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The effects of age on resting state functional connectivity of the basal ganglia from young to middle adulthood

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ABSTRACT

The basal ganglia nuclei are critical for a variety of cognitive and motor functions. Much work has shown age-related structural changes of the basal ganglia. Yet less is known about how the functional interactions of these regions with the cerebral cortex and the cerebellum change throughout the lifespan. Here, we took advantage of a convenient sample and examined resting state functional magnetic resonance imaging data from 250 adults 18 to 49 years of age, focusing specifically on the caudate nucleus, pallidum, putamen, and ventral tegmental area/substantia nigra (VTA/SN). There are a few main findings to report. First, with age, caudate head connectivity increased with a large region of ventromedial prefrontal/medial orbitofrontal cortex. Second, across all subjects, pallidum and putamen showed negative connectivity with default mode network (DMN) regions such as the ventromedial prefrontal cortex and posterior cingulate cortex, in support of anti-correlation of the "task-positive" network (TPN) and DMN. This negative connectivity was reduced with age. Furthermore, pallidum, posterior putamen and VTA/SN connectivity to other TPN regions, such as somatomotor cortex, decreased with age. These results highlight a distinct effect of age on cerebral functional connectivity of the dorsal striatum and VTA/SN from young to middle adulthood and may help research investigating the etiologies or monitoring outcomes of neuropsychiatric conditions that implicate dopaminergic dysfunction.

Introduction

The basal ganglia nuclei play a key role in a variety of cognitive and motor abilities throughout the human lifespan. Based on neurophysiology and anatomical data, it has been proposed that the caudate, putamen, and pallidum are organized into parallel and overlapping "loops" connecting to the cerebral cortex (Alexander et al., 1986; Joel and Weiner, 1997; Middleton and Strick, 2000; Haber, 2003). Similar organization is implicated in humans using probabilistic tractography (Draganski et al., 2008). Modulated by dopaminergic input from the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc), these circuits are implicated in maintenance and updating of working memory (Hazy et al., 2006), control of goal-directed and habitual behavior (Redgrave et al., 2010), reward-based learning (Berridge and Robinson, 1998; Schultz, 2002; Wise, 2004), control of posture and movement (Delong et al., 1983, Mink, 1996), and providing motivational signals to enhance attention and cognition (Pessoa and Engelmann, 2010).

Many of these cognitive and motor functions deteriorate with age (Mark and Rugg, 1998; Smith et al., 1999; Mattay et al., 2002), and co-occur with marked anatomical changes in the basal ganglia. Morphology studies consistently reveal declines in striatal/pallidal volume by 4–8% per decade, starting as early as age 20 (e.g., Brabec et al., 2003; Raz et al., 2003; Walhovd et al., 2011; Goodro et al., 2012). Postmortem studies have shown age-related neuronal loss and changes to basic cellular structure such as the myelin sheath in basal ganglia (for reviews, see Haug, 1985; Kemper, 1994; Peters, 2002). Diffusion tensor imaging demonstrated significant age-related reductions in fractional anisotropy and age-related increases in mean diffusivity in the SN and striatum (Cherubini et al., 2009; Vaillancourt et al., 2012). Accompanying findings of structural changes, age-related differences in functional activation of the basal ganglia nuclei have been consistently reported during cognitive and motor tasks (Mattay et al., 2002; Ward and Frackowiak, 2003; Wu and Hallett, 2005; Rubia et al., 2007; Langenecker et al., 2007). Despite an extensive literature on regional changes in brain activity, little is known about how functional connectivity of the basal ganglia with the cortex and cerebellum changes

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throughout the lifespan. The integrity of these circuits is likely crucial for healthy aging, given their role in a wide range of behaviors (for reviews, see Alexander and Crutcher, 1990; Haber, 2003). The current study addressed this gap of research.

We examined the connectivity of the caudate, putamen, pallidum, and VTA/SN with other brain structures using resting state functional magnetic resonance imaging (rsfMRI) data in a large cohort of young and middle-aged adults. rsfMRI measures the correlations of spontaneous, low-frequency blood oxygenation level dependent (BOLD) signals between brain regions (Biswal et al., 1995; Fox and Raichle, 2007). A proxy for the functional relatedness of neural circuits, resting state functional connectivity has gained wide appeal for its ease of use and reliability within and across individuals (Fox and Raichle, 2007). For example, rsfMRI has been used to delineate subregions of cortical structures (e.g., Mars et al., 2011; Zhang et al., 2012; Zhang and Li, 2012a), predict impulsive behaviors (Davis et al., 2013), and examine changes in developing neural circuits throughout adolescence (Stevens et al., 2009; Tomasi and Volkow, 2012a). Using rsfMRI, Tomasi and Volkow (2012b) demonstrated that from adolescence to young adulthood, VTA connectivity increased with structures in the DMN. Here, we extended this investigation to include seed regions in the dorsal striatum, areas that have received relatively little attention in the adult life-span rsfMRI literature. We posited that functional connectivity of the dorsal striatum and VTA/SN with other brain regions would be significantly altered with age and tested this hypothesis in a convenient sample of slightly older healthy adults (18 to 49 years of age) that we have analyzed extensively in previous work (Zhang et al., 2012; Zhang and Li, 2012a; Li et al., 2014; Zhang and Li, 2014).

