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Journal of Neuroscience Methods 169 (2008) 249–254

JOURNAL OF NEUROSCIENCE METHODS

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Short communication

Network homogeneity reveals decreased integrity of default-mode network in ADHD

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Received 17 October 2007; received in revised form 28 November 2007; accepted 28 November 2007

Abstract

Examination of spontaneous intrinsic brain activity is drawing increasing interest, thus methods for such analyses are rapidly evolving. Here we describe a novel measure, "network homogeneity", that allows for assessment of cohesiveness within a specified functional network, and apply it to resting-state fMRI data from adult ADHD and control participants. We examined the default mode network, a medial-wall based network characterized by high baseline activity that decreases during attention-demanding cognitive tasks. We found reduced network homogeneity within the default mode network in ADHD subjects compared to age-matched controls, particularly between the precuneus and other default mode network regions. This confirms previously published results using seed-based functional connectivity measures, and provides further evidence that altered precuneus connectivity is involved in the neuropathology of ADHD. Network homogeneity provides a potential alternative method for assessing functional connectivity of specific large-scale networks in clinical populations.

Keywords: fMRI; Resting state networks; Functional connectivity; Precuneus; Posterior cingulate; Attention; Attention-deficit/hyperactivity disorder

1. Introduction

The advent of new methods for analyzing functional neuroimaging data in the resting state has enabled the investigation of previously overlooked aspects of intrinsic network organization. In particular, investigators have identified spontaneous coherent fluctuations in functionally distinct networks even in the absence of specific cognitive instruction (De Luca et al., 2006; Fox et al., 2006; Vincent et al., 2006). This "cognitively unbiased" approach appears to be particularly relevant for the study of psychopathological populations, with several recent reports noting disruptions in such intrinsic organization (Greicius et al., 2004; Garrity et al., 2007).

Assessment of resting brain networks can be accomplished using several recently developed methods, although two are most widely employed. These are independent components analysis (ICA) and region-of-interest (ROI) seed-based correlation approaches, each of which has strengths and shortcomings. ICA is a model-free approach whereby a two-dimensional (time points *x* voxels) data matrix is decomposed into a set of independent timeseries and consequently associated spatial maps which describe the temporal and spatial characteristics of the underlying signals (components) (Beckmann et al., 2005). While ICA has the power to estimate largely overlapping spatial processes, there is no clear consensus as to how best to compare components across subjects and/or between groups (Fox and Raichle, 2007) (see (Beckmann and Smith, 2004; Calhoun et al., 2005) for recent advances). Seed-based approaches involve using correlation or regression analyses to determine the temporal coherence between the timeseries for a particular voxel or ROI and the timeseries of all other voxels in the brain in order to identify temporally coherent "functionally connected" networks (Biswal

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doi:10.1016/j.jneumeth.2007.11.031

et al., 1995). This flexible approach is limited by the requirement for an *a priori* ROI seed region, which is typically selected based upon prior findings or theoretical models. Unfortunately, determining optimal ROI seed placement within a network is non-trivial, as brain circuits can encompass a large number of brain regions consisting of multiple functionally differentiable sub-regions (Margulies et al., 2007). The decision to place the ROI seed in one sub-region within this network can be somewhat arbitrary, with no way to determine which placement might be "best". The selection and precise placement of ROI seeds can therefore have considerable impact on the patterns of functional connectivity observed. Consequently, decisions made early in the analytic process concerning seed placement could potentially result in lack of appreciation of abnormalities in functional connectivity in a particular clinical population. For the same reason, if no *a priori* prediction exists for a particular region or ROI, potential abnormalities in the associated networks could be missed.

Alternative approaches are currently being developed to address some of the limitations of the prevailing techniques. In order to overcome the difficulty of sorting ICA components, Greicius et al. have developed a template-matching procedure which identifies a network of interest by its goodness-of-fit to a prespecified template mask (Greicius et al., 2004). Wang et al. have developed a parcellation method, which divides the whole brain into several regions to identify abnormal connectivity by comparing correlation coefficients of each pair of regions between groups (Wang et al., 2007). A similar method of computing regionwise correlation matrices has recently been proposed (Fair et al., 2007). All of these newer approaches share the advantage of simplifying between-group comparisons of resting-state fMRI data. Another approach, "regional homogeneity", measures the similarity of the timeseries of a given voxel to those of its nearest neighbors (Zang et al., 2004). This method has been used to demonstrate abnormalities in a fronto-striatal-cerebellar functional network in attention-deficit/hyperactivity disorder (ADHD) (Cao et al., 2006). While informative, this "regional" method is only sensitive to the temporal synchrony of the BOLD signal within the 26 neighboring voxels for any given voxel, and thus is poorly suited for studying long-range connectivity.

