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Putamen–midbrain functional connectivity is related to striatal dopamine transporter availability in patients with Lewy body diseases

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ABSTRACT

Prior work has shown that functional connectivity between the midbrain and putamen is altered in patients with impairments in the dopamine system. This study examines whether individual differences in midbrain–striatal connectivity are proportional to the integrity of the dopamine system in patients with nigrostriatal dopamine loss (Parkinson's disease and dementia with Lewy bodies). We assessed functional connectivity of the putamen during resting state fMRI and dopamine transporter (DAT) availability in the striatum using 11C-Altropane PET in twenty patients. In line with the hypothesis that functional connectivity between the midbrain and the putamen reflects the integrity of the dopaminergic neurotransmitter system, putamen–midbrain functional connectivity was significantly correlated with striatal DAT availability even after stringent control for effects of head motion. DAT availability did not relate to functional connectivity between the caudate and thalamus/prefrontal areas. As such, resting state functional connectivity in the midbrain–striatal pathway may provide a useful indicator of underlying pathology in patients with nigrostriatal dopamine loss.

1. Introduction

Dopamine cells of the midbrain (substantia nigra and ventral tegmental area) heavily innervate the striatum. Loss of dopaminergic cells in the midbrain is a neuropathological hallmark of age-related Lewy body diseases (LBD) including Parkinson's disease with or without dementia and dementia with Lewy bodies. Nigrostriatal dopamine loss can currently only be measured in vivo using positron emission tomography (PET). Striatal dopamine transporter (DAT) availability measured with PET is one measure of nigrostriatal integrity (see Brooks and Pavese, 2011, for review). DAT binding in putamen and caudate in patients with LBD is reduced by 55–75% compared to age-matched controls (Innis et al., 1993; O'Brien et al., 2004) and correlates with nigrostriatal neuron loss observed post-mortem (Colloby et al., 2012).

Consistent with known projections, the striatum and midbrain are functionally coupled as measured with functional magnetic resonance imaging (fMRI) during resting state in healthy adults (Kelly et al., 2009; Hacker et al., 2012). Studies in patients with Parkinson's disease have shown that midbrain–putamen functional connectivity is reduced compared to age-matched healthy controls (Hacker et al., 2012; Wu et al., 2012), suggesting that loss of striatal resting-state functional connectivity may be reflective of the nigrostriatal dopamine loss in these patients. In line with this hypothesis, Tomasi and Volkow (2014) showed increases in midbrain coupling with ventral striatum and pallidum in children with attention deficit hyperactivity disorder (ADHD), which may parallel the increased levels of markers of the dopamine system that are seen in ADHD (e.g. Spencer et al., 2013). In schizophrenic patients, midbrain connectivity with ventral striatum was decreased (Hadley et al., 2014), again possibly reflecting altered functions of the dopamine system in this patient group (Laruelle et al., 1996).

To date, however, reports have been restricted to group comparisons between patient groups with known pathology of the dopamine system, without an analysis of individual differences in midbrain–striatal connectivity in relation to in vivo assessments of dopamine PET markers. The present study was designed to fill this gap by assessing striatal connectivity with resting-state fMRI and DAT availability with PET in the same group of patients with nigrostriatal dopamine loss. We predicted that weaker functional connectivity MRI between the midbrain and the putamen would be related to lower presynaptic DAT availability in the striatum. If present, such a result would indicate

Abbreviation list: LBD, Lewy body diseases; DAT, dopamine transporter; UPDRS, Unified Parkinson's Disease Rating Scale; ROI, region of interest; DVR, distribution volume ratio.

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that resting-state functional connectivity MRI may function as a useful biomarker of underlying neuropathology.

2. Materials and methods

2.1. Participants

Twenty-six patients (mean age = 68.1 years, SD = 6.7, range 57–81, 9 female) with parkinsonism completed a PET scan, a structural MRI and at least one resting-state fMRI run. Data from six of these patients were excluded from analysis because of head motion (Van Dijk et al., 2012).

Subjects were recruited from the MGH Movement Disorders and Memory Disorders Units. All subjects gave informed consent to participate in the study according to the protocol approved by the ethical review board. Patients were clinically diagnosed with parkinsonism and had, on average, experienced motor symptoms for 9.2 years (SD = 5.6, range 3–22 years). Fourteen patients met diagnostic criteria for idiopathic Parkinson's disease (Hughes et al., 1992) and were non-demented. Six other patients were diagnosed with parkinsonism and cognitive impairment: three had dementia with Lewy bodies (McKeith et al., 2005) and three had Parkinson's disease with dementia (Emre et al., 2007). Although it is worthwhile to study these patient groups separately when large sample sizes permit (e.g. Marquie et al., 2014), in the current study the primary objective was to study striatal functional connectivity in relation to dopamine loss as measured with PET. As all subjects shared the typical motor signs of parkinsonism, and as DAT density was depleted in all patients relative to a healthy reference sample, patients were treated as a single group.

Patients were tested on their prescribed dopamine replacement medication to minimize head motion and a levodopa equivalent dose was calculated (mean = 400.3 mg/day, SD = 376.8; Tomlinson et al., 2010). Motor impairment was classified according to Hoehn and Yahr criteria (mean = 2.5, SD = 0.6, range 2–4) and the Unified Parkinson's Disease Rating Scale motor subscale (UPDRS; mean = 20.7, SD = 8.4, range 8–37; data missing for one individual).

