doi:10.1093/brain/awx053 BRAIN 2017: 140; 1371–1383 | 1371

BRAIN
A JOURNAL OF NEUROLOGY

Neuroimaging and clinical features in adults with a 22q11.2 deletion at risk of Parkinson's disease

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The recurrent 22q11.2 deletion is a genetic risk factor for early-onset Parkinson's disease. Adults with the associated 22q11.2 deletion syndrome (22q11.2DS) may exhibit phenotypes that could help identify those at highest risk and reveal disease trajectories. We investigated clinical and neuroimaging features relevant to Parkinson's disease in 26 adults: 13 with 22q11.2DS at genetic risk of Parkinson's disease (mean age = 41.5 years, standard deviation = 9.7), 12 healthy age and sex-matched controls, and a 22q11.2DS patient with L-DOPA-responsive early-onset Parkinson's disease. Neuroimaging included transcranial sonography and positron emission tomography using ^{11}C-dihydrotetrabenazine (^{11}C-DTBZ), a radioligand that binds to the presynaptic vesicular monoamine transporter. The 22q11.2DS group without Parkinson's disease demonstrated significant motor and olfactory deficits relative to controls. Eight (61.5%) were clinically classified with parkinsonism. Transcranial sonography showed a significantly larger mean area of substantia nigra echogenicity in the 22q11.2DS risk group compared with controls ($P = 0.03$). The 22q11.2DS patient with Parkinson's disease showed the expected pattern of severely reduced striatal ^{11}C-DTBZ binding. The 22q11.2DS group without Parkinson's disease however showed significantly elevated striatal ^{11}C-DTBZ binding relative to controls (~33%; $P < 0.01$). Results were similar within the 22q11.2DS group for those with ($n = 7$) and without ($n = 6$) psychotic illness. These findings suggest that manifestations of parkinsonism and/or evolution to Parkinson's disease in this genetic at-risk population may include a hyperdopaminergic mechanism. Adequately powered longitudinal studies and animal models are needed to evaluate the relevance of the observed clinical and imaging phenotypes to Parkinson's disease and other disorders that are more prevalent in 22q11.2DS, such as schizophrenia.

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Received October 10, 2016. Revised January 20, 2017. Accepted January 23, 2017. Advance Access publication March 24, 2017.

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Keywords: 22q11.2 deletion syndrome; dopamine; neurotoxicity; Parkinson's disease; ^{11}C-DTBZ PET

Abbreviations: BP_{ND} = non-displaceable binding potential; MDS = Movement Disorders Society; UPDRS = Unified Parkinson's Disease Rating Scale

Introduction

Parkinson's disease is a common progressive neurodegenerative disorder, associated with a massive loss of dopaminergic cells that affects about 1% of the population over age 60 years. The study of patients at genetic risk of developing Parkinson's disease provides insight into early disease mechanisms that may help inform early diagnostic and intervention strategies (van der Brug *et al.*, 2015). We reported the recurrent hemizygous 22q11.2 deletion that is associated with 22q11.2 deletion syndrome (22q11.2DS, OMIM #192430, #188400) as a novel genetic risk factor for early-onset Parkinson's disease (Butcher *et al.*, 2013). Nearly 6% of 22q11.2DS patients over the age of 35 years were diagnosed with Parkinson's disease. The deletion has since been found to be enriched in early-onset Parkinson's disease cohorts and may account for ~0.5% of all cases of early-onset Parkinson's disease (Mok *et al.*, 2016). The recurrent 22q11.2 deletion affects an estimated 1 in 4000 live births, usually occurring as a spontaneous mutation (McDonald-McGinn *et al.*, 2015).

The Parkinson's disease phenotype in 22q11.2DS (22q11.2DS-Parkinson's disease) includes classic loss of midbrain dopaminergic neurons and variable Lewy body neuropathology (Booij *et al.*, 2010; Butcher *et al.*, 2013; Mok *et al.*, 2016). Patients with 22q11.2DS-Parkinson's disease identified to date appear to show clinical symptoms, disease course, and treatment response similar to that of typical Parkinson's disease (Zaleski *et al.*, 2009; Booij *et al.*, 2010; Butcher *et al.*, 2013; Rehman *et al.*, 2015; Mok *et al.*, 2016). Manifestations of 22q11.2DS are multi-system and variable between patients, including birth defects, learning disabilities, endocrinological abnormalities, and seizures. Neuropsychiatric disorders, including those thought to involve dopaminergic dysfunction such as attention deficit disorder and schizophrenia, are common (Bassett *et al.*, 2011; Fung *et al.*, 2015; McDonald-McGinn *et al.*, 2015).

There are as yet no systematic data on neuroimaging and clinical features of potential relevance to parkinsonism and Parkinson's disease in individuals with a 22q11.2 deletion. To begin to address this, we investigated adults with 22q11.2DS using standard assessments of motor and non-motor functioning and neuroimaging relevant to Parkinson's disease including transcranial sonography and PET. For the PET, we selected ^{11}C-dihydrotetrabenazine (^{11}C-DTBZ), a vesicular monoamine transporter (VMAT2) radioligand used to assess striatal dopamine neuron density in other populations (Frey *et al.*, 1996; Bohnen *et al.*, 2006; Martin *et al.*, 2008; Christopher *et al.*, 2014). Healthy controls, and a single living patient with 22q11.2DS-Parkinson's disease, were assessed for comparison purposes.

We hypothesized that adults with 22q11.2DS at increased genetic risk of Parkinson's disease would exhibit a higher prevalence and/or severity of motor and non-motor features believed to be associated with Parkinson's disease risk (Postuma *et al.*, 2012; Siderowf and Lang, 2012; Berg *et al.*, 2015) as well as neuroimaging features known to precede the clinical manifestation of Parkinson's disease, relative to healthy controls. These included enlarged substantia nigra echogenicity on transcranial sonography (Berg *et al.*, 2013; Pilotto *et al.*, 2015) and reduced striatal ^{11}C-DTBZ binding on PET neuroimaging (Stoessl *et al.*, 2011). We expected that the 22q11.2DS-Parkinson's disease case would show a similar but more severe profile of symptoms and neuroimaging abnormalities.

Materials and methods

Participants and clinical evaluations

A total of 26 Canadian adults participated in this study. The main comparison groups comprised 13 individuals with 22q11.2DS ('22q11.2DS group') at increased age-related risk of Parkinson's disease ($\geq$30 years) and 12 healthy age and sex-matched controls (Table 1). As a positive control, we also assessed one previously unreported 50-year-old female patient with 22q11.2DS and early-onset Parkinson's disease. All participants were assessed using a battery of standard motor and non-motor assessments (Table 2), transcranial

Table 1 Demographic characteristics and clinical features of 22q11.2 deletion syndrome adults at genetic risk of early-onset Parkinson's disease and age and sex-matched healthy controls

	Healthy controls (n = 12)	At-risk 22q11.2DS (n = 13)	Analyses (P)[a]
Demographic features			
Mean age (years)	42.4 ± 8.7	41.5 ± 7.3	0.79
Male sex	8 (66.7%)	8 (61.5%)	1.00
Caucasian ethnicity	11 (91.7%)	14 (100.0%)	0.48
Right handedness	9 (75.0%)	11 (84.6%)	0.65
Smoker	5 (41.6%)	1 (7.7%)	0.07
Mean years of education (years)[b]	15.3 ± 2.0	12.8 ± 1.8	**0.004**
Mean Montreal Cognitive Assessment (MoCA score 0–30)	27.2 ± 2.6	22.5 ± 3.5	**0.0009**
22q11.2 deletion associated major features			
Congenital heart defect[c]	–	5 (38.5%)	–
Intellectual disability (mild)	–	4 (30.8%)	–
Psychotic disorder	–	7 (53.8%)	–
Other psychiatric disorder[d]	–	9 (69.2%)	–
Recurrent seizures	–	3 (23.1%)	–