When assessing network integrity in clinical populations, one potentially informative approach would be to provide an unbiased survey of a distributed network of interest, looking for regions exhibiting pathology-related decreases in network coherence. Here we present a novel measure for this purpose, which we term "network homogeneity". This is a voxel-wise measure that provides an assessment of a voxel's correlation with all other voxels within a given network of interest. This measure is defined as the mean correlation of any given voxel's timeseries with the timeseries of every other voxel in the network. Brain regions exhibiting compromises in network homogeneity in association with a particular disorder or pathological process can be identified by our method, which enables between-group comparisons. A primary advantage of this approach is that it provides an unbiased survey of a given network, so that group differences may be identified without the need for *a priori* knowledge of where in the network abnormalities might be.

The most prominent network in the clinical neuroscience literature on spontaneous intrinsic brain activity is the default mode network (DMN). The DMN comprises medial (medial prefrontal cortex, posterior cingulate/precuneus) and lateral (posterior parietal) brain regions that routinely exhibit coherent decreases in activity during attention-demanding cognitive tasks (Raichle et al., 2001). Attentional lapses have been found to occur shortly after periods of decreased deactivation of posterior DMN regions (Weissman et al., 2006). ADHD is a heterogeneous developmental condition with multiple potential loci of neural dysfunction. Though there are numerous theoretical reasons for suspecting DMN dysfunction in ADHD, little empirical work has been conducted in this area. In a recent review, DMN interference during task performance was suggested to be a potential underlying cause of performance variability in ADHD (Sonuga-Barke and Castellanos, 2007). In a recent study, examining resting state functional connectivity of the dorsal anterior cingulate cortex using a seed-based approach, we reported a secondary finding of decreased functional connectivity between the precuneus and other DMN regions in adults with ADHD (Castellanos et al., in press). This seed-based approach consisted of extracting the timeseries of specific ROIs selected from previous work (Weissman et al., 2006) and using these as regressors to produce maps of all positively and negatively predicted voxels for each regressor (Margulies et al., 2007). This analysis revealed decreased functional connectivity between the anterior cingulate cortex and precuneus in ADHD subjects. Secondary analyses using the precuneus as a starting point for seeding revealed decreases in connectivity between the precuneus and ventromedial cortex in ADHD participants. Though examination of the DMN was not the primary focus of that study, results suggested that more detailed examination of DMN integrity in ADHD was warranted. Here we apply our network homogeneity measure to the same dataset to demonstrate its efficacy as a complementary method to seed-based functional connectivity and ICA. Based on our previous findings and the functional associations of this network, we hypothesized that we would find abnormal DMN homogeneity in the ADHD group compared to the control group, and that regions of "disconnect" would confirm and extend those previously identified via seed-based approaches.

2. Materials and methods

2.1. Participants

Twenty adults with ADHD were recruited from the New York University School of Medicine Adult ADHD Program, and 20 age-matched comparison subjects were recruited through local media advertisements. All prospective participants were screened with the Symptom Checklist-90-Revised (SCL-90-R) to exclude a broad range of psychiatric psychopathology (Deragotis, 1986). Exclusion criteria for both groups included: (1) lifetime history of psychotic, bipolar or substance use disorders, (2) current history of mood, psychotic, anxiety, or substance use disorders, (3) lifetime history of treatment with

Table 1
Group demographics and ADHD symptom severity

	ADHD	Healthy control
Total subjects	20	20
Mean age (years)	34.9 ± 9.9	31.2 ± 9.0
Inattentive symptoms	7.4 ± 1.6	1.2 ± 0.4
Hyperactive/Impulsive symptoms	5.9 ± 2.6	1.5 ± 0.6
Number (%) treated	9 (45%)	0
Gender		
Male	16	14
Female	4	6

Current DSM-IV inattention and hyperactivity/impulsivity symptoms (lifetime symptoms for healthy comparisons) were assessed using the Adult ADHD Clinical Diagnostic Scale 2.1. Symptom data on this scale were not available for two subjects diagnosed with combined-type ADHD by clinical interview. Age, sex distributions, and educational attainment did not differ significantly between groups ($p > 0.2$).

psychotropics other than stimulants (for ADHD group only), and (4) history of neurological or chronic medical illness. Participants with ADHD were administered the Structured Clinical Interview for DSM-IV (SCID) and met lifetime criteria for Combined Type ADHD. A semi-structured clinical interview was carried out by a psychiatrist for the comparison group. For all participants, intelligence within the normal range was established by educational history and strong right-handedness by self-report. All participants were evaluated with the Adult ADHD Clinical Diagnostic Scale Version1.2 (Adler and Cohen, 2004). Patient characteristics are shown in Table 1. All patients were either untreated for ADHD or washed out of stimulant therapy for at least 24 h at the time of scanning. ADHD participants showed no co-morbidities, and were not taking other psychotropics or non-stimulants for ADHD. Participants provided signed informed consent as approved by the IRBs of NYU and the NYU School of Medicine and received monetary compensation.

