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Neuroimaging

Degradation in intrinsic connectivity networks across the Alzheimer's disease spectrum

Rachel Nuttall[a,b,*], Lorenzo Pasquini[b,c], Martin Scherr[b,d,e], Christian Sorg[b,c,d], for the Alzheimer's Disease Neuroimaging Initiative[1]

[a]Department of Psychology, Ludwig Maximilian University Munich, Munich, Germany
[b]TUM-Neuroimaging Center, Neuro-Kopf-Zentrum, Technische Universität München, Munich, Germany
[c]Department of Neuroradiology, Technische Universität München, Munich, Germany
[d]Department of Psychiatry, Technische Universität München, Munich, Germany
[e]Doppler Klinik, Division of Neuroradiology, Paracelsus Medical University Salzburg, Salzburg, Austria

Abstract

Introduction: Changes in intrinsic functional connectivity (iFC) have been reported at various stages of the Alzheimer's disease (AD) spectrum. We aimed to investigate such alterations over a variety of large-scale intrinsic brain networks (iBNs) across the spectrum of amyloid β positivity and uncover their relation to cognitive impairment.

Methods: Eight iBNs were defined from resting-state functional magnetic resonance imaging data. In amyloid β–positive healthy subjects, prodromal, and AD patients (N = 70), within-network iFC (intra-iFC) and between-network iFC (inter-iFC) were correlated with scores of cognitive impairment.

Results: Across all iBNs, a general degradation in intra-iFC along the scale of cognitive impairment severity was found. Only subtle changes in inter-iFC were identified.

Discussion: Across the AD spectrum, changes in iFC that are strongly related to cognitive impairment occur within an extensive variety of networks.

Keywords: Alzheimer's disease; Intrinsic brain networks; Intrinsic functional connectivity; Resting-state fMRI; Cognitive impairment

1. Introduction

Alzheimer's disease (AD) is the major cause of age-related dementia with 46.8 million people worldwide estimated to be living with dementia [1]. AD is a neurodegenerative disorder characterized by progressive amyloid β (Aβ) pathology, tau-related pathology, and cell loss [2]. In particular, Aβ pathology is characterized by progressive Aβ plaque accumulation, starting in the isocortex several years before first cognitive symptoms arise, and interacting in a complex way with both brain activity and rising tau-related pathology [3]. In the context of manifest Aβ plaques, changes in cortical activity occur, particularly in relation to slowly fluctuating ongoing (i.e., intrinsic) activity and intrinsic functional connectivity (iFC) [4–10]. Changes in

Institution of origin: Klinikum rechts der Isar, Technische Universität München, Ismaninger Strasse 22, 81675 Munich, Germany.

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*Corresponding author. Tel.: +49-89-4140-7666; Fax: +49-89-4140-4887.

E-mail address: rachelnutt3012@hotmail.com

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iFC are detectable in vivo by changes in correlated blood oxygenation level dependent (BOLD) fluctuations as measured by resting-state functional magnetic resonance imaging (rsfMRI).

In more detail, slow (<0.1 Hz) ongoing fluctuations of activity occur in the absence of a task and findings of coherence between these fluctuations across spatially distributed brain regions have led to the proposition of resting-state or so-called intrinsic brain networks (iBNs). A wide variety of primary sensory and motor, default mode, and "attentional" iBNs have been identified, which show high reproducibility [11,12]. One such iBN is the default mode network (DMN), consisting of discrete regions of the bilateral parietal, prefrontal, and temporal cortices that show coherent hemodynamic fluctuations at rest [13].

Alterations in iFC within (intra-iFC) and between (inter-iFC) iBNs have been reported at various stages across the AD spectrum. With increasing mild cognitive impairment (MCI) and dementia, both increases and decreases in intra-iFC have been reported in AD [14–16], alongside decreases in inter-iFC [14,16]. In terms of specific iBNs, iFC changes within the DMN in AD have been extensively studied, showing disruptions both preclinically in Aβ-positive healthy control subjects [6,17] and as a function of cognitive impairment [18].

