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ORIGINAL ARTICLE

Neuroanatomic changes and their association with cognitive decline in mild cognitive impairment: a meta-analysis

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Abstract Mild cognitive impairment (MCI) is an acquired syndrome characterised by cognitive decline not affecting activities of daily living. Using a quantitative meta-analytic approach, we aimed to identify consistent neuroanatomic correlates of MCI and how they are related to cognitive dysfunction. The meta-analysis enrols 22 studies, involving 917 MCI (848 amnestic MCI) patients and 809 healthy controls. Only studies investigating local changes in grey matter and reporting whole-brain results in stereotactic coordinates were included and analysed using the activation likelihood estimation approach. Probabilistic cytoarchitectonic maps were used to compare the localization of the obtained significant effects to histological areas. A correlation between the probability of grey matter changes and cognitive performance of MCI patients was performed. In MCI patients, the meta-analysis revealed three significant clusters of convergent grey matter atrophy, which were mainly situated in the bilateral amygdala and hippocampus, extending to the left medial temporal pole and thalamus, as well as in the bilateral precuneus. A sub-analysis in only amnestic MCI revealed a similar pattern. A voxel-wise analysis revealed a correlation between grey matter reduction and cognitive decline in the right hippocampus and amygdala as well as in the left thalamus. This study provides convergent evidence of a distinct neuroanatomical pattern in MCI. The correlation analysis with cognitive-mnestic decline further highlights the impact of limbic structures and the linkage with data from a functional neuroimaging database provides additional insight into underlying functions. Although different pathologies are underlying MCI, the observed neuroanatomical pattern of structural changes may reflect the common clinical denominator of cognitive impairment.

Keywords Mild cognitive impairment · Meta-analysis · Voxel-based morphometry · Cognitive impairment · Activation likelihood estimation approach · Mini-mental state examination

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Introduction

Mild cognitive impairment (MCI) is as an acquired syndrome defined as cognitive decline greater than expected

for an individual's age and education but that does not interfere notably with activities of daily life (Gauthier et al. 2006). According to Petersen, amnestic MCI (aMCI) is a more specified term describing a subtype of MCI, in which there are memory complaint, objective memory impairment; essentially preserved general cognitive function, largely intact functional activities and no dementia (Petersen 2004). Given the current available morphometric MRI studies selecting MCI and aMCI patients according to the older Petersen criteria (Petersen 2004; Petersen et al. 1999), it has to be noted, that results of this meta-analysis are based on these definitions. In the general elderly population, the prevalence of MCI is estimated between 3.2 and 19.3% (Ritchie et al. 2001). A meta-analysis in cohort studies revealed a yearly rate of progression of MCI to dementia of approximately 5–10% (Mitchell and Shiri-Feshki 2009). However, population-based studies have shown that up to 44% of patients presenting with MCI may return to normal cognitive-mnestic functioning within a year (Ritchie et al. 2001; Ganguli et al. 2004). These findings underline that various, yet not fully understood factors may influence cognitive and mnestic decline in an elderly population (Gauthier et al. 2006). Moreover, MCI is also supposed to originate from various aetiologies (Petersen et al. 2001) involving beginning neurodegenerative disorders but also for example vascular lesions, depression or diverse medical conditions. Thus, a method to distinguish between converters into dementia and non-converters has become one of the interests in MCI research.

Structural MRI studies in MCI patients have revealed grey matter loss in the hippocampus (Muller et al. 2007; Krasuski et al. 1998; Jack et al. 1999) but also have resulted in very heterogeneous findings concerning atrophy in several frontal, parietal and the occipitotemporal regions (Chetelat et al. 2002; Convit et al. 2000; Karas et al. 2004; Killiany et al. 2000; Visser et al. 1999). The question thus emerges whether common neuroanatomical substrates of this widely defined syndrome exist and how neurostructural findings correlate with neuropsychological markers that indicate cognitive-mnestic decline. The aim of the present study was therefore:

(1) to identify regions of consistent brain structure changes as reported in the current literature and relate these findings to cytoarchitectural areas,

(2) to investigate whether the likelihood of finding regional atrophy correlates with neuropsychological markers that indicate cognitive-mnestic decline in the respective studies, and

(3) to assess the physiological functions of brain regions showing consistent atrophy.

