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Review

Parietal cortex matters in Alzheimer's disease: An overview of structural, functional and metabolic findings

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ABSTRACT

Atrophy of the medial temporal lobe, especially the hippocampus and the parahippocampal gyrus, is considered to be the most predictive structural brain biomarker for Alzheimer's Dementia (AD). However, recent neuroimaging studies reported a possible mismatch between structural and metabolic findings, showing medial temporal lobe atrophy and medial parietal hypoperfusion as biomarkers for AD. The role of the parietal lobe in the development of AD is only recently beginning to attract attention. The current review discusses parietal lobe involvement in the early stages of AD, viz. mild cognitive impairment, as reported from structural, functional, perfusion and metabolic neuroimaging studies. The medial and posterior parts of the parietal lobe seem to be preferentially affected, compared to the other parietal lobe parts. On the basis of the reviewed literature we propose a model showing the relationship between the various pathological events, as measured by different neuroimaging techniques, in the development of AD. In this model myelin breakdown is a beginning of the chain of pathological events leading to AD pathology and an AD diagnosis.

Contents

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1. Introduction

Alzheimer's disease (AD), the most common cause of dementia, is characterized by an insidious decline in memory, later affecting language, visuospatial perception, arithmetic abilities and executive functioning. Behavioral and psychiatric symptoms have also been frequently reported (Cummings, 2004). AD is characterized by both the accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles (tau pathology) leading to regional neuronal loss, cortical atrophy and cognitive decline (Braak and Braak, 1991, 1996). Histological studies have shown that neurofibrillary tangle formation occurs in a well-defined order, starting in the medial temporal lobe early in the disease and subsequently progressing towards the lateral temporal and association parietal cortices, the prefrontal cortices and finally the motor and sensory areas (Braak and Braak, 1996). By contrast, amyloid plaques first affect the posterior association cortices in the earliest stage of the disease. The medial temporal lobe areas might then be affected, but this is not very common in the early stages of AD (Braak and Braak, 1991, 1996; Thal et al., 2002).

The amyloid cascade hypothesis has been dominating AD research to date (Korczyn, 2008), stating that extracellular amyloid plaques formed by aggregates of amyloid beta (Abeta) peptide, are central to the AD pathology. In view of the evidence that amyloid deposition most commonly starts in the association neocortex (Braak and Braak, 1991, 1996; Thal et al., 2002), it is therefore rather surprising that the extant literature mainly focuses on pathology in the medial temporal lobe.

While different neuroimaging methods have shown that hippocampal and parahippocampal atrophy could predict conversion from MCI to AD (de Leon et al., 2007; Dickerson and Sperling, 2009; Echavarri et al., 2010; Jacova et al., 2008; van de Pol et al., 2009), the results so far have been equivocal. Medial temporal lobe atrophy has a low specificity, since it has also been observed in patients with other neurodegenerative diseases, such as Lewy Body dementia or Parkinson Disease (Barkhof et al., 2007) and even in healthy aging (Kaye et al., 1997; Raz et al., 2005). Besides grey matter atrophy, loss of regional white matter tissue in the medial temporal lobe areas (Jovicich et al., 2009; Naggara et al., 2006; Salat et al., 2009) has also been associated with AD. Functional imaging studies have shown that medial temporal lobe hyperactivation could be a possible biomarker for AD.

Metabolic imaging studies, however, have revealed a major discrepancy with the above structural and functional studies. Metabolic dysfunction is most frequent reported in tempoparietal association areas, in which hypometabolism in the medial parietal areas appears to be more accurate in discriminating AD patients from control participants (Imabayashi et al., 2004; Ishii et al., 2005; Jagust et al., 2002; Villain et al., 2010b). As for metabolic changes in the medial temporal lobe regions, the findings are less clear, suggesting that the temporal lobe is of less value (Encinas et al., 2003) and that metabolic changes in the medial temporal lobe areas are a better predictor than metabolic changes in the medial parietal areas (Caroli et al., 2007; Karow et al., 2010; Nobili et al., 2009). The medial parietal areas are considered to be the centre of metabolic changes (Jagust et al., 2002; Villain et al., 2010b; Zhang et al., 2011). Thus, there might be a mismatch between structural and metabolic findings (Buckner et al., 2005; Caroli et al., 2010; Hunt et al., 2007; Ishii et al., 2005; Klunk et al., 2004; Matsuda, 2007; Villain et al., 2010b). Understanding this mismatch requires a better comprehension of the relevance of the posterior association areas and their connectivity with the rest of the brain.

This overview summarizes the evidence of structural, functional and metabolic changes in MCI or prodromal AD patients based on the recent neuroimaging literature, with a special focus on posterior association regions, more specifically the parietal lobe areas. Our review of the literature also investigated which parietal region appears to be the most relevant in the development of AD, based on the research results that have been reported.

2. Methods

2.1. Search strategy and selection criteria

Research papers dating from January 2000 to September 2010 were identified in PubMed using the following search terms: {"mild cognitive impairment" or "prodromal Alzheimer" or "predementia Alzheimer"} and {"parietal" or "precuneus" or "posterior cingulate" or "retrosplenial"} and depending on the imaging technique reviewed: {"grey/gray matter" or "white matter" or "functional MRI" or "SPECT" or "PET", or "metabolic"}. Searches were limited to papers written in English. Studies that solely focused on one single brain region of interest, e.g., the medial temporal lobe, were excluded. Because of our focus on parietal lobe regions, at least one parietal lobe structure had to be involved in the results among other cortical regions. Histological or EEG studies were not included.

In addition to a semi-systematic search in PubMed, we also performed hand searching based on reported citations identified to be of interest.

2.2. Data analysis

The articles included in our review are summarized in the tables provided in the supplemental data. We reviewed the data qualitatively and did not perform any quantitative meta-analysis, because different techniques were compared (Region of Interest (ROI), whole brain, different neuroimaging techniques). Comparing findings based on different techniques and analyses methods quantitatively would not result in highly reliable results. We reviewed the specific parietal lobe area that was involved in each study, but not left-right differences or lateralization.

3. Structure of this review

We first summarize the neuroanatomy and functions of the parietal lobe. Then we review the results of the semi-systematic literature search, categorized by neuroimaging technique: structural, functional and metabolic neuroimaging studies. By taking this approach, we did not aim to play down the importance of the medial temporal lobe, but we wanted to highlight the high

relevance of the parietal lobe in the earliest stages of the disease. We also wanted to examine which parietal area is most commonly associated with MCI. We focused on studies using either a multiple ROI approach or a whole brain approach. Furthermore, we limit our discussion to studies comparing controls with either MCI patients, prodromal AD patients or participants with cognitive decline, since all three categories of individuals are considered to be susceptible to AD and this information can thus be of direct relevance for studies investigating diagnostic and therapeutic aims. We do not focus on the comparison between healthy controls and AD, since the brain changes in full-blown AD are no longer region-specific, but widespread. The tables (see Supplemental Data) present an overview of the reviewed studies together with the location of the results with respect to the parietal lobe. The nature of the findings (increased or decreased tissue, activation or perfusion) is discussed in the text. Note that this overview of the extant literature is not exhaustive, although we have tried to include the most relevant studies. The conclusion summarizes the findings within and across the various neuroimaging techniques. Based on these findings, we finally present a model describing the chain of pathological events leading to Alzheimer's dementia.

4. Parietal lobe structure and function

4.1. Parietal lobe structure

The parietal lobe is the region of the cerebral cortex underlying the parietal skull bone. The anterior border of the parietal lobe is formed by the central sulcus and the marginal ramus. The posterior border can be defined by a line along the sulci from the parieto-occipital sulcus into the preoccipital notch. The ventral border can be defined by the insula and a line from the tip of the lateral fissure perpendicular to the curvilinear line from the parieto-occipital sulcus towards the preoccipital notch. The parietal lobe includes the posterior cingulate cortex, so the medial border is at the bottom of the callosal sulcus. The medial border between the parietal cortex and the posterior cingulate cortex is formed by the splenial or subparietal sulcus. The retrosplenial cortex is often considered part of the posterior cingulate gyrus (Jones et al., 2006).

The parietal lobe can be subdivided into the postcentral gyrus (more or less equivalent to the Brodmann Areas (BA) 1, 2 and 3), the superior parietal lobule (∼BA 5 and 7), the parietal operculum (∼BA 43), the inferior parietal lobule formed by the angular gyrus (∼BA 39) and the supramarginal gyrus (∼BA 40), the precuneus (∼BA 7 mesial and a small part of BA 31), the posterior cingulate cortex (∼BA 23 and part of BA 31), the retrosplenial cortex (∼BA 26, 29 and 30) and the posterior part of the paracentral lobule (BA 31) (Nieuwenhuys et al., 2008; Uylings et al., 2005). Functionally, the parietal lobe is often divided into an anterior (BA 1, 2, 3 and 43) and a posterior part (BA 5, 7, 39, and 40). These parts are also often referred to as the somatosensory cortex and the posterior parietal cortex, respectively (Fig. 1).

The medial part of the posterior parietal cortex, i.e., the precuneus, has bilateral reciprocal connections with the posterior cingulate retrosplenial cortices, but also with the other parietal areas, frontal areas (frontal eye fields, dorsolateral prefrontal cortex, premotor area, supplementary motor area and anterior cingulate cortex), the superior temporal sulcus, the thalamus, the striatum and the brainstem. Interestingly, the precuneus has no connections with the somatosensory cortex (Cavanna and Trimble, 2006). The posterior parietal cortex is highly connected with the prefrontal cortex (mainly BA 46, the dorsolateral prefrontal cortex), and is also connected with the paralimbic cortex, the hippocampus, the parahippocampal gyrus and the thalamus (Rushworth et al., 2006). The posterior parietal cortex can therefore be regarded as a polymodal area.

Different fiber bundles connect the posterior parietal cortex with the temporal lobe: one (i.e., the middle longitudinal fasciculus) from the inferior parietal lobule to the rostral middle and caudal portions of the superior temporal region, one to the parahippocampal area, and one (partly along the cingulum) to the presubiculum.

Fibers from the posterior parietal cortex travel along the superior temporal sulcus, the geniculocalcarine tract, the parahippocampal area and the cingulum. The cingulum fibers extend caudally to the parahippocampal gyrus and the presubiculum (Makris and Pandya, 2009; Makris et al., 2009; Seltzer and Pandya, 1984). The superior longitudinal fasciculus (SLF) connects the posterior parietal cortex with the prefrontal cortex. This tract consists of three parts: the SLF1, SLF2 and SLF3 (Schmahmann et al., 2007). The SLF1 connects the superior parietal lobule with premotor and dorsolateral prefrontal areas. The SLF2 connects the inferior parietal lobule with the dorsolateral prefrontal cortex. This almost coincides with the areas innervated by the fronto-occipital fasciculus. The SLF3 connects the inferior parietal lobule and the intraparietal area with the premotor, inferior prefrontal and dorsolateral prefrontal cortices. The SLF1 is believed to be involved in higher order motor behavior, while the SLF2 and SLF3 have been linked to visual attention and working memory. The posterior parietal cortex (BA7, 39, and 40) is also innervated by the dorsal part of the splenium (Chao et al., 2009; Makris et al., 2005; Mori et al., 2005; Schmahmann et al., 2007).

4.2. Parietal lobe functions

Structures within the parietal lobe are thought to bear a specific relation to a variety of cognitive functions. Some of them have to do with spatial information processing, but also non-spatial functions of the parietal lobe have been described (Cabeza, 2008; Husain and Nachev, 2007). The exact functional parcellation of the parietal lobe is still under debate (Culham and Kanwisher, 2001). The somatosensory cortex is primarily involved in somatic sensations and perceptions, while the posterior parietal cortex plays an important role in integrating sensory input from the somatic and visual regions. It also has a role in directing movements in space and detecting stimuli in space. Furthermore, the posterior parietal cortex is part of the dorsal stream and is important for spatial processing. It is also involved in selective attention, independent of modality, and in spatial and non-spatial working memory. Involvement in other important simple and complex functions and processes have been described, notably arithmetic, reading, mental rotation, mental imagery, response inhibition, task switching and the manipulation of visual images (Husain and Nachev, 2007; Zacks, 2008). Also pain processing and meditation have been associated with medial parietal lobe activation (Cavanna and Trimble, 2006). The superior parietal lobule and supramarginal gyrus are involved in the visual guidance of the movements of hands, fingers, limbs, head and eyes. The angular gyrus plays an important role in processes relating to spatial cognition. The intraparietal sulcus, i.e., the border between the superior and inferior parietal lobule, has been associated with saccadic eye movements, attention, reaching, grasping, tactile manipulation of objects, observing hand movements, passive tool use, object matching and object size and orientation discrimination (Gottlieb, 2007; Grefkes et al., 2004, 2002; Pellijeff et al., 2006; Tunik et al., 2007). The precuneus has been suggested to play a role in visuo-spatial imagery, episodic memory retrieval and self-consciousness (Cavanna and Trimble, 2006; Vogt et al., 2006).

Recent studies have parcellated the functions of the parietal lobe in greater detail (Caspers et al., 2006; Eickhoff et al., 2006a,b; Grefkes and Fink, 2005; Sack, 2009; Scheperjans et al., 2008).