Data from twenty-nine clinically normal older adults were used as reference sample to (1) demonstrate that our PET measure accurately separates DAT densities in clinically normal aging from pathological dopamine loss and (2) to identify reference seeds for the functional connectivity analyses. Control subjects were clinically normal older adults (mean = 70.9 years, range 63–80, 11 females) recruited for the Harvard Aging Brain study. Patients and normal controls did not differ in terms of age ($t(47) = 1.0$, $p = 0.34$) or estimated VIQ (mean(±SD) patients = 122.5(11.4), mean(±SD) controls = 120.9(9.6); $t(46) = -0.5$, $p = 0.62$; based on the American National Reading Test; Ryan and Paolo, 1992). Healthy controls were slightly lower in years of education (mean(±SD) patients = 16.2(3.2), mean(±SD) controls = 14.4(2.8); $t(47) = -2.1$, $p = 0.04$). Data from these patients and normal control participants have been presented elsewhere (Marquie et al., 2014; Schultz et al., 2014; Shaw et al., 2015).

2.2. PET acquisition and analysis

Binding of 11C-Altropane, a ligand with high selectivity for striatal DAT (Fischman et al., 2001), was assessed with an HR+ (CTI, Knoxville, TN) PET camera (3D mode, 63 adjacent slices of 2.42 mm interval, 15.2 cm axial field of view, 5.60 mm transaxial resolution). Approximately 15 mCi of 11C-Altropane was intravenously administered as a bolus over 20–30 s. Dynamic images were acquired in 39 frames of increasing duration for a total of 60 min (8×5 s, 4×1 min, 27×2 min). PET data were reconstructed using a filtered back-projection algorithm and standard photon attenuation measurements were used to correct the emission data. The participant's head was stabilized during the scan and correction for residual head motion was performed on the dynamic data to a common reference frame.

PET data were partial volume corrected using an anatomical MRI-based correction method, implemented using PVElab Software and SPM5 (Quarantelli et al., 2004; Meltzer et al., 1990). Then, uptake images (averaged across the first 8 min) were normalized to the SPM8 standard PET template in MNI space using a two-step procedure of an initial 12-parameter affine transformation followed by non-linear warping (http://www.fil.ion.ucl.ac.uk/spm). Normalization parameters were applied to the remaining frames and a striatum region of interest (ROI) was defined as the 1000 voxels (=8 cm^3) with the highest signal intensity on the average emission image (8–60 min, Fig. 1A). The search was constrained to a large search area around the striatum. A central cerebellar region of 1000 voxels was defined in MNI atlas space as a reference region and Logan graphical analysis was used to derive distribution volume ratios (DVRs; Logan et al., 1990) for the striatum. Alternative methods for PET ROI delineation of striatum involve manual or automatic delineation in native PET or MRI space. However, anatomical ROI estimates can be inaccurate due to low spatial resolution or low contrast and also differ in size between individuals, which may introduce dependencies between volume measures and DVR. Our approach ensured that DVR estimation for the striatum is fully automated, of a fixed size, and not affected by moderate errors in the registration to standard space. Even though this approach does not distinguish between sub-regions of the striatum it accurately separates DAT densities in clinically normal aging (mean = 3.38, SD = 0.34) from pathological dopamine loss in the patients (mean = 2.02, SD = 0.29; $t(47) = 14.70$, $p < 0.01$; Fig. 1B) and the DVR estimates correlated significantly with disease duration ($r = -0.45$, $p = 0.02$) and Hoehn–Yahr stage of motor impairment ($r = -0.45$, $p = 0.03$) in the present sample.

2.3. MRI acquisition and analysis

All patients completed a T1-weighted MPRAGE scan (1.0 mm isotropic voxel size, TR = 2300 ms, TE = 2.98 ms, Flip angle 9 deg, 192 slices) and at least one resting state fMRI run of 6 min and 30 s using a T2*-weighted sequence sensitive to blood oxygenation level dependent contrast (2.0 mm isotropic voxel size; TR = 5000 m, TE = 30 ms, flip angle 90 deg, 55 slices). For normal controls, a multiecho MPRAGE (1.20 mm isotropic voxel size, TR = 2200 ms, TI = 1100 ms, Flip angle = 7 deg, 4× acceleration, 144 slices, TE = 1.54, 3.36, 5.18, 7.01 ms) and two resting state fMRI runs of 6 min and 20 s were available (3.0 mm isotropic voxel size, TR = 3000 ms, TE = 30 ms, Flip angle = 85 deg, 47 slices). All MRI scans were acquired on a Siemens 3 T Tim Trio scanner at Massachusetts General Hospital.

From the T1-weighted structural scan, ventricular size was estimated from a volumetric segmentation using Freesurfer (v 5.1.0, e.g. Fischl et al., 2002). Ventricle volume was normalized by intracranial volume following the methods described in Buckner et al. (2004), and used to control for the effects of subcortical atrophy in the association between functional connectivity and striatal DVR.

Pre-processing of the fMRI data followed the procedures of prior studies in this field (di Martino et al., 2008; Hacker et al., 2012) and included slice-timing correction, motion-correction, registration to standard MNI152 space, spatial smoothing, temporal filtering, and intensity normalization. Motion-correction was performed using rigid body translation and rotation of all volumes to the first volume (Jenkinson et al., 2002). To acquire a summary measure of motion, the root-mean-square of the 3 translation and 3 rotation parameters was calculated for each volume relative to the preceding volume and averaged over all volumes of the scan. Following this step, six patients were excluded from further analysis (N = 20 remaining) because they had an average mean displacement of more than 0.25 mm, where 0.25 mm corresponds approximately to 2 SDs above the average mean motion for the healthy older control group (mean = 0.10 mm, SD = 0.07), and/or at least 5 isolated movements of more than 0.5 mm from one brain volume as compared to the previous volume.