Data are mean (SD) or n (%).
[a]P-values from Fisher's exact tests for categorical variables and independent t-tests for continuous variables. Bold font indicates statistically significant P-values.
[b]Includes special education, in the 22q11.2DS group only.
[c]Tetralogy of Fallot/pulmonary atresia/ventricular septal defect, n = 2; tetralogy of Fallot, n = 1; ventricular septal defect, n = 1; sinus of Valsalva fistula/aneurysm, n = 1.
[d]Major depressive disorder, n = 5; generalized anxiety disorder, n = 4; obsessive compulsive disorder, n = 1 (Supplementary Table 1).

sonography, and ^{11}C-DTBZ PET. None of the 26 participants had a first-degree family history of Parkinson's disease.

All patients with 22q11.2DS were recruited from a large cohort of adults with 22q11.2DS primarily ascertained through adult congenital cardiac, psychiatric, and genetic services using active screening and/or clinical referrals, where the 22q11.2 deletion had been molecularly confirmed using standard methods (Bassett *et al.*, 2005; Van *et al.*, 2016). Microarray results available for 12 of the 13 subjects in the 22q11.2DS group showed the typical ~2.5 Mb 22q11.2 deletion (LCR A-D) (Bassett *et al.*, 2005; Costain *et al.*, 2013). The subject without microarray results had a confirmed 22q11.2 deletion with fluorescence *in situ* hybridization (FISH) using standard probes for the typical 22q11.2 deletion region. Healthy controls were recruited using advertisement and confirmed to be free of major neurological, psychiatric, or any other major illness using the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Motor Examination, the Mini-International Neuropsychiatric Interview, the Mini-Mental State Examination, and a comprehensive medical history.

Psychiatric diagnoses in patients with 22q11.2DS were made using DSM-IV criteria, and previously established methods (Chow *et al.*, 2006; Butcher *et al.*, 2012; Van *et al.*, 2016). Nine (64.3%) patients had borderline to normal intellect and the remainder (n = 4, 30.8%) met DSM-IV criteria (Chow *et al.*, 2006; Butcher *et al.*, 2012; Van *et al.*, 2016) for mild intellectual disability (Supplementary Table 1). Seven (53.8%) patients in the 22q11.2DS group were treated with an antipsychotic medication for a psychotic illness (Supplementary Table 2): three patients were diagnosed with schizophrenia, two with schizoaffective disorder, and two with a psychotic mood disorder. Mean age at onset of psychosis was 25.3 [standard deviation (SD) = 7.2] years. Other current psychotropic medications in the 22q11.2DS group (Supplementary Table 1) included antidepressants (n = 9), benzodiazepines (n = 5), and anticonvulsants (n = 1).

The patient with 22q11.2DS-Parkinson's disease had a history of moderate intellectual disability and was treated for an anxiety disorder and a major depressive disorder with an antidepressant (Supplementary Table 1). There was no history of psychosis or treatment with an antipsychotic medication in this patient. The absence of known pathogenic point mutations in *LRRK2*, *PARK2*, *PARK7*/DJ-1, *PINK1*, or *SNCA*, or copy number variants in *PARK2* or *SNCA* was confirmed using previously described methods (Butcher *et al.*, 2013). Clinical microarray testing showed a maternally inherited ~500 kb 3q29 duplication (variant of unknown significance) in addition to the typical 22q11.2 deletion. This patient received a clinical diagnosis of L-DOPA responsive early-onset Parkinson's disease at age ~48 years, following symptom onset at ~45 years. L-DOPA treatment for this participant was withdrawn for 12 h prior to performing PET scanning and motor assessments.

Informed consent was obtained in writing and the study was approved by the research ethics boards at the Centre for Addiction and Mental Health and University Health Network, Toronto, Ontario, Canada.

Transcranial sonography

Bilateral transcranial sonography of the substantia nigra was independently performed by two experienced sonographers using a Siemens Acuson X300 PE and a 2.0–3.5 MHz transducer with a penetration depth of 14–16 cm and a dynamic range of 40–45 dB. Echogenicity measurements were performed off-line by a single sonographer. We selected the larger area of echogenicity in the substantia nigra of each participant or, in cases of an insufficient temporal bone window

Table 2 Motor and non-motor characteristics of 22q11.2 deletion syndrome adults at genetic risk of early-onset Parkinson's disease and age and sex-matched healthy controls

	Healthy controls (n = 12)	At-risk 22q11.2DS (n = 13)	Analyses (P)[a]
Motor phenotypes			
MDS-UPDRS[b] mean scores			
I: Non-motor EDL (score 0–52)	–	11.2 ± 7.6	–
II: Motor EDL (score 0–52)	–	5.6 ± 6.5	–
III: Motor Exam (score 0–132)[c]	0.8 ± 1.2[d]	11.5 ± 9.0	**0.0004**
Bradykinesia subscore (score 0–44)	0.4 ± 0.8	5.8 ± 6.1	**0.008**
Tremor subscore (score 0–36)	0.3 ± 0.6	1.4 ± 1.6	**0.032**
Rigidity subscore (score 0–20)	0 ± 0	0.6 ± 1.0	0.055
Axial impairment subscore (score 0–20)	0 ± 0	1.6 ± 1.4	**0.002**
Hoehn and Yahr Stage			
Stage 1	–	2 (15.4%)	-
Stage 2	–	3 (23.1%)	-
Stage 2.5	–	3 (23.1%)	-
Tremor Rating Scale (score 0–136)	–	9.6 ± 8.9	–
Purdue pegboard (age and sex-adjusted mean z-score)			
Dominant hand	−0.6 ± 1.0	−2.8 ± 1.1	**0.0002**
Non-dominant hand	−0.9 ± 1.3	−2.9 ± 1.1	**0.004**
Non-motor phenotypes			
Hyposmia classification[e] (UPSIT)	4 (33.3%)	10 (76.9%)	**0.047**
UPSIT raw mean score (score 0–40)	33.6 (range 21–40)	29.3 (range 21–40)	**0.094**
Farnsworth-Munsell 100-Hue test error score	124.7 ± 80.4	227.1 ± 77.4	0.30[f]
REM sleep behaviour disorder symptoms[g]	1 (8.3%)	1 (7.1%)	1.00

Data are mean (±SD) or n (%) unless otherwise noted.
EDL = Experiences of Daily Living; MDS-UPDRS = Movement Disorders Society-Unified Parkinson's Disease Rating Scale; UPSIT = University of Pennsylvania Smell Identification Test; Tremor Rating Scale = Modified Fahn-Tolosa-Marin Tremor Rating Scale.
[a]P-values from Fisher's exact tests for categorical variables and independent t-tests for continuous variables unless otherwise noted. Bold font indicates statistically significant P-values.
[b]The MDS-UPDRS scores for the single 22q11.2DS-Parkinson's disease (Hoehn and Yahr stage 3) case following 12-h withdrawal from L-DOPA were as follows: non-motor EDL = 3, motor EDL = 3, and motor exam = 64.
[c]Motor subscores were calculated from the MDS-UPDRS for all subjects as follows: bradykinesia (items 3.4 + 3.5 + 3.6 + 3.7 + 3.8 + 3.14), tremor (items 3.15 + 3.16 + 3.17), rigidity (item 3.3), and axial impairment (items 3.9 + 3.10 + 3.12 + 3.13).
[d]Four healthy controls had slight, clinically insignificant motor features.
[e]Hyposmia classified using age and sex-adjusted normative scores (http://sensonics.com/). Two (50%) of the controls with hyposmia and one (10%) of the 22q11.2DS patients with hyposmia were smokers.
[f]Adjusted for cognitive level (MoCA) due to test sensitivity to mild cognitive deficits (Bertrand et al., 2012). One 22q11.2DS patient was unable to complete the 100-Hue Test due to comprehension difficulties.

on one side (n = 3 each in the 22q11.2DS and control group), the area from the analysable side.

