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Research Paper

Divergent Structural Responses to Pharmacological Interventions in Orbitofronto-Striato-Thalamic and Premotor Circuits in Obsessive-Compulsive Disorder

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ABSTRACT

Prior efforts to dissect etiological and pharmacological modulations in brain morphology in obsessive-compulsive disorder (OCD) are often undermined by methodological and sampling constraints, yielding conflicting conclusions and no reliable neuromarkers. Here we evaluated alteration of regional gray matter volume including effect size (Cohen's *d* value) in 95 drug-naïve patients (age range: 18–55) compared to 95 healthy subjects (age: 18–63), then examined pharmacological effects in 65 medicated (age: 18–57) and 73 medication-free patients (age: 18–61). Robustness of statistical outcomes and effect sizes was rigorously tested with Monte Carlo cross-validation. Relative to controls, both drug-naïve and medication-free patients exhibited comparable volumetric increases mainly in the left thalamus ($d = 0.90, 0.82$, respectively), left ventral striatum ($d = 0.88, 0.67$), bilateral medial orbitofrontal cortex ($d = 0.86, 0.71; 0.90, 0.73$), and left inferior temporal gyrus ($d = 0.83, 0.66$), and decreased volumes in left premotor/presupplementary motor areas ($d = -0.83, -0.71$). Interestingly, abnormalities in the thalamus and medial orbitofrontal cortex were present in medicated patients whereas entirely absent in premotor and ventral striatum. It suggests that pharmacotherapy elicited divergent responses in orbitofronto-striato-thalamic and premotor circuits, which warrants the design of longitudinal studies investigating the potential of these neuromarkers in stratified treatments of OCD.

1. Introduction

Although rapid advances in structural neuroimaging studies using voxel-based morphometry (VBM) have enabled systematic assessment of the structural substrates underlying obsessive-compulsive related disorders (Ashburner and Friston, 2000; Lerch et al., 2017), our understanding of these pathological alterations remains shaded by conflicting and inconclusive prior findings. These apparent discrepancies may partially be due to insufficient power, clinical heterogeneity, mixed statistical analytic methods and medication confounds (Abi-Dargham and Horga, 2016; Blackford, 2017; Button et al., 2013; Poldrack et al., 2017; van den Heuvel et al., 2009). Among those confounding factors, pharmacological intervention has thus far received insufficient attention, as yields extremely limited (yet still diverging) evidence regarding the modulatory activity of therapeutics such as selective serotonin reuptake inhibitors (SSRIs) in OCD (Pine and Freedman, 2017; Skapinakis et al., 2016). Early studies selectively analyzed abnormally increased volumes of the thalamus and amygdala in drug-naïve pediatric patients, both of which were normalized by pharmacotherapy (Gilbert et al., 2000; Szeszko et al., 2004). Two whole-brain VBM studies on over a dozen patients found volume reductions in the left putamen (Hoexter et al., 2012) and parietal lobes (Lazaro et al., 2009) that became comparable to controls after medication. To date, the underlying circuit-level therapeutic mechanisms of pharmacotherapy remain essentially unclear while as many as half of patients diagnosed with OCD fail to

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respond adequately to serotonergic-based drugs (Bloch et al., 2006, 2010; Hirschtritt et al., 2017). Understanding the brain-modulatory effects of medication treatment may help to match the pathological deficits in brain morphology of patients with therapeutic network fingerprints of specific drugs, thereby leading to improved treatment efficacy.

It is known that evidence generated from small sample sizes is especially prone to error: both false negatives due to inadequate power and false positives due to biased samples (Button et al., 2013). Meta- and mega-analysis of VBM studies combining data from independent studies can substantially improve statistical power, and have demonstrated that brain abnormalities in OCD not only manifest in the orbitofronto-striato-thalamic circuits, but also extend to other regions such as the dorsolateral prefrontal cortex, premotor and parietal areas (Carlisi et al., 2016; de Wit et al., 2014; Eng et al., 2015; Norman et al., 2016; Radua et al., 2010; Rotge et al., 2009, 2010). Nevertheless, even in these large-sample reports, considerable inconsistency with regard to the presence and significance of anatomical abnormalities still exists. For instance, gray matter volume (GMV) of the ventral striatum (VS) has been described as increased (Carlisi et al., 2016; Norman et al., 2016), and unchanged (Eng et al., 2015; Radua et al., 2010; Rotge et al., 2010) in OCD compared to healthy controls. Volume sizes of the dorsolateral prefrontal cortex (dlPFC) and premotor areas were found to be decreased (Carlisi et al., 2016; Norman et al., 2016; Rotge et al., 2010) or normal (Eng et al., 2015; Radua et al., 2010). The validity of meta-analyses heavily relies on the methodological quality of the included studies, the eligibility criteria used for the meta-analysis, and various reporting biases (Finckh and Tramer, 2008; Walkup, 2017). Effect sizes, estimates of population parameters that are independent of sample size and other design decisions, provide a tool for determining whether a finding is not only statistically significant, but also whether a detected difference is substantive (Blackford, 2017). To test the internal validity within a sample and the external validity across multiple samples, cross-validation methods are usually required to provide final parameter estimates that are less biased and more likely to be replicated in independent future studies.

