.org/forum/viewtopic.php?f=3&t=88). When studies included more than one group of MCI patients [Celone et al., 2006; Clément and Belleville, 2010; Clément and Belleville, 2012; Clément et al., 2013; Machulda et al., 2009; Vannini et al., 2007], the different groups were averaged into one pooled group, and the coordinates were also pooled. Two studies exploring therapeutic cholinesterase inhibitors [McGeown et al., 2008; Thiyagesh et al., 2010] were also included because these studies provided baseline fMRI activation coordinates of group comparisons.

Quantitative Meta-Analysis Procedures

All of the Talairach coordinates were first transformed into the corresponding MNI locations [Lancaster et al., 2007]. All of the MNI coordinates were then input into a text file, which was subsequently loaded into a Java-based version of GingerALE 2.3.1 (http://www.brainmap.org). ALE identifies the reported foci as centers of 3D Gaussian probability distributions around the specified coordinates. ALE models aim to assess the spatial uncertainty of coordinates within a study and detect convergence across studies [Laird et al., 2005; Turkeltaub et al., 2002]. Statistical significance was determined via a permutation test using randomly distributed foci. We computed 5,000 permutations using subject-based FWHM values and the same number of foci were used to compute ALE values [Turkeltaub et al., 2012]. The thresholds of the final ALE maps were set at $P < 0.05$, and the maps were corrected for multiple comparisons using the false discovery rate (FDR pN) method. Minimal clusters were required to exceed

200 mm^3 in volume. The Talairach Daemon identified the anatomical labels of the maximum of ALE values and the weighted centers of their coordinates [Lancaster et al., 2007].

We conducted several separate meta-analyses: (1) comparisons between MCI patients and healthy controls across all of the task-based fMRI studies; (2) comparisons between AD patients and healthy controls across all of the task-based fMRI studies. We also investigated the functional activation and neuronal networks in specific cognitive tasks in MCI and AD, respectively. These tasks included memory encoding, memory retrieval, executive function and working memory, attention and visuospatial, language processing, and emotional processing. The MCI-related and AD-related resting-state fMRI meta-analyses were also investigated as a supplement of this review.

Relationship with Neuronal Networks

According to the ALE results, we separately calculated the number of significant voxels that overlapped the masks generated for the seven large-scale neural networks [Buckner et al., 2011; Choi et al., 2012; Yeo et al., 2011] in MCI-related and AD-related changes. The results calculated from the cortical, cerebellar, and striatal networks were then merged. Chi-square analyses were finally performed to compare the proportions of voxels exhibiting increased and decreased brain activity in the seven neural networks.

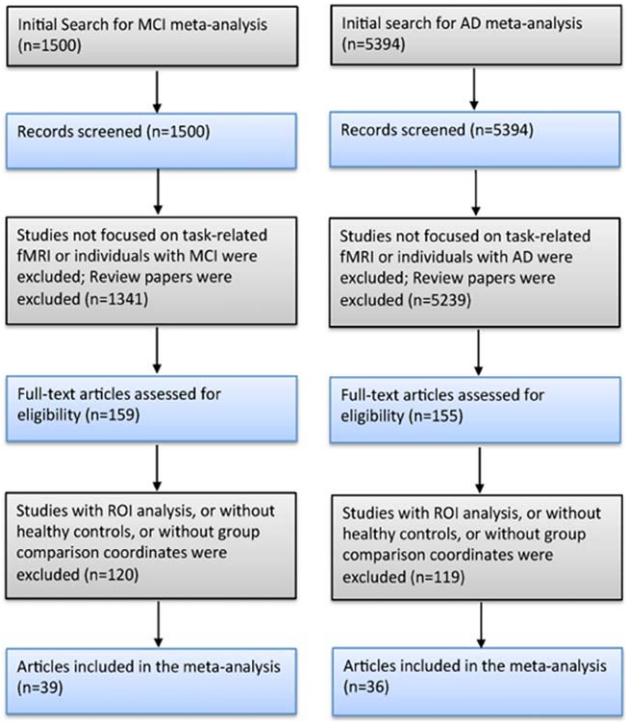

Figure 1.
Flow chart of the study selection process for MCI-related and AD-related task-based fMRI meta-analyses. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

RESULTS

Search Results

The results of the initial reference search and study exclusion for task-based fMRI meta-analyses are presented in Figure 1. There were 39 and 36 studies reporting contrast coordinates of MCI patients and healthy controls, and AD patients and healthy controls, respectively. The MCI-related meta-analysis included 697 individuals with MCI and 628 healthy controls while the AD-related meta-analysis included 421 AD patients and 512 healthy controls. The characteristics of the included studies are summarized in Table I. There were 17 and 8 studies included in the MCI-related and AD-related resting-state fMRI meta-analyses, respectively (details please see the Supporting Information). The characteristics of the included studies are summarized in Supporting Information Table I.

MCI-Related Meta-Analysis

In the overall meta-analysis of task-based fMRI studies, MCI-related hypoactivation relative to healthy elderly was observed in the right putamen, right insula, right hippocampus, left inferior and middle frontal gyrus, and left middle temporal gyrus; MCI-related hyperactivation relative to healthy elderly was mainly found in the left superior temporal gyrus, bilateral insula, left claustrum, right inferior frontal gyrus, right middle frontal gyrus, left parahippocampus, right inferior parietal lobule, and right supramarginal gyrus (Table II, Fig. 2).

