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White matter disruption at the prodromal stage of Alzheimer's disease: Relationships with hippocampal atrophy and episodic memory performance

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ABSTRACT

White matter tract alterations have been consistently described in Alzheimer's disease (AD). In particular, limbic fronto-temporal connections, which are critical to episodic memory function, may degenerate early in the course of the disease. However the relation between white matter tract degeneration, hippocampal atrophy and episodic memory impairment at the earliest stages of AD is still unclear. In this magnetic resonance imaging study, white matter integrity and hippocampal volumes were evaluated in patients with amnestic mild cognitive impairment due to AD (Albert et al., 2011) ($n = 22$) and healthy controls ($n = 15$). Performance in various episodic memory tasks was also evaluated in each participant. Relative to controls, patients showed a significant reduction of white matter fractional anisotropy (FA) and increase of radial diffusivity (RD) in the bilateral uncinate fasciculus, parahippocampal cingulum and fornix. Within the patient group, significant intra-hemispheric correlations were notably found between hippocampal grey matter volume and FA in the uncinate fasciculus, suggesting a relationship between atrophy and disconnection of the hippocampus. Moreover, episodic recognition scores were related with uncinate fasciculus FA across patients. These results indicate that fronto-hippocampal connectivity is reduced from the earliest pre-demential stages of AD. Disruption of fronto-hippocampal connections may occur progressively, in parallel with hippocampal atrophy, and may specifically contribute to early initial impairment in episodic memory.

1. Introduction

In vivo detection of the earliest physiological changes that occur in Alzheimer's disease (AD) is currently the focus of a large body of research. To identify the earliest cerebral biomarkers, imaging results are reported in patients with amnestic mild cognitive impairment (aMCI). These patients present with progressive episodic memory deficit and have a high risk to convert to AD dementia (Petersen et al., 1999). In aMCI patients relative to age-matched controls, significant medial temporal grey matter (GM) atrophy and hypometabolism at rest have been consistently reported (De Santi et al., 2001; Du et al., 2004; Jack et al., 1999; Pengas et al., 2010), coherent with the earliest neurofibrillary tangle deposition in the hippocampus and entorhinal cortex in AD (Braak and Braak, 1991). Besides, reduced metabolism has been reported in posterior cerebral regions, most consistently in the posterior cingulate cortex (PCC), in early AD (Chételat et al., 2003) and aMCI patients (Herholz et al., 2002; Minoshima et al., 1997; Nestor et al., 2003). Accordingly, several authors proposed that these functional changes may result from reduced connectivity of posterior regions with the hippocampus (Chételat et al., 2008, 2003; Minoshima et al., 1997; Nestor et al., 2003; Smith, 2002). Hippocampal disconnection may occur from very early stages of the disease, thus affecting large-scale neural networks critical to episodic memory, such as the limbic network (Callen et al., 2001; Huang et al., 2012; Nestor et al., 2003; Pengas et al., 2010). On the basis of this disconnection hypothesis (Chételat et al., 2003; Smith, 2002), an interesting approach is to evaluate potential changes in white matter (WM) tracts from the earliest stages of AD. The present study aimed at measuring WM changes in aMCI patients, who responded to strict physiological criteria typical of AD pathology, i.e. patients with aMCI due to AD (Albert et al., 2011; Dubois et al., 2014). Our objective was to identify the earliest alterations in WM connections that could contribute to the initial episodic memory impairment.

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Using magnetic resonance diffusion tensor imaging (MR-DTI) (Basser and Jones, 2002; Le Bihan et al., 2001), WM microstructural changes in aMCI patients have been most consistently reported in temporal and parietal regions (for review see Chua et al., 2008; Sexton et al., 2011), although frontal and occipital WM may also undergo changes (Bosch et al., 2012; Zhuang et al., 2010). These WM alterations could be more important as pathology evolves, as suggested in studies comparing aMCI and mild AD patients with controls (Bosch et al., 2012; Fellgiebel et al., 2005; Kiuchi et al., 2009; Liu et al., 2011; Medina et al., 2006; Mielke et al., 2009; Zhang et al., 2007). In particular, limbic WM tracts may be altered in aMCI, and further in AD patients. To date, the most consistent finding has been a significant alteration of the cingulum (Acosta-Cabronero et al., 2012; Bosch et al., 2012; Fellgiebel et al., 2005; Kiuchi et al., 2009; Liu et al., 2011; Medina et al., 2006; Rose et al., 2006; Stenset et al., 2011; Zhang et al., 2007; Zhuang et al., 2013), which connects the hippocampal formation with the cingulate gyrus (Catani and Thiebaut de Schotten, 2008). In AD patients, hippocampal volume has been related with alteration of the cingulum micro-structure (Choo et al., 2010; Xie et al., 2005), as well as with cingulum bundle volume (Villain et al., 2008), suggesting a causal link between the hippocampus and cingulum anatomical changes. Also, alteration of the cingulum is consistent with early PCC hypometabolism at rest (Chételat et al., 2003; Minoshima et al., 1997), and may in particular explain the relationship between hippocampal atrophy and PCC/temporo-parietal hypometabolism, which has been reported in AD (Meguro et al., 2001; Villain et al., 2008) and aMCI (Guedj et al., 2009) patients. Apart from the cingulum, other limbic tracts may as well undergo changes in early AD. Alterations of the fornix have been reported in aMCI patients (Mielke et al., 2009; Zhuang et al., 2013, 2010), and these alterations may be more important in patients with short-term progression to AD (Douaud et al., 2013). Also, damage of the uncinate fasciculus has been recently reported in 'late' aMCI (Zhuang et al., 2013) and more consistently in mild AD patients (Bosch et al., 2012; Damoiseaux et al., 2009; Kiuchi et al., 2009), this limbic tract connecting the temporal pole with the lower medial and lateral inferior frontal cortices (Catani and Thiebaut de Schotten, 2008). Notably, causal links were established between hippocampal GM atrophy, cingulum and uncinate fasciculus WM atrophy, and hypometabolism in the cingulate gyrus and lower frontal cortex (Villain et al., 2010). Together with the fornix, the cingulum and uncinate fasciculus are temporo-frontal limbic connections that underlie episodic memory function in healthy subjects (Metzler-Baddeley et al., 2011; Sepulcre et al., 2008). These WM tracts may get altered from the earliest prodromal stage of AD, leading to hippocampal disconnection with posterior and anterior cortical regions.

