Behavioral and neural correlates of memory suppression in PTSD

Danielle R. Sullivan[a,b,*], Brian Marx[a,b], May S. Chen[c], Brendan E. Depue[d,e], Scott M. Hayes[b,f,g], Jasmeet P. Hayes[a,b,f]

[a] National Center for PTSD, VA Boston Healthcare System, Boston, MA, USA
[b] Department of Psychiatry, Boston University School of Medicine, Boston, MA, USA
[c] Department of Health Behavior, University of North Carolina at Chapel Hill, NC, USA
[d] Department of Psychological and Brain Sciences, University of Louisville, KY, USA
[e] Department of Anatomical Sciences and Neurobiology, University of Louisville, KY, USA
[f] Neuroimaging Research for Veterans Center, VA Boston Healthcare System, Boston, MA, USA
[g] Memory Disorders Research Center, VA Boston Healthcare System, Boston, MA, USA

ARTICLE INFO

ABSTRACT

Previous work has shown that healthy individuals can actively suppress emotional memories through recruitment of the lateral prefrontal cortex. By contrast, individuals with posttraumatic stress disorder (PTSD) frequently experience unwanted memories of their traumatic experiences, even when making explicit efforts to avoid them. However, little is known regarding the behavioral and neural effects of memory suppression among individuals with PTSD. We examined memory suppression associated with PTSD using the Think-No-Think paradigm in an event-related functional magnetic resonance imaging (fMRI) study. We studied three groups: PTSD (n = 16), trauma exposure without PTSD (n = 19), and controls (i.e., no trauma exposure or PTSD; n = 13). There was a main effect of memory suppression such that participants remembered fewer face-picture pairs during the suppress condition than the remember condition. However, trauma-exposed participants (regardless of PTSD status) were less likely to successfully suppress memory than non-trauma-exposed controls. Neuroimaging data revealed that trauma-exposed individuals showed reduced activation in the right middle frontal gyrus during memory suppression. These results suggest that trauma exposure is associated with neural and behavioral disruptions in memory suppression and point to the possibility that difficulty in active suppression of memories may be just one of several likely factors contributing to the development of PTSD.

1. Introduction

The powerful influence of emotions on human memory has been well documented (LaBar and Cabeza, 2006). Although emotional enhancement of memory is important for survival, such as within the context of learning to avoid dangerous stimuli, *forgetting* emotionally-charged information is equally important and adaptive. Mounting evidence has shown that healthy individuals can successfully suppress emotional memories with repeated attempts (Anderson and Green, 2001; Depue et al., 2006, 2007). However, the inability to forget is a hallmark symptom of posttraumatic stress disorder (PTSD), which develops after exposure to a life-threatening event. PTSD is characterized by intense reliving of the trauma that is repetitive, intrusive, and incapacitating. The intrusive nature of these hallmark symptoms suggests that the inability to suppress unwanted memories may be a strong contributor to the behavioral manifestation of PTSD.

The notion that PTSD is associated with impaired ability to suppress unwanted information is supported by long-standing experimental work using both directed forgetting and thought suppression paradigms (Geraerts and McNally, 2008; Hayes et al., 2012). For example, in the directed forgetting task, participants are instructed to either remember or forget words in a list and then are asked to recall or recognize list words irrespective of whether they were to-be-remembered or to-be-forgotten. Generally, healthy participants remember fewer items in the 'forget' condition than the 'remember' condition, demonstrating successful control of memory. However, patients with PTSD recall proportionally more words in the 'forget' condition than controls, suggesting difficulty with forgetting (Cottencin et al., 2006; Zoellner et al., 2003).

Similarly, research examining the effects of suppression of a particular thought has demonstrated that patients with PTSD have more trauma-related thoughts after a thought suppression period relative to

baseline, known as the rebound effect (Shipherd and Beck, 1999, 2005). The link between PTSD and disrupted thought suppression is also evident in patient self-reported engagement in thought suppression as measured by the White Bear Suppression Inventory (WBSI; Wegner and Zanakos, 1994). The WBSI is a questionnaire that assesses an individual's trait-like tendency to suppress unwanted thoughts in everyday life (Nickerson et al., 2016). Paradoxically, more attempts at thought suppression may actually lead to more intrusive thoughts (Amstadter and Vernon, 2006; McNally and Ricciardi, 1996) and thus may lend itself to a chronic cycle of intrusive and avoidance symptoms characteristic of PTSD (Wenzlaff and Wegner, 2000). Not surprisingly, patients with greater PTSD symptom severity endorse a greater number of items on the WBSI (Nickerson et al., 2016; Vázquez et al., 2008; Vincken et al., 2012). Taken together, the evidence suggests that individuals with PTSD have difficulty inhibiting memories despite greater attempts at suppression of the trauma memory.

Despite the body of evidence suggesting that PTSD is associated with difficulties in suppressing unwanted memories, little is known regarding the neural basis of memory suppression failure associated with PTSD. The Think-No-Think task (Anderson and Green, 2001; Anderson et al., 2004; Depue et al., 2007) has been used to examine active memory suppression within the context of functional magnetic resonance imaging (fMRI). In this task, participants are instructed to suppress a memory by not letting it enter consciousness (No-Think condition) or to retrieve a memory by elaborating it (Think condition). The difference in brain activity for No-Think trials versus Think trials constitutes a neural measure of memory suppression. In healthy individuals, memory suppression is associated with greater activation of the lateral prefrontal cortex (LPFC) including the middle frontal gyrus (MFG) and inferior frontal gyrus (IFG; Anderson and Hanslmayr, 2014; Anderson et al., 2004; Depue et al., 2007; Levy and Anderson, 2008). LPFC may modulate memory suppression by down-regulating key encoding and retrieval systems (i.e., the hippocampus) and sensory components of memory (Depue et al., 2007).

In this study, we examined the neural correlates of memory suppression among individuals diagnosed with PTSD (PTSD group), individuals with trauma exposure without PTSD (trauma-exposed group), and individuals who had neither trauma exposure nor PTSD (controls). The primary goals of this study were: (1) to examine the function of the LPFC in PTSD during an event-related fMRI Think-No-Think task (Depue et al., 2007); (2) to examine the effect of PTSD on trait suppression and (3) to assess the relation between trait suppression and the neural processes engaged during an active state of suppression (i.e., the Think-No-Think task), thereby, predicting possible brain-behavior correlates. We hypothesized that individuals with PTSD would have difficulties suppressing negative information and show disrupted LPFC activity during active attempts at memory suppression relative to both the trauma-exposed and control groups. Further, we hypothesized that individuals with PTSD would endorse greater trait-like suppression than trauma-exposed and control groups and that this would be associated with alterations in the neural processes engaged during an active state of memory suppression.