We also compared the functional activation between MCI patients and healthy elderly during several cognitive tasks. In tasks related to memory encoding, MCI-related hypoactivation relative to healthy elderly was observed in left inferior frontal gyrus, left insula, right fusiform gyrus, left superior temporal gyrus, and left inferior parietal lobule while MCI-related hyperactivation relative to healthy elderly was found in the left lateral globus pallidus, left parahippocampus, right inferior frontal gyrus, and right middle frontal gyrus (Supporting Information Table II). The meta-analysis of memory-retrieval tasks revealed MCI-related hypoactivation of bilateral hippocampus, right parahippocampus, bilateral middle frontal gyrus, right insula, left inferior parietal lobule, and the left precuneus while no hyperactivation cluster was found in MCI (Supporting Information Table III). In executive function and working memory tasks, no MCI-related hypoactivation brain regions were found, whereas MCI-related

TABLE I. Characteristics of task-fMRI studies included in the meta-analysis of MCI and AD

Study	*N*	Age (SD)	Education (SD)	MMSE (SD)	fMRI task type	Group contrasts	Number of foci
MCI versus healthy controls							
Alichniewicz et al. (2012)	39 MCI	62.3 (8.6)	13.1 (3.0)	28.6 (1.2)	Working memory	MCI < Controls	5
	24 controls	60.7 (7.2)	13.7 (2.0)	29.2 (0.9)			
Baglio et al. (2012)	16 MCI	71.0 (5.8)	9.9 (4.8)	27.0 (1.8)	Theory of mind	MCI < Controls	1
	15 controls	66.9 (6.4)	10.8 (3.5)	29.0 (1.3)		MCI > Controls	7
Bokde et al. (2008)	16 MCI	69.9 (7.8)	13.2 (3.3)	27.2 (1.5)	Visuospatial	MCI > Controls	16
	17 controls	66.7 (4.2)	12.8 (2.9)	29.2 (1.0)			
Bokde et al. (2010a)	8 MCI	70.8 (5.3)		26.6 (1.3)	Working memory	MCI < Controls	8
	8 controls	66.6 (3.9)		30.0 (0.0)		MCI > Controls	18
Bosch et al. (2010)	15 MCI	74.6 (6.9)		25.5 (2.0)	Language processing	MCI > Controls	3
	15 controls	72.2 (5.8)		27.7 (1.5)			
Celone et al. (2006)	27 MCI	77.3 (6.1)	16.3 (3.1)	29.0 (1.0)	Memory encoding	MCI > Controls	6
	15 controls	75.5 (6.0)	16.5 (2.1)	29.5 (0.5)			
Clément and Belleville (2010)	26 MCI	67.9 (8.5)	14.4 (3.9)	27.7 (1.6)	Memory encoding	MCI > Controls	6
	14 controls	67.2 (6.8)	14.6 (3.8)	29.3 (1.1)		MCI < Controls	2
Clément and Belleville (2012)	26 MCI	67.9 (8.5)	14.5 (3.9)	27.7 (1.6)	Memory retrieval	MCI < Controls	1
	14 controls	67.2 (6.8)	14.6 (3.8)	29.3 (1.1)		MCI > Controls	10
Clément et al. (2013)	24 MCI	68.4 (9.1)	14.5 (4.1)	28.0 (1.8)	Executive function	MCI < Controls	3
	14 controls	67.2 (6.8)	14.6 (3.8)	29.3 (1.1)		MCI > Controls	7
Dannhauser et al. (2005)	10 MCI	72.0 (7.7)	10.3 (1.8)	24.5 (1.5)	Divided attention	MCI < Controls	1
	10 controls	68.0 (13.5)	10.1 (1.4)	28.3 (1.6)			
Dannhauser et al. (2008)	10 MCI	72.0 (7.7)	10.3 (1.8)	24.5 (1.5)	Memory encoding	MCI < Controls	1
	10 controls	68.0 (13.5)	10.1 (1.4)	28.3 (1.6)			
Faraco et al. (2013)	16 MCI	75.1 (6.5)	14.2 (3.5)		Visuoattention	MCI < Controls	7
	24 controls	74.2 (5.5)	17.0 (2.3)		Working memory	MCI > Controls	94
Giovanello et al. (2012)	12 MCI	75.2 (4.3)	16.3 (2.9)	27.8 (1.7)	Memory retrieval	MCI < Controls	7
	12 controls	72.6 (5.9)	15.6 (3.1)	29.5 (0.9)		MCI > Controls	4
Hämäläinen et al. (2007)	14 MCI	72.4 (7.3)	8.1 (2.6)	25.6 (3.1)	Memory encoding	MCI < Controls	1
	21 controls	71.2 (4.9)	7.9 (2.9)	27.7 (2.0)		MCI > Controls	13
Hanseeuw et al. (2011)	16 MCI	72.6 (7.9)	13.5 (2.7)	27.3 (1.6)	Memory encoding	MCI < Controls	5
	15 controls	69.4 (4.8)	14.9 (2.4)	28.7 (1.5)			
Heun et al. (2007)	20 MCI	69.7 (7.1)		26.6 (1.5)	Memory retrieval	MCI > Controls	3
	28 controls	67.5 (5.4)		28.9 (1.1)			
Jacobs et al. (2012)	18 MCI	65.1 (4.5)		27.6 (2.3)	Visuospatial	MCI > Controls	10
	18 controls	64.6 (3.4)		28.9 (1.0)			
Jin et al. (2012)	8 MCI	60.9 (3.2)	16.9 (1.9)	28.1 (1.1)	Memory encoding	MCI < Controls	10
	8 controls	60.6 (8.3)	16.9 (2.1)	29.6 (0.5)	Memory retrieval	MCI > Controls	5
Johnson et al. (2006)	14 MCI	73.7 (6.9)	16.2 (2.7)	28.6 (1.5)	Memory retrieval	MCI < Controls	6
	14 controls	72.5 (5.7)	17.3 (2.9)	29.4 (0.8)			
Kaufmann et al. (2008)	6 MCI	69.8 (5.3)		24.8 (1.2)	Executive function	MCI > Controls	24
	9 controls	68.3 (7.5)		29.0 (1.2)			
Kircher et al. (2007)	29 MCI	69.7 (7.0)		26.6 (1.4)	Memory encoding	MCI > Controls	4
	21 controls	67.8 (5.4)		28.8 (1.2)			
Kochan et al. (2011)	35 MCI	78.0 (3.9)	12.6 (3.9)	27.9 (1.6)	Working memory	MCI < Controls	5
	22 controls	77.2 (3.3)	11.4 (3.7)	29.3 (1.0)		MCI > Controls	2
Lenzi et al. (2011)	15 MCI	72.5	10.3	25.1	Language processing/ memory retrieval/ attention	MCI > Controls	3
	14 controls	64.3	13.6	28.6			
LeyHe et al. (2009)	11 MCI	75.0 (6.7)	13.4 (3.3)	27.6 (1.4)	Executive function	MCI < Controls	1
	15 controls	70.6 (11.8)	13.7 (3.0)	29.7 (0.5)		MCI > Controls	7
Li et al. (2013)	34 MCI	64.4 (7.5)	11.1 (2.4)	26.0 (2.0)	Memory encoding	MCI < Controls	9
	25 controls	62.5 (5.4)	11.4 (3.3)	28.6 (1.4)			
Machulda et al. (2009)	31 MCI	76.6 (6.8)	14.9 (3.4)		memory encoding	MCI < Controls	33
	29 controls	73.0 (7.0)	14.1 (2.4)		Memory retrieval		
Mandzia et al. (2009)	14 MCI	68.6 (7.4)	13.4 (2.8)	27.7 (1.1)	Memory encoding	MCI < Controls	36

TABLE I. (continued).

