



Neural correlates of processing harmonic expectancy violations in children and adolescents with OCD



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ABSTRACT

It has been suggested that patients with obsessive–compulsive disorder (OCD) exhibit enhanced awareness of embedded stimulus patterns as well as enhanced allocation of attention towards unexpected stimuli. Our study aimed at investigating these OCD characteristics by running the harmonic expectancy violation paradigm in 21 boys with OCD and 29 healthy controls matched for age, gender and IQ during a functional magnetic resonance imaging (fMRI) scan. Each trial consisted of a chord sequence in which the first four chords induced a strong expectancy for a harmonic chord at the next position. In 70% of the trials the fifth chord fulfilled this expectancy (harmonic condition), while in 30% the expectancy was violated (disharmonic condition). Overall, the harmonic condition elicited blood-oxygen-level dependent (BOLD) activation in the auditory cortex, while during the disharmonic condition the precuneus, the auditory cortex, the medial frontal gyrus, the premotor cortex, the lingual gyrus, the inferior frontal gyrus and the superior frontal gyrus were activated. In a cluster extending from the right superior temporal gyrus to the inferior frontal gyrus, boys with OCD exhibited increased activation compared to healthy controls in the harmonic condition and decreased activation in the disharmonic condition. Our findings might indicate that patients with OCD are excessively engaged in processing the implicit structure embedded in music stimuli, but they speak against the suggestion that OCD is associated with a misallocation of attention towards the processing of unexpected stimuli.

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1. Introduction

Obsessive–compulsive disorder (OCD) is characterized by intrusive thoughts and time-consuming repetitive behaviors often causing significant impairment. Approximately 2% of the population are affected (Ruscio et al., 2010). Many patients with OCD report about sensations of incompleteness or something being “not-just-right” accompanying their symptoms. These sensations – often referred to as Not-just-right experiences (NJRE) – can be evoked by visual, auditory or tactile perceptions and often entail the urge to perform a compensatory compulsion (Leckman et al., 1994; Prado et al., 2007; Summerfeldt, 2004).

NJRE are more frequent in patients with early-onset OCD (Rosario-Campos et al., 2001), which has been suggested to represent a distinct subtype of OCD (Chabane et al., 2005). Besides the higher frequency of NJRE, early onset OCD is also associated with a higher frequency of tic-like compulsions, a greater familial aggregation of OCD and tic disorders

and a male predominance (Chabane et al., 2005; Geller et al., 2007; Nestadt et al., 2003; Roessner et al., 2005; Rosario-Campos et al., 2001).

Although NJRE have gained some attention in recent years, most studies have not gone beyond a description of their phenomenology and prevalence and the underlying mechanisms of NJRE remain elusive.

Rauch and Savage (2000) proposed that cognitive intrusions in OCD might stem from a misallocation of attention towards stimuli that would normally be processed without conscious awareness. The underlying neural mechanism might be a disbalance between the direct cortico–pallido–thalamic pathway, which amplifies attention towards salient stimuli and the indirect pathway, which helps to inhibit distraction from nonsalient cues. This assumption got empiric support from a study utilizing an implicit procedural learning task. While patients with OCD had deficits in implicit procedural learning, they showed enhanced awareness of the stimulus pattern that was embedded in the implicit learning task (Goldman et al., 2008).

It has also been proposed that patients with OCD exhibit a hypersensitivity of the stimulus-driven attentional system (Mathews and Mackintosh, 1998), assessable in the orienting response towards unexpected stimuli. An enhanced cortical orienting response is reflected in enhanced P3 event-related potential amplitudes. Indeed, a heightened P3b and shortened P3b latencies following target sounds have been found in patients with OCD (Gohle et al., 2008; Ischebeck et al.,

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2011; Johannes et al., 2001; Mavrogiorgou et al., 2002). The P3b is largely generated in temporal-parietal regions as well as in the hippocampus (Huang et al., 2015; Molnár, 1994).

An ideal probe for studying how patients with OCD a) process implicit structures of stimuli and b) respond to the presentation of unexpected stimuli might be the harmonic expectancy violation paradigm by Koelsch et al. (2000, 2005). The harmonic expectancy violation paradigm is based on tonal music constructed in accordance to specific regularities, sometimes called the musical syntax. Listeners brought up in a western culture are familiar with these regularities and detect violations of the expected harmonic structure (Koelsch, 2005; Koelsch et al., 2000). In a previous study it was shown that the violation of music-syntactic regularities by disharmonic chord sequences provokes feelings in healthy controls that are similar to NJRE reported in the context of obsessive-compulsive (OC) symptomatology (Buse et al., 2015).

