Relationship Between Neuroanatomical and Serotonergic Hypotheses of Obsessive-Compulsive Disorder:

A Combined Functional Magnetic Resonance Imaging–Evoked Potential Study

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ABSTRACT

Objective: The so-called neuroanatomical hypothesis (with an increased activity of orbitofrontal cortex [OFC]) and the serotonergic hypothesis (with low activity in this system) have been discussed regarding the pathogenesis of obsessive-compulsive disorder (OCD) for decades. This study aimed to look for a relationship between the 2 pathogenetic concepts.

Methods: Nineteen OCD patients (8 female, 11 male, mean ± SD age = 33.37 ± 11.73 years, Yale-Brown Obsessive Compulsive Scale: 21.79 ± 6.59; diagnosed by *ICD-10/DSM-IV-TR*) were compared to 19 matched healthy controls (8 female, 11 male, mean ± SD age = 31.63 ± 10.79 years) and investigated (2012–2014) with the loudness dependence of auditory-evoked potentials (LDAEP) as a marker of the synaptic serotonergic activity and functional magnetic resonance imaging (fMRI) during the delay discounting paradigm, inducing OFC blood-oxygen level–dependent activity in the 2 groups.

Results: There were significant correlation coefficients between LDAEP (eLORETA right side) and fMRI OFC activities (anatomic region of interest) within the delay discounting paradigm (immediate vs control) in patients with OCD ($r = -0.554$; $P = .014$). LDAEP differed between the 2 groups with larger LDAEP at Cz in OCD patients indicating low serotonergic activity (0.28 ± 0.14 vs 0.20 ± 0.10 µV/10 dB, $F_{2,35} = 4.66$, $P = .016$). fMRI activations of dorsolateral and medial prefrontal cortex as well as ventral striatum (functional region of interest) were different between OCD and healthy volunteers.

Conclusions: The 2 main pathophysiologic hypotheses of OCD seem to be related to each other as measured by LDAEP and fMRI OFC activity during the delay discounting task. This could be interpreted as a further hint that low serotonergic activity induces altered OFC responsivity, which has to be treated in each patient with OCD by a serotonin agonist.

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Over the past 30 years, obsessive-compulsive disorder (OCD) has been the focus of research in biological psychiatry. Technological advances such as in neuroimaging contributed to a better understanding of the pathogenesis of this disorder, but findings were not consistent across all studies. Although efficacious treatments have been developed and established, patients in clinical settings often report inadequate response. However, there is still a relatively limited understanding of OCD pathophysiology, especially concerning the brain pathways involved.

Several research studies provided growing evidence for a neurobiological basis of OCD resulting in 2 main hypotheses: the so-called neuroanatomical hypothesis and the serotonergic hypothesis. Thus, neurochemical and neuroimaging studies have shown that various neurotransmitters are implicated in the pathophysiology of this disorder, including serotonin,[1] dopamine,[2] and glutamate.[3] The highest impact today is made by the neurochemical model of OCD that postulates a central serotonergic dysfunction, a finding that has been based mainly on the efficacy of SSRIs in OCD.[1] However, the underlying therapeutic mechanism of SSRIs in OCD remains unclear, since there are many discrepant findings across studies of structural and functional brain changes in OCD patients before and after SSRI treatment.[4] On the other hand, peripheral measures, such as levels of serotonin metabolites (blood, cerebrospinal fluid), have not been proven to be sufficiently valid in reflecting the central serotonergic activity.[5,6] Furthermore, the use of imaging methods that reflect the availability of the binding potentials of 5-HT receptors or serotonin transporter (SERT), such as positron emission tomography (PET)[7] and single-photon emission computed tomography (SPECT), is not appropriate for daily clinical practice to characterize all patients with OCD.[8–10]

In the continuing search for biological markers of psychiatric disorders such as OCD, auditory evoked potentials now constitute a prime target of investigation. The so-called intensity dependence of sensory-evoked potentials denotes the increase or decrease of the amplitude of a late component because of the increase of a stimulus intensity, ie, loudness. There is strong evidence indicating that the loudness dependence of auditory-evoked potentials (LDAEP), especially of the primary auditory cortex, is closely related to the central serotonergic function in an inverse manner: a strong LDAEP is related to low serotonergic activity, and vice versa.[5,6,11,12] During the last decade, several studies have documented a weaker LDAEP in, for example, schizophrenia, indicating high serotonergic activity[13–15] or a strong LDAEP corresponding to a low serotonergic level

Clinical Points

- Clinicians and researchers in the field of OCD have long discussed the 2 main hypotheses of OCD—the serotonergic and the neuroanatomical—but no study has yet explored their relationship.
- These 2 hypotheses seem to be related as measured by loudness dependence of auditory-evoked potentials and fMRI orbitofrontal cortex activity during a delay discounting task, with low serotonergic activity associated with altered orbitofrontal cortical responsivity.

in affective disorders.[16–18] In contrast, only a few studies focus on LDAEP in OCD, which have partially shown a strong LDAEP, indicating low serotonergic functioning in medication-free patients with OCD in comparison to healthy controls.[6,19,20] It was further found that patients with early onset OCD exhibit lower serotonergic activity levels, which were stable also under treatment.