2.2. fMRI parameters

A resting state scan consisting of 197 contiguous whole-brain functional volumes using echo planar imaging on a Siemens 3.0 Tesla Allegra (TR = 2000 ms; TE = 25 ms; flip angle = 90, 39 slices, matrix = 64 × 64; FOV = 192 mm; acquisition voxel size = 3 mm × 3 mm × 3 mm; 6:38 min) was collected from each participant. A separate functional connectivity analysis of this dataset has been published elsewhere (Castellanos et al., in press). Subsets of this dataset have also been published separately (Kelly et al., 2008; Margulies et al., 2007). Participants were verbally instructed to relax and remain awake while the word "Relax" was centrally displayed. A T1-weighted anatomical image was also acquired for registration purposes (MP-RAGE, TR = 2500 ms; TE = 4.35 ms; TI = 900 ms; Flip angle = 8; 176 slices; FOV = 256 mm).

2.3. Data analysis

Initial image preprocessing, including motion correction, despiking, and slice time correction, was done using AFNI (http://www.afni.nimh.nih.gov/afni). Subsequent preprocessing, including spatial filtering (FWHM = 6 mm), temporal bandpass filtering, spatial normalization, and registration to the MNI template was performed using FSL (http://www.fmrib.ox.ac.uk/fsl).

2.4. Network homogeneity

Network homogeneity analyses were implemented using Matlab. We used a template mask derived using a seed-based approach from a previous study (Uddin et al., in press) to identify the default mode network and limited our analyses to only those voxels within the mask (see Fig. 1). The default mode network template mask was derived from resting-state fMRI data collected from 26 normal adult subjects, most of whom are included in the present analysis. The mask was created from a functional connectivity analysis, and represents voxels positively correlated with a spherical seed ROI (10 3 mm × 3 mm × 3 mm voxels, volume = 270 mm3) centered in posterior cingulate cortex (PCC: Talairach coordinates = −2, −51, 27). Previous work has shown that seeding the PCC produces the most comprehensive map of the default mode network (Greicius et al., 2004). Preprocessed data from each participant was subjected to the following procedure. For each participant, we calculated voxel-wise network homogeneity (NH) measures using the following equation:

$$NH_i = \sum_{j=1}^{n} \frac{r(TS_i, TS_j)}{n-1} \quad \text{where } i \neq j$$

Simply put, for the timeseries (TS) of each voxel i, a Pearson's correlation coefficient, r, was computed with the timeseries of each of the other $n-1$ voxels in the network as defined by the mask, and averaged to provide the network homogeneity measure for that voxel. In order to take into account the potential contributions of inter-individual and group differences in overall homogeneity, a global default mode network homogeneity measure was also calculated for usage as a covariate in group-level analyses. This global DMN homogeneity measure was obtained for each subject by calculating the sum of the network homogeneity scores across voxels for each subject's DMN.

2.5. Between group comparison

Using a random effects model implemented in SPM2, voxel-wise group differences were detected by testing the null hypothesis that the two groups do not differ with respect to a given voxel's network homogeneity score. Subject age was included as a covariate, as well as each subject's global DMN homogeneity measure (the mean network homogeneity for the subject's default mode network) to adjust for overall differences in homogeneity. Corrections for multiple comparisons were carried out at the cluster level using Gaussian random field theory ($Z > 2.3$, cluster significance: $p < 0.01$, corrected).

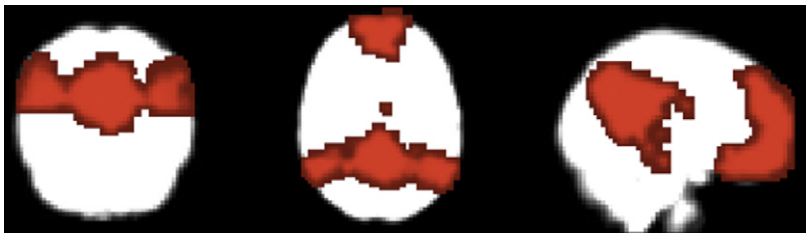

Fig. 1. Mask used to define the Default Mode Network in each subject for NH calculation.

