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Maturation trajectories of cortical resting-state networks depend on the mediating frequency band

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ABSTRACT

The functional significance of resting state networks and their abnormal manifestations in psychiatric disorders are firmly established, as is the importance of the cortical rhythms in mediating these networks. Resting state networks are known to undergo substantial reorganization from childhood to adulthood, but whether distinct cortical rhythms, which are generated by separable neural mechanisms and are often manifested abnormally in psychiatric conditions, mediate maturation differentially, remains unknown. Using magnetoencephalography (MEG) to map frequency band specific maturation of resting state networks from age 7 to 29 in 162 participants (31 independent), we found significant changes with age in networks mediated by the beta (13–30 Hz) and gamma (31–80 Hz) bands. More specifically, gamma band mediated networks followed an expected asymptotic trajectory, but beta band mediated networks followed a linear trajectory. Network integration increased with age in gamma band mediated networks, while local segregation increased with age in beta band mediated networks. Spatially, the hubs that changed in importance with age in the beta band mediated networks had relatively little overlap with those that showed the greatest changes in the gamma band mediated networks. These findings are relevant for our understanding of the neural mechanisms of cortical maturation, in both typical and atypical development.

Introduction

Synchronous neuronal activity in the brain gives rise to rhythms, that are known to be functionally significant. These rhythms are commonly divided into five fundamental frequency bands, most commonly classified as delta (1–2 Hz), theta (3–7 Hz), alpha (8–12 Hz), beta (13–30 Hz), and gamma (31–80 Hz) (Buzsáki, 2006). One of the hypothesized roles of these rhythms is in forming neuronal ensembles, or networks, via local and longer-range synchronization, across spatially distributed regions (Fries, 2005, 2015; Siegel et al., 2012; Bastos et al., 2015). Brain networks that emerge in the absence of any directive task or stimulus, referred to as resting state networks (Raichle et al., 2001; Raichle, 2015),

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have attracted particular interest due to their consistency across and within individuals. Abnormalities in these networks are also emerging as a hallmark of psychiatric and developmental disorders (Broyd et al., 2009; Toussaint et al., 2014; Kitzbichler et al., 2015), further underscoring their functional significance. While resting state networks have been studied extensively using fcMRI (functional connectivity MRI), a technique that relies on the slow hemodynamic signal and thus has a maximal temporal resolution of about 1 Hz, studies using high temporal resolution magnetoencephalography (MEG), have confirmed that the five fundamental faster rhythms mediate these networks in non-overlapping patterns (de Pasquale et al., 2010; Hipp et al., 2012).

As part of understanding the function of resting state networks in general, and their role in cognitive development and neurodevelopmental disorders in particular, it is important to map their maturational trajectories, from childhood to adulthood. To date, our knowledge of maturational changes in macro-scale functional networks in the developing brain is largely based on task-free fcMRI studies. Several such studies have shown developmental changes in resting state brain networks, where regions associated with separate networks become connected while closely linked local subnetworks lose some of their connections with maturation (Dosenbach et al., 2010; Sato et al., 2014, 2015). Most of these studies have concluded that network integration, how well different components of the network are connected, increases with maturation, while network segregation, the differentiation of the network into modules, or clusters, decreases with maturation. The spatial distribution of hubs, the most highly connected brain regions, also changes with maturation. Another feature examined in prior studies is the small-world property of brain networks. Small world networks optimize the balance between local and global efficiency. fcMRI studies have not documented a change in the small world property of brain networks with maturation from childhood, around age 7, to adulthood, around age 31 (Fair et al., 2009). Network resilience, a measure of the robustness of the network as hubs are removed, which has been used to assess robustness in psychiatric disorders (Lo et al., 2015), has been shown to be age dependent in infants (Gao et al., 2011), but age dependency through maturation has not been studied. It has also been shown that the association between global graph metrics characterizing network properties and the ages of the participants follows an asymptotic growth curve (Dosenbach et al., 2010).