Methods and materials

Literature search and selection

PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and BrainMap (http://brainmap.org/) databases were searched by using the following search string "smci + vbm", "mci + voxel", "mild + cognitive + impairment + voxel", "mild + cognitive + impairment + vbm" to identify morphometric MRI studies investigating MCI. BrainMap provides a database that establishes structure–function correspondence in the brain through the combined application of experimental psychology, human neuroscience, and non-invasive neuroimaging (Laird et al. 2005b). Inclusion criteria for this meta-analysis were: (1) original peer-reviewed studies, (2) selection of MCI patients according to the Petersen criteria (Petersen 2004; Petersen et al. 1999), (3) quantitative automated MRI whole-brain grey matter assessment using voxel-based morphometry (VBM), (4) comparison of MCI patients to a matched healthy control group, (5) reporting of results as coordinates in stereotactic space (Talairach/MNI).

In total, 22 studies published between 2002 and 2010 fit these criteria and were included in our meta-analysis (see Table 1). Out of the 917 included MCI patients, 848 subjects were classified as amnestic MCI (aMCI). The remaining "non-amnestic" MCI subjects were subdivided in 36 subjects with multi-cognitive domain MCI (MCD-MCI) and 33 single-cognitive domain MCI (SCD-MCI) (Schmidt-Wilcke et al. 2009; Bell-McGinty et al. 2005; Pa et al. 2009; Jauhiainen et al. 2008). By now, there have been various re-definitions of (a) MCI and/or prodromal stages of Alzheimer's disease (AD), but all of our included studies referred to the criteria according to Petersen (Petersen et al. 1999; Petersen 2004). These criteria are: (1) memory complaint usually corroborated by an informant, (2) objective memory impairment for age, (3) essentially preserved general cognitive function, (4) largely intact functional activities, (5) not demented. Overall, 130 MCI patients were reported to have converted to AD during follow-up, but separate VBM data for converters were only reported for three studies encompassing 41 subjects. None of the included studies reported increased grey matter changes in MCI patients compared to healthy controls.

Anatomic likelihood estimation meta-analysis procedure

The meta-analysis was carried out using a revised version (Eickhoff et al. 2009) of the activation likelihood estimation (ALE) approach for coordinate-based meta-analysis of neuroimaging results (Laird et al. 2005a; Turkeltaub et al. 2002). This algorithm aims at identifying areas showing a

