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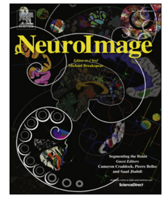
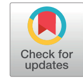


Detecting stable individual differences in the functional organization of the human basal ganglia



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ABSTRACT

Moving from group level to individual level functional parcellation maps is a critical step for developing a rich understanding of the links between individual variation in functional network architecture and cognitive and clinical phenotypes. Still, the identification of functional units in the brain based on intrinsic functional connectivity and its dynamic variations between and within subjects remains challenging. Recently, the bootstrap analysis of stable clusters (BASC) framework was developed to quantify the stability of functional brain networks both across and within subjects. This multi-level approach utilizes bootstrap resampling for both individual and group-level clustering to delineate functional units based on their consistency across and within subjects, while providing a measure of their stability. Here, we optimized the BASC framework for functional parcellation of the basal ganglia by investigating a variety of clustering algorithms and similarity measures. Reproducibility and test-retest reliability were computed to validate this analytic framework as a tool to describe inter-individual differences in the stability of functional networks. The functional parcellation revealed by stable clusters replicated previous divisions found in the basal ganglia based on intrinsic functional connectivity. While we found moderate to high reproducibility, test-retest reliability was high at the boundaries of the functional units as well as within their cores. This is interesting because the boundaries between functional networks have been shown to explain most individual phenotypic variability. The current study provides evidence for the consistency of the parcellation of the basal ganglia, and provides the first group level parcellation built from individual-level cluster solutions. These novel results demonstrate the utility of BASC for quantifying inter-individual differences in the functional organization of brain regions, and encourage usage in future studies.

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1. Introduction

The basal ganglia (BG) is a functionally heterogeneous structure that interacts with the cortex to produce a wide range of motor, cognitive, and affective functions (Alexander et al., 1986; Coxon et al., 2016; Goble et al., 2011, 2012; Graybiel, 2008; Hikosaka et al., 2002; Hoshi et al., 2005; Postuma and Dagher, 2006). The BG's functional diversity is also supported by its involvement in a wide range of psychiatric and neurological dysfunction (e.g., Parkinson disease, Huntington disease, major depression, OCD, Tourette Disorder, addiction (Albin et al., 1989; DeLong and Wichmann, 2007; Dogan et al., 2015; Graybiel, 2008; Hyman et al., 2006; Ikemoto et al., 2015; Simpson et al., 2010; Worbe et al., 2015; Yu et al., 2013). Understanding how the BG supports these myriad functions requires a detailed understanding of the architecture of this complex brain region. While discrete anatomical nuclei have been identified by post-mortem studies, such findings provide little insight into variations among individuals in cortical interactions that could contribute to differences in cognitive, motor, and affective function and dysfunction.

Such anatomical brain parcellations can present significant confounds to the specification of functional networks (Blumensath et al., 2013; Smith et al., 2011) and have been demonstrated to be not detailed enough to result in adequate models of functional data (Thirion et al., 2014). Due to these issues, efforts have focused on the delineation of BG sub-regions based upon patterns of functional co-activation

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or connectivity and have proven to be particularly promising (Postuma and Dagher, 2006). Task based meta-analytic approaches have used large sets of coactivation maps to clusters of BG voxels (Pauli, O'Reilly, Yarkoni and Wager, 2016; Postuma and Dagher, 2006). Other studies, such as Di Martino et al., 2008 used functional connectivity based methods for delineating subdivisions of the BG in resting state fMRI. Following this initial study of BG connectivity, a number of papers have generated voxel-level connectivity-based parcellations of the BG using a range of techniques, including independent component analysis (Kim et al., 2013), graph theory (Barnes et al., 2010), network-based voting strategies (Choi et al., 2012), and cluster analysis (Jung et al., 2014). Despite differences in methodologies, the results of these studies have been largely consistent with one another, with the findings of the previously discussed co-activation studies, and with the larger body of work from animal models. While an important step beyond anatomical atlases, group level functional parcellations do not accurately reflect an individual subject's functional anatomy (Blumensath et al., 2013; Smith et al., 2011). Obtaining functional atlases at the individual level is a critical step towards understanding the organization of the functional anatomy and relationship with phenotypic variation (Devlin and Poldrack, 2007; Laumann et al., 2015).

Individual level maps of the brain's functional architecture are fundamental for deriving how individual differences in cognition are associated with functional brain architecture (Cohen et al., 2008; Di Martino et al., 2009a,b; Kelly et al., 2009). In clinical realms, where individuals can vary dramatically from group atlases, the development of individual level functional maps become an important source of in-vivo information about the brain for a range of clinical procedures such as surgery and brain stimulation (Fox et al., 2014; Fox et al., 2013; Frost et al., 1997; Goulas et al., 2012; Opitz et al., 2016; Wang et al., 2015). Furthermore, for successful application in cognitive and clinical domains, within-subject reproducibility is an important criterion for individual level functional mapping (LaConte et al., 2003; Thirion et al., 2014; Wang et al., 2015). Defining inter-individual variation in BG connectivity patterns may yield important insight into putative biomarkers for BG dysfunction. Prior efforts have targeted the establishment of individual level functional mapping of the cortex (Wang et al., 2015; Blumensath et al., 2013), though establishing individual level parcellations of the basal ganglia remains elusive.