In addition to this serotonergic hypothesis of OCD, it has been suggested that OCD is caused by abnormal activity in the cortico-striato-thalamo-cortical circuits, including the orbitofrontal cortex (OFC), the striatum within basal ganglia, and the thalamus,[21,22] which is summarized as the neuroanatomical hypothesis of this disease. In particular, it was postulated that obsessive-compulsive symptoms may be represented by increased activity in the OFC as a consequence of diminished inhibitory effects of the striatum (especially the globus pallidus internus) on the thalamus. The OFC plays a crucial role in reward-guided learning and decision-making, especially for impulsive choice procedures.[23–25] Previous decision-making studies using difficult-decision tasks, such as the Iowa Gambling Task (IGT)[26] (IGT review[27]) and the Game of Dice Task,[28] have shown abnormal performances in OCD patients,[29–32] but do not clarify what basic process is impaired. Delayed reward discounting is a behavioral economic index of impulsivity, and numerous studies have examined delayed reward discounting in substance use disorder,[33,34] but little information is available about delay discounting in patients with OCD.[35] A series of functional magnetic resonance imaging (fMRI) studies have employed delay discounting task activities primarily within the OFC.[24] Therefore, this task can be used for assessing the activity state within the OFC. However, it remains unclear whether neurotransmitters, especially serotonin, are involved in the abnormalities of the cortico-striato-thalamo-cortical circuit in OCD. Moreover, the relationship between serotonin neural activity and delayed reward remains unclear.[36] A first study by the authors was able to demonstrate a significant relationship between the synaptically released serotonin as measured by the LDAEP and the activity of the medial OFC determined as fMRI blood-oxygen level–dependent (BOLD) response during the delay discounting task in healthy volunteers.[37]

Thus, the present study aimed to combine the 2 major hypotheses regarding OCD: the neuroanatomical hypothesis with hyperactivity in the OFC, which was measured as fMRI activation within the delay discounting task paradigm, and the serotonergic deficit hypothesis of OCD, which was measured by the LDAEP.

Table 1. Sociodemographic and Clinical Characteristics of OCD Patients and Healthy Controls

	OCD (n = 19)	Controls (n = 19)
Sociodemographic characteristics, n (%)		
Gender		
Female	8 (42.1)	8 (42.1)
Male	11 (57.9)	11 (57.9)
Age, y[a]	33.37 ± 11.73	31.63 ± 10.79
Marital status		
Married	3 (15.8)	4 (21.1)
Cohabitating	10 (52.6)	8 (42.1)
Single	6 (31.6)	7 (36.8)
Education		
Upper grade	15 (78.9)	16 (84.2)
Middle grade	4 (21.1)	3 (15.8)
Lower grade	0	0
Occupational status		
Employed	8 (42.1)	13 (68.4)
Unemployed	3 (15.8)	0
Student	6 (31.6)	6 (31.6)
Retired, unable to work (sickness)	2 (10.5)	0
Clinical characteristics, mean ± SD		
Duration of illness, y	14.27 ± 12.39	…
Age at onset, y	19.21 ± 6.71	…
HDRS	12.42 ± 6.13	0
BDI	14.68 ± 10.12	1.42 ± 2.01
YBOCS obsessions	10.74 ± 2.53	0
YBOCS compulsions	10.53 ± 3.73	0
YBOCS total	21.79 ± 6.59	0
MOCI	14.84 ± 5.93	3.89 ± 2.96
STAI I	42.89 ± 13.72	30.21 ± 5.06
STAI II	50.26 ± 11.75	30.58 ± 7.95
CGI	4.58 ± 0.69	1.00 ± 0
MWT-IQ	109.63 ± 12.08	119.58 ± 13.22[b]
NEO-FFI total	2.77 ± 0.55	2.69 ± 0.69
BIS-11 total	59.00 ± 8.72	56.37 ± 7.43
PSP	67.16 ± 14.08	100

[a]Age is expressed as mean ± SD.
[b]$P = .02$.
Abbreviations: BDI = Beck Depression Inventory, BIS-11 = Barratt Impulsiveness Scale, CGI = Clinical Global Impressions, HDRS = Hamilton Depression Rating Scale, MOCI = Maudsley Obsessive-Compulsive Inventory, MWT-IQ = Mehrfachwahl-Wortschatz-Intelligenztest, NEO-FFI = NEO–Five-Factor Inventory, OCD = obsessive-compulsive disorder, PSP = Personal and Social Performance Scale, SD = standard deviation, STAI = State-Trait Anxiety Inventory, YBOCS = Yale-Brown Obsessive Compulsive Scale.

METHODS

Subjects

Nineteen patients (8 female, 11 male, mean age = 33.37 ± 11.73 years) with unequivocal diagnosis of OCD were recruited (May 2012–June 2014) from the outpatient clinic for OCD at the Department of Psychiatry, Ruhr University Bochum. Diagnosis was based on the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*[38]) and *ICD-10* (F42.X[39]).

