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Investigations into within- and between-subject resting-state amplitude variations

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ABSTRACT

The amplitudes of spontaneous fluctuations in brain activity may be a significant source of within-subject and between-subject variability, and this variability is likely to be carried through into functional connectivity (FC) estimates (whether directly or indirectly). Therefore, improving our understanding of amplitude fluctuations over the course of a resting state scan and variation in amplitude across individuals is of great relevance to the interpretation of FC findings. We investigate resting state amplitudes in two large-scale studies (HCP and UK Biobank), with the aim of determining between-subject and within-subject variability. Between-subject clustering distinguished between two groups of brain networks whose amplitude variation across subjects were highly correlated with each other, revealing a clear distinction between primary sensory and motor regions ('primary sensory/motor cluster') and cognitive networks. Within subjects, all networks in the primary sensory/motor cluster showed a consistent increase in amplitudes from the start to the end of the scan. In addition to the strong increases in primary sensory/motor amplitude, a large number of changes in FC were found when comparing the two scans acquired on the same day (HCP data). Additive signal change analysis confirmed that all of the observed FC changes could be fully explained by changes in amplitude. Between-subject correlations in UK Biobank data showed a negative correlation between primary sensory/motor amplitude and average sleep duration, suggesting a role of arousal. Our findings additionally reveal complex relationships between amplitude and head motion. These results suggest that network amplitude is a source of significant variability both across subjects, and within subjects on a within-session timescale. Future rfMRI studies may benefit from obtaining arousal-related (self report) measures, and may wish to consider the influence of amplitude changes on measures of (dynamic) functional connectivity.

1. Introduction

The Human Connectome Project (HCP) is a unique neuroimaging research resource, consisting of an extensive set of high quality imaging data from a large number of healthy subjects (Van Essen et al., 2013). For the first time, we have access to four repeat resting-state fMRI (rfMRI) scans per subject (a total of 60 min), from a very large group of study participants, alongside extensive demographic and behavioural subject measures. The combined availability of multiple long scans per subject, and a high number of subjects, offers a valuable opportunity to investigate and differentiate between within-subject and between-subject variability. Gaining a better understanding of the types of variability that we observe in rfMRI data across subjects, and whether or not we see the same types of variability within subjects over time, is important in relation to the biomarker potential of rfMRI. If the aim is to develop rfMRI to the point where it can be used on a single case basis for diagnosis, prognosis or individualised treatment, it is essential to differentiate between artifactual variability, within-subject (state) variability and between-subject (trait) variability.

Several studies have been published that use the wealth of between-subject information available in the HCP data. These studies have, for example, identified brain correlates of a positive-negative behavioural mode of population variation (Smith et al., 2015), and have showed that connectivity profiles can be used to predict fluid intelligence (Finn et al., 2015). However, analysing and interpreting such between-subject correlations is challenging, partly because many of the demographic

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measures of interest (including IQ and BMI) are also correlated with motion (Siegel et al., 2016). A recent study has revealed that the within-subject patterns of associations between functional connectivity and motion are very similar to the between-subject patterns of associations between functional connectivity and motion (Siegel et al., 2016). This suggests that subject head motion forms an important potential confound for correlational studies.

In addition to these types of between-subject correlational research, several studies have also investigated within-subject changes in rfMRI. Data acquired from the same individual subject over approximately 18 months has shown that within-subject variability of functional connectivity over time is especially high in visual and sensorimotor cortices, whereas the same is not true for between-subject variability (Laumann et al., 2015; Poldrack et al., 2015). The same dataset was also used to identify two different functional connectivity patterns (meta-states) that occurred repeatedly over time and were associated with significant differences in self reported levels of attention and tiredness (Shine et al., 2016). These findings point to the presence of significant variability within subjects over time. This type of within-subject variability is currently poorly characterized and understood, and may add a further confound to both between-subject correlational studies and to dynamic functional connectivity studies, that is commonly overlooked.

In this work, we focus primarily on the amplitudes of resting state BOLD signal fluctuations (i.e., the standard deviation of time series), because the amplitudes provide a localised summary measure for each resting state network that is relatively easy to estimate and interpret, and also has a direct, albeit complex impact on correlations between different regions' timeseries (i.e., apparent functional connectivity) (Cole et al., 2016). The primary index of amplitude used in this paper is a measure of the relative size of BOLD fluctuations. This timeseries amplitude measure is closely related to the (fractional) amplitude of low frequency fluctuation (ALFF), which is a measure of low frequency power rather than of time series variance (Kannurpatti and Biswal, 2008; Zang et al., 2007; Zou et al., 2008). Previous work has linked between-subject variability in regional (f)ALFF to inter-individual difference in various aspects of behaviour, such as working memory, executive control and response inhibition (Mennes et al., 2011; Xu et al., 2014; Zou et al., 2013). Here, we extend this work by estimating associations between regional amplitude and a comprehensive set of measures including behaviour and lifestyle factors, subject head motion, and functional connectivity. We explicitly do not assume that the timeseries amplitude measure adopted in this work is driven exclusively by neuronal signal fluctuations (an assumption that is often made in the fALFF literature). In fact, we extensively test the influence of subject head motion on within and between subject variability in amplitude, as well as the indirect influence of head motion on functional connectivity estimates.