The detection of music-syntactically irregular chords is reflected in a negative Event-Related Potential (ERP) that occurs at about 200 ms after onset of the disharmonic chord and is strongest over right-frontal electrode leads (Koelsch, 2005; Koelsch et al., 2000). Functional neuroimaging studies show that the processing of harmonic expectancy violations is located in the inferior frontolateral cortex (often denoted as 'Broca's area', an area that has also been implicated in the processing of linguistic syntax) (Koelsch, 2005; Maess et al., 2001) but also the superior temporal gyrus and the premotor cortex (Koelsch et al., 2002, 2005).

The aim of the current study was to investigate the neural correlates of a) the processing of music-syntactic regularities and b) the detection of violations of those regularities in children and adolescents with OCD.

We hypothesized that boys with OCD exhibit altered BOLD activation as compared to healthy controls during the harmonic expectancy violation paradigm in the inferior fronto-lateral cortex, the superior temporal gyrus and the premotor cortex, but potentially also in temporal-parietal regions and in the hippocampus.

2. Methods

2.1. Sample characteristics

Participants with OCD were recruited among referrals to the Child and Adolescent Psychiatry of the University Medical Centre Dresden. The OCD diagnoses were made by board certified child and adolescents psychiatrists using ICD-10 criteria. Additionally, all potential participants were screened for psychiatric disorders with the Mini International Neuropsychiatric Interview for Children and Adolescents (M.I.N.I.-Kid, Sheehan et al. (1998)).

The recruitment was restricted to boys aged between 11–17 years. We chose to examine only children and adolescent, because the phenomena of interest are particularly present in the early-onset OCD subtype.

Initially, 21 boys with OCD and 29 healthy controls were recruited. The healthy controls were matched with the patients with regard to age, sex and IQ. We excluded patients with any comorbid diagnosis to OCD, except related disorders such as phobia ($n = 3$), panic disorder ($n = 1$) and depressive episode in the past ($n = 1$) since they were no current source of impairment. Four boys with OCD had to be excluded because of movement artifacts, resulting in a total of 17 boys with OCD. One of the controls had to be excluded because of claustrophobia, one because of a previously undetected large intracranial cyst and one because he exhibited motor tics during the examination. Three controls were excluded because of movement artifacts, resulting in a total of 23 boys in the control group.

Two boys with OCD were currently taking medication (both fluoxetine).

Written informed consent was obtained from both the participants and their parents after the procedure had been fully explained. The study was approved by the ethics committee of the TU Dresden and

Table 1
Demographics and clinical characteristics of the sample.

		Boys with OCD N = 17	Healthy control boys N = 23		
		Mean (SD)	Mean (SD)	t(38)	p
Age (in years)		14.88 (1.73)	14.26 (1.89)	1.07	.293
IQ		114 (27.66)	110 (13.08)	0.60	.553
Age at OCD onset		10.47 (3.32)			
Duration of OCD		4.41 (2.94)			
CY-BOCS	Obsessions	7.59 (5.29)	–	–	–
	Compulsions	8.29 (5.02)	–	–	–
	Total score	15.88 (8.58)	–	–	–
OCI-R	Global score	21.35 (19.82)	4.35 (6.01)	3.90	<0.001
OCTCDQR	Harm	6.77 (4.48)	1.78 (2.81)	4.32	<0.001
	avoidance				
	Incompleteness	11.41 (8.46)	3.13 (4.61)	4.00	<0.001
ZWIK-E	Total score	82.65 (18.57)	24.13 (25.23)	8.07	<0.001
ZWIK-K	Total score	65.59 (32.52)	21.44 (25.48)	4.82	<0.001

IQ = assessed with the short version of the Hamburg-Wechsler-Test for Intelligence for children (HAWIK-IV, German version of the WISC-IV) (Petermann and Petermann, 2010), CY-BOCS = Children's Yale-Brown Obsessive-Compulsive Scale (Scahill et al., 1997), OCI-R = Obsessive-Compulsive Inventory (Foa et al., 2002), OCTCDQR = Obsessive-Compulsive Trait Core Dimensions Questionnaire – Revision (Summerfeldt et al., 2001), ZWIK = Zwangsinventar für Kinder und Jugendliche (Goletz and Döpfner, 2011) (ZWIK-E = parent-report version, ZWIK-K = self-report version).

was carried out in accordance with the latest version of the Declaration of Helsinki. The demographics and clinical characteristics of the sample are presented in Table 1.

2.2. Assessment of OC symptoms and motivational core dimensions

The Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) (Scahill et al., 1997) was obtained from all boys with OCD. The CY-BOCS is a half-structured interview to determine the severity of symptoms in pediatric OCD.

Both boys with OCD and healthy controls completed the Obsessive-Compulsive Inventory (OCI-R) ((Foa et al., 2002), German version by Gönner et al. (2007)), a self-report instrument measuring dimensional OC symptoms on six subscales (washing, obsessing, hoarding, ordering, checking and neutralizing) and one global symptom scale.