2. Materials and methods

2.1. Participants

A total of 48 participants with either PTSD, trauma exposure without PTSD, or no trauma exposure or PTSD (i.e., participants did not meet the DSM-IV A1 and A2 criteria for a traumatic event) were included in the final analyses of this study. Recruitment and exclusion criteria are listed in the Supplementary Materials. Of the 48 participants included in the study, 13 were in the control group, 19 were in the trauma-exposed group, and 16 were in the PTSD group. Demographics are described in Table 1.

All participants provided written consent after study procedures had

been fully explained and prior to participation in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board at the VA Boston Healthcare System.

2.2. Clinical and behavioral assessments

PTSD diagnosis and symptom severity were assessed using the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995) for DSM-IV by a doctoral-level clinician. The CAPS is a structured interview that assesses the intensity and frequency of PTSD symptoms (with higher scores reflecting higher symptom severity) and is currently the gold standard for PTSD diagnosis and assessment.

Trait suppression was assessed with the WBSI (Wegner and Zanakos, 1994). The WBSI is a self-report questionnaire that measures an individual's general tendency to suppress unwanted negative thoughts. Military-related trauma exposure was measured with the Deployment Risk and Resilience Inventory (DRRI) Section I-Combat Experiences and Section J-Post-Battle Experiences (King et al., 2006) for trauma-exposed individuals only. The DRRI is a self-report questionnaire that measures experiences before, during, and after military deployment. Depression symptomatology was measured with the Beck Depression Inventory (BDI)-II. The BDI-II is a self-report questionnaire that assess 21 groups of statements related to depression on a 0–3 point scale. More details about these measures are reported in the Supplementary Materials.

2.3. Think-No-think task

A Think-No-Think task with face-picture pairs (Depue et al., 2007, 2010) was administered in the scanner in an event-related fMRI paradigm (stimuli and task were based on Depue et al., 2007). Forty faces with neutral expressions (20 female and 20 male faces; normed by ~500 individuals as having a neutral rating on a Likert scale of 1–7 (mean = 3.46, SD = 0.21) based on Depue et al., 2006) were paired with images from the International Affective Picture System (IAPS; Lang et al., 2008) that were rated moderately negative in content (mean valence = 2.9; SD = 0.6). IAPS images were selected by two independent raters to have minimal content relatedness to minimize potential for overlap during the recall phase of the experiment. Visual stimuli were presented with E-Prime software (Psychology Software Tools, Pittsburgh, PA) and viewed with MRI-compatible goggles. The experiment took part in three phases: training, experimental and testing (see Fig. 1).

In-depth details describing this task are reported in the Supplementary Materials. In brief, in the training phase, participants were instructed to view and remember 40 face-picture pairs. This procedure was repeated until the participant achieved 97.5% accuracy. After the participant successfully learned the face-picture pairs, 32 of the 40 faces were presented to the participant 12 times across four runs during the experimental phase. Half of the faces were assigned to the Think condition (designated with a green frame around the face), while the other half were assigned to the No-Think condition (designated with a red frame around the face). During the Think trials, participants were asked to "think of the picture previously associated with the face." During No-Think trials, participants were told to "not let the previously associated picture come into consciousness." The remaining eight faces of the original set of 40 served as a zero-repetition baseline for memory recall (i.e., Baseline trials) and were presented in the testing phase only. In the testing phase, participants were presented with each face and asked to write a short description of the picture associated with it. Recall accuracy from this testing phase served as our behavioral measure of memory suppression.

2.4. Imaging acquisition

T2*-weighted functional scans were acquired on a 3-T Siemens TIM Trio scanner using a 12-channel head coil (TR = 2000 ms, TE = 30 ms,

Table 1
Summary of demographic and clinical characteristics of participants.

	Control (*n* = 13)	Trauma-exposed (*n* = 19)	PTSD (*n* = 16)	Group Comparison
Age in years, *M (SD)*	24.8 (6.3)	29.7 (8.4)	30.2 (5.4)	$F(2,45) = 2.6, p > 0.08$
Males, *no. (%)*	11 (84.6)	18 (94.7)	15 (93.8)	$\chi^2(2) = 1.2, p > 0.5$
Taking psychotropic medication, *no. (%)*	0 (0.0)	1 (5.3)	8 (50.0)	$\chi^2(2) = 15.5, p < 0.001$[a]
CAPS, *M (SD)*	0.9 (2.1)	15.1 (12.9)	69.6 (14.9)	$F(2,42) = 142.7, p < 0.001$[b]
CAPS re-experiencing, *M (SD)*	0.8 (1.9)	3.9 (4.0)	18.6 (5.9)	$F(2,45) = 74.2, p < 0.001$[b]
CAPS avoidance/numbing, *M (SD)*	0.1 (0.3)	4.6 (5.6)	26.6 (7.1)	$F(2,45) = 105.9, p < 0.001$[b]
CAPS hyperarousal, *M (SD)*	0.0 (0.0)	6.6 (7.0)	24.4 (7.1)	$F(2,45) = 66.7, p < 0.001$[b]
BDI-II, *M (SD)*[c]	3.7 (3.8)	6.7 (6.0)	24.81 (9.8)	$F(2,44) = 39.6, p < 0.001$[a]
Military-related trauma exposure, *M (SD)*[d]		13.4 (8.4)	17.7 (6.8)	$t(30) = 1.6, p > 0.1$
Type of Criterion A event, *no. (%)*				$\chi^2(5) = 6.1, p > 0.2$
Combat		7 (36.8)	10 (62.5)	
Child physical/sexual abuse		2 (10.5)	0 (0.0)	
Adult physical/sexual assault		1 (5.3)	1 (6.3)	
Accident/MVA/fire		3 (15.8)	4 (25.0)	
Domestic violence		0 (0.0)	0 (0.0)	
Death of someone		5 (26.3)	1 (6.3)	
Witness/experience violence, adult[e]		0 (0.0)	0 (0.0)	
Natural disaster		0 (0.0)	0 (0.0)	
Witness/experience violence, child[e]		0 (0.0)	0 (0.0)	
Other[f]		1 (5.3)	0 (0.0)	
Number of Criterion A events, *M (SD)*		1.7 (0.7)	1.9 (0.7)	$t(33) = -1.1, p > 0.2$
Proximity of Criterion A event, *no (%)*				$\chi^2(2) = 1.1, p > 0.5$
Happened to me		10 (52.6)	11 (68.8)	
Witnessed it		8 (42.1)	4 (25.0)	
Learned about it		1 (5.3)	1 (6.3)	

BDI-II = Beck Depression Inventory-II; CAPS = Clinician-Administered PTSD Scale; MVA = motor vehicle accident; PTSD = posttraumatic stress disorder.

