Published in final edited form as:

J Affect Disord. 2016 May 15; 196: 87–96. doi:10.1016/j.jad.2016.02.021.

OCD is associated with an altered association between sensorimotor gating and cortical and subcortical 5-HT_{1B} receptor binding

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Abstract

Obsessive-compulsive disorder (OCD) is characterized by impaired sensorimotor gating, as measured using prepulse inhibition (PPI). This effect may be related to abnormalities in the serotonin (5-HT) system. 5-HT_{1B} agonists can impair PPI, produce OCD-like behaviors in animals, and exacerbate OCD symptoms in humans. We measured 5-HT_{1B} receptor availability using ¹¹C-P943 positron emission tomography (PET) in unmedicated, non-depressed OCD patients ($n = 12$) and matched healthy controls (HC; $n = 12$). Usable PPI data were obtained from 20 of these subjects (10 from each group). There were no significant main effects of OCD diagnosis on 5-HT_{1B} receptor availability (¹¹C-P943 BP_{ND}); however, the relationship between PPI and ¹¹C-P943 BP_{ND} differed dramatically and significantly between groups. 5-HT_{1B} receptor availability in the basal ganglia and thalamus correlated positively with PPI in controls; these correlations were lost or even reversed in the OCD group. In cortical regions there were no significant correlations with PPI in controls, but widespread positive correlations in OCD patients. Positive correlations between 5-HT_{1B} receptor availability and PPI were consistent across

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diagnostic groups only in two structures, the orbitofrontal cortex and the amygdala. Differential associations of 5-HT_{1B} receptor availability with PPI in patients suggest functionally important alterations in the serotonergic regulation of cortical/subcortical balance in OCD.

INTRODUCTION

Obsessive compulsive disorder (OCD) affects approximately one person in 40 (1, 2) and is commonly severe (3, 4). Its underlying biology is not well understood (5); alterations in both cortical and basal ganglia circuitries have been documented (e.g. 6, 7). Selective serotonin reuptake inhibitors (SSRIs), along with the relatively serotonin-specific tricyclic antidepressant clomipramine, form the backbone of pharmacotherapy and are efficacious in 50-60% of patients (3, 8). However, refractory disease is common; approximately 30% of patients show little meaningful response to available treatments, either pharmacological or psychotherapeutic, and many who are classified as 'responders' continue to experience substantial residual symptomatology and attendant morbidity (4, 9-12).

Recent studies have identified a number of behavioral and neuropsychological candidate endophenotypes in OCD (7, 13, 14). These include behavioral inflexibility (15), an over-reliance on habit-based decision-making (16, 17), difficulties with response inhibition (18), and abnormalities in sensorimotor gating. Sensorimotor gating, typically assayed using prepulse inhibition (PPI), has been shown to be deficient in patients with OCD in several studies (19-23), though not in all (24). It has been speculated (19) that these PPI abnormalities may be related to dysfunction of the cortico-basal ganglia circuitry; the basal ganglia, especially the ventral striatum and medial, have been implicated in PPI in animal studies (25-27). PPI deficits may relate to patients' inability to filter out obsessive thoughts and compulsive urges (19, 20).

The efficacy of the SSRIs has motivated interest in the integrity of the serotonergic modulatory system in patients with OCD, but no clear abnormalities have been documented, suggesting that any disease-associated abnormalities are likely to be subtle and/or masked by phenotypic heterogeneity within the OCD patient population. An early study found increased 5-HT in peripheral blood of OCD patients (28); this was replicated in one subsequent study (29), but not in others (30-33). CSF studies have not shown consistent changes in 5-HT or its metabolites (34). Genetically, variants in the promoter of the 5-HT transporter (5-HTT) and in the 5-HT_{2A} receptor have been associated with OCD in candidate gene studies, but with very small effects (35). Recent genome-wide association studies have not implicated serotonergic genes as major risk factors at the population level (36, 37).

Platelet measures of 5-HTT have been fairly consistent in showing reduced ligand binding in patients with OCD (31, 38-43), which in some cases has been shown to correlate with symptom severity (41). In the brain, however, positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies of 5-HTT have yielded more equivocal results, with individual studies showing decreased, increased, or unchanged binding in patients (44). Binding to the 5-HT_{2A} receptor has similarly been reported to be increased (45, 46), decreased (47), or unchanged (48) in OCD.

The 5-HT_{1B} receptor, formerly called 5-HT_{1Dβ}, has been a focus of recent interest. 5-HT_{1B} is a seven transmembrane receptor coupled to G_qi. It functions as a presynaptic autoreceptor on serotonergic neurons (49-53), as well as a presynaptic heteroreceptor on other neuron types. It is highly expressed in basal ganglia and in regions of cortex (54-60). Several polymorphisms in the 5-HT_{1B} gene have been characterized; to date, there is no statistically convincing evidence associating them with OCD risk (35). However, the 5-HT_{1B/1D} agonist sumatriptan has been reported to worsen OCD symptoms in a number of studies (61-63), though not in all (64, 65).

In rodents, agonists of the 5-HT_{1B} receptor have been reported to impair PPI (66, 67) and to lead to increased locomotion, anxiety, and perseverative behaviors (68, 69); this has been proposed to be a behavioral model for OCD. In support of this, the effects of 5-HT_{1B} agonist challenge are attenuated by chronic SSRI treatment but not by chronic treatment with the tricyclic imipramine (68, 69), which is generally inefficacious in OCD. The observed behavioral effects depend on drug actions in the orbitofrontal cortex (OFC), which has been implicated as a key node of pathology in OCD (70).

5-HT_{1B} receptor availability can be assessed *in vivo* in humans using the PET ligands ¹¹C-P943 (71-74) and ¹¹C-AZ10419369 (75). ¹¹C-P943 has recently been used to document receptor abnormalities in several psychiatric conditions (76-78). We used ¹¹C-P943 PET imaging to examine 5-HT_{1B} receptor availability in unmedicated, non-depressed patients with OCD and matched healthy controls. Because of the relationship between 5-HT_{1B} activity and PPI in rodents (67, 68), we also examined PPI in all participants and examined its relationship to ¹¹C-P943 binding both within and between diagnostic groups. We assessed two primary hypotheses. First, because 5-HT_{1B} agonists can worsen OCD symptomatology, we hypothesized that regional ¹¹C-P943 binding would differ between patients with OCD and controls in cortical and subcortical regions previously implicated in OCD (see Methods). Second, because 5-HT_{1B} activation both produces OCD-like behaviors and impairs PPI in animals (67, 68), we hypothesized that the relationship between ¹¹C-P943 binding and PPI would differ between the two groups.

EXPERIMENTAL PROCEDURES

Subjects

Adults with a primary DSM-IV diagnosis of OCD and healthy controls (HC) matched for age, body mass index, and sex were recruited through the Yale OCD Research Clinic (ocd.yale.edu). All subjects completed signed informed consent, approved by the Yale Human Investigations Committee. OCD diagnosis was established by clinical interview with a doctoral level clinician; diagnosis was confirmed (in both OCD and control groups) using the Structured Clinical Interview for DSM-IV (79). Subjects were unmedicated; no use of psychoactive medications within 8 weeks of scanning was permitted. Because 5-HT_{1B} receptor binding abnormalities have been documented in major depressive disorder (77), individuals with comorbid depression, indicated by a DSM diagnosis or by a Hamilton Depressive Rating Scale (HDRS-17) score of ≥ 12 (80), were excluded. Individuals with active substance abuse or dependence (within the past 6 months), history of mania or of psychosis, autism, major neurological disease, and pregnancy were also excluded. Subject

demographic and clinical characteristics are presented in **Table 1**. There was a weak trend towards more years of education in the control group ($p = 0.074$ without correction for multiple comparisons); there were no differences in any other demographic variables.

