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Comparative Multimodal Meta-analysis of Structural and Functional Brain Abnormalities in Autism Spectrum Disorder and Obsessive-Compulsive Disorder

Christina O. Carlisi, Luke J. Norman, Steve S. Lukito, Joaquim Radua, David Mataix-Cols, and Katya Rubia

ABSTRACT

BACKGROUND: Autism spectrum disorder (ASD) and obsessive-compulsive disorder (OCD) share inhibitory control deficits possibly underlying poor control over stereotyped and repetitive and compulsive behaviors, respectively. However, it is unclear whether these symptom profiles are mediated by common or distinct neural profiles. This comparative multimodal meta-analysis assessed shared and disorder-specific neuroanatomy and neurofunction of inhibitory functions.

METHODS: A comparative meta-analysis of 62 voxel-based morphometry and 26 functional magnetic resonance imaging (fMRI) studies of inhibitory control was conducted comparing gray matter volume and activation abnormalities between patients with ASD (structural MRI: 911; fMRI: 188) and OCD (structural MRI: 928; fMRI: 247) and control subjects. Multimodal meta-analysis compared groups across voxel-based morphometry and fMRI.

RESULTS: Both disorders shared reduced function and structure in the rostral and dorsomedial prefrontal cortex including the anterior cingulate. OCD patients had a disorder-specific increase in structure and function of left basal ganglia (BG) and insula relative to control subjects and ASD patients, who had reduced right BG and insula volumes versus OCD patients. In fMRI, ASD patients showed disorder-specific reduced left dorsolateral-prefrontal activation and reduced posterior cingulate deactivation, whereas OCD patients showed temporoparietal underactivation.

CONCLUSIONS: The multimodal comparative meta-analysis shows shared and disorder-specific abnormalities. Whereas the rostrodorsomedial prefrontal cortex was smaller in structure and function in both disorders, this was concomitant with increased structure and function in BG and insula in OCD patients, but a reduction in ASD patients, presumably reflecting a disorder-specific frontostriatoinsular dysregulation in OCD in the form of poor frontal control over overactive BG, and a frontostriatoinsular maldevelopment in ASD with reduced structure and function in this network. Disorder-differential mechanisms appear to drive overlapping phenotypes of inhibitory control abnormalities in patients with ASD and OCD.

Keywords: Autism, Cognitive control, fMRI, Meta-analysis, OCD, VBM

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Autism spectrum disorder (ASD) is a predominantly male neurodevelopmental disorder characterized by difficulties in reciprocal social communication and stereotyped repetitive behaviors (1) with a prevalence of 0.6% to 1% (2).

Obsessive-compulsive disorder (OCD) is characterized by recurrent intrusive and distressing thoughts (obsessions) and repetitive mental and behavioral rituals (compulsions) (1), affecting 1% to 3% of the population, with a slightly higher prevalence among pediatric male and adult female subjects (3).

Both disorders are highly heterogeneous (4), carry >25% comorbidity with one another (5) and can be clinically difficult to separate. Both disorders are thought to be associated with poor top-down behavioral and neurocognitive inhibitory control (6), which may underlie poor control over stereotyped repetitive behaviors in ASD (7) over compulsions and intrusive thoughts in OCD (8). Inhibitory control is typically measured in motor and interference inhibition or switching tasks (9). Motor response inhibition tasks including go/no-go and stop tasks measure selective inhibition or withdrawal of a built-up prepotent response to frequent stimuli after presentation of an infrequent no-go or stop signal, respectively (10). Stroop, Simon, or Erikson flanker interference inhibition tasks measure the ability to inhibit a prepotent response tendency that conflicts with the primary intended action, and switching measures the ability to inhibit previously valid stimulus-response associations to engage in new ones (10). Whereas in stop, go/no-go, and interference inhibition tasks, a prepotent motor response has to be inhibited, switching

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requires, in addition to motor inhibition, reengagement in a different response. However, all these tasks share inhibitory processes (11) which are mediated in adults and children by overlapping inferior and medial frontostriatothalamoparietal networks, including ventrolateral prefrontal cortex (VLPFC), anterior insula, supplementary motor area, anterior cingulate cortex (ACC), caudate, subthalamic nucleus, and inferior parietal lobe (IPL) (11–15). Both OCD (8,16,17) and ASD (18–20) are characterized by deficits in performance and frontostriatoparietal activation during these inhibitory control tasks, suggesting that impaired inhibition could be a transdiagnostic behavioral phenotype.