[a] PTSD group significantly differed from trauma-exposed and control groups.

[b] PTSD group significantly differed from trauma-exposed and control groups and trauma-exposed group significantly differed from control group.

[c] Data for one participant in the trauma-exposed group was unavailable for this analysis (*n* = 18).

[d] data for three participants in the trauma-exposed group were unavailable for this analysis (*n* = 16).

[e] The witness/experience violence category of type of Criterion A events included robberies, assault, fights, and shootings.

[f] The other category for type of Criterion A event included events such as witnessing severe human suffering.
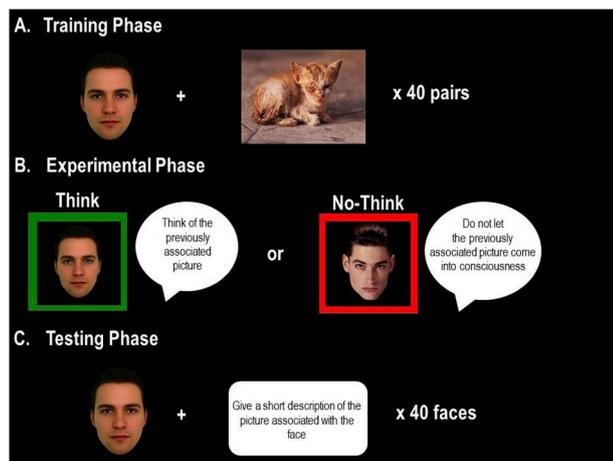

Fig. 1. Think-No-Think Paradigm. **(A)** During the training phase, participants were trained on 40 face-picture pairs until they reached 97.5% accuracy. **(B)** During the experimental phase, participants viewed 32 out of the 40 faces 12 times each. Faces were either surrounded by a green border (Think condition), in which participants were instructed to think of the previously associated picture or with a red border (No-Think condition), in which participants were instructed to not let the previously associated picture come into consciousness. **(C)** During the testing phase, participants were presented with the 40 faces and were asked to write a short description of the picture associated with each face. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

FOV = 192 mm², matrix = 64 × 64, flip angle = 90°, 33 slices, 3 × 3 × 3.75 mm voxels). Slices were oriented obliquely along the anterior commissure-posterior commissure plane. To improve localization and registration of functional images to the standard MNI template, T1-weighted structural scans were also obtained for each participant (TR = 2530 ms, TE = 3.32 ms, FOV = 256 mm², matrix = 256 × 256, slice thickness = 1 × 1 × 1 mm voxels, 128 slices).

2.5. Behavioral analysis

Statistical analyses were performed with SPSS version 25 (IBM Corp., Armonk, NY). Demographic variables were analyzed with analysis of variance (ANOVA) and independent samples *t*-test for continuous variables or chi-square tests for categorical variables. To examine performance on the No-Think trials relative to Think trials, age was entered as a covariate in a 3 (group: control, trauma-exposed, PTSD) x 2 (condition: No-Think, Think) repeated measures analysis of covariance (ANCOVA) in which percentage recalled was the dependent measure.

In addition, we examined No-Think performance in relation to Baseline with a procedure similar to Paz-Alonso et al. (2013), in which participants were subdivided into suppressors or non-suppressors as a function of their capacity for mnemonic control with a mnemonic control index. The mnemonic control index is based on a ratio of retrieval suppression in which performance on No-Think trials is compared with Baseline ((Baseline-No-Think)/Baseline). Suppressors have positive mnemonic control indexes reflecting suppression of the No-Think stimuli relative to Baseline (n = 23), whereas non-suppressors have zero or negative values suggesting failure to suppress items in the No-Think condition relative to Baseline (n = 25). To examine the association between PTSD group status and mnemonic control group status, we performed a hierarchical binomial logistic regression in which mnemonic control group (suppressor or non-suppressor) was the dependent variable. Age was entered into the first step of the model and group (control, trauma-exposed, or PTSD) was entered into the second step as a categorical variable with the control group as the indicator.

Next, we performed an ANCOVA to analyze group differences in

trait suppression with total score on the WBSI as the dependent variable, group (control, trauma-exposed, or PTSD) as the independent variable and age as a covariate.

Finally, follow-up analyses examined whether state suppression (as measured by the mnemonic control capacity) was associated with trait suppression or military-related trauma exposure. These analyses and results are reported in the Supplementary Materials.

2.6. Imaging analysis

All image preprocessing and analysis was carried out using FEAT (fMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software package, Version 5.0.9; http://www.fmrib.ox.ac.uk/fsl). Details of preprocessing are provided in the Supplementary Materials.

Functional analysis of memory retrieval and suppression was performed using a Think > No-Think or No-Think > Think contrast, respectively, for all trials. Higher-level analyses were carried out using FMRIB's Local Analysis of Mixed Effects (FLAME) stage 1 (Beckmann et al., 2003; Woolrich, 2008; Woolrich et al., 2004). Runs were combined for each participant and group level activation maps were generated for the contrasts. Z statistic images were thresholded using clusters determined by $Z > 3.1$ ($p < 0.001$) and a corrected cluster significance threshold of $p = 0.05$ for all analyses.

Given that previous work by Depue et al. (2007) has shown that the LPFC is primarily involved in the cognitive control of emotional memory suppression and is specifically related to an increase in activity in No-Think trials rather than a decrease in activation for Think trials, we focused on LPFC activation for the memory suppression analyses. To provide as unbiased of a LPFC region of interest (ROI) as possible, data for all participants were combined and the bilateral activation encompassing the LPFC in the No-Think > Think contrast was selected as an ROI for further analyses (peak MNI coordinates = 34 34 36, Z Max = 7.36; see Fig. 2, Table 2). Using this LPFC ROI as a mask, we compared groups (control v. PTSD, control v. trauma-exposed, PTSD v. trauma-exposed) in a voxel-wise ROI analysis for the No-Think > Think contrast. Age was entered into the model as a covariate. Z statistic images were thresholded using clusters determined by $Z > 3.1$ ($p < 0.001$) and a corrected cluster significance threshold of $p = 0.05$.

To examine associations between brain activation and trait suppression (as measured by the WBSI), parameter estimates of significant clusters in each group contrast (control v. PTSD, control v. trauma-exposed, PTSD v. trauma-exposed) for the No-Think > Think ROI analysis were extracted from individual level activation maps and entered into SPSS. Partial Pearson correlations were calculated between these parameter estimates and WBSI total score across all participants, controlling for age.

Table 2
Significant brain regions for full sample group mean in whole brain analyses.