Prepulse inhibition

Startle and PPI were measured in all subjects, in most cases within 1 week of the date of PET imaging. White noise startle stimuli and prepulses were presented binaurally through headphones (TDH-39-P; Maico; Minneapolis). The eyeblink component of the acoustic startle response was assessed by recording the electromyogram (EMG) of the left orbicularis oculi muscle, using a commercial system (EMG-SR-LAB; San Diego Instruments). Background white noise (65 dB) was presented during a 4-minute acclimatization period and throughout the trial. Startle stimuli consisted of a 50 msec, 102 dB white noise burst. On prepulse trials, this startle stimulus was preceded by 120 msec by a 5 msec white noise burst 15 dB above background (i.e. 80 dB). Three initial startle pulse alone (PA) trials constituted a habituation block. Next, a total of 16 PA trials and 16 prepulse (PP) trials were intermingled pseudorandomly, with an inter-trial interval of 14-22 seconds (mean 18.56, SD 3.0). PPI was calculated using the proportion of difference method (81) as % reduction of EMG startle response on PP trials compared to PA trials.

Structural MRI imaging

All subjects underwent a structural MRI imaging scan prior to PET imaging for anatomical registration of PET data. Imaging was on a 3T Trio MRI scanner (Siemens) with a circularly polarized head coil.

Radioligand synthesis

The synthesis of ^{11}C -P943 at our center has recently been described (82). ^{11}C -P943 was prepared by N-methylation using ^{11}C -methyltriflate produced using a PETtrace cyclotron and a FxC automated synthesizer (GE Healthcare, Chalfont S. Giles, United Kingdom). Injection parameters are presented in **Table 2**.

PET imaging

PET imaging using ^{11}C -P943 was performed as described in recent studies from our center (72, 78, 83). The antecubital vein was cannulated for radiotracer delivery. ^{11}C -P943 was injected over one minute using an infusion pump. PET imaging was performed using the High Resolution Research Tomograph (HRRT; Siemens/CTI, Knoxville, TN). Image size was $256 \times 256 \times 207$ voxels, voxel size was $1.23 \text{ mm} \times 1.23 \text{ mm} \times 1.2 \text{ mm}$, and the reconstructed image resolution was about 3 mm (isotropic). Acquisition began with injection; list mode data were acquired for a total of 120 minutes.

PET imaging analysis

Kinetic modeling of ^{11}C -P943 binding has recently been described (72). Dynamic PET scan data were reconstructed with all corrections (attenuation, normalization, scatter, randoms, deadtime, and motion) using the MOLAR algorithm (84). A sequence of 33 frames was reconstructed. Parametric images of binding potential were calculated with MRTM2, using

the cerebellum grey matter as a reference region. The 5-HT_{1B} receptor is present in deep cerebellar nuclei but not in the cerebellar cortex in animals (57, 85) and in human post-mortem tissue (58, 59), justifying the use of the cerebellum grey matter as a reference region; further discussion of this issue is presented in ref. 73. A summed PET image (0-10 min post-injection) was created from motion-corrected data for each subject and then registered to the subject's T1-weighted MR image (6-parameter registration), and then to a common MR template using a nonlinear grid transformation (based on (86), as modified in (87)), using Bioimagesuite software (<http://bioimagesuite.yale.edu>; version 2.5). Regional values of non-displaceable binding potential (BP_{ND}) (88) were derived for multiple brain regions of interest (ROIs), defined using the AAL template (see **Supplementary Table 1**). *A priori* regions of interest were the OFC, due to its implication in the effects of 5-HT_{1B} agonists in animals (70), and other components of the CSTC circuitry in which hypermetabolism has been consistently reported in patients with OCD (7, 89): the ventromedial prefrontal cortex (PFC), anterior cingulate cortex (ACC), the subnuclei of the basal ganglia, and the thalamus; all ROIs were analyzed by mixed ANOVA, and then these *a priori* ROIs were analyzed by one-way ANOVA.

Statistical analysis

All data are presented as mean $\pm$ SEM, or SD as indicated (e.g. **Table 3**). All statistical analysis other than mixed modeling were performed in SPSS. Mixed modeling analyses were performed with SAS. All data were tested for normality prior to use of parametric statistics. Demographic and clinical data, startle, and PPI were analyzed using one-way ANOVA. Initial analysis of ¹¹C-P943 BP_{ND} across *a priori* ROIs was performed using t-tests, with false discovery rate (FDR) correction for multiple comparisons; between-group comparisons across other ROIs was considered exploratory. Correlations between regional ¹¹C-P943 BP_{ND} and Y-BOCS, and between BP_{ND} and PPI, were performed using Pearson's correlation for normally distributed data. Principal component analysis (PCA) of ¹¹C-P943 binding across ROIs (**Supplementary Table 2**) was performed in SPSS using oblique Oblimin factor rotations; factors for analysis were selected by inspection of the resulting Scree plot (**Supplementary Figure 1**).

RESULTS

Prepulse inhibition

Two subjects in each group did not yield reliable startle data and were therefore excluded from PPI analysis, prior to any group-level data analysis; usable PPI data were therefore analyzed on 10 subjects with OCD and 10 controls. One-way ANOVA revealed comparable PPI in patients ($43 \pm 6\%$) and controls ($41 \pm 8\%$), with no significant difference between groups ($p > 0.8$).

¹¹C-P943 PET imaging

High-quality ¹¹C-P943 binding (72) and structural MRI data were collected for all 12 subjects in each group (**Figure 1**). A mixed between (diagnosis)-within (ROIs) ANOVA revealed no significant main effect of OCD diagnosis on ¹¹C-P943 BP_{ND} ($F [1, 22] = 0.01$, $p = .98$) or diagnosis by ROI interaction ($F [14, 308] = 1.04$, $p = .41$). In our *a priori* regions

of interest (**Figure 2A**), ^{11}C -P943 BP_{ND} in the thalamus was nominally lower for OCD patients than controls ($F [1,22] = 4.76, p = .045$ before correction for multiple comparisons, $d = .93$; **Table 3**). Trend-level differences were also seen in the ACC ($F [1,22] = 3.07, p = .09$ uncorrected, $d = .75$) and ventromedial PFC ($F [1,22] = 2.89, p = .10$ uncorrected, $d = .72$), with OCD subjects showing higher BP_{ND} . Outside of the *a priori* regions of interest, the strongest trend-level between-group difference was in the calcarine cortex ($F [1,22] = 3.40, p = .08$ uncorrected, $d = .79$). However, none of these effects were significant after controlling for false discovery rate (FDR; e.g. .90). If our largest effect, in the thalamus ($d = 0.93$), were specified *a priori*, confirming this result in a replication study would require $N = 15$ subjects per group for 80% power.

