Psychiatry Research: Neuroimaging 283 (2019) 135–144

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Individual OCD-provoking stimuli activate disorder-related and self-related neuronal networks in fMRI

Kathrin Viol[a,b,*], Benjamin Aas[a,b,c], Anna Kastinger[a,b], Martin Kronbichler[d,e], Helmut Schöller[a,b,c], Eva-Maria Reiter[f], Sarah Said-Yürekli[d,e,g], Lisa Kronbichler[d,e], Brigitte Kravanja-Spannberger[b], Barbara Stöger-Schmidinger[b], Wolfgang Aichhorn[a,b], Günter Schiepek[a,b,c]

[a] Institute of Synergetics and Psychotherapy Research, Paracelsus Medical University, Salzburg, Austria
[b] Department of Psychosomatics and Inpatient Psychotherapy, University Hospital for Psychiatry, Psychotherapy and Psychosomatics, Paracelsus Medical University, Salzburg, Austria
[c] Department of Psychology, Ludwig Maximilians University, Munich, Germany
[d] Centre for Cognitive Neuroscience and Department of Psychology, Paris Lodron University of Salzburg, Salzburg, Austria
[e] Neuroscience Institute, Christian-Doppler Medical Center, Paracelsus Medical University, Salzburg, Austria
[f] Department for Radiotherapy and Radio-Oncology, Christian-Doppler University Hospital of the Paracelsus Medical University, Salzburg, Austria
[g] Department for Neurology, Christian-Doppler University Hospital of the Paracelsus Medical University, Salzburg, Austria

ARTICLE INFO

Keywords:
Symptom provocation
Individualized stimuli
Standardized stimuli
MOCSS
Cortical midline structure

ABSTRACT

For patients with Obsessive-Compulsive Disorder (OCD), whose triggers are highly idiosyncratic, individual stimulus material has been used in several fMRI studies. This study aims at comparing individual to standardized picture sets and at investigating a possible overlap of the former with the self-referential neuronal network. During fMRI-scanning, 17 inpatients with OCD and 17 healthy controls were exposed to pictures of their personal triggers, photographed in their domestic environments, to standardized pictures designed to provoke OCD symptoms, and to neutral pictures. Whole-brain analyses were calculated and the pictures were rated by both patients and controls with respect to valence, arousal, and coping. Patients rated the individualized stimuli lower in valence and coping and higher in arousal compared to controls, and also compared to standardized OCD- and neutral stimuli. The individual stimuli elicited neuronal activity in the cingulate cortex, hippocampus, insula, middle frontal/precentral gyrus, superior/inferior parietal lobe, and precuneus, while no group difference was detected by the standardized OCD-stimuli. In conclusion, individual picture sets facilitate the detection of neuronal activity, but the results might be confounded due to the overlap with the network of self-referential processing and memory retrieval. The use of individual symptom-provoking and individual neutral stimuli would therefore be optimal.

1. Introduction

1.1. Importance of stimuli for fMRI

Choosing the right stimulus material is highly relevant in fMRI research in order to answer the hypotheses under investigation. In studies aimed at examining neuronal correlates for psychiatric disorders, patients are usually confronted with disorder-specific triggers in the imaging environment, e.g., by passively viewing pictures designed to evoke symptom-related emotions and cognitions. The BOLD-signal of the fMRI scan, however, is composed of a baseline neuronal activity (comparable to resting-state activity), plus the activity due to visual processes when viewing pictures of any kind, plus the activity representing the neuropathological mechanisms of a disorder. Therefore, most analyses use contrasts of two conditions by subtracting the measured signal when viewing the symptom provoking pictures (condition 1) from the measured signal when viewing neutral pictures (condition 2). The difference (contrast) can then be interpreted as the neuronal activity evoked by specific aspects of condition 2 in comparison to condition 1 (e.g., disgust-provoking stimuli). The same procedure is conducted for all participants, and the averages for each group (patients and controls) are calculated. The difference between patients and controls can then be determined by subtracting the mean contrast of the controls from the mean contrast of the patients. The remaining signal can be interpreted as the pathological activity. Considering this procedure of analysis, it becomes clear that the choice of stimulus

* Corresponding author.
E-mail address: k.viol@salk.at (K. Viol).

https://doi.org/10.1016/j.pscychresns.2018.12.008
Received 31 August 2018; Received in revised form 11 December 2018; Accepted 11 December 2018
Available online 14 December 2018
0925-4927/

material is not to be underestimated and could alter the results considerably.

1.2. Obsessive-Compulsive Disorder (OCD)

Individuals with Obsessive-Compulsive Disorder (OCD) experience a persistent intrusion of unwanted thoughts or images (obsessions) and/or the urge for repetitive, ritualistic behaviors or mental acts (compulsions) that need to be neutralized in order to reduce anxiety or distress (American Psychiatric Association, 2013). With a prevalence of 2–3%, OCD is one of the most common psychiatric diseases and has a serious impact on the quality of life (Crino et al., 2005). The illness is very heterogeneous, i.e. patients experience a wide range of different situations, objects and/or thoughts as triggering. Four general subtypes have been identified: symmetry/ordering, hoarding, washing/cleaning and checking (Mataix-Cols et al., 2004). Still, even within the subtypes, the exact nature of the symptom provoking stimuli can differ immensely.

1.3. Possible stimulus material for OCD

Choosing stimuli for the scanning environment that appropriately address the disorder's heterogeneity is a challenge. Researchers have therefore addressed the cognitive aspects of the illness (for a review see Del Casale et al., 2015), or its emotional side (e.g., Thorsen et al., 2018). Others have adressed the problem by focusing on specific subtypes of OCD, e.g., showing disgusting pictures to a sample of patients with fear of contamination (washing subtype, e.g., Shapira et al., 2003). After Mataix-Cols and his co-workers published their standardized Maudsley Obsessive-Compulsive Stimulus Set (MOCSS), many researchers have used the 50 pictures for each subtype category for their studies (Mataix-Cols et al., 2004). Even though the standardization can be seen as a clear advantage to science in terms of reproducibility and validation, the stimulus set was able to provoke mild to moderate OCD symptoms only (Simon et al., 2012). In consequence, many paradigms used some kind of individualization in order to reflect each subject's primary OCD triggers, e.g., individual words related to the symptoms like “door/key/switch” for a patient from the controlling/checking subtype, or – most commonly – individual pictures (e.g., Schienle et al., 2005; Schiepek et al., 2009, 2013; Simon et al., 2012).

1.4. Self-related processing

While individual stimulus sets clearly account for the diversity of OCD phenomenology and the idiosyncrasy of obsessions (Baioui et al., 2013a), one has to take into account that these are classical stimuli used to investigate self-relatedness (Northoff, 2014). In an activation-likelihood-estimation (ALE) meta-analysis, Hu et al. (2016) found several areas to be consistently active in self-related processing, including the cortical midline structure (bilateral anterior cingulate cortex (ACC)/medial frontal gyrus, left precuneus), left middle frontal gyrus, inferior parietal lobule and bilateral superior temporal gyrus.

Some of these regions, especially the ACC and the prefrontal cortex, has also been revealed to be significantly altered in OCD. Despite this obvious possible confound, a direct comparison between the neuronal activation for individual versus standardized stimulus sets has hardly been considered by researchers. Baioui et al. (2013b) used both conditions, but did not conduct a whole-brain analysis and instead used a mask with regions known to be part of the cortico-striatal network model of OCD.

