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The neural basis of improved cognitive performance by threat of shock

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Abstract

Anxiety can have both detrimental and facilitatory cognitive effects. This study investigates the neural substrates of a replicated facilitatory effect of anxiety on sustained attention and response inhibition. This effect consisted of improved performance on the Sustained Attention to Response Task (a Go–NoGo task consisting of 91% Go and 9% NoGo trials) in threat (unpredictable electrical shock) vs safe (no shock) conditions. This study uses the same experimental design with fMRI and relies on an event-related analysis of BOLD signal changes. Findings reveal that threat-related cognitive facilitation (improved NoGo accuracy) is associated with greater activation of a right-lateralized frontoparietal group of regions previously implicated in sustained attention and response inhibition. Moreover, these same regions show decreased activation in the Go trials preceding NoGo errors. During NoGo trials, striatal activity is also greater in the threat vs safe condition, consistent with the notion of enhanced inhibitory processing under threat. These findings identify potential mechanisms by which threat of unpredictable shock can facilitate distinct cognitive functions. A greater understanding of the complex interaction of the anxious state and cognitive processes may have critical clinical implications.

Key words: sustained attention; response inhibition; Go/NoGo; threat of shock; fMRI

Introduction

Anxiety is known to alter behavioral and cognitive functions. While anxiety can impair performance through cognitive interference (Eysenck *et al.*, 2007; Robinson *et al.*, 2013b), it can also improve performance, putatively through heightened arousal (Malmo, 1957), sensory processing (Baas *et al.*, 2006; Grillon and Charney, 2011) or facilitated motor inhibition (Sehlmeyer *et al.*, 2010; Robinson *et al.*, 2013a; Chiu *et al.*, 2014). This study tests the neural mechanisms underlying such effects. We recently showed in two separate cohorts that anxiety induced by threat of shock improved NoGo performance accuracy (reduced NoGo commission errors) on the Sustained Attention to Response Task (SART) by possibly facilitating vigilance and/or behavioral inhibition (Robinson *et al.*, 2013a; Grillon *et al.*, 2015). Using a similar task, Sehlmeyer *et al.* (2010) found that high trait anxiety was also associated with reduced NoGo commission errors and concluded that anxiety enhanced response inhibition. Anxiety-induced behavioral inhibition is consistent with models according to which anxiety prompts hypervigilance and inhibition of prepotent responses (Gray and McNaughton, 2000) and with the observation that anxiety causes freezing and avoidance behaviors (Lang *et al.*, 2000). This study provides novel data on the neural mechanisms underlying these effects, using our same empirical approach, but in the fMRI environment.

SART consists of the presentation of frequent 'Go' stimuli interspersed with rare 'NoGo' stimuli, which require withdrawing prepotent 'Go' responses. Accordingly, SART probes two main cognitive processes, *sustained attention* and *motor inhibition* (Robertson *et al.*, 1997; Helton, 2009). The engagement of sustained attention is required to maintain task goals, while inhibition is required to withhold prepotent responses. The high repetitiveness of Go stimuli endows responses to these stimuli with prepotency, and, consequently, requires strong response

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inhibition to withdraw motor responses to rare NoGo stimuli (Peebles and Bothell, 2004; Helton, 2009). This design also requires the maintenance of a state of preparedness for the NoGo stimuli. Therefore, during the long succession of sequential Go trials, sustained attention is the dominant active process, and response inhibition is in a primed state. Conversely, during NoGo trials, motor inhibition is the primary active process.

Sustained attention and response inhibition have been mapped to specific neural networks (here we use 'network' to refer to consistent coactivations and acknowledge that a more appropriate use of this word necessitates structural or functional connectivity analyses). The sustained attentional network has typically been assigned to right-lateralized prefrontal and parietal regions (Manly *et al.*, 2003; Fassbender *et al.*, 2004; O'Connor *et al.*, 2011; Sakai *et al.*, 2013). The response inhibition network involves regions in the right inferior frontal cortex, dorsal anterior cingulate cortex (dACC) and basal ganglia (Bush *et al.*, 2000; Garavan *et al.*, 2006; Aron *et al.*, 2014). Accordingly, neuroimaging studies have shown that SART engages right-lateralized regions (Helton *et al.*, 2010; Stevenson *et al.*, 2011) localized to the right inferior frontal cortex, dACC, parietal cortex and basal ganglia (Manly *et al.*, 2003; Fassbender *et al.*, 2004; Sakai *et al.*, 2013).