Exclusion criteria included so-called organic disorders according to *ICD-10* (F0X) or recent concomitant neurologic or other medical disorders and the presence of severe alcohol or substance abuse. No patient met the criteria for Tourette syndrome or any psychotic disorder. Table 1 shows the

demographic and clinical data of the 19 patients included in the study. Of the patients, 17 were taking medication at the time of the assessment, of which 13 were taking SSRIs (fluoxetine [40–60 mg/d]; sertraline [50–150 mg/d]; escitalopram [10 mg/d]; citalopram [20–60 mg/d]), 1 patient received clomipramine (200 mg/d), and 3 received a serotonin-norepinephrine reuptake inhibitor (venlafaxine [300 mg/d; n = 2] or duloxetine [90 mg/d; n = 1]). None of the patients was engaged in cognitive-behavioral therapy during the study period.

Nineteen healthy volunteers (8 female, 11 male, mean age = 31.63 ± 10.79 years) with no neurologic or psychiatric disorders in their personal or family history served as a control group matched for age, sex, education level, and handedness (18 right-handed, 1 left-handed). These 19 volunteers underwent the Mini-International Neuropsychiatric-Structured Diagnostic Interview for *DSM-IV* and *ICD-10* disorders (MINI-PLUS)[40,41] and the psychometric tests for obsessive-compulsive symptoms as well as depressive and anxiety symptoms.

All subjects gave written informed consent after the study was fully explained to them. In accordance with the Helsinki Declaration of 1975, the study was approved by the local university ethics committee of the Ruhr University Bochum, Germany.

Clinical Assessment

Severity of obsessive-compulsive symptoms was assessed by the Yale-Brown Obsessive Compulsive Scale (YBOCS)[42,43] and Maudsley Obsessive-Compulsive Inventory.[44] To validate the presence of OCD (sub)symptoms, we used the YBOCS symptom checklist.

Severity of depressive symptoms was assessed using the Hamilton Depression Rating Scale,[45] and self-ratings with the Beck Depression Inventory.[46] Anxiety symptoms were measured using the State-Trait Anxiety Inventory I and II.[47,48]

The overall severity of the psychiatric disorder was quantified using the Clinical Global Impressions score.[49]

Psychosocial functioning was measured by the Personal and Social Performance Scale.[50]

Impulsivity was assessed by the Barratt Impulsiveness Scale.[51,52] Moreover, the NEO–Five-Factor Inventory[53] was used to assess personality characteristics, such as extraversion, neuroticism, and conscientiousness. Participants' verbal intelligence was estimated with the Mehrfachwahl-Wortschatz-Intelligenztest.[54]

Loudness Dependence of Auditory Evoked Potentials

Subjects sat in a comfortable armchair in an electrically shielded and sound-attenuated room. They were instructed to avoid movements and blinking throughout the testing. Auditory evoked potentials were recorded with 32 non-polarizable Ag-AgCl electrodes referred to as FCz, placed according to the International 10/20 System. All further methodological procedures were the same as reported in Mavrogiorgou et al.[37]

eLORETA Region-of-Interest Analysis

A region-of-interest (ROI) analysis was performed to investigate the electric neuronal activity as current source density in the right and left Heschl gyrus (Brodmann area [BA] 41) for the LDAEP of the 5 intensities between 50 and 250 ms using the exact low-resolution brain electromagnetic tomography (eLORETA) software.[55] In this study, the BA 41-ROI covered a region extended in Talairach space from *x*: 35 to 55 and −35 to −55, *y*: −15 to −40, *z*: 5 to 15 and included all voxels of BA 41. The ROI analysis was done with the ROI-Extractor tool, which averages the current source density values in the specified voxels. The brain model of eLORETA is based on the Montreal Neurological Institute average MRI brain map (MNI 152), while the solution space is limited to the cortical gray matter, comprising 6,239 voxels of 5-mm^3 resolution. The validity of the eLORETA approach as a reliable and effective tool for examining brain activations has been confirmed by several neuroimaging studies using intracranial electroencephalography (EEG),[56] EEG,[57] structural MRI,[58] and fMRI.[59,60]

Behavioral Practice Session of Delay Discounting

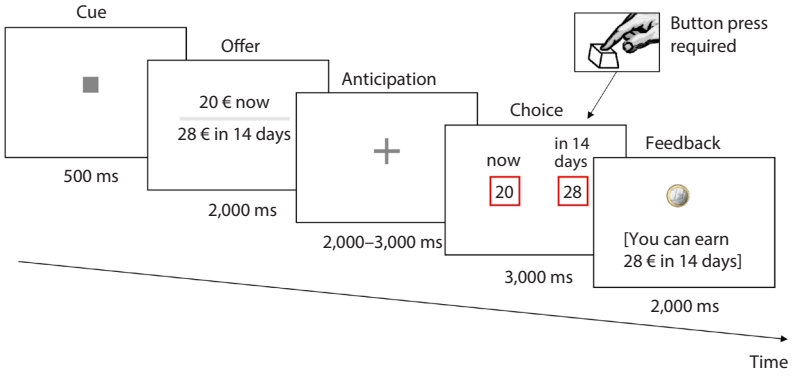
Before scanning, all subjects completed an identical practice version of the task to become familiar with the experiment and to confirm short-term stability of discounting. The results of the pretest were used to adequately compute monetary reward offers (€20 [US $20.13] immediately or €28 [US $32.38] in 14 days) for the fMRI sessions and for estimation of the individual discounting rate k. A detailed description of the applied paradigm is given below and in Figure 1.