1.5. Hypotheses

In our study, we did not limit the analysis to predefined regions but were hypothesizing that hyperactivation of some of the regions often reported in OCD patients with individual stimuli are due to an overlap with a network for self-referential processes activated by recognition (cortical midline structures including the cingulate cortex and the precuneus, see Cavanna and Trimble, (2006) and Northoff et al., (2006)). This could be a confound in studies using individual compared to neutral pictures only and might explain some of the diverging results in neuronal correlates found for OCD. We also assumed that the two approaches provoked partly different OCD relevant processes and therefore different regional activity as suggested by Baioui et al. (2013a). Furthermore, in comparison to standardized OCD pictures, we expected the individual stimuli to evoke higher neuronal responses in regions central to the OCD etiology, i.e., the cortico-striato-thalamo-cortical circuit including cingulate, insular, and parts of the frontal and parietal cortices (e.g., Schiepek et al., 2011; Del Casale et al., 2015).

2. Methods

2.1. Participants

The sample of this study consisted of 17 inpatients (6 men and 11 women, mean age 43.5 years (SD = 10.7)) from the Christian-Doppler University Hospital, Salzburg, Austria, as well as 17 healthy controls (HC) matched by age and gender. Patients were eligible to participate in the study if obsessive-compulsive disorder was the main illness by clinical judgement based on ICD-10 and DSM-IV criteria and on the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I, First, Spitzer, Miriam, and Williams, 2002). Exclusion criteria consisted of neurological impairment and/or neurological diseases, acute psychosis, substance abuse, and/or suicidality. As commonly found in OCD patients, comorbidities of the sample included depression (8 patients), social phobia (2 patients, in addition to depression) and one each from the schizophrenic spectrum, alcohol and substance abuse (currently abstinent), and posttraumatic stress disorder (PTSD). For results of the psychological assessment see Section 3.1. All but one patient took some kind of antidepressant (mostly SSRI), 7 of them in addition neuroleptics, 3 anticonvulsants, 2 benzodiazepine and 1 lithium. One patient also had to be medicated for high blood pressure, thyroid dysfunction and incontinence. The study was approved by the Ethics Commission Salzburg (Ethikkommission Land Salzburg, No. 415-E/1203/5-2012).

OCD subtypes were determined by their total score on their MOCSS picture rating (see 3.2 *picture rating*). As expected, all patients scored in all categories, confirming prior findings in the literature on the overlap of subtypes (for a review see Rowsell and Francis, 2015). Out of the 17 participants, 11 scored highest in the category *washing*, 3 in *symmetry/ordering*, 1 in *hoarding* and 2 in *checking*.

2.2. Study procedures

As preparation, detailed information on the study was provided and written informed consent was obtained from all participants according to the Declaration of Helsinki. After the acquisition of individual stimulus pictures, a picture rating of the individual and standard MOCSS stimulus pictures was obtained in order to determine the most relevant pictures for each individual that were then shown during the fMRI scan. The scans were realized within the first week of hospitalization and were followed by another picture rating. In addition, all participants filled in the Symptom Checklist-90-R (SCL-90-R, Derogatis et al., 1977; German Version: Gloeckner-Rist and Stieglitz, 2011) and the Beck Depression Inventory II (BDI-II, Beck et al., 1996; German Version: Hautzinger et al., 2009).

The study is part of a larger multi-level longitudinal project with 4-5 fMRI scans during inpatient treatment, accompanied by venipunctures for assessment of several immune and endocrinological parameters, and real-time monitoring of the psychotherapeutic process, aiming at investigating the changes during psychotherapy. Please note that the results reported here focus on the above mentioned hypotheses only and are based on the data acquired at admission to the hospital.

Fig. 1. Exemplary pictures of individual stimulus pictures of OCD patients.

2.3. Stimuli

As mentioned before, our approach to individualize the stimulus pictures goes beyond the selection of individually triggering material, but includes taking photos from the patients' domestic environment. Two members of the study group accompanied each patient to their homes and took pictures of symptom-provoking situations presented by the patient. Exemplary pictures are shown in Fig. 1. Compliance was very high, since the patients themselves confirmed our assumption that the most problematic situations occur at home. The visit was often perceived as part of the therapy.

The standard pictures were taken from the Maudsley Obsessive-Compulsive Stimulus Set (MOCCS, Mataix-Cols et al., 2009), a validated picture set targeting the 4 subgroups of OCD (for examples see Fig. 2). It should be noted that the picture set is based on a dimensional approach, i.e. especially the washing subgroup evokes responses also in healthy controls, but on a lower level (Mataix-Cols et al., 2003).

For creating contrasts, neutral pictures from the International Affective Pictures Set (IAPS, Lang et al., 2008) were used (for examples see Fig. 3). In addition, participants were exposed to pictures from the IAPS-category 'disgust'.

2.4. Picture rating

The procedure of the picture ratings consisted of two parts. The first one aimed at choosing the 40 most triggering pictures for stimulation in the scanner, the second part aimed at collecting psychological data. Ratings were conducted computer-based with the E-Prime 2.0 presentation software (http://www.pstnet.com). First, the concepts of valence and arousal were explained to the patients, followed by a short introduction and training on the software. Then, all photos taken at the domestic settings were displayed on the computer screen and patients rated each picture on a Likert-scale from 1-9 with respect to the dimensions arousal and valence. The same was repeated for the pictures from the MOC stimulus set and the neutral pictures from the IAPS. The inverse value for valence and the value for arousal were added for each picture to obtain a total score and create a ranking, one for individual and one for standardized photos (over all subcategories). The top 40 pictures of each list, i.e. the most triggering ones, were chosen to be shown during the fMRI scan. For the healthy controls, the pictures of their respective patients were used.

In the post-scan ratings, only the pictures shown in the scanner (i.e., the top 40 of each list) were rated again, with a supplementary question on "coping", i.e. how well the participants felt that they could handle the situation shown. 2-sided *t*-tests and ANOVA were calculated for differences in groups and categories; all *p*-values were corrected for false-discovery rates (FDR, Radua and Albajes-Eizagirre, 2010).

2.5. fMRI Data Acquisition

Images were acquired with a 3T Siemens TIM TRIO whole-body scanner (Siemens Symphony, Erlangen, Germany) with a 32-channel head coil. First, a high-resolution scan was acquired for anatomical referencing using a T1-weighted MPRAGE sequence (FoV = : 256 mm, slice thickness = 1.0 mm, TR = 2300 ms, flip angle = 9°, resolution =1x1x1 mm). Functional images were obtained in two sessions with a

Fig. 2. Examples of standardized pictures from the MOCSS (Mataix-Cols et al., 2004).