PET neuroimaging

Each subject had PET imaging using ^{11}C-DTBZ, a radioligand that binds to VMAT2. VMAT2 is a vesicular membrane protein that transports cytosolic dopamine (and other monoamines) into presynaptic vesicles (Lawal and Krantz, 2013). The majority (>95%) of VMAT2-related activity in the striatum derives from dopaminergic presynaptic terminals (Vander Borght *et al.*, 1995; Wilson *et al.*, 1996*b*). VMAT2 binding is an established index of striatal dopamine neuron density in other populations (Frey *et al.*, 1996; Bohnen *et al.*, 2006; Martin *et al.*, 2008; Stoessl, 2011; Christopher *et al.*, 2014), based on evidence that striatal VMAT2 levels are a linear function of the number of dopaminergic neurons in the substantia nigra pars compacta (Vander Borght *et al.*, 1995; Sun *et al.*, 2012), its strong correlation with striatal levels of the dopamine transporter, another presynaptic dopamine terminal marker, in healthy subjects (Sun *et al.*, 2012), and its robustness to both disease and drug compensatory regulation mechanisms (Vander Borght *et al.*, 1995; Kilbourn *et al.*, 1996; Wilson *et al.*, 1996*a*; Kemmerer *et al.*, 2003).

PET scans were performed using a 3D high-resolution research brain tomograph (Siemens) as previously described (Christopher *et al.*, 2014). Following a 10-min transmission scan, the emission scans started with the bolus injection of ^{11}C-DTBZ (dose injected: 22q11.2DS group 9.91 ± 0.52 mCi versus control group 9.91 ± 0.81 mCi, P = 0.99; specific activity at time of injection: 22q11.2DS group 1674.8 ± 802.6 versus control group 2104.3 ± 1043.3 mCi/μmol, P = 0.26). Acquisition of emission data occurred over a period of 60 min. The emission list mode data were rebinned into a series of 3D sinograms. The data were normalized with attenuation and scatter correction before applying Fourier rebinning to convert the 3D sinograms into 2D sinograms, which were then reconstructed into image space using a 2D filtered back projection algorithm.

A region of interest analysis was performed for ^{11}C-DTBZ as described in Rusjan *et al.* (2006) using ROMI software. Our primary region of interest was the sensorimotor striatum (posterior putamen), which shows the earliest signs of dopamine depletion in Parkinson's disease. We also examined the

associative (anterior putamen and caudate nucleus) and limbic (ventral striatum) striatal subdivisions (Martinez *et al.*, 2003). A standard brain template (International Consortium for Brain Mapping/Montreal Neurological Institute 152 MRI) containing predefined cortical and subcortical regions of interest (Talairach and Tournoux, 1988; Kabani *et al.*, 1998) was non-linearly transformed using Statistical Parametric Mapping software (SPM8) to fit the individual high-resolution proton density weighted structural MRI scans (GE 3 T, oblique axial scan with 1 mm slice thickness).

Regions of interest were aligned and resliced to match the dimension of the PET images using a normalized mutual information algorithm.^{11}C-DTBZ binding to VMAT2 (non-displaceable binding potential, BP_{ND}) was estimated in each region of interest using the simplified reference tissue model (SRTM) (Lammertsma and Hume, 1996) and the occipital cortex time activity curve as an input function (Koeppe *et al.*, 1996; Chan *et al.*, 1999) using an in-house MATLAB script. The occipital cortex is the established region of reference (i.e. devoid of significant levels of VMAT2) (Tong *et al.*, 2011) for ^{11}C-DTBZ imaging studies. The SRTM has been established as an appropriate model to quantify ^{11}C-DTBZ without arterial input function (Koeppe *et al.*, 1996; Chan *et al.*, 1999). ^{11}C-DTBZ binding after partial volume effects correction on time activity curve data using the Rousset algorithm (Rousset *et al.*, 1998) was also assessed.

Statistical analyses

To compare demographic and clinical variables between the 22q11.2DS group and healthy controls, we used *t*-tests for independent continuous variables and Fisher's exact tests for independent categorical variables. ^{11}C-DTBZ binding in the regions of interest was contrasted between groups with analysis of covariance and corrected for multiple testing using a Bonferroni correction. An absolute lateralization index was calculated to investigate possible hemispheric asymmetry of ^{11}C-DTBZ binding (|right − left| / [right + left] / 2) for each region of interest and compared between groups using the same analysis of covariance approach. Spearman rank-order correlation coefficients were used to examine the putative relationships between regional ^{11}C-DTBZ binding and clinical symptoms. All statistical analyses were two-tailed and performed with SAS version 9.4 software (SAS Institute, Cary, NC), with statistical significance defined as $P < 0.05$.

Results

Demographic and clinical features of the 22q11.2DS group at genetic risk of early-onset Parkinson's disease and healthy controls are presented in Table 1. There were no significant between-group differences in age, sex, ethnicity, or handedness. The proportion of smokers was non-significantly greater in the control group. Patients with 22q11.2DS had a lower level of education and performed significantly worse on the Montreal Cognitive Assessment (MoCA) than controls, consistent with limitations in intellectual functioning as expected in 22q11.2DS (Chow *et al.*, 2006; Bassett *et al.*, 2011; Fung *et al.*, 2015).

Motor findings

Compared with the control group (Table 2), the 22q11.2DS group had a significantly higher mean score on the MDS-UPDRS Motor Exam subscale ($P = 0.0004$) and the associated bradykinesia ($P = 0.008$), tremor ($P = 0.032$), and axial impairment ($P = 0.002$) subscores and performed significantly worse on the Purdue Pegboard test (dominant hand, $P = 0.0002$; non-dominant hand, $P = 0.004$).

Each subject in the 22q11.2DS group exhibited at least one parkinsonian sign on the MDS-UPDRS motor exam (Supplementary Table 2). Bradykinesia was the most commonly observed, affecting 11 (84.6%) of the 13 patients, including all six with no history of antipsychotic treatment. Four subjects (23.1%) had rigidity, four (30.8%) postural instability, and eight (61.5%) action tremor, of whom one, three, and four, respectively, had no antipsychotic treatment. Eight patients (61.5%), and no healthy controls, were clinically classified by the assessing movement disorders specialist to have parkinsonism (Supplementary Table 2). Of these, two had no antipsychotic treatment.