Table 1 Demographic and clinical characteristics of the included VBM studies

Study	Subjects	Sex (male)	Age (mean ± SD)	MMSE (mean ± SD)	Scanner	Gaussian kernel width (mm)
Barbeau et al. Neuropsychologia, 2008	MCI (28*[28]*[a])	12	69.3 ± 8.6	27.4 ± 1.4	1.5 T S	6
	HC (28)	15	63.3 ± 7.2			
Bell-McGinty et al. Arch Neurol, 2005	MCI (37*[9]*)	17	71.9 ± 7.6	25.5 ± 3.2	1.5 T GE	8
	HC (47)	27	66.9 ± 7.3			
Bozzali et al. Neurology, 2006	MCI (22*[22]*)	10	70.5 ± 10.5	25.3 ± 1.6	1.5 T S	12
	HC (20)	7	65.8 ± 6.8			
Caroli et al. J Neurol, 2007	MCI (23*[23]*)	13	70.0 ± 5.5	26.9 ± 1.9	1 T P	12
	HC (17)	8	69.0 ± 3.0			
Chetelat et al. Neuroreport, 2002	MCI (22*[22]*)	10	71.0 ± 8.0	27.3 ± 1.5	1.5 T GE	12
	HC (22)	10	66.6 ± 7.2			
Hamalainen et al. Neuroimage, 2007	MCI (56*[56]*)	15	72.4 ± 4.2	23.6 ± 2.5	1.5 T S	8
	HC (22)	11	72.9 ± 4.5			
Hirata et al. Neurosci Lett, 2005	MCI (30*[30]*)	NS	70.6 ± 8.4	26.0 ± 1.5	1 T S	12
	HC (41)	NS	71.1 ± 7.7			
Jauhiainen et al. DGCD, 2008	MCI (14*[7]*)	7	76.6 ± 1.7	25.7 ± 0.8	1.5 T S	12
	HC (13)	7	74.4 ± 1.2			
Morbelli et al. Eur J Nucl Med Mol Imaging, 2009	MCI (20*[20]*)	8	75.6 ± 5.6	27.8 ± 1.2	1.5 T P	8
	HC (12)	2	70.4 ± 7.3			
Pa et al. Ann Neurol, 2009	MCI (58*[26]*)	33	65.9 ± 7.2	28.8 ± 1.3	1.5 T S	12
	HC (36)	13	64.8 ± 8.2			
Pennanen et al. JNNP, 2005	MCI (51[51])	17	72.0 ± 5.0	24.0 ± 2.0	1.5 T S	12
	HC (32)	13	74.0 ± 4.0			
Rami et al. Int J Geriatr Psychiatry, 2009	MCI (16*[16]*)	4	72.9 ± 4.8	26.0 ± 2.0	1.5 T GE	10
	HC (27)	10	74.3 ± 5.3			
Risacher et al. Curr Alzheimer Res, 2009	MCI (339*[339]*)	214	74.7 ± 0.7	26.9 ± 0.2	1.5 T GE, P, S	10
	HC (206)	107	76.0 ± 0.5			
Saykin et al. Neurology, 2006	MCI (40*[40]*)	23	72.9 ± 7.1	27.2 ± 2.2	1.5 T GE	12
	HC (40)	12	71.0 ± 5.1			
Shiino et al. Neuroimage, 2006	MCI (20*[20]*)	10	67.7 ± 9.0	26.8 ± 1.9	1.5 T GE	12
	HC (88)	40	68.7 ± 8.7			
Stoub et al. PNAS, 2006	MCI (40*[40]*)	16	77.9 ± 7.5	27.2 ± 1.6	1.5 T GE	12
	HC (50)	15	78.1 ± 6.0			
Trivedi et al. Alzheimers Dement, 2006	MCI (15*[15]*)	9	73.3 ± 6.7	27.8 ± 1.8	3 T S	12
	HC (15)	9	73.6 ± 7.1			
Wang et al. Eur J Radiol, 2009	MCI (14*[14]*)	6	71.8 ± 7.3	26.6 ± 0.3	3 T GE	8
	HC (14)	6	70.4 ± 5.8			
Schmidt-Wilcke et al. Neuroimage, 2009	MCI (18*[16]*)	10	65.7 ± 7.2	n.a.	1.5 T S	10
	HC (18)	10	63.0 ± 10.7			
Bonekamp et al. Neuroreport, 2010	MCI (10*[10]*)	5	72.7 ± 5.3	26.3 ± 2.9	1.5 T GE	8
	HC (20)	10	75.3 ± 4.8			
Brambati et al. DGCD, 2009	MCI (25*[25]*)	8	73.6 ± 7.0	27.5 ± 1.4	3 T S	8
	HC (13)	5	75.0 ± 5.0			
Guedj et al. Eur J Nucl Med Mol Imaging, 2009	MCI (19*[19]*)	9	69.9 ± 9.5	27.1 ± 1.1	1.5 T S	6
	HC (28)	14	66.7 ± 6.9			

MCI mild cognitive impairment, *GR* general electrics, *HC* healthy controls, *MMSE* mini-mental state examination, *n.a.* not available, *P* Philips, *S* Siemens, *SD* standard deviation, *T* Tesla, *S* Siemens

[a] [aMCI]

convergence of findings across studies, which is higher than expected under a spatially random spatial association. The key idea behind ALE is to treat the reported foci as centres of 3D Gaussian probability distributions reflecting the spatial uncertainty associated with each reported set of coordinates. The probabilities of all foci reported in a given study were combined for each voxel, resulting in a modelled anatomical effects map (paralleling the modelled activation maps in functional imaging meta-analyses). Taking the union across these yielded voxel-wise ALE scores describing the convergence of results at each particular location. To distinguish 'true' convergence between studies from random convergence, i.e., noise, ALE scores were compared to an empirical null-distribution reflecting a random spatial association between experiments. Hereby, a random-effects inference is invoked, focussing on inference on the above-chance convergence between studies, not clustering of foci within a particular study. Computationally, deriving this null-hypothesis involved sampling a voxel at random from each of the anatomical effects maps and taking the union of these values in the same manner as done for the (spatially contingent) voxels in the true analysis. The p value of a 'true' ALE was then given by the proportion of equal or higher values obtained under the null-distribution. The resulting non-parametric p values were transformed into Z scores and thresholded at a cluster level corrected threshold of $p < 0.05$.

