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Common intrinsic connectivity states among posteromedial cortex subdivisions: Insights from analysis of temporal dynamics

Zhen Yang [a,b,c], R. Cameron Craddock [a,b], Daniel S. Margulies [d], Chao-Gan Yan [a,b,c], Michael P. Milham [a,b,*]

[a] Center for the Developing Brain, Child Mind Institute, New York, NY 10022, USA
[b] Nathan Kline Institute for Psychiatric Research, Orangeburg, NY 10962, USA
[c] The Phyllis Green and Randolph Cowen Institute for Pediatric Neuroscience, New York University Child Study Center, New York, NY 10016, USA
[d] Max Planck Research Group for Neuroanatomy & Connectivity, Max Planck Institute for Human Cognitive and Brain Sciences, 04103 Leipzig, Germany

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ABSTRACT

Perspectives of human brain functional connectivity continue to evolve. Static representations of functional interactions between brain regions are rapidly giving way to dynamic perspectives, which emphasize non-random temporal variations in intrinsic functional connectivity (iFC) patterns. Here, we bring this dynamic perspective to our understanding of iFC patterns for posteromedial cortex (PMC), a cortical hub known for its functional diversity. Previous work has consistently differentiated iFC patterns among PMC subregions, though assumed static iFC over time. Here, we assessed iFC as a function of time utilizing a sliding-window correlation approach, and applied hierarchical clustering to detect representative iFC states from the windowed iFC. Across subregions, five iFC states were detected over time. Although with differing frequencies, each subregion was associated with each of the states, suggesting that these iFC states are "common" to PMC subregions. Importantly, each subregion possessed a unique preferred state(s) and distinct transition patterns, explaining previously observed iFC differentiations. These results resonate with task-based fMRI studies suggesting that large-scale functional networks can be flexibly reconfigured in response to changing task-demands. Additionally, we used retest scans (~1 week later) to demonstrate the reproducibility of the iFC states identified, and establish moderate to high test–retest reliability for various metrics used to quantify switching behaviors. We also demonstrate the ability of dynamic properties in the visual PMC subregion to index inter-individual differences in a measure of concept formation and mental flexibility. These findings suggest functional relevance of dynamic iFC and its potential utility in biomarker identification over time, as d-iFC methodologies are refined and mature.

Introduction

Posteromedial cortex (PMC), a cortical hub commonly referred to as 'posterior cingulate/precuneus', is implicated in a diverse range of higher-order cognitive and affective functions (Cavanna and Trimble, 2006). Efforts to understand the heterogeneity of the roles ascribed to PMC have increasingly highlighted the presence of functionally differentiable subdivisions. Initially reliant on cytoarchitectonic (Brodmann, 1909; Vogt, 1911) and animal tract-tracing studies (Pandya and Seltzer, 1982; Parvizi et al., 2006), models positing PMC subregions have gained support from resting-state fMRI (R-fMRI) studies of intrinsic functional connectivity (iFC). For example, seed-based correlation analysis of iFC differentiated the PMC into four distinct subregions (three in precuneus and one in posterior cingulate cortex) associated with unique functional systems (visual, cognitive, sensorimotor, and limbic) (Margulies et al., 2009). Recent data-driven approaches (e.g., cluster analysis), which avoid potential biases of *a priori* models, confirmed the presence of PMC subdivisions (Cauda et al., 2010; Zhang and Li, 2012; Zhang et al., 2012). However, in describing the connectivity of these subregions, prior studies have relied on a key assumption—namely, that iFC patterns are static during an R-fMRI scan.

