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Amygdala hyperactivation during symptom provocation in obsessive–compulsive disorder and its modulation by distraction

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ABSTRACT

Anxiety disorders have been linked to a hyperactivated cortico-amygdalar circuitry. Recent findings highlight the amygdala's role in mediating elevated anxiety in obsessive–compulsive disorder (OCD). However, modulation of amygdala hyperactivation by attentional distraction – an effective emotion regulation strategy in healthy individuals – has not yet been examined. While undergoing functional magnetic resonance imaging twenty-one unmedicated OCD patients and 21 controls performed an evaluation and a distraction task during symptom provocation with individually tailored OCD-relevant pictures. To test the specificity of responses, additional aversive and neutral stimuli were included. Significant group-by-picture type interactions were observed within fronto–striato–limbic circuits including the amygdala. In these regions patients showed increased BOLD responses during processing of OCD triggers relative to healthy controls. Amygdala hyperactivation was present across OCD symptom dimensions indicating that it represents a common neural correlate. During distraction, we observed dampening of patients' amygdala hyperactivity to OCD-relevant stimuli. Augmented amygdala involvement in patients during symptom provocation, present across OCD symptom dimensions, might constitute a correlate of fear expression in OCD linking it to other anxiety disorders. Attentional distraction seemed to dampen emotional processing of disorder-relevant stimuli via amygdala downregulation. The clinical impact of this strategy to manage anxiety in OCD should be further elucidated.

1. Introduction

Obsessive–compulsive disorder (OCD) is characterized by unwanted intrusive thoughts (obsessions) and/or repetitive ritualistic behaviors (compulsions), generally performed to relieve distress and anxiety accompanying obsessions. The amygdala shows exaggerated responses in various anxiety disorders, such as post-traumatic stress disorder (PTSD) or phobias (Etkin and Wager, 2007). Imaging studies investigating the neural mechanism underlying OCD symptoms highlight the role of overactive frontostriatal pathways in mediating obsessions. Elevated anxiety caused by these intrusive thoughts has rather been linked to hyperactivity in the anterior cingulate cortex (ACC) than to aberrant amygdala function (Deckersbach et al., 2006). Limited evidence for limbic hypersensitivity has been provided to date (Breiter et al., 1996; Simon et al., 2010) and has solely been assumed for a subgroup of OCD patients with prominent contamination fear (e.g., van den Heuvel et al., 2004). However, we recently provided evidence for amygdala hyperactivation also in a multisymptomatic, unmedicated patient sample, when using individually tailored stimuli (Simon et al., 2010), and by using a symptom provocation paradigm better accounting for rapid onsets and fast attenuation of amygdala responses. Taken together, these studies highlight the role of amygdalocortical, in addition to corticostriatal circuitry, in mediating anxiety in OCD (Milad and Rauch, 2012) that needs to be further elucidated.

Patients' ability to distract themselves from intrusive thoughts, behaviors and accompanying elevated anxiety – and thus regulate amygdala hyperactivity – is essential for functioning in situations when compulsions cannot be performed. Indeed, when requested the use of attentional distraction as coping behavior is an effective technique for managing clinically significant intrusive thoughts (Najmi et al., 2009). Distraction alters emotional processing via attentional shift before elaborate processing of an emotional situation has occurred. While in healthy individuals as well as in patients with mood disorders distraction effectively attenuates emotional processing by down-regulation of amygdala activity (Kanske et al., 2012), amygdala hyperactivation in anxiety disorders is also present under distraction or masking conditions (Rauch et al., 2000; Straube et al., 2011). It has also been demonstrated that the effectiveness of distraction increases with attentional load of the task in healthy individuals

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(Pessoa et al., 2005), whereas phobics show automatic amygdalar engagement independent from attentional load (Straube et al., 2011). Whether amygdala hypersensitivity in OCD resembles this mechanism found in other anxiety disorders has not yet been explored. One OCD symptom provocation study reports amygdala hyperactivity during a distraction task with low attentional load (categorization of indoor or outdoor scene (van den Heuvel et al., 2004)); pointing towards an impaired ability to down-regulate this response through distraction. However, before definite conclusions can be drawn, distraction should be investigated by using a task with higher attentional load.

Our first aim was to confirm findings of frontostriatal and amygdala hyperactivity during provocation with individually tailored OCD-related pictures in a medication-free, multisymptomatic sample of OCD patients. Second, we examined whether amygdala hyperactivity is predicted by OCD symptom dimension scores. Third, we investigated whether distraction damps amygdala hyperactivity to OCD-related stimuli.

2. Materials and methods

2.1. Participants

Twenty-one medication-free patients with OCD (13 females) were recruited from the outpatient clinic at the Humboldt-Universität zu Berlin, Germany. Diagnoses were established using the Structured Clinical Interview for DMS-IV (First et al., 1995). Severity and characteristics of OCD symptoms were assessed with the clinician-rated Yale–Brown Obsessive–Compulsive Scale (Y-BOCS), the Y-BOCS Symptom Checklist (Goodman et al., 1989a; Goodman et al., 1989b) and the Obsessive–Compulsive Inventory—Revised (OCI-R) (Foa et al., 2002). Only patients with a total score of 12 or higher on the Y-BOCS were included in the present study. All patients fulfilled the criteria of OCD at the time of the study. Exclusion criteria were the presence of neurological illness and other major psychiatric disorders. Nine patients had one or more comorbid Axis I disorders comprising major depressive disorder ($n = 4$), generalized anxiety disorder ($n = 1$), panic disorder ($n = 1$), specific phobia ($n = 4$), binge eating disorder ($n = 1$), and social phobia ($n = 1$). Seven patients received cognitive-behavioral therapy at the time of testing (only three had already undergone exposure and response prevention treatment). In addition, twenty-one case-by-case matched healthy controls (HCs; 13 females) entered the analysis (Table 1). Participants furthermore completed the Beck Depression Inventory (BDI-II), the Montgomery–Asberg Depression Rating Scale (MADRS) (Beck et al., 1961; Montgomery and Asberg, 1979) and the State–Trait Anxiety Inventory (STAI) (Spielberger, 1983). Subjects were right-handed, had normal or corrected-to-normal vision and provided written informed consent after complete description of the study protocol, which was approved by the local ethical review board.

2.2. Stimuli and procedure

During scanning participants were exposed to individually tailored OCD-relevant pictures (Simon et al., 2012) as well as generally aversive (Lang et al., 2005) and neutral control stimuli (Fig. 1A). Generally aversive pictures were introduced in order to examine possible hyperresponsivity to these stimuli in OCD patients. Patients and controls evaluated arousal, unpleasantness and anxiety induced by OC, AV and NE pictures one week prior to scanning. Additionally, patients rated the OCD symptoms provoked by each picture (1 = “no” to 9 = “extreme”). Based on these symptom ratings an individualized stimulus set comprising the 12 most relevant OC pictures was created for each patient (Supplementary Table S1) that was also presented to the yoked control subject. All stimuli were carefully matched on visual complexity based on subjective ratings (1 = “low” to 9 = “high”) of an independent sample.

In the scanner, participants performed either a self-referential evaluation or a distracting bar orientation task while viewing pictures, which were presented along with central bars in the picture foreground, either aligned in parallel or not (Fig. 1B). During evaluation, subjects attended to the target stimulus and indicated whether the depicted scene made them feel unpleasant or not by pressing one of two buttons. During distraction, subjects indicated again via button press whether the bars in the foreground of the picture are aligned in parallel or not. This task still constituted a relatively easy task with respect to attentional load but was more challenging than the one used by van den Heuvel et al. (2004) due to the fact that the content of the picture was task-irrelevant and had to be ignored. Since immediate ratings would force participants to concentrate on their emotional response and invoke deeper processing during distraction, we did not request an online rating after each picture. Instead participants provided a mean post-scan rating of unpleasantness for picture type by strategy. The experimental design consisted of two runs containing eighteen blocks each starting with an initial instruction screen indicating the type of condition and six trials of one picture category (OC, AV or NE). Each trial started with a green fixation cross (200 ms) followed by the target picture (1000 ms) and ended with a white fixation cross shown for 2500 ms plus variable inter-trial interval (mean: 530 ms). Block and picture order was pseudo-randomized.

2.3. Data acquisition

Stimuli were presented using Presentation® (Neurobehavioral Systems) and were viewed by means of a mirror system attached to the head coil. In order to reduce head motion, participants' head was immobilized by a vacuum head cushion. Prior to functional runs, 176 anatomical MDEFT slices (Deichmann et al., 2004) were acquired (spatial resolution 1 × 1 × 1 mm, TR = 12.24 ms, TE = 3.56 ms, flip angle = 23°, 256 × 224 matrix) on a 1.5 T Siemens Sonata scanner. A total of 353 whole-brain volumes (T2*-weighted single-shot gradient EPI sequence) were acquired in each of the two runs using the following parameters: TR = 2120 ms, TE = 40 ms, 38 consecutive axial slices, 3 × 3 × 3 mm voxel, flip angle = 90°, FOV = 192 mm, 64 × 64 matrix.

2.4. Data analysis

2.4.1. Self-report and behavioral data

Analysis of ratings and reaction time (RT) was performed using repeated measures analyses of variance (ANOVAs) with a Greenhouse–Geisser correction when necessary. Due to technical problems during response acquisition RT of one patient is missing.

2.4.2. Brain imaging data

Imaging data were analyzed using BrainVoyagerQX (Brain Innovation). The first four volumes of each functional run were discarded to allow for T1 equilibration. Preprocessing included slice-time correction, realignment, motion correction, co-registration, smoothing (8-mm Gaussian kernel), temporal smoothing (high-pass filter: 5 cycles per run) and spatial normalization into the Talairach space (Talairach and Tournoux, 1988).

First, a separate general linear model (GLM) was specified for each subject including parameter estimates of event-related activity at each voxel for each regressor. Movement parameters were included as regressors of no interest. The expected blood oxygenation level-dependent (BOLD)-signal change was modeled by a canonical hemodynamic response function. Contrast images were generated and parameter estimates for the parametric regressors were computed for each individual. Second, the random effects group analysis was then performed on the regression coefficients from the analyses

Table 1
Demographic and clinical characteristics of both groups.

	OCD patients ($N = 21$)		Healthy controls ($N = 21$)		Statistic	
	Mean	SD	Mean	SD	t (df = 40)	p
Education, years	12.1	1.5	12.1	1.5	0.10	0.92
Verbal intelligence	107.3	10.1	110.2	12.4	−0.82	0.42
Age, years	33.1	10.8	33.1	10.1	−0.02	0.99
Illness duration, years	12.1	10.8				
STAI-S[a]	41.8	8.3	28.6	4.8	6.28	<0.001
STAI-T[b]	48.0	8.0	33.9	6.3	6.34	<0.001
BDI-II[c]	12.8	8.8	2.6	3.1	5.00	<0.001
MADRS[d]	8.4	6.3	–			
OCI-R[e]	29.8	10.8	4.2	4.3	10.11	<0.001
Y-BOCS[f]	21.2	6.8	–			

[a] STAI-S = State version of State–Trait Anxiety Inventory.
[b] STAI-T = Trait version of State–Trait Anxiety Inventory.
[c] BDI-II = Beck Depression Inventory II.
[d] MADRS = Montgomery-Asberg Depression Rating Scale.
[e] OCI-R = Obsessive–Compulsive Inventory—Revised.
[f] Y-BOCS = Yale–Brown Obsessive–Compulsive Scale.

for the individual subjects by means of a 3 × 2 × 2 analysis of variance (ANOVA). The three variables were picture type (AV, OC, NE), strategy (evaluation, distraction), and group (OCD, HC). This analysis produced statistical maps of the main effects and interactions. Our main interests were in testing the group-by-picture type and the three-way group-by-strategy-by-picture type interaction in order to test the degree to which OCD-specific responses to OC stimuli change during distraction. The significance threshold was initially set at $p < 0.005$. To correct for multiple comparisons, a spatial clustering operation was then performed using the cluster threshold estimator plugin for BrainVoyagerQX with 1000 Monte Carlo simulations. The minimum cluster size threshold that yielded a false-positive probability of $p < 0.05$ was applied to the statistical maps. Since we had specific hypothesis for the amygdalae, we performed a region of interest (ROI) analysis of these a priori anatomically defined structures (Talairach and Tournoux, 1988) using a significance level of $p < 0.05$ corrected for the specific volume of interest. For each significantly active cluster yielded by the ANOVA, we conducted follow-up analyses to delineate the nature of the main and interaction effects.

Symptom dimension scores of OCD were determined using the Y-BOCS Symptom Checklist (Goodman et al., 1989a) according to a previously described item-based factor-analytic method (Katerberg et al., 2010). Symptoms were coded with 1 when endorsed currently or in the past, and with 0 if the patient never experienced the symptom. The five resulting dimensional scores are: taboo, contamination/cleaning, doubt, rituals/superstitious and hoarding/symmetry. Mean scale scores were computed by summing up item scores and dividing the sum by the total number of items of the respective dimension. This resulted in five scores (ranging from 0 to 1) for each patient. Multiple regression analyses for the OCD group were performed analyzing the prediction of amygdala response to OCD-triggers relative to neutral stimuli ($OC_{evaluation\ +\ distraction} - NE_{evaluation\ +\ distraction}$) by the symptom dimension scores from the Y-BOCS Symptom Checklist.

3. Results

3.1. Clinical characteristics

Most patients were multisymptomatic, reported moderate symptoms, showed symptoms of mild depression (MADRS), and differed significantly from controls on the BDI (Table 1). While groups did not statistically differ with respect to demographic variables, OCD patients reported higher levels of anxiety (STAI).

3.2. Self-report data

Arousal and unpleasantness ratings showed a main effect of picture type (AV = OC > NE; $ps < .001$; for complete F-statistics see Supplementary Fig. S1) group (OCD > HC), and an interaction of group-by-picture type (OCD > HC:OC only). For anxiety ratings also a main effect of picture type (OC > AV > NE; $ps \leq .015$), group (OCD > HC), and an interaction of group-by-picture type was observed (OCD > HC:OC and AV only). Symptom ratings within the OCD group showed a main effect of picture type (OC > AV > NE; $ps \leq .001$). Post-scan unpleasantness ratings confirmed the described effects of picture type and group. The analysis regarding strategy showed a main effect ($F = 73.4$, df = 1,40, $p < .001$, $\eta^2 = .65$; evaluation > distraction) and interaction of picture type-by- strategy ($F = 22.3$, df = 2,80, $p < .001$, $\eta^2 = .36$) due to the fact that only OCD-related and aversive stimuli were rated less unpleasant during distraction ($p < .001$). Overall, these results validated the intended manipulation of affective states.

3.3. Behavioral data

Performance in the distraction task (accuracy overall: 96.7% ± 2.5) revealed a main effect of group ($F = 4.5$, df = 1,39, $p = .041$, $\eta^2 = .10$; OCD mean = 97.5% ± 2.1 > HC mean = 95.9% ± 2.7). Mean accuracy rates were comparable across all picture types. Analysis of RTs revealed a main effect of strategy (evaluation > distraction; see Supplementary Table S2) and picture type (OC = AV > NE; both $ps \leq .001$). Furthermore, a three-way interaction was detected (HC: evaluation > distraction for OC only; $p = .006$).

3.4. Brain imaging data

As noted, our main interest was in statistical tests of group-by-picture type and group-by-picture type-by-strategy interactions. Table 2 summarizes regions showing these significant interactions. Results of the main effect of group, picture type, strategy (see data supplement), and picture type-by-strategy interaction are provided in

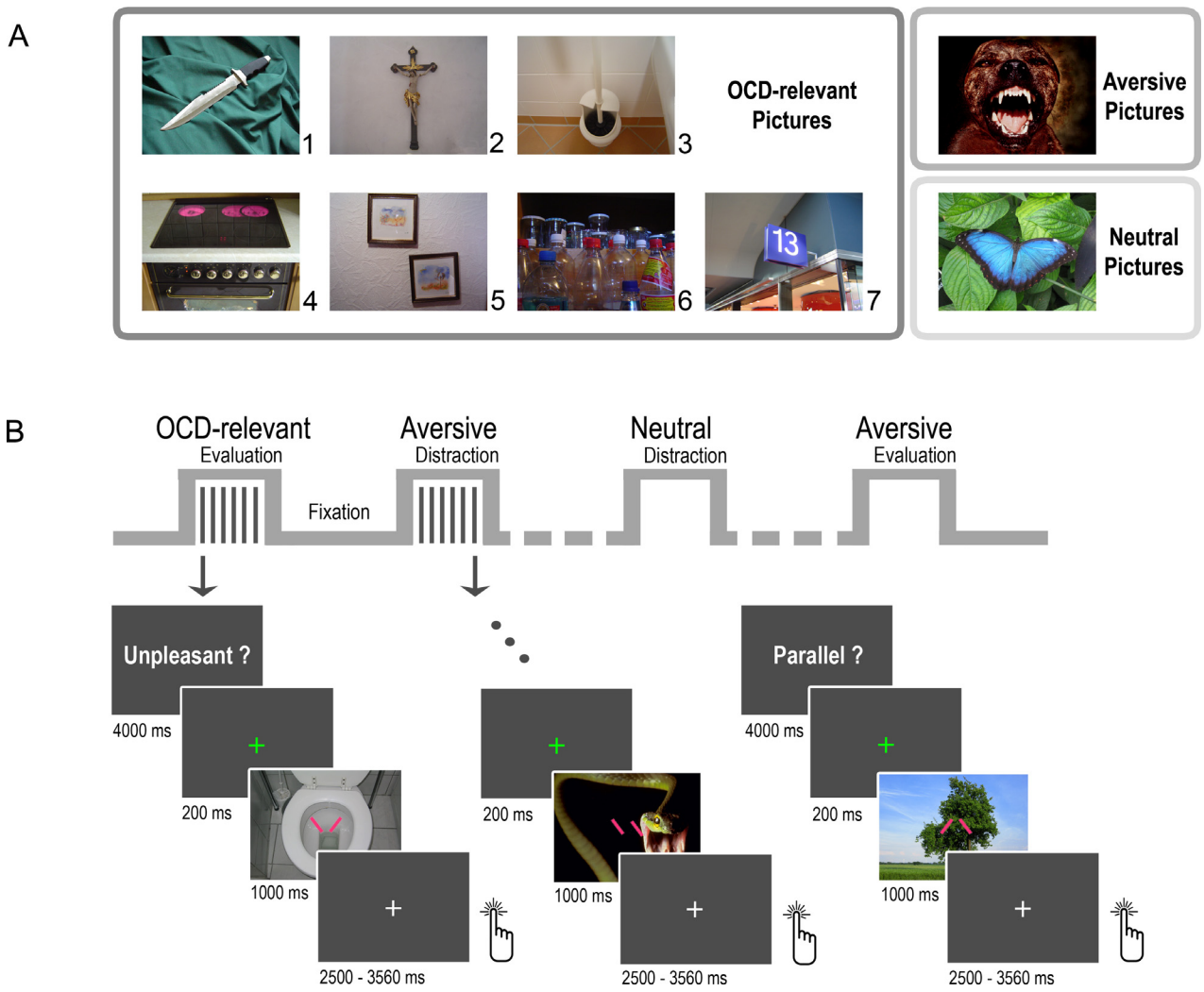

Fig. 1. Stimuli and experimental design. The top panel (A) depicts examples from the stimulus set including OCD-relevant, generally aversive* and neutral pictures. [1]Aggressive obsessions, [2]religious obsessions, [3]contamination/washing, [4]checking, [5]symmetry/ordering, [6]hoarding and [7]counting. *The IAPS identification numbers of the selected pictures are: 1030, 1050, 1070, 1080, 1111, 1113, 1201, 1220, 1300, 1302, 1321, 1930, 1931, 2053, 2692, 2700, 2722, 2752, 2800, 2900, 6020, 9160, 9421, 9440, and 9560. The experimental design (B) consisted of two runs containing eighteen blocks (approximately 32,000 ms) each separated by a fixation condition (14,000 ms). Blocks contained an initial instruction screen (4000 ms) indicating the type of condition ("unpleasant?" vs. "parallel?") and six trials of one picture category (OCD-relevant, aversive or neutral pictures). Each trial started with a green fixation cross (200 ms) followed by the target picture (1000 ms) and ended with a white fixation cross shown for 2500 ms plus variable inter-trial interval (mean: 530 ms). Block and picture order was pseudo-randomized.

Supplementary Table S3. No regions survived correction for multiple comparisons from the group-by-strategy statistical map.

3.4.1. *Group-by-picture type interaction*

Consistent with our predictions, the group-by-picture type interaction identified the amygdala bilaterally (Table 2 and Fig. 2). Further examination of the interaction revealed that for the right amygdala this was due to greater activation to aversive relative to neutral ($p = .043$) and OCD-relevant stimuli ($p = .049$) in healthy subjects only ($F = 3.38$, df = 2,40, $p = .044$). For the left amygdala patients only ($F = 3.61$, df = 2,40, $p = .036$) showed increased activation for OCD-triggers relative to neutral ($p = .043$) and aversive stimuli ($p = .03$). An analysis of covariance (ANCOVA) performed on extracted data with individual trait and state anxiety scores as the covariate revealed that the amygdala group difference for OCD-triggers was independent from anxiety. Moreover, the results of the multiple regression analyses in patients showed that none of the symptom dimensions uniquely predicted amygdala activity to OCD triggers relative to neutral stimuli ($ps = .27$–$.50$). Further regions identified by this interaction were the left thalamus, caudate nucleus, subthalamic nucleus, globus pallidus, middle temporal gyrus, the right OFC, ventrolateral PFC, precuneus/PCC and anterior insula, and bilateral parahippocampal gyri and cuneus. Follow-up analyses revealed that this was due to different patterns of picture type effects in healthy comparison subjects and patients (F range = 3.38–22.58; $p < .03$–$.001$). Namely, in controls increased BOLD responses to aversive relative to neutral/both stimulus categories were observed in the left thalamus, caudate nucleus, subthalamic nucleus, globus pallidus, ventrolateral PFC, anterior insula, right parahippocampal gyrus and bilateral cuneus (p range $< .036$ to $.001$; see Fig. 2 and Supplementary Fig. S2). Patients showed greater responses to OCD-triggers compared to neutral (right cuneus; $p < .001$), aversive (globus pallidus; $p = .019$, OFC; $p = .05$) or both stimulus categories (thalamus, caudate nucleus, subthalamic nucleus, anterior insula, parahippocampal gyri, middle temporal gyrus and precuneus; p range $< .05$ to $.001$). The effect in patients' ventrolateral PFC, however, was due to increased activation to neutral relative to aversive ($p = .007$) and OCD-related stimuli ($p = .013$), whereas controls again showed stronger responses to aversive stimuli relative to both picture categories.

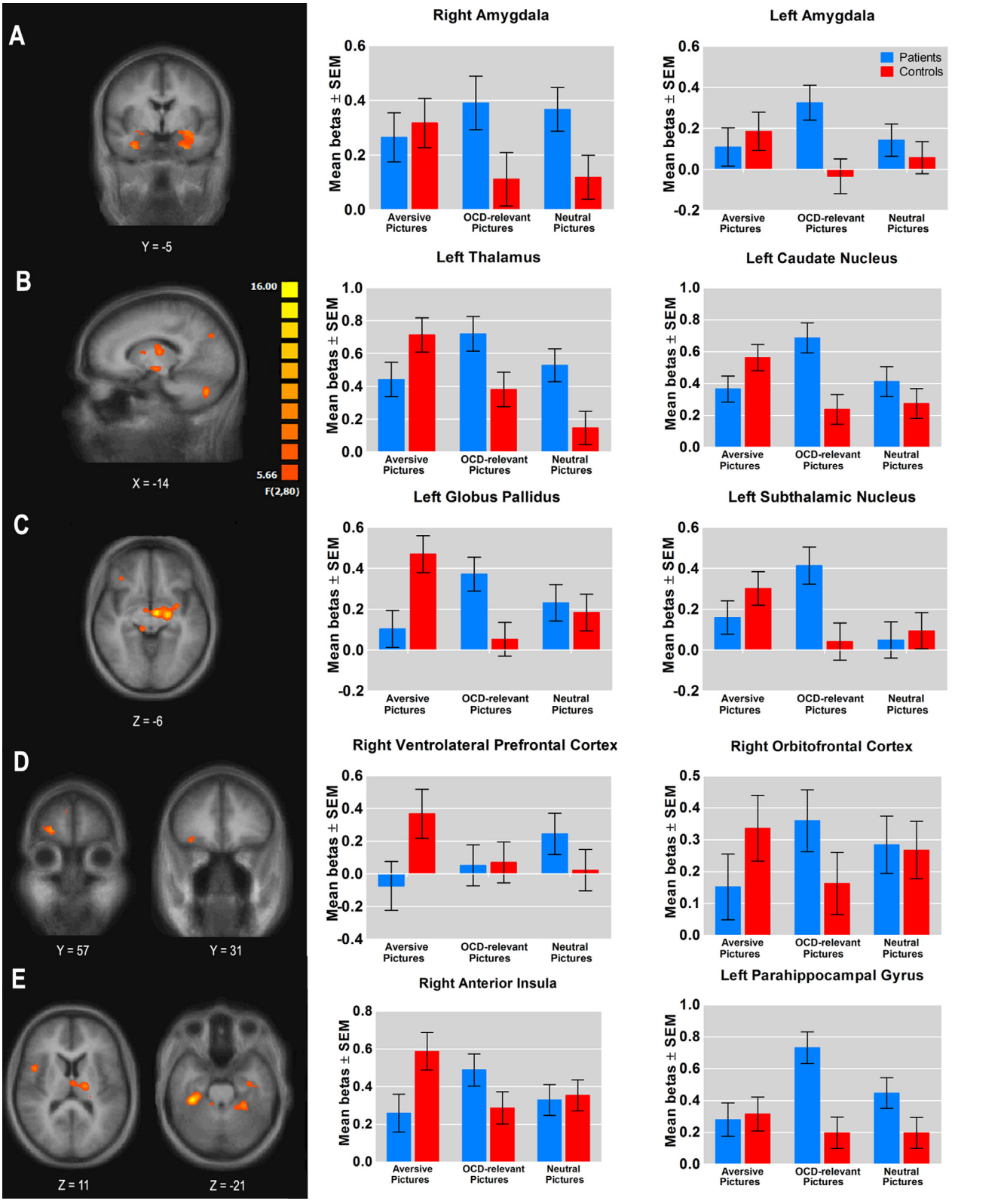

Fig. 2. Group × picture type interaction during individually tailored symptom provocation in 21 unmedicated OCD patients and 21 healthy controls. Blood oxygenation level-dependent (BOLD) responses overlaid on an averaged T1 scan (radiological convention: left = right; $p(cor) < 0.05$; see Table 2) in the amygdala (A), thalamus and caudate nucleus (B), globus pallidus and subthalamic nucleus (C), ventrolateral prefrontal (left panel) and orbitofrontal cortex (right panel) (D), and anterior insula (left panel) and parahippocampal gyri (right panel) (E) were significantly greater during OCD-relevant stimuli compared with aversive and/or neutral control stimuli in OCD patients relative to healthy controls. Plots display parameter estimates and error bars represent standard errors (mean ± SEM).

Table 2
Brain regions demonstrating differential BOLD responses during individually tailored symptom provocation in OCD.

Brain regions[a]	Side	Coordinates: Brodmann area[a]	x	y	z	Volume, mm³	*F* value[b]
Group-by-picture type interaction							
Subcortical							
Thalamus	L		−14	−11	14	1198	10.46
Caudate nucleus/body	L		−15	−11	18	193*	7.93
Subthalamic nucleus	L		−7	−11	−6	274	17.93
Lentiform/globus pallidus	L		−19	−12	−6	260	14.58
Amygdala	R		26	−2	−12	558	8.81
	L		−28	−8	−12	937	9.01
Frontal lobes							
Orbitofrontal cortex	R	47	35	31	−6	162*	7.75
Ventrolateral prefrontal cortex	R	10	26	58	3	517	10.83
Anterior insula	R	13	44	7	12	276	9.43
Temporal lobes							
Parahippocampal gyrus	R	36	35	−29	−21	1182	15.81
	L	27	−22	−32	−1	984	9.11
Middle temporal gyrus	L	19	−37	−80	21	710	9.68
Occipital lobes							
Posterior cingulate cortex/precuneus	R	31	11	−53	27	317	7.99
Cuneus	R	7	11	−68	33	540	9.83
	L	18	−4	−92	21	287	7.94
Group-by-picture type-by-strategy interaction							
Subcortical							
Amygdala	L		−28	−5	−11	108	6.42
Anterior cerebellum	R		8	−56	0	334	9.56
Frontal lobes							
Dorsal anterior cingulate cortex	L	24, 31	−10	−11	45	362	7.65
Parietal lobes							
Insulo-opercular region	L	13, 40	−55	−32	18	455	9.88

[a] According to the Talairach Daemon atlas (http://www.nitrc.org/projects/tal-daemon/).
[b] All activations are effects observed in whole-brain analyses significant at $p < 0.005$ corrected for multiple comparisons p (cor)clusterwise < 0.05
*Significant at $p < 0.005$ uncorrected.

3.4.2. Group-by-picture type-by-strategy interaction

The ROI-driven analysis confirmed a three-way interaction for the left amygdala (Table 2 and Fig. 3) in patients ($F = 5.61$, df = 2,40, $p = .007$). Thus, in patients only detailed evaluation elicited significantly stronger BOLD-response relative to both control conditions and dampening of amygdala activation to OC-triggers occurred during distraction (evaluation > distraction; $p = .001$). This was also the case for neutral ($p = .003$) but not for aversive stimuli. No interaction of picture type and strategy was observed for healthy subjects ($p = .32$). Moreover, whole-brain analysis identified a three-way interaction also in the right cerebellum, left dorsal ACC and postcentral gyrus including the insula (insulo-opercular region). In all regions an interaction of picture type-by-strategy was present for patients only (F range = 6.29–8.11; $p \leq .004$–.001, Supplementary Fig. S3). While no such interaction in healthy subjects occurred in the cerebellum and dorsal ACC it was observed for the insulo-opercular region ($F = 5.36$; $p = .018$) due to stronger activation to neutral stimuli relative to aversive during distraction only ($p < .001$). Similarly to the amygdala, within the insulo-opercular region and dorsal ACC patients showed greater responses to OCD-triggers compared to aversive control stimuli during evaluation only ($ps \leq .011$). In the cerebellum, patients showed an increased response to neutral relative to aversive and OCD-related stimuli during evaluation only ($ps < .003$), while HCs showed no such response.

Further investigation using an analysis of covariance (ANCOVA) procedure to explore the influence of comorbid anxiety and depression using individual trait anxiety and BDI scores as the covariate revealed that all main findings remained significant. Additionally, a post-hoc subsample analysis excluding all OCD patients with comorbid anxiety disorders ($N = 6$) was performed to further explore the impact of comorbidity on the results. As demonstrated by Supplementary Table S4, our key findings including amygdala hyperactivation remained unchanged.

4. Discussion

The present study investigates amygdala hyperactivity during symptom provocation in a multisymptomatic sample of unmedicated patients reporting moderate symptoms. It also aimed at yielding insights into the effectiveness of distraction in dampening this response and thereby the resemblance between OCD and other anxiety disorders.

Consistent with our first hypothesis, we extend previous findings of left-hemispheric amygdala hyperactivation in patients during passive viewing (Simon et al., 2010) to self-referential processing of symptom-related compared to aversive and neutral pictures. This finding was independent from individual anxiety and depression scores. The observed group difference did also correspond to patients' subjective ratings of arousal, unpleasantness, anxiety and symptoms. Using the multidimensional approach (Mataix-cols et al., 2005), we showed that increased amygdala engagement was present across OCD symptom dimensions, indicating that it represents a common, anxiety-related neural response pattern.

The between-group comparison moreover revealed that relative to healthy controls, patients showed increased neural responses for OCD-relevant relative to neutral and aversive pictures in thalamo-basal ganglia circuits (thalamus, caudate nucleus, subthalamic nucleus), areas implicated in emotion (Phillips et al., 2003) (anterior insula, parahippocampal gyrus and middle temporal gyrus) and visual attention (PCC). Compared to aversive stimuli patients additionally showed greater BOLD signal in the globus pallidus and the OFC, and compared to neutral stimuli in a visual attention area (cuneus) during viewing of OCD triggers.

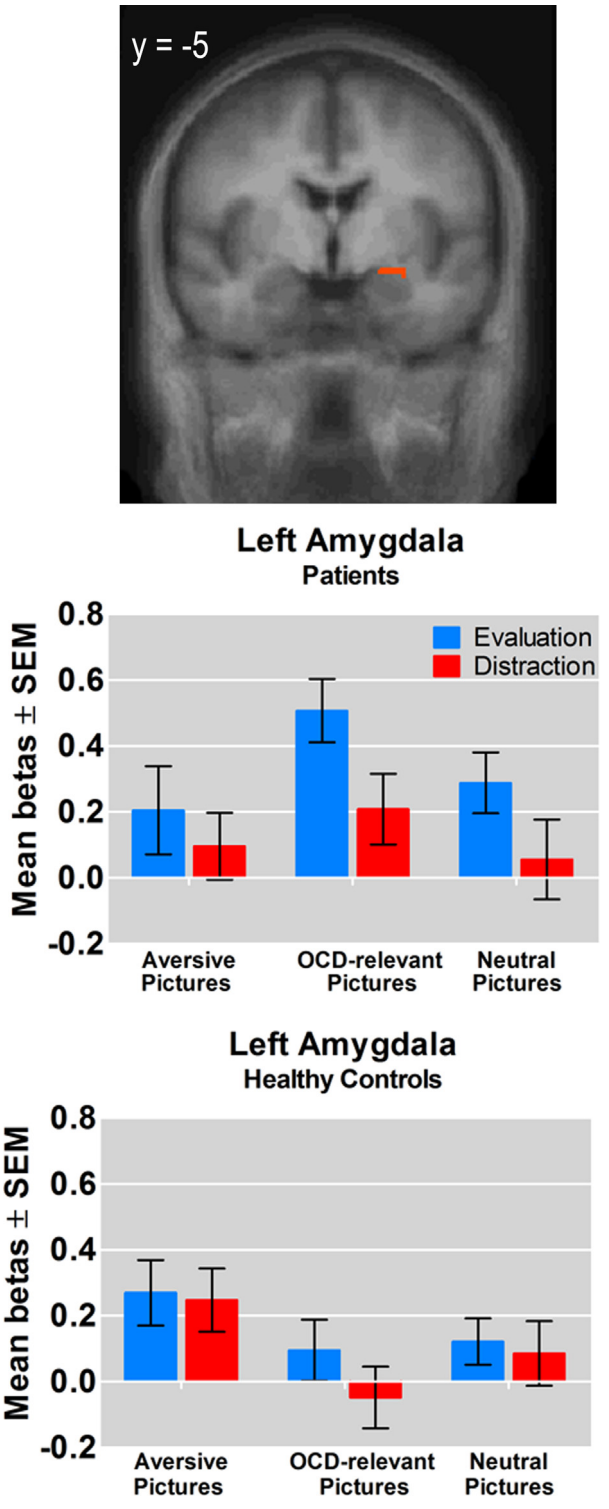

Fig. 3. Group × picture type × strategy interaction in the left amygdala during individually tailored symptom provocation in 21 unmedicated OCD patients and 21 healthy controls. Blood oxygenation level-dependent (BOLD) response observed in the ROI-driven analysis overlaid on an averaged T1 scan (radiological convention: left = right; $p(\text{cor}) < 0.05$; see Table 2). Plots display parameter estimates and error bars represent standard errors (mean ± SEM).

These results converge with findings of hyperactivity in fronto–striato–limbic circuits during OCD symptom provocation (Milad and Rauch, 2012). Based on these and previous findings (Breiter et al., 1996; Simon et al., 2010; van den Heuvel et al., 2004), amygdala hyper-responsivity to disorder-specific stimuli might hence constitute a correlate of fear expression in OCD linking it to other anxiety disorders (Etkin and Wager, 2007). Since comorbid anxiety disorders did not impact this finding, we assume that it is not due to non-specific group effects. However, aberrant amygdala activity is also reported e.g., in mood disorders (Sheline et al., 2001), and is possibly not specific to anxiety disorders. A distinction from other anxiety disorders with respect to frontostriatal hyperactivity and attenuated amygdala response to disorder-independent threat stimuli (faces, scenes) has been suggested (Stein et al., 2010). Indeed, although affective control stimuli were rated as more anxiety inducing, arousing and unpleasant than neutral ones by both groups and patients even reported more anxiety to aversive pictures than controls, they did not show increased amygdala responses to these stimuli. In controls, however, enhanced amygdala engagement in concert with other areas implicated in negative emotion reactivity (Phillips et al., 2003) (e.g., amygdala, striatum, insula, parahippocampal gyrus, ventrolateral prefrontal cortex), as well as in visual processing and maintenance of visuospatial attention was observed in line with the described main effect of picture type. The laterality of the amygdala responses converges with findings of right-hemispheric amygdala activation when the emotional property of a stimulus is visual in nature and obvious to the subjects (e.g., generally aversive), and of left-sided amygdala engagement when the emotional property of a stimulus is cognitively learned and depends on subjects interpretation (Phelps et al., 2001).

Besides amygdala hyperactivity, disorder-specific pictures reliably elicited an enhanced response in thalamo–striato–cortical pathways in patients including the thalamus, globus pallidus, subthalamic nucleus, caudate nucleus and OFC. This is in line with their roles in gating cortical in- and output, in the preservative nature of obsessions and compulsions (Deckersbach et al., 2006), and in decoding reward and punishment values of events (Kringelbach and Rolls, 2004), respectively. Activation of the insula, a paralimbic structure associated with bodily arousal states (Phillips et al., 2003), together with limbic hyperactivation, including the amygdala and parahippocampal gyrus might mediate the clinical expression of anxiety symptoms during viewing of OCD-triggers. Patients' increased BOLD-responses found in the parieto-occipital network (cuneus, PCC), known to be involved in the active reallocation of attentional resources, could be related to patients' effort to shift their attention away from the distressing stimulus (Rotge et al., 2008).

As intended by the paradigm and demonstrated by the strategy main effect both groups showed extensive recruitment of regions implicated in cognitive control, self-referential processing, emotion, visual processing and visuospatial attention as a function of evaluation. Distraction was characterized by stronger activation especially in attention areas including the dorsal ACC (Kanske et al., 2011). However, a group-by-picture type-by-strategy interaction was observed. We demonstrate dampening of patients' amygdala hyperactivity to OCD-related pictures during distraction. Moreover, as revealed by the three-way interaction in the dorsal ACC and operculo-insular region, hyperactivity to OCD-triggers in patients was only present during evaluation and was dampened through distraction. Patients' activation within the dorsal ACC might reflect elevated arousal during evaluation of individually relevant stimuli (Deckersbach et al., 2006). The operculo-insular system is known to process sensory inflow before reaching the amygdala (Schnitzler et al., 2000). Its hyperactivity could point towards deficient filtering of sensory stimulation which might result in excessive input into the amygdala.

In contrast to one previous PET study (van den Heuvel et al., 2004) that detected amygdala activation also during distraction, our task implicated higher attentional load since the picture content was task-irrelevant and had to be ignored. Thus, higher task-related demands might have exhausted patients' capacity to emotionally process OCD triggers (Pessoa et al., 2005). In contrast to the neuronal level, performance and reaction times during distraction did not point towards

patient's difficulties to disengage attention from symptom-related stimuli. However, studies on the attentional bias in OCD have yielded conflicting results (e.g., Moritz et al., 2008) and a similar mismatch between behavioral and neural level in OCD has been reported by van den Heuvel et al. (2005). We assume that the block design may have enabled subjects to reach near perfect task performance. Our results are consistent with prior findings of extended down-regulation of the amygdala response to emotional stimuli in healthy subjects (Kanske et al., 2011; McRae et al., 2010) and patients with remitted depression (Kanske et al., 2012). Thus, as confirmed by post-scan ratings, attentional distraction also appears to be effective in OCD patients and thereby distinguishes OCD from other anxiety disorders showing amygdala hyperactivation also under distraction or masking conditions (Rauch et al., 2000; Straube et al., 2011). However, it has to be pointed out that patients' decrease of amygdala activity achieved by distraction was comparable to the activation level of healthy controls when viewing aversive pictures. One could assume that the observed amygdala down-regulation might thus not be sufficient which could also be related to the fact that only few patients received treatment at the time of the study. Although patients performed with higher accuracy in the distraction task without group difference regarding reaction time, they did not show compensatory hyperactivation in the regulatory network during distraction found in other psychiatric disorders (Kanske et al., 2012). However, it has to be pointed out that the strategy applied in this study might be better called *guided* attentional distraction, while other studies request participants to use self-generated distraction. It has been reported that OCD patients use self-generated distraction less frequently than controls (Amir et al., 1997) although this technique was proofed to be effective for managing clinically significant intrusive thoughts (Najmi et al., 2009).

The lack of patients' differential amygdala activation during evaluation of generally aversive stimuli might also be explained by their increased activation to neutral stimuli. Apart from the above mentioned role, the amygdala is associated with broader dimensions of information processing, including ambiguity (Pessoa and Adolphs, 2010). Hence, amygdala activity to neutral stimuli could reflect patients' uncertainty in the decision (Is the picture unpleasant/disorder-relevant?) that contained no objective uncertainty for controls (Stern et al., 2012). In line with this interpretation, patients exhibited increased BOLD-responses during evaluation of neutral pictures relative to aversive and OCD-relevant stimuli in the cerebellum—a region involved in somatosensory-motor-related functioning and emotional processing (Stoodley and Schmahmann, 2009). Consistent with established ipsilateral cerebellar somatotopy the right-lateralized activation during the right-handed task could reflect patients' increased effort to perform the requested motor action despite the perceived uncertainty. Additionally, given the evidence for functional integration of cognition and emotion in the lateral prefrontal cortex (Pessoa, 2008), increased ventrolateral prefrontal activation to neutral stimuli, found in patients across strategies, might reflect top-down regulation to reduce the impact of these ambiguous distractors during performance.

In contrast to previous findings, controls showed no amygdala down-regulation to aversive stimuli during distraction (Kanske et al., 2011). This might be explained by the relatively easy task since effectiveness of distraction increases with attentional load of a task in healthy individuals (Pessoa et al., 2005).

The following limitations of the present study should be considered when interpreting the findings. First, the small sample size of 21 patients and the fact that not all symptom dimensions (e.g., hoarding) were equally present in our sample limits definitive conclusions regarding the multidimensional approach, and warrants replication and extension of findings. Second, our results may be biased by comorbidity. However, the presence of comorbid disorders was not an exclusion criterion since it is common and considered a natural phenomenon in OCD patients. A post-hoc subsample analysis to rule out that group differences are systematically due to comorbid anxiety disorders showed that the main findings remained significant after exclusion and suggested that our results can be attributed to the main diagnostic entity of OCD. However, these subsample findings should merely be considered exploratory and preliminary. In order to answer the question of specificity of these findings a clinical control group should be included in future studies. Third, in contrast to real-life situations, where fully developed emotional responses need to be regulated, our distraction–instruction was presented at once with the OCD-trigger. Hence, effectiveness of distraction during OCD symptom provocation should also be investigated *after* induction of an emotional response (Kanske et al., 2012). Moreover, further clinically relevant self-generated distraction strategies with higher attentional load that can be performed in everyday situations (e.g., mental task) should be tested and their long-term effect examined.

In conclusion, the observed hyperactivity within corticosubcortical loops during symptom provocation seems to reflect the neural basis underlying the emergence of OCD symptoms. Increased parieto-occipital activation may be involved in OCD patients' attempts to turn their attention away from their obsessive thoughts. Amygdala hyperactivity in concert with increased activation detected in the insula, anterior cingulate cortex (during evaluation) and parahippocampal gyri may mediate the clinical expression of anxiety symptoms in OCD (Milad and Rauch, 2012). This aberrant amygdala response was independent from symptom expression on established dimensions and dampened by attentional distraction. The clinical impact of distraction to manage states of immediate intense feelings of anxiety should be further elucidated and alternative emotion regulation strategies involving enhanced cognitive modulation (e.g., reappraisal) and their effects on brain activity patterns should be investigated.

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Appendix A. Supplementary material

Supplementary material associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.nicl.2014.03.011.

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