Non-motor findings

There was a significantly greater proportion of 22q11.2DS patients with hyposmia ($n = 10$, 76.9%) compared with controls ($n = 4$, 33.3%; $P = 0.047$), although results were non-significant if smokers ($n = 1$ 22q11.2DS; $n = 5$ controls) were excluded ($n = 9$ hyposmia, 75.0% versus $n = 2$, 28.5%; $P = 0.074$). Hyposmia was absent ($n = 2$) or mild ($n = 3$) in the 22q11.2DS patients without parkinsonism. In contrast, six of the eight patients with parkinsonism had moderate to severe hyposmia, and the patient with 22q11.2DS-Parkinson's disease met criteria for anosmia (Supplementary Table 2). Although performance was worse on the 100-Hue test of colour discrimination in the 22q11.2DS group (Table 2), there was no significant between-group difference after adjusting for cognitive level (MoCA scores). One participant in each group self-reported symptoms of REM sleep behaviour disorder (Nightingale *et al.*, 2005) by endorsing that they moved while asleep as if acting out their dreams, that they had injured themselves or a bed partner while asleep, and that those movements woke them from sleep.

Neuroimaging findings

As hypothesized, the mean area of substantia nigra echogenicity on transcranial sonography was significantly larger in the 22q11.2DS at-risk of Parkinson's disease group than the healthy control group (0.18 cm^2, SD = 0.06; 0.11 cm^2, SD = 0.07, respectively; $P = 0.03$; Fig. 1). Substantia nigra echogenicity did not correlate with any motor symptoms or with ^{11}C-DTBZ binding results (data not shown).

The 22q11.2DS patient with Parkinson's disease showed the expected pattern of severely reduced striatal ^{11}C-DTBZ

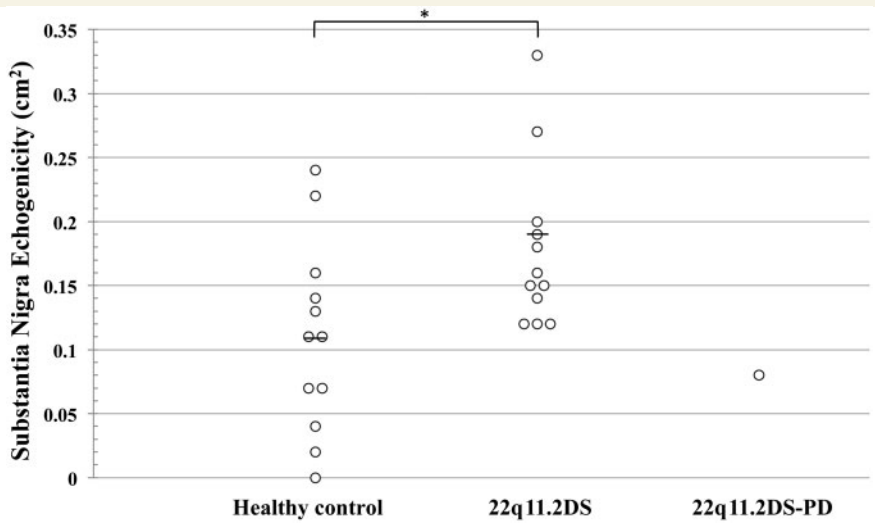

Figure 1 Transcranial sonography findings in adults with 22q11.2 deletion syndrome (22q11.2DS) at genetic risk of early-onset Parkinson's disease and one with 22q11.2DS and Parkinson's disease (22q11.2DS-PD). The mean echogenic area (horizontal line) corresponding to the anatomical location of the substantia nigra was significantly larger in the 22q11.2DS at-risk group compared with the age and sex-matched control group. The area of echogenicity in the substantia nigra in the 22q11.2DS-PD case is shown for comparison purposes. Zero measurements indicate instances where the mesencephalic brainstem was clearly visualized but there was no measurable echogenic signal in the location of the substantia nigra. The bilateral temporal bone window was insufficient in one 22q11.2DS patient. *$P \leqslant 0.05$.

binding. However, contrary to our hypothesis, the 22q11.2DS group had significantly higher mean overall striatal ^{11}C-DTBZ BP_{ND} values (3.24, SD = 0.61) compared with healthy controls (2.43, SD = 0.40; $P = 0.007$; Fig. 1). Mean ^{11}C-DTBZ binding was 36.7% higher in the sensorimotor striatum (3.50, SD = 0.96) relative to the control group (2.56, SD = 0.48; $P = 0.006$), 34.9% higher in the associative striatum (22q11.2DS 3.40, SD = 0.70; controls 2.52, SD = 0.43; $P = 0.001$), and 30.9% higher in the limbic striatum (22q11.2DS 2.71, SD = 0.42; controls 2.07, SD = 0.30; $P = 0.0003$). Results were similar after implementing a partial volume effects correction on time activity curve data (results not shown). Also, within the 22q11.2DS group, comparing patients with and without psychosis, there were no significant differences for striatal BP_{ND} values ($P > 0.6$), or laterality index calculated for hemispheric ^{11}C-DTBZ binding ($P > 0.3$), for any of the three striatal subdivisions. Median ^{11}C-DTBZ binding was similar in patients with 22q11.2DS at-risk of Parkinson's disease with ($n = 9$) and without ($n = 4$) treatment with an antidepressant medication (sensorimotor striatum, 3.81 versus 3.74; associative striatum, 3.39 versus 3.78; limbic striatum, 2.68 versus 2.56, respectively). There were no gross structural abnormalities in the striatum or the occipital lobe reference region in the 22q11.2DS or control groups as assessed with MRI. As expected, time-activity curves calculated using decay-corrected standard uptake values for the occipital reference region showed no significant difference between patients and controls (two-way repeated measures ANOVA, $P = 0.26$; Supplementary Fig. 1).

There was no support for a correlation between MDS-UPDRS bradykinesia subscores and ^{11}C-DTBZ binding in the associative (r = 0.03, $P = 0.92$) or limbic (r = −0.13, $P = 0.68$) striatum. In the sensorimotor striatum, there was a negative, though non-significant, correlation (r = −0.43, $P = 0.14$; Fig. 3). Including the patient with 22q11.2DS-Parkinson's disease as a measure of an advanced motor disease state strengthened the linear relationship between bradykinesia and ^{11}C-DTBZ binding (r = −0.54, $P = 0.04$) in the sensorimotor striatum. No relationships were found between ^{11}C-DTBZ binding in the three striatal regions and other motor measures.

Discussion

Here we report the results of the first investigation of phenotypes relevant to Parkinson's disease in individuals with a hemizygous 22q11.2 deletion, a genetic risk factor for early-onset Parkinson's disease (Butcher *et al.*, 2013; Mok *et al.*, 2016). As hypothesized, we found that parkinsonian features and olfactory deficits were more common in adults with 22q11.2DS relative to healthy age and sex-matched controls. Transcranial sonography, a proposed neuroimaging risk marker of Parkinson's disease (Berg *et al.*, 2013; Pilotto *et al.*, 2015), revealed significantly greater substantia nigra echogenicity in the 22q11.2DS group relative to controls. PET neuroimaging with ^{11}C-DTBZ, an established index of striatal dopamine neuron density in other populations (Frey *et al.*, 1996; Bohnen *et al.*, 2006; Martin *et al.*, 2008; Christopher *et al.*, 2014), showed a novel result: elevated ^{11}C-DTBZ binding

