

Impaired right inferior frontal gyrus response to contextual cues in male veterans with PTSD during response inhibition

Sanne J.H. van Rooij, MSc; Arthur R. Rademaker, PhD; Mitzy Kennis, MSc; Matthijs Vink, PhD; René S. Kahn, MD, PhD; Elbert Geuze, PhD

van Rooij, Rademaker, Kennis, Vink, Kahn, Geuze — Brain Center Rudolf Magnus, Department of Psychiatry, University Medical Center Utrecht, the Netherlands; van Rooij, Rademaker, Kennis, Geuze — Research Centre, Military Mental Healthcare, Ministry of Defence, the Netherlands

Background: Posttraumatic stress disorder (PTSD) is often associated with impaired fear inhibition and decreased safety cue processing; however, studies capturing the cognitive aspect of inhibition and contextual cue processing are limited. In this fMRI study, the role of contextual cues in response inhibition was investigated. **Methods:** Male medication-naïve war veterans with PTSD, male control veterans (combat controls) and healthy nonmilitary men (healthy controls) underwent fMRI while performing the stop-signal anticipation task (SSAT). The SSAT evokes 2 forms of response inhibition: reactive inhibition (outright stopping) and proactive inhibition (anticipation of stopping based on contextual cues). **Results:** We enrolled 28 veterans with PTSD, 26 combat controls and 25 healthy controls in our study. Reduced reactive inhibition was observed in all veterans, both with and without PTSD, but not in nonmilitary controls, whereas decreased inhibition of the left pre/postcentral gyrus appeared to be specifically associated with PTSD. Impaired behavioural proactive inhibition was also specific to PTSD. Furthermore, the PTSD group showed a reduced right inferior frontal gyrus response during proactive inhibition compared with the combat control group. **Limitations:** Most patients with PTSD had comorbid psychiatric disorders, but such comorbidity is common in patients with PTSD. Also, the education level (estimate of intelligence) of participants, but not of their parents, differed among the groups. **Conclusion:** Our findings of reduced proactive inhibition imply that patients with PTSD show reduced contextual cue processing. These results complement previous findings on fear inhibition and demonstrate that contextual cue processing in patients with PTSD is also reduced during cognitive processes, indicating a more general deficit.

Introduction

Posttraumatic stress disorder (PTSD) is an anxiety disorder that can develop after a traumatic event.¹ Two of the core PTSD features include re-experiencing of the traumatic event and increased arousal. Studies have suggested that diminished inhibition of the fear response underlies these PTSD symptoms.²⁻⁴ Impaired fear inhibition is a well-known and well-studied issue in patients with PTSD,²⁻⁶ but studies capturing the cognitive aspect of inhibition are limited. Inhibition is an essential component of several cognitive processes⁷ and can be measured by assessing response inhibition. Response inhibition pertains to the suppression of an initial response and the adjustment of the behavioural response accordingly.⁸ In addition,

PTSD has been associated with decreased inhibition of brain areas; reduced inhibition of the amygdala by the ventromedial prefrontal cortex mediates decreased fear inhibition in patients with PTSD.⁵ Therefore, applying functional imaging during the investigation of response inhibition in patients with PTSD is highly relevant.

Response inhibition can be measured with the go/no-go task or the stop-signal task (SST). In inhibition tasks, the response to a go stimulus has to be inhibited when an infrequent no-go or stop signal is presented.⁹ With an adapted version of the SST, the stop-signal anticipation task (SSAT),¹⁰ a differentiation between reactive inhibition and proactive inhibition can be made. Reactive inhibition is the outright stopping of a response and is the result of inhibition of the motor areas.^{11,12} Impaired reactive

Correspondence to: S.J.H. van Rooij, Heidelberglaan 100 (HPN B01.2.06), 3584 CX, Utrecht, the Netherlands; SJHvanRooij@gmail.com or S.J.H.vanRooij-3@umcutrecht.nl

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response inhibition has been demonstrated in patients with PTSD compared with healthy controls, but not compared with trauma controls.^{13–15} Functional MRI has shown activation in the prefrontal cortex and motor cortex during response inhibition, which was decreased in patients with PTSD compared with healthy controls.¹⁵ Another fMRI study demonstrated reduced activation in the ventromedial prefrontal cortex in patients with PTSD during a response inhibition task.¹⁵