fMRI Task and Procedures

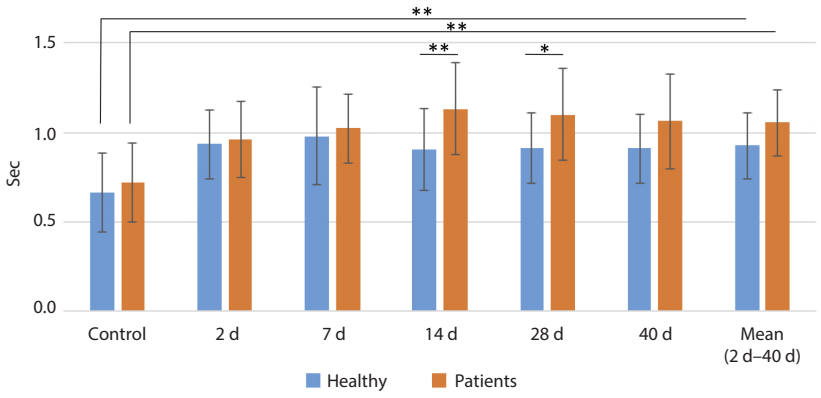
We used a slightly modified version of an established decision-making paradigm previously described by Peters and Büchel.[24] Briefly, participants have to choose between a fixed immediate reward of €20 and larger but delayed rewards delivered after 2, 7, 14, 28, and 40 days. The delayed rewards were computed individually for each subject to ensure that the delayed offer was chosen in approximately 50% of all trials. A detailed description is given in a previous publication from our group.[37] Functional data were collected using a 3-Tesla whole body MRI system (Philips Achieva 3.0T TX) equipped with a 32-channel Philips SENSE head coil. A total of 32 T2*-weighted echo-planar images (EPI) per volume with BOLD contrast were obtained using a sensitivity encoded single-shot EPI protocol (SENSE-sshEPI, 595 volumes per run, matrix 112 × 112 mm^2, FoV 220 × 220 mm^2, spatial resolution 1.96 × 1.96 × 3 mm^3, tilted by 30° with reference to the bicommisural plane; see reference 37 for all further details of fMRI procedures). The functional data were preprocessed and statistically analyzed using SPM8 (Wellcome Department of Cognitive Neuroscience, University College London, United Kingdom; http://www.fil.ion.ucl.ac.uk) and MATLAB 7.11 (The Mathworks Inc, Natick, Massachusetts). The statistical analyses followed the general linear model approach. Briefly, changes in the

Figure 1. Depiction of the Paradigm Used, Reaction Times, and fMRI Anatomical Location

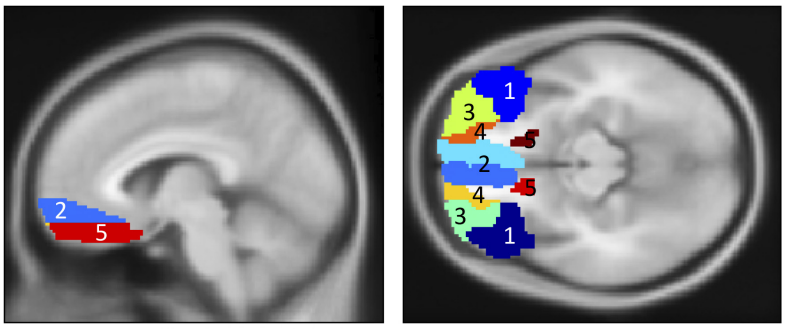
A. Structure of the applied fMRI paradigm[a]



B. Reaction times in healthy subjects and OCD patients[b,c]



C. Parcellation of the orbitofrontal cortex[a,d]



[a]Modified with permission from Mavrogiorgou et al.[37]
[b]Error bar represents standard deviation.
[c]OCD patients showed longer reaction times compared to healthy controls (14 d: $t_{36}=2.833$, $P=.008$; 28 d: $t_{36}=2.461$, $P=.019$; 40 d: $t_{36}=1.943$, $P=.06$). Both groups showed faster reaction times in control trials than in reward trials (healthy: paired $t_{18}=5.474$, $P<.001$; OCD: paired $t_{18}=8.879$, $P<.001$).
[d](1) Dark blue: inferior frontal gyrus, orbital part; (2) light blue: superior frontal gyrus, medial orbital part; (3) green/light green: middle frontal gyrus, orbital part; (4) yellow/orange: superior frontal gyrus, orbital part; (5) red: gyrus rectus.
*$P<.05$.
**$P<.01$.
Abbreviations: fMRI = functional magnetic resonance imaging, OCD = obsessive-compulsive disorder.

