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Brain functional connectivity in stimulant drug dependence and obsessive–compulsive disorder

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ABSTRACT

There are reasons for thinking that obsessive–compulsive disorder (OCD) and drug dependence, although conventionally distinct diagnostic categories, might share important cognitive and neurobiological substrates. We tested this hypothesis directly by comparing brain functional connectivity measures between patients with OCD, stimulant dependent individuals (SDIs; many of whom were non-dependent users of other recreational drugs) and healthy volunteers. We measured functional connectivity between each possible pair of 506 brain regional functional MRI time series representing low frequency (0.03–0.06 Hz) spontaneous brain hemodynamics in healthy volunteers (N = 18), patients with OCD (N = 18) and SDIs (N = 18). We used permutation tests to identify i) brain regions where strength of connectivity was significantly different in both patient groups compared to healthy volunteers; and ii) brain regions and connections which had significantly different functional connectivity between patient groups. We found that functional connectivity of right inferior and superior orbitofrontal cortex (OFC) was abnormally reduced in both disorders. Whether diagnosed as OCD or SDI, patients with higher scores on measures of compulsive symptom severity showed greater reductions of right orbitofrontal connectivity. Functional connections specifically between OFC and dorsal medial pre-motor and cingulate cortex were attenuated in both patient groups. However, patients with OCD demonstrated more severe and extensive reductions of functional connectivity compared to SDIs. OCD and stimulant dependence are not identical at the level of brain functional systems but they have some important abnormalities in common compared with healthy volunteers. Orbitofrontal connectivity may serve as a human brain systems biomarker for compulsivity across diagnostic categories.

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Introduction

Obsessive–compulsive disorder (OCD) and stimulant drug dependence are usually regarded as distinct species in the standard taxonomies of psychiatric disorders. This diagnostic speciation is reflected in specific therapeutic approaches, and different moral and legal attitudes to the two disorders. These marked differences in current clinical orientation can be contrasted to findings from recent cognitive neuroscientific reviews, which suggest that OCD and stimulant drug dependence share important features in common (Everitt and Robbins, 2005), including a persistent pattern of maladaptive, compulsive behavior. Compulsions are a core symptom of OCD, characterized by perseverative, ritualistic or repetitive behaviors or mental acts, which are often accompanied by troubling intrusive thoughts (American Psychiatric Association, 2000). Compulsivity is also a hallmark of drug addiction, represented by the persistence with which drug-dependent individuals act to obtain and consume drugs despite the risk of job loss, family break-up or imprisonment precipitated by further drug use (American Psychiatric Association, 2000). Compulsivity, thus defined as a perseverative pattern of maladaptive behavior, is different from impulsivity, which is defined as a tendency to respond without normal inhibitory control.

How could compulsivity emerge from abnormal brain function, especially functional dysconnectivity between components of large-scale brain systems? There is strong evidence, from pre-clinical models and human neuroimaging studies of both OCD and stimulant dependence, that compulsivity is related to abnormal structure and function of the orbitofrontal cortex (OFC) as a key component of fronto–striato–thalamic networks (Fineberg et al., 2010; Menzies et al., 2008b). For example, structural and functional magnetic resonance imaging (MRI) studies have demonstrated structural deficits of gray matter volume

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(Menzies et al., 2007), and functional abnormalities of task-related activation in the orbitofrontal cortex in patients with OCD (Chamberlain et al., 2008; Figee et al., in press). There is also growing evidence for abnormal OFC function in stimulant-dependent individuals, including reduced brain metabolism at rest (Volkow et al., 1993, 2001), decreased gray-matter density (Franklin et al., 2002; Matochik et al., 2003), and increased activation in response to drug-related cues (Bonson et al., 2002). It has been suggested that the compulsive features of addiction are mediated by abnormal function in the OFC (Volkow and Fowler, 2000).

In short, compulsivity is a behavioral phenotype that seems to cut across diagnostic boundaries between OCD and stimulant dependence. Despite this overlap, no studies have directly compared the two disorders in relation to the same group of healthy comparison volunteers, using functional neuroimaging to test the hypothesis that abnormalities of OFC function might consistently underlie compulsivity in both disorders. We tested this hypothesis directly on the basis of fMRI data collected identically from balanced groups of well-characterized patients with OCD (N = 18), stimulant dependent individuals (SDI, N = 18), and healthy volunteers (N = 18). Specifically, we predicted on the basis of prior data (Harrison et al., 2009) that functional connectivity of the orbitofrontal cortex would be abnormal in both OCD and stimulant dependence, and that the degree of abnormal orbitofrontal connectivity would be related to individual differences in compulsivity. We also explored the hypothesis that the different patient groups might demonstrate differences in OFC function related to the broader, diagnostically specific clinical contexts within which compulsivity emerges in OCD and stimulant dependence.