Proactive inhibition pertains to the anticipation of stopping and relies on the processing of contextual cues.¹⁶ Patients with PTSD are unable to fully recognize cues that signal a safe environment (contextual cues),^{5,6} and this deficit represents an essential component of impaired fear inhibition. It is not known, however, if reduced contextual cue processing is also apparent in other (cognitive) domains. If so, this would represent a more general deficit in patients with PTSD. Investigating the role of contextual cues during response inhibition would elucidate this issue. The right inferior frontal gyrus (rIFG) has often been associated with response inhibition¹⁷ and may be particularly important for proactive inhibition, because it is involved in regulating attention^{11,17} and outcome expectancies.¹² The striatum is involved in the anticipation of stopping the response.¹²

In the present study both reactive and proactive inhibition were investigated; participants performed the SSAT inhibition task¹⁰ during fMRI. Two previous fMRI studies on response inhibition in patients with PTSD investigated reactive inhibition in small samples^{13,15} but did not control for task performance. Moreover, to our knowledge, proactive inhibition has never been investigated in a PTSD sample. As it is important to differentiate PTSD-related alterations from consequences of stress/trauma exposure,¹⁸ we included male war veterans with PTSD, male war veterans without a current psychiatric

disorder (combat controls), and a nonmilitary healthy male sample (healthy controls). We hypothesized that reactive inhibition would be impaired in patients with PTSD and that these patients would have increased stop-signal reaction times. In line with previous studies,^{13,15} we expected the differences to be in contrast to the healthy control and not the combat control group. We also hypothesized that the patients with PTSD would show decreased inhibition of the motor cortex during response inhibition. Furthermore, we expected that patients with PTSD would show decreased behavioural proactive inhibition, indicated by a smaller increase in response time to increasing stop-signal probability levels, and that they would show decreased activation of the rIFG and right striatum compared with both the combat controls and healthy controls during proactive inhibition.

Methods

Participants

We recruited male veterans with PTSD from the Military Mental Health Care outpatient clinics, Ministry of Defence, the Netherlands. Through advertisements, we recruited veterans without a current psychiatric illness (combat controls) and nonmilitary men without a current psychiatric illness (healthy controls) as 2 separate control groups. We used the clinician-administered PTSD scale¹⁹ to quantify the severity of PTSD in the patient group and to confirm that both control groups had no clinically significant PTSD symptoms. The structured clinical interview for DSM-IV Axis I disorders²⁰ was administered to examine (comorbid) psychiatric disorders. Individuals with a history of neurologic illness were not included. After the

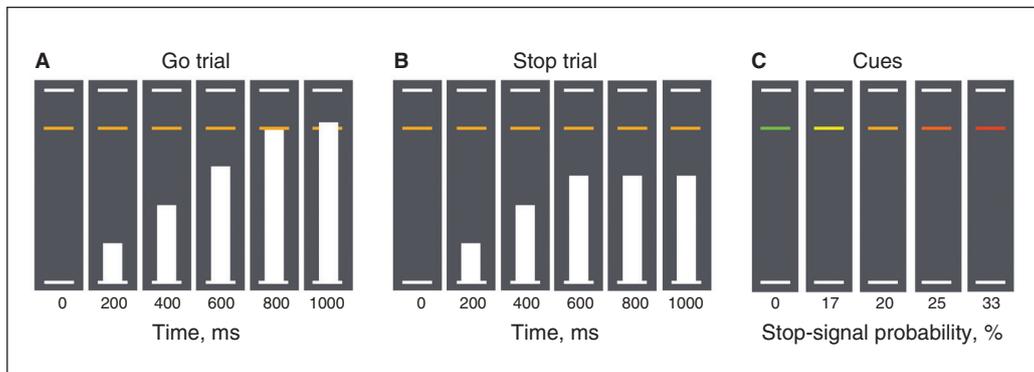


Fig. 1: Stop-signal anticipation task (SSAT). Three horizontal lines are displayed. A bar moves in 1000 ms from the bottom line to the top. The intertrial interval is also 1000 ms. The moving bar has to be stopped at the middle colored line at 800 ms. These trials are referred to as “go trials” (A). In a subpart of the trials the moving bar will stop on its own before reaching the middle colored line (stop signal). The stop response has to be withheld in these trials, and they are therefore referred to as “stop trials” (B). The colour of the middle line indicates the stop-signal probability: green 0%, yellow 17%, amber 20%, orange 25% and red 33% (C). The task consists of 414 go trials (0%, $n = 234$; 17%, $n = 30$; 20%, $n = 48$, 25%, $n = 54$; 33%, $n = 48$) and 60 top trials (17%, $n = 6$; 20%, $n = 12$, 25%, $n = 18$; 33%, $n = 24$). These trials were presented in pseudo-random order. The time before the stop signal appears (i.e., stop-signal delay [SSD]) was set at 550 ms, but varies in accordance with stop performance to generate a reasonably similar number of correct and incorrect trials. When stopping was successful, SSD was increased by 25 ms, making stopping more difficult. Vice versa, SSD was decreased by 25 ms each time the participant failed to stop. The SSD was adjusted for each stop-signal probability separately. For more details on the task, see the study by Zandbelt and Vink.¹⁰