Brain Region	Cluster Size	Peak Voxel (MNI coordinates)	Z-statistic
Think > No-Think full sample map			
Right Occipital Fusiform Gyrus/Lingual Gyrus	497	18 -84 -4	3.72
Left Superior Parietal Lobule/Angular Gyrus	363	−30 -56 38	4.46
Left Inferior Frontal Gyrus/Middle Frontal Gyrus	240	−40 28 16	4.38
Left Posterior Cingulate Cortex	155	−4 -32 28	2.48
Left Occipital Pole/Lateral Occipital Cortex	123	−8 -98 -10	3.43
Right Precuneus/Supracalcarine Cortex	94	16 -58 20	3.62
No-Think > Think full sample map			
Right Middle Frontal Gyrus	3488	34 32 36	5.04
Right Angular Gyrus/Supramarginal Gyrus	2595	60 -48 36	4.96
Left Supramarginal Gyrus	1499	−58 -34 32	4.29
Right Temporal Pole	1324	52 12 -8	4.12
Left Cerebellum	1095	−6 -70 -16	4.20
Right Posterior Cingulate Cortex	1080	6 -24 40	4.22
Left Frontal Pole	659	−28 42 30	4.12
Left Lateral Occipital Cortex	478	−18 -80 16	3.88
Right Supracalcarine Cortex	446	26 -62 12	4.31
Left Precuneus/Posterior Cingulate Cortex	411	−14 -44 48	3.91
Right/Left Paracingulate Gyrus	240	0 52 16	3.79
Left Precentral Gyrus	202	−56 2 16	3.81
Left Insular Cortex	171	−32 6 2	3.89
Left Lateral Occipital Cortex	165	−38 -74 8	3.94
Left Inferior Temporal Gyrus	161	−58 -18 -32	3.78

Note: Cluster size is number of voxels. Only clusters are reported; sub-clusters are not reported.

3. Results

3.1. Behavioral performance

3.1.1. Memory performance

A 3 × 2 repeated measures ANCOVA of recall accuracy with group (controls, trauma-exposed, and PTSD) as the between subjects factor and condition (No-Think, Think) as the within subjects factor revealed no main effect of group ($F(2,44) = 0.5$, $p > 0.4$), but a main effect of condition ($F(1,44) = 4.5$, $p < 0.04$), with higher scores for the Think condition than the No-Think condition (see Table 3, Supplementary Material Figure S1). The group by condition interaction was not significant ($F(1,44) < 1$, $p > 0.9$).
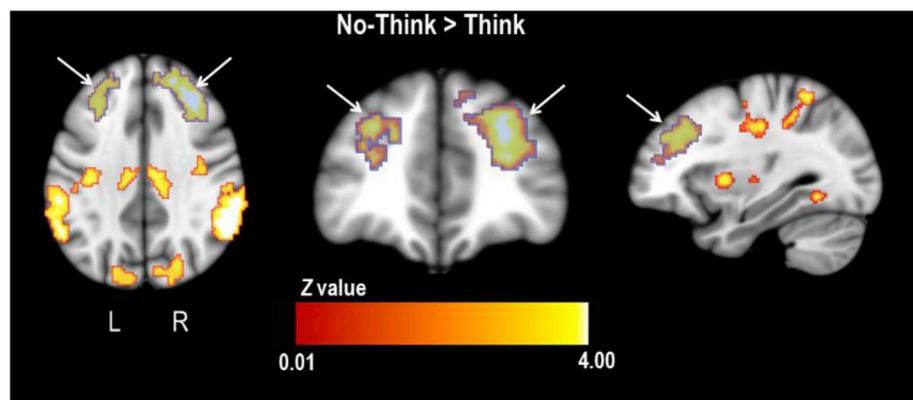

Fig. 2. Average activation across the full sample for the No-Think > Think contrast. White arrows pointing to the areas shaded and outlined in blue indicate the PFC mask used in the ROI analysis. L = left; PFC = prefrontal cortex; R = right; ROI = region of interest. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Think-No-Think task performance by group.

	Control (n = 13)	Trauma-exposed (n = 19)	PTSD (n = 16)	Total (n = 48)
Think %, *M (SD)*	65.4 (25.2)	55.3 (20.4)	56.6 (20.0)	58.5 (21.6)
No-Think %, *M (SD)*	44.7 (21.0)	37.2 (21.3)	37.5 (19.1)	39.3 (20.3)

Note: Performance is listed in percent. There was no significant effect of group, but there was a main effect of condition ($p < 0.04$). PTSD = posttraumatic stress disorder.

3.1.2. Mnemonic control capacity

To examine whether groups differed in mnemonic control capacity, a hierarchical binomial logistic regression was performed in which mnemonic control group (suppressors and non-suppressors) was the dependent variable. Age was entered into the first step of the model followed by group (controls, trauma-exposed, and PTSD) in the second step. Results revealed that group status was the only significant predictor with a significant overall model ($\chi^2(3)$, $N = 48$) = 8.2, $p = 0.04$, Negelkerke $R^2 = 0.2$) and a significant change in the chi-square equation ($\chi^2(2)$, $N = 48$) = 8.1, $p < 0.02$). Both the trauma-exposed and PTSD groups had lesser odds of being classified as a suppressor than the control group (trauma-exposed: OR = 0.1, $p = 0.01$; PTSD: OR = 0.2, $p < 0.05$). The trauma-exposed and PTSD groups did not significantly differ from one another ($p > 0.4$). Further inspection revealed that 77% of controls were classified as suppressors, while only 32% of trauma-exposed and 44% of PTSD participants were classified as suppressors (see Fig. 3A). Fig. 3B displays the number of participants within each group that scored in the suppressor (positive) or non-suppressor (zero and negative) range on the mnemonic control index.

3.1.3. Trait suppression

Examination of trait suppression revealed a significant effect of group ($F(2,44) = 22.1$, $p < 0.001$) on WBSI total score. Post-hoc tests revealed that the PTSD group had significantly higher WBSI scores than either the trauma-exposed ($t(33) = -7.1$, $p < 0.001$) or control ($t(27) = -5.7$, $p < 0.001$) group (see Supplementary Material Figure S2). The trauma-exposed and control groups did not significantly differ from one another ($t(30) = 0.2$, $p > 0.8$).

3.2. Imaging results

3.2.1. Memory retrieval

First, we performed a whole brain analysis for the Think > No-Think contrast in the entire sample. Results were in line with our expectations, with greater activation in the occipital cortex and fusiform gyrus in the Think relative to the No-Think condition (see Table 2 for full set of results). Examination of group differences in brain activation for the Think > No-Think contrast revealed that there were no significant whole brain differences between any group.