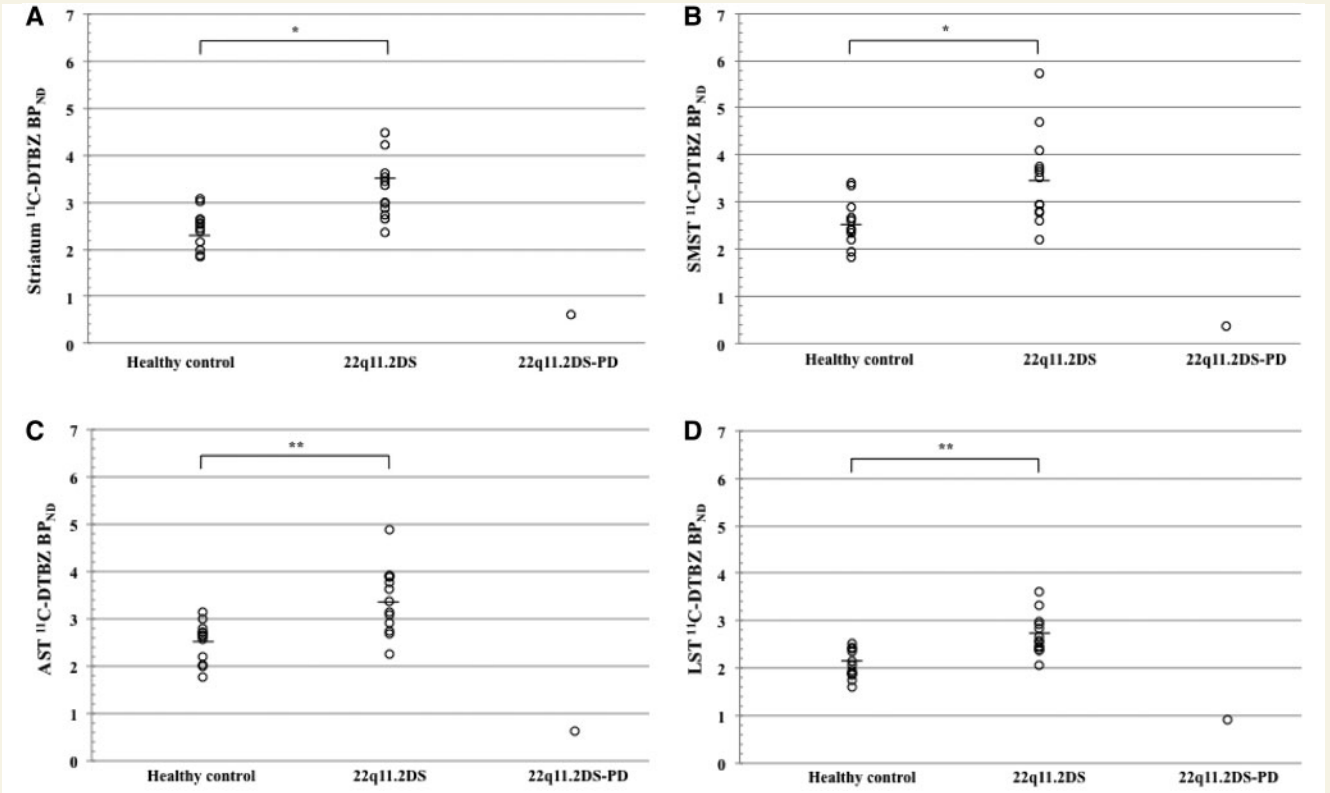

Figure 2 ^{11}C-DTBZ binding in adults with 22q11.2 deletion syndrome (22q11.2DS) at genetic risk of Parkinson's disease and one with 22q11.2DS and Parkinson's disease. Adults with 22q11.2 deletion syndrome (22q11.2DS) show significantly elevated ^{11}C-DTBZ binding potential (BP_{ND}), compared with healthy age and sex-matched control subjects (n = 12) using PET, in the (**A**) striatum and in each of the three striatal subdivisions: (**B**) the sensorimotor striatum (SMST; posterior putamen), (**C**) the associative striatum (AST; anterior putamen and caudate nucleus), and (**D**) the limbic striatum (LST; ventral striatum). The single 22q11.2DS patient with Parkinson's disease (22q11.2DS-PD) shows the expected pattern of grossly reduced ^{11}C-DTBZ binding (**A** to **D**). *$P < 0.01$, **$P \leqslant 0.001$; horizontal line indicates group mean.

levels in the striatum in the 22q11.2DS group relative to healthy age and sex-matched controls. Interestingly, we found that a PET study using a presynaptic dopamine transporter ligand (^{18}F-PRO4.MZ) of a 45-year-old female with 22q11.2DS and parkinsonism with severe periodic limb movement disorder from another centre showed similarly elevated (by 30%) bilateral uptake in the putamen and caudate nuclei (see Supplementary material for case history). We propose that these initial findings suggest that manifestations of parkinsonism and/or evolution to Parkinson's disease in this genetic population may include a hyperdopaminergic mechanism. We discuss the findings and potential implications below.

Motor and olfactory dysfunction in 22q11.2DS

The motor functioning deficits documented in this study in individuals with 22q11.2DS, most notably bradykinesia and postural and/or kinetic tremor, may help inform clinical care of the growing adult 22q11.2DS population and could potentially help to identify predictive markers of Parkinson's disease in 22q11.2DS. The deficits observed could represent clinical manifestations of 22q11.2DS in adulthood in the absence of Parkinson's disease risk. Only a small subset of individuals might be expected to progress to Parkinson's disease given the reduced penetrance of Parkinson's disease in 22q11.2DS (Butcher *et al.*, 2013). A spectrum of motor dysfunction may therefore be part of the variable clinical presentation of 22q11.2DS (Boot *et al.*, 2015), in keeping with the variable expressivity of other 22q11.2DS phenotypes (Fung *et al.*, 2015).

Other 22q11.2DS-associated comorbidities and/or treatments, including most notably schizophrenia, epilepsy, and neuroendocrine disorders, may contribute to observed abnormalities in motor functioning in adulthood. These will require careful study to evaluate their relative contributions to the neurological presentation of adults with 22q11.2DS (Boot *et al.*, 2015; Fung *et al.*, 2015). Motor deficits were not, however, wholly attributable to antipsychotic treatment as they were also observed in patients who were not receiving these medications. Longitudinal follow-up of the patients studied may help reveal which,

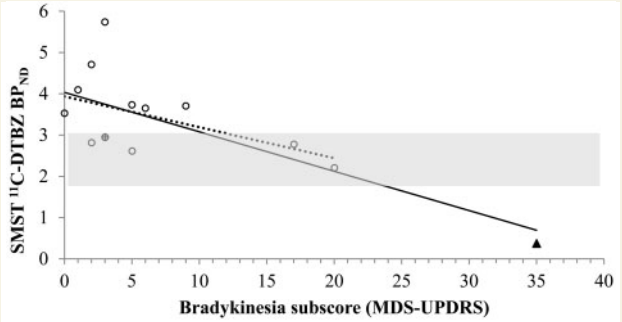

Figure 3 Bradykinesia severity and ^{11}C-DTBZ binding potential (BP_{ND}) correlation result in the sensorimotor striatum (SMST) of adults with 22q11.2 deletion syndrome (22q11.2DS). Circles indicate PET results for adults with 22q11.2DS at-risk of Parkinson's disease with varying severity of bradykinesia, as measured using the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS); the circle with a plus sign indicates two overlapping subjects. The triangle indicates result for the 22q11.2DS subject with Parkinson's disease (22q11.2DS-Parkinson's disease). The dashed line indicates the low non-significant correlation result ($r = -0.43$, $P = 0.14$) for the at-risk 22q11.2DS group and the solid line indicates the moderate correlation result ($r = -0.54$, $P = 0.04$) including the 22q11.DS-Parkinson's disease patient as a measure of an advanced motor disease state. The shaded grey area represents the range of ^{11}C-DTBZ binding observed in the sensorimotor striatum of healthy age and sex-matched control subjects.

if any, of the observed motor phenotypes may be useful predictors of risk of progression to Parkinson's disease in patients with 22q11.2DS (Postuma *et al.*, 2012; Berg *et al.*, 2015).