To date, the link between limbic WM damage and episodic memory impairment remains unclear. Whole-brain WM DTI metrics in aMCI patients have been previously related with cognitive status (Acosta-Cabronero et al., 2012; Mielke et al., 2009; Nir et al., 2013) and memory scores (Bosch et al., 2012; Fellgiebel et al., 2005). Note that most of the latter correlations were obtained across groups of subjects, pooling aMCI and AD patients (and sometimes controls), and this may artificially increase the correlation strength. Besides, episodic recall performance in aMCI patients has been related to DTI metrics in pre-defined regions of interest of the retrosplenial (Walhovd et al., 2009) and temporal WM (Goldstein et al., 2009), regions that could comprise the posterior and parahippocampal parts of the cingulum, respectively. However, clear relationships between damage of specific WM tracts and early episodic memory deficit in aMCI patients remain to be established. In particular, episodic *recognition* and *recall* of verbal/visual materials, which are both impaired early in AD, could rely on separate neural networks involving distinct hippocampal tracts. Whereas episodic recognition of previously-encoded items could be mostly based on item familiarity and involve hippocampal connections with anterior temporal and frontal regions (Gour et al., 2011), episodic recall may additionally recruit posterior regions, such as the PCC and temporo-parietal cortex (Wang et al., 2010), thus involving the cingulum tract.

In the present study, DTI-derived parameters in whole-brain WM tracts were measured in patients with aMCI due to AD (Albert et al., 2011; Dubois et al., 2014), and in age-matched controls. By selecting patients according to strict inclusion criteria, we expected to measure group differences specifically related to the earliest stages of AD pathology. It was previously reported that hippocampal connectivity with distant posterior and anterior brain regions could be reduced in early AD, as a consequence of hippocampal atrophy (Villain et al., 2010). We aimed at supporting this hypothesis using whole-brain WM DTI and hippocampal GM volumetry. Differences in WM micro-structure between patients and controls were assessed, and fibre tractography was computed from medial temporal regions showing significant changes, allowing for clear identification of altered tracts in patients. Correlations between hippocampal volumes and DTI metrics were then assessed in these regions. Moreover, performance in episodic recognition and recall of verbal and visual items was assessed in each participant. We hypothesized that initial impairment in episodic memory tasks may rely on early hippocampal disconnection, from the pre-demential stage of AD. Disruption of tracts connecting the hippocampus with anterior regions may mainly affect item recognition, whereas episodic recall deficit could be related with alterations of hippocampal tracts projecting to posterior regions.

2. Materials & methods

2.1. Participants

Twenty-two patients diagnosed with aMCI due to AD (see inclusion criteria below) and 15 age- and gender-matched control subjects were recruited for the study (Table 1). The study was approved by the regional Ethics committee (Comité de Protection des Personnes Sud-Ouest et Outre-Mer I, no. AFSSAPS A90605-58) and written informed consent was given by all participants.

2.2. Inclusion criteria

2.2.1. Patients with MCI due to AD

Pre-inclusion assessment and inclusion criteria have been extensively described in a previous report (Saint-Aubert et al., 2013). Briefly, patients over 65 years old, with a memory complaint dating from more than 6 months and without any neurologic or psychiatric disease history, were initially recruited ($n = 34$). After pre-inclusion assessment, which included neuropsychological tests (Clinical Dementia Rating (CDR) scale and Free and Cued Selective Reminding Test (FCSRT)), MRI examination, ^{18}F-FDG Positron Emission Tomography (PET) examination and cerebrospinal fluid (CSF) biomarker sampling, inclusion was decided according to the following criteria:

- CDR = 0.5, i.e. autonomy in daily life,
- Sum of the three free recalls ≤17/48 and/or sum of the three free and cued recalls ≤40/48 on the FCSRT, i.e. significant verbal episodic memory impairment (Sarazin et al., 2007),
- One or more of the following criteria:
  - Scheltens score for medial temporal GM atrophy >1 in at least one hemisphere, based on visual T_1-weighted MRI scan examination (Scheltens et al., 1992).
  - Temporo-parietal and/or PCC hypometabolism at rest suggestive of AD, based on visual FDG-PET scan examination.
  - Level of phospho-tau (P-tau) ≥60 pg/ml and Innotest Amyloid Tau Index (IATI) ≤ 0.8. In case of ambiguous profile, i.e. P-tau < 60 pg/ml or IATI > 0.8, the Aβ42/Aβ40 level ratio was calculated and a ratio <0.045 was considered compatible with AD diagnosis (Wiltfang et al., 2007).

Moreover, patients with significant white matter hyperintensities on the T2-weighted MRI scan (Fazekas and Schmidt (F&S) score > 2 (Fazekas et al., 2002)) were excluded.