MRI scan, we used the Dissociative State Symptom scale — short form (DSS)²¹ to check for the presence of dissociative symptoms during the scan. All participants gave written informed consent after having received complete written and verbal explanations of the study, in accordance with procedures approved by the University Medical Center Utrecht (UMCU) ethics committee and the declaration of Helsinki.²²

Inhibition task

Participants underwent fMRI while performing the SSAT (Fig. 1). The SSAT measures reactive and proactive inhibition. Three horizontal lines are displayed continuously throughout the task. During each trial, a bar moves from the lower to the upper line in 1000 ms. The main task is to press the button to stop this moving bar as close as possible to the middle colored line, which is around 800 ms (go trials). In a subpart of the trials the moving bar stops on its own before it has reached this middle colored line (stop signal), indicating that the stop response has to be withheld (stop trials). The probability that the bar stops on its own was manipulated across trials and was indicated by the colour of the middle line: green 0%, yellow 17%, amber 20%, orange 25% and red 33% (stop-signal probability). In total, 234 go trials with stop-signal probability of 0%, 180 go trials with stop-signal probability greater than 0% and 60 stop trials were presented. Two rest blocks of 24 seconds each, where only the background was displayed, were applied at one-third and two-thirds of the task. The interval between trial onset and presentation of the stop signal, the stop-signal delay (SSD), was initially set at 550 ms. However, the SSD was adjusted (in steps of 25 ms) based on the individual participant's performance to obtain equal performance among participants. In this way, the interpretation of the fMRI results is not confounded by (large) differences in task performance.

Before the fMRI experiment, participants were trained on the SSAT. They were instructed that the first goal was to stop the bar as close to the middle line as possible, and the second goal was to avoid stopping the bar when it had stopped on its own. They were instructed that both goals were equally important. Participants were informed that the stop trial would never occur when the green line was presented. Participants were told that the stop-signal was least likely when the yellow line was presented and most likely during the presentation of the red line, and that the amber and orange cues represented intermediate stop chances. The exact stop-signal probabilities were not revealed. For more details on the task, see the study by Zandbelt and Vink.¹⁰

Image acquisition

Functional images were acquired using a 3.0 T MRI scanner (Philips Medical Systems) at the UMCU. A total of 622 whole brain, T_2^* -weighted echo planar images with blood oxygen level-dependent contrast (repetition time [TR] 1600 ms, echo time [TE] 23.5 ms, flip angle 72.5°) were collected in a single run. Each scan lasted 16 minutes and 36 seconds. A T_1 -weighed image (200 slices, TR 10 ms, TE 3.8 ms, flip angle 8°, field of view 240 × 240 × 160 mm, matrix 304 × 299 mm) was used for within-subject registration purposes.

Statistical analysis

Behavioural performance

Reactive inhibition was measured as the speed of inhibition, and was indicated by the stop-signal reaction time (SSRT¹⁰). The SSRT was computed according to the integration method and calculated across the 4 stop-signal probability levels (17%–33%). It reflects the latency of the inhibition process.⁹ A smaller SSRT reflects a faster speed of inhibition, indicating better reactive inhibition. We compared the SSRT for the 3 groups, and post hoc tests with least significant difference (LSD) correction were performed when group differences were significant.

Proactive inhibition was taken as a measure for contextual cue processing. It was defined as the anticipation of inhibition based on contextual cues. In this task this means that when the participant expects that the bar will stop on its own — based on the colour of the line in the middle of the screen — the participant needs to wait to respond. This waiting, or the slowing of the response, will result in larger response times to the trials with larger stop-signal probability levels. This “slowing” is proactive inhibition and is measured as the slope of increasing response time to increasing stop-signal probability levels (0%–33%). Thus, better proactive inhibition is indicated by larger response times to increasing stop-signal probability levels. We compared this slope for the 3 groups with a univariate general linear model (GLM) with post hoc (LSD-corrected) tests. Proactive inhibition could be influenced by task baseline differences (response time to go 0% trials). To rule out this possibility, we compared baseline response time among the 3 groups and included it as a covariate for the behavioural and region of interest (ROI) proactive inhibition analyses.

Functional MRI

Functional MRI data were preprocessed and analyzed with SPM 5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm/>). Preprocessing included slice time correction, realignment, coregistration of the anatomic image to the mean functional image, spatial normalization to a 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 greater than 0%. Furthermore, response time and stop-signal probability were included as parametric regressors for go trials. To correct for head motion, the 6 realignment parameters were included as regressors of no interest. We applied a high-pass filter with a cutoff of 128 ms to the data to correct for slow signal drifts.