BOLD response for each subject were assessed by linear combinations of the estimated β values. This analysis was performed by modeling the offer periods as explanatory variables convolved with a standard hemodynamic response function implemented in SPM8. Realignment parameters were included as additional regressors in the statistical model. All relevant conditions, ie, "accepted immediate reward," "accepted delayed reward," and "control," were modeled for each subject. Regarding the second-level analysis, we used SPM's "full factorial" option and concentrated the analysis on the *F*-contrast "main effect of task," ie, "immediate reward: accepted" versus "delayed reward: accepted" collapsed over

Table 2. Activations in Healthy Subjects and OCD Patients[a]

Region		Coordinates (MNI)	Extent k	Statistical Value[b]	z Value
F-contrast (main effect of task) collapsed over groups					
L	Inferior frontal gyrus, opercular part	−38, 6, 28	24	16.89	4.94
L	Supramarginal gyrus	−58, −34, 34	69	17.93	5.09
R	Supramarginal gyrus	60, −38, 34	81	18.91	5.23
L	Middle frontal gyrus/dlPFC	−34, 28, 38	31	16.51	4.88
R	Inferior frontal gyrus, opercular part[c]	56, 12, 8	16	9.06	3.51
L	Middle occipital cortex[d]	−30, −76, 22	50	12.64	4.24
R	Angular gyrus[d]	28, −54, 42	12	11.13	3.95
t-contrast [interaction group × task], ie, "immediate reward: accepted" vs "delayed reward: accepted" in healthy vs OCD patients					
L	Putamen/ventral striatum[c]	−22, 16, −2	12	3.67	3.56
R	dlPFC (BA 8)[c]	16, 20, 56	52	3.8	3.68

[a]Initial threshold *P* uncorrected < .001 for an extent k > 10 voxel or *F* > 10.0 for k > 10. Only activations surviving P_{FWE} < .05 for k > 10 voxel were considered as significant (unless otherwise indicated).
[b]*t* or *F* value.
[c]P_{FWE} < .05 after small volume correction with 5-mm radius.
[d]P_{FWE} < .05 on cluster level.
Abbreviations: BA = Brodmann area, dlPFC = dorsolateral prefrontal cortex, FWE = familywise error, L = left, MNI = Montreal Neurological Institute, OCD = obsessive-compulsive disorder, R = right.

both groups, and on the interaction *t*-contrast [task × group], ie, "immediate reward: accepted" versus "delayed reward: accepted" in healthy controls versus OCD patients. The initial threshold was set to *P* [uncorrected] < .001 for an extent k > 10. Regarding the multiple testing problem, we reported only activations surviving voxel- or clusterwise familywise error correction or small volume correction. In addition, anatomically based ROIs were generated using the AAL atlas and the WFU PickAtlas software.

Statistical Analysis

Further statistical analyses of the neuropsychological, behavioral, and fMRI data were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp, Armonk, New York). Statistical analyses were performed with appropriate parametric or nonparametric tests (*t* test, analysis of variance, and Pearson or Spearman correlation coefficients). Statistical significance was defined as $P < .05$. A value of $P < .10$ was regarded as statistical tendency.

RESULTS

LDAEP Findings

The LDAEP (median slope of the Cz electrode) in OCD patients (mean = 0.28 ± 0.14) differed from LDAEP of healthy controls (mean = 0.20 ± 0.10) as a statistical trend ($P = .070$). This association became significant after controlling for verbal IQ ($F_{2/35} = 4.66$, $P = .016$). In contrast, LDAEP values as a result of eLORETA (left and right side) were not found to be significantly different between OCD patients and healthy volunteers with and without partialling out verbal IQ.

Behavioral Data: Comparison of Delay Discounting and Reaction Times

To assess short-term stability of delay discounting behavior across all subjects, we compared the discounting rates derived from the pre-fMRI practice session with those obtained during the fMRI experiment and received stable results for the whole group (k-values $mean_{pre} = 0.0271 \pm 0.0185$; $mean_{fMRI} = 0.0288 \pm 0.0189$; $r = 0.864$). Furthermore, OCD patients showed significantly higher k-values in the fMRI experiment compared to healthy controls ($mean_{fMRI}$ healthy $= 0.0191 \pm 0.01$; $mean_{fMRI}$ OCD $= 0.0385 \pm 0.021$; $t_{2\text{-samples}} = -3.686$, $P = .001$) reflecting a higher degree of discounting, and thus an increased impulsivity, in patients suffering from OCD. In addition, we were able to observe a significant positive correlation between the pretest k-values and the k-values obtained during fMRI. Regarding the reaction times (RT), we observed a significant [group × RT] interaction ($F_{4,33} = 3.901$; $P = .011$) and a statistical trend concerning group ($F_{1,36} = 3.945$; $P = .055$) (Figure 1).

