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Altered structural network organization in cognitively normal individuals with amyloid pathology

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ABSTRACT

Recent findings show that structural network topology is disrupted in Alzheimer's disease (AD), with changes occurring already at the prodromal disease stages. Amyloid accumulation, a hallmark of AD, begins several decades before symptom onset, and its effects on brain connectivity at the earliest disease stages are not fully known. We studied global and local network changes in a large cohort of cognitively healthy individuals (N = 299, Swedish BioFINDER study) with and without amyloid-β (Aβ) pathology (based on cerebrospinal fluid Aβ42/Aβ40 levels). Structural correlation matrices were constructed based on magnetic resonance imaging cortical thickness data. Despite the fact that no significant regional cortical atrophy was found in the Aβ-positive group, this group exhibited an altered global network organization, including decreased global efficiency and modularity. At the local level, Aβ-positive individuals displayed fewer and more disorganized modules as well as a loss of hubs. Our findings suggest that changes in network topology occur already at the presymptomatic (preclinical) stage of AD and may precede detectable cortical thinning.

1. Introduction

In Alzheimer's disease (AD), the loss of gray matter follows a characteristic pattern over time, spreading from medial temporal regions to temporoparietal association cortices, then to the neocortical areas (Thompson et al., 2003). A number of recent studies have proposed that cognitive decline in AD is a consequence of disruptions in the structural and functional connections between brain regions (Delbeuck et al., 2003). Studying brain structural covariance may expand our understanding of the organization of the brain at the different stages of disease progression.

AD begins 1 to 2 decades before any symptoms become apparent (Bateman et al., 2012). Asymptomatic individuals at risk for AD can be identified using validated pathophysiological biomarkers, such as cerebrospinal fluid markers of amyloid-β (Aβ) (Rosen et al., 2013). Cognitively healthy individuals with abnormal Aβ levels are considered to have preclinical AD (Sperling et al., 2011). Several studies have shown that asymptomatic individuals with evidence of cerebral amyloidosis have an increased risk of subsequent cognitive decline, including development of AD dementia (Insel et al., 2016; Jagust, 2016; Vos et al., 2013). Whether cognitively normal individuals with high amyloid burden display other abnormalities consistent with AD pathophysiology has been investigated across different magnetic resonance imaging (MRI) modalities. Most structural MRI (s-MRI) studies do not detect atrophy in normal individuals harboring brain amyloid. Some, however, have found a subtle degree of cortical thinning in asymptomatic amyloid-positive older controls (Dickerson et al., 2009). Further, high amyloid burden does not seem to influence white matter integrity measures in the absence of neurodegeneration in nondemented adults (Kantarci et al., 2014). Functional MRI (fMRI) studies have found that increased brain amyloid load (Sheline et al., 2010) and lower cerebrospinal fluid (CSF) Aβ42 levels (Wang et al., 2013) are associated with decreases in functional connectivity in regions that belong to the default mode network (DMN) in cognitively healthy older individuals.

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Gray matter networks are thought to reflect both actual connections via white matter tracts (as measured by diffusion tensor imaging) as well as intrinsic functional connectivity (as inferred from the blood-oxygen-level-dependent signal in fMRI) (Alexander-Bloch et al., 2013; Spreng and Turner, 2013). In neurodegeneration, cortical atrophy patterns give rise to covariance networks, which differ depending on the underlying pathology (Seeley et al., 2009). AD patients as well as asymptomatic adults at risk of developing AD (carriers of the apolipoprotein E [APOE] ε4 allele) have previously shown to display a different structural network organization compared to controls (Alexander et al., 2012; He et al., 2008). The extent of these network changes tends to reflect the magnitude of the underlying pathology, disease severity, and duration (Stam, 2014).

A widely used framework for investigating structural covariance networks is graph analysis. A graph theoretical approach allows assessing brain connectivity and network organization by representing the brain as a set of nodes connected by edges. When applied to s-MRI data, the nodes of a network correspond to anatomical regions (segmented/parcellated structures), and the edges are measures of the "connection" (i.e., structural dependence or covariance) between these regions estimated using statistical correlations (Rubinov and Sporns, 2010). Using graph theory, these brain networks can be described by a number of parameters, such as global efficiency, clustering coefficient, transitivity, modularity, and the existence of hubs (Mijalkov et al., 2017; Rubinov and Sporns, 2010). Global efficiency is a measure of integration that indicates how fast information is transmitted across the nodes of a network. Clustering, transitivity, and modularity are segregation measures that indicate how strongly a network is organized into clearly distinguishable different modules. Hubs are regions of a network that play a critical role in regulating the flow of information.