Anatomical allocation by probabilistic maps

We used the SPM Anatomy Toolbox v1.5 (Eickhoff et al. 2007) to compare the localisation of the significant effects to histological areas as described in probabilistic cytoarchitectonic maps, which were summarised in a maximum probability map (MPM). The latter attributes each voxel of the reference space to the most likely cytoarchitectonic area or myeloarchitectonically defined fibre tract (Table 2) at this position and allows the definition of non-overlapping representations of all areas from a set of inevitably overlapping probabilistic maps (Amunts and Zilles 2001; Eickhoff et al. 2006; Zilles et al. 2002; Eickhoff et al. 2005). For all clusters in regions that have not yet been histologically examined, we used the MPM of macroanatomical regions provided in the "Harvard-Oxford cortical and subcortical structural atlas" (Desikan et al. 2006; Makris et al. 2006).

Correlations between MMSE and likelihood of grey matter changes

The Mini-Mental State Examination (MMSE) (Folstein et al. 1975) is the most commonly used bedside test to screen for cognitive impairments. We aimed to investigate whether assessment of an MCI sample with lower MMSE scores increases the probability of finding grey matter reduction in a particular brain region. Thus, mean MMSE scores reported in the original studies were correlated on a voxel-wise level with the modelled anatomical effects values using a Spearman rank correlation ($p < 0.05$).

Functional analysis by Behavioural Domains

In order to determine structure–function relationships, we used the BrainMap database (Laird et al. 2005b) to assess the physiological functions of brain regions showing consistent atrophy in MCI. The BrainMap database archives peak coordinates of activations of functional imaging studies and their corresponding metadata (e.g. number of subjects, analysis technique, paradigm, cognitive domain, etc.). Metadata on the domain of the behavioural system is

Table 2 Main findings of grey matter reductions in MCI patients relative to healthy controls and correlation with MMSE performance

Cluster	k_E	Side	MNI coordinates			Region
			x	*y*	*z*	
MCI < HC						
Cluster 1	2407	L	−22	−8	−22	Amygdala (LB); hippocampus (CA); thalamus; medial temporal pole
Cluster 2	1984	R	24	−8	−20	Amygdala (LB); hippocampus (FD); parahippocampal gyrus; hippocampus (EC)
Cluster 3	269	L/R	2	−54	32	Parietal precuneus; dorsal cingulate cortex
Correlation with MMSE						
Cluster 1	120	R	18	−4	−18	Amygdala (SF)
Cluster 2	33	L	−16	−24	8	Thalamus
Cluster 3	28	R	32	−14	−38	Hippocampus (EC)

MCI mild cognitive impairment, *HC* healthy controls, *GM* grey matter, *MMSE* mini-mental state examination, *MNI* Montreal Neurological Institute, *Lat.* laterality, *R* right, *L* left, *LB* laterobasal, *FD* fascia dentate, *CA* cornu ammonis, *SF* superficial, *EC* entorhinal cortex

classified according to six main categories and their related subcategories: cognition, action, perception, emotion, interoception or pharmacology (a complete list of BrainMap's behavioural domains can be found at http://brainmap.org/scribe/). To determine possible functional consequences of the structural changes, we analysed the behavioural domain metadata associated with each cluster from the ALE results to determine frequency of domain hits relative to its distribution across the whole brain (i.e. the entire database) as described before (Laird et al. 2009).

Results

Study characteristics

The mean age of subjects across the twenty-two VBM studies ranged from 65.4 to 77.9 years in the MCI group ($n = 917$ MCI patients, mean age 71.7 ± 3.2 (SD) years) and from 63 to 78.1 years in the control group ($n = 809$ healthy controls, mean age: 70.8 ± 4.4 (SD) years). Mean performance (within each study) in MMSE ranged from 23.5 to 28.8 points in MCI patients. The subgroup of aMCI compromised 848 subjects (mean age 72 ± 2.5(SD) years; age range of 67.7–77.9) and 778 healthy controls (mean age 71.1 ± 4.2 (SD) years; age range 63.3–78.1). Mean performance in MMSE ranged from 23.1 to 28.7 points in aMCI patients. The demographic and clinical data are also summarised in Table 1.

Regions with significant grey matter differences between subjects with MCI and healthy controls

Across studies, we found in total three clusters of consistent grey matter reduction in MCI patients (Table 2, Fig. 1). The two largest clusters were situated in the medial temporal lobes. Analysis by cytoarchitectural probability showed that the largest cluster was mainly situated in the laterobasal part of the left amygdala, the left thalamus, the left medial temporal pole and the cornu ammonis region of the left hippocampus. The second largest cluster in the contralateral temporal lobe was primarily located in the right laterobasal amygdala and extended to the fascia dentate region of the right hippocampus. The third largest cluster was to be found in the parietal precuneus broadening to the posterior cingulate cortex bilaterally, accentuated on the right side.