Correlations between ^{11}C -P943 binding and clinical measures

We performed exploratory correlation of regional ^{11}C -P943 BP_{ND} with clinical measures of OCD symptom severity within the OCD group. Total Y-BOCS was negatively correlated with BP_{ND} in the ventromedial PFC ($r = -.60, p = .04$; **Figure 2B**) and, at trend level, in the OFC ($r = -.52, p = .08$). There was a positive correlation between BP_{ND} in the hippocampus and the obsessions subscale of the Y-BOCS ($r = .61, p = .04$; **Figure 2C**). There were negative correlations between the compulsions subscale of the Y-BOCS and BP_{ND} in the ACC ($r = -.67, p = .02$; **Figure 2D**) and ventromedial PFC ($r = -.69, p = .01$). There was also a trend-level correlation between compulsion severity and ^{11}C -P943 BP_{ND} in the OFC ($r = -.54, p = .07$). These correlations were exploratory and were not significant following FDR correction; they should therefore be regarded as provisional findings in need of replication.

Correlations between ^{11}C -P943 binding and PPI

We next examined correlations between ^{11}C -P943 BP_{ND} and PPI. Looking across correlations in all analyzed ROIs, a striking pattern emerged (**Figure 3**). Across subcortical regions, PPI correlated positively with BP_{ND} in controls, but these correlations were lost or even reversed in OCD patients. Across cortical regions, on the other hand, PPI correlated positively with BP_{ND} in patients but showed no significant correlation in controls. The only exceptions to these patterns were the OFC and the amygdala, in which positive correlations were seen in both groups (at trend level in the case of the amygdala; **Figure 3**).

To capture the overall pattern of these correlations across multiple ROIs we performed a dimensional reduction, applying principal component analysis (PCA) with oblique (Oblimin) factor rotations to ^{11}C -P943 BP_{ND} values, across diagnoses and irrespective of PPI. Two major factors emerged that accounted for 69% of variance across ROIs (**Supplementary Figure 1**). The 11 cortical ROIs loaded heavily onto the first factor (eigenvalue 8.10; all factor loadings > 0.50), while the 7 subcortical ROIs loaded heavily onto the second factor (eigenvalue 4.32; all factor loadings > 0.50 ; **Supplementary Table 2**). There were several salient (> 0.30) complex loadings, with ACC (0.42) and ventromedial PFC (0.36) also loading onto the subcortical factor and amygdala (0.43) cross-loading onto the cortical factor.

Cortical and subcortical ^{11}C -P943 BP_{ND} factor scores were calculated for each subject. Cortical and subcortical factors were not significantly correlated with one another in either control ($r = 0.31$, $p = 0.33$) or OCD subjects ($r = -0.20$, $p = 0.54$; **Supplementary Figure 2**) and did not differ between diagnostic groups (2X2 mixed ANOVA: main effect of diagnosis, $F[1,22] = 0.26$, $p = 0.62$; factor X diagnosis interaction, $F[1,22] = 0.28$, $p = 0.6$). They did not correlate with symptoms within the OCD group (R^2 values 0.003-0.155, n.s.).

The cortical ^{11}C -P943 binding factor was a significant positive predictor of PPI among OCD subjects ($r = .75$, $p = .01$) but not among controls ($r = .17$, $p = .64$). Conversely, the subcortical ^{11}C -P943 binding factor was a marginally significant positive predictor of PPI among control subjects ($r = .58$, $p = .08$) but was a non-significant negative predictor among OCD subjects ($r = -.41$, $p = .23$). This recapitulates the pattern of correlations that is evident in the individual ROIs (**Figure 3**).

We performed a mixed model analysis with ^{11}C -P943 binding as the dependent variable, diagnostic group (OCD vs. controls) as a between-subject fixed factor, brain region (cortical vs. subcortical principal component) as a within-subject factor, and PPI as a continuous covariate, to test the significance of the interaction between diagnosis and region on the relationship between ^{11}C -P943 binding and PPI. There was a significant 3-way (group X region X PPI) interaction [$F(1,16) = 10.30$, $p = .0055$] indicating that the relationship between ^{11}C -P943 BP_{ND} and PPI varied across diagnostic groups and regions. Lower-order post-hoc analyses confirmed that correlations between regional ^{11}C -P943 BP_{ND} and PPI differed between controls (**Figure 4A**) and patients (**Figure 4B**), confirming the effect seen by inspection of individual ROI correlations (**Figure 3**).

DISCUSSION

We present the first *in vivo* analysis of the 5-HT_{1B} receptor in patients with OCD, in relation to diagnosis, symptomatology, and prepulse inhibition. We find some evidence for between-group differences in 5-HT_{1B} receptor availability in patients, most strongly in the thalamus, but this does not survive correction for multiple comparisons. More strikingly, we find a dramatic alteration of the relationship between 5-HT_{1B} availability and PPI in patients with OCD, consistent with the motivating hypothesis derived from animal data (68-70). This represents a novel finding that may suggest a reorganization of serotonergic modulation of cortical and subcortical structures.

We have focused on the 5-HT_{1B} receptor, using PET imaging with ^{11}C -P943. While no previous studies have directly examined the 5-HT_{1B} receptor in patients with OCD, indirect evidence suggests that it may play an important role. Challenge with 5-HT_{1B/1D} agonists has been shown to worsen OCD symptoms in several studies (61-63). In mice, 5-HT_{1B} agonists produce a range of behavioral abnormalities that have been argued to recapitulate phenomenology of OCD and that respond to chronic SSRI treatment (68-70). Prominent among these effects is a disruption in PPI; PPI is deficient in patients with OCD (19, 20, 24).

We find several intriguing nominal differences between patients and controls in 5-HT_{1B} receptor availability, though none were sufficiently large to survive correction for multiple

comparisons in our sample. Within the circuitry canonically associated with OCD, we find reduced ^{11}C -P943 BP_{ND} in thalamus ($p = 0.04$), with an apparent effect size of $d = 0.93$. BP_{ND} in several regions was correlated with OCD symptom severity (**Figure 2**), suggesting a functional role, though again these correlations did not survive correction for multiple comparisons and should be considered provisional and in need of replication. In particular, abnormalities in medial PFC have been documented in OCD patients in fMRI functional connectivity studies (6, 91), functional studies of error responses (92), and structural MRI (93). The observation of a nominal correlation between ^{11}C -P943 binding and OCD symptom severity in this region is intriguing in light of these observations.

Prepulse inhibition

We did not find significantly reduced PPI in our patients. However, we were not well powered to detect this difference. Furthermore, recent analyses (19) have suggested that the PPI deficit in patients with OCD may be seen primarily in those with past or current tics or Tourette syndrome. Among the 10 OCD patients in whom we were able to measure PPI, only one had past (and current) tics (see **Table 1**). This, together with the small sample, may have attenuated our ability to detect between-group differences in PPI.

Brain structures involved in PPI have been well delineated in animals (21). The acoustic startle is mediated by circuitry in the midbrain. Descending projections from ventral and dorsomedial striatum (25), amygdala, hippocampus, and medial PFC and OFC modulate PPI (21). We therefore anticipated relationships between 5-HT_{1B} receptor availability and PPI in these structures; and that is for the most part what we observed in control subjects. PPI correlated with 5-HT_{1B} binding in ventral striatum, caudate (i.e. dorsomedial striatum), amygdala, hippocampus, and OFC (**Figure 3**).