While fMRI studies have greatly increased our understanding of the development of resting state networks from childhood to adulthood, the relative temporal coarseness of fcMRI makes it impossible to differentiate maturational trajectories by frequency bands (Hipp and Siegel, 2015). Mapping the contributions of distinct frequency bands to maturational trajectories is critical because these rhythms are associated with distinct neurophysiological generators (Uhlhaas et al., 2008; Ronnqvist et al., 2013), have been mapped to a multitude of cognitive functions (Harris and Gordon, 2015), are known to themselves change in power and phase synchrony with maturation (Uhlhaas et al., 2009, 2010).

To better understand the contribution of individual rhythms to network maturation, we used MEG, which measures magnetic fields associated with neural currents with millisecond time resolution, and has a spatial resolution on the order of a centimeter (Lin et al., 2006a). We chose to use graph theory with connectivity measured using envelope correlations (Hipp et al., 2012) as the core metric, to analyze cortical resting state (relaxed fixation) MEG signals from 131 individuals (64 females), ages 7 to 29, in each of the five fundamental frequency bands. We focused on five well-studied graph theory metrics because the approach is well-suited for studying global network properties also in the functional domain (Bullmore and Sporns, 2009, 2012; Rubinov and Sporns, 2010; Misic et al., 2016; Bassett and Sporns, 2017). The results were then validated using similar data from 31 individuals (16 females, ages 21–28) from an independent early adulthood resting state data set (Niso et al., 2015). The full distribution of participants is shown in Fig. S1 in SM. Lastly, to determine the relevance of these graph metrics to the maturation of resting state networks within each frequency band, we used machine learning to quantify the extent to which the MEG derived graph metrics can be used to predict age, similarly to a prior resting state networks study that used fMRI data (Dosenbach et al., 2010). We then assessed whether the data from the independent dataset fit on the same curves.

Materials and methods

The analysis stream we followed is illustrated in Fig. 1.

Experimental paradigm

The resting state paradigm consisted of a red fixation cross at the center of the screen, presented for 5 min continuously, while participants were seated and instructed to fixate on the cross. The fixation stimulus was generated and presented using the psychophysics toolbox (Brainard and Vision, 1997; Pelli, 1997), and projected through an opening in the wall onto a back-projection screen placed 100 cm in front of the participant, inside a magnetically shielded room.

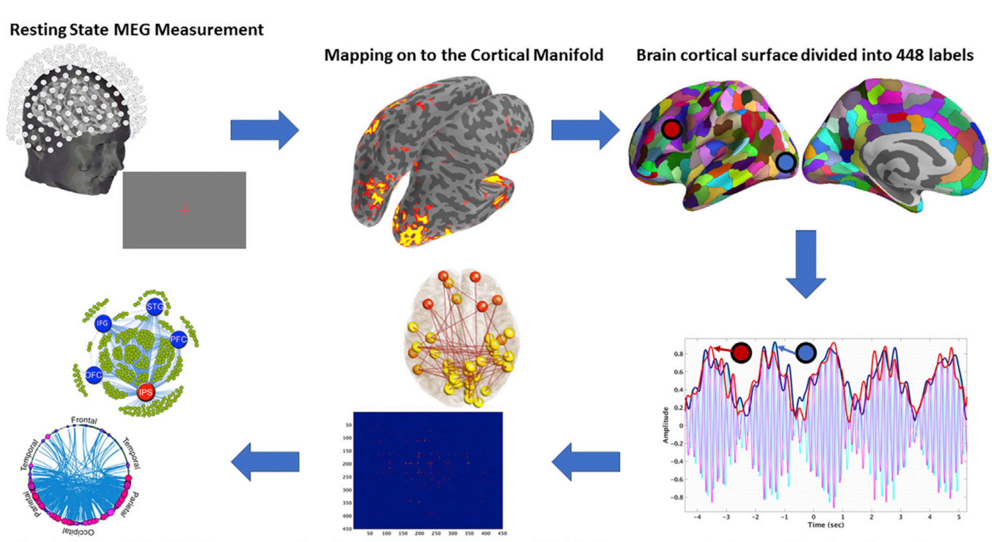

Fig. 1. Schematic illustration of pipeline. From top left in a clockwise direction: Resting state data are acquired using MEG, and then mapped to the cortical surface. The surface is then divided into regions (parcellated), and envelopes are calculated for each frequency band, in each region. The connectivity between the regions is then computed from the envelopes, and, finally, connectivity metrics are derived.