Psychiatry Research: Neuroimaging 249 (2016) 12–19

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Brain parcellation choice affects disease-related topology differences increasingly from global to local network levels

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ARTICLE INFO

Article history:
Received 13 May 2015
Received in revised form
15 January 2016
Accepted 4 February 2016
Available online 12 February 2016

Keywords:
Anorexia nervosa
Resting state
Graph metrics
fMRI

ABSTRACT

Network-based analyses of deviant brain function have become extremely popular in psychiatric neuroimaging. Underpinning brain network analyses is the selection of appropriate regions of interest (ROIs). Although ROI selection is fundamental in network analysis, its impact on detecting disease effects remains unclear. We investigated the impact of parcellation choice when comparing results from different studies. We investigated the effects of anatomical (AAL) and literature-based (Dosenbach) parcellation schemes on comparability of group differences in 35 female patients with anorexia nervosa and 35 age- and sex-matched healthy controls. Global and local network properties, including network-based statistics (NBS), were assessed on resting state functional magnetic resonance imaging data obtained at 3 T. Parcellation schemes were comparably consistent on global network properties, while NBS and local metrics differed in location, but not metric type. Location of local metric alterations varied for AAL (parietal and cingulate cortices) versus Dosenbach (insula, thalamus) parcellation approaches. However, consistency was observed for the occipital cortex. Patient-specific global network properties can be robustly observed using different parcellation schemes, while graph metrics characterizing impairments of individual nodes vary considerably. Therefore, the impact of parcellation choice on specific group differences varies depending on the level of network organization.

1. Introduction

Functional brain connectivity is known to form complex networks, both during tasks and at rest. Due to the complex network structure observed, deviations due to disease are likely to involve intricate pathways and may not be observed using traditional functional connectivity (FC) analysis. As a result, graph theoretical analyses have been applied to functional magnetic resonance imaging (fMRI) data in an attempt to quantify complex connectivity patterns. Previous studies have shown that brain networks efficiently connect functionally similar regions without substantially increasing the overall cost of communication (Van den Heuvel et al., 2008). Other properties of network structure are also routinely used to describe the characteristics of individual regions within the network, such as local efficiency (Latora and Marchiori, 2001) and path length (Watts and Strogatz, 1998). Between the global and local alterations linked to disease, recent studies have found that network alterations may contain a number of interconnected nodes. To this end, Zalesky et al. developed a technique to identify these altered subnetworks, known as network-based statistics (NBS) (Zalesky et al., 2010a).

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http://dx.doi.org/10.1016/j.pscychresns.2016.02.001
0925-4927/

Due to their ease of use and potential for standardized acquisition, large-scale data bases and meta-analyses of resting state data have become increasingly prominent in defining robust measures of abnormal brain network topologies in patients. A major drawback to assess validity in a greater context of multiple studies is related to the methodological variations that appear during preprocessing and analysis. Preprocessing methods have been heavily emphasized for their impact on resting state measures in general (Weissenbacher et al., 2009; Saad et al., 2012) and graph measures in particular (Braun et al., 2012; Liang et al., 2012). The choice of a suitable parcellation scheme is, however, much less supported by specific investigations, and insufficient evidence exists for researchers to assess how much a specific parcellation scheme would allow comparison with previously reported findings. Recent evidence suggests the placement of regions of interest (ROIs) crossing functional boundaries severely impacts the specificity of the affected ROI time series (Smith et al., 2011). Although ROIs not sharing a common boundary do not suffer from a common noise source, the specificity of such signals may potentially still be compromised by the increased noise in ROI time series. Such information is not only necessary to relate convergent as well as divergent findings of a specific study to prior work, but also to make concise decisions in, for example, meta-analyses of existing data in which results of different studies can be pooled to enhance confidence in results with, in principle, comparable outcomes.

While a number of theoretical articles arguing for specific parcellation schemes exist, we found that no work so far was dedicated to a specific comparison of different, but frequently used parcellation schemes, in their outcomes on group differences between neuropsychiatric and healthy control samples.

One group for which abnormal resting state findings have been reported is anorexia nervosa (AN). AN is an eating disorder predominantly affecting adolescent women, characterized by excessive food restriction, a fear of weight gain and distorted body self-image. This disorder has an extremely high mortality rate (Steinhausen, 2002) and is known to contain a high genetic component (Kaye et al., 2009).

There have been several recent studies examining whole brain alterations in functional correlations in AN patients. Seed-based approaches have identified increased functional connectivity (FC) in various areas such as the dorsal anterior cingulate cortex and the precuneus (Lee et al., 2014), the left anterior insula and the inferior frontal gyrus (Kim et al., 2012), as well as increased connectivity in the bilateral putamen (Favaro et al., 2014) and dorsolateral prefrontal cortex (PFC). However, all these investigations were limited to only a few seed regions. In previous studies, we showed reduced correlations in FC within a predominantly subcortical network involving the bilateral posterior insula as well as the (left) thalamus, amygdala (left), fusiform gyrus (right) and bilateral putamen using the AAL atlas to define our ROIs (Ehrlich et al., 2015). Furthermore, in another recent study (Geisler et al., 2016), we identified changes in global (characteristic path length and assortativity) and local (strength, degree and local path length) network metrics in acute AN.