Changes in signal amplitude in either (or both) of two regions' resting-state timeseries can result in changes in correlation (functional connectivity) between the two time series (Friston, 2011). For example, a change in correlation between two regions can be observed when a shared signal is added to both time series (leading to increased amplitude of both time series and increased correlation between them), or when an unshared signal is added to one of the time series (leading to increased amplitude in one of the time series and decreased correlation between the two time series). Therefore, many differences in functional connectivity that are observed between subject groups or within a subject across multiple scans may be explained by the existence of shared or unshared additive signals (Cole et al., 2016; Duff et al., 2017). Such additive signals can result from a variety of different sources, including: changes in neural processing, changes in non-neural noise sources, and changes in the local signal to noise ratio. For example, previous work has shown that differences in preprocessing strategies can significantly alter functional connectivity estimates (Gavrilescu et al., 2008; Weissenbacher et al., 2009). Therefore, understanding the variability in the amplitude of resting state networks plays an important role in functional connectivity more generally.

The aim of this work was to characterise between-subject and within-subject variability in resting state network amplitudes. We hypothesised that some aspects of variability are common both across subjects and within subjects (i.e., variability caused by state differences), whereas other types of variability may only be present across subjects, and not within subjects (i.e., variability caused by trait differences). We show that differences in the subjects' arousal state can drive amplitude variability both across subjects and within subjects, particularly in visual, somatosensory, and motor networks. Additionally, we reveal a complex relationship between network amplitudes, behaviour and subject head motion.

2. Material and methods

2.1. Data

This study primarily uses data from the Human Connectome Project S900 release of resting state fMRI data from 819 subjects (452 male, mean age 28.8 ± 3.7 years old) (Van Essen et al., 2013). Each subject underwent a total of 4 resting state scans of 15 min duration over 2 days. Multiband echo planar imaging was used with an acceleration factor of 8 to achieve whole brain imaging at 2 mm isotropic resolution with a TR of 0.73 s (Moeller et al., 2010; Ugurbil et al., 2013).

In addition to HCP data, data from UK Biobank was used in order to replicate findings, and to perform between-subject correlations between BOLD signal amplitude and between-subject measures relating to arousal. Resting state scans (one per subject) were acquired using similar parameters to HCP for a duration of 6.10 min (2.4 mm spatial resolution, TR = 0.735 s, multiband acceleration factor of 8) (Miller et al., 2016). Data from 5847 UK Biobank subjects were used (2774 male, mean age 62.3 ± 7.5 years old).

2.2. Data pre-processing

The HCP data were preprocessed following HCP minimal preprocessing pipelines, containing tools from FSL, Freesurfer and HCP workbench (Fischl et al., 1999; Glasser et al., 2013; Jenkinson et al., 2012; Marcus et al., 2013; Smith et al., 2013a). ICA was performed for each run independently, and FIX (FMRIB's ICA-based X-noiseifier) was used to identify and regress out spatially structured noise components (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014). Following spatial and temporal preprocessing, the data were in a grayordinate coordinate system that combines surface-based cortical regions and volumetrically represented subcortical regions (Glasser et al., 2013).

Biobank data preprocessing included correction for motion and distortions, high pass filtering, and FIX cleaning (Miller et al., 2016). The biobank data were analysed in volumetric space, as cortical modelling has not yet been applied to this huge dataset.

2.3. Group ICA and dual regression

For both HCP and UK Biobank data, temporal concatenation group ICA was performed to extract maps for 25 group-level ICA networks (and separately for 200 group-level ICA components in HCP data). The primary analyses presented in this work are based on the 25-dimensional group ICA results, because this dimensionality is commonly adopted in the literature and the resulting network structure closely matches commonly studied resting state networks (and can be easily matched between HCP and UK Biobank data by qualitative inspection). Multiple regression of these group ICA maps onto the rfMRI data from each run was performed to obtain time series for each resting state network for each run (1200 timepoints per run, 4800 timepoints in total per subject for the HCP data; 490 timepoints per subject for the Biobank data). Note that the post-processed HCP900 Parcellation + Timeseries + Netmats (PTN) data are publicly available (https://db.humanconnectome.org).