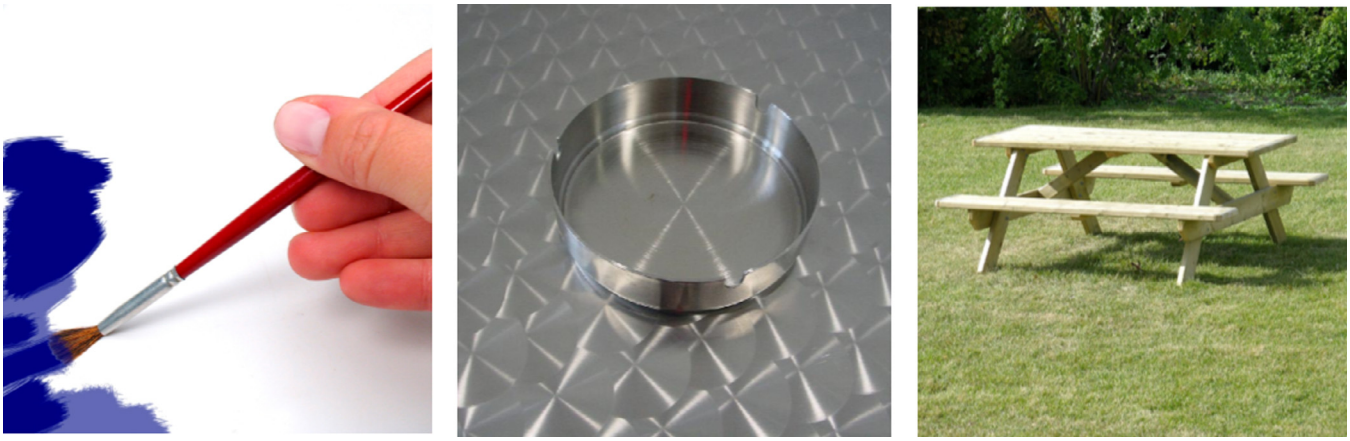

Fig. 3. Examples of neutral pictures from the IAPS (Lang et al., 2008).

short pause in between. A total of 552 volumes were acquired using a T2*-weighted gradient echo EPI with 36 slices (slice thickness = 3 mm, descending slice order, TR = 2250 ms, TE = 30 ms, flip angle = 70°, FoV = 192 mm). The first 6 volumes of each functional session were discarded due to saturation effects (Sarty, 2007), leaving a total of 540 volumes. The 40 most triggering pictures from the categories, as determined by the pre-scan picture rating (see 2.4), plus 40 neutral pictures were presented with the E-Prime 2.0 presentation software (http://www.pstnet.com) as an event-related design in a pseudo-randomized order in 2 sessions (20 pictures of each category in each session). The pictures were shown for 4 seconds each, separated by a fixation cross; the inter-stimulus interval was 2 seconds. The resulting DICOM files were converted to 4D-NIfTI-files with the tools *MRIConvert* (University of Oregon, 2016) and *dcm2nii* (Rorden, 2010).

2.6. Preprocessing

Preprocessing and statistical analyses were performed using the Statistical Parametric Mapping software package SPM12 (Wellcome Department of Cognitive Neurology, London) implemented in Matlab (Mathworks, Inc., Natick, MA, USA, release 13a). Functional images were realigned to the first image, de-spiked with the AFNI 3d-despike function (https://afni.nimh.nih.gov), unwarped, corrected for geometric distortions using the fieldmap of each participant, and slice time corrected.

The high resolution structural T1-weighted image of each participant was processed and normalized with the CAT12 toolbox (http://dbm.neuro.uni-jena.de/cat) using default settings. Each structural image was segmented into gray matter, white matter and CSF, and denoised, then warped into MNI space by registration to the DARTEL template provided by the CAT12 toolbox via the high-dimensional DARTEL registration algorithm (Ashburner, 2007). Based on these steps, a skull stripped version of each image in native space was created. To normalize functional images into MNI space, the functional images were coregistered to the skull stripped structural image and the parameters from the DARTEL registration were used to warp the functional images, which were resampled to 3x3x3 mm voxels and smoothed with a 6 mm FWHM Gaussian kernel. The quality of the preprocessing was checked using the tools *BXH* (Duke University, 2014) and *tsdiffana* (University of Cambridge, 2009).

2.7. Model specifications

Since SPM uses a mass-univariate approach, the effect of the conditions were modeled for each voxel with the general linear model (Kiebel and Holmes, 2008). The movement parameters gained from the realignment procedure during preprocessing were used as regressors. Corresponding to the 4 categories of pictures shown during scanning, the four conditions “Individual OCD pictures (OCD_Ind)”, “Standard OCD pictures (OCD_MOCSS)”, “Disgust (Disgust)” and “Neutral (Neutral) were modeled. The effects of the OCD pictures were investigated by calculating the *t*-contrasts “OCD_Ind > Neutral”, “OCD_MOCSS > Neutral” and “OCD_Ind > OCD_MOCSS” for each participant. These contrasts were then used to calculate two-sample *t*-tests on the group level.

In order to illustrate the differences in activation of the 7 most relevant regions (i.e., with voxels that survived FWE-correction on peak-level, see Table 5) between groups, the eigenvariates were calculated separately for each participant for both individual and neutral pictures. The eigenvariates were extracted using SPM's inbuilt functionality by specifying a sphere with r = 6 mm around the peak voxels and adjusting for effects of interest.

3. Results

3.1. Psychological Assessment

The psychological assessment of patients and controls confirms the clinically relevant symptoms of the patients and the mental health of the controls (Table 1). The mean of 26.7 (*SD* = 8.8) on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS, Goodman et al., 1989; German version: Hand and Buettner-Westphal, 1991) ranks the sample in the

Table 1
Arithmetic means (standard deviation) and *p*-values confirm significant differences in the psychological assessments of patients and controls. Ranges: Y-BOCS: 0–40; Beck Depression Inventory (BDI-II): 0–63; Symptom Checklist (SCL-90-R), scaled values: 0–4.

Psychological assessment

Questionnaire	Patients	Controls	*p*
Y-BOCS			
Total	26.7 (8.8)	n.a.	
BDI-II			
Total	29 (9.4)	1.2 (1.5)	< 0.001
SCL-90-R			
Somatization	1.1 (0.7)	0.2 (0.3)	< 0.001
Obsessive-Compulsive	2.4 (0.8)	0.1 (0.2)	< 0.001
Interpersonal sensitivity	1.9 (0.9)	0.1 (0.1)	< 0.001
Depression	2.1 (0.6)	0.1 (0.1)	< 0.001
Anxiety	1.5 (0.8)	0.1 (0.2)	< 0.001
Hostility	0.9 (0.8)	0.1 (0.2)	0.001
Phobic anxiety	1.2 (0.8)	0.0 (0.0)	< 0.001
Paranoid ideation	1.4 (0.7)	0.1 (0.1)	< 0.001
Psychoticism	1.0 (0.7)	0.0 (0.1)	< 0.001
Additional items	1.6 (0.9)	0.1 (0.1)	< 0.001

Table 2
Arithmetic mean values of the picture rating for all stimulus categories for valence, arousal and ability to cope. In brackets: *SD. p: p*-values (FDR-corrected) of 2-sided *t*-test with H_0: mean (patients) = mean (controls).

Post-scan picture ratings: significance between groups			
Stimulus	Patients	Controls	*p*
Individual OCD			
Valence	2.50 (1.04)	5.30 (1.03)	< 0.0001*
Arousal	6.96 (1.80)	2.14 (1.39)	< 0.0001*
Coping	3.32 (1.96)	8.17 (1.34)	< 0.0001*
MOCSS OCD			
Valence	2.94 (.86)	4.87 (.85)	< 0.0001*
Arousal	6.21 (1.88)	2.53 (1.59)	< 0.0001*
Coping	4.5 (2.14)	7.88 (1.56)	< 0.0001*
Disgust			
Valence	3.08 (1.69)	3.51 (1.18)	0.48
Arousal	5.92 (2.09)	3.71 (2.47)	0.03*
Coping	4.63 (2.34)	6.85 (2.44)	0.03*
Neutral			
Valence	6.72 (1.33)	6.59 (1.05)	0.75
Arousal	2.38 (1.11)	1.65 (.84)	0.08
Coping	8.15 (.83)	8.57 (.67)	0.17

middle to upper range of OCD symptom severity. Patients rated their strains significantly higher than controls on the BDI-II and on all subscales of the SCL-90-R. Next to the obsessive-compulsive subscale, depression was rated highest by the patients.