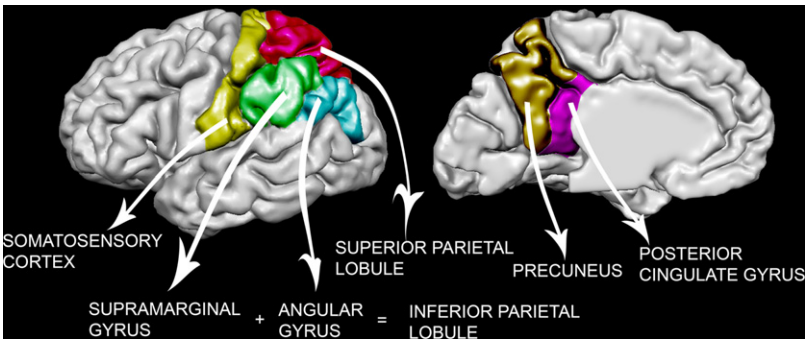

Fig. 1. Structure of the parietal lobe. The various anatomical regions of the parietal lobe are shown: the somatosensory cortex (yellow), the superior parietal lobule (pink), the supramarginal gyrus (green), the angular gyrus (blue), the precuneus (brown) and the posterior cingulate gyrus (purple). The supramarginal and the angular gyri together form the inferior parietal lobule. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

4.3. Relevance of the parietal lobe to neuropsychological deficits in AD

Early AD is primarily characterized by episodic memory functions, but other memory impairments, such as semantic memory impairments can also be present (Cummings, 2004; Lindeboom and Weinstein, 2004). Memory problems in AD have received a great deal of attention. However, early AD is also characterized by subtle language deficits, visuo-spatial dysfunctions and impairments in executive functions (Cummings, 2004; Lindeboom and Weinstein, 2004). In view of the prominent memory problems, many studies have focused on medial temporal lobe changes in AD (Dickerson and Sperling, 2008). However, the parietal lobe also plays a role in memory retrieval (Cabeza et al., 2008). Furthermore, other cognitive functions associated with parietal lobe functions are impaired in early AD, e.g., attention, naming or executive dysfunctions (Lindeboom and Weinstein, 2004).

The involvement of the parietal lobe in neurodegenerative diseases such as AD is likely to be due to the strong connectivity between the parietal lobe and other brain areas, and to the wide range of cognitive functions relying on parietal lobe functioning.

5. Involvement of the parietal lobe during conversion from MCI to AD in neuroimaging studies

5.1. Structural neuroimaging

5.1.1. Grey matter studies

Table 1 (see Supplemental Data) summarizes the findings with respect to grey matter loss in the parietal lobe in MCI patients. Most studies ($n = 10$ out of 20) so far have used a voxel-based morphometry (VBM) approach, and far fewer have applied cortical thickness analyses ($n = 6$), a technique that gained popularity in recent years.

Studies comparing MCI patients with controls at one particular time point have reported varying results. Grey matter loss in MCI groups has been found in the following regions: the precuneus, supramarginal gyrus, angular gryus, superior parietal lobule, paracentral lobule posterior cingulate cortex and inferior parietal lobule (Chetelat et al., 2002; Hamalainen et al., 2007b; Pennanen et al., 2005; Scahill et al., 2002; Singh et al., 2006; Wang et al., 2009). This was found regardless of the technique used, whether volumetry, cortical thickness analyses or VBM. Taken together, these studies indicated that patients with mild cognitive impairment show grey matter loss in the posterior parietal cortex, compared to healthy counterparts. These patterns might differ depending on the subgroup of mild cognitive impairment. Few studies ($n = 3$) have investigated differences in grey matter loss between single domain amnestic MCI patients and multi-domain MCI patients. Since the pattern of grey matter loss in the multi-domain MCI group is more widespread, but overlaps with that in the amnestic MCI group, it has been suggested that multi-domain MCI might be a stage in the continuum between amnestic MCI and AD (Fennema-Notestine et al., 2009).

Amnestic MCI has been associated with grey matter loss in the inferior parietal lobule, the precuneus, the superior parietal lobule, the posterior cingulate cortex (Apostolova et al., 2007; Fennema-Notestine et al., 2009) and the angular gyrus (Saykin et al., 2006). In addition, multi-domain MCI has been associated with cortical thinning in the inferior parietal lobule, the precuneus, the posterior cingulate cortex, the retrosplenial cortex, the superior parietal lobule, the supramarginal gyrus and the paracentral lobule (Fennema-Notestine et al., 2009; Seo et al., 2007).

Other studies have also investigated grey matter differences in relation to the severity of the disease, either by comparing patients with different scores ($n = 1$) (McDonald et al., 2009), or by making longitudinal comparisons, in terms of conversion rates to AD ($n = 10$). One study compared different stages of the disease, based on Clinical Dementia Rating (CDR) scores of patients and found a negative relationship between severity and grey matter volumes in the superior parietal lobule and the supramarginal gyrus. The grey matter volumes of the inferior parietal lobule and the precuneus were reduced even in the early stages (McDonald et al., 2009). Longitudinal studies that investigated possible conversion to AD showed grey matter loss in the superior parietal lobule, the supramarginal gyrus, the angular gyrus, the precuneus, the posterior cingulate gyrus, the retrosplenial cortex, and the inferior parietal lobule (Bakkour et al., 2009; Bozzali et al., 2006; Chetelat et al., 2005; Desikan et al., 2009, 2008; Hamalainen et al., 2007b; Julkunen et al., 2009; Karas et al., 2008; Whitwell et al., 2008). The most consistent finding in these studies was atrophy of the precuneus and inferior parietal lobule. However, the suggestion that parietal lobe atrophy is associated with conversion to AD and is not present in the very early stages of AD, possibly before MCI, is contradicted by studies investigating individuals without an MCI diagnosis. Such studies, comparing individuals without a diagnosis of MCI or AD, but with cognitive complaints or cognitive decline, have already shown involvement of the posterior parietal lobe, more specifically the angular gyrus (Saykin et al., 2006; Smith et al., 2007; Tisserand et al., 2004).

Overall, these studies show that the somatosensory cortex is least affected in MCI, and the precuneus/posterior cingulate gyrus is most commonly affected.

5.1.2. White matter studies

Most studies ($n = 14$ out of 17) examining the white matter in patients with mild cognitive impairment have used diffusion tensor imaging (DTI). DTI is a method for quantitative evaluation of white matter tissue microstructure at each imaging voxel throughout the

brain and might be more sensitive to subtle white matter damage affecting cognition (Burgmans et al., 2009; Vernooij et al., 2009). Three different approaches are widely used: the ROI-based approach ($n = 8$), the voxel-based approach ($n = 3$) and Tract-Based Spatial Statistics (TBSS) ($n = 3$). Each approach has its advantages and disadvantages, which were recently described (Chua et al., 2008). So far, a comparison between amnestic and non-amnestic MCI patients on the one hand and controls on the other has not yielded consistent differences (see Supplemental Data, Table 2). White matter integrity in MCI patients, regardless of the type, is compromised in several tracts innervating the parietal lobe: the splenium, the superior longitudinal fasciculus, the inferior longitudinal fasciculus, the posterior cingulate fibers and the occipitofrontal fasciculus (Bai et al., 2009b; Bosch et al., 2010; Cho et al., 2008; Chua et al., 2008; Huang and Auchus, 2007; Huang et al., 2007; Liao et al., 2010; Medina et al., 2006; Parente et al., 2008; Rose et al., 2006; Scola et al., 2010; Stahl et al., 2007; Teipel et al., 2010). Furthermore, several studies ($n = 7$) have reported reduced white matter integrity in the normal appearing parietal white matter (Bai et al., 2009b; Huang and Auchus, 2007; Huang et al., 2007; Liao et al., 2010; Medina et al., 2006; Rose et al., 2006; Stahl et al., 2007). These patterns were independent of the DTI technique used.

It should be noted that some other studies were unable to find differences between control participants and MCI patients, in terms of parietal white matter (Balthazar et al., 2009; Kantarci et al., 2001). This could be due to the sample size, the fact that the parietal lobe was not selected as an ROI, or because the description of the results was not detailed enough (e.g., centrum semi-ovale or total white matter). Recently, a few studies ($n = 2$) investigated white matter differences between cognitively healthy older participants and MCI patients in more detail, beyond the tracts. Apart from the affected tracts documented earlier, these studies showed loss of white matter integrity in the superior parietal lobule, the precuneus, the angular gyrus and the supramarginal gyrus (Bai et al., 2009b; Zhuang et al., 2010). Only a few studies ($n = 4$) were found that used other techniques than DTI. Studies using VBM have shown less white matter density in the angular gyrus, the paracentral region and postcentral white matter in MCI patients (Teipel et al., 2010; Wang et al., 2010). A study using magnetization transfer imaging, a technique able to estimate structural damage in the brain, found a reduced white matter height peak in the parietal white matter in MCI patients (van Es et al., 2006). Less white matter volumes in very mild AD patients were found in the inferior parietal lobule, the superior parietal lobule, the supramarginal gyrus, the somatosensory cortex, the precuneus and the retrosplenial cortex compared to healthy counterparts (Salat et al., 2009). Finally, parietal white matter hyperintensities (WMH) are very prominent in MCI patients (Targosz-Gajniak et al., 2009). Most studies investigating WMH divide such abnormalities into subcortical and periventricular WMH, rather than by lobe or region. In our own work, we showed that parietal WMH could differentiate cognitively declining from non-declining MCI patients (Jacobs et al., 2010). We did not identify any studies investigating WMH volumes in specific brain regions, such as parietal lobe regions.

Overall, these white matter studies suggest a widespread pattern of loss of white matter volume or integrity, affecting all parietal areas and many tracts connecting these areas.

5.2. Functional neuroimaging

5.2.1. Resting state activity studies

The default mode network comprises a group of brain regions – encompassing the posterior cingulate cortex, the adjacent precuneus, retrosplenial cortex, inferior parietal cortex, medial prefrontal cortex and sometimes also the medial temporal lobe – which is active during rest and deactivates during externally oriented tasks (Andrews-Hanna et al., 2010; Buckner et al., 2008; Greicius et al., 2003; Raichle et al., 2001). Comparisons between MCI patients and healthy controls regarding parietal lobe differences have consistently shown a reduced deactivation of the inferior parietal lobule, the posterior cingulate gyrus, the retrosplenial cortex, and the precuneus (Bai et al., 2008; Koch et al., 2010; Pihlajamaki and Sperling, 2009; Qi et al., 2010; Sorg et al., 2007) Several studies ($n = 5$) reported loss of connectivity or even no connectivity between the posterior cingulate cortex and other brain regions, such as the medial temporal lobe, other parietal regions and the prefrontal lobe regions (Bai et al., 2009a, 2008; Gili et al., 2010; Koch et al., 2010; Sorg et al., 2007).

Overall, resting state studies in MCI patients show reduced deactivation and loss of connectivity in the precuneus and posterior cingulate gyrus.

5.2.2. Task-related activity studies

Table 3 (see Supplemental Data) summarizes studies that found task-related activation changes in MCI patients for the parietal lobe. Some studies ($n = 2$) summarized their parietal lobe findings at a general level, without focusing on the different parts of this lobe (Machulda et al., 2009; Rosano et al., 2005).

Increased activation in the precuneus in MCI patients compared to controls was found with visual and verbal episodic memory tasks, visual and verbal working memory tasks, autobiographic tasks, semantic memory tasks and visuospatial tasks (angle discrimination) (Bai et al., 2009c; Bokde et al., 2010; Celone et al., 2006; Dohnel et al., 2008; Petrella et al., 2007; Poettrich et al., 2009; Vannini et al., 2007; Woodard et al., 2009; Yetkin et al., 2006). Most of these memory tasks concerned encoding processes. Decreased activation in the precuneus seems to be associated with retrieval processes (Bokde et al., 2010; Johnson et al., 2006). The relevance of the precuneus for memory has been suggested before and Goekoop et al. (2004) showed that treating MCI patients with galantamine, a cholinergic drug, increased activation in the precuneus (Goekoop et al., 2004). Apart from the precuneus, many studies ($n = 6$) also found increased activation in the inferior parietal lobule (Bartres-Faz et al., 2008; Bokde et al., 2006; Kircher et al., 2007; Leyhe et al., 2009; Woodard et al., 2009; Yetkin et al., 2006), the posterior cingulate gyrus ($n = 5$) (Bokde et al., 2010; Celone et al., 2006; Johnson et al., 2006; Petrella et al., 2007; Woodard et al., 2009) the superior parietal lobule ($n = 4$) (Bartres-Faz et al., 2008; Bokde et al., 2006; Leyhe et al., 2009; Vannini et al., 2007) and the supramarginal gyrus ($n = 3$) (Kircher et al., 2007; Woodard et al., 2009; Yetkin et al., 2006) in memory and non-memory tasks. Finally, encoding has also been associated with increased activation in the intraparietal sulcus (Hamalainen et al., 2007a).

Taken together, the studies showed that increased activity in the precuneus clearly stands out as a universal finding, and is found independent of method or task design. Memory processes show a differential activation effect, i.e., encoding was associated with increased precuneal activation, while retrieval was associated with decreased activation in the precuneus.

5.3. Metabolic neuroimaging

Table 4 (see Supplemental Data) summarizes studies showing parietal involvement in MCI using either SPECT or PET imaging methods. Most SPECT studies ($n = 11$) have shown hypoperfusion in MCI patients compared to controls in the inferior parietal lobule and the posterior cingulate cortex (Alegret et al., 2010; Borroni et al., 2006; Caffarra et al., 2008; Hirao et al., 2005; Huang et al., 2003, 2002; Ishiwata et al., 2006; Johnson et al., 2007; Nobili et al., 2009, 2008; Pappata et al., 2010). So far, both cross-sectional and longitudinal study designs have demonstrated hypoperfusion in all parietal areas in MCI patients. This means that group differences

were not only reported in the posterior cingulate cortex or the inferior parietal lobule, but also in the precuneus, the angular gyrus and the superior parietal lobule (Borroni et al., 2006; Devanand et al., 2010; Encinas et al., 2003; Hirao et al., 2005; Huang et al., 2003; Ishiwata et al., 2006; Nobili et al., 2009, 2008; Pappata et al., 2010).