A sub-analysis in only aMCI subject compared to healthy controls revealed a similar pattern of brain structure changes with a slightly different quantity and size of clusters. The three clusters observed in the above-described

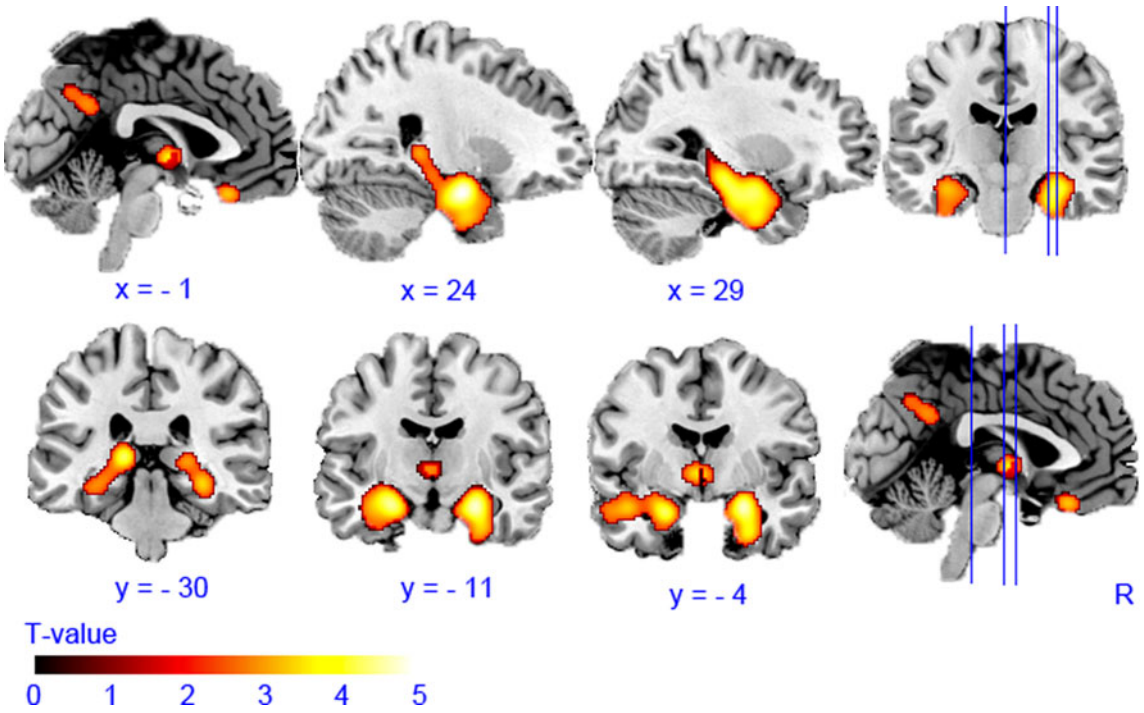

Fig. 1 Convergent areas of grey matter loss in MCI patients compared to healthy controls. Grey matter changes were found bilaterally in the amygdala/hippocampus region extending to the thalamus and medial temporal pole on the left side and to the parahippocampal gyrus on the right side. The third cluster was found accentuated on the right side in the parietal precuneus broadening to the posterior cingulate cortex

analysis were almost identically found in this analysis again. However, the analysis in the aMCI subsample revealed two additional mid-sized clusters, one in the left superior temporal gyrus and the other one in the left thalamus (please see Supplementary Table 1; Supplementary Fig. 1).

Correlation of grey matter changes with MMSE performance

A voxel-wise analysis whether grey matter changes correlated with MMSE performance yielded three clusters indicating an increased probability of finding brain atrophy in these regions in patients with lower MMSE scores (Table 2, Fig. 2). The largest and the smallest cluster indicated at a correlation of grey matter volume reductions with MMSE performance in the right superficial parts of the amygdala and the right parahippocampal gyrus. The third cluster was primarily situated in the left thalamus. The MMSE correlation analysis in the aMCI group revealed one larger cluster in the right amygdala and one smaller cluster in the right thalamus (please see Supplementary Table 1; Supplementary Fig. 2).