3.2. Picture Ratings

3.2.1. Comparison between groups

The pictures that were finally chosen and used during the scanning procedure were rated again after the scan including the question "ability to cope". As expected, individual and OCD-pictures were perceived significantly different by patients and controls in all dimensions (i.e. valence, arousal and coping, see Table 2). Neutral pictures were perceived comparably.

3.2.2. Post-scan ratings: comparison between categories

Furthermore, we tested for significant differences between the categories within each group. For patients, Table 3 shows that neutral pictures are perceived clearly different to all other categories in all dimensions. Perception of individual OCD-pictures was also significantly different in all dimensions compared to the standardized pictures, but not to the disgusting pictures. Also, the difference between standardized and disgusting pictures was not significant.

The ratings of the controls were significantly different between all categories for all dimensions apart from the ability to cope, which was rated comparable for individual and neutral pictures (Table 3).

Table 3
Significant differences between the categories (*p*-values, FDR-corrected) for paired *t*-test (2-sided).

Post-scan picture ratings: Significance between categories						
	I-M	I-D	I-N	M-D	M-N	D-N
Patients						
Valence	0.03*	0.39	0.00*	0.84	<0.01*	<0.01*
Arousal	0.01*	0.18	0.00*	0.73	<0.01*	<0.01*
Coping	0.01*	0.15	0.00*	0.85	<0.01*	<0.01*
Controls						
Valence	< 0.01*	< 0.01*	< 0.01*	< 0.01*	< 0.01*	< 0.01*
Arousal	0.01*	< 0.01*	0.03*	< 0.01*	< 0.01*	< 0.01*
Coping	0.01*	< 0.01*	0.07	< 0.01*	0.01*	< 0.01*

I: individual OCD-pictures, M: MOCSS OCD pictures, D: disgusting pictures, N: neutral pictures.
* $p < 0.05$.

Table 4
Results of the ANOVA for the picture rating for the three dimensions.

	F	*df*	*p*	η_p^2
Valence	35.38	7	< 0.001	0.66
Group	40.10	1	< 0.001	0.24
Category	57.71	3	< 0.001	0.58
Group*category	11.49	3	< 0.001	0.21
Arousal	25.68	7	< 0.001	0.58
Group	94.27	1	< 0.001	0.42
Category	19.35	3	< 0.001	0.31
Group*category	9.14	3	< 0.001	0.18
Coping	22.62	7	< 0.001	0.55
Group	79.41	1	< 0.001	0.38
Category	16.90	3	< 0.001	0.28
Group*category	9.41	3	< 0.001	0.18

A univariate ANOVA with the factors "group" and "category" confirmed the significance of the differences (Table 4; see Nieuwenhuis et al., 2011).

All factors and the interaction between group and category were significant.

3.2.3. Variability within groups

In Fig. 4, the results are displayed in boxplots in order to show the variability within the groups. Arousal and coping reveals the most specific reactions (within the negative stimuli) for the individualized stimuli for both patients and controls, while valence was most specific for the standardized pictures in both groups.

3.3. Brain imaging data

The anatomical regions were determined by the Anatomy Toolbox implemented in SPM (Eickhoff et al., 2005).

3.3.1. OCD-stimuli vs. neutral pictures

First, we were interested in the differences between both OCD-stimuli sets compared to neutral pictures. The individual pictures revealed a group difference in several clusters, including the cingulate cortex, insula, hippocampus, middle/precentral gyrus, and superior/inferior parietal lobe (Fig. 5 and Table 5). Concerning the expected activation of the cortico-striato-thalamic network of OCD, no group difference was found for the thalamus or the striatum. For the standard OCD stimulus set (MOCSS), no group difference was found. Since this was unexpected and contradicting the results from the literature, we lowered the threshold to $p < 0.001$ without correction for false-positive results. At this level, group differences were found in the left inferior parietal and the right superior frontal gyrus (note that these regions were also significant for the individual pictures at the respective level of significance, i.e., the standard pictures did not activate any additional regions). Only when lowering the threshold even further to $p < 0.005$ uncorrected, activation was found for the MOCSS for the left hippocampus, bilateral middle frontal gyrus, bilateral precuneus, and left superior parietal cortex. However, no group difference was found with this stimulus set for the cluster including the anterior and posterior cingulate cortex/supplementary motor cortex, and the insula. It should be noted again that these results have to be interpreted with great caution due to the missing correction for false-positives. When checking for controls > patients, no significant activation was found for neither the individual pictures nor for the standardized pictures for $p < 0.05$ (FWE).

The contrast "OCD_Ind. vs. Neutral" is illustrated in Fig. 6 by the eigenvariates (interpretable as the height of the neuronal activation) for both groups and both conditions.