3. Results

The ADHD and control groups did not differ on global measures of DMN homogeneity (mean ADHD = 0.0345, mean Control = 0.0357, $t(39) = 2.7$, $p > 0.01$), suggesting against the possibility of diffuse compromises in network integrity. For voxel-wise group differences tested using a random effects model implemented in SPM2, the comparison *Control* > *ADHD* revealed ADHD-related reductions in network homogeneity in the posterior portion of the DMN centered in precuneus (see Fig. 2). The peak difference between the two groups was at $x = 4$, $y = -78$, $z = 42$. No other regions differed significantly between groups for either comparison (*Control* > *ADHD* or *ADHD* > *Control*). The region exhibiting abnormal network homogeneity in the ADHD group overlaps (17,895 voxels) with a region of altered functional connectivity identified previously in this dataset using seed ROI-based measures (Castellanos et al., in press) (see Fig. 3).

4. Discussion

To provide an unbiased survey of within-network coherence capable of detecting specific loci of compromised connectivity, we have developed a novel measure termed "network homogeneity". We applied this measure to resting state fMRI data to directly assess the integrity of the DMN in ADHD. This approach to characterizing DMN integrity revealed that compared to age-matched controls, subjects with ADHD showed decreased network homogeneity, particularly in the region of the precuneus. Importantly, the locus of dysfunction revealed by this approach overlaps with that revealed by seed-based functional connectivity analysis of this dataset (Castellanos et al., in press), thus replicating a finding from seed-based correlation measures.

The method we introduce here has several potential advantages over existing approaches to examining resting state functional connectivity. It allows for an unbiased survey of a specific network and provides a straightforward means of assessing group differences between clinical populations. By adjusting for global differences in NH, it also allows anatomically specific differences in network integrity to be discerned despite substantial between-subject differences in overall coherence. The network homogeneity measure provides a compromise between the two most widely used methods in analysis of resting-state functional connectivity (seed-ROI based correlation and ICA) by enabling hypothesis-driven interrogation of long-range networks of clinical interest. This approach thus combines the advantages of the two previous methods.

The computation of the network homogeneity has some limitations. First is the requirement that a network of interest and its corresponding mask be identified *a priori*. As a result, it will have limited utility in application to pediatric populations where resting state networks are not as well characterized. Additionally, the *a priori* selection of a specific network mask introduces a bias in the analysis. However, while the network homogeneity approach requires *a priori* selection of a specific network, it is not biased in the same way as traditional seed-based approaches that typically focus on a voxel or cluster of voxels (e.g. a seed region) as the starting point of correlation analyses. The network mask chosen for the analysis can in principle be derived in a way that is not based on seed placement or other biased

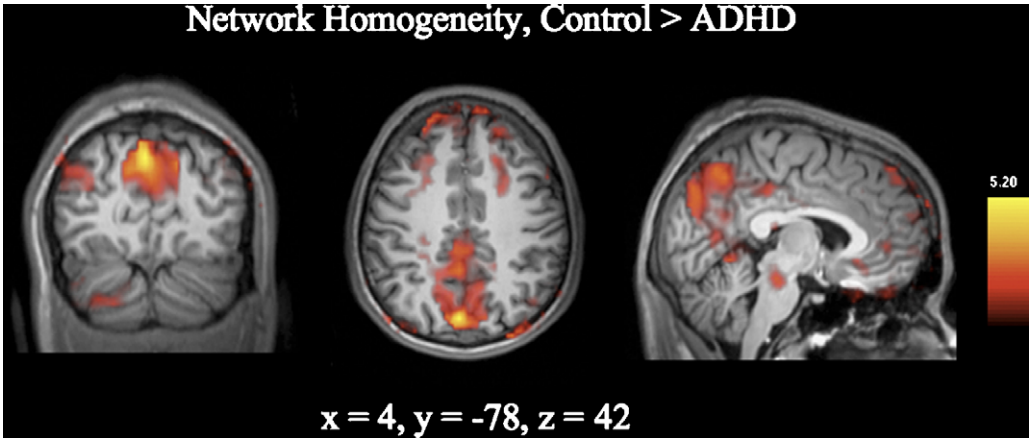

Fig. 2. Network Homogeneity, Control > ADHD. Regions exhibiting decreased NH in DMN in ADHD group compared to control group.