Reorganization of cortical-subcortical relationships in OCD

Our most striking finding is that this relationship between 5-HT_{1B} availability and PPI is completely altered in patients with OCD (**Figure 3, 4**). Correlations between PPI and BP_{ND} are lost or reversed in almost all subcortical structures. In their place, striking correlations emerge with BP_{ND} across almost the entire cortex, where no significant correlations are seen in controls. This suggests that, while the magnitude of 5-HT_{1B} receptor availability is not dramatically altered in patients (**Figure 1, 2**), its functional relationship to sensory gating is quite different.

Previous work has suggested an alteration in the relationship between basal ganglia and cortical circuits in OCD. Early studies of implicit task learning, which is typically subserved by basal ganglia circuitry, showed aberrant recruitment of cortical structures, especially in medial temporal lobe and OFC, in patients; this has been interpreted as a compensatory response to dysregulation of subcortical circuits (94, 95). Similarly, medial frontal/pre-supplementary motor area and anterior frontal hyperactivity during cognitive control tasks has been interpreted as reflecting a compensatory mechanism (96, 97). In a resting-state fMRI study, we found global brain connectivity to be increased in caudate, putamen, and thalamus, but reduced in regions of lateral frontal cortex (6). Such findings suggest an alteration in the functional relationship between subcortical and cortical processing in OCD.

The current results are potentially consistent with such a reorganization, with the cortex taking on functions that would normally be performed by the basal ganglia circuitry. The emergence of positive correlations between ^{11}C -P943 BP_{ND} in patients, and the loss (or even reversal) of these correlations in the basal ganglia, may indicate that PPI is being preserved through the compensatory involvement of cortical structures that would normally not be recruited for this process. The compensation by cortical structures for functions normally mediated by the basal ganglia may be sufficient to preserve function in many contexts but may lead to inefficiencies, overload of available computational resources, and cognitive rigidity, which might contribute to the development of OCD symptomatology. However, this interpretation remains quite speculative.

^{11}C -P943 BP_{ND} provides an index of receptor availability, but it does not distinguish between changes in receptor number, affinity, and occupancy by endogenous serotonin. ^{11}C -P943 binding has been shown to be sensitive to changes in 5-HT levels, as well as variation in receptor density (71). One explanation for our results, therefore, is that they reflect a change in the relationship between basal 5-HT and PPI in OCD. This would imply that increased subcortical 5-HT, corresponding to decreased ^{11}C -P943 BP_{ND} , preserves PPI in patients, while lower cortical 5-HT, corresponding to increased ^{11}C -P943 BP_{ND} , impairs it (or at least fails to rescue it); such a relationship would explain the observed correlations. Alternatively, the observed relationships may reflect changes in 5-HT_{1B} itself, rather than 5-HT.

The correlation between PPI and ^{11}C -P943 BP_{ND} is similar in patients and controls in only two structures: the OFC and the amygdala (**Figure 3**). These are among the small number of telencephalic structures with an established role in PPI under normal circumstances (21). The role of 5-HT_{1B} in the OFC as a modulator of PPI is emphasized by animal studies, in which agonist infusion specifically into OFC is sufficient to disrupt PPI (70). Further study will be needed to clarify why these structures do not follow the overall pattern in the relationship between ^{11}C -P943 BP_{ND} and PPI throughout the rest of the brain.

Limitations and conclusions

These observations are derived from a small sample, which is an important limitation of our results. ^{11}C -P943 PET imaging data were collected in 12 subjects in each group, and usable PPI data in only 10. Consequently, the nominal difference we see in thalamic BP_{ND} (**Figure 2A**) and correlations of regional binding with symptomatology (**Figure 2B-D**) do not survive FDR correction and require replication in larger cohorts. The patients we examined were unmedicated and non-depressed; while this is essential for any conclusions to be made about patients with OCD, since depression has been shown to affect ^{11}C -P943 binding (77), it may limit generalizability to a more realistic and heterogeneous population. It will be interesting to examine the effect of comorbid depression and of medication with serotonergic agents in future studies. While all subjects were free of psychoactive medications for 8 weeks at the time of scanning, several had been treated with serotonergic pharmacotherapy in the past; it is possible that this led to long-lasting alterations in their serotonergic modulatory systems. A final limitation is that our behavioral assessments were limited to clinical measures and PPI. It will be important in future studies

to examine a broader range of behavioral measures that may be modulated by cortical 5-HT_{1B} receptors in OCD.

Despite these limitations, our findings may indicate an important new insight into the pathophysiology of OCD. While there are not statistically significant between-group differences in ¹¹C-P943 binding, as have been seen in depression and alcohol dependence (76, 77), the dramatic shift in the relationship between 5-HT_{1B} receptor availability and PPI that we observe in OCD may be reflective of a reorganization of the functional balance between cortical and subcortical circuits, and their modulation by serotonin. These results reinforce the potential value of examining the effects of 5-HT_{1B} agonist effects in animals (68-70). Such altered relationships with behavioral measures in clinical groups are rare in the PET literature; our findings speak to the power of combining PET measurement of specific receptors with hypothesis-driven behavioral assessment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the staff of the Yale PET Center, and Brian Pittman, MS, for biostatistical support. This work was supported by NIH grants R21MH090555 (CP), K08MH081190 (CP), T32MH062994 (TA; M. Bell, PI), and CTSA Grant Number UL1TR000142 from the National Center for Advancing Translational Science (NCATS). Its content is solely the responsibility of the authors and does not necessarily reflect the official view of NIH. Additional support came from the State of Connecticut through its support of the Ribicoff Research Facilities at the Connecticut Mental Health Center. The authors have no real or apparent conflict of interest of relevance to this work.

REFERENCES

1. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *International journal of methods in psychiatric research*. 2012; 21(3):169–184. [PubMed: 22865617]
2. Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol Psychiatry*. 2010; 15(1):53–63. [PubMed: 18725912]
3. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder. American Psychiatric Association; Arlington, VA: 2007.
4. Jenike MA. Clinical practice. Obsessive-compulsive disorder. *N Engl J Med*. 2004; 350(3):259–265. [PubMed: 14724305]
5. Ahmari, SE.; Simpson, HB. Neurobiology and treatment of OCD. In: Charney, DS.; Buxbaum, JD.; Sklar, P.; Nestler, EJ., editors. *Neurobiology of Mental Illness*. Oxford University Press; New York, NY: 2013. p. 646-661.
6. Anticevic A, et al. Global resting-state functional magnetic resonance imaging analysis identifies frontal cortex, striatal, and cerebellar dysconnectivity in obsessive-compulsive disorder. *Biol Psychiatry*. 2014; 75(8):595–605. [PubMed: 24314349]
7. Menzies L, et al. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. *Neurosci Biobehav Rev*. 2008; 32(3):525–549. [PubMed: 18061263]
8. Soomro GM, Altman D, Rajagopal S, Oakley-Browne M. Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD). *Cochrane Database Syst Rev*. 2008; (1):CD001765. [PubMed: 18253995]