Functional analysis by Behavioural Domains

Functional Behavioural Domain analysis was carried out for all clusters of convergence that indicated significant differences between MCI patients and healthy controls. Behavioural Domains that were most frequently represented in the clusters of convergence were "emotion" (bilateral hippocampus/amygdala, parietal precuneus, left thalamus), "cognition-memory" (bilateral hippocampus/amygdala, parietal precuneus), "cognition-language" (left hippocampus/amygdala) and "emotion-perception" (left thalamus).

Discussion

This quantitative meta-analysis, encompassing 22 whole-brain VBM studies with a total of 917 MCI patients and 809 healthy controls, is the first one presenting consistent regional brain atrophy, and clinical correlation with clinical cognitive-mnestic performance as well as a description of structure–function correspondence in MCI. Our results demonstrate three significant clusters of convergence in MCI patients. These clusters were located bilaterally in the middle temporal lobe, including the hippocampus and the amygdala, and the parietal precuneus. This pattern was confirmed in a sub-analysis of only aMCI (848 out of 917 MCI subjects). Cognitive decline correlated with findings of brain atrophy in the bilateral hippocampus/amygdala region and the left thalamus. Behavioural Domain analysis found that physiologically these regions were mainly associated with emotion, cognition and memory.

The neuropathological substrate of the most common (amnestic) subtype of MCI, was shown to be the medial temporal lobe and concomitant pathologic abnormalities including argyrophilic grain disease, hippocampal sclerosis and vascular disease were found in *post mortem* studies (Petersen et al. 2006). The involvement of the medial temporal lobe in mnestic functions, especially encoding and retrieval of episodic and spatial memory, is well known and has been repeatedly demonstrated in functional neuroimaging, lesion studies and various animal models (Squire 1992; Sauvage et al. 2008; Fortin et al. 2004). Functionally, the observed structures are commonly regarded as key assemblage points in a widespread cerebral network of episodic memory encoding and retrieval that encompasses also ventrolateral temporal, medial and lateral parietal, and medial and lateral frontal isocortical brain (Dickerson and Eichenbaum 2010). Although there is yet no general consensus whether there is a specific topographic organisation in the medial temporal lobe that differentiates the functional neuroanatomy of memory encoding or retrieval, data derived from fMRI studies hint at differential activation in this brain region during respective paradigms. The hippocampus, located in the medial temporal lobe, belongs to the limbic system and is associated with various cortical regions. Together these structures are responsible for the formation of the long-

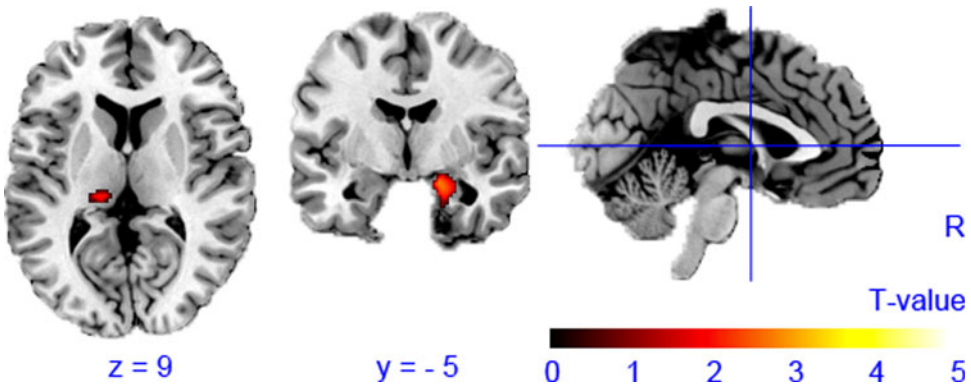

Fig. 2 Voxel-wise correlation analysis with the MMSE scores revealed clusters of convergence in the right hippocampal/amygala region and the left thalamus