The Obsessive-Compulsive Trait Core Dimensions Questionnaire – Revision (OCTCDQ-R) developed by Summerfeldt et al. (2001) assesses the two motivational core dimensions underlying OCD-like symptoms: harm avoidance and incompleteness. We used the German short version of the questionnaire (Ecker et al., 2011). The OCTCDQ-R was obtained from all participants.

In addition, the Zwangsinventar für Kinder und Jugendliche (ZWIK) (Goletz and Döpfner, 2011), a German questionnaire to dimensionally assess pediatric OC symptoms was completed by all participants (ZWIK-K: self-report form) and their parents (ZWIK-E: parent-report form). It provides scores on four subscales (contamination fears and washing compulsions, controlling and repeating, obsessions about the harm or injury of oneself or others, counting and questioning) as well as one total symptom score.

2.3. Task

The harmonic expectancy violation paradigm (e.g. Koelsch et al., 2000) is based on tonal music constructed in accordance to specific implicit regularities. It enables the assessment of reactions to violations of those regularities.

The stimuli were chord sequences, identical to those used by (Koelsch et al., 2005), consisting of five chords each. The first four chords corresponded to the rules of classical harmony with the fourth

chord (a dominant seventh) inducing a strong expectancy for a tonic chord at the fifth position. In 70% of trials this expectancy was fulfilled by the fifth chord being a regular tonic (harmonic condition). In 30% the expectancy was violated by the fifth chord being a disharmonic subdominant variation, so-called Neapolitan sixth chord (disharmonic condition). The first four chords of a sequence were presented for 600 ms and the last chord for 1200 ms, resulting in a total duration of 3600 ms per sequence.

The chord sequences were presented with 20 different melodic outlines, each in a harmonic and a disharmonic version. Those different melodic outlines were presented in different keys. Exactly the same chord sequence (same melodic outline and same key) was never presented twice. Altogether the run consisted of 96 chord sequences (66 harmonic chord sequences and 30 disharmonic chord sequences).

The subjects were instructed to indicate as quickly as possible whether the sequence sounded harmonic or disharmonic by pressing a key with their right or left index finger. The mapping of type of chord sequence (harmonic vs. disharmonic) and response side (right vs. left) was randomized between subjects.

The acoustic stimuli were presented via binaural headphones (MR confon GmbH, Magdeburg, Germany) with approximately 70 dB while the participants fixated a cross in the middle of a black screen. The responses were given with NNL fMRI response grips (Nordic Neuro Lab, Bergen, Norway).

Response times (RTs) were measured from the onset of the last chord of the sequence to the corresponding response. Only RTs of correct responses were analyzed. Trials with RTs longer than two standard deviations above the individual mean as well as trials with RTs shorter than two standard deviations below the individual mean were discarded. In the OCD group an average of 54.94 (SD = 9.18) trials in the harmonic condition and 25.65 (SD = 3.10) trials in the disharmonic condition was used for analyses. In the healthy control group an average of 56.61 (SD = 6.83) trials in the harmonic condition and 26.96 (SD = 1.40) trials in the disharmonic condition was used for analyses.

A mean total RT was calculated for each subject across all trials. In the same way, a mean RT was calculated for harmonic chord sequences and disharmonic chord sequences respectively. A two-factorial repeated measures ANOVA with the factors condition (harmonic vs. disharmonic) and group (patients with OCD vs. healthy controls) was run with IBM SPSS Statistics 23 Software.

2.4. fMRI acquisition, preprocessing and analysis

The functional magnetic resonance imaging (fMRI) scan was performed on a 3 T Siemens Magnetom Trio A Tim. High-resolution structural images (1.0 mm × 1.0 mm × 1.0 mm) were obtained using an MPRAGE T1-weighted sequence (TR = 1900 ms, TE = 2.26 ms, TI = 900 ms, flip = 9). Functional images were acquired with a gradient echo planar T2*-weighted sequence (TR = 2600 ms, TE = 30 ms, flip angle 80°, matrix size = 256 × 256, field of view = 200 mm, 40 transversal slices with 3 mm thickness of slices). The images were acquired in descendent order.

The fMRI data were analyzed using SPM8 software (Wellcome Department of Imaging Neurosciences, UCL, UK, <http://www.fil.ion.ucl.ac.uk/spm>). Preprocessing steps involved slice time correction, realignment (3 translation and 3 rotation parameters), indirect normalization and smoothing (Gaussian Kernel, FWHM = 8 mm). Indirect normalization involved three steps: 1) co-registration of the subjects' functional data sets (EPI images) to their high-resolution structural data sets (T1 images), 2) segmentation of the T1 image into cerebrospinal fluid, white matter and gray matter based on MNI templates, 3) warping of each individual data set into the MNI standard space.

After preprocessing the single-subject (first-level) analyses were performed. For each subject the input functions representing the timing of each event (onset of the last chord in each chord sequence) were convolved with the canonical hemodynamic response function.

