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

David Meunier, Karen D. Ersche, Kevin J. Craig, Alex Fornito, Emilio Merlo-Pich, Naomi A. Fineberg, Shaila S. Shabbir, Trevor W. Robbins, Edward T. Bullmore

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.

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...
Volunteers (N=18), stimulant-dependent individuals (SDI; N=18), and healthy volunteers (N=18) were recruited from the local community and outpatient clinical services: healthy control volunteers, stimulant-dependent individuals, and healthy volunteers. Specifically, we predicted on the basis of prior data 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 healthy volunteers (N=18). Specifically, we predicted on the basis of prior data 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.

#### 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 3T 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 x 64, within-plane voxel dimensions = 3.0 mm x 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. Time series were then extracted using a whole brain, high resolution, regional parcellation of the images which resulted in a set of 506

### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Healthy volunteers</th>
<th>SDI</th>
<th>OCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.7 (±6.9)</td>
<td>34.3 (±7.2)</td>
<td>35.4 (±9.8)</td>
</tr>
<tr>
<td>Gender ratio (male:female)</td>
<td>15:03</td>
<td>15:03</td>
<td>11:07</td>
</tr>
<tr>
<td>Ethnic ratio (Caucasian: Afro-Caribbean)</td>
<td>17:01</td>
<td>16:02</td>
<td>18:00</td>
</tr>
<tr>
<td>Employment ratio (employed : unemployed)</td>
<td>17:01</td>
<td>09:09</td>
<td>11:07</td>
</tr>
<tr>
<td>Verbal intelligence (NART)</td>
<td>108.4 (±6.0)</td>
<td>109.0 (±8.1)</td>
<td>107.9 (±8.8)</td>
</tr>
<tr>
<td>Years of education</td>
<td>12.4 (±1.8)</td>
<td>17.2 (±10.0)</td>
<td>12.3 (±2.0)</td>
</tr>
<tr>
<td>BDI-II (total score)</td>
<td>1.1 (±2.4)</td>
<td>9.3 (±11.1)</td>
<td>18.5 (±10.0)</td>
</tr>
<tr>
<td>MADRS (total score)</td>
<td>0.9 (±2.3)</td>
<td>5.6 (±8.1)</td>
<td>8.1 (±4.8)</td>
</tr>
<tr>
<td>BIS-11 (total score)</td>
<td>62.0 (±7.2)</td>
<td>82.0 (±9.5)</td>
<td>66.9 (±9.7)</td>
</tr>
<tr>
<td>YBOCS (total score)</td>
<td>0.1 (±0.5)</td>
<td>–</td>
<td>24.11 (±13.02)</td>
</tr>
<tr>
<td>OCDUS (total score)</td>
<td>–</td>
<td>26.5 (±7.9)</td>
<td>–</td>
</tr>
</tbody>
</table>

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.

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 tricyclic 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.

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The wavelet correlation was estimated between the wavelet coefficients representing the fMRI time series for each possible pair of nodal regions, $i$ and $j$. This resulted in a $(506 \times 506)$ between-region association matrix, or frequency-dependent functional connectivity matrix $C$ for each subject. From these matrices, we estimated the nodal connectivity strength of each region simply by averaging all the wavelet correlations between the index region and every other regional node in the brain. Between-group differences in nodal connectivity strength were tested for statistical significance by a data permutation algorithm; see Supplemental Material for detail. For the analysis of multiple nodal connectivity differences, the $P$-value for significance was adjusted to $P = 1/506 \times 2 \times 10^{-3}$ so that each cortical map of nodal connectivity differences is expected to include less than one false positive difference.

The following tests were conducted: i) both patient groups combined (OCD and SDIs) were compared to the healthy volunteer group to define regions where nodal connectivity strength was consistently abnormal in both disorders; ii) an ANOVA model, with group as a three level factor, was used to identify regions where nodal connectivity strength was significantly different between groups. For a core region of interest in orbitofrontal cortex (OFC), defined by a significant reduction of nodal connectivity strength in the comparison of both patient groups to the healthy volunteer group (test (i), Fig. 1), we explored the relationship between individual differences in severity of compulsive symptom ratings and nodal connectivity of OFC. Compulsivity scores were rank transformed prior to correlational or regression analysis of their association with OFC connectivity strength.

In addition to these tests of commonality and difference in nodal connectivity strength, we also tested for between-group effects on the pairwise inter-regional connections (wavelet correlations) using the inferential procedures as already described for nodal connectivity analysis. The following tests were conducted: (iii) both groups were compared to volunteers to identify regionally specific connections to OFC that were abnormal in both groups; and (iv) an ANOVA model, with group as a three level factor, was used to identify regional connections to OFC that were differentially affected between groups.