With respect to possible non-motor features associated with Parkinson's disease, the results for hyposmia may suggest that olfactory dysfunction could be associated with Parkinson's disease risk in 22q11.2DS, as in other forms of Parkinson's disease (Siderowf and Lang, 2012; Berg *et al.*, 2015). Olfactory deficits appear to be prevalent in children and adults with 22q11.2DS (Sobin *et al.*, 2006; Bassett *et al.*, 2007; Romanos *et al.*, 2011). In typical Parkinson's disease, the olfactory deficit seems to occur closer to the onset of clinically identifiable parkinsonism than some other premonitory features of Parkinson's disease (Marras *et al.*, 2005). The occurrence of olfactory deficits in patients with 22q11.2DS, even in childhood, may suggest that olfactory deficits could potentially be a useful early feature in evaluating risk of Parkinson's disease in 22q11.2DS. This possibility will need to be evaluated in adequately powered longitudinal studies. Farnsworth-Munsell Hue test results may reflect a tendency for 22q11.2DS patients to have worse colour vision, although it appears that cognitive dysfunction may have compromised performance on this test (Bertrand *et al.*, 2012). Sleep disorders may be a less prevalent early feature of 22q11.2DS-Parkinson's disease and/or represent the pleiotropy that appears to be a normal aspect of this condition (Bassett *et al.*, 2011). Formal sleep studies are needed to clarify this.

The finding of a larger mean echogenic signal in the 22q11.2DS group is consistent with what would be expected for a group at increased risk of developing Parkinson's disease (Berg, 2011; Pilotto *et al.*, 2015) and suggests the potential utility of transcranial sonography as a Parkinson's disease risk assessment tool in this population. However, the relatively small number of subjects and methodological limitations preclude the interpretation of the echogenic signal size as a risk indicator for any individual subject. Although the presence of substantia nigra hyperechogenicity appears to have good positive predictive value in patients with already well-characterized Parkinson's disease (Berg, 2011; Berg *et al.*, 2013), an enlarged echogenic signal is not specific to Parkinson's disease risk and poor diagnostic sensitivity appears to be a particular issue in patients in the early stages of the disease (Bouwmans *et al.*, 2013; Liu *et al.*, 2014). Consistent with these prior findings there was no evidence of an enlargement of the echogenicity signal in the 22q11.2DS Parkinson's disease patient. Adequately powered longitudinal studies are needed.

Imaging of VMAT2 in 22q11.2DS

The 22q11.2DS patient diagnosed with early-onset Parkinson's disease in this study showed the typical pattern found for other patients diagnosed with Parkinson's disease: markedly reduced striatal ^{11}C-DTBZ binding, reflecting loss of dopamine terminals (Frey *et al.*, 1996; Bohnen *et al.*, 2006; Martin *et al.*, 2008; Christopher *et al.*, 2014). This was most prominent in the putamen, as in typical Parkinson's disease (Bohnen *et al.*, 2006; Martin *et al.*, 2008). This finding is also consistent with the severe striatal dopamine denervation observed on neuropathology (Butcher *et al.*, 2013) and dopamine transporter imaging (Booij *et al.*, 2010; Mok *et al.*, 2016) in 22q11.2DS-Parkinson's disease.

How then to interpret the novel finding that the 22q11.2DS at-risk group, many with parkinsonian features but no diagnosis of Parkinson's disease, showed mean elevated striatal ^{11}C-DTBZ binding relative to controls? The clinical features and abnormal ^{11}C-DTBZ binding may possibly suggest the manifestation of a parkinsonian syndrome related to dopaminergic dysfunction in this genetic population. Given that these patients have the potential to develop Parkinson's disease, these results also raise the possibility that early stages of dopaminergic degeneration in 22q11.2DS-associated Parkinson's disease could be masked by higher pre-morbid ^{11}C-DTBZ binding (Fig. 4). A possible implication is that the utility of presynaptic dopaminergic neuroimaging in helping to distinguish between Parkinson's disease and non-degenerative forms of Parkinson's disease (e.g. drug-induced parkinsonism) in patients with 22q11.2DS may be limited to later stages of the disease when significant presynaptic dopaminergic terminal

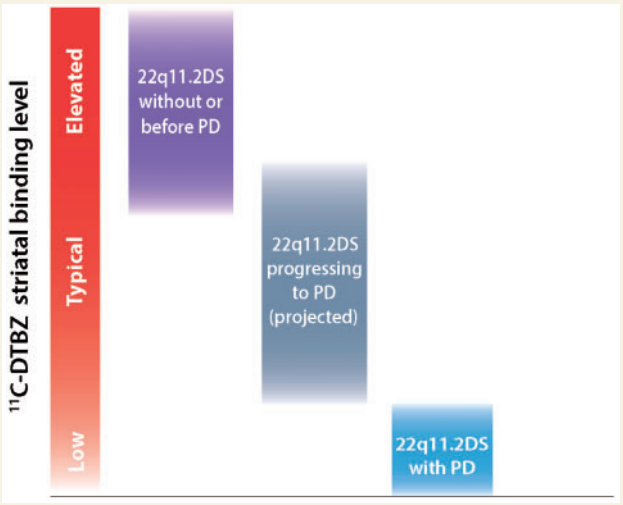

Figure 4 Schematic diagram of presynaptic striatal dopaminergic ^{11}C-DTBZ binding levels in patients with 22q11.2 deletion syndrome (22q11.2DS). Genetically at-risk patients with 22q11.2DS without or before the onset of Parkinson's disease (PD), shown in violet (*left*), may exhibit levels of ^{11}C-DTBZ binding on PET neuroimaging that appear elevated or typical relative to the expected pattern of binding for their age. Those with clinically evident 22q11.2DS-Parkinson's disease, shown in blue (*right*), may exhibit severely reduced striatal ^{11}C-DTBZ binding, indicative of a massive loss of presynaptic dopaminergic terminals in the striatum. It may be projected that patients with 22q11.2DS progressing to clinically manifest Parkinson's disease, shown in grey (*middle*), could appear to show normal or typical levels of ^{11}C-DTBZ binding in the early stages of neurodegeneration, but before profound terminal loss has occurred.

loss has occurred (Booij *et al.*, 2010; Mok *et al.*, 2016). Interestingly, two patients in the 22q11.2DS group at-risk of Parkinson's disease (Cases 7 and 13) would fulfil the new clinical MDS criteria for Parkinson's disease (Postuma *et al.*, 2015), though such a diagnosis would seemingly conflict with the ^{11}C-DTBZ PET results. Both exhibited bradykinesia, rigidity (neck), and hyposmia. Subsequent to the clinical and imaging study assessments, significant decline in motor and cognitive functioning continued in Case 13 (Boot *et al.*, 2015), who notably exhibited the lowest level of striatal ^{11}C-DTBZ binding among the 22q11.2DS at-risk group, but whose ^{11}C-DTBZ binding levels were not reduced relative to healthy controls (Figs 2 and 3). He has shown an unequivocal improvement in symptoms following recent initiation of levodopa/carbidopa treatment (100/25 mg three times a day), approximately 3 years after his ^{11}C-DTBZ PET scan. Improvements included reduced manual bradykinesia, a faster and more fluid gait, and an almost complete resolution of prominent drooling and a jerky upper limb postural and action tremor. His range of facial expression was also slightly improved, together with apparent resolution of facial action myoclonus. These results illustrate the need for larger longitudinal studies to delineate the spectrum and aetiology of the neurological phenotype in adults with 22q11.2DS to help inform diagnostic and treatment strategies for this complex genetic population.