Study	*N*	Age (SD)	Education (SD)	MMSE (SD)	fMRI task type	Group contrasts	Number of foci
	14 controls	72.2 (6.4)	15.4 (2.8)	28.6 (1.1)	Memory retrieval	MCI > Controls	4
Papma et al. (2012)	42 MCI	73.4 (4.4)		27.2 (2.0)	Visuospatial	MCI < Controls	13
	25 controls	71.6 (5.2)		28.8 (1.2)	Working memory	MCI > Controls	6
Petrella et al. (2006)	20 MCI	75.0 (7.6)	15.0 (2.2)	26.7 (1.5)	Memory encoding	MCI < Controls	11
	20 controls	71.2 (4.5)	15.9 (2.9)	28.4 (1.4)	Memory retrieval	MCI > Controls	2
Poettrich et al. (2009)	13 MCI	60.5 (6.6)		28.3 (0.9)	Memory retrieval	MCI > Controls	3
	13 controls	59.8 (5.3)		29.1 (0.9)			
Risacher et al. (2013)	18 MCI	72.3 (6.3)	16.3 (2.9)	26.6 (2.8)	Memory encoding	MCI < Controls	6
	20 controls	71.4 (4.7)	17.1 (2.4)	29.1 (0.9)		MCI > Controls	6
Staffen et al. (2012)	12 MCI	71.8 (5.2)		27.0 (1.8)	Executive function	MCI < Controls	33
	13 controls	68.4 (7.9)		28.0 (1.1)			
Trivedi et al. (2008)	16 MCI	73.1 (5.5)	14.9 (3.3)	26.3 (2.3)	Memory encoding	MCI < Controls	8
	23 controls	77.0 (8.4)	16.2 (3.0)	28.8 (1.2)		MCI > Controls	1
Van Dam et al. (2013)	8 MCI	77.6 (7.0)	14.6 (3.2)	27.1 (1.8)	Executive function	MCI < Controls	20
	8 controls	74.6 (9.2)	16.9 (2.4)	28.8 (1.4)		MCI > Controls	41
Vandenbulcke et al. (2007)	13 MCI	65.8 (6.8)	12.7 (2.7)		Language processing	MCI< Controls	2
	13 controls	65.9 (6.3)	12.9 (2.6)				
van der Meulen et al. (2012)	13 MCI	69.2 (8.2)	13.0 (2.3)	26.7 (2.3)	Memory encoding	MCI < Controls	28
	15 controls	68.1 (7.2)	14.3 (2.6)	29.5 (0.8)	Memory retrieval		
Vannini et al. (2007)	13 MCI	58.6 (5.3)	14.7 (3.5)		Visuospatial	MCI < Controls	2
	13 controls	58.5 (6.4)	15.9 (3.1)			MCI > Controls	5
Xu et al. (2007)	10 MCI	77.0 (4.5)	13.7 (2.7)	27.8 (1.5)	Memory encoding	MCI < Controls	1
	12 controls	70.0 (3.9)	15.6 (2.1)	29.6 (0.8)			
Yetkin et al. (2006)	9 MCI	72.0 (8.0)	13.0 (1.0)	28.4 (1.9)	Working memory	MCI < Controls	11
	8 controls	65.0 (7.0)	16.0 (3.0)	30.0 (0.0)		MCI > Controls	12
AD versus healthy controls							
Bokde et al. (2010b)	12 AD	71.2 (6.9)		25.3 (2.3)	Visuospatial	AD > Controls	18
	14 controls	67.1 (4.0)		29.2 (1.2)			
Bosch et al. (2010)	15 AD	75.3 (5.7)		21.4 (3.1)	Language processing	AD > Controls	2
	15 controls	72.2 (5.8)		27.7 (1.5)			
Celone et al. (2006)	10 AD	77.6 (8.0)		21.1 (3.2)	Memory encoding	AD > Controls	2
	15 controls	75.5 (6.0)		29.5 (0.5)		(ICA)	
Cole et al. (2006)	14 AD	79.0 (5.0)		19.4 (5.7)	Emotion processing	AD > Controls	17
	15 controls	79.0 (4.0)		29.3 (0.1)			
Donix et al. (2013)	12 AD	69.6 (6.1)	14.5 (3.2)	24.5 (2.5)	Episodic encoding	AD < Controls	5
	12 controls	62.1 (5.4)	15.0 (2.2)	29.6 (0.5)			
Golby et al. (2005)	7 AD	69.0 (8.0)		20.8 (2.0)	Memory encoding	AD < Controls	7
	7 controls	66.0 (11.0)		29.4 (0.5)			
Gould et al. (2005)	12 AD	77.3 (4.9)		26.3 (2.1)	Memory encoding	AD < Controls	7
	12 controls	77.3 (4.8)		29.1 (0.9)	Memory retrieval	AD > Controls	11
Grön et al. (2002)	12 AD	61.7 (5.0)		25.9 (3.5)	Memory encoding	AD < Controls	17
	12 controls	59.8 (2.6)		30.0 (0.0)	Memory retrieval	AD > Controls	6
Grossman et al. (2003a)	11 AD	73.0 (4.9)	15.3 (2.9)	20.2 (6.1)	Emotion processing	AD < Controls	7
	16 controls	73.9 (3.6)	13.8 (1.8)	29.7 (0.8)		AD > Controls	2
Grossman et al. (2003b)	11 AD	73.0 (4.9)	15.3 (2.9)	20.2 (6.1)	Memory encoding	AD < Controls	2
	16 controls	73.9 (3.6)	13.8 (1.8)	29.7 (0.8)		AD > Controls	4
Hämäläinen et al. (2007)	15 AD	73.1 (6.7)	8.2 (2.7)	21.7 (3.7)	Memory encoding	AD < Controls	5
	21 controls	71.2 (4.9)	7.9 (2.9)	27.1 (2.0)		AD > Controls	2
Kato et al. (2001)	7 AD	73.6 (2.9)			Memory encoding	AD < Controls	4
	8 controls	65.1 (1.8)					
Kircher et al. (2005)	10 AD	71.8 (12.0)		22.3 (3.9)	Memory encoding	AD < Controls	1
	10 controls	67.2 (5.1)		29.3 (0.6)			
Lee et al. (2013)	12 AD	76.7 (5.2)	1.9 (3.4)	18.3 (3.4)	Emotion processing	AD < Controls	3
	12 controls	72.3 (6.2)	4.7 (4.4)	26.8 (2.9)			
LeyHe et al. (2009)	15 AD	71.5 (7.9)	13.5 (3.2)	22.9 (2.8)	Executive function	AD < Controls	17
	15 controls	70.6 (11.8)	13.7 (3.0)	29.7 (0.5)		AD > Controls	2

