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Changes in resting connectivity with age: a simultaneous electroencephalogram and functional magnetic resonance imaging investigation

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ABSTRACT

Resting fluctuations in the blood oxygenation level-dependent signal have attracted considerable interest for their sensitivity to pathological brain processes. However, these analyses are susceptible to confound by nonneural physiological factors such as vasculature, breathing, and head movement which is a concern when investigating elderly or pathological groups. Here, we used simultaneous electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI) (EEG/fMRI) to constrain the analysis of resting state networks (RSNs) and identify aging differences. Four of 26 RSNs showed fMRI and EEG/fMRI group differences; anterior default-mode network, left frontal-parietal network, bilateral middle frontal, and postcentral gyri. Seven RSNs showed only EEG/fMRI differences suggesting the combination of these 2 methods might be more sensitive to age-related neural changes than fMRI alone. Five RSNs showed only fMRI differences and might reflect nonneural group differences. Activity within some EEG/fMRI RSNs was better explained by neuropsychological measures (Mini Mental State Examination and Stroop) than age. These results support previous studies suggesting that age-related changes in specific RSNs are neural in origin, and show that changes in some RSNs relate better to elderly cognition than age.

1. Introduction

Spontaneous, or resting state, fluctuations in the blood oxygenation level-dependent (BOLD) signal are providing useful insights into functional connectivity between brain regions, and how such connectivity is affected by various pathologies. A characteristic set of coactivating functional systems, typically referred to as resting state networks (RSNs), have been consistently identified in the brain across multiple studies (Allen et al., 2011; Biswal et al., 2010), and clinical populations (Fox and Greicius, 2010; Zhang and Raichle, 2010). These RSNs include basic sensory networks involved in visual, auditory, or sensorimotor processing, or more functionally complex networks such as the default-mode network (DMN) and frontal-parietal attention network (FPN). Numerous resting state studies have been conducted on aging populations and robust differences have been reported, particularly within the DMN (Buckner et al., 2008). However, the interpretation of RSN differences in aging and clinical research is complicated by the fact that the BOLD response is susceptible to nonneural factors including head movement, respiration, and vasculature. The present study explores the utility of electroencephalogram (EEG)-informed functional magnetic resonance imaging (fMRI) to isolate RSN differences that are truly neural in original.

One of the most robust and well-replicated findings in resting state studies of aging is that DMN connectivity decreases with age, an effect that has been observed at rest (Allen et al., 2011; Biswal et al., 2010; Damoiseaux et al., 2008; Lustig et al., 2003) and during task performance (Andrews-Hanna et al., 2007; Grady et al., 2010). Andrews-Hanna et al. (2007) showed that age-related decreases in DMN functional connectivity positively correlated with reduced structural integrity (decreased white matter [WM] integrity in the cingulum) and task performance (semantic memory task). Rather than focusing on the DMN, Damoiseaux et al. (2008) used independent component analysis (ICA) to investigate age-related changes in 13 RSNs common to young and old participants including basic sensory regions and the DMN and FPN. Damoiseaux et al. (2008) found that only the DMN showed a significant aging effect, and unlike Andrews-Hanna et al. (2007) this ICA-based approach did not yield significant differences in the left or right FPN. DMN differences in Damoiseaux et al. (2008) withstood additional correction for gray matter (GM) volume, suggesting a functional rather than a structural deficit, and

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correlated with performance on the trail making test. A number of studies have shed light on the likely origins of DMN activity changes by demonstrating that the structural connections between nodes of the DMN decrease with age (Andrews-Hanna et al., 2007; Damoiseaux et al., 2009; Teipel et al., 2010).

The robust nature of these aging effects has been further underlined using large cohorts of resting state data to increase statistical power. Biswal et al. (2010) collected a sample of 1093 participants and demonstrated decreases in posterior regions of the DMN and left FPN with age. With a sample of 603 participants, Allen et al. (2011) showed that all 28 RSNs within their study were significantly modulated by age (all decreasing with age except for the basal ganglia and medial portion of the superior frontal gyrus which showed increases with age). Allen et al. (2011) also reported the first investigation of the spectral properties of RSN time courses in aging, and the correlations between RSNs. These additional RSN measures (BOLD spectral power and functional network connectivity [FNC]) were equally sensitive to aging because all 28 RSNs show a decrease in spectral power (0.01–0.15 Hz) with age, and connectivity between most RSNs decreased with age.

Though there is general consensus within the literature that connectivity in the DMN decreases with age, the results for other RSNs such as the FPN vary depending on the sample size and the analytical approach taken. Aside from the variability of results for certain RSNs another cause for concern is that RSNs might be susceptible to nonneural factors such as vasculature, breathing, or head movement (Cole et al., 2010; Iannetti and Wise, 2007; Kelly et al., 2012). For example, it is well established that age-related differences in vasculature lead to differences in the hemodynamic response function that can produce false positive results in fMRI studies (D'Esposito et al., 1999; Kannurpatti et al., 2010). It has also been demonstrated that variation in breathing can produce signal variations in regions with high blood volume such as GM (Birn et al., 2006; Wise et al., 2004). Although it has been repeatedly shown that connectivity in the DMN decreases with age, Birn et al. (2006) have also shown that the topography of voxels correlated with respiration variation-induced signal strongly resembles the DMN. Therefore age-related differences in respiration variation, and vasculature, could produce nonneural differences in RSNs. A third confounding variable is head movement. Two recent studies have suggested that differences in resting connectivity, particularly within the DMN and FPN, are partially because of head movement (Power et al., 2012; Van Dijk et al., 2012). Considering that head movement has been shown to differ in studies of aging (Allen et al., 2011; D'Esposito et al., 1999) it is important to ascertain whether differences in head movement are driving differences in RSNs.