The few studies that have examined the effects of "anxiety" on sustained attention have used either exposure to acute threat cues (Wilson *et al.*, 2015), or have studied individuals with high trait anxiety (Righi *et al.*, 2009; Forster *et al.*, 2015) (see Shackman *et al.*, 2006 for caveats to these approaches). Although these works have not directly examined the effects of an enduring state of apprehension, their findings can inform predictions. Specifically, they reported increased activation of the regions involved in sustained attention (Pannu Hayes *et al.*, 2009; Koric *et al.*, 2011; Sylvester *et al.*, 2012). In addition, transient aversive states can improve response inhibition during SART (Wilson *et al.*, 2015). However, studies in high trait anxious individuals have revealed contradictory findings of both improved and impaired response inhibition performance. A study reported that trait anxiety was associated with reduced commission errors during SART, an effect attributed to high level of cognitive control based on measure of brain electrical activity (Sehlmeyer *et al.*, 2010). However, another study reported slower Go reaction time together with reduced activation of cognitive control regions (Bishop, 2008; Forster *et al.*, 2015).

This study uses threat of shock and safety from shock (Alvarez *et al.*, 2011; Robinson *et al.*, 2013b) with the SART to probe sustained attention and response inhibition. Given improved SART performance under threat, three hypotheses are tested separately: (i) activity patterns implicated in sustained attention would be potentiated (i.e. made stronger) by threat of shock in the contrast of threat *vs* safe condition during Go trials; (ii) Errors of commission (EoC) would be preceded by a lesser engagement of these attention-related activations, consistent with attentional lapses. We also predicted that the regions altered in this manner would be consistent with those regions affected by anxiety in the first hypothesis. (iii) Finally, prefrontal regions implicated in motor inhibitory control would be strengthened by threat of shock in the contrast of threat *vs* safe during correct NoGo trials.

Materials and methods

Subjects

Thirty-seven, right-handed, healthy adult volunteers were recruited from a mixed urban and suburban population through Internet listservs, flyers and print advertisements. Exclusion criteria included: (i) current or past Axis I psychiatric disorder as assessed by SCID-I/NP (First *et al.*, 2007), (ii) first degree relative with a known psychotic disorder, (iii) a medical condition conflicting with safety or design of the study, (iv) brain abnormality on MRI as assessed by a radiologist, (v) positive toxicology screen, (vi) MRI contraindication or (vii) excessive head motion during the functional scans. For reasons detailed below, the final analysis included 31 subjects between the ages of 18 and 39. Written, informed consent was approved by the National Institute of Mental Health (NIMH) Combined Neuroscience Institutional Review Board and obtained from all subjects. All subjects were compensated for their time.

Shock procedure

The threat of shock procedure was based on a translational psychophysiology paradigm (Schmitz and Grillon, 2012) adapted for neuroimaging (e.g. Robinson *et al.*, 2012). Prior to the task, subjects completed a work-up procedure to control for individual differences in shock tolerance and to titrate the shock intensity to a level that was highly uncomfortable and aversive but not painful. The subjects were told that they could receive an unpredictable number of randomly generated shocks during the threat conditions. In actuality, one 500-μs shock was delivered to the left wrist (DS7A; Digitimer, UK) twice, during the first half of the two fMRI runs.