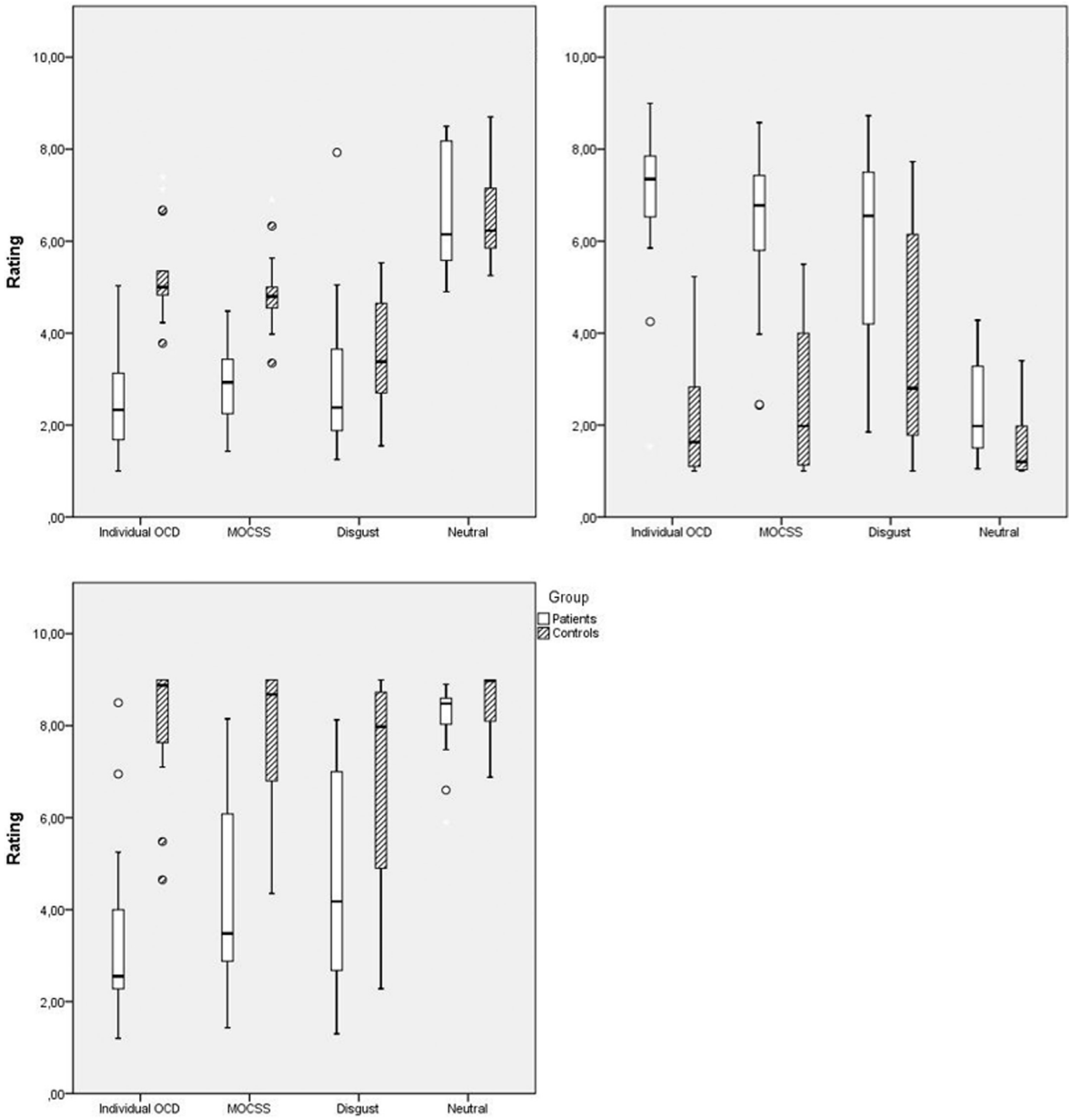

Fig. 4. Boxplots of the picture rating. The pictures were rated for valence (top left), arousal (top right) and coping (bottom). 50% of the answers are within the boxes, with the median marked as a horizontal line. The upper and lower 25% are indicated by the whiskers.

3.3.2. Individual vs. standardized OCD-stimuli

While Table 5 shows a listed comparison of the two conditions, the statistically significant difference between individual and standardized pictures was calculated using the contrast "OCD_Ind > OCD_MOCSS". The result for patients > controls reveals the precuneus (left and right) as the region with highest alteration in neuronal activity (Table 6). For $p < 0.001$ (uncorr.), also the other regions with high differences in significance from Table 5 become significant, especially regions of the cortical midline-structures like the ACC, MCC and the supplementary motor cortex (SMC). Both contrasts are depicted in Fig. 7.

For controls > patients, no significant activation was found for $p < 0.05$ (FWE) on peak- or cluster level.

It should be mentioned that considerable activation was detected in voxels assigned to white matter (corpus callosum). This phenomenon has been reported before (Mazerolle et al., 2010) and is still an open research question.

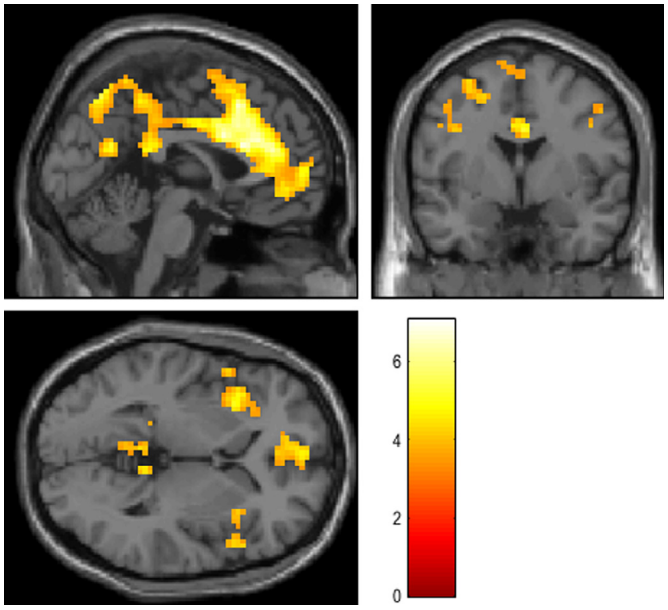

Fig. 5. Heightened activation for "OCD_Ind > Neutral" for patients > controls ($p < 0.001$ on peak-level with FWE cluster correction of $p < 0.05$).

Table 5
Brain regions (clusters) with increased activations for patients > controls for contrast "OCD_Ind > Neutral".

Brain region(s)	L/R	*x*	*y*	*z*	*T*	k
ACC/SMC	L	−3	17	37	6.56**	132
	-	0	17	46	6.56**	
	R	6	26	25	7.06**	
Hippocampus	L	−30	−34	−8	4.96*	52
Insula	L	−39	14	−5	6.65**	19
	R	33	17	−11	6.36**	6
MFG/PrG	L	−45	5	37	4.48*	69
	R	45	8	43	4.96*	58
PCC	L	−3	−46	10	6.16**	3
Precuneus	L	−12	−61	16	6.17**	4
SPL/IPL	L	−36	−55	49	6.17**	7
	R	51	−34	49	4.05*	65

k: number of significant voxels within the cluster for the respective threshold. ACC: anterior cingulate cortex, IPL: inferior parietal lobe, MFG: middle frontal gyrus, PCC: posterior cingulate cortex, PrG: precentral gyrus, SMC: supplementary motor cortex, SPL: superior parietal lobe.

* $p < 0.001$ on peak-level with $p < 0.05$ FWE-corrected on cluster-level,

** $p < 0.05$ FWE corrected on peak-level.

4. Discussion

4.1. Individual pictures are rated most relevant for OCD patients

As expected, the differences between groups in the picture ratings were very clear for the individual and standardized OCD-specific pictures in all three dimensions (Table 2). The significant difference between the categories "individual" and "standardized" OCD-pictures (Table 3) confirm prior findings on the enhanced psychological reactivity of OCD patients to individually tailored pictures (e.g., Schienle et al., 2005; Baioui et al., 2013b; Schiepek et al., 2013). The fact that the neutral pictures are indeed rated as neutral by the OCD patients (Tables 2 and 3) is an important prerequisite for creating meaningful contrasts, since OCD triggers are usually objects considered as "normal" by healthy controls.

The evaluation of the specificity of the categories (Table 3) for the patients showed clear differences for all categories compared to neutral pictures, and to a lesser extend also for the contrast "individual versus standardized" pictures, but neither between individual and disgusting nor between standardized and disgusting pictures. At first glance, one could conclude that disgusting pictures are just as suitable as stimuli as individual pictures. When interested in group differences, however, this does not hold true for the valence, as shown in Table 2. The only result not expected is the significant difference between individual and neutral pictures for valence and arousal for the controls. This might be because of the patients' choice of pictures with toilets, dirt etc., which of course are less pleasant than neutral pictures for healthy individuals, too.

4.2. Enhanced neuronal activity for individual stimuli

The aim of this study was to investigate differences in the activation of an individual compared to a standardized stimulus set. While the individual pictures were able to reveal neuronal activation in regions commonly reported in fMRI-studies of OCD patients (e.g., Schiepek et al., 2011; Del Casale et al., 2015), this was not the case for the standardized Maudsley Obsessive-Compulsive Stimulus Set. It seems like – in accordance with the picture rating – the enhanced psychological reaction is reflected by a heightened neuronal activity in the individual pictures. Concerning the missing difference in activation when corrected for false-positives for the standardized pictures between groups, one has to keep in mind that the MOCSS was designed on a dimensional scale, i.e., especially the pictures for the washing subset are also provocative for healthy controls (Mataix-Cols et al., 2004), as confirmed by our picture ratings (Table 3). In contrast, the individual pictures of our sample did not provoke any different neuronal response than the neutral pictures in the control group (not reported), i.e., they were well suited to elicit group differences between patients and controls. The missing activation for the standardized pictures could therefore be due to the fact that the difference between groups is not as strong as in the individual picture set.