3.2.2. Memory suppression

To examine the neural correlates of memory suppression, we first performed a whole brain analysis for the No-Think > Think contrast in the entire sample. As expected, results showed greater activation in the LPFC, bilaterally, in the No-Think vs. Think condition (see Table 2 for full set of results). We next used the bilateral PFC as an ROI to probe for group differences in memory suppression (see Fig. 2). Results for the No-Think > Think contrast showed that the control group had greater activity in the right MFG than the trauma-exposed (peak MNI coordinates = 34 32 42, Z Max = 3.85) and PTSD (peak MNI coordinates = 34 32 36, Z Max = 4.06; see Fig. 4) groups. Notably, there were no group differences in the left PFC. Neither trauma-exposed nor PTSD groups displayed greater activation than the control group. Further, there were no significant differences between the trauma-exposed and PTSD groups when they were compared directly, nor were there any significant effects of age on activation. Significant brain regions for each group in the No-Think > Think ROI analysis are reported separately in Table 4.
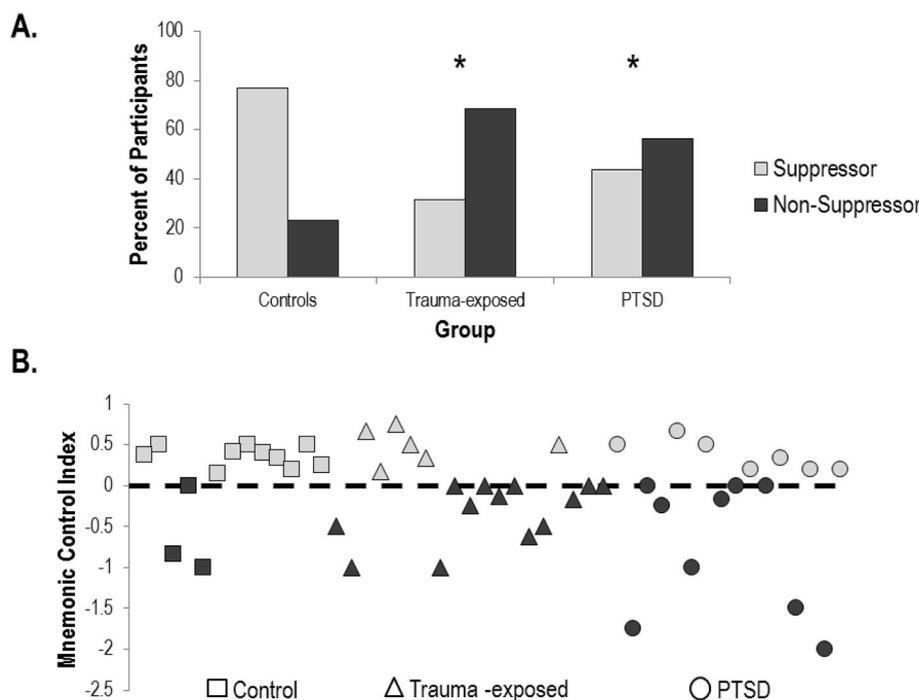

Fig. 3. Mnemonic control by group. **(A)** Percent of individuals within each group (control, trauma-exposed, or PTSD) that were defined as either suppressors (light gray) or non-suppressors (dark gray). * = significantly different from the control group ($p < 0.05$). **(B)** Participants in each group that were in either the suppressor (light gray) or non-suppressor (dark gray) range on the mnemonic control index. Squares represent control participants, triangles represent trauma-exposed participants, and circles represent PTSD participants. PTSD = posttraumatic stress disorder.
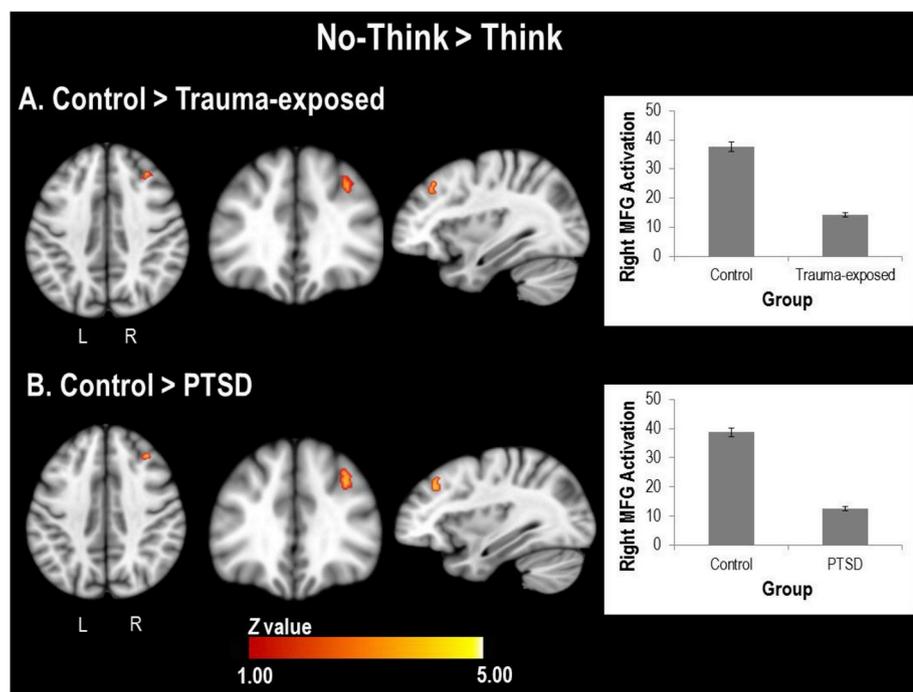
Fig. 4. Group differences in No-Think > Think ROI analysis. The control group had significantly greater activation in the right MFG compared to the **(A)** trauma-exposed and **(B)** PTSD groups. Bar graphs to the right display average cope of parameter estimates for the right MFG region in each group. Scale represents Z score. All images were thresholded at $Z > 3.1$ (p < 0.001) and cluster corrected at $p = 0.05$. L = left; MFG = middle frontal gyrus; PTSD = posttraumatic stress disorder; R = right; ROI = region of interest.

Table 4
Significant brain regions for No-Think > Think ROI analysis in each group.

