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Gray matter network disruptions and amyloid beta in cognitively normal adults

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ABSTRACT

Gray matter networks are disrupted in Alzheimer's disease (AD). It is unclear when these disruptions start during the development of AD. Amyloid beta 1–42 ($A\beta_{42}$) is among the earliest changes in AD. We studied, in cognitively healthy adults, the relationship between $A\beta_{42}$ levels in cerebrospinal fluid (CSF) and single-subject cortical gray matter network measures. Single-subject gray matter networks were extracted from structural magnetic resonance imaging scans in a sample of cognitively healthy adults (N = 185; age range 39–79, mini–mental state examination >25, N = 12 showed abnormal $A\beta_{42}$ < 550 pg/mL). Degree, clustering coefficient, and path length were computed at whole brain level and for 90 anatomical areas. Associations between continuous $A\beta_{42}$ CSF levels and single-subject cortical gray matter network measures were tested. Smoothing splines were used to determine whether a linear or nonlinear relationship gave a better fit to the data. Lower $A\beta_{42}$ CSF levels were linearly associated at whole brain level with lower connectivity density, and nonlinearly with lower clustering values and higher path length values, which is indicative of a less-efficient network organization. These relationships were specific to medial temporal areas, precuneus, and the middle frontal gyrus (all $p < 0.05$). These results suggest that mostly within the normal spectrum of amyloid, lower $A\beta_{42}$ levels can be related to gray matter networks disruptions.

1. Introduction

Coordinated patterns of gray matter morphology as measured with magnetic resonance imaging (MRI) can be concisely described as a network (Alexander-Bloch et al., 2013a; Bassett et al., 2008; Evans, 2013; He et al., 2007; Lerch et al., 2006; Mechelli et al., 2005; Sanabria-Diaz et al., 2010; Tijms et al., 2012). Although the precise biological meaning of these patterns is still unclear, they can be partially explained by functional coactivation and/or mechanical tension from axonal connectivity (Alexander-Bloch et al., 2013b, 2013a; van Essen et al., 1997). Brain areas that correlate in size are often involved in subnetworks that underlie specific cognitive functions (Amunts et al., 1997; Bailey et al., 2014; Fauvel et al., 2014; Hyde et al., 2009; Maguire et al., 2000; Mechelli et al., 2004; Voss and Zatorre, 2015; Woollett and Maguire, 2011). For example, areas involved in visual processing grow in a coordinated way (Andrews et al., 1997; Voss and Zatorre, 2015). In Alzheimer's disease (AD), such gray matter networks become disorganized (He et al., 2008; Li et al., 2012; Tijms et al., 2013a; Yao et al., 2010), and these disruptions have been associated with cognitive dysfunction (Tijms et al., 2013a, 2014). This suggests that gray matter networks capture pathologically relevant information. It is still unclear, however, at which point during the development of AD gray matter networks become disrupted.

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AD pathological processes start as early as 20 years before the onset of dementia, with amyloid deposition being among the earliest changes (Hardy and Selkoe, 2002; Jansen et al., 2015; Mormino, 2014; Villemagne et al., 2013, 2011). Low values of amyloid-beta 1–42 ($A\beta_{42}$) in cerebrospinal fluid (CSF) are indicative of a higher amyloid plaque load in the brain, which is a strong predictor for future development of AD (Vos et al., 2013; van Harten et al., 2012).

$A\beta_{42}$ plaque deposition between neurons disrupts their synaptic communication, resulting in disintegration of neuronal networks. We hypothesized that lower $A\beta_{42}$ CSF levels in cognitively healthy adults may be associated with path length and clustering values that are more like those obtained in randomly organized networks. Recent studies suggest that the presence of $A\beta_{42}$ pathology as measured by CSF or by amyloid positron emission tomography is associated with disruptions in gray matter networks in cognitively normal subjects (Oh et al., 2011; Spreng and Turner, 2013). But, the network results of Oh et al. (2011) could not be associated with interindividual measures of $A\beta_{42}$ pathology because those networks were derived at a group level, which results in 1 value per group. As such, the relationship between interindividual values in $A\beta_{42}$ levels and gray matter network property values remains unclear. Spreng and Turner (2013) derived single-subject scores from group-derived gray matter networks and found that a decrease in gray matter connectivity over time was related to more CSF $A\beta_{42}$ pathology at the baseline of the study. However, in that study, the correlation was assessed across diagnostic groups, and so, it remains unclear if this relationship was present in cognitively normal people.

We recently developed a novel method to extract whole brain gray matter networks from single-subjects structural magnetic resonance images (Tijms et al., 2012). With this method, we investigated whether $A\beta_{42}$ CSF levels are related to disruptions in single-subject gray matter networks in cognitively normal adults.