4.3. Regions concerned with self-related processes and memory

Another hypothesis concerned the interpretation of Baioui et al. (2013a), who proposed that the two OCD-stimulus sets will elicit responses in different aspects of the pathology. Our results, however, suggest another approach. As reported in the results section, the standardized pictures did not reveal group differences in any additional regions, even when the correction for multiple comparisons was disregarded. Although Baioui et al. do not discuss this possibility, their reported results for the standardized pictures at the level of $p < 0.05$ with FWE correction are limited to one region only (nucleus caudatus), while the individual set detected pathological activation also in additional regions (nucleus accumbens, pallidum). Instead of interpreting the difference in activation as some kind of functional difference, it could well be a matter of effect size.

In contrast, some of the regions found for the individual pictures were not significant for the standard set even at the very loose uncorrected threshold of $p < 0.005$. It therefore seems unlikely that the activation of ACC/PCC/SMC and insula with the individual stimuli only is due to different aspects of OCD symptoms. A more plausible explanation might be that they are active because of effects of recognition. The direct comparison of the two stimuli sets revealed the precuneus as the region with the biggest difference. The precuneus belongs to the associative cortices with numerous connections to other cortical and subcortical regions, thus permits the brain to integrate both external and internal information (Cavanna and Trimble, 2006; Northoff, 2014). In a review study, Cavanna and Trimble categorized the functional correlates of the precuneus found in fMRI and PET studies into the three domains "visuo-spatial imagery", "episodic memory retrieval" and "self-processing". Similar roles can be found for the cingulate cortex (ACC/SMC and PCC), which is known to be part of the cortical midline region responsible for self-referential processes (Northoff, 2014). Also,

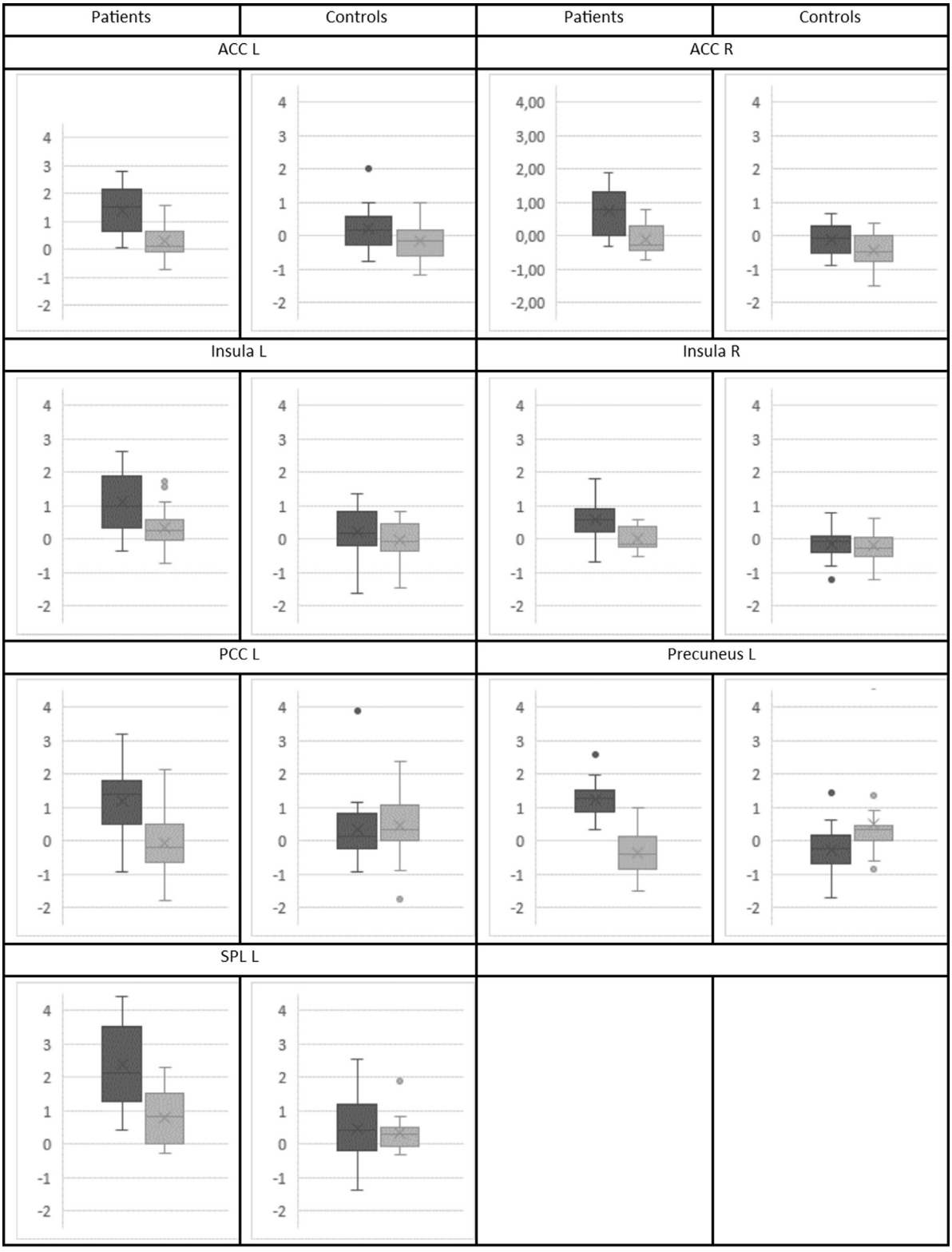

Fig. 6. Eigenvariates for patients and controls for the 7 most relevant brain regions for both individual OCD pictures (dark grey) and neutral pictures (light grey).

the left insula has recently been shown to play an important role in autobiographic memory retrieval (Parlar et al., 2018) and might be additionally activated through its connectivity to the ACC (Chang, 2012). Still, it should be noted that these regions could per se be altered in psychiatric disorders, reflecting an abnormal processing of self-related information and memory retrieval, as shown for depression (Northoff, 2014; Parlar et al., 2018). The paradigm presented here, however, was not aimed at and does not allow differentiating between "normal" and "abnormal" self-processing.

4.4. Limitations

Some limitations have to be taken into consideration with regard to this study. First, a sample size of 17 patients and 17 controls is assumed

Table 6
Contrast "OCD_Ind >. OCD_MOCSS" for patients > controls.

Brain region	L/R	*x*	*y*	*z*	*T*	k
ACC	R	9	17	22	6.70*	291
MCC/SMC	R	3	11	31	6.59*	119
		0	17	49	4.99*	
MFG/PrG	R	48	8	46	5.03*	49
		54	5	40	4.87*	
N. Caudatus/Thalamus	L	−9	8	1	5.72*	53
		−12	−4	1	4.95*	
Precuneus	L	−12	−61	19	9.09**	18
	R	9	−61	25	8.01**	7
Precuneus/MTG/SOG	L	−36	−76	34	6.48*	102
		−42	−76	22	5.36*	
		−30	−82	28	4.43*	
	R	36	−76	34	4.74*	99
		42	−79	16	4.69*	
		42	−67	16	4.56*	
SPL/IPL	R	39	−58	55	4.51*	171
		39	−40	43	5.37*	

k: number of significant voxels within the cluster for the respective threshold. ACC: anterior cingulate cortex, IPL: inferior parietal lobe, MCC: middle cingulate cortex, MFG: middle frontal gyrus, MTG: middle temporal gyrus, PrG: precentral gyrus, SMC: supplementary motor cortex, SOG: superior occipital gyrus, SPL: superior parietal lobe.