Methods and materials

Study sample

Three groups of right-handed participants were recruited from the local community and outpatient clinical services: healthy control volunteers (N = 18), stimulant-dependent individuals (SDI; N = 18) and patients with obsessive–compulsive disorder (OCD; N = 18). Stimulant-dependent individuals had a minimum 2-year history of dependence on illicit stimulants satisfying the DSM-IV-TR criteria for dependence on cocaine/crack (N = 10) or amphetamines (N = 8) (American Psychiatric Association, 2000). On average, they had been using stimulant drugs for 11.7 years (±7.42 standard deviation [SD]), starting at the age of 20.5 years (±5.40 SD). On average, OCD was diagnosed at the age of 17.1 years (±11.0 SD), which meant that patients had diagnosed disorder for 18.3 years (±10.6 SD). Diagnoses of stimulant dependence and OCD were ascertained by Structured Clinical Interview for the DSM-IV-TR (First et al., 2002). Demographic and clinical data are summarized for all groups in Table 1.

All participants were screened to exclude any other current Axis I psychiatric disorder according to the DSM-IV-TR criteria. Concomitant medications (except selective serotonin reuptake inhibitor (SSRI) drugs in OCD patients), and the illicit use of drugs (except in the drug user group), were exclusion criteria. In addition, participants were excluded if they had a current or past history of any serious medical disorder or any contra-indications to MRI; see Supplementary Material for details.

The study was approved by the Cambridge Research Ethics Committee (REC06/Q0108/130; PI: TW Robbins) and all participants provided informed consent in writing.

Psychometric and clinical assessment

All participants underwent an assessment of their general health, including a physical examination, baseline clinical blood tests and urine analysis for illicit drug use prior to study enrolment; see Supplementary Material for details. The severity of compulsive symptoms was assessed in OCD and healthy volunteers using the Yale–Brown Obsessive–Compulsive Scale (YBOCS; Goodman et al., 1989), which is a standard subjective instrument for measuring obsessive–compulsive symptom severity in OCD. We administered the Obsessive–Compulsive Drug Use Scale (OCDUS; Franken et al., 2002) to SDIs only, as patients with OCD and the control volunteers did not have a significant drug-taking history.

Table 1
Demographic, clinical and personality measures for the groups of healthy volunteers (N = 18), stimulant dependent individuals (SDIs; N = 18) and patients with obsessive–compulsive disorder (OCD; N = 18).

Group	Healthy volunteers	SDI	OCD
Age (years)	32.7 (±6.9)	34.33 (±7.2)	35.4 (±9.8)
Gender ratio (male:female)	15:03	15:03	11:07
Ethnic ratio (Caucasian: Afro-Caribbean)	17:01	16:02	18:00
Employment ratio (employed : unemployed)	17:01	09:09	11:07
Verbal intelligence (NART)	108.4 (±6.0)	109.0 (±8.1)	107.9 (±8.8)
Years of education	12.4 (±1.8)	11.2 (±1.0)	12.3 (±2.0)
BDI-II (total score)	1.1 (±2.4)	9.3 (±11.1)	18.5 (±10.0)
MADRS (total score)	0.9 (±2.3)	5.6 (±8.1)	8.1 (±4.8)
BIS-11 (total score)	62.0 (±7.2)	82.0 (±9.5)	66.9 (±9.7)
YBOCS (total score)	0.1 (±0.5)	–	24.11 (±13.02)
OCDUS (total score)	–	26.5 (±7.9)	–

Depressive mood was assessed at baseline using the self-rated Beck Depression Inventory (BDI-II; Beck et al., 1996) and the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979), which is a widely used observer-rated depression scale. We assessed trait-impulsivity because of the hypothesized association between impulsivity and compulsive behaviors (Belin et al., 2008; Everitt and Robbins, 2005; Potenza and Taylor, 2009). Impulsivity was measured using the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995), which is the most widely used self-report measure of impulsive personality traits (see Table 1 for details). BIS-11 scores for one OCD patient were unavailable.

All participants provided a urine sample that was tested for the following drugs: cocaine, amphetamines, morphine, methadone, buprenorphine, barbiturates, benzodiazepines and tricyclides antidepressants. All urine samples provided by SDIs tested positive for stimulants; additional substances tested positive in this group were: cannabis 56%, morphine 28%, benzodiazepines 11%, and tricyclic antidepressants 11%. The urine samples provided by OCD patients and control volunteers were negative for all drugs tested.

Functional MRI data acquisition, pre-processing and analysis

Whole-brain echoplanar imaging (EPI) data depicting blood oxygenation level dependent (BOLD) contrast were acquired at the Wolfson Brain Imaging Centre, University of Cambridge, UK, using a Siemens Magnetom Tim Trio whole body scanner operating at 3 T with a birdcage head transmit/receive coil. Gradient-echo, echoplanar imaging (EPI) data were acquired for the whole brain with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 78°, slice thickness = 3 mm plus 0.75 mm interslice gap, 32 slices parallel to the inter-commissural (AC-PC) line, image matrix size = 64 × 64, within-plane voxel dimensions = 3.0 mm × 3.0 mm. Participants were asked to lie quietly in the scanner with eyes closed during the acquisition of 300 images. The first four EPI images were discarded to account for T1 equilibration effects, resulting in a series of 296 images, of which the first 256 images were used to estimate wavelet correlations.

The individual images were corrected for motion and registered to the standard stereotactic space of the Montreal Neurological Institute EPI template image using an affine transform (Suckling et al., 2006). Time series were then extracted using a whole brain, high resolution, regional parcellation of the images which resulted in a set of 506

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