Recent studies have questioned the temporal invariance of iFC patterns. Using a growing list of data-driven methods, investigators have found that the constituents of intrinsic connectivity networks (ICNs), as well as their within- and between-network connectivity vary over time (Chang and Glover, 2010; Handwerker et al., 2012; see Hutchison et al., 2013, for a review; Kang et al., 2011; Kiviniemi et al., 2011; Smith et al., 2012). Rather than interpreting such variations as random noise, most posit that they reflect meaningful dynamic properties of iFC. In particular, Allen et al. (2012) found that iFC alternates among a finite number of states—each characterized by a highly structured and quasi-stable connectivity pattern that emerges and dissolves with periods of tens of seconds to minutes. Concerns about potential confounds such as motion were alleviated by finding iFC dynamics in anesthetized nonhuman primates (Hutchison et al., 2012) and

* Corresponding author at: Center for the Developing Brain, Child Mind Institute, 445 Park Avenue, New York, NY 10022, USA. Fax: +1 646 625 4348.
E-mail address: Michael.Milham@childmind.org (M.P. Milham).

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rodents (Keilholz et al., 2013; Majeed et al., 2011). The validity of transient functional interactions is supported by neuronal (Popa et al., 2009) and neurophysiological (Chang et al., 2013; de Pasquale et al., 2012) approaches as well.

Here, we revisit previously established iFC differentiations among PMC subregions, now taking into account temporal dynamics. Specifically, we explore the possibility that PMC subregions have a common set of iFC states (i.e., highly structured and quasi-stable connectivity patterns), the existence of which would emphasize the flexibility of network associations and would resonate with task-based phenomena. To identify common iFC states, we: 1) used a sliding-window correlation approach to characterize iFC over time for each seed, 2) pooled iFC windows across seeds and participants, and 3) grouped them using hierarchical clustering. Temporal profiles for each subregion were then reconstructed from the cluster assignments and used to determine the extent to which iFC states are "common" to PMC subdivisions, and characterize potential differences in transition behaviors. Finally, we assessed the reproducibility and test–retest reliability of these state-related findings—properties commonly assumed, but not yet tested.

Methods

Dataset and data acquisition

The current study utilized the Nathan Kline Institute (NKI) test–retest (TRT) dataset publically available via the International Neuroimaging Data-Sharing Initiative (INDI: http://fcon_1000.projects.nitrc.org/indi/pro/eNKI_RS_TRT/FrontPage.html). Two participants were excluded from the original release due to either brain atrophy or a missing retest session, leaving a final sample of 22 participants (16 males, age range of 19–60, mean = 33.45, SD = 12.53). An MPRAGE structural image and two 10-minute resting scans (at least one week apart) were collected for each participant in a Siemens Trio 3.0 T scanner. Participants were instructed to keep their eyes open and fixate on a central cross on the screen. The resting scans were collected using a multiband EPI sequence (TE = 30 ms, flip angle = 60°, slice thickness = 3.0 mm, field of view = 222 mm, matrix size = 74 × 74, TR = 645 ms; no gap, resolution = 3.0 × 3.0 × 3.0 mm^3) (Moeller et al., 2010). In addition to these resting state scans, test–retest resting state scans using two different scanning protocols (2 × 2 × 2 mm resolution, TR = 1400 ms; and 3 × 3 × 3 mm resolution, TR = 2500 ms), and three non-repeated task scans (i.e. visual check-board stimulation, breath holding, eye movement calibration) following resting scans were acquired on these participants. These additional scans were not used in the current study.

As part of the NKI-Rockland protocol, phenotypic characterizations (http://fcon_1000.projects.nitrc.org/indi/pro/eNKI_RS_TRT/FrontPage.html) were obtained for 16 of the 22 participants. Psychiatric assessments using the Structured Clinical Interview for DSM-IV Axis I Disorders/ Non-patient Edition (SCID-I/NP, First et al., 2002) indicated that three of the participants met criteria for a current episode of major depressive disorder. We verified in our dynamic iFC (d-iFC) analyses and neuropsychological assessments that these individuals did not represent extreme outliers. For each of the state dynamic metrics, and each of the neuropsychological scores, extreme outliers were identified using the corresponding three inter-quartile range. Results indicated that no depressive patients were outliers in any of the indices (see Inline Supplementary Table S1 for details). As such, they were included in all analyses to increase the statistical power for this exploratory study. All data were collected according to protocols approved by the institutional review board of the NKI. Informed consent was obtained from each participant prior to participation.