The evidence of increased levels of ^{11}C-DTBZ binding in 22q11.2DS could be a finding unique to this particular patient population at-risk of developing Parkinson's disease. As yet, there have been few studies of patients at high risk of Parkinson's disease prior to clinical onset using ^{11}C-DTBZ PET neuroimaging (Adams *et al.*, 2005; Sossi *et al.*, 2010). Relative to controls, asymptomatic *LRRK2* mutation carriers (Adams *et al.*, 2005; Sossi *et al.*, 2010) and individuals with REM sleep behaviour disorder (Albin *et al.*, 2000), who are known to be at-risk for Parkinson's disease, show evidence of reduced striatal VMAT2 levels using ^{11}C-DTBZ, consistent with a prodromal loss of striatal dopaminergic innervation (Albin *et al.*, 2000; Adams *et al.*, 2005; Sossi *et al.*, 2010). The unexpected finding here of increased average striatal ^{11}C-DTBZ binding levels in young/middle-aged adults with 22q11.2DS could perhaps be a general feature of 22q11.2DS that is unrelated to the pathogenesis of parkinsonism or Parkinson's disease. Given the plausibility of hyperdopaminergia as a potential pathophysiologic mechanism of Parkinson's disease (Bisaglia *et al.*, 2013; Goldstein *et al.*, 2014) however, it is possible that these 22q11.2DS patients may have been studied at an earlier stage than other at-risk groups along a trajectory toward the typical hypodopaminergia of manifest Parkinson's disease. Also, advances in genetics suggest there are likely to be numerous molecular pathways to the common endpoint of clinically manifest Parkinson's disease (Lin and Farrer, 2014; van der Brug *et al.*, 2015). Hyperdopaminergia may be but one of these.

If in 22q11.2DS there is a baseline hyperdopaminergic state that precedes the onset of dopaminergic denervation, this could be consistent with the chronic exposure to the neurotoxic properties of dopamine and its metabolites that has been proposed to be involved in Parkinson's disease pathogenesis (Bisaglia *et al.*, 2013; Goldstein *et al.*, 2014). Animal models have shown that dopamine autotoxicity can lead to progressive neurodegeneration of nigrostriatal neurons through mechanisms involving increased oxidative stress (Hastings *et al.*, 1996; Goldstein *et al.*, 2014). In 22q11.2DS, the increased availability of presynaptic dopamine in the striatum suggested by the finding of elevated ^{11}C-DTBZ binding may be interacting with, or compounded by, a deficient dopamine clearing mechanism related to the effects of missing one copy of the *COMT* gene that is located in 22q11.2 deletion region (Boot *et al.*, 2008, 2011). *COMT* encodes an enzyme involved in dopamine degradation. Also, impaired mitochondrial function related to hemizygosity of the six genes in the deletion region that are involved in mitochondrial function (*MRPL40*, *PRODH*, *SLC25A1*, *TANGO2*, *TXNRD2*, and *ZDDHC8*) may further contribute to increased oxidative stress and vulnerability to dopaminergic cell death in

22q11.2DS. The finding of a significantly larger area of substantia nigra echogenicity in the 22q11.2DS group relative to controls could be consistent with a mechanism involving oxidative stress, given the association of such echogenicity with higher iron tissue levels that may enhance the generation of reactive oxygen species (Berg *et al.*, 2002).

There are several possible mechanisms that could mediate the finding of elevated ^{11}C-DTBZ binding in 22q11.2DS. In other populations, ^{11}C-DTBZ binding to VMAT2 is a well-established index of striatal dopamine neuron density (Frey *et al.*, 1996; Bohnen *et al.*, 2006; Martin *et al.*, 2008; Christopher *et al.*, 2014). Our findings could therefore represent a consequence of excess striatal dopaminergic innervation in 22q11.2DS. If true, increased binding of radioligands specific to the presynaptic plasmalemma dopamine transporter, another measure of striatal presynaptic terminal density (Stoessl, 2011; Sun *et al.*, 2012), would also be expected. The observation of increased ^{18}F-PRO4.MZ binding in a patient with 22q11.2DS (Supplementary material) from an independent centre is consistent with this prediction. Abnormal striatal innervation could occur, for example, through a neurodevelopmental mechanism such as reduced pruning in 22q11.2DS (Gothelf *et al.*, 2007). Elevated ^{11}C-DTBZ binding in 22q11.2DS could also reflect increased availability of presynaptic dopamine storage vesicles through an increase in the number of dopamine storage vesicles per synaptic terminal, more densely packed vesicles, or larger synaptic terminals in 22q11.2DS. Post-mortem studies in patients with 22q11.2DS without Parkinson's disease could clarify these findings. Brain tissue of adults with 22q11.2DS, however, remains an extremely rare resource (Butcher *et al.*, 2013).

Alternatively, it could be hypothesized that elevated ^{11}C-DTBZ binding (and ^{18}F-PRO4.MZ binding) is the result of compensatory changes that may occur in response to a deficient dopamine clearing mechanism in 22q11.2DS (Boot *et al.*, 2008, 2011), as noted above, related to *COMT* haploinsufficiency, and to potential cytotoxic effects of dopamine. Overexpression of VMAT2 in mice has been found to increase vesicular capacity for dopamine and confer a protective effect against dopamine terminal damage and nigral cell loss induced by the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Lohr *et al.*, 2014). Under normal conditions, COMT seems to play a relatively minor role in dopamine clearance in the striatum, and striatal dopamine levels in *Comt* knockout mice have been shown to be normal (Huotari *et al.*, 2002). However, the role of COMT in striatal dopamine degradation may be more important under some challenged conditions. For example, rats treated with a COMT-selective inhibitor showed larger increases in striatal dopamine when challenged with L-DOPA compared with controls (Brannan *et al.*, 1992). It is possible that our findings were influenced by altered striatal VMAT2 expression in 22q11.2DS related to *COMT* haploinsufficiency or other 22q11.2DS-associated conditions and/or their treatments. However, there are extensive animal data suggesting that levels of VMAT2 are relatively resistant to compensatory regulation, e.g. when compared with other dopamine markers such as the dopamine transporter (Vander Borght *et al.*, 1995; Kilbourn *et al.*, 1996; Wilson *et al.*, 1996*a*; Kemmerer *et al.*, 2003).

There is no evidence as far as we are aware to suggest that the 22q11.2 deletion confers a reduction in presynaptic intravesicular dopamine concentration and reduced competition for the same binding site on VMAT2 that could lead to the elevated ^{11}C-DTBZ binding observed in patients with L-DOPA responsive dystonia or in recently abstinent methamphetamine users (De La Fuente-Fernandez *et al.*, 2003; Boileau *et al.*, 2008). A resting state study that used single-photon emission computed tomography and ^{123}I-IBZM to investigate postsynaptic striatal dopamine D_2 receptor binding showed no abnormalities in adults with 22q11.2DS without psychotic illness or Parkinson's disease (Boot *et al.*, 2010). One could speculate that low vesicular dopamine levels would predict poor tolerability of antipsychotics, particularly those with high affinity to the dopamine D_2 receptor; these medications are widely used to successfully treat psychotic illness in 22q11.2DS (Fung *et al.*, 2015).