Comparison of fMRI Activation Differences in Immediate and Delayed Choices

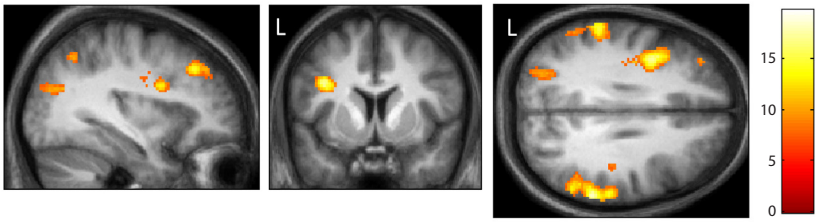
Regarding the fMRI data, we used the *F*-contrast [main effect of task] collapsed over both groups for validation of our experimental paradigm. Both groups showed activity in a set of cortical brain regions, including the bilateral inferior frontal gyrus, the bilateral supramarginal gyrus, the left-middle frontal gyrus, and the angular gyrus (Table 2, Figure 2A). For the investigation of group effects, the *t*-contrast [interaction group × task] was calculated, which revealed activations located in the left ventral striatum/putamen and the right dorsolateral prefrontal cortex (dlPFC)/BA 8 (Table 2, Figure 2).

Correlations Between LDAEP and fMRI BOLD Answers

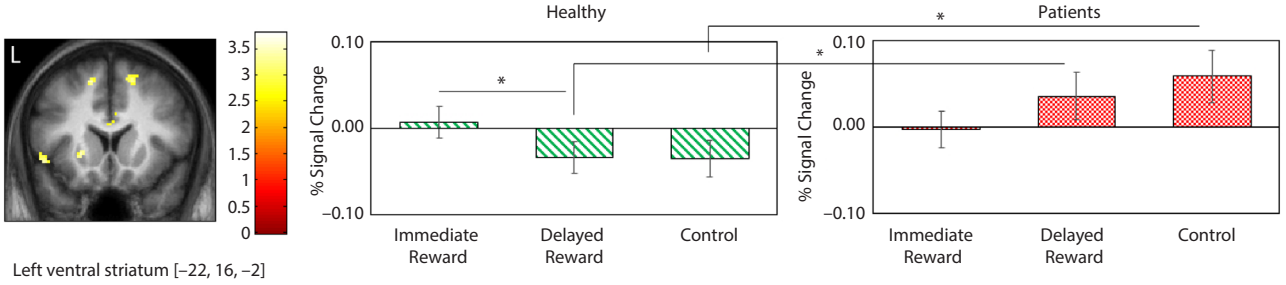
Within the patient group, LDAEP at Cz did not significantly correlate to anatomic BOLD responses. Regarding a possible relationship between reward-related neuronal activity located in the OFC and LDAEP, we used (Pearson) correlations (controlled for age) between

Figure 2. fMRI Activation Differences in Immediate and Delayed Choices

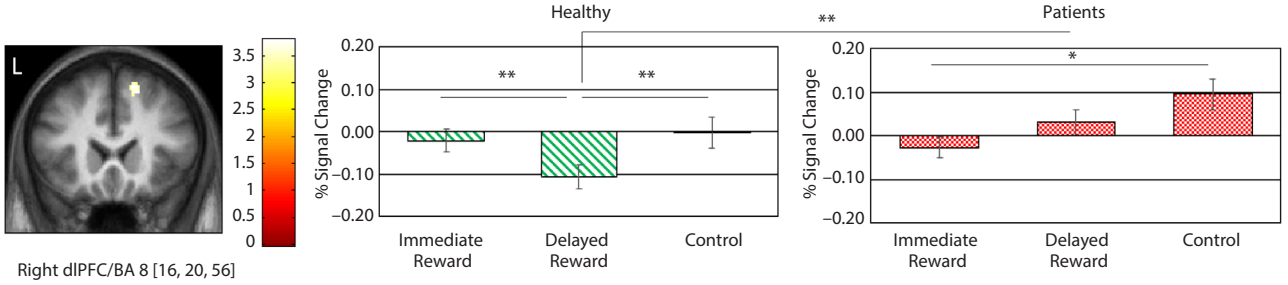
A. Total map: Statistical parametric map (SPM) representing the *F*-contrast [main effect of task] collapsed over groups at $P_{FWE} < .05$ for k > 10



B. Basal ganglia: SPM and percent signal change derived from the left ventral striatum[a]



C. Cortex: SPM and percent signal change derived from the right dorsolateral prefrontal cortex[a]



[a]Error bar represents standard error of means.
*$P < .05$.
**$P < .01$.
Abbreviations: BA = Brodmann area, dlPFC = dorsolateral prefrontal cortex, fMRI = functional magnetic resonance imaging, FWE = familywise error.