Materials and methods

Resting state data

The resting state fMRI (rsfMRI) scans were pooled from three datasets (Leiden_2180/Leiden_2200, Newark, and Beijing_Zang, n = 144) downloadable from the 1000 Functional Connectomes Project (Biswal et al., 2010) and our own data (n = 106). Individual participants' images were viewed one by one to ensure that the whole brain was covered. A total of 250 healthy participants' resting state data (3-Tesla magnet; 18–49 (mean = 24.6 +/− 6.5) years of age; 104 men; one scan per participant; duration: 4.5–10 min; eyes closed during resting) were analyzed. Table 1 summarizes the scan characteristics and demographics of subjects of the data set.

Imaging data preprocessing

Standard image preprocessing was performed on the brain imaging data using Statistical Parametric Mapping (SPM 8, Wellcome Department of Imaging Neuroscience, University College London, U.K.), as described in our previous work (Zhang et al., 2012). Images of each individual participant were first realigned (motion corrected) and corrected for slice timing. Each individual's structural image was coregistered to the mean EPI for each individual (i.e., the mean EPI was used as the reference image). Each individual structural image was then segmented and normalized to an MNI (Montreal Neurological Institute) EPI (echo-planar imaging) template with affine registration followed by nonlinear transformation (Ashburner and Friston, 1999; Friston et al., 1995). The normalization parameters determined for the structural volume were then applied to the corresponding functional image volumes for each participant. The voxels are 3 × 3 × 3 mm. Finally, the images were smoothed with a Gaussian kernel of 8 mm at full width at half maximum.

Additional preprocessing was applied to reduce spurious BOLD variances that were unlikely to reflect neuronal activity (Fair et al., 2007; Fox and Raichle, 2007; Fox et al., 2005; Rombouts et al., 2003). The sources of spurious variance were removed through linear regression by including the signal from the ventricular system, the white matter, and the whole brain, in addition to the six parameters obtained by rigid body head motion correction. First-order derivatives of the whole brain, ventricular and white matter signals were also included in the regression.

Cordes et al. suggested that BOLD fluctuations below a frequency of 0.1 Hz contribute to regionally specific BOLD correlations (Cordes et al., 2001). The majority of resting state studies low-pass filtered BOLD signal at a cut-off of 0.08 or 0.1 Hz (Fox and Raichle, 2007). Thus, we applied a temporal band-pass filter (0.009 Hz < f < 0.08 Hz) to the time course in order to obtain low-frequency fluctuations (Fair et al., 2007; Fox and Raichle, 2007; Fox et al., 2005).

Head motion

As extensively investigated in Van Dijk et al., 2012, micro head motion (>0.1 mm) is an important source of spurious correlations in resting state functional connectivity analysis. Therefore, we applied a "scrubbing" method proposed by Power et al. (2012) and successfully applied in previous studies (Smyser et al., 2010; Power et al., 2012; Tomasi and Volkow, 2012b) to remove time points affected by head motions. Briefly, for every time point t, we computed the *framewise displacement* given by $FD(t) = |\Delta d_x(t)| + |\Delta d_y(t)| + |\Delta d_z(t)| + r|\alpha(t)| + r|\beta(t)| + r|\gamma(t)|$, where (d_x, d_y, d_z) and (α, β, γ) are the translational and rotational movements, respectively, and r (= 50 mm) is a constant that approximates the mean distance between center of MNI space and the cortex and transform rotations into displacements (Power et al., 2012). The second head movement metric was the root mean square variance (DVARS) of the differences in % BOLD intensity $I(t)$ between consecutive time points across brain voxels, computed as follows: $\mathrm{DVARS}(t) = \sqrt{|I(t) - I(t-1)|^2}$, where the brackets indicate the mean across brain voxels. Finally, to compute each subject's correlation map, we removed every time point that exceeded the head motion limit $FD(t) > 0.5$ mm or $\mathrm{DVARS}(t) > 0.5\%$ (Power et al., 2012; Tomasi and Volkow, 2012b). On average, 1% of the time points were removed across subjects.

Seed-based functional connectivity: linear correlations

We used the caudate, pallidum, and putamen templates from the Anatomical Automatic Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) and the maximum probability maps template for the VTA/SN seed (Hammers et al., 2003; Ahsan et al., 2007). The VTA/SN seed was derived from the structural MRIs of 30 healthy adults; after spatial normalization and averaging across subjects the size of the left VTA/SN seed was 561 mm^3 and the right VTA/SN seed was 545 mm^3 (Ahsan et al., 2007). The putamen and the caudate were bisected into anterior and posterior regions based on boundaries from previous studies; the putamen was divided along the coronal slice containing the anterior

Table 1
Available demographic data and imaging parameters for the selected resting state functional MRI datasets from the image repository for the 1000 Functional Connectomes Project and for our own dataset.

Dataset	Subjects	Age (years)	Timepoints	TR (s)	Slice acquisition order
Beijing_Zang	31 M/66 F	18–26	225	2	Interleaved ascending
Leiden_2180	10 M/0 F	20–27	215	2.18	Sequential descending
Leiden_2200	11 M/8 F	18–28	215	2.22	Sequential descending
Newark	9 M/9 F	21–39	135	2	Interleaved ascending
Our own	63 M/43 F	19–49	295	2	Interleaved ascending

Note: M—males; F—females.