Additionally, regressors of temporal and dispersion derivatives were included in the statistical model to account for slight deviations of onset time and response width in the individual BOLD response relative to its canonical form (Friston et al., 1998). Data were filtered by means of a high-pass filter with a cut-off period of 128 s. Two BOLD contrasts (planned t-contrasts) were modeled: 1) harmonic chord sequences > implicit baseline and 2) disharmonic chord sequences > implicit baseline. Motion parameters of the realignment step during preprocessing were introduced as additional covariates of no interest to control for residual movement-related variance from the time series.

Using the parameter estimates obtained by single-subject analyses, we performed a second-level random effects analysis to analyze the functional BOLD activation in the two experimental conditions (harmonic and disharmonic) compared to the implicit baseline for both the control and the OCD group separately. A full factorial design was performed to analyze the main effect of condition (harmonic vs. disharmonic), the main effect of group (OCD vs. controls) and the interaction effect between condition and group. We limited both the random effect analysis and the full factorial analysis to gray matter by using an inclusive gray matter mask that was created with the wfu pickatlas software (<http://fmri.wfubmc.edu/software/pickatlas>). Clusters with a significant interaction effect between condition and group on the BOLD activation were determined as functional regions of interest (ROIs) with the MarsBaR toolbox for SPM (Brett et al., 2002). Contrast estimates (arbitrary units) in the identified ROIs were estimated with the rfxplot toolbox (Gläscher, 2009) and exported to IBM SPSS Statistics 21 Software. In order to test whether the age range of the participants or their task performance (i.e. reaction time) had an influence on the BOLD activation in the ROIs, we conducted ANCOVAs on the contrast estimates including the factors condition (harmonic vs. disharmonic) and group (OCD vs. controls) as well as age and reaction time as a covariate. In addition, the contrast estimates were used to conduct post-hoc tests.

3. Results

3.1. Response times (RT) and error rates

The two-factorial repeated measures ANOVA revealed a main effect of condition, indicating that the RT to disharmonic chord sequences was significantly faster than the RT to harmonic chord sequences (876 ms (SD = 270) vs. 996 ms (SD = 291), $F(1, 38) = 37.6$, $p < 0.001$). There was no main effect of group. There was a trend for an interaction effect between condition and group ($F(1, 38) = 3.27$, $p = 0.078$), indicating that there was a trend for a larger difference of RT between both conditions in the healthy controls compared to the patients with OCD (see Fig. 1).

The two-factorial repeated measures ANOVA on the error rates revealed a main effect of condition, indicating that the error rates in the disharmonic condition were significantly smaller than in the harmonic condition (11.33% (SD = 12.73) vs. 3.91% (SD = 3.68), $F(1, 38) =$

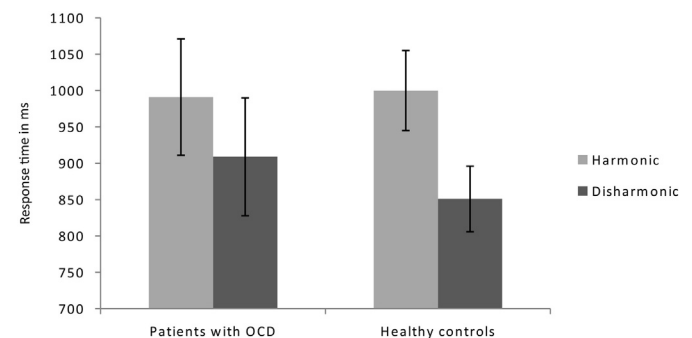


Fig. 1. Response times to harmonic and disharmonic chords in patients. Error bars represent one standard error of the mean.

18.63, $p < 0.001$). There was neither a main effect of group nor an interaction effect between condition and group.

3.2. Random effect analysis (fMRI data)

The gray-matter random effect analysis of the whole sample (healthy controls and patients with OCD combined) showed significant BOLD activations during the presentation of harmonic chord sequences compared to the implicit baseline in the bilateral auditory cortex (threshold at $p < 0.05$, FWE corrected, extent threshold of 50 voxels).

For the contrast disharmonic chord sequences compared to implicit baseline significant BOLD activations were found in the bilateral precuneus, the bilateral auditory cortex, the bilateral medial frontal gyrus, the left premotor cortex, the bilateral lingual gyrus, the bilateral inferior frontal gyrus and the right superior frontal gyrus (threshold at $p < 0.05$, FWE corrected, extent threshold of 50 voxels).

Details of the results of the random effect analysis are displayed in Table 2.

3.3. Full factorial analysis (fMRI data)

There was a pronounced main effect for condition (threshold at $p < 0.05$, FWE corrected, extent threshold of 50 voxels) in the right precuneus. Other activation clusters were found in the right lingual gyrus, the bilateral middle frontal gyrus, the right occipital gyrus, the bilateral cerebellum, the left middle temporal gyrus, the left thalamus, the left inferior frontal gyrus, and the bilateral premotor cortex (BA 6) (see Table 3).

