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Mapping brain volumetric abnormalities in never-treated pathological gamblers

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ABSTRACT

Several magnetic resonance imaging (MRI) studies to date have investigated brain abnormalities in association with the diagnosis of pathological gambling (PG), but very few of these have specifically searched for brain volume differences between PG patients and healthy volunteers (HV). To investigate brain volume differences between PG patients and HV, 30 male never-treated PG patients (DSM-IV-TR criteria) and 30 closely matched HV without history of psychiatric disorders in the past 2 years underwent structural magnetic resonance imaging with a 1.5-T instrument. Using Freesurfer software, we performed an exploratory whole-brain voxelwise volume comparison between the PG group and the HV group, with false-discovery rate correction for multiple comparisons ($p < 0.05$). Using a more flexible statistical threshold ($p < 0.01$, uncorrected for multiple comparisons), we also measured absolute and regional volumes of several brain structures separately. The voxelwise analysis showed no clusters of significant regional differences between the PG and HV groups. The additional analyses of absolute and regional brain volumes showed increased absolute global gray matter volumes in PG patients relative to the HV group, as well as relatively decreased volumes specifically in the left putamen, right thalamus and right hippocampus (corrected for total gray matter). Our findings indicate that structural brain abnormalities may contribute to the functional changes associated with the symptoms of PG, and they highlight the relevance of the brain reward system to the pathophysiology of this disorder.

1. Introduction

Pathological gambling (PG) is a disorder characterized by gambling behaviors that disturb interpersonal relationships and adversely affect both financial and socioeconomic status (Potenza, 2001). In the 1980s, PG became part of the medical nosography, being classified within the realm of impulse control disorders (American Psychiatric Association, 2000). Epidemiological studies have indicated an increasing prevalence of PG (Petry and Armentano, 1999; Shaffer et al., 1999), with the most recent estimates pointing to a prevalence of 1–4% of PG in the general population (Shaffer et al., 1999; Potenza, 2001; Shaffer and Korn, 2002). Maladaptative and persistent gambling behaviors such as excessive preoccupation with gambling, lying to conceal the extent of involvement with gambling, need to gamble with increasing amounts of money, unsuccessful efforts to stop gambling, and chasing one's losses, are all related to the difficulties in social adjustment faced by people with PG (Reuter et al., 2005).

The neurobiological basis of PG remains unclear, although functional neuroimaging techniques have consistently indicated the presence of regional brain activity abnormalities underlying the symptoms of PG. Recent studies using functional magnetic resonance imaging (fMRI) have demonstrated lower activity of the prefrontal cortex, orbitofrontal cortex, insula and striatum in PG patients relative to healthy volunteers during the performance of tasks involving control inhibition, visual presentation of gambling

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cues, and delay discounting (Eber and Shaffer, 2000; Knutson et al., 2003; Volkow et al., 2003; Crockford et al., 2005; Tanabe et al., 2007; Beck et al., 2009; Frascella et al., 2010; Choi et al., 2012; Sescousse et al., 2013). Complementary studies using positron emission tomography (PET) suggested enhanced dopamine release in PG subjects in response to pharmacological challenge and gambling (Joutsa et al., 2012; Boileau et al., 2014). Even though these studies suggest the existence of a relationship between abnormal brain functioning and PG symptoms, all of the studies have methodological limitations, such as their relatively small sample sizes (ranging from 7 to 18 PG subjects) and the potentially confounding influence of pharmacological treatment (Balodis et al., 2012). Nevertheless, they provide evidence that the presence of functional abnormalities in the fronto-striatal reward system might be associated with the vulnerability to develop PG. Alternatively, the identified abnormalities in brain function might be a consequence of the repetitive behavior of pathological gaming.

Much less is known about morphological brain changes possibly associated with PG, given the small number of investigations to date and their inconsistent findings. One recent morphometric MRI investigation showed reduced volumes of the amygdala and hippocampus in a PG sample including untreated patients with comorbid alcohol/drug abuse relative to healthy controls (Rahman et al., 2014), while a different MRI study reported increased volumes of the ventral striatum and right prefrontal cortex in a mixed sample of mixed treated and non-treated PG patients relative to healthy controls (Koehler et al., 2015). On the other hand, in two MRI studies investigating volumetric changes in samples of never-treated PG patients with no history of comorbid alcohol/drug abuse, no differences from healthy controls were detected in the measurements of either gray or white brain matter volumes (Joutsa et al., 2011; van Holst et al., 2012).

Previous studies have associated PG with poorer performance on neuropsychological tests involving decision-making, cognitive control and flexibility (Goudriaan et al., 2005; Fuentes et al., 2006; Odlaug et al., 2011; Grant et al., 2012; Goudriaan et al., 2014), indicating an impairment of reward processing and a potential abnormality of related brain structures such as the prefrontal cortex and ventral striatum (Boog et al., 2014).

Given the scarcity of previous morphometric MRI studies of PG, we carried out the present study with the purpose of comparing brain volumetric measurements between never-treated PG patients and healthy volunteers. We aimed to investigate if morphological abnormalities would distinguish PG individuals from controls in fronto-striatal circuits and medial temporal regions implicated in recent brain volumetric studies of PG (Rahman et al., 2014).

2. Methods

2.1. Participants

Thirty-seven male subjects consecutively admitted to the Gambling Outpatient Unit of the Institute of Psychiatry of the University of São Paulo were invited to take part in the study. They had never received psychotherapeutic support or pharmacological treatment for psychiatric or neurological disorders. Eight (26.6%) subjects had previously attended Gamblers Anonymous meetings.