9. Bloch MH, et al. A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Mol Psychiatry*. 2006; 11(7):622–632. [PubMed: 16585942]
10. Pittenger C, Bloch MH. Pharmacological treatment of obsessive-compulsive disorder. *The Psychiatric clinics of North America*. 2014; 37(3):375–391. [PubMed: 25150568]
11. Pittenger C, Bloch MH, Williams K. Glutamate abnormalities in obsessive compulsive disorder: neurobiology, pathophysiology, and treatment. *Pharmacology & therapeutics*. 2011; 132(3):314–332. [PubMed: 21963369]
12. Pallanti S, Quercioli L. Treatment-refractory obsessive-compulsive disorder: methodological issues, operational definitions and therapeutic lines. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006; 30(3):400–412. [PubMed: 16503369]
13. Abramovitch A, Abramowitz JS, Mittelman A. The neuropsychology of adult obsessive-compulsive disorder: a meta-analysis. *Clinical psychology review*. 2013; 33(8):1163–1171. [PubMed: 24128603]
14. Chamberlain SR, Menzies L. Endophenotypes of obsessive-compulsive disorder: rationale, evidence and future potential. *Expert review of neurotherapeutics*. 2009; 9(8):1133–1146. [PubMed: 19673603]
15. Chamberlain SR, et al. Orbitofrontal dysfunction in patients with obsessive-compulsive disorder and their unaffected relatives. *Science*. 2008; 321(5887):421–422. [PubMed: 18635808]
16. Gillan CM, Robbins TW. Goal-directed learning and obsessive-compulsive disorder. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*. 2014; 369(1655)
17. Gruner P, Anticevic A, Lee D, Pittenger C. Arbitration between Action Strategies in Obsessive-Compulsive Disorder. *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry*. 2015
18. Abramovitch A, Abramowitz JS. Improbability of response inhibition as a causal etiological factor of obsessive-compulsive disorder. *Psychiatry Res*. 2014; 217(3):253–254. [PubMed: 24835846]
19. Ahmari SE, Risbrough VB, Geyer MA, Simpson HB. Impaired sensorimotor gating in unmedicated adults with obsessive-compulsive disorder. *Neuropsychopharmacology*. 2012; 37(5):1216–1223. [PubMed: 22218093]
20. Hoenig K, Hochrein A, Quednow BB, Maier W, Wagner M. Impaired prepulse inhibition of acoustic startle in obsessive-compulsive disorder. *Biol Psychiatry*. 2005; 57(10):1153–1158. [PubMed: 15866555]
21. Kohl S, Heekeren K, Klosterkotter J, Kuhn J. Prepulse inhibition in psychiatric disorders--apart from schizophrenia. *Journal of psychiatric research*. 2013; 47(4):445–452. [PubMed: 23287742]
22. Schall U, Schon A, Zerbin D, Eggers C, Oades RD. Event-related potentials during an auditory discrimination with prepulse inhibition in patients with schizophrenia, obsessive-compulsive disorder and healthy subjects. *The International journal of neuroscience*. 1996; 84(1-4):15–33. [PubMed: 8707477]
23. Swedlow NR, Benbow CH, Zisook S, Geyer MA, Braff DL. A preliminary assessment of sensorimotor gating in patients with obsessive compulsive disorder. *Biol Psychiatry*. 1993; 33(4):298–301. [PubMed: 8471686]
24. de Leeuw AS, Oranje B, van Megen HJ, Kemner C, Westenberg HG. Sensory gating and sensorimotor gating in medication-free obsessive-compulsive disorder patients. *International clinical psychopharmacology*. 2010; 25(4):232–240. [PubMed: 20568657]
25. Baldan Ramsey LC, Xu M, Wood N, Pittenger C. Lesions of the dorsomedial striatum disrupt prepulse inhibition. *Neuroscience*. 2011; 180:222–228. [PubMed: 21315809]
26. Koch M, Schnitzler HU. The acoustic startle response in rats--circuits mediating evocation, inhibition and potentiation. *Behavioural brain research*. 1997; 89(1-2):35–49. [PubMed: 9475613]
27. Swedlow NR, Geyer MA, Braff DL. Neural circuit regulation of prepulse inhibition of startle in the rat: current knowledge and future challenges. *Psychopharmacology (Berl)*. 2001; 156(2-3):194–215. [PubMed: 11549223]
28. Yaryura-Tobias, JA.; Neziroglu, F.; Bhagavan, HN. Obsessive-compulsive disorders: a serotonergic hypothesis. In: Saletu, B.; Berner, P.; Hollister, L., editors. *Neuropsychopharmacology: Proceedings of the 11th Congress of the CNIP*. Pergamon; Oxford, UK: 1979. p. 117-125.

29. Delorme R, et al. Platelet serotonergic markers as endophenotypes for obsessive-compulsive disorder. *Neuropsychopharmacology*. 2005; 30(8):1539–1547. [PubMed: 15886722]
30. Cath DC, Spinhoven P, Landman AD, van Kempen GM. Psychopathology and personality characteristics in relation to blood serotonin in Tourette's syndrome and obsessive-compulsive disorder. *J Psychopharmacol*. 2001; 15(2):111–119. [PubMed: 11448084]
31. Delorme R, et al. Platelet serotonergic predictors of clinical improvement in obsessive compulsive disorder. *J Clin Psychopharmacol*. 2004; 24(1):18–23. [PubMed: 14709942]
32. Flament MF, Rapoport JL, Murphy DL, Berg CJ, Lake CR. Biochemical changes during clomipramine treatment of childhood obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1987; 44(3):219–225. [PubMed: 3548637]
33. Hanna GL, Yuwiler A, Cantwell DP. Whole blood serotonin in juvenile obsessive-compulsive disorder. *Biol Psychiatry*. 1991; 29(8):738–744. [PubMed: 2054448]
34. Baumgarten HG, Grozdanovic Z. Role of serotonin in obsessive-compulsive disorder. *The British journal of psychiatry. Supplement*. 1998; (35):13–20. [PubMed: 9829022]
35. Taylor S. Molecular genetics of obsessive-compulsive disorder: a comprehensive meta-analysis of genetic association studies. *Mol Psychiatry*. 2013; 18(7):799–805. [PubMed: 22665263]
36. Mattheisen M, et al. Genome-wide association study in obsessive-compulsive disorder: results from the OCGAS. *Mol Psychiatry*. 2015; 20(3):337–344. [PubMed: 24821223]
37. Stewart SE, et al. Genome-wide association study of obsessive-compulsive disorder. *Mol Psychiatry*. 2013; 18(7):788–798. [PubMed: 22889921]
38. Bastani B, Arora RC, Meltzer HY. Serotonin uptake and imipramine binding in the blood platelets of obsessive-compulsive disorder patients. *Biol Psychiatry*. 1991; 30(2):131–139. [PubMed: 1655071]
39. Marazziti D, et al. Platelet [3H]paroxetine binding in patients with OCD-related disorders. *Psychiatry Res*. 1999; 89(3):223–228. [PubMed: 10708268]
40. Marazziti D, Hollander E, Lensi P, Ravagli S, Cassano GB. Peripheral markers of serotonin and dopamine function in obsessive-compulsive disorder. *Psychiatry Res*. 1992; 42(1):41–51. [PubMed: 1603880]
41. Marazziti D, et al. Changes in platelet markers of obsessive-compulsive patients during a double-blind trial of fluvoxamine versus clomipramine. *Pharmacopsychiatry*. 1997; 30(6):245–249. [PubMed: 9442546]
42. Sallee FR, Richman H, Beach K, Sethuraman G, Nesbitt L. Platelet serotonin transporter in children and adolescents with obsessive-compulsive disorder or Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry*. 1996; 35(12):1647–1656. [PubMed: 8973072]
43. Weizman A, et al. Decreased platelet imipramine binding in Tourette syndrome children with obsessive-compulsive disorder. *Biol Psychiatry*. 1992; 31(7):705–711. [PubMed: 1318082]
44. Nikolaus S, Muller HW, Hautzel H. Different patterns of 5-HT receptor and transporter dysfunction in neuropsychiatric disorders - a comparative analysis of in vivo imaging findings. *Reviews in the neurosciences*. 2015
45. Adams KH, et al. Patients with obsessive-compulsive disorder have increased 5-HT_{2A} receptor binding in the caudate nuclei. *Int J Neuropsychopharmacol*. 2005; 8(3):391–401. [PubMed: 15801987]
46. Wong DF, et al. Mechanisms of dopaminergic and serotonergic neurotransmission in Tourette syndrome: clues from an in vivo neurochemistry study with PET. *Neuropsychopharmacology*. 2008; 33(6):1239–1251. [PubMed: 17987065]
47. Perani D, et al. In vivo PET study of 5HT(2A) serotonin and D(2) dopamine dysfunction in drug-naïve obsessive-compulsive disorder. *NeuroImage*. 2008; 42(1):306–314. [PubMed: 18511303]
48. Simpson HB, et al. Serotonin 2A receptors in obsessive-compulsive disorder: a positron emission tomography study with [11C]MDL 100907. *Biol Psychiatry*. 2011; 70(9):897–904. [PubMed: 21855857]
49. Boschert U, Amara DA, Segu L, Hen R. The mouse 5-hydroxytryptamine_{1B} receptor is localized predominantly on axon terminals. *Neuroscience*. 1994; 58(1):167–182. [PubMed: 8159291]