* $p < 0.001$ on peak-level with $p < 0.05$ FWE-corrected on cluster-level,

** $p < 0.05$ FWE corrected on peak-level.

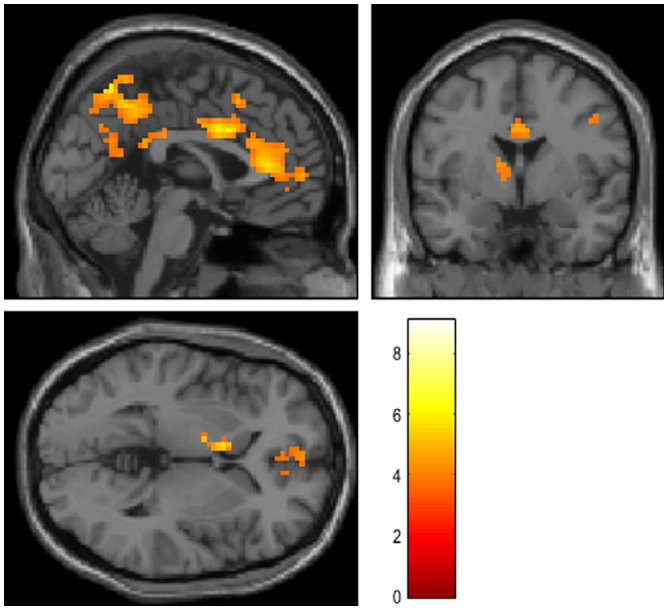

Fig. 7. The contrast "OCD_Ind > OCD_MOCSS" for patients > controls reveals highest activation in the left and right precuneus ($p < 0.001$ on peak-level with FWE cluster correction of $p < 0.05$).

to detect large effects only (Carp, 2012). However, the same author found the median in his review of 234 fMRI studies to be 14.75 for two-group analyses. Although this should not be an excuse for limited statistical power, bigger sample sizes hardly seem to be practically feasible (note that the results presented here are part of a longitudinal study with four to five measurements per participant). Second, the patients were not medication-naïve. Even though psychotropic drugs are specifically designed to alter neuronal activity, it can be assumed that – if the patient still meets the criteria for OCD – the drug was not able to change the disease-specific activation to an extend that normalized the brain function. Third, comorbidities, especially with major depressive disorder, are common in OCD (Schiepek et al., 2011). In consequence, it cannot be excluded that some of the pictures – though specifically designed to provoke OCD symptoms – also provoked altered neuronal activation due to a comorbidity in depression.

To conclude, the study confirms the enhanced psychological and neuronal reactivity of OCD pictures when confronted with individual stimuli compared to standardized stimuli and thereby stresses and confirms the advantages of individually tailored symptom provocation in fMRI. Only when choosing stimuli that appropriately address the unique patterns of symptom manifestation in patients, brain regions were significant with family-wise error correction applied.

When using individual stimuli in fMRI, one yet has to take into account that validity might be affected when using these stimuli only, since the aspect of recognition cannot be subtracted by contrasts if the patients' stimuli are used for the control as well, for whom they are unknown. As a result, parts of the self-referential network were significant, too, and could easily be misinterpreted as neuronal correlate of the illness under consideration.

4.5. Future research

An idiographic, individualized approach should also be considered for other studies, especially with a clinical questions at hand, to account for the considerable intra-individual variation in neuronal activity. Using such stimuli would be an important step towards replicability and validity of fMRI results, as they are able to detect effects that would have been discarded when using the standard stimulus set only. However, it is important to use individual pictures in the neutral condition, too, so that the overlap with processes of recognition and self-reference will be eliminated. Another approach to enhanced effects while avoiding this confound might be given by a standardized set of stimuli that can be individualized by choosing the most triggering images, as proposed by Simon et al. (2012).

Author's Contributions

KV analyzed the data and wrote the manuscript. BA and AK took the individual pictures with the patients at their homes, conducted the psychological tests and interviews and realized the picture ratings. MK set up the fMRI procedure and helped analyzing the data. HS advised on the statistical analysis of the picture ratings. EMR realized the fMRI scans. SSY and LK prepared the scripts for fMRI analyses. BKS and BSS recruited the participants and gave information about the study. WA supervised the study. GS designed and supervised the study.

Declaration of competing interests

All authors declare no competing interests.

References

American Psychiatric Association, 2013. fifth ed. American Psychiatric Association, Washington, DC.

Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. NeuroImage 38 (1), 95–113. https://doi.org/10.1016/j.neuroimage.2007.07.007.

Baioui, A., Pilgramm, J., Kagerer, S., Walter, B., Vaitl, D., Stark, R., 2013a. Neural correlates of symptom reduction after CBT in obsessive-compulsive washers - an fMRI symptom provocation study. J. Obsess-Compuls. Rel. 3, 322–330. https://doi.org/10.1016/j.jocrd.2013.04.006.

Baioui, A., Pilgramm, J., Merz, C.J., Walter, B., Vaitl, D., Stark, R., 2013b. Neural response in obsessive-compulsive washers depends on individual fit of triggers. Front. Hum. Neurosci. 7, 143. https://doi.org/10.3389/fnhum.2013.00143.

Beck, A.T., Steer, R.A., Brown, G.K., 1996. Beck depression inventory-II. PsycTESTS dataset. American Psychological Association. https://doi.org/10.1037/t00742-000.

Carp, J., 2012. The secret lives of experiments: methods reporting in the fMRI literature. NeuroImage 63, 289–300.

Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129, 564–583. https://doi.org/10.1093/brain/awl004.

Chang, L.J., 2012. Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference. Cereb. Cortex 23 (3), 739–749. https://doi.org/10.1093/cercor/bhs065.