Brain Region	Cluster Size	Peak Voxel (MNI coordinates)	Z-statistic
Control group map			
Right Middle Frontal Gyrus/ Frontal Pole	1453	34 34 36	6.57
Right Frontal Pole	214	4 60 6	4.54
Left Frontal Pole	169	−18 42 28	4.47
Left Superior Frontal Gyrus/ Middle Frontal Gyrus	115	−24 30 44	3.53
Right Superior Frontal Gyrus	113	20 2 62	4.42
Right Middle Frontal Gyrus/ Precentral Gyrus	45	40 0 54	4.17
Trauma-exposed group map			
Right Middle Frontal Gyrus/ Frontal Pole	639	34 34 32	5.14
Right Superior Frontal Gyrus	637	20 2 56	4.92
Left Frontal Pole/Middle Frontal Gyrus	163	−32 44 30	4.21
PTSD group map			
Right Middle Frontal Gyrus/ Superior Frontal Gyrus	22	30 34 38	3.71

Note: Cluster size is number of voxels. Only clusters are reported; sub-clusters are not reported. PTSD = posttraumatic stress disorder; ROI = region of interest.

3.2.3. Successful suppression of memory

We next examined brain activity for successfully suppressed images using the subsequent memory paradigm. To do this, we classified fMRI trials not only as a function of condition (No-Think, Think), but also as a function of participants' subsequent memory (forgotten, remembered) for face-picture pairs on the memory test conducted after the scan. A comparison between successful suppression (No-Think-forgotten) and successful retrieval (Think-remembered) using the bilateral PFC ROI mask created from the whole-brain No-Think > Think analysis that included all participants and all trials revealed similar results. Specifically, the control group had significantly increased activation in the right MFG compared with both trauma-exposed and PTSD groups (trauma-exposed: peak MNI coordinates = 34 32 40, Z Max = 4.14;

PTSD: peak MNI coordinates = 34 32 42, Z Max = 4.29). Again, there were no significant group differences in the left PFC. Neither trauma-exposed nor PTSD groups displayed greater activation than the control group and there were no significant differences between the trauma-exposed and PTSD groups when they were compared directly.

3.2.4. Correlations between brain activity and trait suppression

To examine whether brain activity during an active, transient state of suppression was associated with trait suppression, we conducted a partial Pearson correlation between the right MFG (both clusters that were significantly different between groups in the No-Think > Think all trials ROI analysis) and WBSI total score across participants. Results revealed a significant negative correlation (controls v. PTSD cluster: $r = -0.4$, $p = 0.01$; controls v. trauma-exposed cluster: $r = -0.3$, $p < 0.03$) such that higher scores on trait suppression were associated with lower right MFG activity (see Fig. 5).

4. Discussion

There were three main findings of this study. First, those with trauma exposure (both with and without a PTSD diagnosis) had greater difficulty suppressing negative information than non-trauma-exposed controls. Second, trauma exposure, regardless of PTSD status, was associated with disrupted activity in the right MFG during active attempts at memory suppression. Finally, those with lower right MFG activity reported that they routinely engaged in memory suppression in everyday life to a greater extent than individuals with higher right MFG activity. Taken together, these findings suggest that trauma exposure, even in the absence of PTSD, is associated with neural and behavioral disruptions in memory suppression, and that right MFG activity is associated with both online attempts at suppression as well as trait suppression.

Our results add to the growing literature implicating the right, but not left, MFG in memory suppression and motivated forgetting (Benoit and Anderson, 2012; Depue et al., 2007, 2015). Disruptions in this region have been associated with poor memory suppression performance in ADHD, another disorder of inhibitory control (Depue et al., 2010). Here, we show that right MFG activity is disrupted with trauma exposure, and that those with trauma exposure were less likely to be
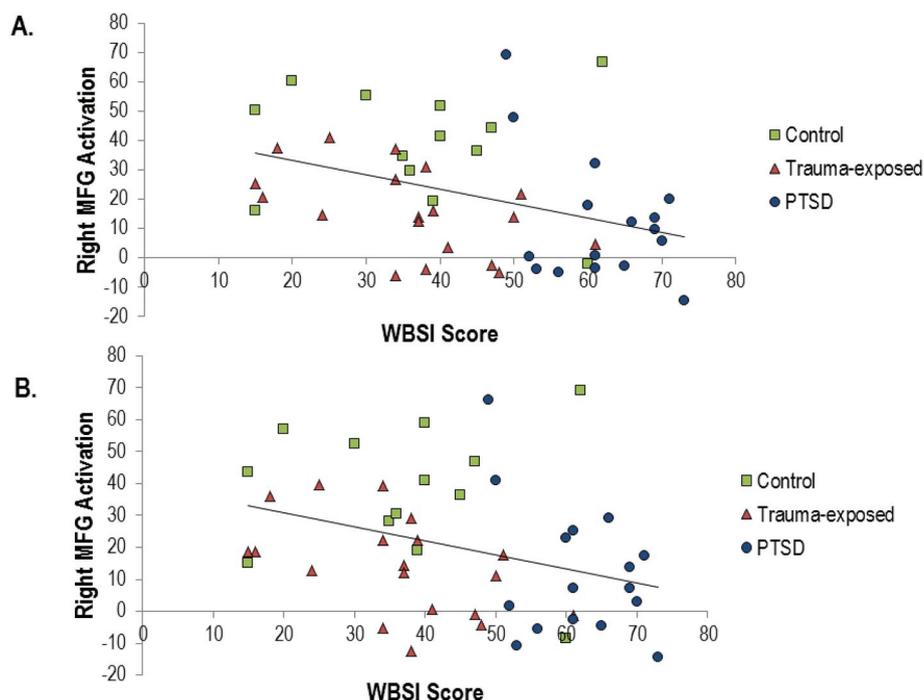
Fig. 5. Trait Suppression is negatively associated with activation in the right MFG. Lower activation in the right MFG for clusters that were significantly different between groups in the No-Think > Think ROI analysis comparing controls to **(A)** PTSD and **(B)** trauma-exposed groups was significantly associated with higher scores on the WBSI. Green squares represent control participants, red triangles represent trauma-exposed participants, and blue circles represent PTSD participants. MFG = middle frontal gyrus; PTSD = posttraumatic stress disorder; ROI = region of interest; WBSI = White Bear Suppression Inventory. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

categorized behaviorally as successful memory suppressors compared with non-traumatized controls. We interpret these findings as suggesting that trauma exposure itself induces greater difficulty in voluntary suppression of negative images. Thus, it is possible that prior trauma may place an individual at increased risk for disruptions in memory suppression processes via the right middle frontal gyrus, potentially contributing to later development of PTSD. This is consistent with work investigating early-life trauma that suggests that childhood trauma may place individuals at increased risk for later-onset clinical disorders and that aberrant neural processes related to trauma exposure itself may underlie vulnerabilities to psychopathology (Herringa et al., 2013; Marusak et al., 2015). However, despite greater difficulty in active memory suppression, trauma-exposed individuals without PTSD do not show elevated trait suppression nor do they report intrusive memories that interfere with everyday life. Thus, disrupted right MFG activity does not appear to be sufficient to induce re-experiencing symptoms that define PTSD. Further studies are necessary to determine the larger brain dynamics involved in elevated thought suppression attempts that characterize PTSD and differentiate those who develop PTSD from those who were trauma-exposed but did not develop PTSD.

