Parkinsonism and Related Disorders 20 (2014) 1209–1214

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Cortical volume and folding abnormalities in Parkinson's disease patients with pathological gambling

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ARTICLE INFO

Article history:
Received 8 May 2014
Received in revised form
28 August 2014
Accepted 1 September 2014

Keywords:
Pathological gambling
Parkinson's disease
Voxel-based morphometry
Cortical folding
Orbitofrontal cortex

ABSTRACT

Purpose: Pathological gambling (PG) is one of the most devastating non-motor complications of Parkinson's disease (PD). Neuroanatomical abnormalities in PD patients with PG are poorly understood.
Methods: In the current study we investigated PD patients with and without PG using Voxel Based Morphometry (VBM) and local Gyrification Index (*l*GI), two neuroimaging techniques useful for detecting complementary morphological metrics in the brain. Twelve PD patients with PG were compared to 12 clinically-matched PD patients without PG and 24 healthy controls.
Results: PD patients with PG showed grey matter volume loss specifically in the orbitofrontal cortex (OFC) when compared to patients without PG, with the atrophy of this region correlating with the increase of gambling symptoms (G-SAS). Surface-based analysis complemented this evidence revealing that the OFC in the PD patients with PG was also characterized by a reduced *l*GI. Moreover, when compared to controls, PD patients with PG showed a more widespread anatomical neurodegeneration involving several limbic regions such as: the OFC, cingulate cortex, inferior frontal cortex and insular cortex. Otherwise, demographically-/clinically-matched PD patients without PG did not display significant anatomical changes.
Discussion: Our study demonstrates that combined grey matter atrophy and reduced *l*GI in the OFC differentiates PD patients with PG from those without PG, suggesting that this cortical area may play a critical role in the development of this drug-induced behavioral disorder.

1. Introduction

Pathological gambling (PG) is defined as persistent and maladaptive gaming behavior, generally considered in the broader psychiatric category of impulsive control disorders (ICDs) which also include compulsive buying, compulsive sexual behavior and binge eating [1]. Recently the DOMINION study [2], where a total cohort of 3090 PD patients was enrolled, showed that ICD occurred in 13.6% of PD patients (gambling in 5.0%, compulsive sexual behavior in 3.5%, compulsive buying in 5.7% and binge-eating disorder in 4.3%).

Although the occurrence of PG has been strongly associated with the use of dopamine agonist medication [3], the neural mechanisms of this neuropsychiatric disorder are still partially obscure. For this reason, in recent years many efforts have been made to try to understand the neurobiological basis of this non-motor complication.

Several authors using positron emission tomography (PET) and functional magnetic functional imaging (fMRI) on PD patients with PG found altered neurofunctional regulation of the "reward pathways" including the dorsal/ventral striatum, thalamus, insular cortex, anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC) [3–5]. However, whether these brain functional abnormalities are dependent upon underlying morphological abnormalities in the brain is still unknown.

The purpose of our study was to investigate neuroanatomical correlates of PD patients with PG in comparison with PD patients without PG and with control subjects. We combined two well-known structural whole brain MR metrics in a multimethod

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http://dx.doi.org/10.1016/j.parkreldis.2014.09.001
1353-8020/

unbiased approach. We used whole brain voxel-based morphometry (VBM) [6] to identify gross differences in morphometry, we then investigated the local gyrification index (*l*GI) [7], an additional specific morphometric feature not completely revealed by VBM, useful for detecting the degree of cortical folding.

2. Participants and methods

2.1. Subjects

Our initial sample consisted of 256 patients meeting UK Brain Bank criteria for the diagnosis of idiopathic PD [8] recruited from the Neurology Unit of the University "Magna Graecia" of Catanzaro. Exclusion criteria were: (1) no evidence of clinical symptoms affecting brain anatomy, such as hallucinations, levodopa-induced dyskinesias, freezing of gait and mild cognitive impairment; (2) no evidence of structural abnormalities in the brain and (3) no evidence of dementia according to DSM-IV criteria. According to these criteria, 131 patients were excluded from the study. Among the cohort of the remaining 125 PD patients we identified 12 PD patients who developed PG subsequent to taking dopamine agonists, confirmed by psychiatric assessment.