In dementia studies, PET imaging usually involves the investigation of glucose metabolism, through 18F-2-fluoro-2-deoxy-glucose (FDG) or tracers to identify amyloid deposition, usually the Pittsburg Compound B (PiB). Progression of dementia is associated with a reduced metabolic rate of glucose or an increased uptake of PiB. A reduced metabolic rate of glucose metabolism rate indicates reduced neuronal function or reduced synaptic activity, whereas an increased PiB uptake reflects increased amyloid accumulation. PiB uptake correlates highly with CSF markers (Jagust et al., 2009). Overall, nearly every study using either or both of these methods showed involvement of the posterior cingulate cortex. Comparable to the SPECT findings, PET studies have found significant group differences in all parietal areas (Anchisi et al., 2005; Chen et al., 2010; Chetelat et al., 2003; Del Sole et al., 2008; Drzezga et al., 2003; Forsberg et al., 2008; Fouquet et al., 2009; Furukawa et al., 2010; Kemppainen et al., 2007; Li et al., 2008; Morbelli et al., 2010; Nestor et al., 2003a,b).

To summarize, these studies show hypoperfusion, hypometabolism and increased amyloid accumulation in MCI patients in all parietal areas, but most commonly in the posterior cingulate gyrus and the inferior parietal lobule.

5.4. Multimodal neuroimaging: MRI and PET

The number of studies that combine MRI and PET techniques in early AD recently has grown (see Table 5, supplemental data) ($n = 14$) (Ishii et al., 2005; Jack et al., 2008; Karow et al., 2010; Morbelli et al., 2010; Walhovd et al., 2010a,b; Zhang et al., 2011) Only few also included white matter measures (Villain et al., 2008, 2010b; Walhovd et al., 2009). These studies showed grey matter differences between the groups under investigation for all parietal areas, also in longitudinal neuroimaging measurements (Matsuda et al., 2002; Morbelli et al., 2010; Villain et al., 2010b). However, three studies did not found structural differences in the parietal lobe (Ishii et al., 2005; Morbelli et al., 2010; Zhang et al., 2011), which might indicate that the structural findings in the parietal lobe are less outspoken than in the temporal lobe (all these studies found structural differences in the temporal lobe, however as the temporal lobe is not part of our focus, we did not include these results in the table.). But the structural temporal changes correlate with metabolic parietal changes, possibly indicating a remote interaction (Tosun et al., 2011; Villain et al., 2008, 2010b). As for the metabolic differences between the groups, effects were most frequently reported in the posterior cingulate gyrus (including the retrosplenial cortex) and the precuneus (Chetelat et al., 2008; Ishii et al., 2005; Jack et al., 2008; Karow et al., 2010; Morbelli et al., 2010; Villain et al., 2008, 2010b; Walhovd et al., 2009, 2010a,b; Zhang et al., 2011).

6. Discussion

6.1. Involvement of the parietal lobe in various neuroimaging studies in early AD

This review examined studies of the involvement of the parietal lobe areas in early AD. For years the medial temporal lobe has been the main research region of interest, because of the good predictive value of structural measures derived from this region in MRI studies. In recent years, however, metabolic imaging results have slowly shifted the focus towards the posterior association areas, because of the assumed mismatch with the structural MRI findings discussed above.

Two main conclusions emerge from this review: (1) the parietal lobe is clearly involved in the early stage of AD and (2) the precuneus/posterior cingulate gyrus is the region most commonly affected.

With regards to the first conclusion, structural, functional, perfusion and metabolic imaging methods have demonstrated that areas within the parietal lobe show changes that indicate an ongoing degenerative process. The mismatch often reported in the literature implies that structural changes are most strong in medial temporal lobe areas, whereas metabolic changes appear to be the strongest and most prevalent in posterior parietal areas (Buckner et al., 2005; Caroli et al., 2010; Hunt et al., 2007; Ishii et al., 2005; Klunk et al., 2004; Matsuda, 2007; Villain et al., 2010b; Zhang et al., 2011). This effect of metabolic dominance in the parietal lobe was also present in most of the multimodal neuroimaging techniques (except for example (Karow et al., 2010)). This difference could possibly be explained by a difference in the timing of the onset and peak of the pathology. Amyloid deposition could lead to neuronal and synaptic loss (Chetelat et al., 2010). Remarkably, studies of patients with subjective cognitive impairment, had already found a direct relationship between atrophy and amyloid deposition in the precuneus and posterior cingulate areas, but not in the hippocampus. However, hippocampal atrophy correlated well with neocortical amyloid deposition, suggesting that a cortico-hippocampal disconnection is already present in the earliest stages. These results have been interpreted as two different pathological processes: one in which the metabolic changes, the deposition of amyloid, evolve in a constant slow rate and reach a plateau phase very early in the disease, and one where the structural changes accelerate in the more advanced stages (Chetelat et al., 2010). Such a two-phasic pathological model suggests that metabolic changes precede structural changes (De Santi et al., 2001; Jack et al., 2010). However, there are other alternatives to this hypothesis. Other studies have suggested that grey matter loss underlies metabolic changes (Jagust et al., 2002; Karow et al., 2010) or that amyloid deposition is only partially related to morphometric changes in AD (Fjell et al., 2010b). It might also be that these brain alterations occur parallel as two distinct effects, in which various brain regions have different susceptibilities to different pathological AD-related processes. Even if these pathological processes would interact or activate a cascade of events, several mechanisms can be considered. Distant white matter tract disruption as a result of wallerian degeneration causing hypometabolism and/or grey matter atrophy could be considered, but the opposite direction would also be possible. This suggests that AD is rather related to remote mechanisms than local changes (Jack et al., 2008; Tosun et al., 2011), but local changes of the various processes should not be excluded (Villain et al., 2008, 2010b). For example, the structural–metabolic discordance might result from the fact that atrophy in the medial temporal lobe regions elicits compensatory sprouting in neighboring unaffected neurons in order to maintain synaptic activity and connectivity. Such a plastic response would result in milder metabolic changes than morphological changes in the medial temporal lobe areas (Ishii et al., 2005; Matsuda et al., 2002).

Our second conclusion concerns the question whether there is a differential involvement of the parietal lobe areas. Although reviewing the different methods did not result in a clear-cut pattern, we can conclude that the somatosensory cortex is an area which is the least affected in the early stages of Alzheimer's disease and that the precuneus and posterior cingulate gyrus are the most commonly affected regions. The posterior cingulate/precuneus areas have unique metabolic, connectivity and vascular characteristics, which make them vulnerable for neurodegenerative processes (McKee et al., 2006). Preservation of the somatosensory cortex is

in agreement with the 'first-developed last-atrophied" principle, which states that parietal areas that are the last to myelinate during development are the first to be affected by pathological processes (Bartzokis, 2004; Braak and Braak, 1996; Echavarri et al., 2010; Flechsig, 1920). The myelin sheath in these late developing areas is thinner and has a different composition, making it more vulnerable to toxic and pathological events (Bartzokis, 2004, 2009).

We can also conclude that even though grey matter structural studies have shown involvement of all parietal areas, the inferior parietal lobule and precuneus are probably the first regions to show atrophy within the parietal lobe (Jacobs et al., 2011). This is based on the finding that participants with cognitive complaints show atrophy in these parietal areas (see Supplemental Data, Table 1) (Saykin et al., 2006; Smith et al., 2007).

White matter integrity loss was found in many tracts innervating the parietal lobe, i.e., the superior longitudinal fasciculus, the inferior longitudinal fasciculus, the fronto-occipital fasciculus, the splenium and the posterior cingulate fibres, but all parietal lobe areas also showed less white matter integrity. Our overview shows that there is a widespread pattern of white matter integrity loss, suggesting that loss of white matter integrity precedes grey matter atrophy (Bartzokis, 2004, 2009). The medial temporal lobe is closely connected with the posterior cingulate gyrus (Damoiseaux and Greicius, 2009; Insausti and Amaral, 2008), and the loss of this connection may well drive the loss of grey matter in the medial temporal lobe (Desikan et al., 2010; Salat et al., 2010). Comparable hypothetical relationships between pathological events with a preference for posterior regions have also been suggested by Buckner et al. (2005). For this review, we could not find many studies reporting specific changes in the retrosplenial cortex. This might be due to the fact that the retrosplenial cortex is often included into the posterior cingulate gyrus. However, because of its connectivity with the entorhinal cortex, this area deserves more attention in future studies (Nestor et al., 2003a).

This loss of connection between the medial temporal lobe areas and the posterior cingulate gyrus was confirmed by the reviewed resting state studies (Bai et al., 2009a, 2008; Gili et al., 2010; Koch et al., 2010; Pihlajamaki and Sperling, 2009; Qi et al., 2010; Sorg et al., 2007). Reduced deactivation in the inferior parietal lobule, precuneus and posterior cingulate cortex was found in MCI patients. But more importantly, these studies also reported loss of connectivity between the posteriomedial brain regions, i.e., the posterior cingulate gyrus and other brain regions, including the medial temporal lobe areas, frontal and parietal regions in MCI patients. This suggests that posterior connectivity alterations in the default mode network in early AD may be due to structural white matter changes.

The importance of the default mode network in understanding neuroimaging findings can also be observed in the results of the task-related functional imaging studies. In the reviewed fMRI studies, the precuneus, a posteriomedial brain region, is the area that emerges most often with respect to differences between cognitively healthy older people and MCI patients. Nonetheless, activation changes in the other parietal areas were also reported. Our overview shows a dissociation of activity in the precuneus. Increased activation was reported in patients with mild cognitive impairment during memory encoding, while deactivation was reported during memory retrieval processes. This is in contrast with the literature about healthy participants, where encoding was associated with deactivation and retrieval with increased activation (Vannini et al., 2010). The latter study found a significant negative correlation between the two processes, so that a greater deactivation during encoding was associated with higher activation during retrieval. The disconnection in the posteriomedial regions of the default mode network might result in less activation during encoding in the precuneus. This reduction in encoding activation might induce less activation during retrieval. The paradoxical increase reported in hippocampal activation in mild cognitive impairment (Dickerson and Sperling, 2009) has been interpreted as a compensatory mechanism in response to this disconnection. A strong correlation has been found between hippocampal activation and posteriomedial deactivation (Celone et al., 2006).

Although perfusion and metabolic imaging studies also showed involvement of all parietal areas, changes in the posterior cingulate cortex and the inferior parietal lobule were most prominent. Whether the metabolic changes in the parietal lobe areas precede metabolic changes in the temporal lobe is not clear from the literature, as most studies are cross-sectional or refer to changes in these areas as 'tempoparietal' changes. Some studies have suggested that parietal metabolic changes precede temporal metabolic changes (Fouquet et al., 2009; Matsuda et al., 2002; Villain et al., 2010a,b, 2008), but this deserves further attention in the future. Nonetheless, the fact that the parietal changes are so strong in metabolic and perfusion studies is consistent with the findings in the reviewed studies using other neuroimaging techniques. Klunk et al. (2004) found a strong inverse correlation between FDG-PET and PiB-PET results in parietal areas in mild AD patients, suggesting a close relationship between neuronal dysfunctions and amyloid deposition (Klunk et al., 2004). Several studies have hinted at the possibility that amyloid deposition reaches a plateau very early in the disease possibly before the MCI stage (Chetelat et al., 2010; Engler et al., 2006; Jack et al., 2010). No correlation was found between amyloid deposition, as measured by PiB-PET, and cognition (Engler et al., 2006; Jagust et al., 2009; Yokokura et al., 2010), suggesting that amyloid might not always be so detrimental to cognitive performance and possibly not an essential feature of Alzheimer's disease.

In contrast to amyloid deposition, glucose metabolism continues to decrease during the disease process and correlates with cognitive function (Engler et al., 2006; Yokokura et al., 2010). This suggests that amyloid accumulation precedes decline in glucose metabolism, and thus also neuronal and cognitive dysfunctions. Microglia activation in turn precedes amyloid accumulation and is especially increased in the early stage of amyloid production (Yokokura et al., 2010). Neuroinflammatory mechanisms, which modulate the disease together with genetic and environmental factors, are considered a driving force in AD. However, the therapeutic potentials remain unclear (Wyss-Coray, 2006).

6.2. Investigating the parietal lobe as a next step in early AD detection

What makes the parietal lobe vulnerable for pathology and thus, relevant for research into early AD biomarkers? The parietal lobe in humans is almost 20 times larger than in the macaque. Other brain regions do not show such a large difference (Culham and Kanwisher, 2001; Van Essen et al., 2001). This is due to the inferior parietal lobule being particularly more developed in humans than in monkeys, where no equivalent to the human supramarginal gyrus has been identified (Karnath et al., 2001). These posterior and medial parts of the parietal lobe are not only late in the phylogenetic development, but were also late in the ontogenetic development. Together with the other association cortices of the cerebral cortex, these areas are the last to become myelinated. As stated earlier, these areas are possibly also the most vulnerable to myelin breakdown, toxic and neuropathological mechanisms, such as amyloid deposition, because of their thinner myelin sheaths (Bartzokis, 2009; Stricker et al., 2009). This might explain why the somatosensory cortex is not implicated in the early stages of AD, in contrast to the posterior parietal cortex. Furthermore, the white matter integrity of the parietal lobe is highly heritable (Chiang et al., 2009), possibly explaining the high intra-individual variability between neuropathology load and degree of cognitive deficits.