In ASD, functional magnetic resonance imaging (fMRI) studies of motor and cognitive interference inhibition and switching report abnormalities in frontostriatoparietal areas including dorsolateral prefrontal cortex (DLPFC) and VLPFC (19,21–23), rostral and dorsal ACC and medial prefrontal cortex (r/dACC/MPFC) (24,25), insula (23,26,27), parietal regions (19,28), and caudate (22,24), as also are shown in meta-analyses of nonsocial processes that included inhibitory control tasks (17,29,30). Structural meta-analyses of gray matter volume (GMV) in ASD implicate frontolimbic and frontoparietal abnormalities, reporting decreased GMV in cerebellar, hippocampal, amygdala and parietal regions but increased GMV in superior frontal, striatal, and temporal regions (31–33), with basal ganglia (BG) abnormalities associated with symptom severity (34).

fMRI studies of response and interference inhibition and switching in children and adults with OCD have consistently shown hypoactivation in r/dACC/MPFC, VLPFC, and DLPFC, as well as altered striatal activation (16,35), supported by a recent meta-analysis and review (8,18). Structural meta- and mega-analyses of whole-brain voxel-based morphometry (VBM) studies in OCD patients report decreased GMVs in r/dACC/MPFC and ventromedial orbitofrontal cortex but increased GMV in bilateral striatum (18,36–38), which furthermore has been linked to poor inhibitory performance, suggesting frontostriatal dysregulation (39).

Despite apparent overlap in frontal and striatal abnormalities between the two disorders, no neuroimaging studies have directly compared ASD and OCD patients. Given the similarities in clinical phenotypes between these disorders (6), establishing common and distinct neuroanatomical and neurofunctional biomarkers may help with future differential diagnosis and treatment development.

The aim of this study was therefore to investigate whether a common behavioral phenotype may be underpinned by either common or distinct neural signatures in the two disorders, or by both common and distinct neural signatures. For this purpose, we conducted a quantitative meta-analysis comparing OCD and ASD in brain function and structural abnormalities using whole-brain VBM and fMRI studies of inhibitory control, and we compared multimodal structural and functional neural abnormalities.

We hypothesized that OCD patients would show disorder-specific frontostriatal dysregulation, that is, increased BG but decreased ventromedial and r/dACC/MPFC GMV activation (8,36), and ASD patients would show disorder-specific reductions in lateral frontostriatolimbic volumes and activations (31,32). We further predicted shared underactivation and reduced structure in medial prefrontal regions (18,24,25).

METHODS AND MATERIALS

Study Selection

A comprehensive literature search was conducted by COC, LJN, and SSL for papers published up to December 2015 for whole-brain imaging studies using VBM or fMRI of inhibitory control in pediatric and adult ASD and OCD subjects (using stop, go/no-go, Simon, Stroop, Eriksen flanker, or switching tasks). For details and search terms see the Supplement. Studies meeting the following criteria were included: 1) comparison with a control group; 2) for fMRI, use of a task investigating inhibitory control (see above for tasks included); 3) included minimum of 10 patients; 4) used standardized measures to assess OCD or ASD; 5) reported sufficient information to calculate effect sizes (i.e., software and coordinates for relevant contrasts); and 6) within one study, used the same significance or extent threshold throughout the whole brain in all analyses. Authors were contacted for additional information if necessary. Studies were excluded if they 1) used region-of-interest (ROI) approaches, 2) did not perform statistical comparisons between case and control subjects, and 3) did not report peak coordinates for relevant contrasts. ROI approaches may be more appropriate than whole-brain investigations when researchers are interested in the activation of a specific brain region. However, ROI studies were excluded from this meta-analysis because when conducting a voxel-wise whole-brain meta-analysis, inclusion of ROI analyses would bias the results, as voxels within ROIs would be set to have the effect sizes reported in the publications, whereas the voxels in the rest of the brain would be unfairly set to have no effect size. The exclusion of ROI studies is therefore recommended practice in structural and functional MRI whole-brain meta-analyses (see, e.g., 31,36,40–50). Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines for meta-analyses of observational studies were followed (51). To avoid duplication, conjunctive group differences across tasks or conditions or main group effects across task conditions were excluded. Peak coordinates and effect sizes of significant activation differences between patients and control subjects (or statistical maps where possible) were extracted from contrasts of interest for each study.

Statistical Methods

Meta-analyses of regional differences in activation or GMV were conducted using voxel-wise anisotropic effect-size seed-based *d* mapping (SDM; http://www.sdmproject.com). Methods employed by SDM are described elsewhere (47,52) and summarized briefly here. SDM uses reported peak coordinates and effect sizes from each study to recreate effect-size maps and an effect-size variance map of the signed (positive or negative) GMV or activation differences between patients and control subjects, converting the *t* value of each peak to Hedges effect size and applying an anisotropic nonnormalized Gaussian kernel so voxels more correlated with the peak have higher effect sizes. All maps were combined with a standard random-effects model, accounting for sample size, intrastudy variability and between-study heterogeneity (53). Statistical significance was determined by permutation tests and default thresholds (52).

Some studies included different fMRI tasks in identical or largely overlapping samples (27,54–56), or compared patient