term memory and spatial navigation. Specific activation of the hippocampal cornu ammonis (CA) areas was reported during episodic memory encoding, while retrieval related activation was mainly found in the subiculum (Zeineh et al. 2003). Item-based (e.g. item recollection, distinction between new and previously shown items) and associative memory processes also seem to involve different functional topographies. The hippocampal formation is primarily engaged in recollection or associative memories, while the entorhinal cortex was found to be activated for familiarity or for item-based non-associative memory (Davachi et al. 2003; Eichenbaum et al. 2007; Squire 2004). Spatial memory functions have been shown to be associated with posterior parahippocampal and perirhinal activity (Davachi et al. 2003; Maguire 1997; Stern et al. 1996). Mirroring these findings of the current literature on hippocampal involvement in episodic memory, our Behavioural Domain analysis of the clusters in the medial temporal lobes was able to verify this association over a large sample of studies. Remarkably, the larger of the two clusters situated in the cornu ammonis region of the hippocampus was on the right side. Lesion studies in humans and animals suggest a lateralization of hippocampal functions in spatial memory with positional memory and object-location memory more impaired by lesions of the right hippocampal formation (Cipolotti and Bird 2006; Kessels et al. 2001). Both memory systems have been shown to be impaired in MCI patients compared to normally ageing individuals (Kessels et al. 2010a), but were also able to validly discriminate MCI from AD patients, thus supporting the notion that tests enrolling visual and spatial features may have better diagnostic value than those relying on verbal memory (Kessels et al. 2010b). Recently, a VBM meta-analysis of MCI patients which converted to AD, proposed atrophy of the left medial temporal lobe as a neurostructural biomarker to predict conversion from amnestic MCI to AD (Ferreira et al. 2009). In this context, our meta-analysis findings of the hippocampal atrophy in patients with MCI further emphasise the important role of the hippocampus in MCI pathobiology.

The two largest clusters of convergence also comprised the amygdalae on either hemisphere. The role of the amygdalae in emotion processing and emotional memory has been highlighted by functional imaging experiments and lesion studies in animal models (Maren and Fanselow 1995; Pape and Pare 2010; Roozendaal et al. 2009). Studies in humans have further demonstrated the essential role of the amygdala in the modulation of emotions, emotional memory processes and storage (Aldolphs 1999; Sarter and Markowitsch 1985; Fine and Blair 2000). On a cytoarchitectonic level, one of the most widely accepted subparcellation schemes distinguishes the superficial, the laterobasal and the centromedial part of the amygdala (Amunts et al. 2005; de Olmos and Heimer 1999). The basal and lateral nuclei of the amygdala receive projections from associative visual and auditory cortical regions, the orbital and the cingulate cortex and from the hippocampus and the entorhinal cortex. Besides projections to higher cortical regions, the efferences of the basolateral group are directed towards the centromedial complex of the amygdala. The centromedial amygdala itself sends efferences to the paraventricular and the lateral nuclei of the hypothalamus, the locus coeruleus, the periaqueductal grey region and the parabrachial nucleus, thus mediating autonomic responses to aversive stimuli (Pitkanen et al. 1997; Pitkanen et al. 1995). Given the functional role of the amygdala involving the storage of emotional memory contents, our findings in the meta-analysis emphasise the crucial role in mild cognitive impairment.

Interestingly, our meta-analysis and the correlation with the MMSE revealed clusters in the thalamus. From the neuropathological perspective, the limbic thalamus is strongly involved in AD (Braak and Braak 1991). Amyloid deposits and neurofibrillary tangles have been found in the thalamus (Braak and Braak 1991) as well as a significant loss of its grey matter in patients with MCI and AD (Karas et al. 2004). Functional neuroimaging studies underline the essential role in dynamical interactions of thalamocortical networks (Lopes da Silva 1991). In patients with MCI, thalamic dysfunctions have been reported, which likely affect the thalamocortical integrity (Cantero et al. 2009). These findings are not surprising given the role of the thalamus in declarative memory (de Rover et al. 2008; Van der Werf et al. 2003) and postulate a mild involvement of this subcortical structure in neurodegenerative processes.

The third cluster was mainly located in the posterior cingulate/precuneus region, accentuated on the left side in the MCI group. The precuneus located in the posteromedial portion of the parietal lobe, has a complex set of interconnections, namely multiple reciprocal and afferent/efferent cortical connections to the cingulate, the adjacent parietal and frontal cortex and subcortical projections to the thalamus, striatum, claustrum as well as the brainstem (Cavanna and Trimble 2006). According to the interwoven network, the precuneus most likely plays an important role in the modulation of self-processing, consciousness, episodic memory retrieval and visuo-spatial imagery (Cavanna and Trimble 2006). Alterations in the posterior cingulate/precuneus region in patients with MCI have not only been reported on the structural level (Lo et al. 2010; Derflinger et al. 2011) but also implications for the default mode network (DMN). The DMN includes the posterior cingulate extending into the precuneus, lateral parietal and medial prefrontal regions. Regional activity levels and network connectivity of resting brain function in MCI and AD feature additional default-related changes particulary

in the posterior cingulate/precunues and hippocampal region (Beason-Held 2011). Interestingly, these regions demonstrating the aberrant default network activity also overlap the anatomy of regions with highly amyloid burden in early AD (Klunk et al. 2004). Moreover, the posterior cingulate/precuneus region may play a role in cognitive reserve, which has been claimed as a factor mitigating the clinical manifestation of AD (Serra et al. 2011).