TABLE I. (continued).

Study	*N*	Age (SD)	Education (SD)	MMSE (SD)	fMRI task type	Group contrasts	Number of foci
Lim et al. (2008)	12 AD	69.5 (5.6)	10.8 (4.3)	20.3 (1.4)	Working memory	AD < Controls	4
	12 controls	68.6 (6.2)	11.3 (3.1)	29.1 (1.2)		AD > Controls	2
McGeown et al. (2008)	11 AD	79.0 (7.4)	11.6 (3.3)	21–26	Language processing	AD < Controls	3
	9 controls	75.1 (1.6)	11.7 (2.3)	27–30	Working memory	AD > Controls	6
Meulenbroek et al. (2010)	21 AD	72.4 (7.1)	16.1 (3.9)	24.8 (3.4)	Memory retrieval	AD > Controls	4
	22 controls	69.6 (8.6)	16.5 (3.2)				
Olichney et al. (2010)	15 AD	72.9 (8.6)	14.7 (2.3)	24.4	Language processing	AD < Controls	7
	15 controls	68.7 (12.1)	15.5 (2.4)			AD > Controls	20
Pariente et al. (2005)	12 AD	70.9 (6.4)	12.9 (2.3)	25.1 (1.8)	Memory encoding	AD < Controls	7
	17 controls	70.6 (5.6)	13.20 (3.8)	29.0 (1.0)	Memory retrieval	AD > Controls	13
Parra et al. (2013)	10 AD	78.0 (7.56)		23.6 (3.37)	Emotional retrieval	AD < Controls	2
	10 controls	74.0 (8.89)		29.1 (1.60)			
Peelle et al. (2014)	12 AD	68.8 (10.18)	16.7 (2.99)	22.5 (6.1)	Semantic processing	AD < Controls	3
	21 controls	65.0 (9.22)	15.2 (2.3)	28.0 (1.3)			
Petrella et al. (2007)	13 AD	71.4 (6.8)	12.7 (2.3)	24.6 (2.4)	Memory encoding	AD < Controls	8
	28 controls	72.0 (4.9)	16.3 (2.8)	28.3 (1.4)		AD > Controls	10
Pihlajamaki et al. (2008)	15 AD	78.3 (6.9)	13.3 (3.2)	23.3 (4.2)	Memory encoding	AD < Controls	4
	29 controls	74.2 (5.6)	15.6 (2.6)	29.7 (0.5)		AD > Controls	6
Pihlajamaki et al. (2010)	15 AD	78.3 (7.1)	13.3 (3.2)		Memory encoding	AD > Controls	14
	30 controls	74.0 (5.5)	15.6 (2.7)				
Rémy et al. (2004)	7 AD	70.4 (10.3)	13.1 (2.8)	20.7 (7.4)	Executive function	AD < Controls	8
	11 controls	65.9 (5.7)	13.3 (2.6)	29.4 (0.5)		AD > Controls	1
Rémy et al. (2005)	8 AD	72.2 (10.8)	13.1 (2.8)	21.2 (6.4)	Memory encoding	AD < Controls	24
	11 controls	65.9 (5.7)	13.3 (2.6)	29.4 (0.5)	Memory retrieval	AD > Controls	8
Saykin et al. (1999)	9 AD	79.0 (5.0)	17.0 (2.0)		Language processing	AD < Controls	11
	6 controls	71.0 (4.0)	16.0 (2.0)			AD > Controls	10
Shanks et al. (2007)	9 AD	74.9 (10.1)	12.2 (3.7)	27–30	Selective attention	AD < Controls	3
	9 controls	75.1 (1.6)	11.7 (2.3)	27–30		AD > Controls	3
Sperling et al. (2003)	7 AD	80.6 (6.9)		22.6 (2.2)	Memory encoding	AD < Controls	15
	10 controls	74.1 (7.3)				AD > Controls	16
Thiyagesh et al. (2009)	12 AD	76.4 (7.0)	9.9 (1.4)	22.6 (4.0)	Visuospatial	AD < Controls	12
	13 controls	71.2 (4.9)	11.5 (2.0)	28.5 (1.0)		AD > Controls	3
Thiyagesh et al. (2010)	10 AD	76.0 (6.5)	9.8 (1.3)	24.1 (3.5)	Visuospatial	AD > Controls	3
	11 controls	70.2 (4.4)	11.3 (1.9)	28.8 (0.8)			
Vannini et al. (2008)	13 AD	68.9 (6.9)	12.5 (3.6)	25.5 (2.3)	Visuospatial	AD < Controls	22
	13 controls	68.7 (7.8)	13.2 (3.9)			AD > Controls	1
Vidoni et al. (2012)	9 AD	69.0 (7.2)	14.8 (7.9)	21.7 (3.4)	Visuomotor	AD < Controls	2
	10 controls	73.6 (6.3)	16.1 (2.8)	29.8 (0.4)		AD > Controls	9
Yetkin et al. (2006)	9 AD	68.0 (10.0)	14.0 (3.0)	23.1 (3.1)	Working memory	AD < Controls	7
	8 controls	65.0 (7.0)	13.0 (1.0)	30.0 (0.0)		AD > Controls	19
Zamboni et al. (2013)	17 AD	76.7 (5.4)	14.3 (4.0)	22.2 (3.0)	Self-awareness	AD < Controls	12
	17 controls	75.5 (4.8)	14.9 (2.8)	29.85 (0.7)			

