



## EEG–BOLD correlations during (post-)adolescent brain maturation

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### ABSTRACT

The transition from adolescence to adulthood is a critical stage in the human lifespan during which the brain still undergoes substantial structural and functional change. The changing frequency composition of the resting state EEG reflects maturation of brain function. This study investigated (post)adolescent brain maturation captured by two independently but simultaneously recorded neuronal signals: EEG and fMRI. Data were collected in a 20 min eyes-open/eyes-closed resting state paradigm. EEG, fMRI–BOLD signal and EEG–BOLD correlations were compared between groups of adults, age 25 ( $n = 18$ ), and adolescents, age 15 ( $n = 18$ ). A typical developmental decrease of low-frequency EEG power was observed even at this late stage of brain maturation. Frequency and condition specific EEG–fMRI correlations proved robust for multiple brain regions. However, no consistent change in the EEG–BOLD correlations was identified that would correspond to the neuronal maturation captured by the EEG. This result indicates that the EEG–BOLD correlation measures a distinct aspect of neurophysiological activity that presumably matures earlier, since it is less sensitive to late maturation than the neuronal activity captured by low-frequency EEG.

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### Introduction

Adolescence and the transition into adulthood are critical stages in the human lifespan. The typical emergence of some major mental illnesses during adolescence further indicates fundamental maturational reorganization (Paus et al., 2008) and stresses the importance of understanding late brain maturation. Since the major developmental changes occur during infancy and childhood, specific research on late maturation has often been neglected. However, late maturation, during and after adolescence, has attracted increasing attention in recent years (Blakemore and Choudhury, 2006; Sisk and Foster, 2004). A growing body of evidence suggests that there are still substantial structural (Paus, 2005) and functional (Luna et al., 2010) changes in the brain during this time. Gray matter loss and white

matter increase in adolescence were found to be consistent with the basic processes of neuronal maturation, i.e. synaptic pruning and myelination (Giedd et al., 1999; Gogtay et al., 2004; Sowell et al., 2001). Apart from these structural aspects, executive functioning commonly associated with changes in the prefrontal cortex undergoes late brain maturation (Luna et al., 2010; Stevens, 2009). Recent brain imaging research has also investigated brain function at rest (where no stimulus or task is involved) to identify resting state networks (RSNs) of functional connectivity (Beckmann et al., 2005; Damoiseaux et al., 2006; van den Heuvel and Hulshoff Pol, 2010). In terms of the development of functional connectivity, basic principles such as successive neural segregation and hierarchical organization have been described (Fair et al., 2007; Stevens, 2009).

Converging evidence for late brain maturation comes from electroencephalogram (EEG) research. The EEG noninvasively measures electrical mass activity of neurons. An advantage over other functional methods such as fMRI is that the EEG measures neuronal activity directly and in absolute terms, i.e. in physical units (microvolts,  $\mu\text{V}$ ). Consequently EEG research has focused on resting state brain functioning since its discovery (Berger, 1929) long before the advent of fMRI. The resting EEG is typically characterized by oscillations of different amplitudes and frequencies. One of the major findings since the beginning of resting EEG research is that children's EEG is dominated by slower rhythms which diminish with further brain maturation (Boord et al., 2007; Clarke et al., 2001; Dustman et al., 1999; Gasser et al., 1988; Gibbs and Knott, 1949; John et al., 1980; Matousek and Petersen, 1973; Wackermann and

**Abbreviations:** EEG, electroencephalogram; (MEG), magnetoencephalography; fMRI, functional magnetic resonance imaging; BOLD, blood oxygen-level dependency; RSNs, resting state networks; ICA, independent component analysis; ECG, electrocardiogram; EPI, echo planar imaging; FOV, field of vision; TR, time of repetition; TE, time of echo; GFP, global field power; BCG, ballistocardiogram; FFT, fast Fourier transformation; GSP, global spectral power; SPM, statistical parametric mapping; MNI, Montreal neurological institute; FWHM, full width at half maximum; HRF, hemodynamic response function, GLM, general linear model; ANOVA, analysis of variance; FWE, family wise error rate; ROI, region of interest; DMN, default mode network; LFP, local field potentials.

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Matousek, 1998). This effect also extends to sleep (Campbell and Feinberg, 2009; Feinberg and Campbell, 2010), and has been suspected to mirror the development of higher cognitive functions (Case, 1992; Thatcher, 1994), and deviations from normal oscillatory patterns has been associated with lagged or abnormal brain maturation (John et al., 1980). That these developmental amplitude reductions are frequency specific, and are also found with magnetoencephalography (MEG) which is insensitive to changes in physical properties such as bone conductivity (Puligheddu et al., 2005; Takeshita et al., 2002), corroborates their neurodevelopmental nature. Again, very few studies specifically focused on late maturational changes (Whitford et al., 2007) although many studies investigated (or included) EEG changes during childhood, when most dramatic changes occur. Typically, linear or curvilinear regression analyses are used to assess developmental effects from childhood to adulthood. Overall age-related changes are well captured using such models but the drawback is a lack of sensitivity to changes during specific, short periods. In particular, (post-)adolescent changes are rarely treated as a maturational step of its own and thus tend to be obscured by stronger developmental effects in childhood. For example, several scientists (Boord et al., 2007; Gasser et al., 1988; Whitford et al., 2007) found low-frequency EEG amplitude reduction associated with late maturation, but the curvilinear developmental regression effects appear to be driven mainly by the younger subjects. The specific contribution of the presumably more subtle changes due to late maturation remains unclear unless studied in a smaller age range confined to the specific (post-)adolescent transition from adolescence to adulthood using regression or age group contrasts. Whitford et al. suggested gray matter loss or synaptic pruning as a candidate to explain developmental EEG amplitude reduction (Whitford et al., 2007). Despite these structural changes that parallel the changes in EEG, the question remains whether there are also functional changes related to the EEG amplitude reduction with increasing age.

