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Test-retest variability of resting-state networks in healthy aging and prodromal Alzheimer's disease

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ABSTRACT

In recent years, changes in resting-state networks (RSN), identified by functional magnetic resonance imaging (fMRI), have gained increasing attention as potential biomarkers and trackers of neurological disorders such as Alzheimer's disease (AD). Intersession reliability of RSN is fundamental to this approach.

In this study, we investigated the test-retest reliability of three memory related RSN (i.e., the default mode, salience, and executive control network) in 15 young, 15 healthy seniors (HS), and 15 subjects affected by mild cognitive impairment (MCI) with positive biomarkers suggestive of incipient AD (6 females each). FMRI was conducted on three separate occasions. Independent Component Analysis decomposed the resting-state data into RSNs. Comparisons of variation in functional connectivity between groups were made applying different thresholds in an explorative approach. Intersession test-retest reliability was evaluated by intraclass correlation coefficient (ICC) comparisons. To assess the effect of gray matter volume loss, motion, cerebrospinal fluid based biomarkers and the time gap between sessions on intersession variation, the former four were correlated separately with the latter.

Data showed that i) young subjects ICCs (relative to HS/MCI-subjects) had higher intersession reliability, ii) stringent statistical thresholds need to be applied to prevent false-positives, iii) both HS and MCI-subjects (relative to young) showed significantly more clusters of intersession variation in all three RSN, iv) while intersession variation was highly correlated with head motion, it was also correlated with biomarkers (especially phospho-tau), the time gap between sessions and local GMV. Results indicate that time gaps between sessions should be kept constant and that head motion must be taken into account when using RSN to assess aging and neurodegeneration. In patients with prodromal AD, re-test reliability may be increased by accouting for overall disease burden by including biomarkers of neuronal injury (especially phospho-tau) in statistical analyses. Local atrophy however, does not seem to play a major role in regards to reliability, but should be used as covariate depending on the research question.

1. Introduction

Mild cognitive impairment (MCI) is a disorder along the spectrum of normal aging and Alzheimer's disease (AD) (Petersen et al., 1999). The diagnostic entity MCI encompasses a heterogeneous group of patients ranging from subjects with mild depression to prodromal AD. All MCI subjects, but particularly those with a positive biomarker-status, have an increased probability of developing AD (Petersen et al., 2001; Grundman et al., 2004; Mitchell and Shiri-Feshki, 2009). With drug development efforts shifting from the treatment of symptomatic AD to therapeutic interventions at preclinical stages (Vellas et al., 2011; Salomone et al., 2012), early detection of individuals at risk of AD has become increasingly important.

Efforts to use resting-state (RS) functional Magnetic Resonance Imaging (fMRI) for these purposes are in progress, as RS-fMRI is a radiation-free, non-invasive method that does not require active participation of the subject. RS-fMRI reveals functionally connected but anatomically distant brain regions (Barkhof et al., 2014). These regions have consistently been classified into resting-state networks (RSN) as they represent reproducible, large-scale functional brain systems. RSN include but are not limited to the default mode network (DMN), attention network, executive control network (ECN), visual network,

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motor network, auditory-phonological network, and the salience network (SN) (Biswal et al., 1995; Hampson et al., 2002; Fox et al., 2005; Yeo et al., 2011; Buckner et al., 2013). Alterations in these RSN are thought to precede symptoms and structural changes in neurodegeneration by several years, and might allow the identification and quantification of preclinical disease stages (Jack Jr. et al., 2010; Sperling, 2011; Gomez-Ramirez and Wu, 2014).

Since functional connectivity within the DMN of MCI patients shows alterations that differ from general aging-related effects, DMN functional connectivity has become a focus of studies investigating AD-related changes (Sorg et al., 2007; Agosta et al., 2012; Cha et al., 2013). Notably, the DMN comprises the hippocampus and the precuneus, regions well-known to be involved in early stages of AD. However, the scope of RSN studies extends beyond the DMN and it has been suggested that two RSN may prove particularly suitable for assessing early AD-related changes: the salience network and the executive control network (Seeley et al., 2007, Menon and Uddin, 2010).

A reproducible and reliable baseline is a mandatory prerequisite for the use of RSN as biomarkers (Zhang et al., 2010) and trackers of treatment effects (Goekoop et al., 2004; Dickerson and Sperling, 2005). Test-retest (TRT) reliability of RSN might be, at least in part, influenced by various factors, such as physiological confounds, scanning conditions, data analysis strategy, differences in brain anatomy or gray matter volume, head motion, disease progression, cerebralspinal fluid based biomarkers, and so forth. To date, only a few studies have investigated the TRT reliability of RSN (Damoiseaux et al., 2006; Shehzad et al., 2009; Meindl et al., 2010; Zuo et al., 2010; Chou et al., 2012; Guo et al., 2012). These studies either focused on one age group or compared the TRT reliability between healthy seniors and MCI patients over a period of one year (Blautzik et al., 2013).