Task design

Go/NoGo trials were presented for 500 ms in an event-related design with a centered "=" symbol representing Go trials and "o" representing NoGo trials. The distribution of trial types consisted of 91% Gos and 9% NoGos distributed across two runs. Each trial was separated by 1500–2500 ms of jittered inter-trial-interval (blank slide that varied in presentation time). Each run consisted of six 2-min blocks of two conditions (three blocks of *safe from shock*, and three blocks of *threat of shock*) and the order of condition presentation was counterbalanced across subjects. The phrases "You are now safe from shock" or "You are now at risk of shock" were shown at the start of each condition and, after these instructions, a blue border surrounded safe trials and a red border surrounded threat trials. Each run was 13 min 12 s (26 min 24 s total). Subjects were asked to rate their subjective anxiety, fear and happiness over the intercom after each run (scale: 1 not at all to10 extremely). Stimuli were presented on a projection screen with E-Prime 2.0 (Psychological Software Tools, Pittsburgh, PA) including 20 s of fixation at the beginning and end for estimating baseline.

Behavior: threat *vs*. safe conditions

Subjective measures, performance measures [accuracy, response time (RT) and response time variability (RTV)] were compared between threat and safe conditions using paired *t*-tests across both runs. Correlations were calculated between percent NoGo accuracy and Go response time variability.

In addition, for the second analysis, the RT of the four trials preceded NoGos was averaged, partitioned according to whether they preceded EoC or correct NoGos, and a repeated measures 2 × 2 ANOVA with the factors condition (threat/safe) × accuracy (EoC/correct) was performed. Behavior analyses were conducted in Microsoft Excel 2011 (Redmond, WA) or SPSS v. 21 (Armonk, NY: IBM Corp.).

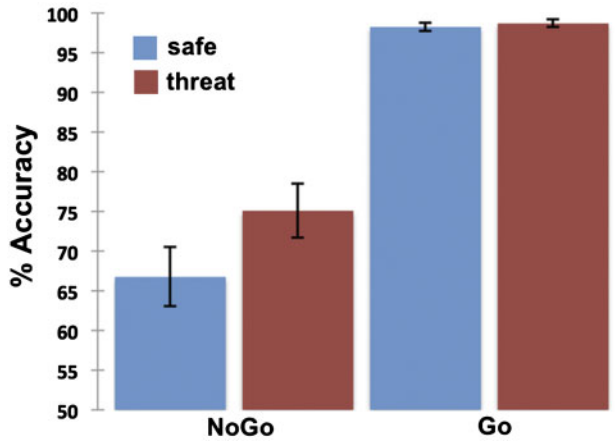

Fig. 1. Percent accuracy within trial type and condition. Error bars = s.e.m.

Functional image acquisition and preprocessing

Scanning was performed on a 3-T Siemens Magnetom Skyra with a 32-channel head coil. The 1-mm isotropic structural scan was a T1-weighted MPRAGE with the following parameters: TR = 1.9 s, TE = 2.13, acquisition matrix = 256 × 256, Slice thickness 0.9 mm, flip angle 9°. The functional EPI had a TR of 2 s, TE = 30 ms, flip angle 70°, 35 slices, acquisition matrix = 64 × 64, 3 × 3 × 3 mm voxels, and 396 images collected for each run. Subjects were provided earplugs, a pillow beneath their knees for stability, and foam padding was used to further constrain head movement.

All preprocessing and analyses were performed with AFNI (Cox, 1996). Subjects' functional volumes were slice-time and motion corrected, coregistered to their structurals using a Local Pearson Correlation algorithm optimized for EPI and T1-weighted scans (Saad *et al.*, 2009), normalized to the N27-Talairach template, and smoothed with a 6-mm FWHM Gaussian kernel within a mask of voxels that had valid data at every TR. Adjacent TRs with a Euclidean Norm motion derivative >0.3 mm were censored (3.1 ± 2.4% TRs per participant). Furthermore, subjects with >10% of their TRs censored from such head motion were removed from the study, leaving 31 of 37 total scanned subjects. This final group of 31 consisted of 14 females and 17 males (average age = 28 ± 6).