Five contrasts were created for each participant: correct go trials with a stop-signal probability of 0% compared with rest to investigate potential baseline differences; successful stop trials versus go trials in the 0% stop-signal probability context to investigate reactive inhibition; the parametric effect of stop-signal probability on go-signal activation for a stop-signal probability of 17%–33% to investigate proactive inhibition; correct go 17%, 20%, 25% and 33% versus correct go 0%

to investigate the average increase in activation across all 4 stop-signal probability levels versus go trials; and correct go 17% versus correct go 0% to measure the response to the smallest stop-signal probability level (a stop chance) versus go trials (no stop chance), as 2 additional measures for proactive inhibition.

For all 5 contrasts, mean activation levels were extracted from predefined ROIs. The ROIs were based on an activation map of an independent sample of 24 healthy volunteers who performed the SSAT in a previous study.¹⁰ For reactive inhibition, we analyzed the left pre/postcentral gyrus. For proactive inhibition, we used the right striatum and the rIFG as ROIs. To test if brain regions outside these ROIs were involved in reactive or proactive inhibition, we performed a whole brain group analysis using a 1-way analysis of variance for each contrast. The resulting maps were tested for significance at a cluster-defined threshold of $p < 0.005$, and a $p < 0.05$, family-wise error-corrected critical cluster size of 42 voxels for the reactive inhibition contrast and of 45 voxels for the baseline and proactive inhibition contrasts. These parameters were determined using SPM and a script (CorrClusTh.m; www2.warwick.ac.uk/fac/sci/statistics/staff/academic-research/nichols/scripts/spm), which uses estimated smoothness (estimated FWHM $3.56 \times 3.65 \times 3.46$ voxels = estimated FWHM 8 mm) and random field theory to find these corrected thresholds.

Results

Participants

We included 28 patients with PTSD in our study. Although 29 were recruited, 1 patient was removed from our analysis because of excessive head movement (> 3 mm). The patients with PTSD were medication-naïve, except for 1 patient who used benzodiazepines occasionally up to 2 weeks before the MRI scan. We also included 26 combat controls and 25 healthy controls in our study. Although 26 healthy controls were recruited, 1 was removed from our analyses because his behavioural performance deviated significantly (> 3 standard deviations) from the group average. The demographic characteristics of participants are summarized in Table 1.

Most of the patients with PTSD had a comorbid psychiatric disorder: mood disorder ($n = 15$), anxiety disorder other than PTSD ($n = 7$), and somatoform/pain disorder ($n = 2$). None of the controls had a current psychiatric disorder. The 3 groups did not differ in age and handedness (according to Edinburgh Handedness Inventory²³). Participants' education level differed significantly among the groups ($F_{2,76} = 8.72$, $p < 0.001$). The education level of the healthy control group was higher than that of the PTSD ($p < 0.001$) and combat control groups ($p = 0.002$), but the PTSD and combat control groups did not differ from one another. Parental education level was comparable among the 3 groups. Year and country of deployment, number of military missions and time since deployment were comparable between the combat control and PTSD groups. The most common military deployments included missions to Lebanon, the Balkans, Iraq and Afghanistan. No evidence for

dissociation during the MRI scan was obtained from the DSS for any of the participants.

Baseline responding

Baseline response time was similar among the groups ($F_{2,76} = 0.83$, $p = 0.44$; Table 2). Furthermore, activation did not differ among the groups in any of the 3 ROIs (left pre/postcentral gyrus: $F_{2,76} = 0.31$, $p = 0.74$; rIFG: $F_{2,76} = 0.27$, $p = 0.77$; right striatum: $F_{2,76} = 0.55$, $p = 0.58$; Table 2). Whole brain analyses did not reveal group differences outside the ROIs.

Reactive inhibition

Behavioural performance

Speed of inhibition (SSRT) differed significantly among the groups ($F_{2,76} = 16.97$, $p < 0.001$), with the healthy control group being faster than both the combat control ($p < 0.001$) and the PTSD groups ($p < 0.001$; Table 2).

Functional MRI

The level of activation of the left pre/postcentral gyrus during correct stop trials compared with go trials was significantly different among the groups ($F_{2,76} = 3.86$, $p = 0.025$). All participants showed reduced activation when stop trials were contrasted to go trials, but post hoc tests revealed that patients with PTSD showed less reduction in activation (inhibition) of the left pre/postcentral gyrus than the combat control group ($p = 0.011$) and healthy control group ($p = 0.041$), as can be seen in Table 2. As there were differences in education level, we tested if there was a correlation between education and SSRT within each group; there were no significant correlations (PTSD: $r = -0.066$, $p = 0.74$; combat control: $r = -0.05$, $p = 0.80$; healthy control: $r = -0.24$, $p = 0.24$).