Inline Supplementary Table S1 can be found online at http://dx.doi.org/10.1016/j.neuroimage.2014.02.014.

Imaging preprocessing

Data were preprocessed using the Data Processing Assistant for Resting-State fMRI (DPARSF, Yan and Zang, 2010, http://www.restfmri.net), which is based on Statistical Parametric Mapping (SPM8) (http://www.fil.ion.ucl.ac.uk/spm) and Resting-State fMRI Data Analysis Toolkit (REST, Song et al., 2011, http://www.restfmri.net). The first 10 s of data were removed to allow data to reach T1 equilibrium, leaving a total of 884 volumes for final analysis. The time series were realigned to the first image and then to the mean of all functional images using a six-parameter (rigid body) linear transformation. After realignment, individual structural images (T1-weighted MPRAGE) were co-registered to the mean functional image using a 6 degrees-of-freedom linear transformation without re-sampling. The registered T1 images were segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using the New Segment module (Ashburner and Friston, 2005) in SPM8.

The realigned data were regressed on 27 nuisance covariates (signals from WM, CSF, global signal, and Friston-24 motion parameters) to reduce the potential effects of physiological processes (e.g. respiration and cardiac processes) and motion. Linear and quadratic trends were removed to account for scanner drift. The Friston 24-parameter model (i.e., 6 head motion parameters, 6 head motion parameters one time point before, and the 12 corresponding squared items) (Friston et al., 1996) was used to regress out head motion based on recent reports demonstrating that higher-order models were more effective at removing head motion effects (Satterthwaite et al., 2012; Yan et al., 2013a). The individual 4D residual volume was spatially normalized to the Montreal Neurological Institute (MNI) space using Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) in SPM8 (Ashburner, 2007). The time series of each voxel were then standardized to zero mean and unit variance.

After preprocessing, normalized time series for 4 spherical seed regions (radius: 3 mm) and 156 target regions of interests (ROIs) were extracted in MNI space. The seed locations were selected based on a previous study (Margulies et al., 2009) to represent one posterior cingulate cortex (PCC) subregion, retrosplenial region (seed 1, location: −2/−36/35) and three subdivisions of precuneus with different functional roles: sensorimotor anterior (seed 2, location: −2/−47/58), cognitive/associative central (seed 3, location: −2/−64/45), and visual posterior precuneal region (seed 4, location: −1/−78/43). These four seeds correspond to seeds 4, 6, 14, and 17 in Margulies et al. (2009), respectively. They were previously determined to be representative of four distinct PMC subdivisions based upon their unique iFC patterns. The specific iFC patterns associated with these seeds corresponded to limbic (seed 4), motor (seed 6), cognitive (seed 14), and visual (seed 17) networks predicted from prior tract-tracing studies in the macaque monkey.

Target regions were defined using an atlas derived from the spatially constrained functional parcellation of an independent dataset (Craddock et al., 2012). Twenty-one ROIs corresponding to brain stem and cerebellum and 23 ROIs corresponding to PMC (i.e. precuneus and PCC) were removed from the atlas, leaving a total of 156 target ROIs for the analysis. Imaging of the brainstem and cerebellum is particularly susceptible to motion induced by physiological processes such as cardiac pulsation and respiration, and inconsistent slice coverage across individuals. Given the lack of physiological monitoring (e.g., respiration, cardiac cycle) in our acquisition, we removed these regions from the analysis to minimize potential confounds in the dynamic patterns revealed. PMC regions were also removed from the set of target regions to be conservative and avoid influences between PMC subregions with respect to their findings. Static and dynamic iFC analyses that specifically examined the connectivity between the four representative PMC seed regions are reported in Supplementary Materials (see Supporting Information, Inline Supplementary Table S2, and Figure S1).

Inline Supplementary Table S2 and Fig. S1 can be found online at http://dx.doi.org/10.1016/j.neuroimage.2014.02.014.