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Resting state functional connectivity changes induced by prior brain state are not network specific

Chris Tailby [a,b,*], Richard A.J. Masterton [a,c], Jenny Y. Huang [c], Graeme D. Jackson [a,c,1], David F. Abbott [a,c,1,*]

[a] The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Austin Hospital, Victoria, Australia
[b] Department of Psychology, The University of Melbourne, Victoria, Australia
[c] Department of Medicine, The University of Melbourne, Victoria, Australia

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ABSTRACT

Resting state functional connectivity (rFC) is used to identify functionally related brain areas without requiring subjects to perform specific tasks. Previous work suggests that prior brain state, as determined by the activity engaged in immediately prior to collection of resting state data, can influence the networks recovered by rFC analyses.

We determined the prevalence and network specificity of rFC changes induced by manipulations of prior state (including an unstructured (unconstrained) state, and language and motor tasks). Three blocks of rest data (one after each of the specified prior states) were acquired on each of 25 subjects. We hypothesised that prior state induced changes in rFC would be greatest within the networks most actively recruited by that prior state. Changes in rFC were greatest following the motor task and, contrary to our hypothesis, were not network specific. This was demonstrated by comparing (1) the timecourses within a set of ROIs selected on the basis of task-related de/activation, and (2) seed-based whole brain voxel-wise connectivity maps, seeded from local maxima in the task-related de/activation maps. Changes in connectivity strength tended to manifest as increases in rFC relative to that in the unstructured rest state, with change maps resembling partially complete maps of the primary sensory cortices and the cognitive control network. The majority of rFC changes occurred in areas moderately (but not weakly) connected to the seeds. Constrained prior states were associated with lower across-participant variance in rFC.

This systematic investigation of the effect of prior brain state on rFC indicates that the rFC changes induced by prior brain state occur both in brain networks related to that brain activity *and* in networks nominally unrelated to that brain activity.

Introduction

Resting state functional connectivity (rFC) has assumed a prominent position in the investigation of large scale neural networks in the human brain (Bandettini, 2009; Fox and Raichle, 2007; Greicius, 2008; van den Heuvel and Pol, 2010; Zuo et al., 2010). The networks revealed by rFC resemble those identified via task-related activation studies (Biswal et al., 1995). Further, rFC analyses are appealing as the data are comparatively easily acquired, and they can be performed even in clinical populations in whom task execution is compromised.

It is now apparent that rFC maps are not fixed, stable entities but rather exhibit variation across a variety of timescales, from seconds to minutes to days (Chang and Glover, 2010; Guo et al., 2012; Hasson et al., 2009; Kang et al., 2011; Mannfolk et al., 2011; Shehzad et al., 2009; Soares et al., 2013; Stevens et al., 2010; Wang et al., 2012; Zuo et al., 2010). In the present study we focus on rFC changes occurring over periods of minutes. Prior studies examining changes in connectivity at this time scale have compared rFC before and after some manipulation, such as execution of a motor task (Duff et al., 2008; Peltier et al., 2005), or a cognitive task such as language (Waites et al., 2005) or working memory task (Gordon et al., 2014). Such studies converge on evidence that prior brain state can influence subsequent rFC, with the changes hypothesised to reflect factors such as fatigue (Esposito et al., 2014; Peltier et al., 2005), changes in cognitive set (Waites et al., 2005) and/or learning/consolidation (Gordon et al., 2014).

The potential influence of prior brain state on rs-fcMRI has important ramifications for group studies. Many research centres uniformly collect rest data across otherwise different experimental protocols, and there is a strong attraction to pool such data in order to increase power. The potential bias introduced by such pooling could also influence analyses based upon large, multicentre data sharing initiatives,

* Corresponding authors at: The Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre, 245 Burgundy Street Heidelberg, Victoria 3084, Australia. Fax: +61 3 9035 7307.
E-mail addresses: ctailby@brain.org.au (C. Tailby), r.masterton@brain.org.au (R.A.J. Masterton), jyhuang84@gmail.com (J.Y. Huang), g.jackson@brain.org.au (G.D. Jackson), david.abbott@florey.edu.au (D.F. Abbott).
[1] Joint senior authors.

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such as the 1000 Functional Connectomes Project (www.nitrc.org/projects/fcon_1000/).

These hypothesised mechanisms by which prior brain state influences rFC, outlined above, suggest that any rFC changes should be network specific. For instance, if fatigue lies behind the rFC changes observed following a finger movement task (Peltier et al., 2005), then one might hypothesise that such changes are restricted to the motor system. The question of the specificity of these effects remains unclear. Gordon et al. (2014) examined connectivity within and between the task positive network (TPN) and the default mode network (DMN) immediately before and after execution of a working memory task. They observed alterations of rFC both *within* the TPN, and *between* the TPN and DMN. This result is similar to the earlier work of Grigg and Grady (2010), who showed variable connectivity from precuneus (in the DMN) to a set of brain regions resembling the TPN and primary sensory cortices when comparing rest data before and after a period of task execution. These data suggest that both intra- and inter-network changes in rFC can be induced by prior brain state. However comparisons relative to the DMN may constitute a special case of inter-network change as the DMN has frequently been conceptualised as diametrically opposed to other brain networks, particularly the TPN.