In the main text, we focus on the results of these relatively simple models. However, to investigate the possible confounding effects of group differences in depressive symptoms, we also fitted analysis of covariance models for estimation of between-group differences and commonalities, with BDI scores included as a covariate. We also measured the correlations between OFC connectivity and residual compulsive symptom scores after effects of BDI had been removed by regression on the raw BDI scores. Additionally, we used regression to control statistically for variation in nicotine and cannabis use in the SDI group, and for variation in prescribed concomitant medication in the OCD group, before estimating the correlations between OFC...
connectivity and compulsivity scores in each group. The pattern of results obtained by these additional analyses was consistent with the results obtained by simpler modeling; see Supplementary Material for details.

Results

Demographic and clinical differences between groups

The three groups were matched with regard to age ($F_{2,51} = 0.50$, $P = 0.611$), verbal intelligence ($F_{2,51} = 0.09$, $P = 0.911$), gender (Fisher’s exact test, $P = 0.238$) and years of education ($F_{2,51} = 3.12$, $P = 0.053$). However, the groups differed significantly in employment status (Fisher’s exact test, $P = 0.010$), since a larger number of patients (53% of the SDI group and 41% of the OCD group) were unemployed at the time of the study compared with the healthy volunteers (6%). Both patient groups also scored higher on both measures of depressive mood compared with controls (BDI-II: $F_{2,51} = 20.12$; MADRS: $F_{2,51} = 7.53$, both $P \leq 0.001$). The groups also differed with regard to impulsive personality traits ($F_{2,50} = 24.76$, $P < 0.001$). Since impulsivity is a key feature of substance dependence (Moeller et al., 2001) it is not surprising that the SDIs reported greater levels of impulsivity compared separately to both OCD and healthy volunteer groups (volunteers versus SDIs: $t = −7.10$; SDIs versus OCD: $t = 4.65$; $P < 0.001$ for both tests). Impulsivity levels in OCD patients and controls were not significantly different ($t = −1.69$, $P > 0.1$). We also did not identify a relationship between the measures of impulsivity and compulsivity either in SDIs ($r = −0.30$, $P > 0.05$) or in OCD patients ($r = −0.30$, $P > 0.05$). Not surprisingly, scores on the B-BOCS measure of compulsivity were significantly greater in patients with OCD than healthy volunteers; and patients with stimulant dependence scored higher on the OCDUS than those in the SDI group ($t = −3.13$, $P = 0.004$). We also did not identify a relationship between OFC connectivity and trait-impulsivity measured by the BIS-11 ($r = −0.49$; $P = 0.04$), smoking in the SDI group (Figure S3, Supplemental Material) and for gender and concomitant medication in the OCD group (Figure S4, Supplemental Material). In contrast, there was no significant correlation between OFC connectivity and trait-impulsivity measured by the BIS-11 (see Figure S5, Supplemental Material).

We also tested the difference between combined disorder and healthy volunteer groups for each pairwise wavelet correlation between the core or “seed” OFC regions, identified as above, and all other brain regions. As shown in Fig. 2(A), this demonstrated that}

![Disorder-generic abnormalities of functional connectivity](https://example.com/figure.png)

To address our primary hypothesis that both disorders might have generic abnormalities of orbitofrontal connectivity, we first compared mean nodal connectivity strength between the group of healthy volunteers and the combined group of both patients with OCD and SDIs. The most significant results, and the only ones to survive correction for multiple comparisons, were abnormally reduced strength of functional connectivity of inferior and superior components of right orbitofrontal cortex, at stereotactic (MNI) $[x, y, z]$ coordinates, $mm$: {10, 38, −16} and {10, 62, 8}; see Fig. 1. In post-hoc analyses, we found that each group considered separately had abnormally reduced mean connectivity of these right orbitofrontal regions compared to the healthy volunteers, although the extent of abnormality was greater and less variable in patients with OCD than in stimulant dependent individuals ($t(31.3) = 2.2$, $P = 0.03$).