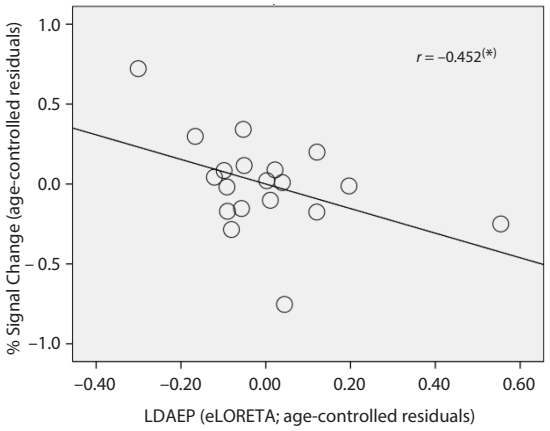
the fMRI signal for [Δ immediate reward – control] and LDAEP (eLORETA values). Smoking had no influence. In the orbital part of the right middle frontal gyrus and in the medial orbital part of the superior frontal gyrus, we were able to detect a significant negative correlation between [Δ immediate reward – control] and LDAEP in OCD patients (right middle frontal gyrus, orbital part: $r = –0.554$; $P = .014$; right superior frontal gyrus, medial orbital part: $r = –0.496$; $P = .032$), whereas healthy subjects showed a significant positive correlation only in the medial orbital part of the right superior frontal gyrus ($r = 0.551$; $P = .014$). In OCD patients, these results were extended by a (trendwise) significant negative correlation between [Δ immediate reward – control] and LDAEP located in the orbital part of the superior frontal gyrus ($r = –0.452$; $P = .052$) (Figure 3). In contrast to our finding in males, we found a closer relationship between LDAEP from both eLORETA sides with fMRI left and right medial OFC activities to immediate responses in females ($r = –0.72$ to $–0.76$, $P < .01$).

DISCUSSION

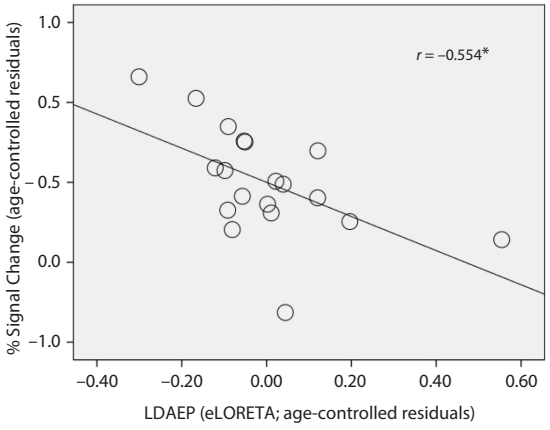
The present study investigated the relationship between a strong LDAEP indicating a low serotonergic activity level and fMRI activation of OFC in a delay discounting task in patients with OCD. There were significant correlation coefficients between LDAEP using all recording sites and eLORETA and fMRI OFC activity within the delay discounting paradigm. Thus, the 2 main pathophysiologic hypotheses of OCD seem to be related to each other as measured by LDAEP and fMRI OFC activity during a delay discounting task. This could mean that there is a conditional relationship with, for example, low serotonergic activity inducing high OFC responsivity in the pathophysiology of OCD. Furthermore, one can assume that the 2 measurements used here were suitable to reflect such a relationship between OFC and serotonergic system. Although there is substantial influence of other neurotransmitter or neuromodulator systems such as acetylcholine on LDAEP[61] and the LDAEP is

Figure 3. Correlation Between [Δ Immediate Reward – Control] and LDAEP in OCD Patients

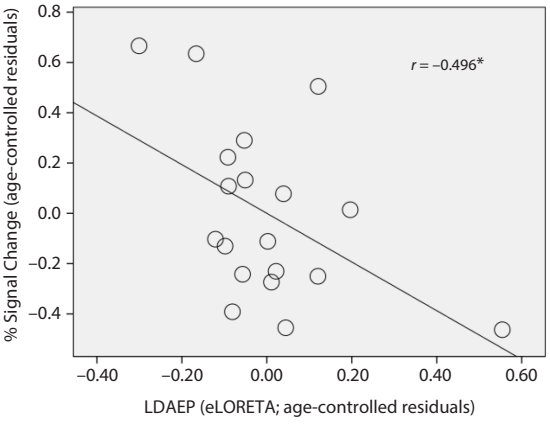
A. Right superior frontal gyrus, orbital part



B. Right middle frontal gyrus, orbital part



C. Right superior frontal gyrus, medial orbital



*$P < .05$. Asterisk in parentheses (*) indicates trend-level significance.
Abbreviations: eLORETA = exact low-resolution brain electromagnetic tomography, fMRI = functional magnetic resonance imaging, LDAEP = loudness dependence of auditory-evoked potentials, OCD = obsessive-compulsive disorder.

limited in human studies due to various reasons, eg, smoking, gender, and personality disorder,[5] broad evidence exists that LDAEP reflects synaptically released serotonin and is a valid indicator of LDAEP for the serotonergic system. On the other hand, the delay discounting task, which demasks impulsive behavior and therefore activates OFC in fMRI, also involves other brain regions, so that one can discuss whether or not this task is able to induce a highly specific activation pattern of the OFC. However, better methodological validated approaches for both the serotonergic and fMRI OFC activity are not known. Working with radioligands for SPECT or PET would have been an alternative, but would also exhibit other disadvantages.