For the main effect of group and the interaction effect between condition and group no FWE corrected results were found, therefore the threshold was lowered to $p < 0.001$, uncorrected. An extent threshold of 10 voxels was used in order to ignore minor clusters with only few activated voxels.

However, still no main effect of group could be found in any brain region (threshold at $p < 0.001$, uncorrected, extent threshold of 10 voxels).

But there was an interaction effect between condition and group (threshold at $p < 0.001$, uncorrected, extent threshold of 10 voxels) on BOLD activation in four clusters. The main activation cluster had its peak in the right superior temporal gyrus, extending to the right inferior frontal gyrus and the right insula (subsequently referred to as superior temporal/inferior frontal cluster). The second largest activation cluster was found in the left parahippocampal gyrus. The other activations

Table 3
Full factorial analysis.

Brain region	Side	Number of voxels	Brodmann area	Talairach coordinates (in mm)		
				x	y	z
Main effect of condition**						
Precuneus	Right	5977	7	4	-48	44
Lingual gyrus	Right	433	18	12	-74	2
Middle frontal gyrus	Right	295	46	50	22	26
Occipital gyrus	Right	288	19	42	-80	10
Middle frontal gyrus	Right	282	8	26	28	46
Cerebellum	Left	171		-36	-50	-16
Middle temporal gyrus	Left	166	39	-54	-64	18
Middle frontal gyrus	Left	151	6	-22	20	52
Thalamus	Left	140		-20	-30	2
Cerebellum	Right	127		48	-46	-20
Inferior frontal gyrus	Left	97	9	-44	12	30
Middle frontal gyrus	Left	73	6	-32	2	52
Precentral gyrus	Left	70	6	-40	2	32
Middle frontal gyrus	Right	61	6	28	-4	50
Main effect of group*						
-	-	-	-	-	-	-
Interaction effect between condition and group*						
Superior temporal gyrus	Right	180	22	50	14	-4
Parahippocampal gyrus	Left	30	27	-22	-34	-4
Precuneus	Right	14	7	6	-52	34
Hippocampus	Left	10		-26	-36	-4

Results from the full factorial fMRI analysis. Condition = harmonic vs. disharmonic chord sequences, group = patients with Obsessive-Compulsive Disorder vs. healthy controls. Brain regions are listed in descending order from the largest to the smallest activation cluster.

* Threshold at $p < 0.001$, uncorrected, extent threshold of 10 voxels.

** Threshold at $p < 0.05$, FWE corrected, extent threshold of 50 voxels.

were found in the right precuneus and in the left hippocampus (see Fig. 2 and Table 3).

The ANCOVAs on the extracted contrast estimates in the superior temporal/inferior frontal cluster revealed that neither age nor reaction time had an influence on the BOLD activation. That is, with or without entering age and reaction time as a covariate the interaction effect remained the same.

Contrast estimates in the main activation clusters were also used for post-hoc tests (see Table 4 and Fig. 2). In the superior temporal/inferior frontal cluster healthy controls showed stronger activation during disharmonic compared to harmonic chords, while patients with OCD

Table 2
Random effect analysis.

	Brain region	Side	Number of voxels	Brodmann area	Talairach coordinates (in mm)		
					x	y	z
Harmonic	Superior temporal gyrus	Left	88	22	-48	-2	-2
	Superior temporal gyrus	Right	58	22	52	-10	4
	Transverse temporal gyrus	Right	41	41	54	-16	10
Disharmonic	Precuneus extending to the posterior cingulate	Left	944	7/29	-2	-60	48
	Precuneus extending to the posterior cingulate	Right	767	7/30	4	-64	54
	Superior temporal gyrus extending to the insula	Left	239	41/22/13	-46	-34	10
	Superior temporal gyrus	Right	208	42/41	64	-24	10
	Medial frontal gyrus extending to cingulate gyrus	Right	167	6/32	12	10	50
	Medial frontal gyrus extending to superior frontal gyrus	Left	106	6	-12	6	52
	Precentral gyrus	Left	99	6	-46	0	46
	Lingual gyrus	Right	96	18/19	12	-74	2
	Lingual gyrus extending to Cuneus	Left	89	17/18	-12	-88	2
	Middle frontal gyrus extending to inferior frontal gyrus	Right	70	46/9	50	22	26
	Inferior frontal gyrus	Left	68	9	-44	10	30
	Inferior frontal gyrus	Right	66	45	32	24	4
	Superior frontal gyrus	Right	63	22	58	2	-6

Results from the gray-matter random effect analysis. Brain regions with significant BOLD activations during presentation of harmonic as well as disharmonic chord sequences compared to the implicit baseline (contrast harmonic/disharmonic > baseline) in the whole sample (healthy controls and patients with OCD combined). Brain regions are listed in descending order from the largest to the smallest activation cluster. threshold at $p < 0.05$, FWE corrected, extent threshold of 50 voxels.