Individual subject regressions were performed with AFNI's *3dDeconvolve*. Each trial event was convolved with a gamma HRF and all data was high-pass filtered with six low-frequency polynomial regressors. Covariates of non-interest included six head movement parameters, incorrect NoGo trials, instruction screens and the two electric shocks. Covariates of interest are described below. Group analyses were performed within a whole brain mask created from an average of each subject's individual masks binarized to 95%. The cluster extent (k_e) of corrected statistical results was also estimated within this mask using an average of all subjects' spatial smoothness computed with *3dFWHMx*. A Monte Carlo simulation using *3dClustSim* then determined that voxel level $P = 0.001$, $k_e = 13$ was corrected for multiple comparisons at $P < 0.05$, whole brain. This threshold was also used to establish statistical significance across the following three random-effects, group-level analyses:

To test hypothesis 1, analysis 1 used *3dANOVA2* to compare correct Go trials in a Threat *vs* Safe contrast. Events of interest were correct Gos in the threat and safe conditions. As others have done (Forster *et al.*, 2015), this analysis used activation during Go trials to examine sustained attention and proactive control. Note that the 2-min condition blocks were not directly modeled in these analyses; only contrasts of individual trial types were constructed.

To test the second hypothesis, analysis 2 investigated brain activity preceding EoCs. Our modeling established a primary contrast between the four Go trials preceding incorrect NoGos (4go-I) and the four Go trials preceding correct NoGos (4go-C), as our group and others have previously done (Robertson *et al.*, 1997; Christoff *et al.*, 2009; Robinson *et al.*, 2013a). The main effect of 4go-I *vs* 4go-C was used to examine mechanisms of attention lapses across conditions. Accordingly, two regressors of interest were added for this second analysis, the sets of four Go trials that preceded incorrect NoGos (4go-I) and the sets of four Go trials that preceded correct NoGos (4go-C). Two subjects were eliminated because they made no EoCs during at least one of the conditions, yielding 29 subjects for this analysis. Finally, all other Go trials and all NoGo trials in the threat and safe conditions were included as covariates of no-interest in addition to those covariates mentioned above. Three regions of interest were chosen from the results of Analysis 1 and subsequently probed in a post hoc manner with *3dROIstats* to clarify the direction of Analysis 2 effects via regression betas. We selected those regions from analysis 1 that seemed to overlap with the results of analysis 2 to test the hypothesis that the effects of attention lapses acted on the same or similar network that supported improved sustained attention.

Analysis 3 tested the effects of threat on NoGo trials to probe our hypothesis 3 of the effects of anxiety on response inhibition in the full sample of 31 subjects. This analysis was modeled at the individual subject level identically to the analysis 1, except for using correct NoGo trials instead of Go trials as the regressors of interest.

In addition, we conducted a validation control analysis, for which we constructed a statistical map of the main effects of Go trials across conditions to check that the event timings were modeled correctly and that the combination of TR and range of inter-trial stimulus intervals could capture hemodynamic responses adequately.

Results

State manipulation. As expected, subjects reported more anxiety (5.0 ± 2.2 threat, 2.0 ± 1.3 safe), more fear (3.7 ± 2.1 threat, 1.4 ± 0.9 safe) and less happiness (4.2 ± 2.1 threat, 6.3 ± 1.8 safe) during the threat compared to the safe condition (all $Ps < 0.0001$).

Behavioral performance

Accuracy. Figure 1 shows NoGo and Go accuracy separately for the threat and safe condition. The improved NoGo accuracy during threat (0.75 ± 0.2) compared to safe (0.67 ± 0.2) was significant ($t(30) = 4.45$; $P = 0.0001$; Cohen's $d = 0.42$). Go accuracy was high and tended to also be improved in the threat (0.987 ± 0.03) compared to the safe (0.982 ± 0.03) conditions ($t(30) = 2.01$; $P = 0.053$).

EoCs varied by trial type and condition, with the mean and [range] reported as follows: threat EoCs: 7.2, [1–17], threat correct NoGo trials: 19.7, [10–26], safe EoCs: 9.3, [1–19], and safe correct NoGo trials: 17.7, [8–26]. Note that these numbers should be multiplied by 4 when considering the second analysis probing trials preceding EoC.