In the present analysis, we observed several clusters in which the likelihood of finding differences to control populations depended on the patients' MMSE score, within the right hippocampal/amygdala region and the left thalamus. As already mentioned, MCI has to be regarded as a syndrome with underlying different diseases with distinct pathophysiologies under the main symptom of cognitive decline causing no inference with daily life functioning. Given the pathological heterogeneity, the further course of MCI is often difficult to estimate. In more detail, if MCI patients present in the further course a more severe cognitive decline (e.g. lower MMSE scores) they are more likely to convert to AD. In contrast, MCI patients showing no further reduction of cognitive function will potentially be clinical stable or even improve over time. Since progression to AD seems to be associated with marked deficits in spatial memory subsystems and lesions of the right hippocampal formation are known to be associated with congruent functional impairments, MCI patients on the verge of conversion to AD can be expected to display more atrophy in this region than other patient subgroups. Thus, these regions might provide a viable diagnostic tool for the identification of MCI patients at high risk to convert into dementia using structural neuroimaging. However, this interpretation has several caveats. Firstly, data of human lesion studies is heterogeneous by nature, especially in a small brain region with functionally diverse structures such as the medial temporal lobe. Due to the small sample of "non-amnestic" MCI subjects in our MCI group, a direct comparison between aMCI and "non-amnestic" MCI in order to detect specific regions for each group appeared not to be meaningful, but should be followed-up in future studies with well-balanced sufficient samples. Moreover, since MMSE scores are a rather unspecific measure of cognitive decline, correlations of brain structure changes with more specific memory tests will be a promising goal for future studies once available.

Whereas a previous VBM meta-analysis only found structural abnormalities in the right gyrus rectus, the left temporal pole/anterior superior temporal sulcus and the right amygdala (Schroeter et al. 2009), we found a bilateral involvement of the hippocampus and amygdala, the precuneus as well as of the left thalamus in patients with MCI. In this vein, the regions we found in our MCI group, the previous VBM meta-analysis by Schroeter mainly reported these findings in the AD group (Schroeter et al. 2009). Given the fact that the previous meta-analysis only compromised five MRI studies with 165 patients for the MCI group and nine MRI studies with 177 patients for the AD group, these observed differences might be due to the small sample of the previous meta-analysis.

As any meta-analysis technique, this approach is limited by the details of the primary research articles, including their definition of MCI and reported variables. Overall, most definitions of MCI relate to the concept of "cognitive decline greater than that for an individual's age or education level but that does not interfere notably with activities of daily life" (Gauthier et al. 2006; Dubois et al. 2007). However, clinical outcome can vary considerably due to differences in diagnostic entry criteria that may appear as minor (Dubois and Levy 2004; Gauthier et al. 2006). In consequence, also neuroanatomical findings might vary due to different entry criterion (Dubois and Levy 2004; Gauthier et al. 2006).

Finally and as already mentioned above only a relatively small number of published studies matched our inclusion criteria, we were therefore not able to perform separate analyses on clinical subgroups. Thus, more detailed analyses on structural findings pertaining to clinical subgroups of MCI will be an important topic for future research once additional whole-brain based VBM studies on this population are available.

Conclusion

In the current quantitative meta-analysis of structural neuroimaging data encompassing 917 MCI patients and 809 healthy controls, we identified common neuroanatomic correlates in the clinical syndrome of cognitive impairment. Firstly, we provide objective evidence that limbic and temporo-parietal structures are consistently involved in pathobiology of MCI. Secondly, the correlation analysis with the clinical neuropsychological finding of cognitive-mnestic decline primarily highlights the impact of the hippocampus and amygdala in this clinical syndrome. Thirdly, we demonstrated using a neuroinformatics approach that these consistent regions of brain atrophy are functionally linked to "emotion" and "cognition".

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Conflict of interest The authors declare that they have no conflict of interest.

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