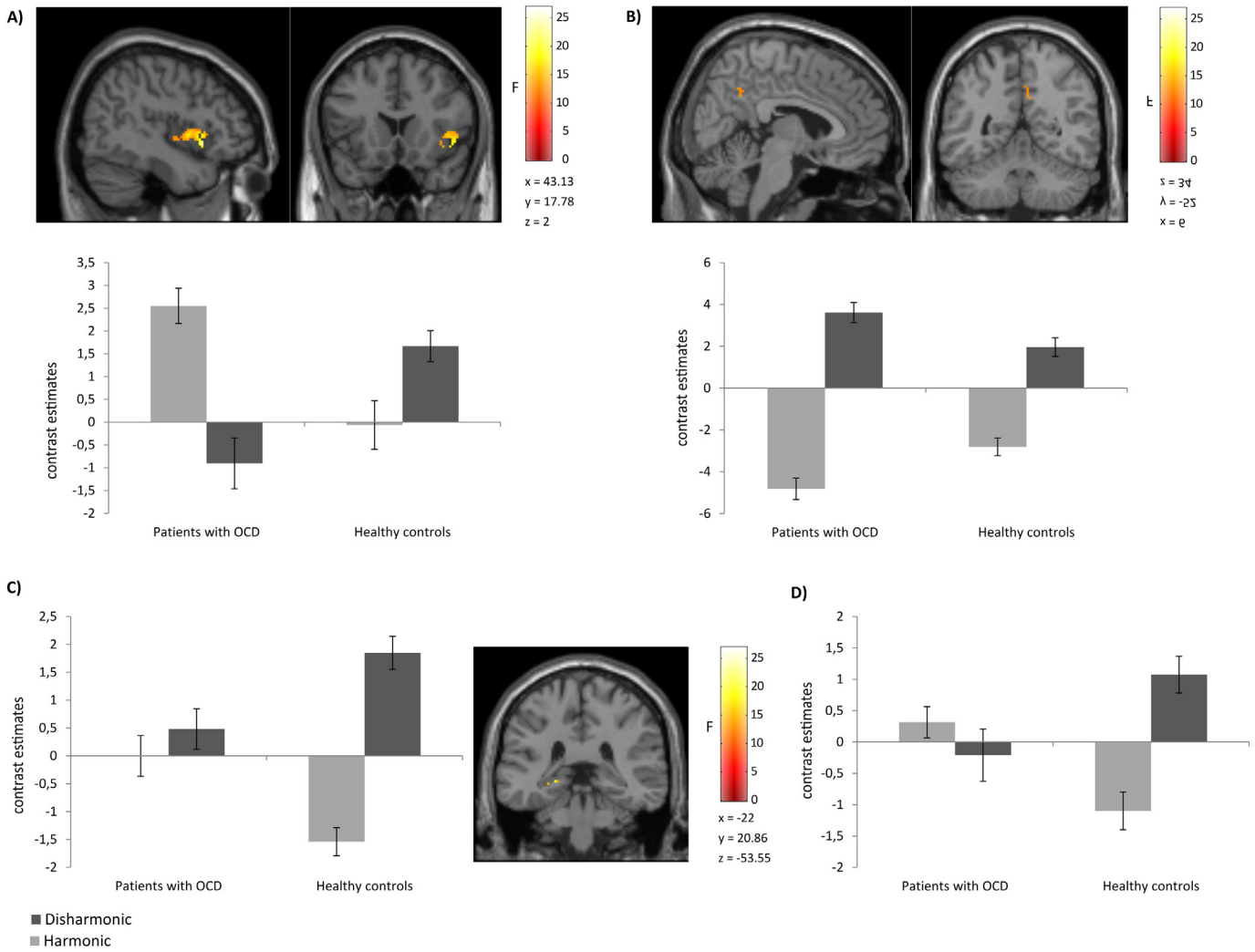


Fig. 2. Interaction effect between condition and group on BOLD activation. Interaction effect in A) the superior temporal/inferior frontal cluster (BA 22/ BA 47), B) the precuneus (BA 7) and C) the parahippocampal gyrus (BA 27) and hippocampus. The bar charts indicate the contrast estimates (arbitrary units) of BOLD activation in the respective brain region during harmonic and disharmonic chords in the OCD and the controls group. Error bars represent one standard error of the mean. Threshold at $p < 0.001$, uncorrected, extent threshold of 10 voxels.

showed stronger activation during harmonic compared to disharmonic chords. In the harmonic condition, patients with OCD had stronger activation than healthy controls, while in the disharmonic condition the activation was higher in healthy controls.