Abbreviations: MMSE, Mini-Mental State Examination; fMRI, functional magnetic resonance imaging; ICA, independent components analysis

hyperactivation was found in the right precentral gyrus, left insula, left postcentral gyrus, left claustrum, left superior temporal gyrus, right precuneus, left fusiform gyrus, right cingulate gyrus, and left paracentral lobule (Supporting Information Table IV). Due to the limited number of relevant studies, no significant hyperactivation or hypoactivation was found in tasks of attention and visuospatial processing, emotional processing, or language processing. The results of resting-state fMRI studies in MCI patients can be found in Supporting Information Results (Supporting Information Table V).

AD-Related Meta-Analysis

The meta-analysis on AD revealed that in the overall meta-analysis of task-based fMRI studies, AD-related hypoactivation relative to healthy elderly was observed

TABLE II. ALE results for MCI-related and AD-related task-based fMRI meta-analyses

		Weighted center				Maximum ALE value				
	Volume (mm^3)	x	y	z	Extrema value	x	y	z	BA	Anatomical label
Healthy controls > MCI (276 foci, 30 experiments)										
1	1552	33.21	16.11	−12.87	0.014661	30	10	−14		Putamen
					0.014532	34	22	−10	47	Insula (frontoparietal)
2	1144	28.25	−33.46	−9.08	0.015837	30	−34	−10		Hippocampus
3	720	−45.42	16.37	−16.16	0.014161	−48	16	−14	47	Inferior frontal gyrus (limbic)
					0.013944	−42	16	−20	47	Inferior frontal gyrus (limbic)
4	624	−60.12	−46.9	0.64	0.014217	−60	−44	0	21	Middle temporal gyrus (default)
					0.010393	−56	−60	2	37	Middle temporal gyrus (dorsal attention)
5	512	−49.44	12.44	35.3	0.012688	−50	12	36	9	Middle frontal gyrus (frontoparietal)
6	448	−41.34	23.04	14.46	0.011563	−44	22	16	46	Middle frontal gyrus (frontoparietal)
MCI > Healthy controls (322 foci, 28 experiments)										
1	1104	−50.46	−17	4.52	0.014216	−50	−16	4	22	Superior temporal gyrus (somatomotor)
					0.011706	−40	−20	2	13	Insula (somatomotor)
					0.011561	−56	−10	4	22	Superior temporal gyrus (somatomotor)
					0.010957	−60	−26	8	41	Superior temporal gyrus (somatomotor)
					0.009894	−38	−12	4		Claustrum (ventral attention)
2	992	49.42	19.95	16.7	0.013785	56	22	20	9	Inferior frontal gyrus (frontoparietal)
					0.012846	46	16	10	13	Insula
					0.011527	46	20	16	46	Middle frontal gyrus
3	824	−15.63	−14.29	−13.01	0.013940	−14	−14	−14	28	Parahippocampal gyrus
					0.013257	−18	−20	−14	35	Parahippocampal gyrus
4	584	62.22	−29.16	24.9	0.014395	62	−30	24	40	Inferior parietal lobule (ventral attention)
5	528	45.71	−36.85	40.11	0.011823	44	−40	42	40	Supramarginal gyrus (dorsal attention)
Healthy controls > AD (244 foci, 29 experiments)										
1	2808	−31.9	−23.39	−15.79	0.013243	−26	−20	−18		Hippocampus
					0.012076	−34	−30	−20	36	Parahippocampal gyrus
					0.009811	−22	−30	−4	27	Parahippocampal gyrus
2	1256	−44.38	−75.59	0.56	0.015756	−46	−74	0	37	Inferior temporal gyrus (visual)
3	1128	−11.14	22.68	49.36	0.012152	−6	26	48	8	Medial frontal gyrus (frontoparietal)
					0.009945	−20	16	48	32	Medial frontal gyrus (default)
					0.009657	−22	22	48	6	Superior frontal gyrus (default)
4	1000	−28.72	−79.51	−6.37	0.016688	−28	−80	−6	19	Lingual gyrus
5	744	29.95	−20.11	−18.4	0.011889	28	−18	−20		Parahippocampal gyrus
					0.011831	32	−20	−16		Parahippocampal gyrus
6	720	−44.68	−21.46	−4.33	0.012743	−44	−20	−6	13	Insula
7	592	−49.36	−3.87	28.36	0.012419	−50	−4	28	6	Precentral gyrus (somatomotor)
8	584	25.49	−23.85	1.51	0.012015	30	−26	0		Thalamus
					0.010222	22	−22	2		Ventral posterior lateral nucleus
AD > Healthy controls (201 foci, 28 experiments)										
1	2240	−12.3	−60.9	40.5	0.013268	−10	−58	46	7	Precuneus (default)
					0.011640	−10	−64	32	31	Precuneus (default)
					0.010246	−20	−64	42	7	Precuneus (dorsal attention)
2	1768	13.7	−61.29	37.95	0.017395	12	−64	38	7	Cuneus (default)
3	856	44.17	14.04	33.89	0.014982	44	14	36	9	Precentral gyrus (frontoparietal)
4	600	9.96	−16.73	37.94	0.013933	10	−16	38	24	Cingulate gyrus (ventral attention)
5	584	−52.46	5.01	16.3	0.012293	−52	6	18	44	Inferior frontal gyrus (ventral attention)
6	544	−21.14	−11.39	−0.79	0.012364	−20	−12	0		Lentiform nucleus
					0.008278	−28	−6	0		Putamen

mainly in subcortical regions, including the left hippocampus, bilateral parahippocampal gyri, right thalamus, left insula, right ventral posterior lateral nucleus, left inferior temporal gyrus, left medial and superior frontal gyrus, left lingual gyrus, and left precentral gyrus. In contrast, AD-related hyperactivation relative to healthy elderly was found mainly in left precuneus, left cuneus, right precentral gyrus, right cingulate gyrus, left inferior frontal gyrus, and left lentiform gyrus/putamen (Table II, Fig. 2).