In this study, we sought to robustly evaluate the regional volumetric brain abnormalities of OCD and to determine the modulation of these pathological alterations by pharmacological treatment. We employed a cross-group design with a total of 328 participants that included three subgroups of patients (drug-naïve, medicated and medication-free) and a group of healthy comparison (HC) subjects. We first identified pathological differences between drug-naive patients and HCs at the whole-brain scale. We then focused on OCD-specific pathological regions to investigate disorder-related pharmacological effects in the medicated group. To demonstrate a robust association of brain volumetric changes with pharmacotherapy, we tested whether the observed structural responses to medication existed in the third sample of medication-free adult patients who had discontinued medication (at least 4 weeks prior). Considering clinical heterogeneity related to variation in disease profile and treatment trajectory, a Monte Carlo cross-validation (MCCV) procedure was employed at each group comparison and the effect sizes were reported correspondingly. Potential modulating effects of demographic, clinical and statistical characteristics on brain volume were regressed out of the present results. With fully cross-validated analysis, we thus expected to identify reliable and reproducible structural substrates of OCD pathophysiology and their network signatures in response to pharmacological therapies.

2. Materials and Methods

2.1. Participants

Between April 2, 2013 and April 13, 2016, patients were recruited through local inpatient and outpatient departments at the OCD Clinics at Ruijin Hospital and Shanghai Mental Health Center. All participants provided written informed consent for study participation after receiving a complete description of the protocols, which were approved by the Institutional Review Boards at Ruijin Hospital and Shanghai Mental Health Center, Shanghai Jiao Tong University and by the Biomedical Research Ethics Committee, Shanghai Institutes for Biological Sciences, and Chinese Academy of Sciences. All patients had received a primary diagnosis of OCD based on clinical evaluation with the Chinese translation of the Structured Clinical Interview for DSM-IV-TR, and were administered the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) to assess OCD symptom severity (Goodman et al., 1989). 233 OCD patients (Five patients who were under the age of 18 were excluded for subsequent analysis) were categorized into 3 subgroups: drug-naïve OCD ($n = 95$), medicated OCD ($n = 65$), and medication-free OCD ($n = 73$). Approximately 97% of OCD patients in the medicated subgroup had received clinical treatment with SSRIs (see Table S1). Patients who had discontinued medication for at least four weeks were considered medication-free. 95 healthy subjects were recruited through local advertisements. Exclusion criteria included age below 18 or over 65 years, any neurological disorders, psychosurgery, current or past substance abuse or dependence, pregnancy or any substantial physical illness such as brain tumor, brain injury, stroke, or epilepsy.

Demographic and clinical data were analyzed for group differences using one-way analysis of variance (ANOVA) and post hoc least significant difference tests (SPSS, version 22). Gender and handedness ratios for each group were analyzed with chi-square and Fisher's exact tests, respectively (Table 1).

2.2. Image Acquisition and Processing

All subjects were scanned using a Siemens Tim Trio 3 T scanner or Siemens Verio scanner (Erlangen, Germany). High-resolution T1-weighted anatomical images were acquired using a 3D magnetization-prepared rapid gradient-echo sequence (repetition time = 2300 ms, TE = 3 ms, TI = 1000 ms, flip angle = 9°, voxel size = 1.0 × 1.0 × 1.0 mm^3). The data were processed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/). All MRI images were visually inspected before data processing to exclude scans exhibiting gross brain pathology, artifacts, or reduced image quality hampering image segmentation. An automated quality check using covariance analysis on the sample homogeneity of segmented GM images was performed in parallel to visual inspection, and did not lead to participant exclusion. T1-weighted images were (a) corrected for field inhomogeneities; (b) registered using a DARTEL (diffeomorphic anatomical registration through exponentiated lie algebra) template (Ashburner, 2007); (c) stripped of non-brain tissue; (d) tissue-segmented into gray matter, white matter and cerebrospinal fluid; (e) modulated for different tissue segments to preserve the regional volumetric information of a particular tissue within a voxel. This was done by multiplying the intensity value of each voxel in the segmented images by the Jacobian determinants (non-linear components only) that were derived from the spatial registration process. To increase the signal-to-noise ratio, images were smoothed with an 8-mm isotropic Gaussian kernel. A gray matter mask was applied before statistical comparison, which was derived from the Desiken-Killinay atlas (Desikan et al., 2006) and contained 34 cortical regions per hemisphere, 14 subcortical regions and the cerebellum (see Table S2).

2.3. Statistical Analysis and Cross Validation

Group effect on regional GMV was investigated by feeding the processed MRI images of drug-naïve OCD and HCs into general linear models that removed the confounding effects of age, sex, education level and total GMV. Clusters of voxels were considered statistically significant if the results of group comparison passed an uncorrected p threshold of 0.005 and withstood Monte Carlo cross-validation (MCCV). The MCCV procedure (repeated random sub-sampling validation) was performed

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