Post-hoc tests of the activation in the hippocampus and the parahippocampal gyrus revealed a similar pattern in both structures: Healthy controls showed deactivation (compared to implicit baseline)

during harmonic chords and activation during disharmonic chords, while there was no difference between both conditions in patients with OCD. The difference between the groups was significant in both conditions.

In the precuneus both groups showed deactivation (compared to implicit baseline) in response to harmonic chords and activations during disharmonic chords. In the harmonic condition patients with OCD

Table 4
Post-hoc tests on contrast estimates in the main activation clusters.

		Harmonic		Disharmonic		t	p
		Mean (SD)		Mean (SD)			
Superior temporal/inferior frontal	Patients with OCD (N = 17)	2.55 (1.6)		-0.91 (2.3)		4.26	0.001
	Healthy controls (N = 23)	-0.06 (2.56)		1.67 (1.62)			
		$t_{(37,2)} = 3.97, p < 0.001$		$t_{(38)} = -4.16, p < 0.001$			
Hippocampus	Patients with OCD (N = 17)	0.32 (1.03)		-0.21 (1.72)		0.96	0.352
	Healthy controls (N = 23)	-1.10 (1.45)		1.07 (1.40)			
		$t_{(38)} = 3.44, p = 0.001$		$t_{(38)} = -2.60, p = 0.013$			
Parahippocampal gyrus	Patients with OCD (N = 17)	-0.002 (1.50)		0.48 (1.50)		-0.75	0.466
	Healthy controls (N = 23)	-1.54 (1.21)		1.85 (1.42)			
		$t_{(38)} = 3.58, p = 0.001$		$t_{(38)} = -2.95, p = 0.005$			
Precuneus	Patients with OCD (N = 17)	-4.82 (2.09)		3.61 (1.98)		-10.71	<0.001
	Healthy controls (N = 23)	-2.81 (2.03)		1.96 (2.13)			
		$t_{(38)} = -3.05, p = 0.004$		$t_{(38)} = 2.49, p = 0.017$			

The comparison between harmonic and disharmonic chord sequences was done with paired-samples t-tests, independent-samples t-tests were used to compare the groups.

showed stronger deactivations as compared to healthy control, while in the disharmonic condition patients with OCD showed stronger activation. This indicates that the difference between both conditions was more pronounced in patients with OCD.

3.4. Correlations between BOLD activation and dimensional OC symptoms

Then, correlations between the contrast estimates in the superior temporal/inferior frontal cluster and the dimensional measures of OC symptoms (OCI-R, OCTCDQ-GR, ZWIK, CY-BOCS) were analyzed for both groups separately. However, neither in healthy controls nor in patients with OCD significant correlations between the contrast estimates in the superior temporal/inferior frontal cluster and any dimensional measure of OC symptoms were found. However, in the OCD group, the correlation between the contrast estimates in the harmonic condition and the incompleteness score of the OCTCDQ-GR reached trend level ($r = 0.448$, $p = 0.071$).

4. Discussion

It has been suggested that patients with OCD exhibit enhanced awareness of embedded stimulus patterns as well as enhanced shifts of attention towards unexpected stimuli. Our study aimed at investigating these OCD characteristics by assessing the neural correlates of a) processing of regularities embedded in musical stimuli and b) the detection of violations of those regularities by disharmonic chords in children and adolescents with OCD.

As expected, in the whole sample the auditory cortex were activated during the presentation of harmonic chord sequences. The presentation of disharmonic chord sequences elicited additional activations in the precuneus, the bilateral medial frontal gyrus, the left premotor cortex, the bilateral lingual gyrus, the bilateral inferior frontal gyrus and the right superior frontal gyrus. Accordingly the full factorial analysis revealed a main effect for condition mainly in the right precuneus, but also in the right lingual gyrus, the bilateral middle frontal gyrus, the right occipital gyrus, the bilateral cerebellum, the left middle temporal gyrus, the left thalamus, the left inferior frontal gyrus, and the bilateral premotor cortex.

Our main interest lay on the question how both groups differ in BOLD activation during the detection of harmonic expectancy violations, i.e. during listening to disharmonic compared to harmonic chord sequences. The main activation cluster of the interaction between condition and group had its peak in the right superior temporal gyrus, extending to the right insula and the right inferior frontal gyrus.

The inferior frontolateral cortex, together with superior temporal regions have been described as the main structures involved in the processing of music-syntactic regularities and their violations (Koelsch, 2005; Koelsch et al., 2002, 2005; Tillmann et al., 2003). A similar pattern of BOLD activation has already been described in children (Koelsch et al., 2005). More generally, the inferior frontal cortex is known to be involved in the processing of semantics and syntactics in both language and music (Huang et al., 2012; Levitin and Menon, 2003; Parsons, 2001; Poldrack et al., 1999; Roskies et al., 2001), whereas the right-hemispheric lateralization is typical for the musical domain (Koelsch, 2005). The inferior frontal cortex has also been referred to as a part of a neural network for perceptual organization, e.g. obeying the regularities of tonal music (Levitin and Menon, 2003).