Here we address the question of the network specificity of rFC changes induced by immediately prior brain state using a novel experimental design. We collected three sets of rest data: an initial rest period acquired upon entering the scanner, a second rest period following execution of an in-scanner language task, and a third rest period following execution of an in-scanner motor task (with order of the language and motor tasks counter-balanced). For each rest block we calculated seeded rFC analyses, with seeds located in the language network, the motor network, and the default mode network. This design enabled us to evaluate two hypotheses: (1) that systematic variation of prior brain state results in systematic group level alterations in rFC; and (2) that alterations in rFC induced by prior brain state exhibit network specificity.

Material and methods

Participants

Twenty-five healthy volunteers participated in the study (17 male; age, mean ± SD: 24.6 ± 5.5 years, range: 17–40). All protocols were approved by the relevant institutional Human Research Ethics Committee.

In-scanner procedures and cognitive activation paradigms

Subjects were scanned continuously for 450 volumes, alternating between periods of "extended rest" (90 volumes) and block design "task" periods (90 volumes) according to the following sequence: rest1, task1, rest2, task2, and rest3. During the extended rest periods, subjects viewed a black screen and were instructed to stay awake with eyes open, and refrain from any overt or covert cognitive or motor activities. During the task periods, subjects performed one of two block design tasks: a language task — Orthographic Lexical Retrieval (OLR), and a motor task — finger tapping (MOTOR); task order was counter-balanced across subjects. Both block design tasks alternated between 10 TRs of active phase and 10 TRs of baseline phase, completing four active phases embedded within five baseline phases. During the baseline phases of both tasks, subjects viewed a black screen with a white cross ("+") at the centre, and were instructed to relax. During the active phase of the OLR task (Wood et al., 2001), a covert adaptation of the Controlled Oral Word Association Test (Strauss et al., 2006), a letter was displayed at the centre of the screen, and then after five TRs another letter was presented. Participants were instructed to think of as many words as possible beginning with the current letter, but to avoid using proper nouns or numbers, repeating words or adding a suffix to a previously retrieved word. During the active phase of the MOTOR task, the word "Move" was presented at the centre of the screen, and subjects were required to tap their left index finger in time with a 1.0 Hz metronome played to them over headphones. The metronome was also played throughout the baseline period of the MOTOR task, during which the words "Don't Move" were presented.

We refer to the resting state data collected during the initial period as *unstructured*, and that collected after the OLR and MOTOR tasks as *post-OLR* and *post-MOTOR*, respectively. Unstructured refers to the fact that, relative to the post-OLR and post-MOTOR rest periods, the prior brain state in the unstructured rest is not as tightly constrained across participants.

Image acquisition

The fMRI studies were carried out with a 3 T GE Signa LX whole body scanner (General Electric, Milwaukee, WI), using a standard birdcage quadrature head coil. Functional images were acquired as a series of gradient-recalled echo planar imaging (GR-EPI) volumes (TE = 40 ms). Images for the first 13 participants were acquired using a TR of 3.6 s at a voxel resolution of 1.95 mm × 1.95 mm × (4 mm thick + 1 mm gap) (25 oblique slices); images for the final 12 participants were acquired using a TR of 3.2 s at a voxel resolution of 3.44 mm × 3.44 mm (3.2 mm thick + 0.2 mm gap) (40 oblique slices). The data from the two different scanners therefore contained the same number of image volumes, corresponding to slightly different total experiment durations. Due to a technical error the initial rest period for one participant contained 50 rather than 90 volumes.

Image processing

The collected images were pre-processed using Statistical Parametric Mapping software (SPM8 release 4667; Wellcome Department of Imaging Neuroscience, London, UK) with the aid of the iBrain™ analysis toolbox for SPM (Abbott et al., 2011) and iBrain™ (Abbott and Jackson, 2001). Images were first slice-time corrected, realigned, then spatially normalised to an in-house EPI template (constructed from 30 healthy control brains not including the present participants, as described in detail in Waites et al. (2005)) that approximates the SPM standard space (Montreal Neurological Institute). Normalised images were written out at 2 × 2 × 2 mm resolution, then smoothed with an isotropic Gaussian kernel (full-width-at-half-maximum = 8 mm).

Analysis of activation paradigms

Statistical analysis of the functional imaging data was conducted in SPM8 with the aid of the iBrain™ analysis toolbox for SPM using a general linear model. Standard single subject analyses were conducted on each participant's OLR and MOTOR tasks. The BOLD response of the task compared to baseline state was modelled assuming the SPM canonical hemodynamic response function (HRF), and comprised the effect of interest. In addition, the six rigid body transformation parameters estimated during image realignment were included in the model as effects of no interest. Prior to estimation, the fMRI data and design matrix were high-pass filtered (cut-off = 128 s) and pre-whitened using a first-order autoregressive process (Friston et al., 2002). Session specific grand mean scaling was used. From these analyses we used contrasts of parameter estimates of task against baseline (OLR-baseline and MOTOR-baseline) as inputs to group level one-sample t-tests of the OLR and MOTOR tasks.

Seed selection

For analyses of rFC we selected seeds on the basis of task-related activation on the OLR and MOTOR paradigms. We adopted this approach for consistency with our previous published work, examining prior brain state effects on functional connectivity in the language system (Waites et al., 2006). Specifically, we defined five motor and five

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