Importantly, we also found that functional connectivity of this right superior OFC region was inversely correlated with the severity of ranked compulsive symptoms in the combined patient group (Spearman’s rank correlation rho = −0.54; $S = 11,983$, $P = 0.0006$); see Fig. 1C as well as specifically in the OCD group (rho = −0.49; $S = 1439.2$, $P = 0.04$) and in the SDIs (rho = −0.64; $S = 1588.6$, $P = 0.004$); see Fig. 1D. In other words, greater attenuation of orbitofrontal functional connectivity was generally associated with higher scores on standard clinical measures of obsessive-compulsive symptoms (YBOCS) and compulsivity of stimulant drug use (OCDUS). These correlations remained significant following additional analyses which controlled for tobacco and cannabis smoking in the SDI group (Figure S3, Supplemental Material) and for gender and concomitant medication in the OCD group (Figure S4, Supplemental Material). In contrast, there was no significant correlation between OFC connectivity and trait-impulsivity measured by the BIS-11 (see Figure S5, Supplemental Material).

...
OFC connections with medial premotor cortex \([0, −36, 64]\), dorsal cingulate cortex \([0, −14, 40]\), right somatosensorymotor cortex \([60, −14, 26]\), and left temporal cortex \([-60, −12, −20]\), were significantly attenuated in both patient groups compared to healthy volunteers.

**Disorder-specific abnormalities of functional connectivity**

To assess the differences among the three groups in nodal connectivity, we used an ANOVA model and data permutation. Two cortical regions demonstrated significant between-group differences in nodal connectivity: a region of right superior orbitofrontal cortex at stereotactic (MNI) \([x, y, z]\) coordinates: \((10, 62, 8)\) and a region of posterior cingulate cortex at \((-14, -58, 20)\). Consistent with the prior analysis on commonality of OFC connectivity deficits across disorders, post-hoc analysis demonstrated that right superior OFC connectivity was significantly different in both groups compared separately to healthy volunteers, but there was no significant difference between the patient groups (Fig. 3). However, posterior cingulate connectivity was significantly reduced only in the OCD group, compared to both healthy volunteers and SDIs (Fig. 3). Connectivity of left dorsal thalamus was also significantly increased in the OCD group compared to SDIs, but was not significantly different in OCD compared to healthy volunteers (Fig. 3).

Finally, we returned to the right OFC region that demonstrated compulsivity-related reduction of functional connectivity in both groups combined; Fig. 2(B). We asked the question: what regionally specific functional connections with right OFC are differently affected in the OCD and SDI groups? We found that connectivity of medial prefrontal cortex at stereotactic coordinates \((0, −6, 58)\) and right postcentral cortex at \((36, −26, 52)\) was attenuated specifically in the OCD group compared to both SDIs and healthy volunteers.

**Discussion**

We have confirmed that two clinically differentiated syndromes – obsessive-compulsive disorder and stimulant drug dependence – are both associated with high levels of compulsive behavior. Our results also show directly for the first time that compulsivity is associated with reduced functional connectivity of orbitofrontal cortex (OFC), suggesting that compulsive aspects of psychopathology in the two disorders may arise from a generic abnormality in functional connectivity of the OFC. Although this is our major result, it should not be taken to mean that OCD and SDI were identical at the level of neurophysiological systems: for example, although connectivity between OFC and dorsal medial cortex was significantly reduced in both disorders, the degree of abnormality was greater in patients with OCD.

**Orobitofrontal compulsivity as a neurocognitive phenotype**

There is abundant evidence implicating orbitofrontal cortex in the ongoing guidance and inhibition of behavior by integrating information about the possible outcomes of events (Bechara et al., 2000; Elliott et al., 2000; Kringelbach and Rolls, 2004; Rubia et al., 2003; Wals, 2007). Patients with lesions to the OFC make decisions without using information about outcomes to guide their behavior (Bechara et al., 1997). Both patients with OCD (Chamberlain et al., 2006; Menzies et al., 2005) and SDIs (Fillmore and Rush, 2002; Monterosso et al., 2005) show significant impairments in suppressing ongoing behavior. It has been suggested that in individuals with poor response inhibition, OFC dysfunction mediates compulsivity (Schoenbaum and Shaham, 2008). Our main new findings in this context are that functional connectivity of OFC – specifically connectivity of OFC with dorsal medial cortex – was abnormally attenuated in patients with OCD and long-term stimulant dependence, and reduced OFC connectivity was correlated with severity of compulsive symptoms.

To the best of our knowledge, this is the first functional neuroimaging study to directly test the hypothetical prediction that orbitofrontally-mediated compulsivity is a neurocognitive phenotype in common to obsessive–compulsive and stimulant-dependent patients. In light of previous results indicating that OFC function and structure are endophenotypes, or markers of genetic risk, for OCD, it would be interesting to test the candidacy of orbitofrontal compulsivity as a marker for obsessive–compulsive and stimulant dependence.