While prior works have demonstrated mapping individual functional differentiations among BG subdivisions driven by group-level connectivity is feasible (Janssen et al., 2015), these individual-level solutions have not yet been examined, nor has the reliability of differences obtained across individuals been established or quantified. We leverage the “bootstrap analysis of stable clusters” (BASC) framework (Bellec et al., 2010) to assess both individual differences in BG parcellations and stability of BG parcellations at the group level. BASC is unique in its ability to provide a probabilistic measure of clustering properties at a single-subject level as well as stable clustering solutions at a group-level. In addition to group-level measures of stability for parcellations, BASC provides measures of stability of individual-level parcellation results. Assessment of test-retest reliability is particularly relevant to efforts focused on biomarker identification. Recent works focused on cortical parcellation have suggested that functional boundaries detected during rest are reliable and may vary meaningfully across individuals (Glasser et al., 2016; Gordon et al., 2015; Van Essen and Glasser, 2014; Xu et al., 2016). Accordingly, the present work emphasizes the test-retest reliability for the findings obtained using the BASC framework. We use BASC to replicate our parcellation across multiple clustering methods, data types, and acquisition parameters to establish a methodologically agnostic map of the stability of BG subdivisions. We demonstrate that BASC can provide individual level functional maps of the BG are reliable across scans, and we establish the basis for cognitive and clinical endeavors that rely on mapping functional architecture at the individual level.

2. Methods

2.1. Datasets

We employed two independent test-retest datasets currently available for open science investigations. The NYU TRT includes data from 25 right-handed participants (11 males; mean age 20.5 $\pm$ 8.4) downloaded from www.nitrc.org/projects/nyu_trt. Participants had no history of psychiatric or neurological illness, as confirmed by a psychiatric assessment. The second dataset, NKI TRT, includes data from 23 participants (17 males; 19 right-handed; mean age 34.4 $\pm$ 12.9) downloaded from http://fcon_1000.projects.nitrc.org/indi/pro/eNKI_RS_TRT. This sample included 6 patients with current or past psychiatric diagnosis, as confirmed by a psychiatric assessment. The institutional review boards of the New York University School of Medicine, New York University, and of the Nathan Kline Institute approved the NYU and NKI studies, respectively. In all cases, signed informed consent was obtained prior to participation, which was compensated.

2.1.1. fMRI acquisition

NYU TRT. Three resting state scans were acquired on each of 25 participants using a Siemens Allegra 3.0 T scanner equipped with echo planar imaging (EPI) (TR = 2000 ms; TE = 25 ms; flip angle = 90; 39 slices, matrix 64 $\times$ 64; FOV = 192 mm; acquisition voxel = 3 $\times$ 3 $\times$ 3 mm; 197 vol; 6 min 34 s). Scans 2 and 3 were acquired in a single scan session 45 min apart, 5–16 months (mean = 11 $\pm$ 4 months) after scan 1 was acquired. During the scans, participants were instructed to rest with eyes open while fixating on the word “Relax” which was centrally projected in white, against a black background. A high-resolution T1-weighted anatomical image was obtained in each session using a magnetization prepared gradient echo sequence (MPRAGE, TR = 2500 ms; TE = 4.35 ms; TI = 900 ms; flip angle = 8; 176 slices, FOV = 256 mm) for spatial normalization and localization.

NKI TRT. Two 10-min resting-state scans were collected from each participant in two different sessions using a 3T Siemens TIM Trio scanner equipped with a 32-channel head coil. The fMRI time-series data were acquired using multiband (MB) accelerated (Moeller et al., 2010) echo-planar imaging, giving a whole-brain temporal resolution of 0.645 s (TE = 30 ms; flip angle = 90; 40 slices; FOV = 222 mm; acquisition voxel = 3 $\times$ 3 $\times$ 3 mm; 930 vol). Scan 1 and scan 2 were completed two weeks apart. A high-resolution T1-weighted anatomical image was also acquired during each session using a magnetization prepared gradient echo sequence (MPRAGE, TR = 2500 ms; TE = 4.35 ms; TI = 900 ms; flip angle = 8; 176 slices, FOV = 256 mm) for spatial normalization and localization.

2.2. fMRI data analysis

2.2.1. Image preprocessing

Data processing was performed using Analysis of Functional NeuroImaging (AFNI; http://afni.nimh.nih.gov/afni) (Cox, 1996) and FMRIB Software Library (FSL; www.fmrib.ox.ac.uk). AFNI image preprocessing comprised slice time correction for interleaved acquisitions (only for the NYU TRT sample); 3-D motion correction with Fourier interpolation; despiking (detection and compression of extreme time series outliers); while FSL preprocessing comprised spatial smoothing using a 6 mm FWHM Gaussian kernel; mean-based intensity normalization of all volumes by the same factor; temporal bandpass filtering (0.009–0.1 Hz); and linear and quadratic detrending.

We used FSL to perform high-resolution structural image registration to the MNI152 template using a two-stage procedure that begins by first calculating a linear transform using the FSL tool *FLIRT* (Jenkinson et al., 2002; Jenkinson and Smith, 2001), which was then refined using *FNIRT* nonlinear registration (Andersson et al., 2007; Andersson, 2007). Linear registration of each

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