One clue that may shed light on potential differences between trauma-exposed and PTSD participants with regard to memory suppression comes from a recent behavioral Think-No-Think study (Catarino et al., 2015), in which trauma-exposed subjects without PTSD showed successful memory suppression relative to those with PTSD. In that study, paired object-scene stimuli were contextually related (i.e., teddy bear + scene with embedded teddy bear) increasing the likelihood that individuals remembered items based on familiarity, unlike the stimuli presented in the current study (i.e. unrelated face + scene pair), which required subjects to form novel episodic associations. It is possible that the ability to suppress *contextually related and familiar* items is the key to preventing intrusive trauma memories from entering consciousness. To fully evaluate this possibility, an fMRI study using contextually related stimuli in trauma-exposed controls versus PTSD would be necessary to test the hypothesis that trauma-exposed individuals without PTSD show intact right MFG activity during suppression attempts of related associative stimuli.

Notwithstanding potential task effects of memory suppression, the PTSD group reported more attempts at memory suppression in everyday life in this study than trauma-exposed and non-trauma-exposed control groups. Research has shown that engaging in thought suppression may paradoxically lead to an increase in intrusive thoughts (Amstadter and Vernon, 2006; McNally and Ricciardi, 1996). Thus, higher scores on the WBSI may indicate not only a greater chronic tendency to suppress, but also less success at suppression (Rassin, 2003). Our results suggest that although trauma exposure by itself may be associated with disrupted state suppression, the chronic tendency to engage in memory suppression, and consequently the chronic difficulties in successfully implementing it, may be specific to PTSD. This is consistent with other research that has examined chronic thought suppression with the WBSI in PTSD and has shown that higher PTSD symptom severity is associated with a greater tendency to suppress unwanted thoughts (Vázquez et al., 2008; Vincken et al., 2012). What remains unclear, however, is whether trait suppression is a predisposing risk factor for, or a consequence of, PTSD. Longitudinal studies will be necessary to shed light onto these unanswered questions.

The results reported in this study should be considered within the context of the limitation of the small sample size of the patient and control groups. It will be important to replicate these findings in studies with larger samples. Another limitation is that chronic trait suppression was based on self-report. However, the WBSI has been widely used to measure chronic thought suppression use, has good psychometric properties (Muris et al., 1996), and has been validated across cultural groups (Altın and Gençöz, 2009). A third limitation of the study is that it did not include a component to probe suppression strategies used by participants. It is possible that the individuals were using varying strategies during the No-Think condition such as rehearsing a distractor, attending to present-moment sensations, etc. However, we have found no observable differences when regressing strategy with fMRI data in the past (Depue et al., 2007, 2015). Nonetheless, it will be beneficial for future research to include an assessment of suppression strategies during the Think-No-Think task. Finally, this study did not assess psychopathology other than depression and PTSD. Although the trauma-exposed group did not exhibit depression symptomatology, it is possible that this group had other psychopathology not measured here, which could potentially limit PTSD-specific findings. More research investigating other psychopathology and PTSD is needed to confirm the findings reported in the current study.

In summary, we report disruptions in the neural processes associated with memory suppression in trauma exposure. In particular, compared to non-traumatized controls, trauma-exposed individuals with and without PTSD had greater difficulty suppressing negative information and had disrupted activation in the right MFG during an active state of memory suppression. In addition, the chronic tendency to engage in thought suppression was specific to PTSD, and was associated with reduced activity in the right MFG. Collectively, our results add to the growing evidence for the role of the right MFG in successful memory suppression and further demonstrate that this region is associated with both state and trait suppression. The results also indicate that trauma exposure itself is related to disruptions in inhibitory control of memory. Thus, trauma exposure appears to be only one factor in the complex and multifactorial process that leads to the development of PTSD. Further research is necessary to evaluate the role that trait suppression has as a risk factor for PTSD.

Conflicts of Interest

Declarations of Interest: none.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.02.015.

References

Altın, M., Gençöz, T., 2009. Psychopathological correlates and psychometric properties of the White Bear Suppression Inventory in a Turkish sample. Eur. J. Psychol. Assess. 25, 23–29. https://doi.org/10.1027/1015-5759.25.1.23.

Amstadter, A.B., Vernon, L.L., 2006. Suppression of neutral and trauma targets: Implications for posttraumatic stress disorder. J. Trauma Stress 19, 517–526. https://doi.org/10.1002/jts.20142.

Anderson, M.C., Green, C., 2001. Suppressing unwanted memories by executive control. Nature 410, 366–369. https://doi.org/10.1038/35066572.

Anderson, M.C., Ochsner, K.N., Kuhl, B., Cooper, J., Robertson, E., Gabrieli, S.W., Glover, G.H., Gabrieli, J.D., 2004. Neural systems underlying the suppression of unwanted memories. Science 303, 232–235. https://doi.org/10.1126/science.1089504.

Anderson, M.C., Hanslmayr, S., 2014. Neural mechanisms of motivated forgetting. Trends Cognit. Sci. 18, 279–292. https://doi.org/10.1016/j.tics.2014.03.002.

Beckmann, C.F., Jenkinson, M., Smith, S.M., 2003. General multilevel linear modeling for group analysis in FMRI. Neuroimage 20, 1052–1063. https://doi.org/10.1016/s1053-8119(03)00435-x.

Benoit, R.G., Anderson, M.C., 2012. Opposing mechanisms support the voluntary forgetting of unwanted memories. Neuron 76, 450–460. https://doi.org/10.1016/j.neuron.2012.07.025.

Blake, D.D., Weathers, F.W., Nagy, L.M., Kaloupek, D.G., Gusman, F.D., Charney, D.S., Keane, T.M., 1995. The development of a Clinician-Administered PTSD Scale. J. Trauma Stress 8, 75–90. https://doi.org/10.1007/bf02105408.

Catarino, A., Küpper, C.S., Werner-Seidler, A., Dalgleish, T., Anderson, M.C., 2015. Failing to forget: Inhibitory-control deficits compromise memory suppression in posttraumatic stress disorder. Psychol. Sci. 26, 604–616. https://doi.org/10.1177/0956797615569889.

Cottencin, O., Vaiva, G., Huron, C., Devos, P., Ducrocq, F., Jouvent, R., Goudemand, M., Thomas, P., 2006. Directed forgetting in PTSD: A comparative study versus normal controls. J. Psychiatr. Res. 40, 70–80. https://doi.org/10.1016/j.jpsychires.2005.04.001.