A number of studies have investigated AD imaging data within the graph theoretical framework (Dai and He, 2014; He et al., 2009; Pereira et al., 2015; Tijms et al., 2013; Yao et al., 2010). Although the results of the studies varied, increased characteristic path length and decreased number of hubs are the most consistent findings (Dai and He, 2014). Studies that included cases with mild cognitive impairment (MCI) found that the MCI network showed similar but less extensive changes compared to AD, presenting intermediate network values between controls and AD (Yao et al., 2010). Only 3 studies have assessed whether gray matter networks are affected by the presence of Aβ pathology in cognitively healthy individuals (Oh et al., 2011; Spreng and Turner, 2013; Tijms et al., 2016), and only the most recent one (Tijms et al., 2016) used a graph-based approach. Tijms et al. investigated the link between amyloid pathology and gray-network measures in cognitively healthy individuals, revealing that lower CSF Aβ42 levels were associated with lower connectivity density, reduced clustering, and higher path length values (Tijms et al., 2016). The authors worked with single-subject brain networks, reporting correlations of various graph theory metrics with continuous CSF Aβ42.

In the present study, we aim to examine the subtle changes in the organization of structural brain networks, which may precede the onset of AD symptoms. We assessed whether amyloid pathology as inferred from CSF Aβ42/40 levels can have detectable effects on global and local connectivity measures. In a large sample of well-characterized cognitively healthy elderly controls originating from the prospective Swedish BioFINDER study, we identified those with no evidence of Aβ pathology (normal CSF Aβ42/40, n = 233) and those with CSF evidence of Aβ pathology (abnormal CSF Aβ42/40, n = 66). To our knowledge, no studies have assessed gray matter network organization in such a high number of cognitively normal subjects with abnormal Aβ42/40 ratio, comparing it to that of individuals with no evidence of amyloid pathology. We hypothesized that network changes would already be present at the asymptomatic disease stages at both the global network level and the local network level. Compared to another recent study that assessed network topology in preclinical AD (Tijms et al., 2016), our study includes a substantially larger number of cognitively normal Aβ+ participants, directly compares Aβ-positive and Aβ-negative groups and uses the CSF Aβ42/40 ratio as a biomarker of amyloid pathology. This ratio has recently shown to be more sensitive to Aβ deposition in prodromal AD than Aβ42, providing a better discrimination from other neurodegenerative disorders such as dementia with Lewy bodies and Parkinson's disease dementia (Janelidze et al., 2016). In addition, in our study, we applied a methodology that overcomes the bias introduced by the varying number of edges when comparing groups (network densities are kept fixed so that the number of connections across groups is equal) and assessed network parameters that have not been previously evaluated in preclinical AD such as the modularity, transitivity, betweenness centrality, and community structure.

2. Materials and methods

2.1. Participants

All participants gave written consent to participate in the study. Ethical approval was given by the Ethical Committee of Lund University, Lund, Sweden.

The study population stemmed from the prospective and longitudinal Swedish BioFinder study (more information available at www.biofinder.se). The cohort consisted of cognitively normal elderly participants who were eligible for inclusion if they (1) were aged ≥60 years; (2) scored 28−30 points on the Mini-Mental State Examination at the screening visit; (3) did not suffer from any subjective cognitive impairment; and (4) were fluent in Swedish. Exclusion criteria included presence of significant neurologic disease (e.g., stroke, Parkinson's disease, and multiple sclerosis), severe psychiatric disease (e.g., severe depression or psychotic syndromes), dementia, or MCI. These subjects underwent a thorough clinical assessment, including a comprehensive neuropsychological evaluation in the executive, visuospatial, language, and memory domains. A medical doctor made a global assessment of whether the individual was cognitively healthy based on the test results in relation to education and age. All subjects had a Clinical Dementia Rating scale score of 0.

For the present study, only participants with CSF analysis and a high-quality MRI scan were selected. This resulted in 233 healthy controls with normal CSF Aβ42/Aβ40 (CSF Aβ−) levels and 66 healthy controls with abnormal CSF Aβ42/Aβ40 levels. CSF Aβ42/Aβ40 ratio ≤0.1 was considered abnormal (Janelidze et al., 2016).

2.2. CSF collection and analysis

The procedure and analysis of the CSF followed the Alzheimer's Association Flow Chart for CSF biomarkers. Lumbar CSF samples were collected at the 3 centers and analyzed in accordance with a standard protocol (Blennow et al., 2010). The CSF levels of Aβ42 and Aβ40 were determined using enzyme-linked immunosorbent assay (EUROIMMUN AG, Lübeck, Germany) (Janelidze et al., 2016).

2.3. MRI acquisition

MRI acquisition was performed on a 3T Siemens TrioTim scanner. The MRI protocol included a high-resolution coronal 3D T1-weighted magnetization-prepared rapid gradient-echo volume