Whole brain analyses per group showed that all groups activated a network of regions commonly associated with response inhibition, consisting of the rIFG, insula, right supramarginal gyrus, right middle frontal gyrus, right supplementary motor area and left superior frontal gyrus. Deactivation of the default mode network (DMN; e.g., left precuneus, left posterior cingulate gyrus) and left pre/postcentral gyrus was observed in all groups (see the Appendix, Table S1, available at jpn.ca). A whole brain analysis performed to investigate group effects outside the predefined ROIs revealed no significant results (Fig. 2A).

Proactive inhibition

Behavioural performance

The increase in response time (proactive inhibition) differed among the 3 groups ($F_{2,75} = 3.87$, $p = 0.025$; Table 2), with the PTSD group showing reduced proactive inhibition compared with the combat control group ($p = 0.044$) and the healthy control group ($p = 0.010$). Correlation analyses were performed between the increase in response time and education, because education level differed among the groups;

there were no significant correlations (PTSD: $r = 0.11, p = 0.58$; combat control: $r = 0.24, p = 0.23$; healthy control: $r = -0.04, p = 0.85$).

Functional MRI

Activation in the rIFG differed among the groups ($F_{2,75} = 3.40, p = 0.039$; Table 2) during the parametric contrast. That is, the slope of the rIFG response to contextual cues was different among groups. Post hoc tests revealed that the PTSD group showed a larger increase in rIFG activation with increasing stop-signal probability levels than the combat control group ($p = 0.012$). This result was not due to an overall difference in

rIFG activation in the PTSD group compared with the combat control group, as the mean increase of rIFG activation across all 4 stop-signal probabilities versus correct go 0% did not differ between the 2 groups ($t_{52} = 0.98, p = 0.33$). However, this rIFG difference can be explained by the significantly larger increase in rIFG activation in the combat control group to the smallest stop-signal probability level (17%) relative to correct go 0% when compared with the PTSD group ($t_{52} = 1.975, p = 0.054$). No significant differences with the healthy control group were observed. There were no group differences in the right striatum for the parametric contrast ($F_{2,75} = 1.16, p = 0.32$; Table 2).

Table 1: Demographic and clinical characteristics of the PTSD, combat control and healthy control groups

Characteristic	Group; mean ± SD*			Statistic	p value
	PTSD, n = 28	Combat control, n = 26	Healthy control, n = 25		
Age, yr	36.6 ± 10.6	37.2 ± 10.1	34.8 ± 9.5	$F = 0.40$	0.67
Handedness, EHI percentage	71 ± 30	72 ± 37	76 ± 23	$F = 0.22$	0.80
Education level, ISCED					
Own	4 ± 2	4 ± 2	5 ± 1	$F = 8.72$	< 0.001
Father	3 ± 2	4 ± 2	3 ± 2	$F = 0.67$	0.52
Mother	2 ± 1	3 ± 1	3 ± 2	$F = 1.57$	0.22
Months since deployment	82 ± 100	79 ± 81		$t = -0.15$	0.88
No. of missions	3 ± 4	2 ± 1		$t = -0.59$	0.56
(1/2/3/> 3)	(12/6/5/5)	(9/7/4/6)			
PTSD symptoms					
Re-experiencing, CAPS B	22 ± 6	1 ± 1	0 ± 1	$F = 275.14$	< 0.001
Avoiding, CAPS C)	21 ± 8	1 ± 2	1 ± 3	$F = 140.97$	< 0.001
Hyperarousal, CAPS D	24 ± 5	3 ± 3	3 ± 4	$F = 229.67$	< 0.001
Total, CAPS total	67 ± 11	5 ± 5	5 ± 4	$F = 656.75$	< 0.001
DSS	3 ± 5	1 ± 4	1 ± 2	$F = 1.35$	0.27

CAPS = Clinician Administered PTSD scale; DSS = Dissociative State Symptom scale; EHI = Edinburgh Handedness Inventory; ISCED = International Standard Classification of Education; PTSD = posttraumatic stress disorder; SD = standard deviation.
 *Unless otherwise indicated.

