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A whole-brain computational modeling approach to explain the alterations in resting-state functional connectivity during progression of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is the most common dementia with dramatic consequences. The research in structural and functional neuroimaging showed altered brain connectivity in AD. In this study, we investigated the whole-brain resting state functional connectivity (FC) of the subjects with preclinical Alzheimer's disease (PAD), mild cognitive impairment due to AD (MCI) and mild dementia due to Alzheimer's disease (AD), the impact of APOE4 carriership, as well as in relation to variations in core AD CSF biomarkers. The synchronization in the whole-brain was monotonously decreasing during the course of the disease progression. Furthermore, in AD patients we found widespread significant decreases in functional connectivity (FC) strengths particularly in the brain regions with high global connectivity. We employed a whole-brain computational modeling approach to study the mechanisms underlying these alterations. To characterize the causal interactions between brain regions, we estimated the effective connectivity (EC) in the model. We found that the significant EC differences in AD were primarily located in left temporal lobe. Then, we systematically manipulated the underlying dynamics of the model to investigate simulated changes in FC based on the healthy control subjects. Furthermore, we found distinct patterns involving CSF biomarkers of amyloid-beta (Aβ1 − 42) total tau (t-tau) and phosphorylated tau (p-tau). CSF Aβ1 − 42 was associated to the contrast between healthy control subjects and clinical groups. Nevertheless, tau CSF biomarkers were associated to the variability in whole-brain synchronization and sensory integration regions. These associations were robust across clinical groups, unlike the associations that were found for CSF Aβ1 − 42. APOE4 carriership showed no significant correlations with the connectivity measures.

1. Introduction

Alzheimer's disease (AD), being the most prevalent dementia, became a major concern in developed countries as a consequence of increasing life expectancy (Blennow et al., 2006; Plassman et al., 2007). During the past two decades advancements in genetics, neurobiology and neuroimaging techniques allowed researchers to study the mechanisms behind the underlying causes of AD. In particular, resting state functional Magnetic Resonance Imaging (rs-fMRI) became a widely used tool to study the alterations in brain activity of AD patients as well as many other clinical conditions (Greicius, 2008). Furthermore, cerebrospinal fluid (CSF) biomarkers have been shown to serve as a proxy to monitor in vivo the neuropathological hallmarks of AD, namely amyloid-β and tau tangles (José Luis Molinuevo et al., 2014).

Various rs-fMRI studies showed altered functional connectivity in AD (Brier et al., 2014; Dennis and Thompson, 2014; Filippi and Agosta, 2011). The studies that used seed-based approach showed widespread decreases in hippocampal (Allen et al., 2007; W. Li et al., 2012; Wang et al., 2006) and posterior cingulate functional connectivity (Bai et al., 2011; Zhang et al., 2009) in AD. In addition, some of these studies

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reported increased FC between prefrontal cortex and hippocampus (Wang et al., 2006), and between prefrontal cortex and posterior cingulate (Bai et al., 2011; Zhang et al., 2009) in AD. The increased connectivity in prefrontal cortex was interpreted as a compensation mechanism during the initial stages of the disease (Dickerson et al., 2004; Filippi and Agosta, 2011; Sanz-Arigita et al., 2010). The studies based on independent component analysis (ICA) showed decreased activation of default mode network (DMN) (Agosta et al., 2012; Koch et al., 2010; Qi et al., 2010; Sorg et al., 2007) and increased activation of frontoparietal network (FPN) (Agosta et al., 2012). Various other studies found impaired deactivation of DMN during task in AD and dementia (Celone et al., 2006; Greicius et al., 2004; Lustig et al., 2003; Petrella et al., 2007; Rombouts et al., 2009, 2005).

Another powerful approach to study AD comprised the relationship between CSF biomarkers and the progression of AD. For example, amyloid-β plaques are known to accumulate decades before the onset of the first disease symptoms in individuals with prolonged phase of "preclinical AD" (Price and Morris, 1999). The analysis of CSF Aβ1 − 42 concentrations has been shown to closely correlate with cerebral pathology. Furthermore, to identify the functional manifestations of CSF biomarkers, rs-fMRI has been proposed as a promising approach (Barkhof et al., 2014). Several studies showed an overlap between the spatial pattern of the DMN and that of Aβ1–42 accumulation that happens in this preclinical phase of AD (Buckner et al., 2008; Hedden et al., 2009). Furthermore, DMN connectivity was decreased in cognitively normal individuals with augmented cerebral amyloid load (Sheline, Raichle, et al., 2010b; Hedden et al., 2009; Oh et al., 2011). In addition to Aβ1 − 42, altered functional connectivity in the DMN have also been associated to abnormal levels of phosphorylated Tau181 (p-tau) in CSF (Wang et al., 2013) as well as the ratio Aβ1–42/p-tau and the AD CSF Index (Jose Luis Molinuevo et al., 2013), both of which constitute well-established markers of disease progression (X. Li et al., 2013). Reduced DMN functional connectivity has also been reported in amyloid-free carriers of at least one copy of the APOE4 allele, which is the strongest genetic risk factor for AD (Sheline, Morris, et al., 2010a). These findings suggested that differences in functional connectivity might even precede amyloid deposition (Sheline and Raichle, 2013).