50. Boulenguez P, Pinard R, Segu L. Subcellular localization of 5-HT1B binding sites in the stratum griseum superficiale of the rat superior colliculus: An electron microscopic quantitative autoradiographic study. *Synapse*. 1996; 24(3):203–212. [PubMed: 8923659]
51. Buhlen M, Fink K, Boing C, Gothert M. Evidence for presynaptic location of inhibitory 5-HT1D beta-like autoreceptors in the guinea-pig brain cortex. *Naunyn Schmiedebergs Arch Pharmacol*. 1996; 353(3):281–289. [PubMed: 8692282]
52. Riad M, et al. Somatodendritic localization of 5-HT1A and preterminal axonal localization of 5-HT1B serotonin receptors in adult rat brain. *J Comp Neurol*. 2000; 417(2):181–194. [PubMed: 10660896]
53. Sari Y. Serotonin1B receptors: from protein to physiological function and behavior. *Neurosci Biobehav Rev*. 2004; 28(6):565–582. [PubMed: 15527863]
54. Bonaventure P, Schotte A, Cras P, Leysen JE. Autoradiographic mapping of 5-HT1B- and 5-HT1D receptors in human brain using [3H]alniditan, a new radioligand. *Receptors Channels*. 1997; 5(3-4):225–230. [PubMed: 9606727]
55. Bruinvels AT, Palacios JM, Hoyer D. Autoradiographic characterisation and localisation of 5-HT1D compared to 5-HT1B binding sites in rat brain. *Naunyn Schmiedebergs Arch Pharmacol*. 1993; 347(6):569–582. [PubMed: 8361548]
56. Palacios JM, Waeber C, Bruinvels AT, Hoyer D. Direct visualization of serotonin1D receptors in the human brain using a new iodinated radioligand. *Brain Res Mol Brain Res*. 1992; 13(1-2):175–178. [PubMed: 1315914]
57. Pazos A, Palacios JM. Quantitative autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-1 receptors. *Brain Res*. 1985; 346(2):205–230. [PubMed: 4052776]
58. Varnas K, Hall H, Bonaventure P, Sedvall G. Autoradiographic mapping of 5-HT(1B) and 5-HT(1D) receptors in the post mortem human brain using [(3)H]GR 125743. *Brain Res*. 2001; 915(1):47–57. [PubMed: 11578619]
59. Varnas K, Halldin C, Hall H. Autoradiographic distribution of serotonin transporters and receptor subtypes in human brain. *Human brain mapping*. 2004; 22(3):246–260. [PubMed: 15195291]
60. Verge D, et al. Quantitative autoradiography of multiple 5-HT1 receptor subtypes in the brain of control or 5,7-dihydroxytryptamine-treated rats. *J Neurosci*. 1986; 6(12):3474–3482. [PubMed: 2947981]
61. Gross-Isseroff R, Cohen R, Sasson Y, Voet H, Zohar J. Serotonergic dissection of obsessive compulsive symptoms: a challenge study with m-chlorophenylpiperazine and sumatriptan. *Neuropsychobiology*. 2004; 50(3):200–205. [PubMed: 15365215]
62. Koran LM, Pallanti S, Quercioli L. Sumatriptan, 5-HT(1D) receptors and obsessive-compulsive disorder. *Eur Neuropsychopharmacol*. 2001; 11(2):169–172. [PubMed: 11313163]
63. Zohar J, Kennedy JL, Hollander E, Koran LM. Serotonin-1D hypothesis of obsessive-compulsive disorder: an update. *J Clin Psychiatry*. 2004; 65(Suppl 14):18–21. [PubMed: 15554784]
64. Boshuisen ML, den Boer JA. Zolmitriptan (a 5-HT1B/1D receptor agonist with central action) does not increase symptoms in obsessive compulsive disorder. *Psychopharmacology (Berl)*. 2000; 152(1):74–79. [PubMed: 11041318]
65. Pian KL, Westenberg HG, van Megen HJ, den Boer JA. Sumatriptan (5-HT1D receptor agonist) does not exacerbate symptoms in obsessive compulsive disorder. *Psychopharmacology (Berl)*. 1998; 140(3):365–370. [PubMed: 9877016]
66. Dulawa SC, Gross C, Stark KL, Hen R, Geyer MA. Knockout mice reveal opposite roles for serotonin 1A and 1B receptors in prepulse inhibition. *Neuropsychopharmacology*. 2000; 22(6):650–659. [PubMed: 10788764]
67. Dulawa SC, Hen R, Scearce-Levie K, Geyer MA. 5-HT1B receptor modulation of prepulse inhibition: recent findings in wild-type and 5-HT1B knockout mice. *Ann N Y Acad Sci*. 1998; 861:79–84. [PubMed: 9928242]
68. Shanahan NA, et al. Chronic reductions in serotonin transporter function prevent 5-HT1B-induced behavioral effects in mice. *Biol Psychiatry*. 2009; 65(5):401–408. [PubMed: 19013555]
69. Woehrle NS, Klenotich SJ, Jamnia N, Ho EV, Dulawa SC. Effects of chronic fluoxetine treatment on serotonin 1B receptor-induced deficits in delayed alternation. *Psychopharmacology (Berl)*. 2013; 227(3):545–551. [PubMed: 23377022]