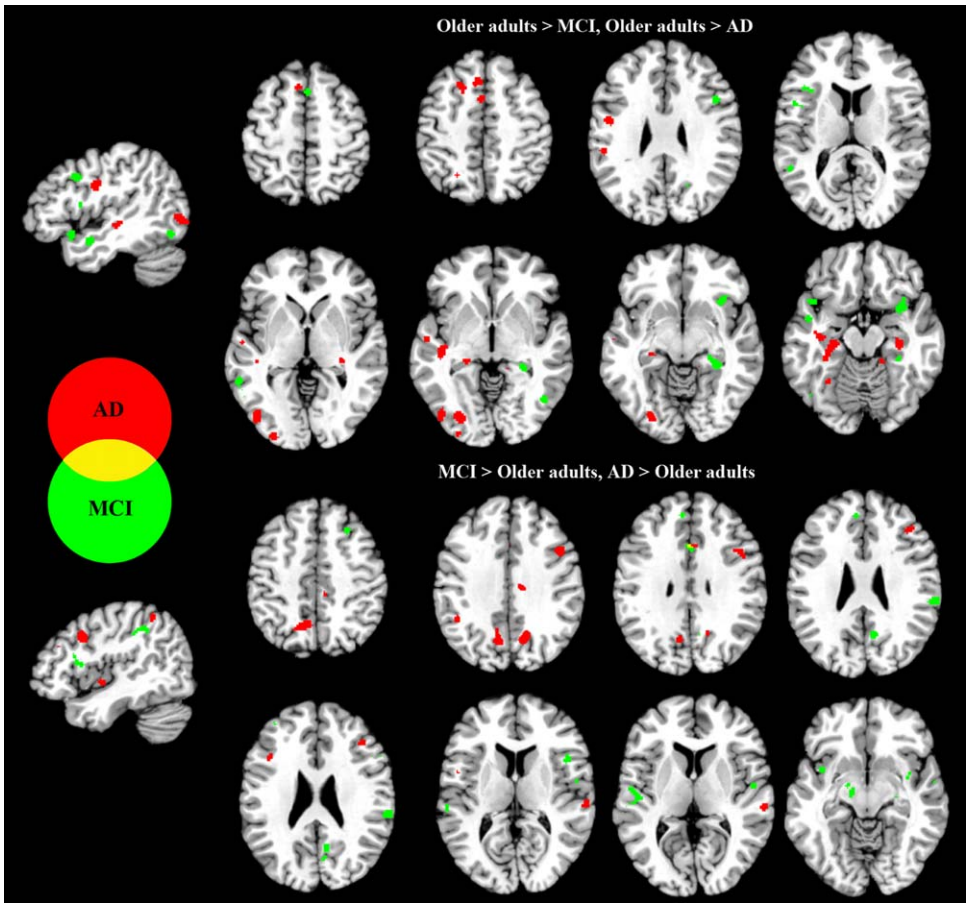

Figure 2.
Regions exhibiting significantly greater activation when comparing MCI patients and healthy older adults, and AD patients and healthy older adults. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

In memory-encoding tasks, AD-related hypoactivation relative to healthy elderly was observed in bilateral hippocampi, left parahippocampus, left putamen, and left inferior parietal lobule; AD-related hyperactivation relative to healthy elderly was observed in right cuneus, bilateral precuneus, left amygdala, and right middle frontal gyrus (Supporting Information Table II). In memory-retrieval tasks, we detected AD-related hypoactivation of the left parahippocampal gyrus, no significant AD-related hyperactivation was found (Supporting Information Table III). For tasks of executive function and working memory, AD-related hypoactivation was observed in the left insula; AD-related hyperactivation was found in left cingulate gyrus (Supporting Information Table IV). Attention and visuospatial processing yielded AD-related hypoactivation mainly in the left inferior temporal gyrus (−46, −72, 2) and no AD-related hyperactivation clusters were found. AD patients exhibited decreased activation of lingual gyrus (−28, −80, −6) in language processing tasks. The results of resting-state fMRI studies in AD patients can be found in Supporting Information Table V.

Relationship with Neuronal Networks

Based on the seven neuronal network parcellations of the human brain, we identified the percentage of significant voxels located in each network. For task-based fMRI meta-analysis, MCI-related hypoactivation was found mainly in the default mode (29.9%) and frontoparietal (24.5%) networks while hyperactivation was found mainly in the ventral attention (29.8%), somatomotor (27.7%), frontoparietal (19.1%), and default mode (16.9%) networks (Fig. 3). The distribution of MCI-related hypoactivation and hyperactivation between the networks differed significantly ($\chi^2 > 100$, $P < 0.0001$).

For task-based fMRI meta-analysis, AD-related hypoactivation voxels were mainly in the visual (42.9%), default