Depue, B., Banich, M., Curran, T., 2006. Suppression of emotional and nonemotional content in memory: Effects of repetition on cognitive control. Psychol. Sci. 17, 441–447. https://doi.org/10.1111/j.1467-9280.2006.01725.x.

Depue, B., Curran, T., Banich, M., 2007. Prefrontal regions orchestrate suppression of emotional memories via a two-phase process. Science 317, 215–219. https://doi.org/10.1126/science.1139560.

Depue, B., Burgess, G., Willcutt, E., Ruzic, L., Banich, M., 2010. Inhibitory control of memory retrieval and motor processing associated with the right lateral prefrontal cortex: Evidence from deficits in individuals with ADHD. Neuropsychologia 48, 3909–3917. https://doi.org/10.1016/j.neuropsychologia.2010.09.013.

Depue, B., Orr, J., Smolker, H., Naaz, F., Banich, M., 2015. The organization of right prefrontal networks reveals common mechanisms of inhibitory regulation across cognitive, emotional, and motor processes. Cerebr. Cortex 26, 1634–1646. https://doi.org/10.1093/cercor/bhu324.

Geraerts, E., McNally, R.J., 2008. Forgetting unwanted memories: Directed forgetting and thought suppression methods. Acta Psychol. 127, 614–622. https://doi.org/10.1016/j.actpsy.2007.11.003.

Hayes, J.P., VanElzakker, M.B., Shin, L.M., 2012. Emotion and cognition interactions in PTSD: A review of neurocognitive and neuroimaging studies. Front. Integr. Neurosci. 6, 89. https://doi.org/10.3389/fnint.2012.00089.

Herringa, R.J., Phillips, M.L., Fournier, J.C., Kronhaus, D.M., Germain, A., 2013. Childhood and adult trauma both correlate with dorsal anterior cingulate activation to threat in combat veterans. Psychol. Med. 43, 1533–1542. https://doi.org/10.1017/s0033291712002310.

King, L.A., King, D.W., Vogt, D.S., Knight, J., Samper, R.E., 2006. Deployment Risk and Resilience Inventory: A collection of measures for studying deployment-related experiences of military personnel and veterans. Mil. Psychol. 18, 89–120. https://doi.org/10.1207/s15327876mp1802_1.

LaBar, K.S., Cabeza, R., 2006. Cognitive neuroscience of emotional memory. Nat. Rev. Neurosci. 7, 54. https://doi.org/10.1038/nrn1825.

Lang, P.J., Bradley, M.M., Cuthbert, B.N., 2008. International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-8. University of Florida, Gainesville, Fl.

Levy, B.J., Anderson, M.C., 2008. Individual differences in the suppression of unwanted memories: The executive deficit hypothesis. Acta Psychol. 127, 623–635. https://doi.org/10.1016/j.actpsy.2007.12.004.

Marusak, H.A., Etkin, A., Thomason, M.E., 2015. Disrupted insula-based neural circuit organization and conflict interference in trauma-exposed youth. Neuroimage: Clinic 8, 516–525. https://doi.org/10.1016/j.nicl.2015.04.007.

McNally, R.J., Ricciardi, J.N., 1996. Suppression of Negative and Neutral Thoughts. Behav.Cogn. Psychother. 24, 17–25. https://doi.org/10.1017/s1352465800016805.

Muris, P., Merckelbach, H., Horselenberg, R., 1996. Individual differences in thought suppression. The White Bear Suppression Inventory: Factor structure, reliability, validity and correlates. Behav. Res. Ther. 34, 501–513. https://doi.org/10.1016/0005-7967(96)00005-8.

Nickerson, A., Garber, B., Ahmed, O., Asnaani, A., Cheung, J., Hofmann, S.G., Huynh, L., Liddell, D., Litz, B.T., Pajak, R., Bryant, R.A., 2016. Emotional suppression in torture survivors: Relationship to posttraumatic stress symptoms and trauma-related negative affect. Psychiatr. Res. 242, 233–239. https://doi.org/10.1016/j.psychres.2016.05.048.

Paz-Alonso, P.M., Bunge, S.A., Anderson, M.C., Ghetti, S., 2013. Strength of coupling within a mnemonic control network differentiates those who can and cannot suppress memory retrieval. J. Neurosci. 33, 5017–5026. https://doi.org/10.1523/jneurosci.3459-12.2013.

Rassin, E., 2003. The White Bear Suppression Inventory (WBSI) Focuses on Failing Suppression Attempts. Eur. J. Personal. 17, 285. https://doi.org/10.1002/per.478.

Shipherd, J.C., Beck, J.G., 1999. The effects of suppressing trauma-related thoughts on women with rape-related posttraumatic stress disorder. Behav. Res. Ther. 37, 99–112. https://doi.org/10.1016/s0005-7967(98)00136-3.

Shipherd, J.C., Beck, J.G., 2005. The role of thought suppression in posttraumatic stress disorder. Behav. Ther. 36, 277–287. https://doi.org/10.1016/s0005-7894(05)80076-0.

Vázquez, C., Hervás, G., Pérez-Sales, P., 2008. Chronic thought suppression and post-traumatic symptoms: Data from the Madrid Marcg 11, 2004 terrorist attack. J. Anxiety Disord. 22, 1326–1336. https://doi.org/10.1016/j.janxdis.2008.01.014.

Vincken, M.J.B., Meesters, C., Engelhard, I.M., Schouten, E., 2012. Psychometric qualities of the White Bear Suppression Inventory in a Dutch sample of children and adolescents. Pers. Indiv. Differ. 52, 301–305. https://doi.org/10.1016/j.paid.2011.10.023.

Wegner, D.M., Zanakos, S., 1994. Chronic thought suppression. J. Pers. 62, 615–640. https://doi.org/10.1111/j.1467-6494.1994.tb00311.x.

Wenzlaff, R.M., Wegner, D.M., 2000. Thought Suppression. Annu. Rev. Psychol. 51, 59–91. https://doi.org/10.1146/annurev.psych.51.1.59.

Woolrich, M.W., Behrens, T.E., Beckmann, C.F., Jenkinson, M., Smith, S.M., 2004. Multilevel linear modelling for FMRI group analysis using Bayesian inference. Neuroimage 21, 1732–1747. https://doi.org/10.1016/j.neuroimage.2003.12.023.

Woolrich, M., 2008. Robust group analysis using outlier inference. Neuroimage 41, 286–301. https://doi.org/10.1016/j.neuroimage.2008.02.042.

Zoellner, L.A., Sacks, M.B., Foa, E.B., 2003. Directed forgetting following mood induction in chronic posttraumatic stress disorder patients. J. Abnorm. Psychol. 112, 508. https://doi.org/10.1037/0021-843x.112.3.508.