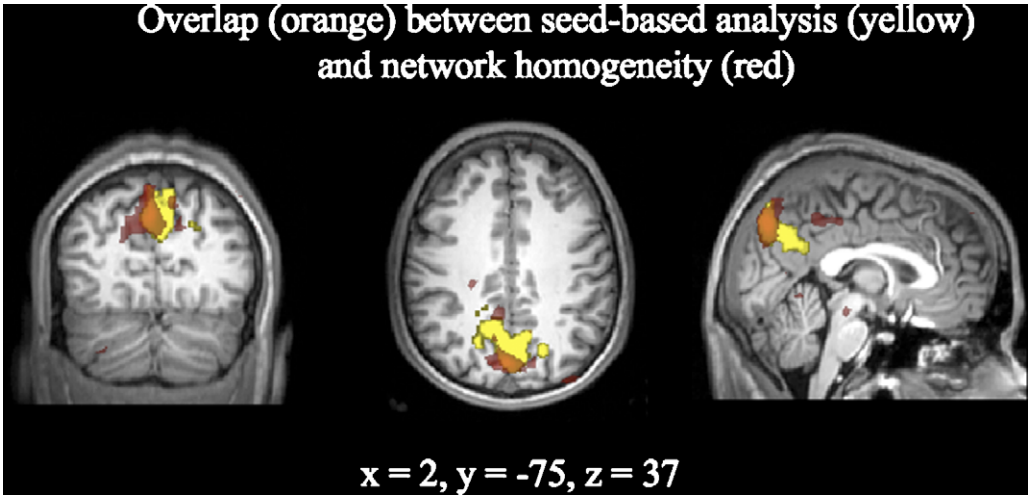

Fig. 3. Overlap with Seed-ROI Based Functional Connectivity Results (Castellanos et al., in press).

methods (for example, networks can be identified using model-free approaches like ICA). Also, computational complexity may also be an issue given the large number of correlations that must be calculated. This can be overcome by parcellating the calculation into smaller units. Another potential limitation is that NH measures detect only differences within a network, and cannot assess between-network interactions and/or dysfunction. As such, NH measures should be used as a complimentary method to the more traditional approaches previously discussed. Lastly, due to inter-individual differences in the spatial extent of the DMN, it is possible that the NH score will sometimes include negative as well as positive correlations when all possible pairwise correlations are computed. As such, network homogeneity is meant to infer not the mere presence of a relationship between any given voxel and others in the network, but consistent directionality as well. Despite these limitations, the advantage that is to be gained from the network homogeneity approach is that it can be readily applied in clinical populations where large-scale within-network abnormalities are suspected (e.g. autism spectrum disorders, schizophrenia, and Alzheimer's disease), yet little consensus exists with respect to localized brain abnormalities.

The DMN is a prime candidate for investigating the neural basis of attentional dysfunction, given its reported antagonistic relationship with task-positive networks engaged during attentionally demanding conditions (Fox et al., 2005). The precuneus is a prominent node in the DMN that has been receiving increasing attention in the ADHD neuroimaging literature. Several studies to date have shown ADHD-related structural abnormalities, including reductions in grey matter volume (Overmeyer et al., 2001; Carmona et al., 2005) in this region. The precuneus is an important integrative structure that demonstrates widespread connectivity with several cortical (anterior cingulate, lateral prefrontal, and inferior and superior parietal) and sub-cortical (thalamus, striatum, and brainstem) regions (Cavanna and Trimble, 2006). Its role in higher order cognitive functions is only recently being explored. That the functional connectivity of this posterior node of the DMN is less homogenous in adults with ADHD is in line with emerging theories of default mode interference as a contributor to attentional dysregulation in ADHD (Sonuga-Barke and Castellanos, 2007). Such ADHD-related decreases in network homogeneity might reflect decreased functional interactions between the precuneus and control regions such as anterior cingulate, and may be a cause of some of the executive function deficits characteristic of this condition (Castellanos et al., 1996).

To summarize, network homogeneity provides an objective means for comparing network integrity between groups. The utility of this approach lies in its ease of application to clinical populations where network integrity is potentially compromised. Dysfunction of the DMN has been hypothesized to contribute to a variety of disorders, including autism (Kennedy et al., 2006), Alzheimer's disease (Greicius et al., 2004), and schizophrenia (Liu et al., 2006). Our approach enables characterization of the precise loci of disconnection within a specific network, and may be useful in analyzing resting-state fMRI data acquired from these and other clinical populations.

Acknowledgments

The authors would like to thank Dr. Andrew Kirsch for conducting clinical assessments. This work was supported by grants provided to FXC by the Stavros S. Niarchos Foundation, NIMH (5R21MH066393 and 5T32MH067763), and the Leon Lowenstein Foundation.

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