Table 2: Behavioural performances and brain activation contrasts in region of interest for PTSD, combat control and healthy control groups

Factor	Group; mean ± SD			F statistic	p value
	PTSD, n = 28	Combat control, n = 26	Healthy control, n = 25		
Baseline*					
Response time	818 ± 20	812 ± 15	816 ± 15	$F = 0.83$	0.44
ROI left pre/postcentral gyrus	0.98 ± 0.88	1.20 ± 1.07	1.06 ± 1.17	$F = 0.31$	0.74
ROI right IFG	0.15 ± 0.96	0.14 ± 0.88	-0.04 ± 1.29	$F = 0.27$	0.77
ROI right striatum	0.05 ± 0.40	0.14 ± 0.39	0.02 ± 0.39	$F = 0.55$	0.58
Reactive inhibition†					
Stop-signal reaction time	330 ± 15	325 ± 18	306 ± 12	$F = 16.97$	< 0.001
ROI left pre/postcentral gyrus	-0.59 ± 0.74	-1.03 ± 0.55	-0.94 ± 0.51	$F = 3.86$	0.025
Proactive inhibition‡					
Slope response time§	46.83 ± 64.31	85.29 ± 88.14	100.10 ± 73.05	$F = 3.87$	0.025
ROI right IFG§	4.59 ± 3.32	1.94 ± 4.22	2.87 ± 4.57	$F = 3.40$	0.039
ROI right striatum§	1.50 ± 1.31	0.68 ± 1.70	1.30 ± 2.50	$F = 1.16$	0.32

IFG = inferior frontal gyrus; PTSD = posttraumatic stress disorder patients; ROI = region of interest; SD = standard deviation.
 *Baseline contrast: correct go trials with a stop-signal probability of 0% versus rest.
 †Reactive inhibition contrast: successful stop trials versus correct go trials.
 ‡Proactive inhibition contrast: the parametric effect of stop-signal probability on go-signal activation for stop-signal probability 17% to 33%.
 §Baseline response time was included as a covariate (set at 815.47).