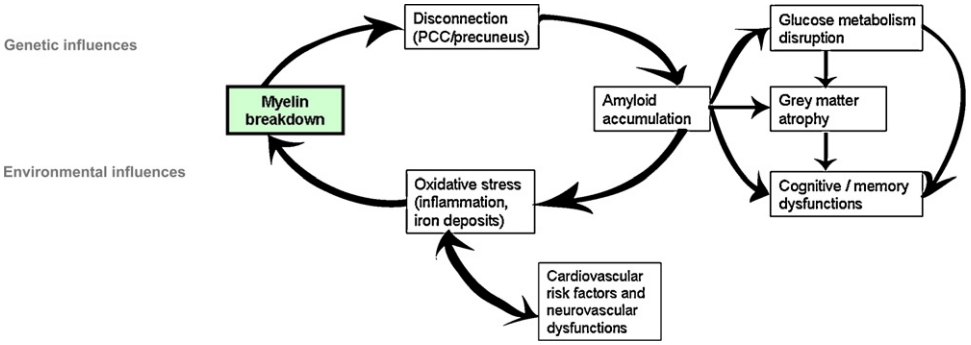

Fig. 2. Hypothetical model of the development of Alzheimer's dementia. This model is a simplification of the hypothesized chain of pathological events leading to Alzheimer's dementia, applied to the parietal lobe, based on ideas by Buckner et al. (2005), Jack et al. (2010) and Bartzokis (2009). When amyloid accumulation, due to myelin breakdown and disconnection reached its peak and crosses a certain threshold, a cascade of events occurs, including glucose metabolism disruption, grey matter atrophy and cognitive changes. At this point, clinical symptoms can be detected. This threshold is variable among individuals and can be influenced by cardiovascular risk factors. Abbreviations: PCC = posterior cingulate cortex.

The possible interrelationships between the different neuroimaging outcome measures, the genetic disposition of the parietal lobe and its vulnerability to oxidative stress, as discussed above, can be summarized in a model representing the putative neurobiological mechanisms of parietal vulnerability in the pathogenesis of AD (see Fig. 2). This model builds on the models proposed by Buckner et al. (2005), Jack et al. (2010) and Bartzokis (2009). The innovative aspect in this model is, firstly, that we combined neurobiological mechanisms with environmental factors and neuroimaging findings and secondly, that this model provides an explanation for the parietal contribution to the development of AD.

In short, this model considers, in agreement with Bartzokis (2009), that myelin breakdown is a critical factor in the development of AD. Ontogenetically late developing areas, the associative areas, are characterized by thinner and more susceptible myelin sheaths, and are therefore more vulnerable (Bartzokis, 2004; Braak and Braak, 1996). Due to the high vulnerability of myelin to toxins and oxidative damage, many genetic and environmental factors can negatively modulate the production and maintenance of the myelin sheath (Bartzokis, 2009). This causes the axons to function less efficiently and to break, and consequently leads to neural disconnection between the posterior cingulate gyrus/precuneus and the medial temporal lobe areas (Chetelat et al., 2010; Desikan et al., 2010; Salat et al., 2010; Villain et al., 2010b).

Myelin repair puts a high demand on metabolic resources. Conductive metabolic conditions are correlated with the default mode network and default mode network studies consistently showed a disconnection between the posterior cingulate gryus/precuneus—medial temporal lobe (Buckner et al., 2005). Rupture of axons increases the deposition of extracellular amyloid, which can bind to toxic-promoting synapse receptors and result in neuritic plaques (Bartzokis, 2009). PiB-PET imaging can detect these plaques, which are often localized in posterior and medial parietal regions.

Amyloid plaques have a negative influence on the functioning of neurons, as was shown by the high correlations between amyloid load, measured with PiB-PET, and neuronal dysfunctions measured with FDG-PET (Klunk et al., 2004). As discussed above, the literature suggests that amyloid accumulations seem to precede neuronal dysfunction (Engler et al., 2006; Jack et al., 2010; Yokokura et al., 2010) (although other suggestions have been discussed above, see (Fjell et al., 2010b; Jagust et al., 2002; Karow et al., 2010)). It has been suggested in prior work that posterior cingulate hypometabolism might be caused by a disruption of the cingulum bundle (Villain et al., 2010b).

Finally, this chain of events and the accumulation of amyloid plaques oversteps a threshold, which is variable among individuals, and leads to a cascade of grey matter atrophy in posterior and medial parietal regions and to cognitive dysfunctions (Buckner et al., 2005; Jack et al., 2010). Therefore, in this model, amyloid accumulation is not considered as essential, but rather as being an epiphenomenon of the AD disease process. As mentioned in the introduction, the parietal lobe is involved in many cognitive functions, including memory, the most prominent dysfunction in AD.

Although not discussed in this review, but worth mentioning, cardiovascular risk factors induce oxidative stress, which causes neurovascular dysfunctions. These vascular changes interact with demylination and the myelin repair mechanisms and can expedite the disease (Bennett et al., 2009; Iadecola, 2010).

This model has some similarities with a recent age-based hypothesis in which amyloid is also not central for the diagnosis of AD (Herrup, 2010). In this hypothesis, three key events are necessary for the development of AD. First, a precipating injury, such as a head trauma or a vascular event must occur, which elicits the second event, a chronic inflammatory process. This results in a major shift in the cellular physiology of brain cells and ultimately leads to cell degenerations, synaptic dysfunction, neuronal death and AD. The author of this hypothesis posits that a vascular event is most likely to be the injury in the first event (Herrup, 2010). In our model, we propose that age-related myelin breakdown and decreased repair mechanisms are the key event (Bartzokis, 2009; Villain et al., 2010b), leading to several neuropathological processes, including neuroinflammation. Vascular events can expedite the disease. Given the fact that progression to dementia is a gradual, long process, it is reasonable to expect a minimal damaging asymptomatic pathogenic process at the start. After an extended period, a threshold is reached and accumulated damage is expressed as dementia. Both models consider amyloid as a by-product or epiphenomenon in the chain of events. That amyloid accumulation is not necessarily causative, but could play a secondary role, is also supported by the fact that Abeta load explains only a fraction of morphometric brain differences between control participants, MCI and AD patients (Fjell et al., 2010b). However, in another study by the same authors, CSF biomaker pathology was related to brain atrophy in areas typically related to very mild AD and not to normal aging (Fjell et al., 2010a). The pathogenesis of AD still remains unclear and needs further investigation, but these findings and the model presented in Fig. 2 provide a framework and new ideas for future research. Most likely, AD has a multi-factorial pathogenesis.

6.3. Future research directions

So far, most studies have tried to investigate differences between cognitively healthy participants and patients in order

to assess which brain areas are affected in cognitive dysfunction. However, little attention has been given to the underlying mechanisms of regional vulnerability in early AD, more specifically in the parietal areas. The following suggestions, based on our model, aim to improve our understanding of the reasons for parietal involvement in MCI and AD.

The key elements in the model are the vulnerability of myelin and the breakdown of myelin in parietal regions. The maintenance of myelin can be affected by various factors, viz. environmental and genetic factors, age-related processes, neuroinflammatory reactions, iron deposits (associated with an increased demand for myelin repair), of which the latter two induce free radical damage. Pharmacological studies using non-steroidal anti-inflammatory drugs (NSAIDS) in the prevention or treatment of AD have yielded conflicting results ranging from no effects to arresting cognitive decline (Hayden et al., 2007; Szekely et al., 2008; Wyss-Coray, 2006). Post-mortem AD brains show less microglial activation when treated with NSAIDS (Mackenzie, 2001). Future studies should investigate interactions between neuroinflammation, genetic changes and brain changes. Considering the fact that the fiber organization in the parietal lobe is highly heritable, these relationships may show a different pattern in the parietal lobe, than in other parts of the brain. The development of new contrast agents for MRI has made it possible to investigate neuroinflammation non-invasively at a cerebral level (Miller et al., 1998; Nighoghossian et al., 2007).

Another aspect besides neuroinflammation that merits more attention is the investigation of iron deposits (Zecca et al., 2004). Late-developing areas, such as the parietal lobe, are more prone to oxidative stress, toxic and pathological events because the myelin repair capacity in these regions is reduced. This repair process relies on the oligodendrocytes, which contain the largest amounts of iron of all brain cell types and which need the highest amounts of energy (Bartzokis, 2009). Some studies have investigated iron deposits in the brain using MRI, but there is need for more studies examining regional differences and interactions with other brain and non-brain factors.

Our model does not include the accumulation of tau and neurofibrillary tangles, because in early AD, these proteins are usually confined to the medial temporal lobe areas. Nonetheless, the interaction between amyloid and tau should be further investigated. Tau also contributes to the myelin repair process and this process could be disturbed by hyperphosphorylated tau (Bartzokis, 2009). The investigation of relationships between tau accumulation and regional loss of white matter integrity by combining PET (Small et al., 2006) with MRI is an intriguing research topic.

Finally, the regional interaction between genes and neuroimaging findings in MCI and AD deserves more attention. We already mentioned the high genetic influence on parietal fiber organization in younger people. It would be interesting to investigate whether neurodegenerative processes in the parietal lobe are also under genetic influence. AD has been associated with many genes, ranging from 20 to 200, but evidence is limited for any of the suggested genes on its own (Zetzsche et al., 2010). A multifactorial genetic process seems more likely. So far, the apolipoprotein E4 (apoE4) genotype is the most investigated risk factor for AD and this is related to myelin production, function and repair mechanisms. ApoE4 carriers have lower myelin repair capacities and have shown higher inflammation risks (Bartzokis et al., 2007; Jack et al., 2010).

6.4. Conclusion

This review discussed structural, functional and metabolic studies showing the involvement of the parietal lobe in early AD. In the preponderance of literature on medial temporal lobe areas, this review offers a complementary perspective by showing the involvement of the parietal lobe in many cognitive functions and by showing the high occurrence of parietal lobe changes in neuroimaging studies. These studies converge on the fact that the posterior cingulate/precuneus area is probably the most relevant of all parietal areas in early AD. Of course, it is untenable to suggest that AD exclusively results from parietal lobe changes. In fact, we argue that the cognitive impairments found in AD should not be considered as the result of changes in one particular brain region. The neurobiological model that we have presented shows that disruptions of the medial temporal lobe—posterior cingulate/precuneus networks are crucial for understanding early AD.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neubiorev.2011.06.009.

References

Alegret, M., Vinyes-Junque, G., Boada, M., Martinez-Lage, P., Cuberas, G., Espinosa, A., Roca, I., Hernandez, I., Valero, S., Rosende-Roca, M., Mauleon, A., Becker And, J.T., Tarraga, L., 2010. Brain perfusion correlates of visuoperceptual deficits in mild cognitive impairment and mild Alzheimer's disease. J. Alzheimers Dis. 21, 557–567.

Anchisi, D., Borroni, B., Franceschi, M., Kerrouche, N., Kalbe, E., Beuthien-Beumann, B., Cappa, S., Lenz, O., Ludecke, S., Marcone, A., Mielke, R., Ortelli, P., Padovani, A., Pelati, O., Pupi, A., Scarpini, E., Weisenbach, S., Herholz, K., Salmon, E., Holthoff, V., Sorbi, S., Fazio, F., Perani, D., 2005. Heterogeneity of brain glucose metabolism in mild cognitive impairment and clinical progression to Alzheimer disease. Arch. Neurol. 62, 1728–1733.

Andrews-Hanna, J.R., Reidler, J.S., Sepulcre, J., Poulin, R., Buckner, R.L., 2010. Functional-anatomic fractionation of the brain's default network. Neuron 65, 550–562.

Apostolova, L.G., Steiner, C.A., Akopyan, G.G., Dutton, R.A., Hayashi, K.M., Toga, A.W., Cummings, J.L., Thompson, P.M., 2007. Three-dimensional gray matter atrophy mapping in mild cognitive impairment and mild Alzheimer disease. Arch. Neurol. 64, 1489–1495.

Bai, F., Watson, D.R., Yu, H., Shi, Y., Yuan, Y., Zhang, Z., 2009a. Abnormal resting-state functional connectivity of posterior cingulate cortex in amnestic type mild cognitive impairment. Brain Res. 1302, 167–174.

Bai, F., Zhang, Z., Watson, D.R., Yu, H., Shi, Y., Yuan, Y., Qian, Y., Jia, J., 2009b. Abnormal integrity of association fiber tracts in amnestic mild cognitive impairment. J. Neurol. Sci. 278, 102–106.

Bai, F., Zhang, Z., Watson, D.R., Yu, H., Shi, Y., Yuan, Y., Zang, Y., Zhu, C., Qian, Y., 2009c. Abnormal functional connectivity of hippocampus during episodic memory retrieval processing network in amnestic mild cognitive impairment. Biol. Psychiatry 65, 951–958.

Bai, F., Zhang, Z., Yu, H., Shi, Y., Yuan, Y., Zhu, W., Zhang, X., Qian, Y., 2008. Default-mode network activity distinguishes amnestic type mild cognitive impairment from healthy aging: a combined structural and resting-state functional MRI study. Neurosci. Lett. 438, 111–115.

Bakkour, A., Morris, J.C., Dickerson, B.C., 2009. The cortical signature of prodromal AD: regional thinning predicts mild AD dementia. Neurology 72, 1048–1055.

Balthazar, M.L., Yasuda, C.L., Pereira, F.R., Pedro, T., Damasceno, B.P., Cendes, F., 2009. Differences in grey and white matter atrophy in amnestic mild cognitive impairment and mild Alzheimer's disease. Eur. J. Neurol. 16, 468–474.