All PG patients were screened to assess the magnitude of their gambling habits as determined by the South Oaks Gambling Screen (SOGS; score ≥ 5 as inclusion criterion) (Lesieur and Blume, 1987). Subsequently, they underwent a clinical interview to assess DSM-IV-TR criteria for PG (American Psychiatric Association, 2000). The Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990) was also administered to exclude other addictive disorders (except tobacco smoking, present in 19 patients) and major current psychiatric disorders. Six subjects were excluded due to comorbidities such as alcohol dependence ($n=3$), depression with suicidal ideation ($n=1$), bipolar disorder ($n=1$), and obsessive–compulsive disorder ($n=1$). One other PG subject was excluded due to claustrophobic anxiety during MRI scanning. The remaining PG patients ($n=30$) were aged from 19 to 59 years (mean $=37.3 \pm 9.6$ years), and all of them were right-handed. There were 28 Caucasian in this group and 22 patients completed, at least, high school, with a mean of 12.1 ± 3.5 years of formal education. Intelligence Quotient in the patients based on the Block Design and Vocabulary subtests of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981) was estimated as 101 ± 9.9.

Thirty male, right-handed healthy volunteers (HV) also took part in the present study. They were recruited through advertisements in a recreational club located in the same neighborhood of the university hospital and were matched to participants in the PG group by age and educational level. They were screened for psychiatric disorders through the Self-Report Questionnaire (Harding et al., 1980) and interviewed with the SCAN (Wing et al., 1990) to exclude current psychiatric diagnoses, except for nicotine dependence. The HV group was aged from 20 to 59 years (mean age $=37.3 \pm 9.7$ years). There were 24 Caucasians in this group, and 25 subjects completed at least high school education (average of 12.6 ± 2.3 years of formal education). The mean estimated Intelligence Quotient for the HV group was 99 ± 8.8.

The local ethics committee approved data assessment, and all participants gave written consent after complete description of the study.

2.2. MRI scanning

Structural MRI data were collected using a 1.5-T scanner (GE Sigma, Milwaukee, WI, USA). Whole-brain images were acquired using a three-dimensional T1-weighted fast field echo sequence (echo time $=5.2$ ms, repetition time $=21.7$ ms, flip angle $=20^{\circ}$, field of view $=220$ mm, 256×256 matrix) in contiguous axial slices with 1.5-mm thickness. An experienced radiologist visually inspected each dataset with the purpose of identifying artifacts during image acquisition and the presence of silent brain lesions. No gross structural brain abnormality was found in any participant.

2.3. Image processing and statistical analyses

Initially, an exploratory whole-brain voxelwise analysis was carried out by means of FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/) (Fischl and Dale, 2000) using a standard image-processing protocol described in detail elsewhere (Dale et al., 1999; Fischl et al., 1999). Briefly, we initially converted the original DICOM images to MGH format. Then, motion correction and conform, non-uniform intensity normalization and Talairach transformation algorithms were applied. Subsequently, intensity normalization, skull stripping, volumetric registration and volumetric labeling were computed to segment and smooth brain tissues. A kernel of 10 mm at the full width at half-maximum (FWHM) was used for spatial smoothing. After that, remaining images were inflated and parameterized into QSphere, which provides a spherical representation of brain tissue, gyri and sulci. Brain topology was then automatically fixed, mapped and registered on spherical parameters. Finally, an average curvature map was calculated to access cortical and sub-cortical parcellation scores. Between-group whole-brain voxelwise comparisons were carried out using an analysis of covariance (ANCOVA) model, considering age as a confounding factor. Also, we carried out a whole-brain voxelwise linear correlation analysis in the PG group between brain volumes and the number of DSM-IV comorbid diagnostic items that the patient presented, used as a measure of disorder severity. For these exploratory whole-brain analyses, we used a strict statistical threshold of $p < 0.05$ with false-discovery rate (FDR) correction for multiple comparisons.

Using the same image-processing protocol above, we also measured the regional volumes of several brain structures separately, including the caudate nucleus, putamen, pallidum, thalamus, hippocampus, amygdala, nucleus accumbens, cingulate gyrus (caudal, posterior, rostral and isthmus portions), frontal lobe (caudal-middle, rostral-middle, lateral-orbital, medial-orbital, superior, frontal-pole, paracentral, precentral, pars opercularis, pars orbitalis and pars triangularis), corpus callosum (posterior, mid-posterior, central, mid-anterior, and anterior portions), and ventricles (third, fourth, lateral and inferior horn). Following these analyses, the absolute volumes of global gray matter, white matter and lateral ventricles were automatically obtained (Fischl et al., 2004).

Regional brain volumes for the above structures were calculated according to Eqs. (1) and (2), considering (1) the total intracranial volume and (2) the total gray matter volume:

$$R_{IC} = \frac{V_{BR}}{V_{IC}} \quad (1)$$

R_{IC} (regional volume relative to the intracranial volume), V_{BR} (absolute volume of a specific brain region), V_{IC} (absolute value of the intracranial volume)

$$R_{GM} = \frac{V_{BR}}{V_{GM}} \quad (2)$$

R_{GM} (regional volume relative to the total gray matter), V_{BR} (absolute volume of a specific brain region), V_{GM} (absolute volume the total gray matter).

For region-of-interest (ROI) inter-group comparisons, we also used ANCOVA considering age as a confounding factor. Findings were reported as significant at a $p < 0.01$ statistical threshold, uncorrected for multiple comparisons. The flexible statistical threshold was applied given the a priori prediction that brain