All of these potential confounds can be addressed to some extent using multi-modal imaging, specifically the fusion of simultaneously recorded EEG and fMRI data. EEG provides a direct measure of postsynaptic neural activity and its combination with fMRI will further support the suggestion that differences in RSNs are neural in origin and not a by-product of vascular or breathing differences in populations. Unfortunately, EEG-informed fMRI is not immune to head movement contamination (Jansen et al., 2012; Moosmann et al., 2009) but steps can be taken to reduce the effect of this confound during the analysis (these procedures are discussed in detail in section 2. Methods).

For the first time we use simultaneous EEG and fMRI (EEG/fMRI) to investigate differences in RSNs that occur with healthy aging. We begin by analyzing EEG and fMRI data separately to replicate previous findings from the literature such as reduced alpha power with age (Babiloni et al., 2006a; Klimesch, 1999) and reduced DMN activity (Allen et al., 2011; Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Lustig et al., 2003). We then use EEG-informed fMRI to determine whether resting state differences are common to both modalities and thus likely to be neural in origin. Finally we correlate changes in RSNs validated using EEG-informed fMRI with changes in neuropsychological variables to better understand how aging effects specific cognitive domains through reduced functional connectivity within and between RSNs.

2. Methods

2.1. Participants

Fifteen young (18–28 years old; mean age, 23.4 ± 3.3 years) and 27 elderly (65–78 years old; mean age, 71 ± 4.49 years) right handed, sex-matched participants were included in this study (see Table 1 for demographic details). Participants gave written informed consent before the study which was approved by the Trinity College Dublin School of Psychology Ethics Committee. On a day separate from the EEG/fMRI testing (elderly group: 163.43 ± 118 days; young group: 161 ± 81 days), participants also underwent a neuropsychological battery consisting of the Mini Mental State Examination (MMSE; Folstein et al., 1975), the National Adult Reading Test (NART; estimate of intelligence; Nelson, 1982), the Stroop test, category fluency (animal), the Logical Memory subtest of the Wechsler Memory Scale III (WMS; Weschler, 1998), and the Hospital Anxiety and Depression Scale (Zigmond and Sims, 1983). Participants who scored more than 8 on either the anxiety or depression subscales of the Hospital Anxiety and Depression Scale were excluded from the study.

Participants were not taking any psychiatric or neurological medications at the time of testing.

2.2. EEG/fMRI acquisition

Participants lay supine in a magnetic resonance imaging (MRI) scanner (Philips 3T Achieva MRI Scanner, Trinity College Dublin) viewing visual stimuli in a mirror positioned above their face. Stimuli were presented using Presentation software v14.2 (Neurobehavioral Systems, Inc). EEG recordings were acquired with a 32-channel magnetic resonance-compatible BrainAmp system (Brainproducts, Munich, Germany). Thirty-three EEG electrodes were placed on the scalp, including the reference electrode positioned at FCz and the ground electrode placed at position AFz. One

Table 1
Participant demographic characteristics

Characteristic	Old ($n = 27$)	Young ($n = 15$)	t	p
Age (y)	71 (0.86)	23.40 (0.86)	−35.86	**<0.001**
Sex	15/27 female	4/15 female	−1.83	0.075
Neuropsychology				
Nart (Z score)	1.32 (0.7)	0.95 (0.12)	−2.76	**0.009**
Logical memory (Z score)	0.66 (0.18)	0.42 (0.3)	−0.7	0.49
MMSE	28.3 (0.21)	29.18 (0.26)	2.43	**0.02**
Animal fluency	45.70 (1.55)	59.45 (1.81)	5.09	**<0.001**
Stroop (T score)	21.33 (0.94)	25.73 (2.69)	1.96	0.058
Structural				
Gray matter (mL)	576.96 (9.09)	664.84 (10.19)	6.1	**<0.001**
White matter (mL)	519.95 (10.09)	539.52 (10.31)	1.25	0.217
Cerebrospinal fluid (mL)	295.19 (7.54)	265.67 (8.48)	−2.47	**0.018**
Total intracranial volume (mL)	1392.1 (20.67)	1470.04 (20.87)	2.36	**0.023**
Head movement				
Translation (mm)	0.087 (0.0074)	0.049 (0.0043)	−3.61	**0.001**
Rotation (radians)	0.0005 (0.00003)	0.0004 (0.00003)	−3.57	**0.001**

Mean values reported, standard error in parentheses. Negative t value indicates old > young. Significant p values are shown in bold.
Key: MMSE, Mini Mental State Examination.