Barkhof, F., Polvikoski, T.M., van Straaten, E.C., Kalaria, R.N., Sulkava, R., Aronen, H.J., Niinisto, L., Rastas, S., Oinas, M., Scheltens, P., Erkinjuntti, T., 2007. The significance of medial temporal lobe atrophy: a postmortem MRI study in the very old. Neurology 69, 1521–1527.

Bartres-Faz, D., Serra-Grabulosa, J.M., Sun, F.T., Sole-Padulles, C., Rami, L., Molinuevo, J.L., Bosch, B., Mercader, J.M., Bargallo, N., Falcon, C., Vendrell, P., Junque, C., D'Esposito, M., 2008. Functional connectivity of the hippocampus in elderly with mild memory dysfunction carrying the APOE epsilon4 allele. Neurobiol. Aging 29, 1644–1653.

Bartzokis, G., 2004. Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. Neurobiol. Aging 25, 5–18, author reply 49–62.

Bartzokis, G., 2009. Alzheimer's disease as homeostatic responses to age-related myelin breakdown. Neurobiol. Aging.

Bartzokis, G., Lu, P.H., Geschwind, D.H., Tingus, K., Huang, D., Mendez, M.F., Edwards, N., Mintz, J., 2007. Apolipoprotein E affects both myelin breakdown and cognition: implications for age-related trajectories of decline into dementia. Biol. Psychiatry 62, 1380–1387.

Bennett, S., Grant, M.M., Aldred, S., 2009. Oxidative stress in vascular dementia and Alzheimer's disease: a common pathology. J. Alzheimers Dis. 17, 245–257.
Bokde, A.L., Karmann, M., Born, C., Teipel, S.J., Omerovic, M., Ewers, M., Frodl, T., Meisenzahl, E., Reiser, M., Moller, H.J., Hampel, H., 2010. Altered brain activation during a verbal working memory task in subjects with amnestic mild cognitive impairment. J. Alzheimers Dis. 21, 103–118.
Bokde, A.L., Lopez-Bayo, P., Meindl, T., Pechler, S., Born, C., Faltraco, F., Teipel, S.J., Moller, H.J., Hampel, H., 2006. Functional connectivity of the fusiform gyrus during a face-matching task in subjects with mild cognitive impairment. Brain 129, 1113–1124.
Borroni, B., Anchisi, D., Paghera, B., Vicini, B., Kerrouche, N., Garibotto, V., Terzi, A., Vignolo, L.A., Di Luca, M., Giubbini, R., Padovani, A., Perani, D., 2006. Combined 99mTc-ECD SPECT and neuropsychological studies in MCI for the assessment of conversion to AD. Neurobiol. Aging 27, 24–31.
Bosch, B., Arenaza-Urquijo, E.M., Rami, L., Sala-Llonch, R., Junque, C., Sole-Padulles, C., Pena-Gomez, C., Bargallo, N., Molinuevo, J.L., Bartres-Faz, D., 2010. Multiple DTI index analysis in normal aging, amnestic MCI and AD. Relationship with neuropsychological performance. Neurobiol. Aging, doi:10.1016/j.neurobiolaging.2010.02.004.
Bozzali, M., Filippi, M., Magnani, G., Cercignani, M., Franceschi, M., Schiatti, E., Castiglioni, S., Mossini, R., Falautano, M., Scotti, G., Comi, G., Falini, A., 2006. The contribution of voxel-based morphometry in staging patients with mild cognitive impairment. Neurology 67, 453–460.
Braak, H., Braak, E., 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. (Berl) 82, 239–259.
Braak, H., Braak, E., 1996. Development of Alzheimer-related neurofibrillary changes in the neocortex inversely recapitulates cortical myelogenesis. Acta Neuropathol. (Berl) 92, 197–201.
Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. Ann. N. Y. Acad. Sci. 1124, 1–38.
Buckner, R.L., Snyder, A.Z., Shannon, B.J., LaRossa, G., Sachs, R., Fotenos, A.F., Sheline, Y.I., Klunk, W.E., Mathis, C.A., Morris, J.C., Mintun, M.A., 2005. Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. J. Neurosci. 25, 7709–7717.
Burgmans, S., van Boxtel, M.P., Gronenschild, E.H., Vuurman, E.F., Hofman, P., Uylings, H.B., Jolles, J., Raz, N., 2009. Multiple indicators of age-related differences in cerebral white matter and the modifying effects of hypertension. Neuroimage 49, 2083–2093.
Cabeza, R., 2008. Role of parietal regions in episodic memory retrieval: the dual attentional processes hypothesis. Neuropsychologia 46, 1813–1827.
Cabeza, R., Ciaramelli, E., Olson, I.R., Moscovitch, M., 2008. The parietal cortex and episodic memory: an attentional account. Nat. Rev. Neurosci. 9, 613–625.
Caffarra, P., Ghetti, C., Concari, L., Venneri, A., 2008. Differential patterns of hypoperfusion in subtypes of mild cognitive impairment. Open Neuroimag. J. 2, 20–28.
Caroli, A., Lorenzi, M., Geroldi, C., Nobili, F., Paghera, B., Bonetti, M., Cotelli, M., Frisoni, G.B., 2010. Metabolic compensation and depression in Alzheimer's disease. Dement. Geriatr. Cogn. Disord. 29, 37–45.
Caroli, A., Testa, C., Geroldi, C., Nobili, F., Barnden, L.R., Guerra, U.P., Bonetti, M., Frisoni, G.B., 2007. Cerebral perfusion correlates of conversion to Alzheimer's disease in amnestic mild cognitive impairment. J. Neurol. 254, 1698–1707.
Caspers, S., Geyer, S., Schleicher, A., Mohlberg, H., Amunts, K., Zilles, K., 2006. The human inferior parietal cortex: cytoarchitectonic parcellation and interindividual variability. Neuroimage 33, 430–448.
Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129, 564–583.
Celone, K.A., Calhoun, V.D., Dickerson, B.C., Atri, A., Chua, E.F., Miller, S.L., DePeau, K., Rentz, D.M., Selkoe, D.J., Blacker, D., Albert, M.S., Sperling, R.A., 2006. Alterations in memory networks in mild cognitive impairment and Alzheimer's disease: an independent component analysis. J. Neurosci. 26, 10222–10231.
Chao, Y.P., Cho, K.H., Yeh, C.H., Chou, K.H., Chen, J.H., Lin, C.P., 2009. Probabilistic topography of human corpus callosum using cytoarchitectural parcellation and high angular resolution diffusion imaging tractography. Hum. Brain Mapp. 30, 3172–3187.
Chen, K., Langbaum, J.B., Fleisher, A.S., Ayutyanont, N., Reschke, C., Lee, W., Liu, X., Bandy, D., Alexander, G.E., Thompson, P.M., Foster, N.L., Harvey, D.J., de Leon, M.J., Koeppe, R.A., Jagust, W.J., Weiner, M.W., Reiman, E.M., 2010. Twelve-month metabolic declines in probable Alzheimer's disease and amnestic mild cognitive impairment assessed using an empirically pre-defined statistical region-of-interest: findings from the Alzheimer's Disease Neuroimaging Initiative. Neuroimage 51, 654–664.
Chetelat, G., Desgranges, B., De La Sayette, V., Viader, F., Eustache, F., Baron, J.C., 2002. Mapping gray matter loss with voxel-based morphometry in mild cognitive impairment. Neuroreport 13, 1939–1943.
Chetelat, G., Desgranges, B., de la Sayette, V., Viader, F., Eustache, F., Baron, J.C., 2003. Mild cognitive impairment: can FDG-PET predict who is to rapidly convert to Alzheimer's disease? Neurology 60, 1374–1377.
Chetelat, G., Desgranges, B., Landeau, B., Mezenge, F., Poline, J.B., de la Sayette, V., Viader, F., Eustache, F., Baron, J.C., 2008. Direct voxel-based comparison between grey matter hypometabolism and atrophy in Alzheimer's disease. Brain 131, 60–71.
Chetelat, G., Landeau, B., Eustache, F., Mezenge, F., Viader, F., de la Sayette, V., Desgranges, B., Baron, J.C., 2005. Using voxel-based morphometry to map the structural changes associated with rapid conversion in MCI: a longitudinal MRI study. Neuroimage 27, 934–946.
Chetelat, G., Villemagne, V.L., Bourgeat, P., Pike, K.E., Jones, G., Ames, D., Ellis, K.A., Szoeke, C., Martins, R.N., O'Keefe, G.J., Salvado, O., Masters, C.L., Rowe, C.C., 2010. Relationship between atrophy and beta-amyloid deposition in Alzheimer disease. Ann. Neurol. 67, 317–324.
Chiang, M.C., Barysheva, M., Shattuck, D.W., Lee, A.D., Madsen, S.K., Avedissian, C., Klunder, A.D., Toga, A.W., McMahon, K.L., de Zubicaray, G.I., Wright, M.J., Srivastava, A., Balov, N., Thompson, P.M., 2009. Genetics of brain fiber architecture and intellectual performance. J. Neurosci. 29, 2212–2224.
Cho, H., Yang, D.W., Shon, Y.M., Kim, B.S., Kim, Y.I., Choi, Y.B., Lee, K.S., Shim, Y.S., Yoon, B., Kim, W., Ahn, K.J., 2008. Abnormal integrity of corticocortical tracts in mild cognitive impairment: a diffusion tensor imaging study. J. Korean Med. Sci. 23, 477–483.
Chua, T.C., Wen, W., Slavin, M.J., Sachdev, P.S., 2008. Diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease: a review. Curr. Opin. Neurol. 21, 83–92.
Culham, J.C., Kanwisher, N.G., 2001. Neuroimaging of cognitive functions in human parietal cortex. Curr. Opin. Neurobiol. 11, 157–163.
Cummings, J.L., 2004. Alzheimer's disease. N. Engl. J. Med. 351, 56–67.
Damoiseaux, J.S., Greicius, M.D., 2009. Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. Brain Struct. Funct. 213, 525–533.
de Leon, M.J., Mosconi, L., Blennow, K., DeSanti, S., Zinkowski, R., Mehta, P.D., Pratico, D., Tsui, W., Saint Louis, L.A., Sobanska, L., Brys, M., Li, Y., Rich, K., Rinne, J., Rusinek, H., 2007. Imaging and CSF studies in the preclinical diagnosis of Alzheimer's disease. Ann. N. Y. Acad. Sci. 1097, 114–145.
De Santi, S., de Leon, M.J., Rusinek, H., Convit, A., Tarshish, C.Y., Roche, A., Tsui, W.H., Kandil, E., Boppana, M., Daisley, K., Wang, G.J., Schlyer, D., Fowler, J., 2001. Hippocampal formation glucose metabolism and volume losses in MCI and AD. Neurobiol. Aging 22, 529–539.
Del Sole, A., Clerici, F., Chiti, A., Lecchi, M., Mariani, C., Maggiore, L., Mosconi, L., Lucignani, G., 2008. Individual cerebral metabolic deficits in Alzheimer's disease and amnestic mild cognitive impairment: an FDG PET study. Eur. J. Nucl. Med. Mol. Imag. 35, 1357–1366.
Desikan, R.S., Cabral, H.J., Fischl, B., Guttmann, C.R., Blacker, D., Hyman, B.T., Albert, M.S., Killiany, R.J., 2009. Temporoparietal MR imaging measures of atrophy in subjects with mild cognitive impairment that predict subsequent diagnosis of Alzheimer disease. AJNR Am. J. Neuroradiol. 30, 532–538.
Desikan, R.S., Fischl, B., Cabral, H.J., Kemper, T.L., Guttmann, C.R., Blacker, D., Hyman, B.T., Albert, M.S., Killiany, R.J., 2008. MRI measures of temporoparietal regions show differential rates of atrophy during prodromal AD. Neurology 71, 819–825.
Desikan, R.S., Sabuncu, M.R., Schmansky, N.J., Reuter, M., Cabral, H.J., Hess, C.P., Weiner, M.W., Biffi, A., Anderson, C.D., Rosand, J., Salat, D.H., Kemper, T.L., Dale, A.M., Sperling, R.A., Fischl, B., 2010. Selective disruption of the cerebral neocortex in Alzheimer's disease. PloS One 5, e12853.
Devanand, D.P., Van Heertum, R.L., Kegeles, L.S., Liu, X., Jin, Z.H., Pradhaban, G., Rusinek, H., Pratap, M., Pelton, G.H., Prohovnik, I., Stern, Y., Mann, J.J., Parsey, R., 2010. 99mTc hexamethyl-propylene-aminoxime single-photon emission computed tomography prediction of conversion from mild cognitive impairment to Alzheimer disease. Am. J. Geriatr. Psychiatry 18, 959–972.
Dickerson, B.C., Sperling, R.A., 2008. Functional abnormalities of the medial temporal lobe memory system in mild cognitive impairment and Alzheimer's disease: insights from functional MRI studies. Neuropsychologia 46, 1624–1635.
Dickerson, B.C., Sperling, R.A., 2009. Large-scale functional brain network abnormalities in Alzheimer's disease: insights from functional neuroimaging. Behav. Neurol. 21, 63–75.
Dohnel, K., Sommer, M., Ibach, B., Rothmayr, C., Meinhardt, J., Hajak, G., 2008. Neural correlates of emotional working memory in patients with mild cognitive impairment. Neuropsychologia 46, 37–48.
Drzezga, A., Lautenschlager, N., Siebner, H., Riemenschneider, M., Willoch, F., Minoshima, S., Schwaiger, M., Kurz, A., 2003. Cerebral metabolic changes accompanying conversion of mild cognitive impairment into Alzheimer's disease: a PET follow-up study. Eur. J. Nucl. Med. Mol. Imag. 30, 1104–1113.
Echavarri, C., Aalten, P., Uylings, H.B., Jacobs, H.I., Visser, P.J., Gronenschild, E.H., Verhey, F.R., Burgmans, S., 2010. Atrophy in the parahippocampal gyrus as an early biomarker of Alzheimer's disease. Brain Struct. Funct., doi:10.1007/s00429-010-0283-8.
Eickhoff, S.B., Amunts, K., Mohlberg, H., Zilles, K., 2006a. The human parietal operculum. II. Stereotaxic maps and correlation with functional imaging results. Cereb. Cortex 16, 268–279.
Eickhoff, S.B., Schleicher, A., Zilles, K., Amunts, K., 2006b. The human parietal operculum. I. Cytoarchitectonic mapping of subdivisions. Cereb. Cortex 16, 254–267.
Encinas, M., De Juan, R., Marcos, A., Gil, P., Barabash, A., Fernandez, C., De Ugarte, C., Cabranes, J.A., 2003. Regional cerebral blood flow assessed with 99mTc-ECD SPET as a marker of progression of mild cognitive impairment to Alzheimer's disease. Eur. J. Nucl. Med. Mol. Imag. 30, 1473–1480.
Engler, H., Forsberg, A., Almkvist, O., Blomquist, G., Larsson, E., Savitcheva, I., Wall, A., Ringheim, A., Langstrom, B., Nordberg, A., 2006. Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. Brain 129, 2856–2866.
Fennema-Notestine, C., Hagler Jr., D.J., McEvoy, L.K., Fleisher, A.S., Wu, E.H., Karow, D.S., Dale, A.M., 2009. Structural MRI biomarkers for preclinical and mild Alzheimer's disease. Hum. Brain Mapp. 30, 3238–3253.
Fjell, A.M., Amlien, I.K., Westlye, L.T., Stenset, V., Fladby, T., Skinningsrud, A., Eilsertsen, D.E., Bjornerud, A., Walhovd, K.B., 2010a. CSF biomarker pathology correlates with a medial temporo-parietal network affected by very mild to moderate Alzheimer's disease but not a fronto-striatal network affected by healthy aging. Neuroimage 49, 1820–1830.

