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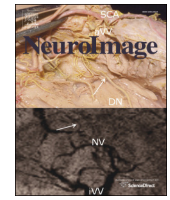

Functional brain network organisation of children between 2 and 5 years derived from reconstructed activity of cortical sources of high-density EEG recordings

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ABSTRACT

There is increasing interest in applying connectivity analysis to brain measures (Rubinov and Sporns, 2010), but most studies have relied on fMRI, which substantially limits the participant groups and numbers that can be studied. High-density EEG recordings offer a comparatively inexpensive easy-to-use alternative, but require channel-level connectivity analysis which currently lacks a common analytic framework and is very limited in spatial resolution. To address this problem, we have developed a new technique for studies of network development that overcomes the spatial constraint and obtains functional networks of cortical areas by using EEG source reconstruction with age-matched average MRI templates (He et al., 1999). In contrast to previously reported channel-level analysis, this approach provides information about the cortical areas most likely to be involved in the network as well as their functional relationship (Babiloni et al., 2005; De Vico Fallani et al., 2007).
In this study, we applied source reconstruction with age-matched templates to task-free high-density EEG recordings in typically-developing children between 2 and 6 years of age (O'Reilly, 2012). Graph theory was then applied to the association strengths of 68 cortical regions of interest based on the Desikan–Killiany atlas. We found linear increases of mean node degree, mean clustering coefficient and maximum betweenness centrality between 2 years and 6 years of age. Characteristic path length was negatively correlated with age. The correlation of the network measures with age indicates network development towards more closely integrated networks similar to reports from other imaging modalities (Fair et al., 2008; Power et al., 2010). We also applied eigenvalue decomposition to obtain functional modules (Clayden et al., 2013). Connection strength within these modules did not change with age, and the modules resembled hub networks previously described for MRI (Hagmann et al., 2010; Power et al., 2010). The high temporal resolution of EEG additionally allowed us to distinguish between frequency bands potentially reflecting dynamic coupling between different neural oscillators. Generally, network parameters were similar for networks based on different frequency bands, but frequency band did emerge as a significant factor for clustering coefficient and characteristic path length. In conclusion, the current analysis shows that source reconstruction of high-density EEG recordings with appropriate head models offers a valuable tool for estimating network parameters in studies of brain development. The findings replicate the pattern of closer functional integration over development described for other imaging modalities (Fair et al., 2008; Power et al., 2010).

Introduction

Recent advances in brain imaging and analysis highlight the importance of interplay between brain regions. Rather than investigating the role of individual brain regions for specific functions, brain connectivity analysis describes the dynamic engagement of multiple brain regions (brain 'networks'). The specific regions identified using various imaging methods differ, probably because the physiological processes underlying different imaging modalities are not the same (Darvas et al., 2004; He et al., 2011). However, graph theory provides a common mathematical framework to compare the network architecture (Rubinov and Sporns, 2010), even when the anatomical regions are not identical. The network architecture was shown to be similar across different scales (Van den Heuvel et al., 2008; Watts and Strogatz, 1998). In this article, we describe a method that allows characterisation of functional cortical networks from high-density EEG recordings in children from 2 years of age.

Functional connectivity measures of the brain can in principle be derived from all functional imaging data such as fMRI, EEG, MEG, and near-infrared spectroscopy (NIRS), but the current literature is

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mostly based on findings from fMRI. A consistent finding in the functional connectivity MRI (fcMRI) literature is the presence of an interconnected network comprising the medial prefrontal cortex, the posterior cingulate, the inferior parietal lobe, the lateral temporal cortex and the hippocampal formation during the resting state (Cherkassky et al., 2006; Fox and Raichle, 2007; Shulman et al., 1997). This network was named the default mode network (DMN). It is thought to be one of the three major networks that are reciprocally regulated (Menon, 2011). The great advantage of the DMN is that it can be investigated even if the participant is not engaged in a task, which is particularly useful in groups with limited cooperative ability like children or developmentally delayed patients. Further, patients and controls can be compared without the assumption that the groups use similar strategies for solving a task. Due to the interplay between functional networks, the characterisation of one network provides an impression of overall functional integrity. Assessment of the resting-state functional connectivity has been widely used to characterise brain development and pathophysiology.

The development of resting-state functional connectivity has been investigated with various techniques. Homae et al. report the development of functional networks in neonates and infants of up to 6 months of age using NIRS (Homae et al., 2010). They collected NIRS data while the children were asleep and calculated correlations between the time series of the channels. They reported an increase in correlation between channels in posterior regions and a decrease in frontal regions. Similarly, Thatcher and colleagues used EEG coherence to investigate the development of cortical functional connectivity in a large sample of age groups between 2 months and 16 years (Thatcher et al., 2008). They report stronger coherences with age, increased anterior–posterior connections and a decrease in overall coherence between electrodes with longer distances (Barry et al., 2004). This is in line with functional connectivity analysis of fMRI data reported by Fair and colleagues that compared the rs-fcMRI architecture of school-age children with adults. The authors found that 7 to 9 year old children display little functional connectivity between the mPFC and posterior cingulate and parietal regions compared to adults. These areas appear highly integrated in adults. In contrast, there is a comparable degree of interhemispheric connections between homotopic regions in both children and adults, e.g. parahippocampal and superior frontal regions. A statistical comparison of connectivity between children and adults shows that the most pronounced differences are generally found in anterior-to-posterior connections. The decrease in correlation between regions is likely to reflect segregation of sub-networks that subserve different functions and integration of areas that mediate the same function (Thatcher et al., 2008). Increased connectivity between regions that are spatially segregated is likely to reflect functional integration (Uhlhaas et al., 2009; Uhlhaas et al., 2010).