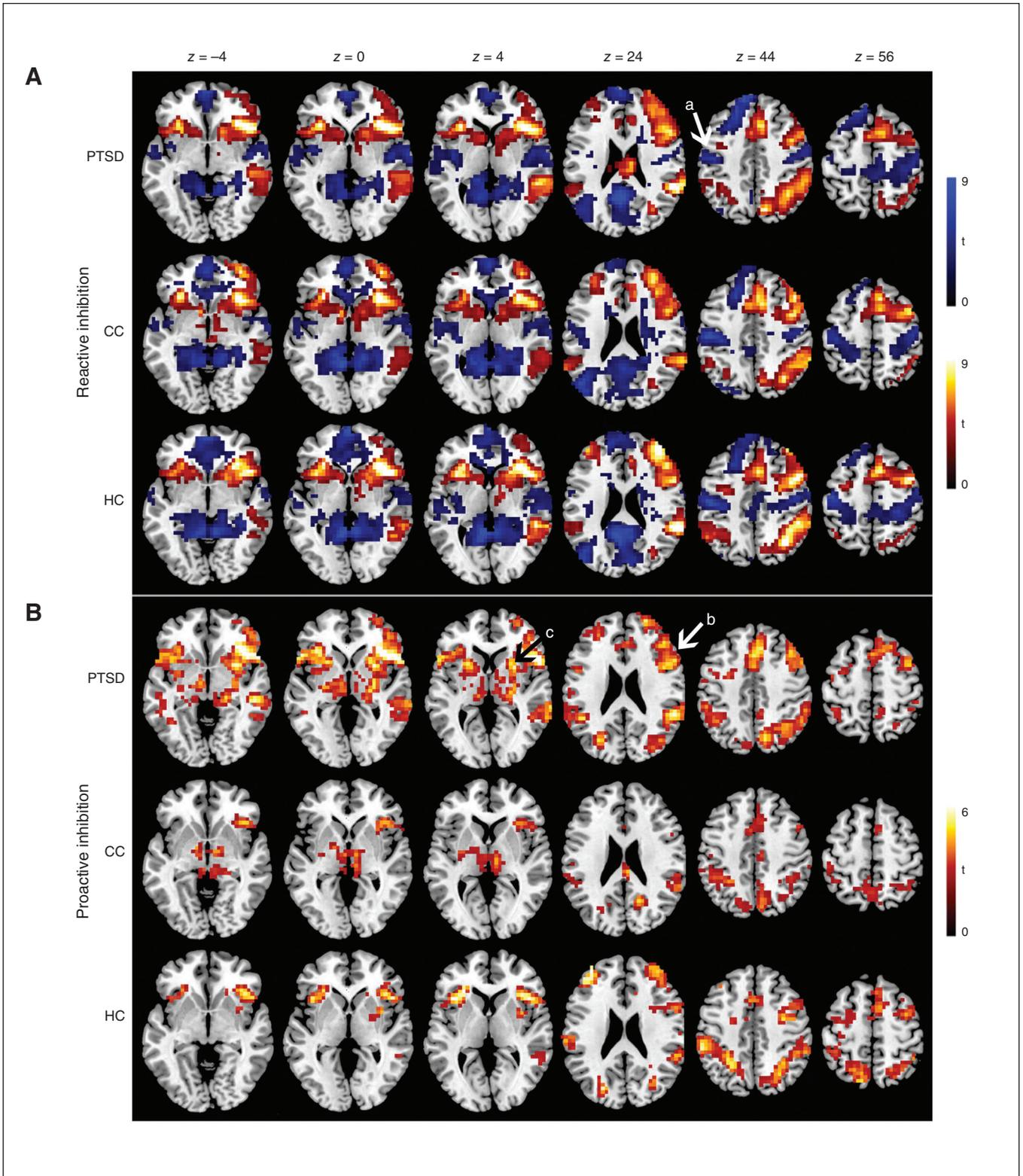


Fig. 2: Whole brain activation during (A) reactive inhibition (successful stop-signal versus go-signal 0% activation) and (B) proactive inhibition (parametric increase in activation as a function of stop-signal probability) in patients with posttraumatic stress disorder patients (PTSD; top panel), combat controls (CC; middle panel) and healthy controls (HC; bottom panel). The arrows point to the regions of interest (a) left pre/postcentral gyrus (b) right inferior frontal gyrus (rIFG) (c) right striatum. Significant (de)activated clusters (1-sample *t* tests; significance tested at cluster-defined threshold of $p < 0.005$, and a $p < 0.05$ family-wise error-corrected critical cluster size) are displayed on a standardized brain (MRIcron).

Areas involved in proactive inhibition (e.g., rIFG, right striatum, right insula) were activated in all groups (Appendix, Table S1). Whole brain analyses did not reveal activation differences outside the predefined ROIs (Fig. 2B).

Discussion

In this fMRI study, the role of contextual cues during response inhibition was investigated. We examined reactive inhibition (outright stopping) and proactive inhibition (anticipation of stopping based on contextual cues) in a male veteran PTSD group, a combat control group and a healthy male nonmilitary control group. Behaviourally, speed of inhibition was decreased in both veteran groups compared with the healthy control group, suggesting that reduced reactive inhibition is not specific to patients with PTSD. Decreased inhibition of the left pre/postcentral gyrus during reactive inhibition, on the other hand, was observed only in patients with PTSD. Furthermore, patients with PTSD showed decreased proactive inhibition, as indicated by a reduced effect of stop-signal probability levels (contextual cues) on response time. Moreover, activation in the right inferior frontal gyrus (rIFG) was reduced during proactive inhibition in the PTSD group compared with the combat control group. Taken together, these results suggest decreased contextual cue processing in patients with PTSD.

Impaired reactive inhibition was demonstrated in patients with PTSD compared with healthy controls, but not combat controls. This finding is in line with those of previous studies on response inhibition in individuals with PTSD.^{13–15} In addition, we found that response inhibition in the combat control group also differed significantly from that in the healthy control group. Therefore, reduced reactive inhibition is not related to PTSD as such, but may reflect effects of military training or stress/trauma exposure during deployment. It seems plausible that exposure to hostile environments, such as combat zones, may increase attention to subtle changes in the environment. Another explanation for reduced reactive inhibition in veterans is the bias in the recruitment of military personnel. Veterans and healthy controls differed in education level, but education level did not correlate with reactive inhibition measures, thus it is unlikely that this difference influenced our results. Reduced response inhibition has previously been related to impulsivity, which in turn has been linked to prefrontal activation during response inhibition.²⁴ This is potentially relevant to PTSD and other psychiatric disorders. Impaired reactive inhibition has been linked to several psychiatric and developmental disorders, such as attention-deficit/hyperactivity disorder, obsessive-compulsive disorder and schizophrenia.²⁵ Indeed, the present study demonstrates that impaired reactive inhibition is not specifically related to PTSD.

Inhibition of the motor areas, which are involved in executing the response, is essential for withholding this response during response inhibition.^{11,12} Inhibition of the left pre/postcentral gyrus is not functioning well in patients with PTSD, as indicated by decreased inhibition of the left pre/postcentral gyrus during correct stop tasks in this study. This is a confirmation of findings from a previous study on response inhibition in patients with PTSD¹³ and extends that

finding by showing that decreased inhibition of the left pre/postcentral gyrus is also observed after controlling for task performance. Across all groups activation was observed in brain areas often associated with response inhibition (e.g., insula, rIFG, supplementary motor area), and deactivation was observed in the motor cortex and medial regions of the DMN. It was previously shown that these DMN regions are deactivated during the performance of a task.²⁶

