Dissociation Between Amygdala and Bed Nucleus of the Stria Terminalis During Threat Anticipation in Female Post-Traumatic Stress Disorder Patients

Leonie Brinkmann ^{1,*} Christine Buff,¹ Paula Neumeister,¹ Sara V. Tupak,¹ Michael P.I. Becker,¹ Martin J. Herrmann,² and Thomas Straube¹

¹*Institute of Medical Psychology and Systems Neuroscience, University of Muenster, Von-Esmarch-Str. 52, D-48149 Muenster, Germany*

²*Department of Psychiatry, Psychosomatics and Psychotherapy, University Hospital Wuerzburg, Margarete-Hoeppel-Platz 1, D-97080 Wuerzburg, Germany*

Abstract: Feelings of uncontrollability and anxiety regarding possibly harmful events are key features of post-traumatic stress disorder (PTSD) symptomatology. Due to a lack of studies, the neural correlates of anticipatory anxiety in PTSD are still poorly understood. During functional magnetic resonance imaging, female PTSD patients with interpersonal violence trauma and healthy controls (HC) anticipated the temporally unpredictable presentation of aversive (human scream) or neutral sounds. Based on separate analysis models, we investigated phasic and sustained brain activations. PTSD patients reported increased anxiety during anticipation of aversive versus neutral sounds. Furthermore, we found both increased initial, phasic amygdala activation and increased sustained activation of the bed nucleus of the stria terminalis (BNST) during anticipation of aversive versus neutral sounds in PTSD patients in comparison to HC. PTSD patients as compared with HC also showed increased phasic responses in mid-cingulate cortex (MCC), posterior cingulate cortex (PCC), mid-insula and lateral prefrontal cortex (PFC) as well as increased sustained responses in MCC, PCC, anterior insula and lateral and medial PFC. Our results demonstrate a relationship between anticipatory anxiety in PTSD patients and hyperresponsiveness of brain regions that have previously been associated with PTSD symptomatology. Additionally, the dissociation between amygdala and BNST indicates distinct temporal and functional characteristics and suggests that phasic fear and sustained anxiety responses are enhanced during unpredictable anticipation of aversive stimuli in PTSD. *Hum Brain Mapp* 38:2190–2205, 2017. © 2017 Wiley Periodicals, Inc.

Key words: anxiety; cingulate cortex; fMRI; insula; prefrontal cortex

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*Correspondence to: Leonie Brinkmann, Institute of Medical Psychology and Systems Neuroscience, University of Muenster,

Von-Esmarch-Str. 52; D-48149 Muenster, Germany. E-mail: leonie.brinkmann@uni-muenster.de

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INTRODUCTION

Post-traumatic stress disorder (PTSD) is characterized by the experience of a traumatic event that is followed by symptoms such as re-experiencing of the event, avoidance of stimuli associated with the trauma, emotional numbing, and hyperarousal [American Psychiatric Association, 2013]. Together with combat, hostage-taking and severe motor vehicle accidents, traumatic experiences most commonly arise from situations involving interpersonal violence [Javidi and Yadollahie, 2012] which frequently comprise violence and abuse within families, between intimate partners, friends, and unknown individuals [WHO, 2004].

The neural correlates of PTSD have been investigated in several symptom provocation studies [for review see Pitman et al., 2012]. A common finding among these studies is increased amygdala activation as well as decreased medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC) activation in PTSD patients compared with healthy control (HC) participants. These findings led to the hypothesis that the mPFC might insufficiently inhibit amygdala activity, leading to emotion regulation deficits and increased fear responses in PTSD [for review see Shin and Liberzon, 2010; Shin et al., 2006].

Anticipation of harmful stimuli or stimuli that are associated with the traumatic experience is particularly important for the maintenance of avoidance behavior and in turn of the disorder itself [Foa, 2006; Rothbaum and Davis, 2003]. To date there are only few studies that investigated neural correlates of anticipatory anxiety in PTSD. Comparing female participants suffering from PTSD after intimate partner violence and HC resulted in increased anterior insula [Aupperle et al., 2012; Simmons et al., 2008] as well as decreased lateral PFC activation [Aupperle et al., 2012] during anticipation of negative versus positive pictures in combination with a continuous performance task. Additionally, therapy studies showed a relationship between PTSD symptomatology and the ability to moderate anticipatory anxiety through a network consisting of insula and cingulate cortex [Aupperle et al., 2013; Simmons et al., 2013b].

A factor that was not taken into account in these anticipation studies is temporal unpredictability, since the anticipatory interval always had the same length (6s) [Aupperle et al., 2012, 2013; Simmons et al., 2008, 2013b]. Startle studies suggest that PTSD patients are hypersensitive to unpredictability [Grillon et al., 1998a,b, 2009] and that uncontrollability is a key factor for the development and maintenance of PTSD symptoms [Foa et al., 1992]. To our knowledge, there is only one study that included temporal unpredictability into an anticipation paradigm. PTSD patients after combat-exposure in comparison to HC showed anterior insula activity during temporally unpredictable versus predictable anticipation of trauma-related images, suggesting that unpredictability enhances the negative experience during anticipatory anxiety [Simmons et al., 2013a]. Taken together, results from anticipation studies in PTSD are in line with studies on anticipation of aversive

stimuli in healthy participants [Alvarez et al., 2011; Carlson et al., 2011; Chua et al., 1999; Drabant et al., 2011; Grupe et al., 2013; Kalisch et al., 2006; Nitschke et al., 2006; Phelps et al., 2001; Ploghaus et al., 1999; Shankman et al., 2014; Simmons et al., 2004, 2006] as well as patients with panic disorder [Boshuisen et al., 2002] and social anxiety disorder [Boehme et al., 2014; Lorberbaum et al., 2004].

Other brain regions that have been discussed in the context of anticipatory anxiety are amygdala and bed nucleus of the stria terminalis (BNST), which is part of the so-called extended amygdala. A growing body of research suggests a dissociation between these two regions, with the amygdala being responsible for phasic threat responses and rapid processing of imminent threat and an involvement of the BNST in sustained anxiety states during unpredictable threat [Davis et al., 2010; Walker et al., 2003]. Anticipatory anxiety studies showed phasic amygdala activation in patients with social anxiety disorder [Boehme et al., 2014; Lorberbaum et al., 2004] and specific phobia [Münsterkötter et al., 2015] as well as sustained enhanced BNST activation in specific phobia [Münsterkötter et al., 2015; Straube et al., 2007]. Furthermore, the dissociation between these regions is also supported by studies reporting phasic amygdala activation and sustained BNST activation during unpredictable anticipation in healthy participants within one and the same experiment [Alvarez et al., 2011; Grupe et al., 2013; Herrmann et al., 2016; Somerville et al., 2013]. So far, the role of phasic and sustained brain responses during anticipation of unpredictable threat has not been investigated in PTSD patients. Unraveling neural correlates of short-term fear and prolonged anxiety responses could provide important insights into the pathophysiology of PTSD [Ahearn et al., 2007]. Especially BNST hyperresponsiveness seems to be involved in maladaptive and chronic anxiety [Avery et al., 2016].

The current functional magnetic resonance imaging (fMRI) study investigated neural correlates of anticipatory anxiety in PTSD patients during unpredictable presentation of auditory aversive or neutral stimuli. Based on previous neuroimaging studies, brain regions of interest included insula, PFC, cingulate cortex, amygdala, and BNST. To investigate phasic and sustained brain responses, we used an initial (first second of anticipatory intervals) as well as a sustained (whole anticipatory interval) model for blood oxygenation level dependent (BOLD) responses. We hypothesized that both phasic amygdala activation and sustained BNST activation would be increased in PTSD patients as compared with healthy controls during anticipation of aversive versus neutral stimuli. Additionally, psychophysiological interaction (PPI) analysis was conducted on differential activations in amygdala and BNST.

METHODS AND MATERIALS

Subjects

Sixteen female PTSD patients and 16 female HC were initially recruited for the study. We only included female

TABLE I. Demographic and clinical characterization of PTSD patients and HC

	PTSD	HC	PTSD vs. HC	
			<i>t</i> -value	<i>P</i> -value
Demographic data				
<i>n</i>	15	16		
Age (in years)	<i>M</i> = 26.6, <i>SD</i> = 5.87	<i>M</i> = 25.44, <i>SD</i> = 3.33	<i>t</i> _[29] = 0.69	<i>P</i> = 0.499
Education (years at school)	<i>M</i> = 12.93, <i>SD</i> = 0.99	<i>M</i> = 12.75, <i>SD</i> = 0.93	<i>t</i> _[28] = 0.51	<i>P</i> = 0.616
Questionnaires				
PDS	<i>M</i> = 23.6, <i>SD</i> = 10.52	<i>M</i> = 1.06, <i>SD</i> = 2.74	<i>t</i> _[15.78] = 8.04	<i>P</i> < 0.001
ASI	<i>M</i> = 42.4, <i>SD</i> = 21.89	<i>M</i> = 12.56, <i>SD</i> = 9.82	<i>t</i> _[19.15] = 4.84	<i>P</i> < 0.001
BDI	<i>M</i> = 19.93, <i>SD</i> = 11.3	<i>M</i> = 1.31, <i>SD</i> = 2.15	<i>t</i> _[14.95] = 6.28	<i>P</i> < 0.001
Type of trauma				
Physical abuse	8			
Sexual abuse	7			
Comorbidities (DSM-IV)				
Depressive disorder	3			
Social anxiety disorder	2			
Specific phobia	1			
Chronic pain disorder	2			
Eating disorder	1			

PTSD, post-traumatic stress disorder; HC, healthy controls; PDS, Posttraumatic Diagnostic Scale [Steil and Ehlers, 2000]; ASI, Anxiety Sensitivity Index [Reiss et al., 1986]; BDI, Beck Depression Inventory-II [Beck et al., 1996].

participants since women are more likely to develop PTSD after a traumatic experience [Shansky, 2015] and have a significantly higher lifetime prevalence of PTSD than men [Tolin and Foa, 2006]. One patient had to be excluded from analysis due to intake of antipsychotic drugs at the time of study participation. The remaining 15 PTSD patients and 16 HC (see Table I) were matched according to age ($t_{[29]} = 0.69$, $P = 0.499$) and education (years at school: $t_{[28]} = 0.51$, $P = 0.616$). Participants were recruited through public advertisements and in collaboration with an outpatient clinic. Participants had no current or history of neurological disorder, traumatic brain injury, psychotic or bipolar disorder and no current drug abuse or dependence. All PTSD patients suffered from trauma related to interpersonal violence (sexual or physical abuse). During a structured clinical interview [SKID; Wittchen et al., 1997] all participants were diagnosed according to DSM-IV criteria, which was the current edition at the time. PTSD patients fulfilled the diagnostic criteria for PTSD and the Posttraumatic Stress Diagnostic Scale confirmed this diagnosis [PDS; Steil and Ehlers, 2000] ($t_{[15.78]} = 8.04$, $P < 0.001$). Furthermore, PTSD patients scored significantly higher than HC on the Anxiety Sensitivity Index [ASI; Reiss et al., 1986] ($t_{[19.15]} = 4.84$, $P < 0.001$) and the Beck Depression Inventory-II [BDI; Beck et al., 1996] ($t_{[14.95]} = 6.28$, $P < 0.001$). Comorbidities among PTSD patients involved recurring depressive disorder ($n = 3$), social anxiety disorder ($n = 2$), specific phobia ($n = 1$), chronic pain disorder ($n = 2$), and eating disorder ($n = 1$) (for participant characterization see Table I). Two PTSD patients took antidepressant medication and were stabilized on such medication at least three months prior to study participation. The study

conforms to the Declaration of Helsinki and was approved by the local ethics committee. All participants gave written informed consent prior to the experiment.

Experimental Design

During scanning, participants anticipated the presentation of aversive or neutral sounds. All sounds were taken from the International Affective Digitized Sounds database [IADS-2; Bradley and Lang, 1999]. Aversive sounds consisted of human screams (#275, 276, 277), while water sounds (#172, 726, 377) served as neutral sounds. We selected representative sequences with a duration of 4 s from these sound clips. Sound intensity was set to a constant level.

Sounds were announced by displaying one of two cues (hash or percent sign) on black background which were shown from the start of the respective trial until the end of sound presentation. Before the start of the experiment, participants heard each of the six sounds once and were instructed about the assignment of the cues to the aversive and neutral conditions, which was counterbalanced across participants. There were 11 aversive and 11 neutral trials, presented in pseudorandomized order. In each condition, there were seven anticipation intervals that lasted 16 s, allowing for investigation of sustained brain responses. By interspersing shorter anticipation intervals (2 * 3 s, 1 * 5 s, 1 * 10 s per condition), we kept the appearance of the stimuli temporally unpredictable. Participants were told that the stimulus could be presented at any time in a given trial after the symbol appeared. Between trials, a white

fixation cross on black background was shown for 15 s. In total the experiment lasted 11 min and 40 s.

After scanning, the participants had to rate the two symbols as well as the six sounds on the dimensions valence (1 = very unpleasant, 9 = very pleasant, with 5 = neutral), anxiety (1 = not anxiety-inducing, 9 = highly anxiety-inducing), and arousal (1 = not arousing, 9 = highly arousing), using a nine-point Likert scale [Self Assessment Manikin; Bradley and Lang, 1994]. Behavioral data were analyzed by means of mixed-model analyses of variance (ANOVA) using IBM SPSS software (Version 22; IBM, Armonk, New York), with group (PTSD vs. HC) as between-subject factor and condition (aversive vs. neutral sounds) as within-subject factor. Post-hoc *t*-tests were used to resolve interactions where necessary. A *P*-value of < 0.05 was considered statistically significant. Data are presented as mean $\pm$ standard error.

FMRI

FMRI data were collected in a 3T magnetic resonance scanner ("Magnetom PRISMA"; Siemens Medical Systems, Erlangen, Germany). A high resolution T1-weighted anatomical scan with 192 slices was acquired. Functional data were then collected with a T2*-weighted echo-planar sequence (TE = 30 ms, flip angle = 90°, matrix = 92×92 , FOV = 208 mm², TR = 2,080 ms) consisting of 340 volumes with 36 axial slices (thickness = 3 mm, gap = 0.3 mm, in plane resolution = 2.26×2.26 mm).

Functional data were preprocessed and analyzed with BrainVoyager QX (Version 2.8; Brain Innovation, Maastricht, the Netherlands). The first four volumes were discarded from each run to ensure adequate saturation. Data were then corrected for slice time errors and controlled for movement artifacts. Anatomical and functional data were co-registered and normalized to fit Talairach space [Talairach and Tournoux, 1988]. Additionally, data were smoothed spatially (6 mm full-width at half maximum [FWHM] Gaussian kernel) and temporally (high pass filter: 10 cycles per run; low pass filter: 2.8 s; linear trend removal).

Statistical analysis consisted of multiple linear regression of the signal time course at each voxel. The expected BOLD signal change for each condition was modeled with a canonical double-gamma hemodynamic response function (HRF). Two separate general linear models (GLMs) were calculated for the anticipatory period. In the first GLM the HRF consisted of the whole anticipatory interval (sustained response GLM). The second GLM modeled a phasic HRF to the onset (first second) of the anticipatory interval (initial response GLM). Sound presentation and six movement parameters were modeled as predictors of no interest in both GLMs. Next, z-standardized predictor estimates based on voxel-wise statistical maps for each participant were calculated. Random effects analysis across the individual predictor estimates for planned contrasts was performed.

Based on previous neuroimaging studies in PTSD and due to the restricted patients sample size, analyses were small-volume-corrected for a-priori defined regions of interest (ROIs). The ROI approach restricts our analyses to a homogeneous search space and thus avoids potential inflation of false-positive clusters due to inhomogeneity of spatial smoothness and spatial autocorrelations. ROIs for amygdala, insula, cingulate cortex (anterior [ACC], middle [MCC], posterior [PCC]), PFC (lateral, medial) were defined on the basis of the Automated Anatomical Labeling (AAL) atlas included in the Wake Forest University (WFU) PickAtlas software [Maldjian et al., 2003, 2004; Tzourio-Mazoyer et al., 2002]. MNI-coordinates were converted into Talairach space with ICBM2tal [Lancaster et al., 2007]. Subdivision of cingulate cortex was based on the anatomically driven model by Vogt [2014]. Consequently, the widely used term of dorsal anterior cingulate cortex (dACC) refers to anterior mid-cingulate cortex (amCC). The BNST ROI was defined based on an anatomical atlas [also see Herrmann et al., 2016; Mai et al., 1997] and was dilated by 1mm to avoid missing relevant activation. For the sake of completeness we additionally conducted whole-brain analyses to detect relevant differential activations outside the ROIs.

PPI analyses were conducted with significantly activated clusters in the amygdala and BNST as seed regions. The contrast anticipation of aversive versus neutral sounds served as the psychological predictor, while the extracted signal time course from these seed regions served as physiological predictors. The PPI GLM contained the signal time course of the seed region and the PPI predictor. Extraction of time courses and convolution with HRF were done with Neuroelf's (www.neuroelf.net) ComputeGLM method.

To correct for multiple comparisons, the cluster-level statistical threshold estimator plugin for BrainVoyager [Goebel et al., 2006] was used. The voxel-level threshold was set to $P < 0.005$ to balance between Type I and II error rates [uncorrected; Lieberman and Cunningham, 2009]. Since we expect large effect sizes of around $d = 1.3$, this threshold provides us with appropriate voxel-level Power (0.80) to detect these effects in normally available patient sample sizes such as ours. A ROI-based mask consisting of predefined amygdala, insula, cingulate cortex and PFC ROIs and a separate mask consisting of bilateral BNST ROIs were applied to the thresholded maps with an estimated FWHM for spatial smoothness [Forman et al., 1995] and an iterative procedure (Monte Carlo simulation) with 1,000 iterations. For the exploratory whole-brain and PPI analyses the threshold was set to $P < 0.001$. The minimum cluster size threshold with a cluster-level false positive rate of $P < 0.05$ was applied to the statistical maps.

To analyze differences in initial versus sustained responses, we first standardized differences in parameter estimates (anticipation of aversive-neutral stimuli) resulting from the initial and sustained model within clusters of

Figure 1.

Ratings for valence (1 = very unpleasant, 9 = very pleasant, with 5 = neutral), arousal (1 = not arousing, 9 = highly arousing) and anxiety (1 = not anxiety-inducing, 9 = highly anxiety-inducing) of post-traumatic stress disorder (PTSD) patients and healthy

controls (HC) for the cue announcing aversive and neutral sounds (a) and for aversive and neutral sounds (b). * $P \leq 0.05$, ** $P \leq 0.001$.

activation in BNST and amygdala. Standardized data were then analyzed by means of an ANOVA with group (PTSD vs. HC) as between-subject factor and model (initial vs. sustained) as within-subject factor. Post-hoc t -tests were used to resolve interactions where necessary. A P -value of < 0.05 was considered statistically significant.

To investigate the relationship between differential brain responses and behavioral measures, ratings regarding valence, arousal, and anxiety for the cues as well as symptom severity as measured by PDS scores [Steil and Ehlers, 2000], level of anxiety as measured by ASI scores [Reiss et al., 1986] and level of depression as measured by BDI scores [Beck et al., 1996] of PTSD patients were correlated with mean beta values for differential activation clusters (anticipation of aversive-neutral sounds) resulting from ROI analyses (Bonferroni-corrected significance level; phasic model: $P \leq 0.0038$; sustained model: $P \leq 0.0022$). Furthermore, subscales of the PDS [Steil and Ehlers, 2000] measuring intrusions, avoidance and hyperarousal were correlated with differential activation in amygdala and BNST (Bonferroni-corrected significance level: $P \leq 0.025$) to investigate the relationship between these regions and specific symptom clusters.

RESULTS

Behavioral Data

Due to technical problems, rating data were only available for 14 PTSD patients and 16 HC (Fig. 1). The ANOVAs for valence, arousal and anxiety ratings for the cues that were presented during anticipation of aversive

versus neutral stimuli resulted in significant main effects for condition (valence: $F_{[1, 28]} = 8.19$, $P = 0.008$; arousal: $F_{[1, 28]} = 16.77$, $P < 0.001$; anxiety: $F_{[1, 28]} = 14.09$, $P = 0.001$) and group (arousal: $F_{[1, 28]} = 14.11$, $P = 0.001$), as well as significant group by condition interactions (valence: $F_{[1, 28]} = 12.1$, $P = 0.002$; arousal: $F_{[1, 28]} = 12.36$, $P = 0.002$; anxiety: $F_{[1, 28]} = 10.01$, $P = 0.004$). Post-hoc analysis revealed that PTSD patients rated the aversive cue as significantly more negative ($t_{[28]} = -2.25$, $P = 0.033$), more arousing ($t_{[28]} = 4.67$, $P < 0.001$), and more anxiety-inducing ($t_{[28]} = 2.93$, $P = 0.007$) than HC, while there were no significant group differences for the neutral cue. Additionally, PTSD patients, but not HC, rated the aversive cue as significantly more negative ($t_{[13]} = -4.28$, $P = 0.001$), more arousing ($t_{[13]} = 4.33$, $P = 0.001$), and more anxiety-inducing ($t_{[13]} = 4.10$, $P = 0.001$) than the neutral cue.

The ANOVAs for valence, arousal and anxiety ratings for aversive versus neutral stimuli yielded significant main effects for condition (valence: $F_{[1, 28]} = 221.39$, $P < 0.001$; arousal: $F_{[1, 28]} = 240.52$, $P < 0.001$; anxiety: $F_{[1, 28]} = 128.98$, $P < 0.001$) and group (valence: $F_{[1, 28]} = 7.20$, $P = 0.012$; arousal: $F_{[1, 28]} = 24.10$, $P < 0.001$; anxiety: $F_{[1, 28]} = 20.59$, $P < 0.001$), as well as significant interaction effects (arousal: $F_{[1, 28]} = 25.17$, $P < 0.001$; anxiety: $F_{[1, 28]} = 18.34$, $P < 0.001$). Post-hoc analysis showed that PTSD patients rated aversive stimuli as significantly more arousing ($t_{[28]} = 5.04$, $P < 0.001$) and more anxiety-inducing ($t_{[28]} = 4.43$, $P < 0.001$) than HC, while there were no significant group differences for the neutral stimuli rating. PTSD patients and HC rated aversive stimuli as more arousing (PTSD: $t_{[13]} = 20.68$, $P < 0.001$; HC: $t_{[15]} = 6.34$, $P < 0.001$) and more anxiety-inducing (PTSD: $t_{[13]} = 13.84$, $P < 0.001$; HC: $t_{[15]} = 4.46$, $P < 0.001$) than neutral stimuli.

TABLE II. Significant initial activations during anticipation of aversive versus neutral sounds as revealed by ROI analysis

Region	Lateralization	PTSD > HC					HC > PTSD				
		<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i> -value	mm ³	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i> -value	mm ³
Amygdala	R	23	1	-17	5.77	856					
Cingulate cortex											
aMCC/pMCC	L/R	0	-1	27	3.94	296					
aMCC/pMCC	L/R	-3	9	42	3.14	112					
pMCC	L/R	0	-27	39	3.51	144					
dPCC	R	9	-43	46	3.55	64					
Insula	R	38	-3	-4	3.80	536					
	L	-44	0	6	3.50	104					
	L	-42	2	-6	3.64	128					
PFC											
dlPFC	R	45	3	29	3.58	504					
	R	41	-1	22	3.81	88					
	R	30	3	56	3.28	96					
	L	-45	-1	30	3.59	104					
dmPFC	R						11	39	28	3.28	72

PTSD, post-traumatic stress disorder; HC, healthy controls; aMCC, anterior midcingulate cortex; pMCC, posterior midcingulate cortex; dPCC, dorsal posterior cingulate cortex; PFC, prefrontal cortex; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; L, left; R, right; (*x,y,z*), Talairach coordinates of maximally activated voxel (activation threshold: $P < 0.05$ corrected).

FMRI Data

Initial response

The comparison between PTSD patients and HC in the initial response GLM for the contrast *anticipation of aversive versus neutral sounds* identified activation differences between groups in several regions (Table II). PTSD patients as compared with HC showed increased activation in the amygdala (right: peak voxel: $x = 23$, $y = 0$, $z = -17$; size: 856 mm³; $t_{[29]} = 5.77$) (Fig. 2). Furthermore, results showed increased activations in anterior/posterior MCC, posterior MCC, dorsal PCC, mid-insula and dorso-lateral PFC (dlPFC), as well as decreased activation in dorso-medial PFC (dmPFC) in PTSD patients in comparison to HC (Fig. 3). Whole-brain analysis additionally showed increased activation in pre- and postcentral gyrus, temporal gyrus, angular gyrus, parietal lobule, operculum and fusiform gyrus as well as decreased activation in cerebellum in PTSD patients relative to HC (Supporting Information Table 1). Correlation analysis revealed a significant positive correlation between BDI score and differential activation in anterior/posterior MCC ($r_{[14]} = 0.726$, $P = 0.002$). Other than that, there were no significant correlations between behavioral measures and differential activations, also with regard to differential activation in the amygdala and subscales of the PDS [Steil and Ehlers, 2000].

Sustained Response

For the sustained response GLM (Table III), the contrast *anticipation of aversive versus neutral sounds* identified

Figure 2.

Post-traumatic stress disorder (PTSD) patients compared with healthy controls (HC) showed increased initial activation in right amygdala and increased sustained activation in bilateral bed nucleus of the stria terminalis (BNST) during anticipation of aversive in contrast to neutral sounds. Statistical parametric maps are overlaid on an averaged T1 scan (radiological convention: left = right). Graphs display contrasts of parameter estimates (anticipation of aversive versus neutral sounds; mean $\pm$ standard error for activation cluster). R, right; L, left. [Color figure can be viewed at wileyonlinelibrary.com]

Figure 3.

Post-traumatic stress disorder (PTSD) patients compared with healthy controls (HC) showed increased initial activation during anticipation of aversive in contrast to neutral sounds in anterior mid-cingulate cortex (aMCC)/posterior mid-cingulate cortex (pMCC), bilateral mid-insula, and dorsolateral prefrontal cortex

(dlPFC). Statistical parametric maps are overlaid on an averaged T1 scan (radiological convention: left = right). Graphs display contrasts of parameter estimates (anticipation of aversive versus neutral sounds; mean $\pm$ standard error for activation cluster). R, right; L, left. [Color figure can be viewed at wileyonlinelibrary.com]

increased activation in PTSD patients as compared with HC in bilateral BNST (right: peak voxel: $x = 4$, $y = 3$, $z = 4$; size: 360 mm^3 ; $t_{[29]} = 3.99$; left: peak voxel: $x = -9$, $y = 3$, $z = 4$; size: 112 mm^3 ; $t_{[29]} = 3.54$) (Fig. 2). Furthermore, we found hyperactivations in aMCC, posterior MCC/dorsal PCC, dorsal/ventral PCC, anterior insula, and several increased activations in dlPFC, dlPFC/dmPFC, ventrolateral PFC (vlPFC), dlPFC/vlPFC, dmPFC, and ventromedial PFC in PTSD patients in comparison to HC (Fig. 4). Whole-brain analysis additionally showed increased activation in PTSD patients as compared with HC in hippocampus, precuneus, temporal gyrus, angular gyrus, occipital gyrus, and cerebellum (Supporting Information Table 1). Correlation analysis revealed positive correlation between valence ratings and differential activation in left vlPFC ($r_{[14]} = 0.75$, $P = 0.002$). Differential activations in BNST showed no significant correlation with subscales of the PDS [Steil and Ehlers, 2000].

Initial Versus Sustained Response

The ANOVA for the analysis of initial versus sustained responses resulted in significant main effects for group (right BNST: $F_{[1,29]} = 7.160$, $P = 0.012$; left BNST:

$F_{[1,29]} = 5.892$, $P = 0.022$; right amygdala: $F_{[1,29]} = 9.806$, $P = 0.004$) and significant group by model interactions (right BNST: $F_{[1,29]} = 4.334$, $P = 0.046$; right amygdala: $F_{[1,29]} = 8.631$, $P = 0.006$). Post-hoc tests revealed that PTSD patients in contrast to HC showed significantly higher parameter estimates in the right BNST for the sustained relative to the initial model ($t_{[29]} = 3.618$, $P = 0.001$) and significantly higher parameter estimates in the right amygdala for the initial relative to the sustained model ($t_{[29]} = 4.890$, $P < 0.001$).

PPI

The initial response GLM resulted in a cluster of increased activation in the right amygdala, which served as seed region for PPI analyses (Table IV, Fig. 5). The time course of this seed showed decreased functional connectivity with left amygdala, dlPFC, and dmPFC in PTSD patients compared with HC. The sustained response GLM resulted in activation clusters in the right and left BNST. PTSD patients in contrast to HC showed hyperconnectivity between the right BNST seed and vmPFC. Seeding the left BNST cluster showed increased functional connectivity with insula and decreased functional connectivity with dmPFC (Table IV, Fig. 5).

TABLE III. Significant sustained activations during anticipation of aversive versus neutral sounds as revealed by ROI analysis

Region	Lateralization	PTSD > HC			<i>t</i> -value	mm ³
		<i>x</i>	<i>y</i>	<i>z</i>		
BNST	R	4	3	4	3.99	360
	L	-9	3	4	3.54	112
Cingulate cortex						
	aMCC	-7	8	28	3.92	328
	pMCC/dPCC	-10	-29	34	3.45	280
dPCC/vPCC	L/R	-1	-45	17	3.35	352
	L	-29	23	-4	4.14	320
Insula						
PFC						
	dIPFC					
	R	35	-15	49	3.81	128
	R	30	15	41	3.24	248
	R	23	49	34	3.26	72
	L	-20	-5	43	4.44	136
	L	-24	21	46	3.36	144
	dIPFC/dmPFC	-14	26	39	5.22	2672
	vlPFC					
	R	28	46	-1	4.69	1968
dIPFC/vIPFC						
	R	52	21	0	4.44	832
	L	-48	21	0	3.04	120
	L	-41	27	-14	4.08	280
	L	-18	13	-12	4.01	264
	dIPFC/vIPFC	-29	45	4	5.02	9040
	dmPFC					
	R	9	29	47	4.38	336
	L	-7	35	39	3.20	96
	vmPFC					
	L/R	-10	56	-10	5.22	1104
	R	10	41	-2	3.83	736

PTSD, post-traumatic stress disorder; HC, healthy controls; BNST, bed nucleus of the stria terminalis; aMCC, anterior midcingulate cortex; pMCC, posterior midcingulate cortex; dPCC, dorsal posterior cingulate cortex; vPCC, ventral posterior cingulate cortex; PFC, prefrontal cortex; dIPFC, dorsolateral prefrontal cortex; vlPFC, ventrolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; vmPFC, ventromedial prefrontal cortex; L, left; R, right; (*x,y,z*), Talairach coordinates of maximally activated voxel (activation threshold: $P < 0.05$ corrected).

DISCUSSION

The current study investigated phasic and sustained brain responses during threat anticipation in PTSD patients. We found phasic, initial activation of amygdala and sustained activation of BNST in PTSD patients compared with HC. Additionally, PTSD patients in comparison to HC showed initial hyperactivation in MCC, PCC, mid-insula, and lateral PFC as well as increased sustained responses in MCC, PCC, anterior insula, and lateral and medial PFC. Functional connectivity analyses revealed distinct phasic and sustained functional connectivity patterns.

This is the first study showing dissociation between BNST and amygdala activation in PTSD patients during unpredictable threat anticipation. The amygdala showed phasic activation to the onset of the anticipatory interval, while the BNST showed sustained activation across the anticipatory interval. Using two different analysis models,

we were able to differentiate between these responses. Our findings thus suggest that, besides other regions, different temporal and functional characteristics of BNST and amygdala during anticipation of unpredictable aversive stimuli have to be taken into account in PTSD. Our behavioral data revealed that PTSD patients perceived the anticipation of aversive stimuli as more anxiety-inducing, arousing, and negative than HC. Together with the temporal unpredictability of stimulus onsets, our methodology seems suitable for the investigation of hypersensitivity to uncontrollability and anticipatory anxiety in PTSD.

The involvement of both, BNST and amygdala could reflect the complex emotional states associated with PTSD that consist of phasic fear and prolonged anxiety responses [Ahearn et al., 2007]. We did not detect a relationship between differential activation in these areas and symptom clusters, which would allow for a more detailed interpretation. However, our results are in line with independent systems for fear and anxiety, with phasic threat detection in the amygdala and sustained threat responding of the BNST [Davis et al., 2010; Walker et al., 2003, 2009]. PTSD patients seem to be hypersensitive to cues signaling unpredictable threat and to contexts of unpredictable threat anticipation. Therefore, amygdala and BNST could be promising targets for treatment of PTSD symptomatology [Avery et al., 2016], such as hyperarousal and avoidance behavior regarding threat stimuli [American Psychiatric Association, 2013].

Phasic amygdala activation was found at cue onset for the anticipation of aversive stimuli, which is in line with the role of the amygdala in rapid, cue-related threat processing [Alvarez et al., 2011; Grupe et al., 2013; Herrmann et al., 2016]. Current and previous findings point toward an amygdala hyperresponsiveness to trauma-related but also trauma-unrelated affective stimuli as well as the anticipation of such stimuli in PTSD [Shin et al., 2006]. This is in accordance with a role of the amygdala in enhanced threat detection resulting in heightened threat expectancies [Grupe and Nitschke, 2013; LeDoux, 1998, 2000; Öhman and Mineka, 2001]. The increased phasic, initial response of the amygdala in PTSD patients suggests that they are more alert during anticipation of aversive stimuli. This initial reaction might trigger exaggerated attentional deployment and biased threat expectancies [Grupe and Nitschke, 2013; LeDoux, 2000].

Interestingly, our findings show unilateral initial activation in the right amygdala. Studies on lateralization effects in the amygdala are rather inconclusive, showing lateralization toward left and right during processing of negative stimuli [Baas et al., 2004; Beraha et al., 2012]. However, converging evidence suggests a tendency for rapid and automatic stimulus detection in the right amygdala, while stimulus processing is more elaborate in the left amygdala [Sergeyev et al., 2008; Wright et al., 2003]. This could be a possible explanation, why we only found initial activation in the right amygdala. At least, right and left amygdala

Figure 4.

Post-traumatic stress disorder (PTSD) patients compared with healthy controls (HC) showed increased sustained activation during anticipation of aversive in contrast to neutral sounds in anterior mid-cingulate cortex (aMCC), posterior mid-cingulate cortex (pMCC)/dorsal posterior cingulate cortex (dPCC), anterior insula, ventromedial prefrontal cortex (vmPFC), dorsolateral prefrontal cortex (dlPFC)/dorsomedial prefrontal cortex

(dmPFC) and ventrolateral prefrontal cortex (vlPFC). Statistical parametric maps are overlaid on an averaged T1 scan (radiological convention: left = right). Graphs display contrasts of parameter estimates (anticipation of aversive vs. neutral sounds; mean $\pm$ standard error for activation cluster). [Color figure can be viewed at wileyonlinelibrary.com]

seem to be functionally distinct during threat anticipation in PTSD.

In contrast to the phasic amygdala response, we detected sustained activation of bilateral BNST. Our findings suggest increased sustained anxiety reflected by hyperactivation of BNST in response to anticipation of unpredictable aversive stimuli in PTSD. This is in accordance with startle studies, suggesting hypersensitivity and sustained anxiety in PTSD patients in response to unpredictable aversive stimuli [Davis et al., 2010; Grillon et al.,

1998a,b,]. A recent review stresses the potential involvement of BNST in anxiety disorders in general, but also with regard to PTSD [Lebow and Chen, 2016]. PTSD symptomatology has been shown to be related to BNST corticotropin-releasing factor receptor type 2 levels in mice, which is thought to reflect maladaptive coping with stressors after traumatic events [Lebow et al., 2012]. Furthermore, animal research proposed a role of BNST in anxious responding and hypervigilance under sustained threat [Davis et al., 2010]. Accordingly, BNST represents a

TABLE IV. Significant functional connectivity differences between PTSD and HC during anticipation of aversive versus neutral sounds

Region	Lateralization	PTSD > HC					HC > PTSD				
		<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i> -value	mm ³	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i> -value	mm ³
<i>Seed: amygdala</i>											
Amygdala	L						−29	−5	−12	4.18	40
dIPFC	R						21	−9	47	4.13	64
dmPFC	R						13	−3	60	4.73	48
dIPFC/dmPFC	R						15	19	48	4.22	56
	L						−15	15	47	4.38	176
<i>Seed: right BNST</i>											
vmPFC	L	−8	29	−8	4.18	64					
<i>Seed: left BNST</i>											
Insula	R	29	13	5	4.30	120					
dmPFC	R/L						−3	17	54	4.68	56

PTSD, post-traumatic stress disorder; HC, healthy controls; BNST, bed nucleus of the stria terminalis; pACC, pregenual anterior cingulate cortex; sACC, subgenual anterior cingulate cortex; aMCC, anterior midcingulate cortex; pMCC, posterior midcingulate cortex; dPCC, dorsal posterior cingulate cortex; dIPFC, dorsolateral prefrontal cortex; vIPFC, ventrolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; vmPFC, ventromedial prefrontal cortex; L, left; R, right; (*x,y,z*), Talairach coordinates of maximally activated voxel (activation threshold amygdala seed: $P < 0.025$ corrected; activation threshold BNST seeds: $P < 0.0125$ corrected).

promising target for the treatment of PTSD symptomatology [Lebow and Chen, 2016]. BNST activation was previously shown during unpredictable anticipation of phobia-specific stimuli in spider phobia [Münsterkötter et al., 2015; Straube et al., 2007]. Other than that, there is still a lack of studies investigating BNST hyperresponsiveness in stress-related or anxiety disorders. Studies in healthy humans showed BNST hyperactivation in response to increasing proximity to threat [Mobbs et al., 2010; Somerville et al., 2010] and within different unpredictable threat contexts [Alvarez et al., 2011; Grupe et al., 2013; Herrmann et al., 2016; Somerville et al., 2013].

Although the BNST is a rather small structure, it is known to be a very heterogeneous region with up to 18 subregions [Bota et al., 2012], various subnuclei and different receptors [Avery et al., 2016; Gungor and Pare, 2016; Lebow and Chen, 2016]. A broad subdivision is the differentiation between anterior and posterior BNST. In rodents, the anterior part of the BNST is suggested to be involved in emotion processing [Dong et al., 2001; Dong and Swanson, 2004] and stress responses [Choi et al., 2008]. The anterolateral region, for example, is thought to integrate information to assess the possibility of an anxiety-like versus a positive experience [Lebow and Chen, 2016]. In contrast, the posterior part of the BNST seems to regulate and inhibit stress responses [Kim et al., 2013; Lebow and Chen, 2016]. Coherently, the activation clusters found in our study correspond to the anterolateral part of the BNST. However, effects have to be interpreted with caution and the identification of precise anatomical locations requires high-resolution imaging in humans.

The current findings revealed increased initial activation in mid-insula regions and sustained activation in anterior insula in PTSD patients compared with HC. These

findings are in line with several anticipation studies showing insula activation in patients with specific phobia [Straube et al., 2007], social phobia [Boehme et al., 2014; Lorberbaum et al., 2004], panic disorder [Wittmann et al., 2014] and HC [e.g., Carlson et al., 2011; Chua et al., 1999; Ploghaus et al., 1999; Shankman et al., 2014; Simmons et al., 2004, 2006]. In our study, increased insula activation in PTSD patients might reflect an initially enhanced internal and external focus [Craig, 2010] that possibly progresses into the facilitation of attentional and behavioral processes that are essential during expectation of an aversive stimulus [Grupe and Nitschke, 2013; Lindquist and Barrett, 2012]. This is additionally supported by the increased functional connectivity of BNST and insula in the current study, since both regions are involved in hypervigilant threat monitoring [Somerville et al., 2010] and are suggested to interact for the expression of aversive emotions during threat anticipation [Avery et al., 2016; Kinnison et al., 2012].

We also detected initial and sustained hyperactivations in MCC and PCC in PTSD patients in contrast to HC. Cingulate cortex activation was also found in HC during anticipation of aversive stimuli [Alvarez et al., 2011; Chua et al., 1999; Drabant et al., 2011; Grupe et al., 2013; Kalisch et al., 2006; Nitschke et al., 2006] and patients with panic disorder expecting a panic attack [Boshuisen et al., 2002] or disorder-related pictures [Wittmann et al., 2014]. In PTSD, hyperactivations in MCC have been found during fear conditioning [Rougemont-Buckling et al., 2011], recall of extinction learning [Milad et al., 2009], and auditory oddball paradigms [Bryant et al., 2005; Felmingham et al., 2009; Pannu Hayes et al., 2009]. Additionally, a meta-analysis of neuroimaging studies in PTSD provided evidence for MCC hyperresponsiveness in PTSD [Shin and

a) functional connectivity seeded from phasic amygdala response

b) functional connectivity seeded from sustained BNST response

Figure 5.

Differential phasic activation in the right amygdala showed decreased functional connectivity with left amygdala, dorsolateral prefrontal cortex (dlPFC) and dorsomedial prefrontal cortex (dmPFC) in post-traumatic stress disorder (PTSD) patients compared with healthy controls (HC) during anticipation of aversive in contrast to neutral sounds. Differential sustained activation in the right bed nucleus of the stria terminalis (BNST) showed increased functional connectivity with ventromedial prefrontal cortex (vmPFC) in PTSD patients compared with HC.

Differential sustained activation in the left BNST showed increased functional connectivity with insula and decreased functional connectivity with dmPFC in PTSD patients compared with HC. Statistical parametric maps are overlaid on an averaged T1 scan (radiological convention: left = right). Graphs display contrasts of parameter estimates (anticipation of aversive vs. neutral sounds; mean $\pm$ standard error for activation cluster). R, right; L, left. [Color figure can be viewed at wileyonlinelibrary.com]

Liberzon, 2010]. Our findings include both initial and sustained activation increases in MCC and PCC, which is in line with previous anticipation studies in HC demonstrating that MCC activation can be robustly separated into two different components reflecting phasic and sustained activation [Grupe et al., 2013; Herrmann et al., 2016]. Taken together, our findings suggest an early onset of increased cingulate cortex activation that continues to persist over the course of the anticipatory interval during anticipation of aversive stimuli in PTSD patients. This hyperactivation might reflect increased levels of attention and appraisal during threat anticipation [Etkin et al., 2011; Hayes et al., 2012; Kalisch and Gerlicher, 2014; Maier

et al., 2012] as well as selection of an appropriate response to the anticipated aversive stimuli in PTSD [Leech and Sharp, 2014; Vogt, 2014].

Finally, the current study found several initial and sustained activation increases in lateral and medial PFC and one small cluster of decreased activation in dmPFC in PTSD patients compared with HC. Previous anticipatory anxiety studies in PTSD reported no differential activation of PFC [Simmons et al., 2008, 2013a] or decreased IPFC activation [Aupperle et al., 2012]. Deactivation of PFC is also commonly found during symptom provocation [e.g., Gold et al., 2011; Lindauer et al., 2004; Shin et al., 2004, 2005; Williams et al., 2006] and is suggested to reflect

attentional deficits and problems to regulate emotional responding of the limbic system, involving the amygdala [Francati et al., 2007; Hayes et al., 2012; Lanius et al., 2006]. Our study, however, found both PFC and amygdala hyperactivations. One explanation for these inconsistencies could be distinct study designs, for example the combination of anticipation and a continuous performance task [Aupperle et al., 2012; Simmons et al., 2008]. Additionally, subregions of PFC serve a variety of functions and the PFC has both inhibitory and excitatory circuits [Quirk and Beer, 2006]. The initial and sustained lateral PFC hyperactivation in the current study might indicate evaluation of the presented cue as well as expectation of aversive stimuli in response to this cue [Otto et al., 2014], which is also in line with the positive correlation between cue valence rating and vLPFC activation in PTSD patients. Medial PFC regions, on the other hand, are suggested to play a role in emotion regulation through attentional, appraisal, monitoring and executive processes that determine subjective emotional experiences [Etkin, 2010]. Together, medial and lateral PFC are implicated in top-down emotion regulation but also generation processes [Ochsner and Gross, 2005; Otto et al., 2014]. We found sustained increased activation in both medial and lateral PFC regions, possibly indicating the emergence of increased subjective negative emotions during anticipation of aversive stimuli in PTSD patients.

Amygdala and BNST showed functional connectivity with several PFC regions, which is in line with a modulatory interaction between these regions [Duval et al., 2015; Engel et al., 2009; Motzkin et al., 2015]. Decreased functional connectivity between amygdala and lateral and medial PFC could be interpreted as a failure of PFC regions to inhibit aversive responding in the amygdala [Davidson, 2002; Motzkin et al., 2015; Rauch et al., 2003], especially with regard to PTSD [Shin and Liberzon, 2010; Shin et al., 2006]. Furthermore, right BNST showed increased functional connectivity with vmPFC, while left BNST showed decreased functional connectivity with dmPFC. The BNST is known to have close connections to mPFC regions [Avery et al., 2014; Torrisi et al., 2015] and it has been suggested that BNST and mPFC work in concert to express aversive emotional states in contexts of threat anticipation [Avery et al., 2016].

Interestingly, the right amygdala activation that was used as seed region for functional connectivity analysis showed a tendency to be associated with right PFC regions. It should be noted that lateralization has most widely been studied in the domain of language [Corballis, 2015], while hemispheric asymmetry with regard to emotional processing is fairly understudied. There is some evidence for right-sided asymmetry in the neurocircuitry of PTSD, although this has only been discussed in the context of EEG [Meyer et al., 2015]. Generally, the right relative to the left hemisphere is associated with anxious arousal, including vigilance and physiological hyperarousal [Engels et al., 2007], as well as the detection of salient stimuli

[Corbetta and Shulman, 2002] and affective and emotional processing [Cerqueira et al., 2008]. Furthermore, the right prefrontal cortex is implicated in negative affect regulation [Baeken et al., 2014] and it has been shown that the right dlPFC is involved in negative rather than positive stimulus processing [Beraha et al., 2012].

Finally, some limitations of our study should be addressed. The current sample included only female participants and a potential gender-specific effect cannot be excluded. Women are more likely to develop PTSD after a traumatic experience [Shansky, 2015] and have a significantly higher lifetime prevalence of PTSD than men [Tolin and Foa, 2006], which increases the representativeness of our sample. Including only female participants also makes our study more comparable to other relevant studies [Aupperle et al., 2012; Simmons et al., 2008]. Still, the generalizability of our results to male PTSD patients and to PTSD patients in general is unknown. Regarding our control group, our conclusions are limited by the fact that we did not include a trauma-exposed control group. Several studies showed differences between trauma-exposed participants with and without PTSD during processing of affective stimuli [Britton et al., 2005; Shin et al., 2005] and threat anticipation [Simmons et al., 2013a]. In contrast, a large number of relevant fMRI studies in PTSD did not include a trauma-exposed control group [for meta-analysis see Hayes et al., 2012] and anticipation studies with and without trauma-exposed controls yielded similar results [Aupperle et al., 2012; Simmons et al., 2008, 2013a]. Taken together, the inclusion of a trauma-exposed control group would have enabled us to specifically investigate whether differential brain activations and especially those associated with hypervigilance are related to PTSD or trauma-exposure alone. Another potential limitation is the sample size, since fMRI studies on between-group differences with lower-bound sample sizes might be biased toward the detection of only the most powerful effects, while they might be underpowered with regard to less powerful effects [Yarkoni and Braver, 2010]. However, especially our results for amygdala and BNST are based on a clear research line and well-defined *a priori* hypotheses that support the relevance of the current findings. Furthermore, comorbidities constitute a possible confound of our study. However, we carefully ensured that PTSD is the main diagnosis for all patients and since PTSD patients commonly present comorbidities [Javidi and Yadollahie, 2012], the exclusion of patients with comorbid diagnoses would have limited the representativeness and generalizability of our findings. Taken together, the specificity of our findings has to be tested in future studies with larger, mixed samples including trauma-exposed participants without PTSD. Finally, even though our findings suggest specifically altered brain responses on PTSD patients during unpredictable threat anticipation, our methodology does not allow for a comparison with predictable threat anticipation. Future studies should therefore manipulate the level of predictability to investigate this in more detail.

CONCLUSION

This is the first study investigating phasic and sustained brain responses during anticipation of aversive stimuli in PTSD patients. Our results demonstrate dissociation between amygdala and BNST activation in PTSD during phasic and sustained anticipatory anxiety. Additionally, threat anticipation led to phasic and sustained hyperactivations in brain regions that have been shown to be important for PTSD symptomatology, such as cingulate cortex, insula and PFC. Taken together, these findings highlight the importance of different temporal and functional characteristics of brain regions involved in anticipation of aversive stimuli in order to understand hypersensitivity during anticipatory anxiety in PTSD.

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