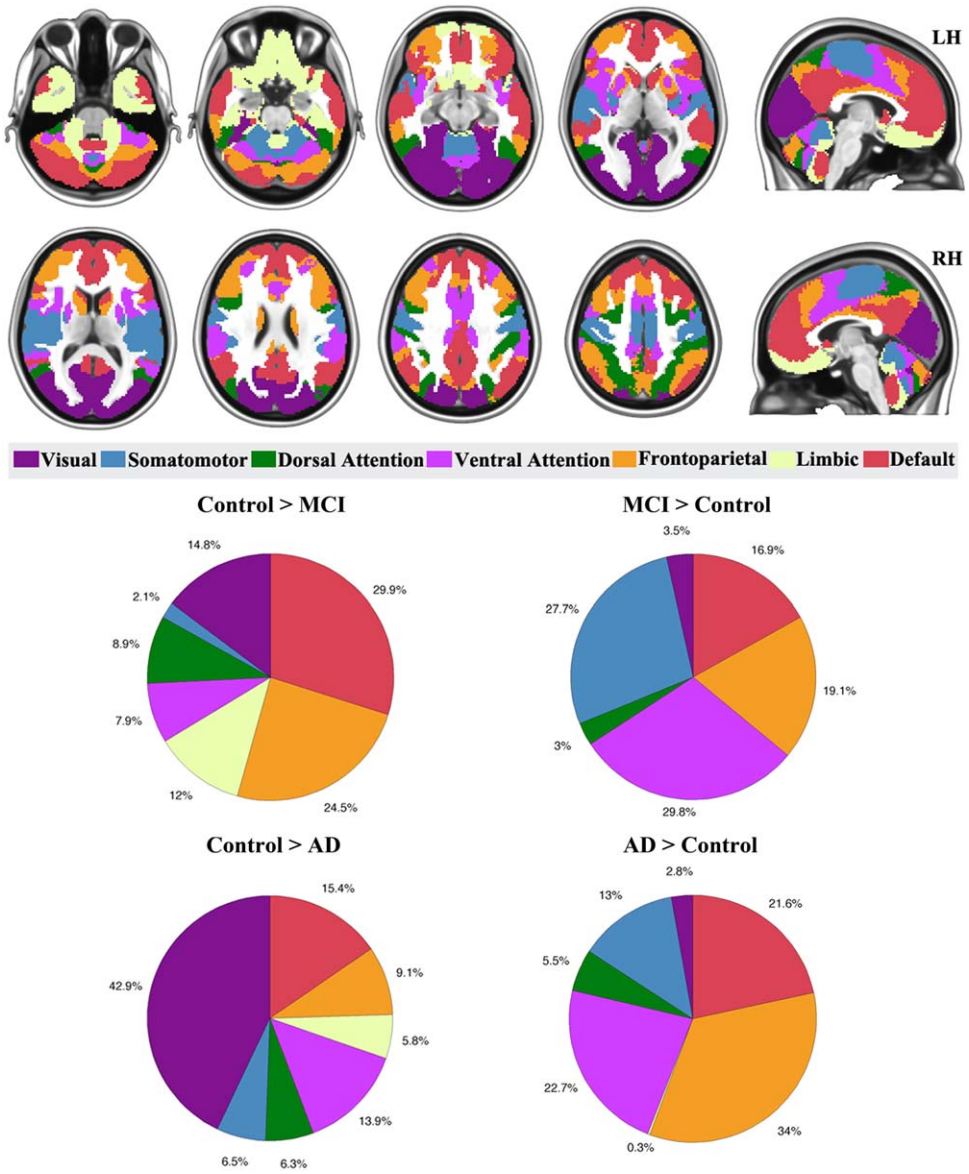

Figure 3.

Proportions of MCI-related, and AD-related hypoactivation or hyperactivation in the overall meta-analyses of task-based fMRI studies, merged from cortical, cerebellar, and striatal networks. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

mode network (15.4%), and ventral attention (13.9%) networks. AD-related hyperactivation voxels were found mainly in frontoparietal (34%), ventral attention (22.7%), and default mode (21.6%) networks (Fig. 3). The distribution of hypoactivation and hyperactivation between the networks differed significantly ($\chi^2 > 100$, $P < 0.0001$).

The neuronal network results of the specific tasks and resting state in MCI and AD patients can be found in Supporting Information Results.

DISCUSSION

To the best of our knowledge, this work is the first meta-analysis exploring the large-scale neuronal network dysfunctions in MCI and AD. The results revealed that MCI and AD patients presented different pathological while shared similar compensatory mechanisms in large-scale networks during fulfilling the cognitive tasks.

MCI- and AD-Related Task-Based fMRI Meta-Analysis

MCI and AD patients presented different decreased patterns, implying that the neuronal network dysfunctions might be a consequence of the disease progression. MCI individuals showed hypoactivation in regions within the frontoparietal and default mode network relative to controls while AD patients showed hypoactivation in regions within the visual network relative to controls. Frontoparietal network was considered to be an important flexible hub for initiating and modulating cognitive control [Cole et al., 2013; Dosenbach et al., 2008]. The decreased activation in frontoparietal network suggested the reduced cognitive control ability in MCI patients. Moreover, further task-specific analysis revealed that the decreased frontoparietal network in MCI was mainly contributed by the memory-retrieval tasks. The findings were partly consistent with previous memory retrieval meta-analysis [Schwindt and Black, 2009], perhaps reflecting worse self-monitoring in MCI individuals [Christoff and Gabrieli, 2000]. With the progression to AD, patients presented decreased activation in visual network. Visual cortex has been reported dysfunctional in AD; the underlying pathology might be due to the neurofibrillary tangles and amyloid plaques [Lewis et al., 1987; Morrison et al., 1991]. Other studies also suggested that the reduction choline acetyltransferase activity in primary visual cortex resulted in the cognitive deficits in AD [Ikonomovic et al., 2005]. These findings indicated that the visual network deficits might be due to the consequence of the disease, meanwhile, inefficiently visual network activation might interfere the following higher cognitive processing in AD patients. Many fMRI studies have reported decreased activity of the default network in MCI [Cha et al., 2013; Jin et al., 2012; Zhu et al., 2013] and AD [Brier et al., 2012; Greicius et al., 2004; Wang et al., 2006; Zhou et al., 2010]. In this MCI- and AD-related meta-analyses, we found most of the decreased regions located in the posterior aspect of the default network, these parts were considered to be related to memory retrieval [Buckner et al., 2008] and played neurodegenerative roles during cognitive decline [Jacobs et al., 2013].