However, the pattern of alterations in iFC within and between an extensive variety of iBNs across the whole AD spectrum of Aβ positivity remains unknown.

Consequently, the present study focused on three main questions: (1) How do changes in iFC within iBNs (i.e., intra-iFC) relate to cognitive impairment across the whole AD spectrum? (2) How do changes in iFC between iBNs (i.e., inter-iFC) relate to cognitive impairment across the whole AD spectrum? (3) How do these intra-iFC and inter-iFC changes relate to one another?

To test these questions, a sample (N = 161) of multimodal imaging and neuropsychological data sets from Aβ-negative, Aβ-positive preclinical, prodromal, and clinically manifest AD subjects were analyzed. Statistical analyses were restricted to Aβ-positive subjects only to restrict the analysis to subjects on an AD-related trajectory of cognitive impairment. A spatial independent component analysis (ICA) was used to estimate iFC across eight iBNs in rsfMRI data. Scores of intra-iFC and inter-iFC were correlated with scores on a continuous measure of AD-related cognitive impairment and with one another.

2. Methods

Data were retrieved from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). Launched in 2003, ADNI supports the investigation and development of treatments against the progression of AD via a $60 million 5-year partnership between various institutes and organizations. This longitudinal multisite study aims to combine various findings of clinical, genetic, imaging, and biospecimen biomarkers across the MCI and AD spectrum to work toward a cohesive understanding of AD and the development of efficacious treatment options against MCI and AD progression. For further information, see https://adni.loni.usc.edu/.

2.1. Participants

Subject data sets complete with rsfMRI, structural MRI, and F^{18}-AV-45-PET (positron emission tomography) scans were retrieved from the ADNI-GO and ADNI2 study phase databases of ADNI, reaping a starting sample size of 161 subjects. When more than one rsfMRI or structural MRI scan was available, those that were acquired within 3 months of one another and met quality control measures were chosen. Subjects whose scans were more than 3 months apart were excluded (n = 12). After visual inspection of the data, subjects were excluded because of imaging artifacts (n = 20), field-of-view cuts (n = 6), and excessive head motion parameters (n = 2) (for exact criteria see subsequently). Patients identified as Aβ negative (see Section 2.3.1 for identification criteria) were also excluded (n = 31). Thus, a high-quality sample of 90 subjects was further analyzed, representing a range of healthy control subjects and the whole spectrum of AD-related cognitive impairment: Aβ-negative healthy control subjects (HC−; n = 20), Aβ-positive healthy control subjects (HC+; n = 9), early MCI (eMCI+; n = 21) and late MCI (lMCI+; n = 18), and AD patients (AD+; n = 22). Healthy control subjects are in a preclinical stage in which there are no signs of depression, MCI, or dementia, with or without the presence of Aβ accumulation (HC+ and HC−, respectively) [19]. MCI patients present concerns of memory decline but do not surpass the threshold of functional impairment to be classified as demented and do not show impairments in other cognitive domains; hence, these subjects present amnestic MCI. The ADNI database subdivides amnestic MCI into two stages, namely eMCI and lMCI, differentiated on the basis of the severity of episodic memory impairment [20], assessed via the Logical Memory II subscale (Delayed Paragraph Recall, Paragraph A only from the Wechsler Memory Scale-Revised) [21]. Patients in the AD group meet the criteria for probable AD, as stated by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [22]. Further information on the respective inclusion criteria can be found at https://adni.loni.usc.edu/wp-content/adni2-procedures-manual.pdf.

All patients were Aβ positive, defined using a cutoff of 1.11 composite cortical standard uptake value ratio (SUVR) using the cerebellum as a reference [23] (for details see subsequently). Thus, all patients were following an AD-related dementia trajectory. See demographic information in Table 1. Further details on the ADNI guidelines in terms of clinical diagnosis and inclusion criteria can be found at http://adni.loni.usc.edu/methods/.