Interestingly, a hyperdopaminergic dysfunction mechanism could contribute to vulnerability to neurodevelopmental disorders such as schizophrenia and attention deficit disorder that are associated with 22q11.2DS (Bassett *et al.*, 2011; Fung *et al.*, 2015; McDonald-McGinn *et al.*, 2015). One could posit that in 22q11.2DS there may be a developmental deficit in pruning of dopaminergic neurons associated with increased risk for expression of schizophrenia, followed by neurotoxicity related to a relatively hyperdopaminergic state with (later) increased risk for expression of Parkinson's disease. The single previous PET study using ^{11}C-DTBZ binding in patients with idiopathic schizophrenia reported no difference in striatal ^{11}C-DTBZ binding relative to controls (Taylor *et al.*, 2000), in keeping with a recent meta-analysis of dopamine transporter binding studies that found no evidence of altered density of presynaptic dopamine terminals in idiopathic schizophrenia (Fusar-Poli and Meyer-Lindenberg, 2013). The preliminary observation in the current study of similar ^{11}C-DTBZ binding levels between 22q11.2DS patients with and without a psychotic illness warrants investigating in a larger, adequately powered cohort.

Strengths and limitations

The results of this study provide the first assessment of phenotypes relevant to Parkinson's disease in patients at risk of a 22q11.2DS form of Parkinson's disease. The study of patients at genetically increased risk of developing Parkinson's disease can provide the opportunity to investigate early biomarkers of the disease and the natural history of this complex disease and its potential mechanisms (Marras *et al.*, 2011; van der Brug *et al.*, 2015).

Longitudinal studies are needed to evaluate whether the observed motor symptoms, olfactory deficits, and neuroimaging features are relevant to early-onset Parkinson's disease risk in 22q11.2DS and/or their role as part of the variable clinical presentation of 22q11.2DS in adulthood.

The results of this study unexpectedly demonstrated that, on average, ^{11}C-DTBZ binding was elevated in a group of patients with 22q11.2DS relative to a group of healthy controls. As expected given the typical variability observed in PET neuroimaging studies, the ^{11}C-DTBZ binding level values in the 22q11.2DS group overlapped with the binding level of the control subjects. Moreover, variability in expression of phenotypes is common in 22q11.2DS (Bassett *et al.*, 2011; Fung *et al.*, 2015; McDonald-McGinn *et al.*, 2015). Well-powered prospective studies will be needed to determine the normative range of ^{11}C-DTBZ binding in 22q11.2DS and to evaluate any clinical significance of striatal ^{11}C-DTBZ binding levels.

Motor assessments were not completed blind to 22q11.2 deletion status as 22q11.2DS patients are often clinically identifiable from features such as hypernasal speech and mild dysmorphic features. However, all motor assessments were performed blind to olfactory and PET imaging results. It is possible that if patients with 22q11.2DS with motor problems were more likely to volunteer for the study this may have influenced the proportion observed to have motor dysfunction. Although all results were limited by the relatively small sample size of this genetic at-risk group, several significant differences were detectable relative to controls. Larger samples may also reveal differences of smaller effect size.

With respect to the ^{11}C-DTBZ binding potential results, minor structural brain differences in patients with 22q11.2DS relative to controls would not be expected to account for the large differences observed. Moreover, partial volume effects correction on time activity curve data showed similar results. Although several subjects in the 22q11.2DS group at-risk of Parkinson's disease were treated with an antidepressant, results were similar in those with and without antidepressant treatment. It has been previously shown that VMAT2 levels in the rat brain are not modified by chronic treatment with the antidepressant paroxetine (Vilpoux *et al.*, 2000). Importantly, we found no difference in the time activity curve of reference region (occipital cortex) between patients and controls that could have explained our results. This provides some assurance that the finding of elevated striatal ^{11}C-DTBZ binding in the 22q11.2DS group is extremely unlikely to be due to a quantification artefact related to the use of the occipital cortex to calculate BP_{ND}. It has previously been shown that levels of VMAT2 are >100-fold lower in post-mortem human cerebral neocortices than in the striatum, and are unlikely to be detected by ^{11}C-DTBZ (Tong *et al.*, 2011). On the other hand, Koeppe *et al.* (1999) found that ~5% of the cortical ^{11}C-DTBZ PET signal could come from specific binding [BP_{ND}(cortex) = ~0.06]. Thus, conservatively assuming a scenario where the observed differences in binding in our study were affected by this level of specific binding in the occipital cortex [healthy controls, BP_{ND}(occipital cortex) = 0.06 and BP_{ND}(striatum) = 2.5; 22q11.2DS group, cortical BP_{ND}(occipital cortex) = 0 and BP_{ND}(striatum) = 2.5], no more than 11% of the difference observed between 22q11.2DS patients and controls could be explained. If an even higher BP_{ND} of 0.16 was assumed for the occipital region for the healthy control group, the case-control difference in ^{11}C-DTBZ binding would be 23%, which is still lower than the observed differences of > 30%. Neuropathological studies assessing VMAT2 protein distribution and other markers of neurotransmitter systems in patients with 22q11.2DS would further aid the interpretation of our PET findings.

Conclusions

Adults with 22q11.2DS ⩾ 30 years who are at increased risk of developing early-onset Parkinson's disease due to hemizygosity of the 22q11.2 deletion region demonstrate variable expression of features associated with Parkinson's disease. These may include motor and olfactory deficits and larger average echogenicity on transcranial sonography, relative to healthy controls. The finding of elevated levels of striatal ^{11}C-DTBZ binding, a radioligand for presynaptic dopamine vesicles, suggest that this genetically at-risk patient population is affected by a hyperdopaminergic abnormality. We hypothesize that the increased risk for developing Parkinson's disease in individuals with 22q11.2DS may involve an autotoxicity mechanism related to this dopaminergic dysfunction. Longitudinal studies are needed to evaluate the potential prognostic significance of these initial cross-sectional findings in the context of the clinical presentation of 22q11.2DS in adulthood. Animal studies using available 22q11.2DS models could help evaluate mechanisms and test novel treatments.

Acknowledgements

The authors would like to thank the adults with 22q11.2DS and their families involved in this and related research studies. The authors would also like to thank core facility staff at the Centre for Addiction and Mental Health Research Imaging Centre. We also thank the staff of Clinical Genetics Research Program and the Dalglish Family 22q Clinic for Adults with 22q11.2 Deletion Syndrome for study support, especially Fiona Fu, Lucas Ogura, and Monica Torsan. In addition, the authors thank Dr Ekaterina Rogaeva for contributing genetic data on the 22q11.2DS patient with Parkinson's disease.

Funding

This work was supported by the Canadian Institutes of Health Research (A.S.B., MOP #97800, MOP #111238),

Canada Research Chairs program (A.S.B.), a Brain Canada Mental Health Training Award (N.J.B.), FONDECYT-Chile grant # 1130392 (G.M.R.), and a Canadian Institutes of Health Research Frederick Banting and Charles Best Canada Graduate Scholarship (N.J.B.).

Supplementary material

Supplementary material is available at *Brain* online.

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