The PTSD group displayed reduced proactive inhibition compared with the combat control and healthy control groups. This indicates that these abnormalities are specific to patients with PTSD. Reduced proactive inhibition implies that these patients are less influenced by contextual cues during inhibition. Decreased inhibition of an automatic response has previously been identified in fear inhibition.^{2–4} Conditioning theories of PTSD posit that patients with PTSD learn to associate cues with their trauma (fear conditioning).²⁷ “Unlearning” this association, and inhibiting the fear response (fear inhibition) in the face of safety cues (contextual cues), is impaired in patients with PTSD.²⁶ Reduced contextual cue processing has been demonstrated in several fear inhibition studies,^{2,6,28,29} but it was unclear whether this deficit was also apparent in other (cognitive) domains. Here we demonstrate that reduced contextual cue processing reflects a more general deficit in individuals with PTSD, as it was observed during response inhibition.

The rIFG response to increasing stop-signal probability levels (contextual cues) differed between the PTSD and combat control groups. The PTSD group showed a larger increase in rIFG activation to increasing stop-signal probability levels; on the other hand, the combat control group showed a larger rIFG response to the 17% compared with the 0% stop-signal probability level. These results can be explained as follows: the combat control group showed a remarkable rIFG increase to the smallest stop-signal probability level (17%) compared with 0% stop. When the increase in rIFG response to increasing stop-signal probability levels was calculated (17%–33%), the result was a rather flat slope. The PTSD group, on the other hand, did not show this increase to the smallest stop-signal probability level, but only showed an increase in rIFG activation to the larger stop-signal probability levels. The result was a steep slope for rIFG response to increasing stop-signal probability. Accordingly, the slope for increasing stop-signal probability levels differed between the PTSD and combat control groups even though neither of them differed significantly from the healthy control group. This finding suggests a divergent reaction of the combat control and PTSD groups after trauma exposure: both groups appear to have adjusted their rIFG response, but in a different way. For the combat control group, this adjustment could constitute a protective or compensatory mechanism, which is absent in the PTSD group.

The rIFG is thought to play a role in attentional monitoring,^{11,17,30} and/or expectancy violation.¹² Therefore, it can be hypothesized that patients with PTSD expect a stop only when there is a high stop-signal probability and not when the context signals a small stop-signal probability, whereas combat controls do expect a stop when the context signals a small

stop-signal probability. This is in line with cognitive models of PTSD²⁵ and recent empirical findings³¹ that highlight the importance of attentional bias in the etiology of PTSD. Furthermore, patients with PTSD do not behave accordingly when they do expect a stop signal: during the high stop-signal probabilities they do not wait to respond, which results in decreased proactive behavioural inhibition (flat line for go-signal response time to increasing stop-signal probability levels). This could also be related to decreased inhibition of the left pre/postcentral gyrus, which makes it more difficult for them to withhold the stop response. The rIFG has been implicated in PTSD in previous studies. A smaller (structural) rIFG was implicated in PTSD,^{32–34} and the rIFG correlated negatively with symptom severity.³⁴ Interestingly, increased rIFG activity has previously been related to a dissociative response.³⁵ However, no evidence for dissociative states was found in any of the participants in the present study.

Limitations

One limitation is that most of the patients with PTSD had comorbid psychiatric disorders, which could have influenced the results; however, comorbidity is often present in individuals with PTSD. Therefore, the inclusion of patients with PTSD and a comorbid disorder allows for broader generalization of the results. Second, education level differed between the military and civilian groups, but no correlations between education level and the behavioural measures were observed. Moreover, task difficulty was adjusted online after individual task performance to keep error rates fairly equal. The difference in education level is likely related to most military men joining the armed forces after high school, whereas the civilian men continued education. Education level was included as an estimate of intelligence and, importantly, parental education level did not differ among the groups. Future studies (with military samples) could include a more direct measure of intelligence.

An important strength of this study is the inclusion of 2 control groups,¹⁸ because this allowed us to differentiate PTSD symptoms from the effects of military training and deployment. However, the effects of deployment-related exposure to trauma/stress cannot be distinguished from military training or selection, as all veterans in this study experienced both. Additional research to address these issues is recommended. Furthermore, applying a similar design involving patients with PTSD before and after receiving treatment might elucidate whether impaired inhibition and contextual cue processing are state aspects of PTSD or whether they remain after successful treatment

Conclusion

Patients with PTSD showed reduced contextual cue processing and related decreased rIFG activation during response inhibition. These findings support the theory of decreased contextual cue processing during impaired fear inhibition in patients with PTSD and suggest that these deficiencies are also observed during cognitive processes, indicating a more general deficit.

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