70. Shanahan NA, Velez LP, Masten VL, Dulawa SC. Essential role for orbitofrontal serotonin 1B receptors in obsessive-compulsive disorder-like behavior and serotonin reuptake inhibitor response in mice. *Biol Psychiatry*. 2011; 70(11):1039–1048. [PubMed: 21920503]
71. Cosgrove KP, et al. Assessing the sensitivity of [(1)(1)C]p943, a novel 5-HT1B radioligand, to endogenous serotonin release. *Synapse*. 2011; 65(10):1113–1117. [PubMed: 21484884]
72. Gallezot JD, et al. Kinetic modeling of the serotonin 5-HT(1B) receptor radioligand [(11)C]P943 in humans. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2010; 30(1):196–210.
73. Ridler K, et al. Characterization of in vivo pharmacological properties and sensitivity to endogenous serotonin of [11C] P943: a positron emission tomography study in Papio anubis. *Synapse*. 2011; 65(11):1119–1127. [PubMed: 21538549]
74. Saricicek A, et al. Test-retest reliability of the novel 5-HT1B receptor PET radioligand [(11)C]P943. *European journal of nuclear medicine and molecular imaging*. 2015; 42(3):468–477. [PubMed: 25427881]
75. Nord M, Finnema SJ, Schain M, Halldin C, Farde L. Test-retest reliability of [11C]AZ10419369 binding to 5-HT(1B) receptors in human brain. *European journal of nuclear medicine and molecular imaging*. 2014; 41(2):301–307. [PubMed: 24006152]
76. Hu J, et al. Serotonin 1B receptor imaging in alcohol dependence. *Biol Psychiatry*. 2010; 67(9):800–803. [PubMed: 20172504]
77. Murrough JW, et al. Reduced ventral striatal/ventral pallidal serotonin1B receptor binding potential in major depressive disorder. *Psychopharmacology (Berl)*. 2011; 213(2-3):547–553. [PubMed: 20480149]
78. Potenza MN, et al. Serotonin 1B receptor imaging in pathological gambling. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry*. 2013; 14(2):139–145.
79. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version*. American Psychiatric Press, Inc.; Washington, D.C.: 1996.
80. Hamilton M. Development of a rating scale for primary depressive illness. *The British journal of social and clinical psychology*. 1967; 6(4):278–296. [PubMed: 6080235]
81. Blumenthal TD, Elden A, Flaten MA. A comparison of several methods used to quantify prepulse inhibition of eyeblink responding. *Psychophysiology*. 2004; 41(2):326–332. [PubMed: 15032998]
82. Nabulsi N, et al. High-resolution imaging of brain 5-HT 1B receptors in the rhesus monkey using [11C]P943. *Nuclear medicine and biology*. 2010; 37(2):205–214. [PubMed: 20152720]
83. Matuskey D, et al. Reductions in brain 5-HT1B receptor availability in primarily cocaine-dependent humans. *Biol Psychiatry*. 2014; 76(10):816–822. [PubMed: 24433854]
84. Carson, R.; Barker, W.; Liow, J-S.; Adler, S.; Johnson, C. Design of a motion-compensation OSEM List-mode algorithm for resolution-recovery reconstruction of the HRRT. *IEEE Nuclear Science Symposium and Medical Imaging Conference*; Portland, OR. 2003.
85. Sari Y, et al. Cellular and subcellular localization of 5-hydroxytryptamine1B receptors in the rat central nervous system: immunocytochemical, autoradiographic and lesion studies. *Neuroscience*. 1999; 88:899–915. [PubMed: 10363826]
86. Rueckert D, et al. Nonrigid registration using free-form deformations: application to breast MR images. *IEEE transactions on medical imaging*. 1999; 18(8):712–721. [PubMed: 10534053]
87. Papademetris X, Jackowski AP, Schultz RT, Staib LH, Duncan JS. Integrated Intensity and Point-Feature Nonrigid Registration. *Medical image computing and computer-assisted intervention : MICCAI ... International Conference on Medical Image Computing and Computer-Assisted Intervention*. 2001; 3216(2004):763–770.
88. Innis RB, et al. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2007; 27(9):1533–1539.
89. Maia TV, Cooney RE, Peterson BS. The neural bases of obsessive-compulsive disorder in children and adults. *Development and psychopathology*. 2008; 20(4):1251–1283. [PubMed: 18838041]
90. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. Royal Statistical Society, Series B (Methodological)*. 1995; 57(1):289–300.

91. Harrison BJ, et al. Altered corticostriatal functional connectivity in obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2009; 66(11):1189–1200. [PubMed: 19884607]
92. Stern ER, et al. Chronic medication does not affect hyperactive error responses in obsessive-compulsive disorder. *Psychophysiology*. 2010; 47(5):913–920. [PubMed: 20230510]
93. de Wit SJ, et al. Multicenter voxel-based morphometry mega-analysis of structural brain scans in obsessive-compulsive disorder. *Am J Psychiatry*. 2014; 171(3):340–349. [PubMed: 24220667]
94. Rauch SL, et al. Probing striatal function in obsessive-compulsive disorder: a PET study of implicit sequence learning. *The Journal of neuropsychiatry and clinical neurosciences*. 1997; 9(4):568–573. [PubMed: 9447498]
95. Rauch SL, et al. Functional magnetic resonance imaging study of regional brain activation during implicit sequence learning in obsessive-compulsive disorder. *Biol Psychiatry*. 2007; 61(3):330–336. [PubMed: 16497278]
96. Ciesielski KT, et al. Role of medial cortical networks for anticipatory processing in obsessive-compulsive disorder. *Human brain mapping*. 2012; 33(9):2125–2134. [PubMed: 21882299]
97. de Wit SJ, et al. Presupplementary motor area hyperactivity during response inhibition: a candidate endophenotype of obsessive-compulsive disorder. *Am J Psychiatry*. 2012; 169(10):1100–1108. [PubMed: 23032388]
98. Goodman WK, et al. The Yale-Brown Obsessive Compulsive Scale. II. Validity. *Arch Gen Psychiatry*. 1989; 46(11):1012–1016. [PubMed: 2510699]
99. Hamilton, M. Diagnosis and rating of anxiety. In: Lader, M., editor. *Studies of Anxiety*. British Journal of Psychiatry Special Publication; 1969. p. 76-79.

HIGHLIGHTS

Animal and clinical studies suggest abnormalities in the 5-HT1b receptor in obsessive-compulsive disorder

5-HT1b agonists impair sensorimotor gating, measured by prepulse inhibition (PPI); and PPI is impaired in OCD

We measured PPI and 5-HT1b receptor binding using positron emission tomography (PET) in 12 unmedicated individuals with OCD and 12 controls.

The relationship between 5-HT1b binding and PPI in cortex and in subcortical structures was completely altered in individuals with OCD.

In contrast, there were no main effects of OCD diagnosis on 5-HT1b binding.

These results suggest a reorganization of serotonergic modulation of cortical and subcortical function in individuals with OCD.

Figure 1. ^{11}C -P943 BP_{ND} in patients and controls
 Left column shows T1-weighted structural MRI. Middle and right column show averaged BP_{ND} for controls and OCD patients, respectively.