In the current study two parcellation schemes were tested to identify graph metrics that are robust to parcellation alterations. One parcellation scheme was a modified version of the AAL including subdivisions of the cingulate cortex and the insula, resulting in 104 regions (Borchardt et al., 2015). The second, a parcellation scheme using spheres centered around centers of mass identified in a literature search, was based on an approach developed by Dosenbach et al. (2010). Importantly, we did not expect uniform effects of parcellation on the different levels of network organization, normally addressed by graph analysis, thus we specifically investigated their interaction. We assessed the coherence of results between each parcellation scheme on 35 acute AN patients and 35 age-matched healthy controls, all female, in terms of graph metrics across a range of sparsity thresholds as well as using NBS on the fully connected correlation matrices.

2. Methods

2.1. Participants

Our sample consisted of 70 female volunteers: 35 patients with acute anorexia nervosa (AN, 12–23 years old, mean 16.10 ± 2.56) and pairwise age-matched 35 female healthy control subjects (HC, 12–23 years old, mean 16.16 ± 2.64). AN participants were recruited from specialized eating disorder programs of a university child and adolescent psychiatry and psychosomatic medicine department and underwent magnetic resonance imaging (MRI) within 96 h after beginning behaviorally oriented nutritional rehabilitation programs. All participants were diagnosed using the expert version of a semi-structured research interview, the Structured Interview for Anorexia and Bulimia Nervosa for DSM-IV (SIAB-EX) (Fichter et al., 1998). A diagnosis of AN required the patient to have a body-mass index (BMI) below the 10th age percentile (if younger than 16 years) or a BMI below 17.5 kg/m^2 (if older than 16 years) (Hebebrand et al., 2004) and no recent weight gain. Within the AN group, 32 (94.1%) of the patients were of the restrictive and two (5.9%) of the binge/purging subtype; four (11.4%) had comorbid psychiatric disorders (5.7% depressive disorders including dysthymia, 2.9% anxiety disorder and 2.9% obsessive–compulsive disorder). HC participants had to be of normal weight and without any history of psychiatric illness. Participants were excluded if they had a history of bulimia nervosa or “regular” binge eating, psychotropic medications within 6 weeks before the study, substance abuse and neurologic or medical conditions. Case-control age-matching was carried out using the Munkres algorithm (Munkres, 1957), resulting in a maximum difference of 0.9 years between the individuals within one pair. This study was approved by the local Institutional Ethics Review Board, and all participants (and their guardians if participants were underage) gave written informed consent.

2.2. Parcellations

ROIt time series extraction was performed using two parcellation schemes. First, the AAL was used as a basis for one parcellation (Tzourio-Mazoyer et al., 2002); however, recent evidence suggests distinctions exist between subregions of the cingulate cortex, both anatomically (Palomero-Gallagher et al., 2009), and biochemically (Dou et al., 2013). Similarly, the insula has been shown to contain functionally distinct subdivisions, with anterior parts related to autonomic–olfactory–gustatory function, while the posterior insula is functionally related to auditory–somesthetic–skelemotor processes (Mesulam and Mufson, 1982). Due to the lack of functional coherence within these regions, we subdivided the cingulate cortex and insula, in line with Borchardt et al. (Fig. 1) (Borchardt et al., 2015). Another atlas including 160 spherical ROIs, centered at coordinates identified from a literature search of task-based fMRI studies as defined by (Dosenbach et al., 2010), was also used.

2.3. Data acquisition

Images were acquired between 8 and 9 a.m. after an overnight fast on a Siemens 3 T MRI scanner (TRIO; Siemens) with a 12-channel head coil. The T_1-weighted structural brain scans were acquired with a rapid acquisition gradient echo (MP-RAGE) sequence. The T_1 acquisition consisted of 176 slices, with a repetition time (TR) of 1900 ms and an echo time (TE) of 2.26 ms, flip angle of 9°, slice thickness of 1 mm and 1 mm isotropic voxels. The field of view (FoV) was 256*224 mm^2 and a bandwidth of 200 Hz/pixel was used.

Functional images were acquired using a gradient-echo T_2^*-weighted echo planar imaging (EPI) sequence, tilted 30° toward the anterior–posterior commissure line to enhance coverage of orbitofrontal regions. In total, 190 functional volumes, consisting of 40 slices, 2200 ms TR and 30 ms TE were acquired. The flip angle was 75° and the images had a 3.4 mm in-plane resolution, with a slice thickness of 2.4 mm and 1 mm gab between slices. This resulted in a voxel size of 3.4*3.4*2.4 mm^3, FoV 220*220 mm^2, bandwidth 2004 Hz/pixels with a duration of 6:58 min.

2.4. rs-fMRI preprocessing

Functional and structural images were processed using SPM8 toolbox (http://www.fil.ion.ucl.ac.uk/spm/) within the Nipype framework (http://nipy.sourceforge.net/nipype/ Gorgolewski et al. (2011)). Slice time correction was performed to account for the temporal delay in acquisition between volumes (Sladky et al., 2011). The slice time corrected functional data were realigned and registered to their mean. The realigned files were co-registered to the subject's structural brain image. A DARTEL template was created using structural images from all subjects