Despite robust findings addressing altered DMN connectivity in AD, the mechanisms behind this alteration are not clear. Furthermore, dysfunction of DMN is the most common finding in many other mental disorders (Broyd et al., 2009). Therefore, it is crucial to understand the relationship between structure, function and CSF biomarkers in AD (Ramirez et al., 2014; Filippi and Agosta, 2011).

In this study, we investigated the rs-FC alterations in preclinical Alzheimer's disease (PAD), mild cognitive impairment due to AD (MCI) and mild dementia due to Alzheimer's disease (AD). First, we studied the whole-brain connectivity in each group based on the fluctuations in global synchronization level between all brain regions. Then, to understand the role of distinct brain regions, we characterized the rs-FC of each region to the rest of the brain by adapting a previously employed technique to parcellated data (Cole et al., 2010). Moreover, we proposed whole-brain computational model to provide mechanistic understanding of the connectivity alterations in each group. We performed two experiments using the model: First, to understand the role of long-range interactions between regions on the rs-FC alterations in clinical groups, we estimated the effective connectivity in the model. Effective connectivity (EC) refers to the optimal connection strengths between the regions in the model that generate the observed FCs. Second, to test whether a global shift in the optimal dynamics explains the rs-FC alterations, we investigated the predicted changes in rs-FC by manipulating the model parameters in healthy control subjects (Fig. 1). Furthermore, we studied the association between core AD CSF biomarkers and described connectivity measures.

2. Materials and methods

2.1. Subjects

A total of 109 participants (58 HC, 12 PAD, 23 MCI and 16 AD) were recruited at the Alzheimer's disease and other cognitive disorders unit, from the Hospital Clinic of Barcelona. All subjects underwent clinical and neuropsychological assessment, MRI scanning and were submitted to a lumbar puncture to quantify the content of Aβ1–42, p-tau and t-tau in CSF. CSF biomarker quantitation was done at the local laboratory by means of ELISA (Enzyme-Linked ImmunoSorbent Assay kits, Innogenetics, Ghent, Belgium). An interdisciplinary clinical committee formed by two neurologists and one neuropsychologist established the diagnoses. HC and PAD presented no evidence of cognitive impairment on any of the administered neuropsychological tests, but PAD presented an abnormal level of CSF Aβ1–42 (below 500 pg/ml). MCI and AD presented signs of dementia. MCI patients had an objective memory deficit, defined as an abnormal score on the total recall measure of the Free and Cued Selective Reminding Test (FCRST) (over 1.5 × standard deviation), impairment on one or more of the other cognitive tests or preserved activities of daily living, as measured by the Functional Activities Questionnaire (FAQ score < 6). The NINCDS-ADRDA criteria were applied for probable AD diagnosis (Jack et al., 2011), taking into account clinical information and objective measures derived from the FAQ and neuropsychological results. AD patients were all in the mild stages of the disease (Global Deterioration Scale = 4). Diagnostic classification was made independent of CSF results. The local ethics committee approved the study and all participants gave written informed consent to participate in the study. Genomic DNA was extracted from peripheral blood of probands using the QIAamp DNA blood minikit (Qiagen AG, Basel, Switzerland). Apolipoprotein E genotyping was performed by polymerase chain reaction amplification and HhaI restriction enzyme digestion. Average demographic characteristics of the four diagnostic groups are shown in Table 1.

2.2. Image acquisition and preprocessing

Subjects were examined on a 3 T MRI scanner (Magnetom Trio Tim, Siemens, Erlangen, Germany) at the image core facilities of IDIBAPS (Barcelona, Spain). MRI session included a high-resolution three-dimensional structural T1-weighted image (sagittal MPRAGE; TR = 2300 ms, TE = 2.98 ms; matrix size = 256 × 256 × 240; isometric voxel 1 × 1 × 1 mm^3), a 10 min resting state fMRI (rs-fMRI; 300 volumes, TR = 2000 ms, TE = 16 ms, 128 × 128 × 40 matrix, voxel size = 1.72 × 1.72 × 3 mm^3) and two sets of diffusion weighted images (DWI; 30 no-collinear directions with a b value of 1000 s/mm^2 and one volume with a b value of 0; TR = 7700 ms, TE = 89 ms; matrix size = 122 × 122 × 60; voxel size 2.05 × 2.05 × 2 mm^3).

The pre-processing pipeline of rs-fMRI consisted in the slice-timing correction, the realignment and re-slice, smoothing with a Gaussian kernel (FWHM = 5 mm), second order de-trending and regressing out Volterra expanded parameters of movement (24 parameters), mean white matter (WM) signal, mean CSF signal and nulling regressors for bad volumes (Lemieux et al., 2007). Global signal regression (GSR) was not performed, because the known issues about GSR (Murphy et al., 2009) have a prominent impact on the analysis of whole-brain connectivity (Yang et al., 2014). Movement and other nuisance regressions were performed to alleviate the global artifacts. The quality criteria to consider a volume wrong and to override it by a nulling regressor, was that its correlation coefficient (cc) with the mean image of its series were beyond three standard deviations (cc < 0.991) from the mean cc of all the images from all subjects to their corresponding mean image (mean cc = 0.995). No subjects presented > 15% of bad volumes,