2. Methods

2.1. Participants

In total, 408 cognitively normal adults were enrolled in the Gipuzkoa Alzheimer Project (GAP), which is a longitudinal study on predementia AD in people who were recruited from the general population. Inclusion criteria for the GAP study were community-dwelling adults (39–80 years) subjects without dementia and a Clinical Dementia Rating score $\leq$0.5. Exclusion criteria were any significant neurologic, systemic, or psychiatric disorder that could cause cognitive impairment. Subjects were recruited between June 2011 and January 2013 via advertisements in the local media and presentations at the local Alzheimer Family Association. All subjects underwent thorough neurological, neuropsychological, and cardiovascular examination and MRI scanning. All participants were invited for lumbar puncture and cerebrospinal fluid (CSF) sample donation. Blood and CSF samples were obtained at baseline and stored at the Basque Biobank for Research (Basque Foundation for Health Research and Innovation). Apoliprotein E (APOE) genotype was determined using a one-stage polymerase chain reaction as previously described (Blázquez et al., 2007). Subjects were then classified as APOE ε4 carriers (APOE ε4+) if they had $\geq$1 APOE ε4 allele, or as noncarriers (APOE ε4−) otherwise. The local Ethics Committee approved the study protocol, and all subjects gave written informed consent. Inclusion criteria for the present study were the availability of both CSF and structural MRI (N = 185).

2.2. Cerebral spinal fluid analysis

In subjects who gave informed consent, CSF was obtained by lumbar puncture performed by a neurologist at the L3/L4 or L4/L5 intervertebral space with the subjects in left lateral decubitus position, using a 22-gauge atraumatic needle (Whitacre-22G, without introducer) following international consensus recommendations (del Campo et al., 2012). CSF samples were analyzed at the laboratory of Neuroscience of the Hospital Sant Pau in Barcelona. This laboratory is part of the Alzheimer's Association Quality Control Program. Briefly, CSF was collected in the morning between 09:00 and 12:00 hours in polypropylene tubes and immediately centrifuged (1900–2000g × 10 minutes). The first 1–2 cc were discarded to avoid any possible hematic contamination. All samples were aliquoted (0.5 mL) into polypropylene tubes and frozen at −80 °C until analyzed. Commercially available enzyme-linked immunosorbent assay kits were used to determine levels of Aβ42 (InnotestTM β-Amyloid1-42, Fujirebio-Innogenetics). The main objective of this study was to investigate if continuous values of Aβ42 CSF are associated with gray matter network property values. In addition, we classified subjects as amyloid positive using a predefined cutoff of Aβ42 CSF < 550 pg/mL (Alcolea et al., 2015) to determine the proportion of subjects with pathological levels of Aβ42.

2.3. Image acquisition and preprocessing

Whole-brain structural MRI scans were obtained with a Siemens 3T Magnetom TrioTim scanner. Isotropic 3-dimensional T1-weighted images were acquired with a sagittal magnetization-prepared rapid acquisition gradient-echo sequence (MPRAGE, 1.25 × 1.25 × 1.25 mm voxels, repetition time = 2300 ms, echo time = 2.86 ms, inversion time = 900 ms, field of view = 240 mm, flip angle = 9°). The images were segmented into gray matter, white matter, and cerebrospinal fluid with the voxel-based morphometry toolbox version 8 (VBM; University of Jena, Department of Cognitive Neurology, C. Gaser: http://dbm.neuro.uni-jena.de/vbm) implemented in Statistical Parametric Mapping software version 8 (SPM8; Wellcome Department of Cognitive Neurology, London, UK) running in MATLAB 2011a (MathWorks Inc., Natick, MA, USA), with the default settings for all parameters. The quality of all segmentations was visually assessed, and none had to be excluded. In the native space gray matter segmentation of each subject, 90 anatomical areas were identified on the basis of the automated anatomical labelling atlas (AAL; Tzourio-Mazoyer et al., 2002) using the individual brain atlases statistical parametric mapping toolbox in SPM. This toolbox was also used to obtain whole brain gray matter, white matter, and total intracranial volumes (i.e., gray matter + white matter + cerebrospinal fluid volume). After segmentation, the images were resliced into 2 × 2 × 2 mm^3 voxels.

2.4. Single-subject gray matter networks

Single-subject gray matter networks were extracted from native space gray matter segmentations using a fully automated method that was implemented in MATLAB (https://github.com/bettytijms/Single_Subject_Grey_Matter_Networks; Tijms et al., 2012). Nodes were defined as small regions of interest of 3 × 3 × 3 voxel cubes thereby using geometrical information as well as gray matter density values in the voxels. Nodes were connected with edges when they showed similar gray matter structure as determined by calculating the correlation across gray matter values between 2 corresponding voxels of 2 regions of interest: