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Neural Correlates of Inhibition and Contextual Cue Processing Related to Treatment Response in PTSD

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Thirty to fifty percent of posttraumatic stress disorder (PTSD) patients do not respond to treatment. Understanding the neural mechanisms underlying treatment response could contribute to improve response rates. PTSD is often associated with decreased inhibition of fear responses in a safe environment. Importantly, the mechanism of effective treatment (psychotherapy) relies on inhibition and so-called contextual cue processing. Therefore, we investigate inhibition and contextual cue processing in the context of treatment. Forty-one male war veterans with PTSD and 22 healthy male war veterans (combat controls) were scanned twice with a 6- to 8-month interval, in which PTSD patients received treatment (psychotherapy). We distinguished treatment responders from nonresponders on the base of percentage symptom decrease. Inhibition and contextual cue processing were assessed with the stop-signal anticipation task. Behavioral and functional MRI measures were compared between PTSD patients and combat controls, and between responders and nonresponders using repeated measures analyses. PTSD patients showed behavioral and neural deficits in inhibition and contextual cue processing at both time points compared with combat controls. These deficits were unaffected by treatment; therefore, they likely represent vulnerability factors or scar aspects of PTSD. Second, responders showed increased pretreatment activation of the left inferior parietal lobe (IPL) during contextual cue processing compared with nonresponders. Moreover, left IPL activation predicted percentage symptom improvement. The IPL has an important role in contextual cue processing, and may therefore facilitate the effect of psychotherapy. Hence, increased left IPL activation may represent a potential predictive biomarker for PTSD treatment response.
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INTRODUCTION

Posttraumatic stress disorder (PTSD) is a pathological response to experiencing a stressful traumatic event. This trauma- and stress-related disorder highly impacts the life of patients. Symptoms include reexperiencing of the traumatic event, the avoidance of trauma reminders, negative cognitions and mood, and hyperarousal symptoms (APA, 2013).

PTSD patients show exaggerated fear responses to trauma-related stimuli and have difficulties inhibiting their fear response while being in a safe environment. This has been referred to as reduced fear inhibition and decreased contextual cue processing (Jovanovic *et al*, 2012; Rougemont-Bucking *et al*, 2011). Recently, we observed these deficits during cognitive processes unrelated to trauma (van Rooij *et al*, 2014), suggesting more general deficits in PTSD. Response inhibition and contextual cue processing were measured with the stop-signal anticipation task (SSAT, Zandbelt and Vink (2010)). PTSD patients showed less deactivation of the motor cortex during response inhibition, indicating an inhibition deficit (van Rooij *et al*, 2014). Moreover, this inhibition deficit was found to be associated with reduced anticipation of stopping based on contextual cues. This decreased contextual cue processing was coupled with decreased right inferior frontal gyrus (rIFG) activation (van Rooij *et al*, 2014). The rIFG is a region thought to be involved in regulating attention (Duann *et al*, 2009; Hampshire *et al*, 2010) and outcome expectancies (Zandbelt *et al*, 2013). Recently, it is shown that the inferior parietal lobe (IPL) is also crucial in contextual cue processing (Zandbelt *et al*, 2013).

PTSD can be effectively treated with psychotherapy consisting of cognitive behavioral therapy (CBT) with exposure and/or eye movement desensitization and reprocessing (EMDR, Bradley *et al* (2005)). The hypothesized mechanism of this therapy is extinction of learned fear by means of exposure to the traumatic memory (Izquierdo *et al*, 2004; Shipherd and Salters-Pedneault, 2008). Extinction is highly dependent on the context in which it takes place (Shipherd and Salters-Pedneault, 2008), because patients learn to inhibit their fear in a safe environment. Importantly, 30–50% of PTSD patients do not respond to treatment (Bradley *et al*, 2005). As of yet, it is unclear what differentiates PTSD patients who respond to treatment from those who do not.

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Only a few fMRI studies have investigated treatment in PTSD, and they observed associations between treatment outcome and pretreatment striatal and frontal activity during response inhibition, and amygdala and anterior cingulate cortex responses to emotional stimuli (Aupperle *et al*, 2013; Bryant *et al*, 2008; Falconer *et al*, 2013; Felmingham *et al*, 2007; Roy *et al*, 2010; Simmons *et al*, 2013). However, none of the studies included a control group, and in two of these six studies PTSD patients were scanned only prior to the treatment (Bryant *et al*, 2008; Falconer *et al*, 2013). Without a control group treatment effects cannot be separated from the effect of time, learning effects, or habituation. Furthermore, the fMRI signal is hampered by substantial within-subject variability between scan sessions (Zandbelt *et al*, 2008).

Here, we investigate neural mechanisms of inhibition and contextual cue processing related to treatment response in war veterans with PTSD. Inhibition and contextual cue processing were assessed on a cognitive level with the SSAT (Zandbelt and Vink, 2010). In this way we exclude the bias of altered fear processing in PTSD patients, which might be influenced by treatment outcome. Functional MRI scans were collected from PTSD patients before and 6–8 months after treatment. This is the first fMRI study that also scanned healthy war veterans (combat controls) twice with a similar time interval to control for the effect of time and repeated scanning. We first compared PTSD patients with combat controls at both time points to test the hypothesis that treatment improves inhibition and contextual cue processing deficits. Second, within the PTSD group, responders were compared with nonresponders to test the hypothesis that neural correlates of inhibition and contextual cue processing predict treatment response.

MATERIALS AND METHODS

Participants

Veterans with PTSD were recruited from the Military Mental Healthcare outpatient clinics, Ministry of Defence, The Netherlands. PTSD patients were included and examined close to the start of their treatment. All PTSD patients received 'treatment as usual', including CBT with exposure and/or EMDR. The pretreatment scan (T0) was made as close as possible to the starting date of treatment and the posttreatment scan (T6) was made 6–8 months later. Additionally, veterans without a current psychiatric disorder were included as combat controls and also scanned twice with a 6- to 8-month interval.

Results described here are part of a larger study, which was conducted between September 2010 and September 2013. Duration of the study was dependent on the collection of posttreatment scans. Based on a power analysis, our aim was to collect pre and posttreatment scans from 50 PTSD patients and 25 combat controls. The eligibility criteria for inclusion were deployment to a war zone, age 18–60 years and written informed consent. All participants gave written informed consent after having received complete written and verbal explanation of the study, in accordance with procedures approved by the University Medical Center Utrecht ethics committee and the declaration of Helsinki (World Medical Association Declaration of Helsinki, Seoul, 2008). PTSD patients were included when they met the DSM-IV criteria for current PTSD. This was confirmed with a score of $\geqslant 45$ on the clinician-administered PTSD scale (CAPS, Blake *et al* (1990)). The sum of the frequency and intensity of PTSD symptoms was taken as the measure for PTSD severity, ie, CAPS total. Controls were included when they had no current psychiatric disorder and a CAPS $\leqslant 15$. To examine (comorbid) psychiatric disorders at both time points, the structured clinical interview for DSM-IV axis I disorders (First *et al*, 1997) was administered. Subjects were excluded when they had a history of neurological illness, current substance dependence, or when they were suffering from medical or psychological conditions due to which a MRI scan could not be made.

A total of 65 PTSD patients and 31 controls had signed up for the study. As five patients and two controls did not fulfill the eligibility criteria, a total of 60 patients and 29 combat controls were included in the current study. Five patients did not undergo the first MRI scan, because they experienced participation as too much of a burden. Furthermore, four patients and two controls dropped out after the first MRI scan for unknown reasons, two patients did not agree to a second MRI scan and two patients and one control were not scanned a second time, because of poor quality of the first scan. Data from one patient and two controls could not be included in the analyses due to technical issues. Additionally, left-handed participants and the only women were excluded from the current analyses. In sum, T0 and T6 scans were obtained from 41 right-handed male veterans with PTSD and 22 right-handed male veterans without a current psychiatric disorder. For part of the analyses, treatment responders were compared with nonresponders. Based on previous studies, response to treatment was defined as (at least) a 30% reduction of total CAPS score posttreatment (Brady *et al*, 2000; Davidson *et al*, 2001).

Inhibition Task

FMRI scans were made while participants performed the SSAT (Figure 1; van Rooij *et al*, 2014; Zandbelt and Vink, 2010). In the SSAT, three horizontal lines were displayed throughout the task and a moving bar had to be stopped at the middle colored line (Go trial). In a minority of the trials, the bar stopped on its own before the middle colored line and the participant had to withhold their response (stop signal). This is taken as a measure of response inhibition. The color of the middle line indicated the probability that the bar stopped moving on its own: green 0%, yellow 17%, amber 20%, orange 25%, and red 33% (stop-signal probability; contextual cues). Subjects typically slow down their responses when they anticipate that the bar will stop. This slowing is taken as a measure of contextual cue processing. The task lasted for 16 min and 36 s. A total of 234 Go trials with stop-signal probability of 0%, 180 Go trials with stop-signal probability $>0\%$ and 60 stop trials were presented during the task. Each trial lasted 1000 ms with an intertrial interval of 1000 ms. For information on this task see Supplementary Materials and Methods S1 and van Rooij *et al* (2014); Zandbelt and Vink (2010).

Image Acquisition

A 3.0 T MRI scanner (Philips Medical System, Best, The Netherlands) at the University Medical Center Utrecht was

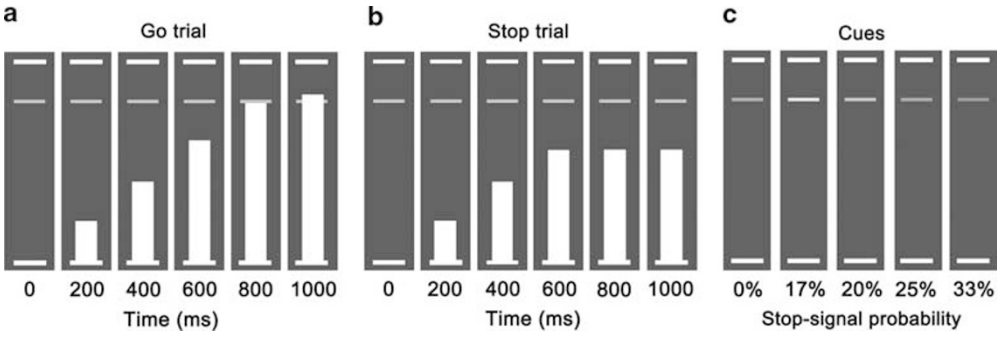

Figure 1 Stop-signal anticipation task (SSAT). Three horizontal lines were displayed throughout the task. A bar moved in 1000 ms from the bottom line to the top. At 800 ms the bar reached the middle colored line and had to be stopped (Go trials, a). In a minority of the trials the bar stopped moving on its own before reaching the middle colored line, consequently, the stop response had to be withheld (stop trials, b). The color of the middle line indicated the stop-signal probability (c). For information on this task see Supplementary Materials and Methods S1 and van Rooij *et al* (2014); Zandbelt and Vink (2010).

used to acquire fMRI images. In total 622 whole brain, T2*-weighted echo planar images with blood oxygen level-dependent contrast (repetition time = 1600 ms, echo time = 23.5 ms, flip angle = 72.5°) were collected in a single run. Each scan lasted 16 min and 36 s. For within-subject registration purposes a T1-weighted image (200 slices, repetition time = 10 ms, echo time = 3.8 ms, flip angle 8, field of view = 240 × 240 × 160 mm, matrix of 304 × 299) was used. For details see Zandbelt and Vink (2010).

Data Analysis

Behavioral performance. Inhibition is the ability to suppress an initial response. Reactive inhibition was measured as speed of inhibition, indicated by the stop-signal reaction time (SSRT, Zandbelt and Vink (2010)). The SSRT was computed according to the integration method and calculated across the four stop-signal probability levels (17–33%). It reflects the latency of the inhibition process (Logan and Cowan, 1984). Better reactive inhibition is indicated by a smaller SSRT.

Contextual cue processing was measured by means of proactive inhibition. Proactive inhibition is the anticipation of stopping based on contextual cues and is measured as the slope of response time to increasing stop-signal probability levels (0–33%). Hence, a steeper slope indicates better proactive inhibition and thus better contextual cue processing.

FMRI. For the preprocessing and analysis of the fMRI data SPM 5 (http://www.fil.ion.ucl.ac.uk/spm/software) was used. Preprocessing and first-level statistical analyses are described elsewhere (Zandbelt and Vink, 2010). In brief, preprocessing included slice time correction, realignment, and coregistration of the anatomical image to the mean functional image, spatial normalization to Montreal Neurological Institute template brain and smoothing (using a 6-mm full-width at half-maximum (FWHM) Gaussian kernel).

A GLM regression analysis was used to estimate task effects (on brain activation). Three regressors were included to model brain activation related to successful stop trials, failed stop trials and Go trials with stop-signal probability >0%. Furthermore, response time and stop-signal probability were included as parametric regressors for Go trials. To correct for head motion, the six realignment parameters were included as regressors of no interest. A high-pass filter with a cutoff of 128 ms was applied to the data to correct for slow signal drifts.

For each participant three contrasts were created: (1) to investigate reactive inhibition, successful stop trials were contrasted to Go trials in the 0% stop-signal probability context; (2) to measure contextual cue processing, the correct Go 17% (CorGo1) was compared with correct Go 0%: the response to cues indicating that a stop-signal could occur *vs* cues indicating Go, and (3) to analyze the effect of different types of contextual cues (indicating an increasing chance of a stop signal), the parametric effect of stop-signal probability on Go-signal activation for stop-signal probability of 17–33% was included as a second measure for contextual cue processing.

Whole brain group analyses were performed for each contrast. The resulting maps were tested for significance at a cluster-defined threshold of $p < 0.001$, and $p < 0.05$ family-wise error-corrected critical cluster size calculated for each contrast. These parameters were determined using SPM and a script (CorrClusTh.m, http://www2.warwick.ac.uk/fac/sci/statistics/staff/academic-research/nichols/scripts/spm), which uses estimated smoothness (estimated FWHM: 8 mm) and Random Field Theory to find these corrected thresholds. The critical cluster sizes for the contrasts (1) reactive inhibition, (2) cues indicating a stop signal, and (3) effect of different types of contextual cues were 18, 20, and 20, respectively, for the CC *vs* PTSD comparison, and 19, 20, and 19, respectively, for the responders *vs* nonresponders group comparison.

Second, mean activation levels (ie, parameter estimates) were extracted from predefined regions of interest (ROIs) for all three contrasts. The ROIs were based on an activation map of independent sample of 24 healthy volunteers who performed the SSAT in a previous study (Zandbelt and Vink, 2010). The same ROIs as in van Rooij *et al* (2014) were used. For reactive inhibition, the left motor cortex was used as ROI. For contextual cue processing, the rIFG and the right striatum were analyzed.

Statistical Analyses

First, all PTSD patients regardless of treatment response were compared with combat controls. Diagnostic group by

time repeated measures analyses were performed for the behavioral and ROI measures. To correct for multiple comparisons, behavioral and ROI analyses were only analyzed individually when the multivariate test (Wilk's lambda) was significant.

Second, PTSD patients were divided into a responder group and nonresponder group, and treatment response group by time repeated measures analyses were performed for the behavioral and fMRI measures of inhibition and contextual cue processing. Again, multivariate tests were performed first. Pretreatment PTSD severity (total CAPS score) was included as a covariate of no interest.

RESULTS

Participants

The participant characteristics are presented in Table 1. Two patients were excluded from analyses: One patient had not received treatment in between the two scans, and the behavior (contextual cue processing) of another patient deviated significantly (>3 SD) from the mean. None of the participants displayed excessive head movement (>4 mm). In total, 39 PTSD patients and 22 combat controls were included in the analyses. The PTSD group was divided into a treatment responder group ($N=22$) and a treatment nonresponder group ($N=17$), using a cutoff of 30% reduction in symptoms (total CAPS score). Pretreatment PTSD symptoms, number of treatment sessions, medication use, and comorbidity did not differ between the two PTSD groups (Table 1).

PTSD *vs* Combat Controls

Behavioral results. Results are presented in Table 2. No interaction between time and diagnostic group was observed for behavioral measures of inhibition and contextual cue processing. Instead, the multivariate test for diagnostic group was significant ($F_{(7,53)}=3.07$, $p=0.01$). A main effect of diagnostic group for contextual cue processing was found ($F_{(1,59)}=5.90$, $p=0.02$). PTSD patients showed a smaller slope of increasing response times to increasing stop-signal probability levels, indicating decreased contextual cue processing compared with combat controls across both time points. Furthermore, a main effect of time was observed for speed of inhibition ($F_{(1,59)}=6.16$, $p=0.02$). Both groups showed a shorter average SSRT at T6, indicating better response inhibition.

FMRI results. Results are shown in Table 2. Neither whole brain analyses nor ROI analyses revealed diagnostic group by time interactions. However, the multivariate test for diagnostic group was significant ($F_{(7,53)}=3.07$, $p=0.01$) and group differences were observed in two ROIs across both time points. PTSD patients showed less deactivation of the left motor cortex during reactive inhibition compared with combat controls ($F_{(1,59)}=4.69$, $p=0.03$). Second, PTSD patients showed less activation in the rIFG during contextual cue processing ($F_{(1,59)}=4.37$, $p=0.04$), ie, when cues indicating a stop-signal could occur were compared with cues indicating Go. Groups did not differ in the right striatum. Additional analyses on the potential effect of medication revealed that current findings were most likely not explained by medication use (Supplementary Results S2).

Responders *vs* Nonresponders

Behavioral results. Findings are presented in Table 2. For behavioral measures of inhibition and contextual cue processing neither a significant interaction between treatment response group and time, nor a significant main effect for treatment response group was observed.

FMRI results. Results are displayed in Figure 2. Whole brain analyses revealed a significant treatment response group by time interaction in the left IPL during contextual cue processing (Figure 2a). Specifically, when cues indicating that a stop signal could occur were compared with cues indicating Go, responders showed more activation in the left IPL than nonresponders before treatment (T0), while the groups did not differ at T6. Mean activation levels were extracted from a sphere around the peak voxel of the difference between the groups and plotted for each group at both time points to visualize this effect (Figure 2b). For inhibition and the second measure of contextual cue processing (ie, effect of increasing stop-signal probability levels), no significant interaction effects or treatment response group differences were observed. ROI analyses showed no treatment response group (by time) effect for inhibition and contextual cue processing.

Post hoc analyses were performed on the extracted sphere around the peak voxel of the difference between the groups. First, paired samples *t*-tests within the responder and nonresponder groups showed a significant pre to posttreatment decrease in the responder group ($t_{(21)}=2.776$, $p=0.011$) and a marginally significant increase in the nonresponder group ($t_{(16)}=2.776$, $p=0.051$). Second, no significant correlations between pretreatment IPL activation and pretreatment severity, and behavioral measures were observed. Third, a *post hoc* regression analysis revealed that pretreatment left IPL activation was a significant predictor for treatment response (expressed in percentage decrease of CAPS), $F_{(1,34)}=7.68$; $p=0.009$; $R=0.44$; $R^2=0.19$ (Figure 2c). The left IPL remained a significant predictor when age, education level, months since deployment, and early traumatic experiences were added as predictors in a second model ($F_{(1,29)}=3.33$; $p=0.017$; $R=0.60$; $R^2=0.36$; left IPL $t=-2.88$; $p=0.007$). Additionally, education level was an independent significant predictor for treatment response ($t=-2.66$, $p=0.013$). Correlation analyses with left pretreatment IPL activation and percentage decrease of the three CAPS symptom clusters revealed a significant correlation with the reexperiencing (CAPS B) cluster ($r^2=-0.40$, $p=0.012$), and a marginally significant correlation with the avoiding and numbing (CAPS C) cluster ($r^2=-0.30$, $p=0.061$).

DISCUSSION

Here, we investigated the neural mechanisms of inhibition and contextual cue processing related to treatment response in PTSD. Analyses comparing PTSD patients with combat controls revealed deficits in contextual cue processing and

Table 1 Participant Characteristics

	Combat controls (N = 22)	PTSD responders (N = 22)	PTSD nonresponders (N = 17)	Test statistic	*p*-value
Age (years)	37.7 ± 10.8	34.3 ± 8.7	38.0 ± 9.8	F = 0.91	0.41
Education level (ISCED)					
Own	3.4 ± 1.9	3.8 ± 1.3	3.1 ± 1.0	F = 1.13	0.33
Father	4.0 ± 1.8	3.7 ± 1.9	3.6 ± 2.1	F = 0.22	0.81
Mother	2.7 ± 1.4	2.4 ± 1.54	2.5 ± 1.7	F = 0.16	0.86
Months since deployment	82.6 ± 87.9	78.0 ± 87.3	100.5 ± 114.1	F = 0.29	0.75
Number of missions (1/2/3/>3)	2.5 ± 1.4 (7/6/4/5)	3.5 ± 4.3 (7/5/3/7)	2.2 ± 1.3 (7/3/5/2)	F = 1.22	0.30
Early traumatic experiences	3.1 ± 2.8	4.3 ± 3.8	4.8 ± 4.8	F = 0.99	0.38
PTSD symptoms pretreatment					
Reexperiencing (CAPS B)	0.5 ± 0.9	23.6 ± 5.2	22.7 ± 6.5	F = 167.67	<0.001
Avoiding (CAPS C)	0.8 ± 2.1	23.8 ± 11.2	22.7 ± 6.4	F = 61.82	<0.001
Hyperarousal (CAPS D)	2.9 ± 3.0	24.3 ± 5.3	24.9 ± 4.6	F = 170.14	<0.001
Total (CAPS total)	4.2 ± 4.1	71.7 ± 15.2	70.3 ± 11.3	F = 253.68	<0.001
PTSD symptoms posttreatment					
Reexperiencing (CAPS B)		8.4 ± 8.1	22.2 ± 6.1	t = −5.85	<0.001
Avoiding (CAPS C)		7.1 ± 6.2	20.7 ± 8.1	t = −5.94	<0.001
Hyperarousal (CAPS D)		12.6 ± 7.1	23.2 ± 6.7	t = −4.78	<0.001
Total (CAPS total)		28.1 ± 17.8	66.1 ± 16.2	t = −6.88	<0.001
Treatment, number of sessions		8.8 ± 5.4	9.8 ± 4.7	t = −0.60	0.55
Range		1–20	3–18		

	PTSD responders (N = 22)		PTSD nonresponders (N = 17)			
	T0	T6	T0	T6	*p*-value T0	*p*-value T6
Medication (number)	10	8	6	10	0.55	0.16
SSRI	3	4	5	9	0.23	0.02
Benzodiazepine	5	5	4	2	0.95	0.38
SARI	2	1	0	0	0.20	0.37
Antipsychotics	2	2	0	2	0.20	0.79
Nicotine antagonist	1	0	0	0	0.37	—
β-Blocker	0	0	2	0	0.10	—
Comorbid disorders (number)	13	4	13	7	0.25	0.11
Mood	11	3	9	2	0.52	0.86
Anxiety	4	2	8	5	0.12	0.10
Somatic	1	0	1	1	0.85	0.25

Abbreviations: CAPS, Clinician-administered PTSD scale (Blake *et al*, 1990); ISCED, International Standard Classification of Education (Schneider, 2013); PTSD, posttraumatic stress disorder patients.T0, pretreatment measurement; T6, posttreatment measurement.
Data are presented as means ± SD.
p-values of medication and comorbid disorder analyses are based on χ^2-analyses.

inhibition across both time points, extending our previous findings (van Rooij *et al*, 2014) by showing that these deficits do not change with treatment. Specifically, PTSD patients showed reduced deactivation of the motor cortex during inhibition, and decreased contextual cue processing coupled with reduced right IFG activation. Within the PTSD group, treatment responders and nonresponders did not differ on any of these measures, providing further support for the notion that these represent general deficits of PTSD. However, compared with nonresponders, responders showed increased activation in the left IPL during contextual cue processing already at baseline, prior to treatment. Furthermore, the responders showed a significant decrease in left IPL activation posttreatment, whereas the nonresponders showed a marginally significant increase. Left IPL activation at baseline significantly predicted treatment response, and was particularly associated with decrease in reexperiencing symptoms. The IPL is involved in contextual cue processing, which is important for psychotherapy and could therefore facilitate the effect of psychotherapy.

Table 2 Behavioral and fMRI Results

	Combat controls (N = 22)		PTSD (N = 39)		Test statistic	*p*-value
	T0	T6	T0	T6		
Reactive inhibition						
SSRT	327 ± 4	318 ± 5	330 ± 3	324 ± 4	$F_{group} = 1.05$	0.31
ROI left motor cortex	− 1.08 ± 0.13	− 1.03 ± 0.34	− 0.61 ± 0.10	− 0.46 ± 0.34	$F_{group} = 4.69$	0.03
Contextual cue processing						
Slope response time	95 ± 17	108 ± 16	56 ± 12	55 ± 12	$F_{group} = 5.90$	0.02
ROI right IFG 0–17%	0.09 ± 0.17	0.05 ± 0.15	− 0.18 ± 0.13	− 0.16 ± 0.11	$F_{group} = 4.37$	0.04
ROI right Striatum 0–17%	0.03 ± 0.06	− 0.02 ± 0.06	− 0.44 ± 0.05	− 0.05 ± 0.05	$F_{group} = 0.91$	0.34
ROI right IFG 17–33%	2.48 ± 0.94	2.74 ± 1.11	2.45 ± 0.71	2.24 ± 0.83	$F_{group} = 0.07$	0.79
ROI right Striatum 17–33%	1.06 ± 0.43	0.01 ± 0.46	0.93 ± 0.32	0.98 ± 0.35	$F_{group} = 1.04$	0.31
	PTSD responders (N = 22)		PTSD nonresponders (N = 17)		Test statistic	*p*-value
	T0	T6	T0	T6		
Reactive inhibition						
SSRT	330 ± 4	324 ± 5	331 ± 5	326 ± 6	$F_{group} = 0.05$	0.82
ROI left motor cortex	− 0.66 ± 0.14	− 0.18 ± 0.39	− 0.55 ± 0.16	− 0.83 ± 0.45	$F_{group} = 0.72$	0.40
Contextual cue processing						
Slope response time	60 ± 16	53 ± 11	51 ± 18	58 ± 12	$F_{group} = 0.02$	0.90
ROI right IFG 0–17%	− 0.08 ± 0.18	− 0.17 ± 0.17	− 0.32 ± 0.20	− 0.15 ± 0.19	$F_{group} = 0.64$	0.43
ROI right Striatum 0–17%	0.06 ± 0.06	− 0.03 ± 0.07	− 0.18 ± 0.07	− 0.07 ± 0.08	$F_{group} = 3.96$	0.05
ROI right IFG 17–33%	2.18 ± 0.98	2.19 ± 1.13	2.81 ± 1.11	2.30 ± 1.28	$F_{group} = 0.10$	0.76
ROI right Striatum 17–33%	0.52 ± 0.43	0.76 ± 0.49	1.46 ± 0.49	1.26 ± 0.56	$F_{group} = 1.77$	0.19

Abbreviations: PTSD, posttraumatic stress disorder patients; Right IFG, right inferior frontal gyrus; SSRT, stop-signal response time (ms).
Data are presented as means ± SD.

PTSD *vs* Combat Controls

Decreased deactivation of the left motor cortex during inhibition, and reduced contextual cue processing coupled with decreased rIFG activation was observed in PTSD patients compared with combat controls before and after (successful) treatment. Previously, we observed these deficits in PTSD patients pretreatment (van Rooij *et al*, 2014), thereby supporting the theory of reduced contextual cue processing during fear inhibition and extending it to cognitive processes. We concluded that reduced inhibition and contextual cue processing represent a more general deficit in PTSD. The current results indicate that inhibition and contextual cue deficits do not recover in PTSD patients despite clinical improvement, and are therefore not related to the state of PTSD. Indeed, even after treatment, responders still showed reduced contextual cue processing compared with controls. These deficits likely represent either vulnerability factors for developing PTSD or consequences of PTSD, ie, scar characteristics of PTSD. Impaired inhibition and decreased contextual cue processing have consistently been observed in PTSD patients during fear processing (Jovanovic *et al*, 2012; Rougemont-Bucking *et al*, 2011; Wessa and Flor, 2007). Studies investigating fear inhibition before trauma exposure consistently found that decreased extinction learning predicts development of PTSD symptoms (Guthrie and Bryant, 2006; Lommen *et al*, 2013; Pole *et al*, 2009). These studies therefore suggest that inhibition deficits may be a vulnerability factor for PTSD rather than a scar aspect. Though, a prospective study investigating inhibition and contextual cue processing pre and posttrauma would be necessary to confirm this. It could then be hypothesized that improving inhibition and contextual cue processing skills might be important for preventing the development of PTSD in high-risk samples. However, our results suggest that it is unlikely that improving inhibition and contextual cue processing deficits is relevant for treatment of PTSD, as these deficits are not affected by treatment. This information contributes to our understanding of treatment effects in PTSD and is highly relevant for future studies and the focus of treatment, because it should not aim at improving inhibition skills.

Although several fMRI treatment studies on PTSD exist (Aupperle *et al*, 2013; Falconer *et al*, 2013; Felmingham *et al*, 2007; Roy *et al*, 2010; Simmons *et al*, 2013), none of these included a control group. Without a control group, the effect of treatment cannot be disentangled from the general effects of time, learning, and habituation effects, as

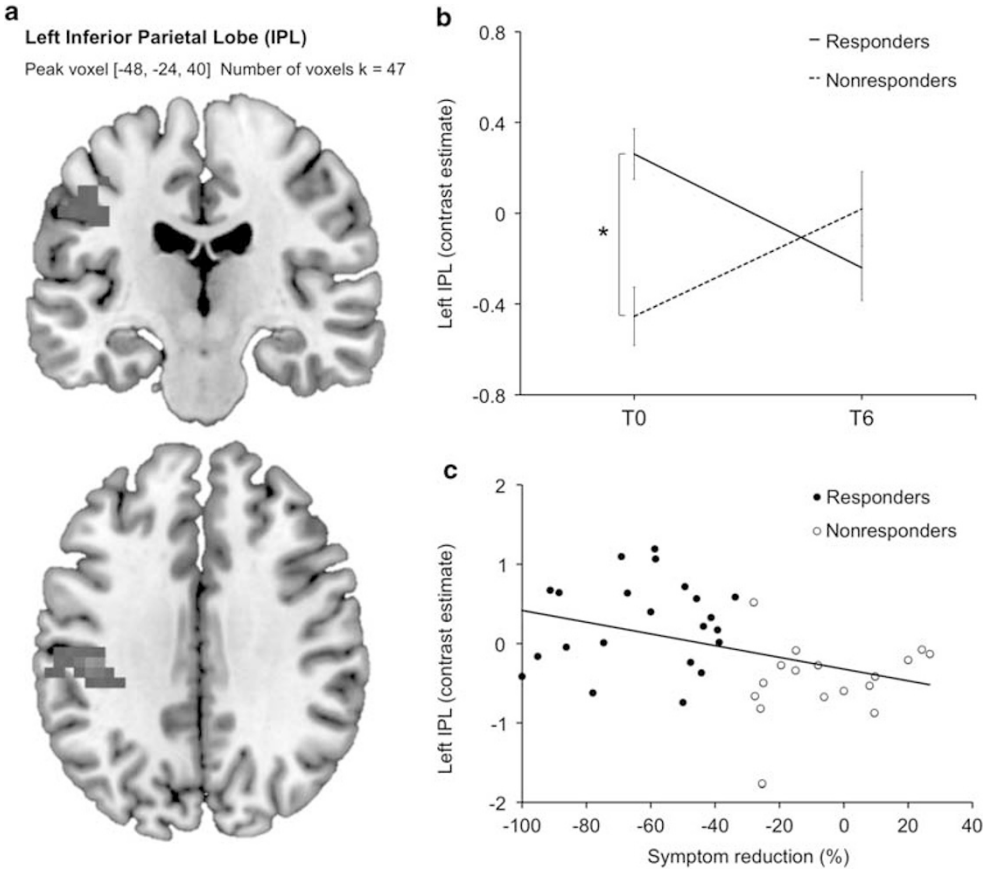

Figure 2 Left inferior parietal lobe (IPL) activation in treatment responders and nonresponders. (a) Whole brain group analysis of contextual cue processing revealed a significant response group by time interaction. The significant cluster is displayed on a standardized brain (MRIcron). Left = left. (b) Mean activation levels of the left IPL plotted for each group pretreatment (T0) and posttreatment (T6). Error bars indicate the standard errors. (c) For each PTSD patient, mean left IPL activation level (T0) was plotted against percentage symptom reduction (based on decrease in CAPS score).

well as within-subject variability between scan sessions of the fMRI signal (Zandbelt *et al*, 2008). For example, in the current study, we observed an effect of time on speed of inhibition. As this effect was observed in both patients and controls, this most likely represents a learning effect. Importantly, in studies without a control group this learning effect can be misinterpreted as an effect of treatment.

Responders *vs* Nonresponders

Whole brain analyses comparing responders and nonresponders revealed increased left IPL activation during contextual cue processing in PTSD patients who subsequently responded to treatment. Indeed, the IPL was recently shown to be crucial for contextual cue processing (Zandbelt *et al*, 2013). Contextual cue processing depends on working memory processing (Travis *et al*, 2013), and working memory processing is known to be affected in PTSD (Vasterling *et al*, 2002). Additionally, the IPL has previously been implicated in PTSD during working memory updating (Clark *et al*, 2003; Moores *et al*, 2008; Shaw *et al*, 2009). Also, during a working memory task weaker connectivity with the IPL and other areas involved in salience and executive functions was observed in PTSD patients compared with controls (Daniels *et al*, 2010). Working memory functioning is thought to underlie the process of learning when to inhibit your response based on contextual information, therefore, appropriate (working) memory functioning is thought to be required for CBT (Shipherd and Salters-Pedneault, 2008). EMDR is thought to depend specifically on working memory updating (Gunter and Bodner, 2008). Taken together, these results and hypotheses are in line with our finding of increased left IPL activation during contextual cue processing in PTSD patients who respond to treatment compared with nonresponders. Moreover, we observed that left IPL activation predicted treatment response and was particularly associated with decrease in reexperiencing symptoms. Higher left IPL activation could facilitate the mechanism of CBT and/or EMDR, eventually resulting in symptom improvement. Replication of these findings is required, however, to further explore and substantiate the predictive value of left IPL activation for psychotherapy. Subsequently, interventions to increase left IPL activation (eg, with transcranial magnetic stimulation or transcranial direct current stimulation, Saunders *et al*, (2014)) before treatment, should be investigated.

Treatment response group differences in IPL activation were only observed pretreatment. The task had been performed twice, which induces learning effects. This can

be observed in the responder group, who showed a significant reduction of left IPL activation over time. In contrast, the nonresponder group showed an (marginally significant) increase in activation, suggesting that their learning process has not been finalized. The IPL is thought to be involved in working memory updating, and at the posttreatment scan this learning has been completed in the responders, which could explain the absence of group differences posttreatment.

Although only marginally significant differences in education level were observed between responders and nonresponders, a higher education level was also a significant predictor for treatment response. Normal to above normal intelligence has been suggested to enhance treatment outcome, because psychotherapies involve verbal-emotional-intellectual processes (Curtis, 1985). In a group of obsessive compulsive disorder patients, higher verbal IQ indeed predicted better treatment response to CBT (D'Alcante *et al*, 2012). PTSD patients who responded to CBT had better verbal memory than nonresponders, although IQ did not explain differences (Wild and Gur, 2008). It can be hypothesized that increased IPL activation and increased IQ both contribute to enhanced cognitive functioning, which could result in a better response to cognitive behavioral therapy. Thus, our findings suggest that a higher education level might be beneficial for treatment outcome, but the exact relationship should be further investigated.

Limitations

In this study all patients received CBT with exposure and/or EMDR, but the number of sessions and the exact nature of treatment was not controlled. Therefore, no conclusions on the effects of, or the predictive values for a specific treatment can be drawn. However, investigating 'treatment as usual' allows for better generalization to actual treatment. In contrast to our previous study, several patients using medication were included in this study. Therefore, the effect of medication use was investigated by comparing medication naive patients and patients using medication at both time points for all the measures that differed between groups. No significant differences were observed, thus it is unlikely that medication confounds these results.

CONCLUSION

Treatment (successful or not) does not improve two of the core deficits of PTSD, impaired inhibition and contextual cue processing. These deficits are therefore thought to represent vulnerability factors or scar aspects of PTSD. Patients who responded to treatment showed increased left IPL activation during contextual cue processing before treatment compared with nonresponders. Moreover, pretreatment levels of left IPL activation predicted percentage symptom improvement and this was particularly associated with decrease in reexperiencing symptoms. The left IPL is implicated in contextual cue processing (Zandbelt *et al*, 2013), a mechanism crucial for effective psychotherapy in PTSD (Shipherd and Salters-Pedneault, 2008). As such, the IPL may facilitate the effect of psychotherapy, resulting in a better treatment outcome. This study reveals an important potential predictive biomarker (Prata *et al*, 2014) for PTSD treatment response although replication of this study is required to further explore and substantiate the predictive value of the left IPL response.

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Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)