**Fig. 3.** Disorder-specific profiles of cortical and subcortical nodal connectivity strength. (A) Between-group differences in nodal connectivity strength, identified by ANOVA, are represented by cortical surface mapping: red voxels indicate significant between-group differences with \(P < 2 \times 10^{-3}\). (B) Boxplots of nodal mean connectivity strength for right superior orbitofrontal cortex \((10, 62, 8)\) and left posterior cingulate area \((-14, -58, 20)\). Asterisks denote statistical significance of pair-wise comparisons by permutation testing, as for Fig. 1. (C) Axial slice representation of the left dorsal thalamus \((-14, -10, 20)\), showing a significant difference in nodal connectivity strength between groups. The boxplot represents mean and variability of left thalamic nodal connectivity strength for each group; asterisks denote statistical significance of pair-wise comparisons by permutation testing, as for Fig. 1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
of genetic risks shared between these disorders. Both disorders are heritable: family studies have shown that OCD is five to seven times (Nestadt et al., 2000) and SDI eight times (Merikangas et al., 1998) more frequent in first-degree relatives of patients than in unrelated controls. Both disorders also seem to co-segregate in families more frequently than expected by their general population prevalences (Manco & et al., 2009). The existence of a generic brain functional system related to compulsivity might also be expected to encourage development of new therapeutics targeting this core psychopathological mechanism across traditional diagnostic indications.

It is notable that, although contemporary neurobiological models of compulsivity are often framed in terms of orbitofrontal systems, there have been relatively few neuroimaging studies of structural or functional brain connectivity in either disorder. Some advanced recent work has directly measured functional connectivity between components of fronto-striatal circuits in OCD. This study showed that connectivity of ventral striatal regions of interest, especially with orbitofrontal cortex, was attenuated in OCD and severity of obsessive-compulsive symptoms was greater in patients with greater reductions in ventral striatal connectivity. We did not find significant changes in striatal connectivity, perhaps because we used a different parcellation scheme for striatum, but our findings of abnormal OFC connectivity seem likely to be related to these results. Future studies might profitably combine a finer-grained anatomical resolution of subcortical nuclei, as done by Harrison et al. (2009), with a comprehensive mapping of all cortical regions, as done here. The broad conclusion from both studies is that functional connectivity is attenuated in OCD and this is echoed by neuroimaging studies of white matter that have been used to assess anatomical (putatively axonal) connectivity between brain regions. These have demonstrated reductions in white matter volume measured by MRI (Duran et al., 2009), and in fractional anisotropy (FA) measured using diffusion tensor imaging (DTI) (Szeszko et al., 2005). White matter abnormalities have also been shown using DTI in first-degree relatives of patients with OCD (Menzies et al., 2008a).

Differences in orbitofrontal connectivity: diagnostic implications

Although our findings support the existence of a generic neurocognitive phenotype in both OCD and stimulant dependence, it is obviously also true that people with OCD and stimulant-dependent individuals are not clinically identical in their expressions of compulsivity. In keeping with these clinical differences in expression of compulsivity, we found that the groups also differed in terms of the severity and anatomical profile of abnormal functional connections with orbitofrontal cortex. Although both groups demonstrated some degree of attenuation of orbitofrontal connectivity, with dorsal medial cortex especially, the OCD group was more severely affected, with significantly reduced orbitofrontal–dorsomedial connectivity compared to SDI groups (Fig. 2). Moreover, the OCD group demonstrated abnormalities in functional connectivity of posterior cingulate (compared to both healthy volunteers and SDI) and dorsal thalamus (compared to SDI). We speculate that these different profiles of orbitofrontal dysconnectivity may be related to the clinical differentiation of compulsivity in these groups. Thus the greater attenuation in OCD of orbitofrontal connectivity to regions of dorsal pre-motor and cingulate cortex may be related to the ritualistic or manneristic movements associated with OCD. This would be consistent with what is known about the importance of these regions for motor planning of goal-directed actions (Koski et al., 2002) and for adjustment of these actions in response to reinforcement or conflict (Weissman & et al., 2005).