PD patients with and without PG were then individually matched by a computer-generated programme according to their age, sex, disease severity and chronic dopaminergic (levodopa and pramipexole) therapy [9]. All PD patients were treated with pramipexole (See Supplementary Materials Table S1). Before MRI examination, patients in OFF condition underwent clinical assessments including Hoehn–Yahr (HY) staging and Unified Parkinson's Disease Rating Scale (UPDRS).

Twenty-four healthy controls (HC) with no previous history of neurological or psychiatric diseases and with normal MRI of the brain were matched for demographical variables with patients. All participants gave written informed consent, which was approved by the Ethical Committee of the University 'Magna Graecia' of Catanzaro, according to the Helsinki Declaration.

2.2. MRI data acquisition

Brain MRI was performed according to our routine protocol by a 3 T scanner with an 8-channel head coil (Discovery MR-750, GE, Milwaukee, WI, USA). Structural MRI data were acquired using a 3D T1-weighted spoiled gradient echo (SPGR) sequence with the following parameters: TR: 3.7 ms, TE: 9.2 ms, flip angle 12°, voxel-size $1 \times 1 \times 1$ mm^3.

2.3. Neuropsychological assessment

All participants completed an extensive series of neuropsychological tests, which were administered by an experienced clinical neuropsychologist blind to any other result. Neuropsychological evaluation was performed at the same time as the MRI and neurological exams after dopaminergic treatment. First of all, all participants underwent a behavioral assessment including: a) the gambling symptom assessment scale (G-SAS) [10], which gives a severity score during a patient's worst week of gambling activity (past gambling) and a severity score for current gambling activity; b) the Barratt Impulsivity Scale (BIS-11) [11], which is a self-reporting 30-item questionnaire of impulsivity traits. Total scores were used for further analysis, with greater scores equating to a more impulsive personality; *c*) the Beck Depression Inventory and the Hamilton Rating Scale Anxiety to assess the presence of depression and anxiety symptoms. Next, additional neuropsychological measures were also evaluated: (1) executive control (Frontal Assessment Battery, Modified Card Sorting Test and Stroop task), (2) attention and working memory (Digit Span Forward and Backward), (3) short- and long-term verbal memory (Rey Auditory Verbal Learning Test), (4) verbal fluency and language comprehension (Word List Generation, Token Test) and (5) visual–spatial skills (Judgment of Line Orientation).

2.4. VBM data processing and analysis

Data were processed and examined using the SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK), where we applied VBM implemented in the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html) with default parameters incorporating the DARTEL toolbox that was used to obtain a high-dimensional normalization protocol. Images were bias-corrected, tissue classified and registered using linear (12-parameter affine) and non-linear transformations (warping), within a unified model [6]. Subsequently, the warped GM segments were affine transformed into Montreal Neurological Institute (MNI) space and were scaled by the Jacobian determinants of the deformations (modulated GM volumes). Finally, the modulated volumes were smoothed with a Gaussian kernel of 10 mm full-width at half maximum (FWHM). The GM volume maps were statistically analyzed using the general linear model (GLM) based on Gaussian random field theory.

Statistical analysis consisted of an analysis of covariance (AnCOVA) used for investigating the main effect of group (statistical F-test). The advantage of an SPM F-map is that increases and decreases of GM volumes are analyzed together to detect morphological changes in all groups. Age and total intracranial volume (ICV) were included in the model as covariates of no-interest. Based on previous findings [2–5], we selected a list of structures as regions of interest (ROIs) for VBM analysis (amygdala, nucleus accumbens, thalamus, basal ganglia, insular cortex, inferior frontal cortex, ACC and OFC). All ROIs were created with the "aal.02" atlas included in the Wake Forest University Pickatlas software version 1.04 (http://www.fmri.wfubmc.edu/download.htm). The statistical threshold was set at $P < 0.05$ with a Family-Wise error (FWE) correction for multiple comparisons within ROIs.