In this study we investigated the TRT reliability of three memory-related RSN (DMN, ECN, SN) in healthy young subjects, healthy seniors, and subjects with prodromal AD across three scanning sessions, with approximately two weeks in-between each scanning session (median 14 days, standard deviation 28 days) for each participant. We examined voxel-wise intersession variations in cortical activation patterns and specifically assessed whether gray matter volume (GMV) loss, biomarkers in cerebrospinal fluid, the time gap between acquired sessions and motion are associated with session differences observed. We expected to find i) a higher TRT reliability in young subjects relative to HS and MCI, ii) an increase in intersession variations due to gray matter volume loss and motion (Marchitelli et al., 2016) and to a lesser degree due to biomarkers and the time gap between sessions.

2. Materials and methods

2.1. Subjects

Fifteen healthy young subjects (age: 24.4 ± 2.8 years; six females), fifteen healthy seniors (HS; age: 67.3 ± 8.1 years; six females), and fifteen patients with MCI (age: 71.1 ± 6.0 years; six females) participated in the study. Healthy participants were recruited via local advertisement. MCI patients were recruited from the memory clinic of the Department of Neurology at the University Hospital Cologne. Prior to participation, informed written consent was obtained from all participants. The local ethical committee (medical faculty, University of Cologne) had approved the study. All subjects were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971) and completed a medical questionnaire to rule out neuropsychiatric diseases, with exception of amnestic deficits in MCI, as well as the intake of CNS-effective medication. To eliminate the possibility of contradictions to MRI scanning, a safety-checklist was completed.

Since MCI is a diagnostic entity that encompasses a heterogeneous group of individuals (Petersen et al., 2001), we decided to only include subjects who are in the stage of prodromal AD according to the IWG-2 criteria and Dubois et al. (2014, 2016), with at least one abnormal biomarker suggestive of AD, i.e., abnormal concentrations of amyloid β42, phospho-tau, total tau, a pathological total tau - amyloid β42 ratio > 0.52 in cerebrospinal fluid (CSF) obtained by lumbar puncture (Duits et al., 2015), or amyloid-plaque deposition assessed with positron emission tomography (PET).

Subjects underwent neuropsychological assessment including the Mini Mental Status Examination (MMSE) (Folstein et al., 1975), the Trail Making Test (TMT) for visual processing speed, executive functioning and task switching (Tombaugh, 2004; Bowie and Harvey, 2006), a test of auditory verbal learning and memory (Verbaler Lern- und Merkfähigkeitstest, VLMT) (Helmstaedter et al., 2001), a test of logical thinking, conception of space and recognition of patterns and irregularities (LPS50 +, Leistungsprüfungssystem für 50- bis 90-jährige, Subtest 7) (Horn, 1983), the Bayer Activity of Daily Living Scale (B-ADL) (Hindmarch et al., 1998), and the Hamilton Depression Rating Scale to measure subjective symptoms of depression (Hamilton, 1960).

2.2. Experimental setup

FMRI measurements were acquired on three separate occasions, with approximately two weeks in-between each scanning session (median 14 days, standard deviation 28 days) for each participant. The minimum interval between two sessions was 3 days. Each participant underwent all three imaging sessions at the same time of day. Participants were instructed to refrain from caffeine consumption before scanning. During each of these measurements, subjects were asked to lay still with their eyes closed, to think of nothing in particular and not to fall asleep. To account for the influence of fatigue and sleep, participants were monitored through a camera system and asked to retrospectively rate the degree of fatigue they had experienced during scanning on a scale from 1 (not tired) to 6 (very tired). Additionally, subjects were asked whether they had fallen asleep at any point throughout the scanning procedure. Only one MCI subject reported to have fallen asleep briefly during one session, and another was unsure whether sleep might have occurred briefly during one session. Since the periods of sleep were brief and had not been detected by the camera-based monitoring, these subjects were not excluded from further analyses.

2.3. Image acquisition

All functional and anatomical imaging was performed using a TRIO 3.0 Tesla whole-body scanner (Siemens, Erlangen, Germany) equipped with a standard head coil for radiofrequency transmission and signal reception. Sequence parameters were: T2*-weighted echoplanar images (EPI) with BOLD contrast, echo time (TE) = 30 ms, repetition time (TR) = 2430 ms, flip angle = 90°, slice thickness 3.0 mm, interslice gap 0.3 mm, field of view (FoV) = 200 mm, matrix size 64 × 64, in-plane resolution = 3.0 mm × 3.0 mm. 40 axial slices per volume, capturing the brain from vertex to cerebellum were acquired sequentially. 155 volumes were acquired and the first 4 functional volumes of the fMRI time series of each session were discarded from analysis to account for T1 saturation effects. As a result, 151 images were subjected to further analysis. Total acquisition time amounted to approximately 6.3 min per session. The slices were positioned at an angle between a line crossing the anterior and posterior commissure (AC-PC line) and a line paralleling the medial tentorium cerebelli. This resulted in a slice orientation previously proposed to reduce susceptibility artifacts in the medial temporal lobe (Deichmann et al., 2003; Weiskopf et al., 2006). For anatomical reference and to control for gray matter density, a high-resolution T1 image was obtained for each subject using a three-dimensional magnetization-prepared, rapid acquisition gradient echo sequence (MP-RAGE). To control for white matter lesions and macroangiopathy, T2-weighted FLAIR and Time of Flight measurements were performed. None of these or any other imaging procedures preceded the RS fMRI scans.