The increased patterns of neuronal networks were similar between MCI and AD patients, implying the similar compensatory mechanisms underlying the functional brain activity. The frontoparietal compensatory hypothesis has been consistently reported in previous meta-analyses in MCI and AD [Browndyke et al., 2013; Schwindt and Black, 2009]. Many previous task-based fMRI studies found that MCI patients recruited more activity than healthy controls in frontal and parietal regions across memory encoding and retrieval, working memory, executive function, and perception tasks [Bokde et al., 2010b; Bokde et al., 2008; Hämäläinen et al., 2007; Kaufmann et al., 2008; LeyHe et al., 2009; Poettrich et al., 2009; Yetkin et al., 2006]. Moreover, increased activity in frontal and parietal areas was consistently found in AD patients across a variety of tasks, including memory encoding and retrieval, working memory, perception, and language processing [Bokde et al., 2010a; Bosch et al., 2010; Hämäläinen et al., 2007; Yetkin et al., 2006]. The present findings implicated that ventral attention, somotomotor, and default networks were also involved in the compensatory processing besides frontoparietal network. Ventral attention network are considered to be responsible for the endogenous attention orienting process [Corbetta and Shulman, 2002]. Somatomotor network is involved in the episodic memory, action recognition, and spatial navigation [Russ et al., 2003]. The increased default network regions were mainly in the anterior regions; the anterior aspect of the default network was more associated with self-referential thoughts and cognitive control [Buckner et al., 2008] and played compensatory roles in the degenerative process [Jacobs et al., 2013].

Meta-Analysis for Specific Task

The large-scale functional network disruptions presented differentially patterns across cognitive tasks in MCI and AD patients. Episodic memory deficit was the core characteristics of cognitive decline in MCI and AD. For memory encoding meta-analyses, MCI patients showed hypoactivation in visual, dorsal attention, and ventral attention networks, more percentages of hypoactivation voxels were found in these networks in AD patients, these results suggested that the reduced visual processing and the attentional orienting might influence subsequent encoding of the stimuli [Corbetta et al., 2008; Corbetta and Shulman, 2002]. Moreover, the hyperactivation voxels in MCI were focused exclusively in frontoparietal network while frontoparietal and default networks occupied 98% of the hyperactivation voxels in AD-related memory encoding meta-analysis, these results implied that frontoparietal network played an important role in dealing with the memory decline in MCI and AD. Moreover, default network was also involved in this compensatory process when the disease progressed to AD. Several other cognitive tasks also revealed interesting and differential results, for AD patients, they presented 94.1% of the hypoactivation voxels in default network in executive function and working memory tasks while demonstrated 92% of the hypoactivation voxels in visual networks in attention and visuospatial tasks; these results reflected that the dysfunctional large-scale networks in MCI and AD are influenced by specific type of cognitive task. However, due to the limited number of studies, the results should be treated cautiously.

MCI- and AD-Related Resting-State fMRI Meta-Analyses

During the resting-state fMRI meta-analysis, MCI patients showed similar lower activation in default,

frontoparietal, and limbic networks than healthy controls, as well as task-based fMRI meta-analysis. The results further suggested that reduced self-monitoring and executive control ability resulted in the cognitive decline in MCI patients. MCI patients presented exclusively higher activity in default network. Recent studies revealed increased functional connectivity in default network might be compensated to disruptions of other networks [De Vogelaere et al., 2012; Esposito et al., 2013; Jin et al., 2012; Li et al., 2012]. Functional differentiation of the default network may result in the bidirectional significant clusters that were observed in MCI patients. People with MCI have been reported to demonstrate both increased and decreased activity in the default network, which suggests that both deficits and functional compensation may coexist in the default network [Qi et al., 2010]. Regarding the fact that only eight resting-state fMRI studies contributed to the AD-related meta-analysis, the results should be treated carefully.

General Discussion

The large-scale brain network approach has become increasingly important in understanding the neural mechanisms of cognitive decline in pathological aging [Bressler and Menon, 2010; Menon, 2011], and it was deemed to be a promising biomarker for disease diagnosis and monitoring of MCI and AD. Actually, varying levels of biomarkers may be related to disease progression from MCI and AD [Jack et al., 2010]. Previous studies have consistently found amyloid-β and tau pathology in the default mode network during the progression of AD [Buckner et al., 2005; Kapogiannis and Mattson, 2011; Small et al., 2006]. Although amyloid-β and tau pathology were considered to be most sensitive biomarkers for AD, however, any single biomarker cannot predict the conversion to AD. Multiple biomarkers must be combined to detect and predict disease progression. The present findings suggested that the functional neuronal networks might be a useful imaging biomarker that may have important implications in elucidating the underlying pathologic mechanisms in pathological aging.

Although cognitive decline is consistently described in pathologically aging populations, meta-analyses of cognitive intervention revealed cognitive plasticity in MCI [Li et al., 2011] and AD patients [Sitzer et al., 2006]. Recent cognitive intervention studies have reported that training-related brain plasticity is observed in individuals with MCI [Belleville et al., 2011; Li et al., 2014]. The present results imply that the neuronal networks may be useful to evaluate the effects of cognitive intervention and investigate the underlying mechanisms of brain plasticity.

Limitations

Several limitations must be considered in this meta-analysis. First, participants across selected studies were heterogeneous, which may potentially influence the meta-analysis results. In the MCI-related and AD-related meta-analyses, diagnostic and inclusion criteria of MCI and AD, age, gender, handedness, behavioral performance, duration of illness, pathology severity, medication dosage, and other clinical symptoms experienced by MCI and AD patients are not the same, and these differences may influence brain activation. Second, this ALE model could not evaluate the relative weights among studies that used differing criteria for statistical significance. Third, we did not concern the scattered deactivation coordinates or studies only focused on deactivation. Because only few studies reported deactivation coordinates, it would not be beneficial to explore deactivation patterns at present. Finally, although these seven neuronal networks cover the cerebral neuronal network and the functional projections to the cortex from the cerebellum and striatum, some important subcortical memory related regions, such as the hippocampus and parahippocampus, were not included in the neuronal networks. These regions played important roles in pathological aging; therefore, the proportions of MCI-related and AD-related hypoactivation and hyperactivation may be influenced due to the lack of consideration memory network regions.

CONCLUSIONS

These meta-analyses demonstrated the extent and nature of the functional abnormal activation and large-scale neuronal network dysfunction in MCI and AD. The decreased activation was mainly detected in frontoparietal and default networks in MCI whereas AD patients showed more hypoactivation voxels in visual network. Similar frontoparietal, ventral attention, somatomotor, and default networks were involved in the compensatory process in these two populations. This large-scale network approach reveals neuronal network changes in cognitive decline and may provide potential insights in evaluating brain pathological aging at a system level.

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