Fjell, A.M., Walhovd, K.B., Fennema-Notestine, C., McEvoy, L.K., Hagler, D.J., Holland, D., Brewer, J.B., Dale, A.M., 2010b. CSF biomarkers in prediction of cerebral and clinical change in mild cognitive impairment and Alzheimer's disease. J. Neurosci. 30, 2088–2101.
Flechsig, P., 1920. Anatomie des menschlichen Gehirns und Ruckenmarks. George Thieme, Leipzig.
Forsberg, A., Engler, H., Almkvist, O., Blomquist, G., Hagman, G., Wall, A., Ringheim, A., Langstrom, B., Nordberg, A., 2008. PET imaging of amyloid deposition in patients with mild cognitive impairment. Neurobiol. Aging 29, 1456–1465.
Fouquet, M., Desgranges, B., Landeau, B., Duchesnay, E., Mezenge, F., de la Sayette, V., Viader, F., Baron, J.C., Eustache, F., Chetelat, G., 2009. Longitudinal brain metabolic changes from amnestic mild cognitive impairment to Alzheimer's disease. Brain 132, 2058–2067.
Furukawa, K., Okamura, N., Tashiro, M., Waragai, M., Furumoto, S., Iwata, R., Yanai, K., Kudo, Y., Arai, H., 2010. Amyloid PET in mild cognitive impairment and Alzheimer's disease with BF-227: comparison to FDG-PET. J. Neurol. 257, 721–727.
Gili, T., Cercignani, M., Serra, L., Perri, R., Giove, F., Maraviglia, B., Caltagirone, C., Bozzali, M., 2010. Regional brain atrophy and functional disconnection across Alzheimer's disease evolution. J. Neurol. Neurosurg. Psychiatry.
Goekoop, R., Rombouts, S.A., Jonker, C., Hibbel, A., Knol, D.L., Truyen, L., Barkhof, F., Scheltens, P., 2004. Challenging the cholinergic system in mild cognitive impairment: a pharmacological fMRI study. Neuroimage 23, 1450–1459.
Gottlieb, J., 2007. From thought to action: the parietal cortex as a bridge between perception, action, and cognition. Neuron 53, 9–16.
Grefkes, C., Fink, G.R., 2005. The functional organization of the intraparietal sulcus in humans and monkeys. J. Anat. 207, 3–17.
Grefkes, C., Ritzl, A., Zilles, K., Fink, G.R., 2004. Human medial intraparietal cortex subserves visuomotor coordinate transformation. Neuroimage 23, 1494–1506.
Grefkes, C., Weiss, P.H., Zilles, K., Fink, G.R., 2002. Crossmodal processing of object features in human anterior intraparietal cortex: an fMRI study implies equivalencies between humans and monkeys. Neuron 35, 173–184.
Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V., 2003. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc. Natl. Acad. Sci. U.S.A. 100, 253–258.
Hamalainen, A., Pihlajamaki, M., Tanila, H., Hanninen, T., Niskanen, E., Tervo, S., Karjalainen, P.A., Vanninen, R.L., Soininen, H., 2007a. Increased fMRI responses during encoding in mild cognitive impairment. Neurobiol. Aging 28, 1889–1903.
Hamalainen, A., Tervo, S., Grau-Olivares, M., Niskanen, E., Pennanen, C., Huuskonen, J., Kivipelto, M., Hanninen, T., Tapiola, M., Vanhanen, M., Hallikainen, M., Helkala, E.L., Nissinen, A., Vanninen, R., Soininen, H., 2007b. Voxel-based morphometry to detect brain atrophy in progressive mild cognitive impairment. Neuroimage 37, 1122–1131.
Hayden, K.M., Zandi, P.P., Khachaturian, A.S., Szekely, C.A., Fotuhi, M., Norton, M.C., Tschanz, J.T., Pieper, C.F., Corcoran, C., Lyketsos, C.G., Breitner, J.C., Welsh-Bohmer, K.A., 2007. Does NSAID use modify cognitive trajectories in the elderly? The Cache County study. Neurology 69, 275–282.
Herrup, K., 2010. Reimagining Alzheimer's disease—an age-based hypothesis. J. Neurosci. 30, 16755–16762.
Hirao, K., Ohnishi, T., Hirata, Y., Yamashita, F., Mori, T., Moriguchi, Y., Matsuda, H., Nemoto, K., Imabayashi, E., Yamada, M., Iwamoto, T., Arima, K., Asada, T., 2005. The prediction of rapid conversion to Alzheimer's disease in mild cognitive impairment using regional cerebral blood flow SPECT. Neuroimage 28, 1014–1021.
Huang, C., Wahlund, L.O., Almkvist, O., Elehu, D., Svensson, L., Jonsson, T., Winblad, B., Julin, P., 2003. Voxel- and VOI-based analysis of SPECT CBF in relation to clinical and psychological heterogeneity of mild cognitive impairment. Neuroimage 19, 1137–1144.
Huang, C., Wahlund, L.O., Svensson, L., Winblad, B., Julin, P., 2002. Cingulate cortex hypoperfusion predicts Alzheimer's disease in mild cognitive impairment. BMC Neurol. 2, 9.
Huang, J., Auchus, A.P., 2007. Diffusion tensor imaging of normal appearing white matter and its correlation with cognitive functioning in mild cognitive impairment and Alzheimer's disease. Ann. N. Y. Acad. Sci. 1097, 259–264.
Huang, J., Friedland, R.P., Auchus, A.P., 2007. Diffusion tensor imaging of normal-appearing white matter in mild cognitive impairment and early Alzheimer disease: preliminary evidence of axonal degeneration in the temporal lobe. AJNR Am. J. Neuroradiol. 28, 1943–1948.
Hunt, A., Schonknecht, P., Henze, M., Seidl, U., Haberkorn, U., Schroder, J., 2007. Reduced cerebral glucose metabolism in patients at risk for Alzheimer's disease. Psychiatry Res. 155, 147–154.
Husain, M., Nachev, P., 2007. Space and the parietal cortex. Trends Cogn. Sci. 11, 30–36.
Iadecola, C., 2010. The overlap between neurodegenerative and vascular factors in the pathogenesis of dementia. Acta Neuropathol. 120, 287–296.
Imabayashi, E., Matsuda, H., Asada, T., Ohnishi, T., Sakamoto, S., Nakano, S., Inoue, T., 2004. Superiority of 3-dimensional stereotactic surface projection analysis over visual inspection in discrimination of patients with very early Alzheimer's disease from controls using brain perfusion SPECT. J. Nucl. Med. 45, 1450–1457.
Insausti, R., Amaral, D.G., 2008. Entorhinal cortex of the monkey: IV. Topographical and laminar organization of cortical afferents. J. Comp. Neurol. 509, 608–641.
Ishii, K., Sasaki, H., Kono, A.K., Miyamoto, N., Fukuda, T., Mori, E., 2005. Comparison of gray matter and metabolic reduction in mild Alzheimer's disease using FDG-PET and voxel-based morphometric MR studies. Eur. J. Nucl. Med. Mol. Imag. 32, 959–963.
Ishiwata, A., Sakayori, O., Minoshima, S., Mizumura, S., Kitamura, S., Katayama, Y., 2006. Preclinical evidence of Alzheimer changes in progressive mild cognitive impairment: a qualitative and quantitative SPECT study. Acta Neurol. Scand. 114, 91–96.
Jack Jr., C.R., Knopman, D.S., Jagust, W.J., Shaw, L.M., Aisen, P.S., Weiner, M.W., Petersen, R.C., Trojanowski, J.Q., 2010. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 9, 119–128.
Jack Jr., C.R., Lowe, V.J., Senjem, M.L., Weigand, S.D., Kemp, B.J., Shiung, M.M., Knopman, D.S., Boeve, B.F., Klunk, W.E., Mathis, C.A., Petersen, R.C., 2008. 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment. Brain 131, 665–680.
Jacobs, H.I.L., Van Boxtel, M.P., Uylings, H.B., Gronenschild, E.H., Verhey, F.R., Jolles, J., 2011. Atrophy of the parietal lobe in preclinical dementia. Brain Cogn. 75, 154–163.
Jacobs, H.I.L., Visser, P.J., Van Boxtel, M.P., Frisoni, G.B., Tsolaki, M., Papapostolou, P., Nobili, F., Wahlund, L.O., Minthon, L., Frolich, L., Hampel, H., Soininen, H., van de Pol, L., Scheltens, P., Tan, F.E., Jolles, J., Verhey, F.R., 2010. The association between white matter hyperintensities and executive decline in mild cognitive impairment is network dependent. Neurobiol. Aging.
Jacova, C., Peters, K.R., Beattie, B.L., Wong, E., Riddehough, A., Foti, D., Scheltens, P., Li, D.K., Feldman, H.H., 2008. Cognitive impairment no dementia—neuropsychological and neuroimaging characterization of an amnestic subgroup. Dement. Geriatr. Cogn. Disord. 25, 238–247.
Jagust, W.J., Eberling, J.L., Wu, C.C., Finkbeiner, A., Mungas, D., Valk, P.E., Haan, M.N., 2002. Brain function and cognition in a community sample of elderly Latinos. Neurology 59, 378–383.
Jagust, W.J., Landau, S.M., Shaw, L.M., Trojanowski, J.Q., Koeppe, R.A., Reiman, E.M., Foster, N.L., Petersen, R.C., Weiner, M.W., Price, J.C., Mathis, C.A., 2009. Relationships between biomarkers in aging and dementia. Neurology 73, 1193–1199.
Johnson, K.A., Moran, E.K., Becker, J.A., Blacker, D., Fischman, A.J., Albert, M.S., 2007. Single photon emission computed tomography perfusion differences in mild cognitive impairment. J. Neurol. Neurosurg. Psychiatry 78, 240–247.
Johnson, S.C., Schmitz, T.W., Moritz, C.H., Meyerand, M.E., Rowley, H.A., Alexander, A.L., Hansen, K.W., Gleason, C.E., Carlsson, C.M., Ries, M.L., Asthana, S., Chen, K., Reiman, E.M., Alexander, G.E., 2006. Activation of brain regions vulnerable to Alzheimer's disease: the effect of mild cognitive impairment. Neurobiol. Aging 27, 1604–1612.
Jones, B.F., Barnes, J., Uylings, H.B., Fox, N.C., Frost, C., Witter, M.P., Scheltens, P., 2006. Differential regional atrophy of the cingulate gyrus in Alzheimer disease: a volumetric MRI study. Cereb. Cortex 16, 1701–1708.
Jovicich, J., Czanner, S., Han, X., Salat, D., van der Kouwe, A., Quinn, B., Pacheco, J., Albert, M., Killiany, R., Blacker, D., Maguire, P., Rosas, D., Makris, N., Gollub, R., Dale, A., Dickerson, B.C., Fischl, B., 2009. MRI-derived measurements of human subcortical, ventricular and intracranial brain volumes: reliability effects of scan sessions, acquisition sequences, data analyses, scanner upgrade, scanner vendors and field strengths. Neuroimage 46, 177–192.
Julkunen, V., Niskanen, E., Muehlboeck, S., Pihlajamaki, M., Kononen, M., Hallikainen, M., Kivipelto, M., Tervo, S., Vanninen, R., Evans, A., Soininen, H., 2009. Cortical thickness analysis to detect progressive mild cognitive impairment: a reference to Alzheimer's disease. Dement. Geriatr. Cogn. Disord. 28, 404–412.
Kantarci, K., Jack Jr., C.R., Xu, Y.C., Campeau, N.G., O'Brien, P.C., Smith, G.E., Ivnik, R.J., Boeve, B.F., Kokmen, E., Tangalos, E.G., Petersen, R.C., 2001. Mild cognitive impairment and Alzheimer disease: regional diffusivity of water. Radiology 219, 101–107.
Karas, G.B., Sluimer, J., Goekoop, R., van der Flier, W., Rombouts, S.A., Vrenken, H., Scheltens, P., Fox, N., Barkhof, F., 2008. Amnestic mild cognitive impairment: structural MR imaging findings predictive of conversion to Alzheimer disease. AJNR Am. J. Neuroradiol. 29, 944–949.
Karnath, H.O., Ferber, S., Himmelbach, M., 2001. Spatial awareness is a function of the temporal not the posterior parietal lobe. Nature 411, 950–953.
Karow, D.S., McEvoy, L.K., Fennema-Notestine, C., Hagler Jr., D.J., Jennings, R.G., Brewer, J.B., Hoh, C.K., Dale, A.M., 2010. Relative capability of MR imaging and FDG PET to depict changes associated with prodromal and early Alzheimer disease. Radiology 256, 932–942.
Kaye, J.A., Swihart, T., Howieson, D., Dame, A., Moore, M.M., Karnos, T., Camicioli, R., Ball, M., Oken, B., Sexton, G., 1997. Volume loss of the hippocampus and temporal lobe in healthy elderly persons destined to develop dementia. Neurology 48, 1297–1304.
Kemppainen, N.M., Aalto, S., Wilson, I.A., Nagren, K., Helin, S., Bruck, A., Oikonen, V., Kailajarvi, M., Scheinin, M., Viitanen, M., Parkkola, R., Rinne, J.O., 2007. PET amyloid ligand [11C]PIB uptake is increased in mild cognitive impairment. Neurology 68, 1603–1606.
Kircher, T.T., Weis, S., Freymann, K., Erb, M., Jessen, F., Grodd, W., Heun, R., Leube, D.T., 2007. Hippocampal activation in patients with mild cognitive impairment is necessary for successful memory encoding. J. Neurol. Neurosurg. Psychiatry 78, 812–818.
Klunk, W.E., Engler, H., Nordberg, A., Wang, Y., Blomqvist, G., Holt, D.P., Bergstrom, M., Savitcheva, I., Huang, G.F., Estrada, S., Ausen, B., Debnath, M.L., Barletta, J., Price, J.C., Sandell, J., Lopresti, B.J., Wall, A., Koivisto, P., Antoni, G., Mathis, C.A., Langstrom, B., 2004. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann. Neurol. 55, 306–319.
Koch, W., Teipel, S., Mueller, S., Benninghoff, J., Wagner, M., Bokde, A.L., Hampel, H., Coates, U., Reiser, M., Meindl, T., 2010. Diagnostic power of default mode network resting state fMRI in the detection of Alzheimer's disease. Neurobiol. Aging.