Figure 2. ^{11}C -P943 BP_{ND} in *a priori* ROIs and correlation with symptoms

A. ^{11}C -P943 BP_{ND} in 8 ROIs selected *a priori* as being associated with known OCD pathology (mean $\pm$ SEM). The greatest group effect was in thalamus ($p = 0.045$), but the significance of this difference did not survive correction for multiple comparisons. **B.** Symptom severity (Y-BOCS total) correlated negatively with BP_{ND} in medial PFC ($p = 0.04$). **C.** Obsessions (Y-BOCS obsessions subscale) correlated positively with BP_{ND} in hippocampus ($p = 0.04$). **D.** Compulsions (Y-BOCS compulsions subscale) correlated negatively with BP_{ND} in ACC ($p = 0.02$).

Figure 3. Differential correlations of PPI with ^{11}C -P943 BP_{ND} across cortical and subcortical ROIs

A. Correlation of PPI with ^{11}C -P943 BP_{ND} across ROIs revealed different patterns of correlation across diagnoses in cortical and subcortical regions. Correlations in individual ROIs were significantly different between diagnoses in caudate and trended towards significance in numerous structures. **B.** In cortex (occipital cortex shown here), there was no significant association between ^{11}C -P943 BP_{ND} and PPI in controls but a markedly positive correlation in OCD. **C.** In subcortical structures (caudate nucleus shown here), there was a positive correlation between BP_{ND} and PPI and controls but no correlation, or even a negative correlation, in OCD. **D.** OFC (shown here) and amygdala were the only structures in which the relationship between BP_{ND} and PPI was not modulated by diagnosis. Uncorrected p-values for correlations: ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$. The correlation between ^{11}C -P943 BP_{ND} and PPI was significantly different between OCD and control subjects in the caudate

Figure 4. Correlation of PPI and ^{11}C -P943 BP_{ND} in controls and patients across cortical and subcortical factors

ROIs were combined into two principal factors (see **Supplementary Figure 1, Supplementary Table 2**), corresponding to cortical and subcortical binding. Mixed-model analysis with BP_{ND} as the dependent variable revealed a significant diagnosis X factor X PPI interaction ($p = 0.0055$), as described in the main text. Post-hoc contrasts revealed significant or near-significant differences between patients and controls in the relationship between subcortical ^{11}C -P943 BP_{ND} and PPI ($t[16] = 2.31, p = 0.03$) and that between cortical ^{11}C -P943 BP_{ND} and PPI ($t[16] = 2.03, p = 0.06$). In OCD patients (**A**), the correlations of cortical and subcortical ^{11}C -P943 BP_{ND} with PPI were significantly different ($t[16] = 3.15, p = 0.006$); this contrast was not significant in controls (**B**; $t[16] = 1.13, p = 0.28$). Subcortical ^{11}C -P943 BP_{ND} was a nearly significant predictor of PPI among control subjects ($t[16] = 2.02, p = 0.06$), but cortical ^{11}C -P943 BP_{ND} was not ($p = 0.63$). Cortical ^{11}C -P943 BP_{ND} was a significant predictor of PPI among OCD patients ($t[16] = 2.87, p = 0.01$), but subcortical ^{11}C -P943 BP_{ND} was not ($p = 0.18$).

Table 1

Subject demographic and clinical characteristics.

	OCD	Control	p-value (2-tail, uncorrected)
Age	31.2±2.6 yr	30.7 ± 2.5 yr	
Sex	4M/8F	4M/8F	
Handedness	2L/10R	3L/9R	
Education	14.2 ± 0.8 yr	16.0 ± 0.6 yr	0.074
Race	10 Caucasian	9 Caucasian	
	1 Asian	1 Caucasian/Native American	
	1 African American/Native American	1 Asian 1 African American	
Ethnicity	3 Hispanic	3 Hispanic	
Age of first OCD sx	10.6 ± 1.5 yr		
Age of OCD dx	23.1 ± 2.7 yr		
Y-BOCS	25.5 ± 1.3		
obsessions	12.6 ± 0.8		
Compulsions	12.9 ± 0.8		
Past depressive sx	5 subjects	1 subject (adjustment disorder, distant, fully resolved)	
HAM-D (24)	6.5 ± 1.5		
HAM-A	5.2 ± 0.7		
Current tics	1 subject		
Trichotillomania	0 subjects		
Excoriation	2 subject		
Other diagnoses	Panic disorder (1) EtOH dependence in remission (1) Attention deficit disorder (1) Panic disorder (2) Social anxiety disorder (1; subclinical)		

All values are mean ± SEM. Y-BOCS – Yale-Brown Obsessive-Compulsive Scale (98). HAM-D = Hamilton Depression Rating Scale, 24-item version (80). HAM-A = Hamilton Anxiety Rating Scale (99). P-values over 0.2 are not shown.

Table 2PET parameters (mean $\pm$ SEM).

	OCD	Control	p-value (uncorrected, 2-tail)
BMI	26.2 $\pm$ 1.9	27.3 $\pm$ 1.9	
Injected dose (MBq)	559 $\pm$ 41	579 $\pm$ 40	
Injected dose (μg)	2.0 $\pm$ 0.43	1.1 $\pm$ 0.29	0.11

BMI – Body mass index. MBq – Mega-Becquerels. P-values over 0.2 are not shown.

Table 3¹¹C-P943 BP_{ND} in regions of interest.

		Controls <i>M</i> (<i>SD</i>)	OCD <i>M</i> (<i>SD</i>)	<i>F</i> -value	Cohen's <i>d</i>
Cortical ROIs	# Orbitrofrontal	.73 (.12)	.79 (.16)	1.06	.42
	# Medial PFC	.74 (.14)	.83 (.12)	2.88 [†]	.72
	Dorsolateral PFC	.96 (.14)	1.03 (.15)	1.32	.48
	Motor/Premotor	.78 (.10)	.79 (.13)	0.08	.09
	Occipital	.84 (.08)	.83 (.13)	.06	.10
	Calcarine	1.30 (.16)	1.16 (.21)	3.33 [†]	.75
	Parietal	.69 (.09)	.72 (.12)	.49	.30
	Temporal	.69 (.09)	.71 (.11)	.15	.17
	# Anterior Cingulate	.80 (.15)	.90 (.11)	3.02 [†]	.75
	Medial Cingulate	.79 (.11)	.83 (.11)	.90	.40
	Posterior Cingulate	.45 (.12)	.48 (.25)	.14	.16
Subcortical ROIs	# Caudate	.49 (.12)	.47 (.09)	.21	.20
	# Putamen	.78 (.08)	.81 (.11)	.35	.25
	# Pallidum	1.53 (.24)	1.50 (.29)	.05	.10
	# Ventral Striatum	1.31 (.27)	1.29 (.22)	.03	.07
	# Thalamus	.45 (.07)	.38 (.09)	4.76 [*]	.93
	Hippocampus	.40 (.09)	.36 (.09)	1.12	.45
	Amygdala	.73 (.18)	.76 (.11)	.17	.18

Regions marked with a # were identified as *a priori* ROIs, as described in the text. No differences were statistically significant following correction for false discovery rate.

[†] = uncorrected $p < .10$;

^{*} = uncorrected $p < .05$