In recent years, simultaneous EEG and fMRI has allowed to link electrophysiological scalp-recorded activity more directly to cortical and subcortical regions. The exact physiological relationship between EEG amplitudes and the fMRI blood oxygen-level dependency (BOLD) signal remains unclear (Laufs, 2008). However, the two signals co-vary during rest in terms of their temporal fluctuation (following appropriate convolution to account for the lag and the lower frequency range of the BOLD signal), indicating that they are functionally coupled. Accordingly, the term coupling as used here does not describe the physiological mechanism underlying their coupling, but the correlation reflecting the statistical similarity between their (convolved) time courses. Research groups have repeatedly verified a thalamocortical circuit associated with alpha (8–13 Hz) oscillations (de Munck et al., 2007; Difrancesco et al., 2008; Feige et al., 2005; Goldman et al., 2002; Goncalves et al., 2006; Moosmann et al., 2003; Tyvaert et al., 2008). Furthermore, Scheeringa and colleagues found the so-called default mode network (Raichle et al., 2001; Raichle and Snyder, 2007) to be (inversely) correlated with frontal midline theta power (Scheeringa et al., 2008). Other authors found that different EEG rhythms reflect different functional networks (Laufs et al., 2006; Laufs et al., 2003b; Mantini et al., 2007). A consistent finding of concurrent EEG–fMRI studies is that at least for the lower frequencies, EEG power is inversely related to the BOLD signal, indicating that these EEG signals become stronger with decreased neuronal activity in associated brain regions. To our knowledge, research on resting state using simultaneous EEG–fMRI has so far been limited to healthy adults. The coupling of EEG rhythms to the BOLD signal has not been studied in developmental or clinical settings. Furthermore, little is known about the coupling during eyes-open resting state. Although eyes-open/eyes-closed protocols were used in prior EEG–fMRI resting state studies (Ben-Simon et al., 2008; Feige et al., 2005; Henning et al., 2006; Yang et al., 2009) (mainly to induce alpha modulation), none of these studies analyzed the eyes-open condition separately except for the work by Scheeringa et al. (Scheeringa et al., 2008) addressing eyes-open-theta

coupling. Also, most of the previous studies exploring the EEG–BOLD coupling during rest were limited to specific components of the EEG such as eyes-closed occipital alpha or eyes-open frontal midline theta power, using selected electrode sites or ICA components. A comprehensive study of resting state EEG–BOLD coupling covering the common spectral frequency bands and resting states has not yet been performed. Such a study is important, because the profile formed by different EEG rhythms is characteristic of different brain states and brain functions, and because eyes-open and eyes-closed states differ substantially in levels of arousal and EEG (Barry et al., 2007; Berger, 1929; Bianciardi et al., 2009; Marx et al., 2004; Marx et al., 2003) as well as in fMRI (Bianciardi et al., 2009; Marx et al., 2004; Marx et al., 2003).

The aim of this study was to investigate late maturation of the brain's resting state using simultaneous EEG–fMRI. In particular, we asked whether changes in EEG–BOLD coupling parallel developmental EEG amplitude decreases. To investigate this question we compare EEG, fMRI and EEG–BOLD coupling differences between adults and adolescents. According to the literature we expected that adolescents have stronger EEG activity, especially in lower frequencies, although at this age the effect was expected to be subtle. We hypothesized that such increased EEG activity would reflect a distinct immature resting state network, and show coupling to different brain regions, or differ in coupling strength, rather than a constant coupling as expected for simple amplitude scaling of the EEG- or BOLD-time series. Although differences were mostly expected in lower frequency bands, we included faster oscillations for comparison. Both eyes-open and eyes-closed conditions were included to provide a comprehensive picture of EEG–BOLD coupling and its late development during common resting states.

## Methods

### Participants

Two sex matched groups participated in this study. The 18 adults (mean age  $24.9 \pm 3.8$  years, 8 males) were recruited by university billboard ads and 18 adolescents (mean age  $15.4 \pm 1.1$  years, 8 males) were recruited in school classes by approaching their teachers. All participants met the MRI safety standards, were healthy with no history of medical or psychiatric disease, and had normal or corrected to normal vision. All were right-hand dominant as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). All participants, as well as the children's parents, gave written informed consent prior to the investigation. The study was approved by the local ethics committee and was conducted in accordance with the guidelines determined in the Helsinki Declaration.

### Procedure

After EEG preparation, participants were introduced to the nature of EEG signals and artifacts produced by movement and muscle tension. EEG and fMRI was recorded simultaneously in two 10 min resting state sessions with a 16 min working memory test (not reported here) in between. Each session consisted of alternating eyes-open (EO) and eyes-closed (EC) blocks of 2.5 min duration. One session started with eyes-open (EO–EC–EO–EC) and one with eyes-closed (EC–EO–EC–EO). The order of the two sessions was counterbalanced across participants by group and sex. A video beamer outside the scanner room projected onto a screen placed in front of the MR table. A mirror mounted on the head coil enabled participants to see through the bore onto the screen. In the eyes-open blocks a fixation star was presented on the screen, and at the end an instruction was given to close the eyes. The instruction to open the eyes after an eyes-closed block was given by a somatosensory stimulus on the left index finger via a pneumatic device. Short stimulation pulses were given already prior to scanning, to prevent subjects from any knee-jerk movements. Participants were instructed to follow the eyes-open/eyes-closed instruction, relax and refrain from any

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