Korczyn, A.D., 2008. The amyloid cascade hypothesis. Alzheimers Dement. 4, 176–178.
Leyhe, T., Erb, M., Milian, M., Eschweiler, G.W., Ethofer, T., Grodd, W., Saur, R., 2009. Changes in cortical activation during retrieval of clock time representations in patients with mild cognitive impairment and early Alzheimer's disease. Dement. Geriatr. Cogn. Disord. 27, 117–132.
Li, Y., Rinne, J.O., Mosconi, L., Pirraglia, E., Rusinek, H., DeSanti, S., Kemppainen, N., Nagren, K., Kim, B.C., Tsui, W., de Leon, M.J., 2008. Regional analysis of FDG and PIB-PET images in normal aging, mild cognitive impairment, and Alzheimer's disease. Eur. J. Nucl. Med. Mol. Imag. 35, 2169–2181.
Liao, J., Zhu, Y., Zhang, M., Yuan, H., Su, M.Y., Yu, X., Wang, H., 2010. Microstructural white matter abnormalities independent of white matter lesion burden in amnestic mild cognitive impairment and early alzheimer disease among Han Chinese elderly. Alzheimer Dis. Assoc. Disord..
Lindeboom, J., Weinstein, H., 2004. Neuropsychology of cognitive ageing, minimal cognitive impairment, Alzheimer's disease, and vascular cognitive impairment. Eur. J. Pharmacol. 490, 83–86.
Machulda, M.M., Senjem, M.L., Weigand, S.D., Smith, G.E., Ivnik, R.J., Boeve, B.F., Knopman, D.S., Petersen, R.C., Jack, C.R., 2009. Functional magnetic resonance imaging changes in amnestic and nonamnestic mild cognitive impairment during encoding and recognition tasks. J. Int. Neuropsychol. Soc. 15, 372–382.
Mackenzie, I.R., 2001. Postmortem studies of the effect of anti-inflammatory drugs on Alzheimer-type pathology and associated inflammation. Neurobiol. Aging 22, 819–822.
Makris, N., Kennedy, D.N., McInerney, S., Sorensen, A.G., Wang, R., Caviness Jr., V.S., Pandya, D.N., 2005. Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. Cereb. Cortex 15, 854–869.
Makris, N., Pandya, D.N., 2009. The extreme capsule in humans and rethinking of the language circuitry. Brain Struct. Funct. 213, 343–358.
Makris, N., Papadimitriou, G.M., Kaiser, J.R., Sorg, S., Kennedy, D.N., Pandya, D.N., 2009. Delineation of the middle longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. Cereb. Cortex 19, 777–785.
Matsuda, H., 2007. Role of neuroimaging in Alzheimer's disease, with emphasis on brain perfusion SPECT. J. Nucl. Med. 48, 1289–1300.
Matsuda, H., Kitayama, N., Ohnishi, T., Asada, T., Nakano, S., Sakamoto, S., Imabayashi, E., Katoh, A., 2002. Longitudinal evaluation of both morphologic and functional changes in the same individuals with Alzheimer's disease. J. Nucl. Med. 43, 304–311.
McDonald, C.R., McEvoy, L.K., Gharapetian, L., Fennema-Notestine, C., Hagler Jr., D.J., Holland, D., Koyama, A., Brewer, J.B., Dale, A.M., 2009. Regional rates of neocortical atrophy from normal aging to early Alzheimer disease. Neurology 73, 457–465.
McKee, A.C., Au, R., Cabral, H.J., Kowall, N.W., Seshadri, S., Kubilus, C.A., Drake, J., Wolf, P.A., 2006. Visual association pathology in preclinical Alzheimer disease. J. Neuropathol. Exp. Neurol. 65, 621–630.
Medina, D., DeToledo-Morrell, L., Urresta, F., Gabrieli, J.D., Moseley, M., Fleischman, D., Bennett, D.A., Leurgans, S., Turner, D.A., Stebbins, G.T., 2006. White matter changes in mild cognitive impairment and AD: a diffusion tensor imaging study. Neurobiol. Aging 27, 663–672.
Miller, D.H., Grossman, R.I., Reingold, S.C., McFarland, H.F., 1998. The role of magnetic resonance techniques in understanding and managing multiple sclerosis. Brain 121 (Pt 1), 3–24.
Morbelli, S., Piccardo, A., Villavecchia, G., Dessi, B., Brugnolo, A., Piccini, A., Caroli, A., Frisoni, G., Rodriguez, G., Nobili, F., 2010. Mapping brain morphological and functional conversion patterns in amnestic MCI: a voxel-based MRI and FDG-PET study. Eur. J. Nucl. Med. Mol. Imag. 37, 36–45.
Mori, S., Wakana, S., Nagae-Poetscher, L.M., van Zijl, P.M., 2005. Atlas of Human White Matter. Elsevier, Amsterdam.
Naggara, O., Oppenheim, C., Rieu, D., Raoux, N., Rodrigo, S., Dalla Barba, G., Meder, J.F., 2006. Diffusion tensor imaging in early Alzheimer's disease. Psychiatry Res. 146, 243–249.
Nestor, P.J., Fryer, T.D., Ikeda, M., Hodges, J.R., 2003a. Retrosplenial cortex (BA 29/30) hypometabolism in mild cognitive impairment (prodromal Alzheimer's disease). Eur. J. Neurosci. 18, 2663–2667.
Nestor, P.J., Fryer, T.D., Smielewski, P., Hodges, J.R., 2003b. Limbic hypometabolism in Alzheimer's disease and mild cognitive impairment. Ann. Neurol. 54, 343–351.
Nieuwenhuys, R., Voogd, J., van Huijzen, C., 2008. The Human Nervous System, 4th ed. Springer Verlag, Berlin, Heidelberg, New York.
Nighoghossian, N., Wiart, M., Cakmak, S., Berthezene, Y., Derex, L., Cho, T.H., Nemoz, C., Chapuis, F., Tisserand, G.L., Pialat, J.B., Trouillas, P., Froment, J.C., Hermier, M., 2007. Inflammatory response after ischemic stroke: a USPIO-enhanced MRI study in patients. Stroke 38, 303–307.
Nobili, F., De Carli, F., Frisoni, G.B., Portet, F., Verhey, F., Rodriguez, G., Caroli, A., Touchon, J., Morbelli, S., Guerra, U.P., Dessi, B., Brugnolo, A., Visser, P.J., 2009. SPECT predictors of cognitive decline and Alzheimer's disease in mild cognitive impairment. J. Alzheimers Dis. 17, 761–772.
Nobili, F., Frisoni, G.B., Portet, F., Verhey, F., Rodriguez, G., Caroli, A., Touchon, J., Calvini, P., Morbelli, S., De Carli, F., Guerra, U.P., Van de Pol, L.A., Visser, P.J., 2008. Brain SPECT in subtypes of mild cognitive impairment. Findings from the DESCRIPA multicenter study. J. Neurol. 255, 1344–1353.
Pappata, S., Varrone, A., Vicidomini, C., Milan, G., De Falco, C., Sansone, V., Iavarone, A., Comerci, M., Lore, E., Panico, M.R., Quarantelli, M., Postiglione, A., Salvatore, M., 2010. SPECT imaging of GABA(A)/benzodiazepine receptors and cerebral perfusion in mild cognitive impairment. Eur. J. Nucl. Med. Mol. Imag. 37, 1156–1163.
Parente, D.B., Gasparetto, E.L., da Cruz Jr., L.C., Domingues, R.C., Baptista, A.C., Carvalho, A.C., Domingues, R.C., 2008. Potential role of diffusion tensor MRI in the differential diagnosis of mild cognitive impairment and Alzheimer's disease. AJR Am. J. Roentgenol. 190, 1369–1374.
Pellijeff, A., Bonilha, L., Morgan, P.S., McKenzie, K., Jackson, S.R., 2006. Parietal updating of limb posture: an event-related fMRI study. Neuropsychologia 44, 2685–2690.
Pennanen, C., Testa, C., Laakso, M.P., Hallikainen, M., Helkala, E.L., Hanninen, T., Kivipelto, M., Kononen, M., Nissinen, A., Tervo, S., Vanhanen, M., Vanninen, R., Frisoni, G.B., Soininen, H., 2005. A voxel based morphometry study on mild cognitive impairment. J. Neurol. Neurosurg. Psychiatry 76, 11–14.
Petrella, J.R., Wang, L., Krishnan, S., Slavin, M.J., Prince, S.E., Tran, T.T., Doraiswamy, P.M., 2007. Cortical deactivation in mild cognitive impairment: high-field-strength functional MR imaging. Radiology 245, 224–235.
Pihlajamaki, M., Sperling, R.A., 2009. Functional MRI assessment of task-induced deactivation of the default mode network in Alzheimer's disease and at-risk older individuals. Behav. Neurol. 21, 77–91.
Poettrich, K., Weiss, P.H., Werner, A., Lux, S., Donix, M., Gerber, J., von Kummer, R., Fink, G.R., Holthoff, V.A., 2009. Altered neural network supporting declarative long-term memory in mild cognitive impairment. Neurobiol. Aging 30, 284–298.
Qi, Z., Wu, X., Wang, Z., Zhang, N., Dong, H., Yao, L., Li, K., 2010. Impairment and compensation coexist in amnestic MCI default mode network. Neuroimage 50, 48–55.
Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proc. Natl. Acad. Sci. U. S. A. 98, 676–682.
Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., Acker, J.D., 2005. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb. Cortex 15, 1676–1689.
Rosano, C., Aizenstein, H.J., Cochran, J.L., Saxton, J.A., De Kosky, S.T., Newman, A.B., Kuller, L.H., Lopez, O.L., Carter, C.S., 2005. Event-related functional magnetic resonance imaging investigation of executive control in very old individuals with mild cognitive impairment. Biol. Psychiatry 57, 761–767.
Rose, S.E., McMahon, K.L., Janke, A.L., O'Dowd, B., de Zubicaray, G., Strudwick, M.W., Chalk, J.B., 2006. Diffusion indices on magnetic resonance imaging and neuropsychological performance in amnestic mild cognitive impairment. J. Neurol. Neurosurg. Psychiatry 77, 1122–1128.
Rushworth, M.F., Behrens, T.E., Johansen-Berg, H., 2006. Connection patterns distinguish 3 regions of human parietal cortex. Cereb. Cortex 16, 1418–1430.
Sack, A.T., 2009. Parietal cortex and spatial cognition. Behav. Brain Res. 202, 153–161.
Salat, D.H., Greve, D.N., Pacheco, J.L., Quinn, B.T., Helmer, K.G., Buckner, R.L., Fischl, B., 2009. Regional white matter volume differences in nondemented aging and Alzheimer's disease. Neuroimage 44, 1247–1258.
Salat, D.H., Tuch, D.S., van der Kouwe, A.J., Greve, D.N., Pappu, V., Lee, S.Y., Hevelone, N.D., Zaleta, A.K., Growdon, J.H., Corkin, S., Fischl, B., Rosas, H.D., 2010. White matter pathology isolates the hippocampal formation in Alzheimer's disease. Neurobiol. Aging 31, 244–256.
Saykin, A.J., Wishart, H.A., Rabin, L.A., Santulli, R.B., Flashman, L.A., West, J.D., McHugh, T.L., Mamourian, A.C., 2006. Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI. Neurology 67, 834–842.
Scahill, R.I., Schott, J.M., Stevens, J.M., Rossor, M.N., Fox, N.C., 2002. Mapping the evolution of regional atrophy in Alzheimer's disease: unbiased analysis of fluid-registered serial MRI. Proc. Natl. Acad. Sci. U. S. A. 99, 4703–4707.
Scheperjans, F., Hermann, K., Eickhoff, S.B., Amunts, K., Schleicher, A., Zilles, K., 2008. Observer-independent cytoarchitectonic mapping of the human superior parietal cortex. Cereb. Cortex 18, 846–867.
Schmahmann, J.D., Pandya, D.N., Wang, R., Dai, G., D'Arceuil, H.E., de Crespigny, A.J., Wedeen, V.J., 2007. Association fibre pathways of the brain: parallel observations from diffusion spectrum imaging and autoradiography. Brain 130, 630–653.
Scola, E., Bozzali, M., Agosta, F., Magnani, G., Franceschi, M., Sormani, M.P., Cercignani, M., Pagani, E., Falautano, M., Filippi, M., Falini, A., 2010. A diffusion tensor MRI study of patients with MCI and AD with a 2-year clinical follow-up. J. Neurol. Neurosurg. Psychiatry 81, 798–805.
Seltzer, B., Pandya, D.N., 1984. Further observations on parieto-temporal connections in the rhesus monkey. Experimental brain research. Experimentelle Hirnforschung 55, 301–312.
Seo, S.W., Im, K., Lee, J.M., Kim, Y.H., Kim, S.T., Kim, S.Y., Yang, D.W., Kim, S.I., Cho, Y.S., Na, D.L., 2007. Cortical thickness in single- versus multiple-domain amnestic mild cognitive impairment. Neuroimage 36, 289–297.
Singh, V., Chertkow, H., Lerch, J.P., Evans, A.C., Dorr, A.E., Kabani, N.J., 2006. Spatial patterns of cortical thinning in mild cognitive impairment and Alzheimer's disease. Brain 129, 2885–2893.
Small, G.W., Kepe, V., Ercoli, L.M., Siddarth, P., Bookheimer, S.Y., Miller, K.J., Lavretsky, H., Burggren, A.C., Cole, G.M., Vinters, H.V., Thompson, P.M., Huang, S.C., Satyamurthy, N., Phelps, M.E., Barrio, J.R., 2006. PET of brain amyloid and tau in mild cognitive impairment. N. Engl. J. Med. 355, 2652–2663.
Smith, C.D., Chebrolu, H., Wekstein, D.R., Schmitt, F.A., Jicha, G.A., Cooper, G., Markesbery, W.R., 2007. Brain structural alterations before mild cognitive impairment. Neurology 68, 1268–1273.
Sorg, C., Riedl, V., Muhlau, M., Calhoun, V.D., Eichele, T., Laer, L., Drzezga, A., Forstl, H., Kurz, A., Zimmer, C., Wohlschlager, A.M., 2007. Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. Proc. Natl. Acad. Sci. U. S. A. 104, 18760–18765.
Stahl, R., Dietrich, O., Teipel, S.J., Hampel, H., Reiser, M.F., Schoenberg, S.O., 2007. White matter damage in Alzheimer disease and mild cognitive impairment:

assessment with diffusion-tensor MR imaging and parallel imaging techniques. Radiology 243, 483–492.
Stricker, N.H., Schweinsburg, B.C., Delano-Wood, L., Wierenga, C.E., Bangen, K.J., Haaland, K.Y., Frank, L.R., Salmon, D.P., Bondi, M.W., 2009. Decreased white matter integrity in late-myelinating fiber pathways in Alzheimer's disease supports retrogenesis. Neuroimage 45, 10–16.
Szekely, C.A., Breitner, J.C., Fitzpatrick, A.L., Rea, T.D., Psaty, B.M., Kuller, L.H., Zandi, P.P., 2008. NSAID use and dementia risk in the Cardiovascular Health Study: role of APOE and NSAID type. Neurology 70, 17–24.
Targosz-Gajniak, M., Siuda, J., Ochudlo, S., Opala, G., 2009. Cerebral white matter lesions in patients with dementia—from MCI to severe Alzheimer's disease. J. Neurol. Sci. 283, 79–82.
Teipel, S.J., Meindl, T., Wagner, M., Stieltjes, B., Reuter, S., Hauenstein, K.H., Filippi, M., Ernemann, U., Reiser, M.F., Hampel, H., 2010. Longitudinal changes in fiber tract integrity in healthy aging and mild cognitive impairment: a DTI follow-up study. J. Alzheimers Dis..
Thal, D.R., Rub, U., Orantes, M., Braak, H., 2002. Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology 58, 1791–1800.
Tisserand, D.J., van Boxtel, M.P., Pruessner, J.C., Hofman, P., Evans, A.C., Jolles, J., 2004. A voxel-based morphometric study to determine individual differences in gray matter density associated with age and cognitive change over time. Cereb. Cortex 14, 966–973.
Tosun, D., Schuff, N., Mathis, C.A., Jagust, W., Weiner, M.W., 2011. Spatial patterns of brain amyloid-beta burden and atrophy rate associations in mild cognitive impairment. Brain 134, 1077–1088.
Tunik, E., Rice, N.J., Hamilton, A., Grafton, S.T., 2007. Beyond grasping: representation of action in human anterior intraparietal sulcus. Neuroimage 36 (Suppl. 2), T77–T86.
Uylings, H.B., Rajkowska, G., Sanz-Arigita, E., Amunts, K., Zilles, K., 2005. Consequences of large interindividual variability for human brain atlases: converging macroscopical imaging and microscopical neuroanatomy. Anat. Embryol. (Berl) 210, 423–431.
van de Pol, L.A., Verhey, F., Frisoni, G.B., Tsolaki, M., Papapostolou, P., Nobili, F., Wahlund, L.O., Minthon, L., Frolich, L., Hampel, H., Soininen, H., Knol, D.L., Barkhof, F., Scheltens, P., Visser, P.J., 2009. White matter hyperintensities and medial temporal lobe atrophy in clinical subtypes of mild cognitive impairment: the DESCRIPA study. J. Neurol. Neurosurg. Psychiatry 80, 1069–1074.
van Es, A.C., van der Flier, W.M., Admiraal-Behloul, F., Olofsen, H., Bollen, E.L., Middelkoop, H.A., Weverling-Rijnsburger, A.W., Westendorp, R.G., van Buchem, M.A., 2006. Magnetization transfer imaging of gray and white matter in mild cognitive impairment and Alzheimer's disease. Neurobiol. Aging 27, 1757–1762.
Van Essen, D.C., Lewis, J.W., Drury, H.A., Hadjikhani, N., Tootell, R.B., Bakircioglu, M., Miller, M.I., 2001. Mapping visual cortex in monkeys and humans using surface-based atlases. Vision Res. 41, 1359–1378.
Vannini, P., Almkvist, O., Dierks, T., Lehmann, C., Wahlund, L.O., 2007. Reduced neuronal efficacy in progressive mild cognitive impairment: a prospective fMRI study on visuospatial processing. Psychiatry Res. 156, 43–57.
Vannini, P., O'Brien, J., O'Keefe, K., Pihlajamaki, M., Laviolette, P., Sperling, R.A., 2010. What goes down must come up: role of the posteromedial cortices in encoding and retrieval. Cereb. Cortex.
Vernooij, M.W., Ikram, M.A., Vrooman, H.A., Wielopolski, P.A., Krestin, G.P., Hofman, A., Niessen, W.J., Van der Lugt, A., Breteler, M.M., 2009. White matter microstructural integrity and cognitive function in a general elderly population. Arch. Gen. Psychiatry 66, 545–553.
Villain, N., Chetelat, G., Desgranges, B., Eustache, F., 2010a. Neuroimaging in Alzheimer's disease: a synthesis and a contribution to the understanding of physiopathological mechanisms. Biologie aujourd'hui 204, 145–158.
Villain, N., Desgranges, B., Viader, F., de la Sayette, V., Mezenge, F., Landeau, B., Baron, J.C., Eustache, F., Chetelat, G., 2008. Relationships between hippocampal atrophy, white matter disruption, and gray matter hypometabolism in Alzheimer's disease. J. Neurosci. 28, 6174–6181.
Villain, N., Fouquet, M., Baron, J.C., Mezenge, F., Landeau, B., de La Sayette, V., Viader, F., Eustache, F., Desgranges, B., Chetelat, G., 2010b. Sequential relationships between grey matter and white matter atrophy and brain metabolic abnormalities in early Alzheimer's disease. Brain 133, 3301–3314.
Vogt, B.A., Vogt, L., Laureys, S., 2006. Cytology and functionally correlated circuits of human posterior cingulate areas. Neuroimage 29, 452–466.
Walhovd, K.B., Fjell, A.M., Amlien, I., Grambaite, R., Stenset, V., Bjornerud, A., Reinvang, I., Gjerstad, L., Cappelen, T., Due-Tonnessen, P., Fladby, T., 2009. Multimodal imaging in mild cognitive impairment: metabolism, morphometry and diffusion of the temporal-parietal memory network. Neuroimage 45, 215–223.
Walhovd, K.B., Fjell, A.M., Brewer, J., McEvoy, L.K., Fennema-Notestine, C., Hagler Jr., D.J., Jennings, R.G., Karow, D., Dale, A.M., 2010a. Combining MR imaging, positron-emission tomography, and CSF biomarkers in the diagnosis and prognosis of Alzheimer Disease. AJNR Am. J. Neuroradiol. 31, 347–354.
Walhovd, K.B., Fjell, A.M., Dale, A.M., McEvoy, L.K., Brewer, J., Karow, D.S., Salmon, D.P., Fennema-Notestine, C., 2010b. Multi-modal imaging predicts memory performance in normal aging and cognitive decline. Neurobiol. Aging 31, 1107–1121.
Wang, L., Goldstein, F.C., Veledar, E., Levey, A.I., Lah, J.J., Meltzer, C.C., Holder, C.A., Mao, H., 2009. Alterations in cortical thickness and white matter integrity in mild cognitive impairment measured by whole-brain cortical thickness mapping and diffusion tensor imaging. AJNR Am. J. Neuroradiol. 30, 893–899.
Wang, Z., Guo, X., Qi, Z., Yao, L., Li, K., 2010. Whole-brain voxel-based morphometry of white matter in mild cognitive impairment. Eur. J. Radiol. 75, 129–133.
Whitwell, J.L., Shiung, M.M., Przybelski, S.A., Weigand, S.D., Knopman, D.S., Boeve, B.F., Petersen, R.C., Jack Jr., C.R., 2008. MRI patterns of atrophy associated with progression to AD in amnestic mild cognitive impairment. Neurology 70, 512–520.
Woodard, J.L., Seidenberg, M., Nielson, K.A., Antuono, P., Guidotti, L., Durgerian, S., Zhang, Q., Lancaster, M., Hantke, N., Butts, A., Rao, S.M., 2009. Semantic memory activation in amnestic mild cognitive impairment. Brain 132, 2068–2078.
Wyss-Coray, T., 2006. Inflammation in Alzheimer disease: driving force, bystander or beneficial response? Nat. Med. 12, 1005–1015.
Yetkin, F.Z., Rosenberg, R.N., Weiner, M.F., Purdy, P.D., Cullum, C.M., 2006. FMRI of working memory in patients with mild cognitive impairment and probable Alzheimer's disease. Eur. Radiol. 16, 193–206.
Yokokura, M., Mori, N., Yagi, S., Yoshikawa, E., Kikuchi, M., Yoshihara, Y., Wakuda, T., Sugihara, G., Takebayashi, K., Suda, S., Iwata, Y., Ueki, T., Tsuchiya, K.J., Suzuki, K., Nakamura, K., Ouchi, Y., 2010. In vivo changes in microglial activation and amyloid deposits in brain regions with hypometabolism in Alzheimer's disease. Eur. J. Nucl. Med. Mol. Imag..
Zacks, J.M., 2008. Neuroimaging studies of mental rotation: a meta-analysis and review. J. Cogn. Neurosci. 20, 1–19.
Zecca, L., Youdim, M.B., Riederer, P., Connor, J.R., Crichton, R.R., 2004. Iron, brain ageing and neurodegenerative disorders. Nat. Rev. Neurosci. 5, 863–873.
Zetzsche, T., Rujescu, D., Hardy, J., Hampel, H., 2010. Advances and perspectives from genetic research: development of biological markers in Alzheimer's disease. Exp. Rev. Mol. Diagn. 10, 667–690.
Zhang, D., Wang, Y., Zhou, L., Yuan, H., Shen, D., 2011. Multimodal classification of Alzheimer's disease and mild cognitive impairment. Neuroimage 55, 856–867.
Zhuang, L., Wen, W., Zhu, W., Trollor, J., Kochan, N., Crawford, J., Reppermund, S., Brodaty, H., Sachdev, P., 2010. White matter integrity in mild cognitive impairment: a tract-based spatial statistics study. Neuroimage 53, 16–25.