The heavy reliance on fMRI to study development of functional connectivity may be due to limitations in the alternative tools. NIRS has been applied to study development of functional networks in sleeping neonates and infants of up to 6 months of age (Homae et al., 2010). However, as NIRS relies on light penetrating through the skull it is limited to infants and not suitable to study the full span of development. MEG offers excellent time and spatial resolution. However, magnetometers are expensive and not widely available. Further, MEG is less sensitive to deep or radially oriented sources (Michel and Murray, 2011). Additionally, the head coils used in magnetometers have a fixed size optimised for adults limiting their use for developmental studies. While these factors may have biased researchers towards fMRI, it also has limitations as very young children often require general anaesthesia or sedation for MRI. Further, MRI is costly and requires dedicated staff. Further, fMRI and NIRS measure differences in properties of oxygenated and de-oxygenated haemoglobin. The relationship between the BOLD signal and neural activity is indirect (Logothetis, 2008; Palmer, 2010) and BOLD response is temporally limited to slow fluctuation.

In contrast to fMRI, MEG, and NIRS, high-density EEG recordings provide several advantages for use in young children as they are not as sensitive to movement artefact, can be obtained across a wide range of age and ability levels, and are generally less costly. EEG directly measures brain electrical activity on the surface of the skull. Most EEG activity is generated by membrane potential fluctuations of cortical pyramidal cells perpendicular to the skull (Buzsàki et al., 2012). The excellent temporal resolution of the EEG, also allows the different physiological processes thought to manifest in different frequency bands to be distinguished. Oscillations in the lower part of the EEG power spectrum are associated with changes in membrane potential (Miller, 2007), whereas fast oscillations (>25 Hz) are linked to local field potentials (Buzsàki et al., 2012; Whittingstall and Logothetis, 2009). Generally, it is reported that the connectivity maps derived from different frequency bands are very similar (Barry et al., 2004; Murias et al., 2007) reflecting similar architectural constraints at different physiological levels (Bullmore and Sporns, 2009; Van den Heuvel et al., 2008). In summary, high-density recordings of EEG are inexpensive, easy to obtain even in young children and offer excellent temporal resolution. A great advantage of functional connectivity based on reconstructed EEG sources is the ease of application in populations that are not able to undergo MR scanning.

In spite of these advantages, one reason why researchers may not have embraced the use of EEG to study functional cortical networks is because of their limited spatial resolution. In order to overcome this barrier and obtain functional networks of cortical areas, we used EEG source reconstruction with age-matched average MRI templates (He et al., 1999). In contrast to previously reported channel-level analyses, this approach provides information about the cortical areas that are most likely to be involved as well as their functional relationship (Babiloni et al., 2005; De Vico Fallani et al., 2007) (Table 2). Further, Q5 the independence of nodes in the network is less confounded than in channel-level analysis, which does not take volume conduction effects into account.

Irrespective of the imaging modality, network analysis results in a measure of association strength between areas of interest. The properties of the resulting networks can be characterised through the mathematical framework of graph theory (Bullmore and Sporns, 2009; De Vico Fallani et al., 2007; Sporns, 2002). We applied commonly used graph measures such as node degree, average path length and clustering coefficient (Bullmore and Sporns, 2009; Chu-Shore et al., 2011). These measures allowed qualitative comparison of the characteristics of functional networks derived from reconstructed EEG sources to the organisation of networks derived in other studies using other imaging modalities like fMRI, NIRS etc. Furthermore, graph theory has been used to quantify the efficiency of a variety of networks. Most networks display a characteristic network organisation that is optimised for a) maximal processing speed b) minimal wiring cost and c) resilience (Watts and Strogatz, 1998). These networks all display a high level of local connectivity with some long-range connections. This has been described as a small-world architecture. Network analysis of structural and functional MRI data reveals that the human brain shares this organisation with other biological and non-biological networks, like neurons in *Caenorhabditis elegans* and Q6 traffic on the world-wide web (Bullmore and Sporns, 2012; Watts and Strogatz, 1998; Yu et al., 2008). We obtained measures so that the plausibility of functional networks derived from reconstructed EEG sources can be assessed qualitatively by comparing them to the characteristics of networks described in previously published reports that were derived from these other imaging modalities.

Materials and methods

Participant sample

The data were collected as a control sample for a study of children with epilepsy (O'Reilly, 2012). The control sample consisted of 47

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