Interestingly, the finding concerning the significant relationship between LDAEP from the eLORETA analyses and fMRI BOLD answers was mainly located on the right hemisphere in patients with OCD. This is rather surprising and difficult to explain, but it could be a result of changes in the natural brain asymmetry in patients with OCD. Thus, several studies have found an impaired laterality suggesting a right hemisphere dysfunction in OCD.[62,63] This is in contrast to our study results in healthy volunteers,[37] in which a significant relationship between LDAEP at Cz and from LORETA analyses was found for both brain sides. Furthermore, we found a distinctive anatomic relationship of LDAEP only with the medial orbitofrontal part of the superior frontal gyrus in the healthy subjects, stronger for females than for males. Here in the patient cohort, we found relationships across the medial, middle, and supraorbitofrontal cortex, stronger in males than in females. And there was a positive correlation coefficient in the healthy subjects, while we have now found negative correlation coefficients in the patients with OCD. In our opinion, this all supports the assumption that the OCD disease process affects the impulsivity control and reward decision mechanism[37] in a deeper way than originally hypothesized for this study in OCD patients. Although the "typical" patient suffering from OCD is characterized as risk aversive and doubtful, accompanied by excessive self-control, the role of impulsivity in OCD remains elusive. Low serotonergic activity as measured by a strong LDAEP seems to be related to a reduced responsiveness to immediate versus control or delayed choices expressed as weak fMRI BOLD activity in OFC regions. This could reflect a stronger rigidity and impulse control in OCD patients, which fits very well to the clinical picture,[64,65] since OCD patients regularly show repetitive behavior of closed loops in thoughts and actions. This could also be a reason why OCD patients have shown longer reaction times with the delay discounting task. Patients with OCD tend to have more doubts and skepticism; therefore, they are slower.

The fMRI data of the present study revealed different BOLD responses in ventral striatum and DLPFC between OCD patients and healthy controls during immediate versus delayed choices. Cortico-striatal circuits are central to reward processing, action selection, and motor control.[66,67] Including ventral striatum as a part of basal ganglia, many previous neuroimaging studies demonstrated aberrant

ventral striatum activity and suggest that this brain region may play a crucial role in the pathophysiology of OCD. For example, Van Laere et al[68] found a correlation between decreases in ventral striatum activity from pre– to post–deep brain stimulation and decreases in OCD symptoms measured by YBOCS. However, Jung et al[69] found aberrant increases in ventral striatum activity for the loss avoidance outcome contrast in OCD patients compared with healthy subjects, similar to results in the study from Kaufmann et al.[70] In contrast to these 2 studies, Figee et al[71] reported attenuated activity within the dorsal striatum in OCD patients during reward anticipation. Abe et al[72] investigated the direct influence of the fronto-striato-thalamic loop in 37 nonmedicated OCD patients compared with 38 healthy controls using a deconvolved Granger Causality analysis and detected the hyperinfluence of the OFC to the ventral striatum. The authors discussed this finding in connection with glutamatergic projections from the frontal cortex to the striatum as well as the increase of glutamate releasing in the OFC and finally with the therapeutic benefits of glutamate modulators in OCD (see also reference 3).

There are some limitations in our study. First, our sample consists of patients receiving SSRI medication, which may have affected the results. Thus, it cannot be excluded that the serotonergic activity levels were not examined as fully attributed to the illness of OCD. These pharmacologic effects could have prevented a stronger relationship between LDAEP and fMRI OFC activity. Second, the small sample sizes do not enable a meaningful investigation of OCD subgroup specific characteristics. Furthermore, LDAEP as well as fMRI BOLD contrasts of OFC during the delay discounting task are both indirect measures of the central serotonergic activity on the one hand and OFC activity on the other. The LDAEP is, however, currently the best validated measure for synaptically released brain serotonin to the best of our knowledge. Assessing OFC activity using nuclear medicine procedures such as PET and SPECT would have provided additional and other methodological problems, but we are aware that fMRI BOLD contrasts of OFC activity during a broad and a rather nonspecific neuropsychological task, such as delay discounting, can only be regarded as an indirect procedure and measure for real neuronal activity within the OFC. This task is also associated typically with broader reward and motivation networks, including the OFC but also ventral striatum, as well as executive function and inhibitory control networks including DLPFC, inferior frontal cortex, insula, dorsal striatum, and parietal cortex. In addition, delay discounting is a well-validated task and measure for impulsivity, and while impaired performance has been demonstrated in disorders of impulsivity such as addiction, obesity, and ADHD, delay discounting has been less frequently used in OCD. Finally, both measurements, the neurophysiology and the neuroimaging, were recorded in sequence within a few hours, but not simultaneously, which could also produce a bias. And the percentages of trait and state properties of both parameters, LDAEP and fMRI BOLD contrasts of OFC activity during delay discounting task, still remain difficult to determine exactly.

In conclusion, this study provides further hints for the close relationship between the serotonergic system and OFC activity states in patients with OCD. Therefore, treatment with serotonin agonists seems to be further justified.

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