Crino, R., Slade, T., Andrews, G., 2005. The changing prevalence and severity of

obsessive-compulsive disorder criteria from DSM-III to DSM-IV. Am. J. Psychiatry 162 (5), 876–882. https://doi.org/10.1176/appi.ajp.162.5.876.
Del Casale, A., Rapinesi, C., Kotzalidis, G.D., De Rossi, P., Curto, M., Janiri, D., et al., 2015. Executive functions in obsessive–compulsive disorder: an activation likelihood estimate meta-analysis of fMRI studies. World J. Biol. Psychiatry 17 (5), 378–393. https://doi.org/10.3109/15622975.2015.1102323.
Derogatis, L.R., Lipman, R.S., Covi, L., 1977. SCL-90. Administration, Scoring and Procedures Manual-I for the R (Revised) Version and Other Instruments of the Psychopathology Rating Scales Series. Johns Hopkins University School of Medicine, Chicago.
Duke University BXH/XCEDE Tools. Retrieved from Brain Imaging and Analysis Center: https://wiki.biac.duke.edu/biac:xmlheader (accessed 5 December 2018).
Eickhoff, S., Stephan, K.E., Mohlberg, H., Grefkes, C., Fink, G.R., Amunts, K., et al., 2005. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage 25 (4), 1325–1335.
First, M.B., Spitzer, R.L., Miriam, G., Williams, J.B., 2002. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, research version, non-patient edition. Biometrics Research, New York State Psychiatric Institute, New York.
Gloeckner-Rist, A., Stieglitz, R.-D., 2011. SCL-90-R – Die Symptom-Checkliste von L. R. Derogatis (Deutsche Version). [SCL-90-R - The symptom checklist by L. R. Derogatis (German version)]. Psychol. Rundsch. 63, 73–75. https://doi.org/10.1026/0033-3042/a000103.
Goodman, W.K., Price, L.H., Rasmussen, S.A., Mazure, C., Fleischmann, R.L., Hill, C.L., et al., 1989. Yale-Brown obsessive compulsive scale (Y-BOCS). Arch. Gen. Psychiat. 46, 1006–1011.
Hand, I., Buettner-Westphal, H., 1991. Die Yale-Brown obsessive compulsive scale (Y-BOCS) [The Yale-Brown obsessive compulsive scale (Y-BOCS)]. Verhaltenstherapie 1, 223–225.
Hautzinger, M., Keller, F., Kuehner, C., 2009. BDI-II. Beck-Depressions-Inventar, second ed. Pearson Assessment, Frankfurt Revision.
Hu, C., Di, X., Eickhoff, S.B., Zhang, M., Peng, K., Guo, H., et al., 2016. Distinct and common aspects of physical and psychological self-representation in the brain: a meta-analysis of self-bias in facial and self-referential judgements. Neurosci. Biobehav. R. 61, 197–207. https://doi.org/10.1016/j.neubiorev.2015.12.003.
Kiebel, S.J., Holmes, A.P., 2008. The general linear model. In: Friston, K.J. (Ed.), Statistical Parametric Mapping. Elsevier Acad. Press, Amsterdam, pp. 101–125.
Lang, P.J., Bradley, M.M., Cuthbert, B.N., 2008. International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual. Tech. Rep. A-8. University of Florida, Gainesville.
Mataix-Cols, D., Cullen, S., Lange, K., Zelaya, F., Andrew, C., Amaro, E., et al., 2003. Neural correlates of anxiety associated with obsessive-compulsive symptom dimensions in normal volunteers. Biol. Psychiat. 53 (6), 482–493. https://doi.org/10.1016/S0006-3223(02)01504-4.
Mataix-Cols, D., Lawrence, N.S., Wooderson, S., Speckens, A., Phillips, M.L., 2009. The Maudsley obsessive–compulsive stimuli set: validation of a standardized paradigm for symptom-specific provocation in obsessive–compulsive disorder. Psychiat. Res. 168 (3), 238–241.
Mataix-Cols, D., Wooderson, S., Lawrence, N., Brammer, M.J., Speckens, A., Phillips, M.L., 2004. Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. Arch. Gen. Psychiatry 61 (6), 564–576. https://doi.org/10.1001/archpsyc.61.6.564.
Mazerolle, E.L., Beyea, S.D., Gawryluk, J.R., Brewer, K.D., Bowen, C.V., D'Arcy, R.N., 2010. Confirming white matter fMRI activation in the corpus callosum: co-localization with DTI tractography. Neuroimage 50 (2), 616–621. https://doi.org/10.1016/j.neuroimage.2009.12.102.
Nieuwenhuis, S., Forstmann, B.U., Wagenmakers, E.-J., 2011. Erroneous analyses of interactions in neuroscience: a problem of significance. Nat. Neurosci. 14 (9), 1105–1107. https://doi.org/10.1038/nn.2886.
Northoff, G., 2014. How is our self altered in psychiatric disorders? A neurophenomenal approach to psychopathological symptoms. Psychopathology 47 (6), 365–376. https://doi.org/10.1159/000363351.
Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., Panksepp, J., 2006. Self-referential processing in our brain – a meta-analysis of imaging studies on the self. Neuroimage 31 (1), 440–457. https://doi.org/10.1016/j.neuroimage.2005.12.002.
Parlar, M., Densmore, M., Hall, G.B., Lanius, R., McKinnon, M.C., 2018. Neural and behavioural correlates of autobiographical memory retrieval in patients with major depressive disorder and a history of trauma exposure. Neuropsychologia 110, 148–158. https://doi.org/10.1016/j.neuropsychologia.2017.07.004.
Radua, J., Albajes-Eizagirre, A, 2010. FDR online calculator. Retrieved from Seed-based d-Mapping: https://www.sdmproject.com/utilities/?show=FDR (accessed 5 December 2018).
Rorden, C, 2010. dcm2nii [Software]. University of South Carolina. Retrieved from. http://www.mccauslandcenter.sc.edu/crnl/tools (accessed 5 December 2018).
Rowsell, M., Francis, S.E., 2015. OCD subtypes: which, if any, are valid? Clin. Psychol. Sci. Pr. 22 (4), 414–435. https://doi.org/10.1111/cpsp.12130.
Sarty, G.E., 2007. Computing brain activity maps from fMRI time-series images. University Press, Cambridge.
Schienle, A., Schäfer, A., Stark, R., Walter, B., Vaitl, D., 2005. Neural responses of OCD patients towards disorder-relevant, generally disgust-inducing and fear-inducing pictures. Int. J. Psychophysiol. 57 (1), 69–77. https://doi.org/10.1016/j.ijpsycho.2004.12.013.
Schiepek, G., Karch, S., Tominschek, I., Pogarell, O., 2011. Zwangsstörungen [Obsessive-compulsive disorders]. In: Schiepek, G. (Ed.), Neurobiologie der Psychotherapie [Neurobiology of psychotherapy]. Schattauer, Stuttgart/ Germany, pp. 406–432.
Schiepek, G., Tominschek, I., Heinzel, S., Aigner, M., Dold, M., Unger, A., et al., 2013. Discontinuous patterns of brain activation in the psychotherapy process of obsessive-compulsive disorder: converging results from repeated fMRI and daily self-reports. PLoS One 8 (8), e71863. https://doi.org/10.1371/journal.pone.0071863.
Schiepek, G., Tominschek, I., Karch, S., Lutz, J., Mulert, C., Meindl, T., et al., 2009. A controlled single case study with repeated fMRI measurements during the treatment of a patient with obsessive-compulsive disorder: testing the nonlinear dynamics approach to psychotherapy. World J. Biol. Psychiatry 10 (4), 658–668.
Shapira, N.A., Liu, Y., He, A.G., Bradley, M.M., Lessig, M.C., James, G.A., et al., 2003. Brain activation by disgust-inducing pictures in obsessive-compulsive disorder. Biol. Psychiatry 54 (7), 751–756. https://doi.org/10.1016/s0006-3223(03)00003-9.
Simon, D., Kischkel, E., Spielberg, R., Kathmann, N., 2012. A pilot study on the validity of using pictures and videos for individualized symptom provocation in obsessive–compulsive disorder. Psychiat. Res. 198 (1), 81–88. https://doi.org/10.1016/j.psychres.2011.12.022.
Thorsen, A.L., Hagland, P., Radua, J., Mataix-Cols, D., Kvale, G., Hansen, B., et al., 2018. Emotional processing in obsessive-compulsive disorder: a systematic review and meta-analysis of 25 functional neuroimaging studies. Biol. Psychiat. 3, 563–571. https://doi.org/10.1016/j.bpsc.2018.01.009.
University of Cambridge. Diagnostics for FMRI. Retrieved from MRC Cognition and Brain Sciences Unit: http://imaging.mrc-cbu.cam.ac.uk/imaging/DataDiagnostics (accessed 5 December 2018).
University of Oregon MRIConvert [Software]. Retrieved from https://lcni.uoregon.edu/downloads/mriconvert/mriconvert-and-mcverter (accessed 5 December 2018).