In healthy controls we found activations of the superior temporal/inferior frontal cluster only in response to the disharmonic chord sequences, while in patients with OCD the superior temporal/inferior frontal cluster was only activated during the presentation of harmonic chord sequences. Considering that activations of the inferior frontal cortex have been linked to the processing of musical structure (Koelsch, 2005; Koelsch et al., 2002, 2005; Levitin and Menon, 2003; Poldrack et al., 1999; Tillmann et al., 2003), OCD seems to be related to the processing of musical structure as such and not to violations of musical

structure. It seems that patients with OCD are constantly engaged in processing of the implicit structure of auditory stimuli, while healthy controls are only engaged in the processing of deviations of the regular pattern. This is in line with the suggestion that OCD might be associated with a misallocation of attention towards stimuli that would normally be processed without conscious awareness (Rauch and Savage, 2000).

Our findings might help to elucidate the underlying neural mechanisms of NJRE in patients with OCD. Many patients with OCD report about sensations of incompleteness or something being “not-just-right” accompanying their symptoms (Leckman et al., 1994; Prado et al., 2007; Summerfeldt, 2004). Harmonic expectancy violations by disharmonic chord sequences provoke feelings in healthy controls that are related to those NJRE reported in the context of OC symptomatology (Buse et al., 2015).

Although we fully acknowledge the speculative nature of the following, we suggest that the excessive engagement in the processing of structures in stimuli, e.g. syntactic regularities in music, might be related to the occurrence of NJRE. In line with this suggestion, the correlation between the contrast estimates in the superior temporal/inferior frontal cluster during the presentation of harmonic chords and the incompleteness score of the OCTCDQ-GR, which assesses how much OC symptoms are motivated by a sensation of something being “not-just-right” (Summerfeldt, 2004) reached trend level in the OCD group.

Here it has to bear in mind that this findings may be applicable only to the early-onset OCD subtype, in which NJRE are more frequent, and may not be present in adult OCD samples (Chabane et al., 2005; Roessner et al., 2005; Rosario-Campos et al., 2001).

Besides the activation in the superior temporal/inferior frontal cluster, we found an interaction between condition and group in the hippocampus and in the parahippocampal gyrus. Both, the hippocampus and the parahippocampal gyrus, are activated during the perception of unpleasant music and strongly deactivated in response to pleasant music stimuli (Koelsch et al., 2006). In regard of our healthy controls we had corresponding findings since hippocampus and parahippocampal gyrus were deactivated during harmonic chords, which are usually perceived as more pleasant (Buse et al., 2015), and activated during disharmonic chords, which are usually perceived as more unpleasant (Buse et al., 2015). Interestingly, we found no differences between harmonic and disharmonic chords in hippocampal and parahippocampal activation in patients with OCD.

In the precuneus we found deactivations during the presentation of the harmonic chords and activations during the presentation of disharmonic chords in both groups, but this effect was stronger in patients with OCD. This finding is not easy to interpret and might be explained in different ways since the precuneus is involved in a wide range of cognitive functions, including visuo-spatial imagery, episodic memory retrieval, self processing and consciousness (Cavanna and Trimble, 2006). Signal decreases in the precuneus have also been associated with the performance of a task as compared to a resting state (Cavanna and Trimble, 2006).

Also some limitations have to be taken into account. First, the interaction between condition and group regarding the response times only reached trend level. That is, the behavioral data do not fully reflect the interaction we found in the fMRI data, which substantially weakens the conclusiveness of our results. Second, three patients had related disorders such as phobia, panic disorder and depressive episode and two patients were medicated, which might have confounded the results. However, the exclusion criteria were still considerable strict (only boys, only two on medication, no comorbid externalizing disorder). Thus, potential confounding by medication, gender or comorbidities was limited to a minimum. Finally, the small sample further limits the conclusiveness of our results.

In sum, we found that patients with OCD showed stronger activations in brain regions associated with the processing of music-syntactic regularities, irrespectively of the violation of those regularities. This might indicate that patients with OCD are constantly engaged in processing of the

implicit structure embedded in the music stimuli, while healthy controls are more engaged in the processing of unexpected violations of the implicit structure. Our findings are well in line with the heuristic model by Rauch and Savage (2000), suggesting that OCD is associated with a misallocation of attention towards stimuli that would normally be processed without conscious awareness. Our findings speak against the suggestion that patients with OCD exhibit a misallocation of attention towards the processing of unexpected stimuli.

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Conflict of interest

None of the authors had any financial, personal or other relationship with other people or organizations within three years of beginning the submitted work that inappropriately influenced the submitted work.

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