Moreover, to evaluate co-variation between GM volume changes and behavioral data, we performed a correlation analysis using the multiple regression function of SPM8. Specifically, we were interested in investigating the effects of the GSAS and BIS-11 scores on the detected anatomical changes. Correlation analyses were performed within ROIs using a statistical threshold corrected for multiple comparisons (FWE < 0.05).

2.5. Gyrification index

To further characterize VBM findings and to deeply investigate morphological differences in PD patients with PG with respect to PD without PG, we performed surface-based measurements assessing the degree of the *l*GI. Schaer and colleagues have recently developed this measure of cortical folding [7], which is now freely distributed as a part of the FreeSurfer package (v 5.1; http://surfer.nmr.mgh.harvard.edu/). Before calculating *l*GI, we pre-processed structural MRIs using FreeSurfer with a well-established methodology [12,13]. In brief, the method involves identification, segmentation and tessellation of the cerebral white matter, followed by a deformation of this surface to produce an accurate and smooth representation of the cortical surface. The *l*GI measures the ratio of a vertex-based, 25-mm radius circular region of interest of folded pial surface area to the corresponding surface area of a tight-fitting contour enveloping the cortex's outer perimeter [14]. The resulting cortical surface maps of *l*GI represent the amount of cortical folding: that is, the extent of the cortex buried within the sulcal folds, at each pial surface location. Finally, cortical maps were smoothed with a 10-mm full-width at half maximum Gaussian kernel. Surface-based group analysis was performed using FreeSurfer's GLM tools. Age was included in the model as covariate of no-interest. Statistical significance of between-group *l*GI differences evaluated using a clusterwise correction for multiple comparisons from Monte Carlo z-field simulation. To correct for multiple comparisons, spatial clusters of folding differences were defined as continuous patches of vertices with *P*-values less than 0.05 (two-tailed). The *P*-values for these clusters were determined by Monte Carlo simulation (10,000 iterations). Only clusters that survived this correction with *P*-values less than 0.05 (two-tailed) were deemed significant. Simulation analysis was performed within a specific *a priori* label automatically generated by the Freesurfer pipeline (the OFC consisting of the lateral and medial parts). To constrain analysis within the label, the command *mri_glmfit-sim* was used. Furthermore, a vertex by vertex multiple linear regression analysis was carried out to investigate the relationship between *l*GI and critical clinical symptoms (G-SAS and BIS-11 scores). This analysis was performed within ROI, selected in the cortical region (i.e, OFC) where the PD with PG group had significantly folding changes.

2.6. Statistical analysis

Statistical analyses were performed with Statistica Version 6.0 (www.statsoft.com). ANOVAs, Mann–Whitney, unpaired *t*-test and χ^2 were used to assess potential differences between groups for all demographic and clinical variables. All statistical analyses had a two-tailed alpha level of <0.05 for defining significance.

3. Results

3.1. Participants

Demographic and clinical features of all subjects are listed in Table 1. No significant differences were detected in any demographical and clinical data between groups. PD patients with PG showed significant levels of compulsivity and impulsivity as revealed by G-SAS ($F_{2,45} = 125.3$; p-level < 0.001) and BIS-11 ($F_{2,45} = 3.91$; p-level = 0.03), respectively. Post-hoc analysis (Duncan *t*-test) confirmed that these effects were detected either with respect to PD patients without PG (p-level = 0.0001) or controls (p-level = 0.00006) considering the measures of pathological gambling (G-SAS). Otherwise, PD patients with PG showed significantly greater impulsivity scores (BIS-11) only in the comparison with the other PD group (p-level = 0.01), but not with respect to controls (p-level = 0.08). Overall, compulsivity and impulsivity scores (as defined by G-SAS and BIS-11) within the PG group, showed a significant positive correlation ($r = 0.59$; p-level = 0.006), thus confirming that increasing PG was associated with loss of inhibitory control.