Methodological issues

There are a number of limitations to bear in mind when evaluating these results. The sample size is modest and this is likely to have resulted in some loss of statistical power in the context of the multiple comparisons entailed in a whole brain survey of nodal connectivity differences between groups. Such type 2 errors are most likely to have arisen in relation to analyses involving only one patient group, and especially the SDI group given its greater variability. We have therefore focused here on the most robust results but we anticipate that future studies involving larger samples might be expected to identify functional disconnection in a more extensively distributed system of regions. Although the two groups were matched on several variables, they were not matched in terms of drug exposure: the SDIs were actively using stimulant drugs whereas the majority of the OCD patients were being treated with SSRIs. This factor seems unlikely to explain the commonalities in OFC connectivity between groups, future studies, perhaps involving the first-degree relatives of both SDIs and patients with OCD, will be needed to disambiguate drug effects from disorder-specific effects in accounting for the between-group differences in functional connectivity. Additionally, we recognize that there was heterogeneity in the SDI group in terms of their history of nicotine and cannabis use, and there was heterogeneity in the OCD group in terms of prescribed concomitant medication. However, we have addressed the potentially confounding effects of these factors by supplementary analyses which demonstrated that the correlations between compulsivity and OFC connectivity in each group were substantially unaffected by variation between individuals in their exposure to prescribed or non-stimulant recreational drugs. We note that our focus on compulsivity of stimulant drug use as a continuous trait variable within the group of stimulant dependent individuals further mitigates any possible concern that categorical differences between control and SDI groups might be driven by co-morbid drug abuse by the SDI group.

It is also an issue that compulsivity was measured using different clinical rating scales in the two diagnostic groups: patients with OCD completed the YBOCS scale but stimulant-dependent individuals completed the OCUSS scale. This procedure was designed to measure compulsivity in the most diagnostically appropriate way for each group but it limits direct comparability, requiring rank transformation of compulsivity scores within each group prior to their collation across groups. It will be important, in future, to develop objectively behavioral measures of compulsivity that are applicable across diagnostic groups to validate the individual differences in compulsivity as measured here by group-specific self-report instruments, i.e. OCUUS and YBOCS.

Impulsivity has been hypothesized to mediate the development of compulsive behaviors (Belin & et al., 2008; Dalley & et al., 2007; Potenzo & Taylor, 2009). However, in the present study, we did not find associations between the self-reported measures of impulsivity and compulsivity in either patient group. Impulsivity assessed by the BIS–11 score has been linked with dopamine release in the striatum (Buckholtz & et al., 2010; Lee & et al., 2009) but not with orbitofrontal function. This is consistent with our finding that OFC connectivity was not correlated with trait-impulsivity (Figure S3, Supplemental Material). It will be an important issue for future studies to clarify the theoretically expected relationships between impulsivity, compulsivity and underlying fronto-striatal systems in OCD and drug dependence.

There is also some controversy about the sources of variation in endogenous fMRI dynamics measured in resting state paradigms, which likely include cardiorespiratory pulsation and head movement effects as well as neurophysiologically more interesting changes in cortical activity. The correlation between OFC connectivity and trait impulsivity argues against the interpretation that disorder-related dysconnectivity is trivially attributable to group differences in non-neural sources of fMRI signal variation. However, we did not acquire simultaneous measurements of cardiorespiratory data that would allow statistical correction for such effects in these fMRI data. Moreover, the cognitively uncontrolled nature of the resting state paradigm allows the interpretation that OCD patients demonstrated greater functional dysconnectivity because they were in a more symptomatic state than the SDIs during scanning. Future studies of
functional connectivity in these groups might usefully adopt additional measures to control interpretation of resting state data and/or investigate OFC connectivity under experimentally controlled conditions.

Conclusion

The present study provides preliminary evidence that OCD and stimulant dependence are not identical at the level of brain functional systems but they share some important abnormalities compared with healthy volunteers. Specifically, orbitofrontal connectivity may serve as a human brain systems biomarker for compulsivity across diagnostic categories.

Financial disclosures

EMP and SSS are full-time employees and stockholders of GlaxoSmithKline. ETB is employed half-time by GlaxoSmithKline and half-time by University of Cambridge; he is a stockholder of GSK. KJC is full-time employed by Pivital Ltd. NAF has consulted for Lundbeck, Glaxo-SmithKline, Servier, and Bristol Myers Squibb; has received research support from Lundbeck, GlaxoSmithKline, Astra Zeneca, Wellcome, ECNP, Cephalon; has received honoraria and support to attend and/or lecture at scientific meetings from Janssen, Jazz, Lundbeck, Servier, Astra Zeneca, Cephalon, Wyeth. TWR has provided consulting services for Cambridge Cognition Ltd., and the pharmaceutical industry including E. Lilly and GlaxoSmithKline. He has also received honoraria from Roche, Merck Sharp and Dohme, Lundbeck and GlaxoSmithKline. He is a past recipient of research grants from GlaxoSmithKline and Pfizer, and holds shares from CeNeS, and share options from Cambridge Cognition, and Allon Therapeutics. He also receives an editorial honorarium from the Springer-Verlag (Psychopharmacology). KDE, DM, and AF declare that they have no financial conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2011.08.003.

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