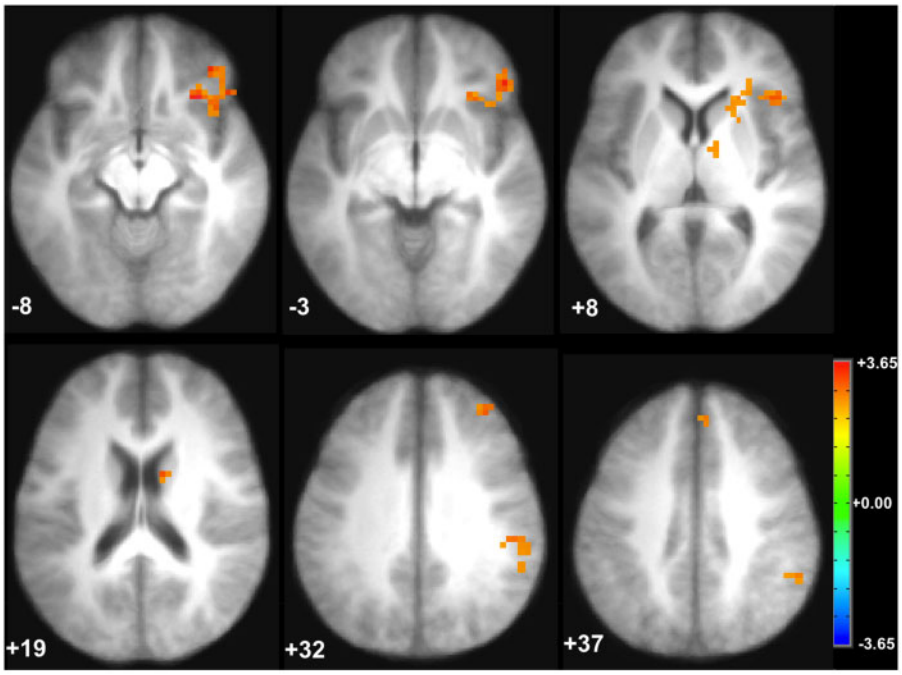

Fig. 2. All Go trials, in a Threat *vs* Safe contrast. Maps corrected at $T > \pm 3.65$, $P < 0.001$, $k = 13$, $N = 31$. Results in this and subsequent figures are overlaid on an average of all subject's normalized structural scans. Numbers represent Z levels in Talairach space. See also Table 1A.

Response time (RT). Three measures of response time are reported:

Go-RT: There was no significant difference of overall Go response time (Go-RT) between the threat and safe conditions ($t = 0.62(30)$; $P = 0.54$), indicating that the improved NoGo accuracy during threat was not due to a speed-accuracy trade off. Furthermore, Go-RT was not correlated with Go-accuracy in either condition (threat: $r = -0.05$, ns; safe: $r = -0.11$, ns).

Go-RTV: Overall Go-RTV was also not influenced by threat. However, greater Go-RTV was associated with worse NoGo accuracy, both in the threat ($r = -0.54$, $P = 0.002$) and safe ($r = -0.57$, $P = 0.0009$) conditions. Therefore, lower RT variability was indicative of better performance.

4Go-RT: For RT of the four trials preceding either incorrect (4go-I) or correct (4go-C) NoGo trials, a 2-way (NoGo Accuracy, Condition) repeated measures ANOVA revealed a significant main effect of NoGo accuracy [$F_{(1,\ 28)} = 16.46$, $P < 0.001$; $\eta^2 = 0.37$], indicating faster 4go-I than 4Go-C. No other effects were significant.

Functional imaging

Analysis 1: This first analysis examined the effects of threat *vs* safe on correct Go trials. Results showed greater activation in threat *vs* safe in regions previously associated with inhibition and sustained attention (Figure 2). Specifically, these threat-related effects were segregated to the right hemisphere: middle frontal gyrus (MFG), medial frontal pole, ventrolateral prefrontal cortex (vlPFC), inferior parietal lobule (IPL), anterior insula, and caudate nucleus (Table 1).

Analysis 2: This second analysis examined neural predictors of EoCs. Four Go trials immediately preceding NoGo EoCs (4go-I) were compared to four Go trials preceding NoGo correct responses (4go-C). Whole brain results showed greater deactivations in 4go-I trials relative to 4go-C trials in right MFG (Brodmann's Area (BA) 9), bilateral IPL (BA40), and bilateral vlPFC/anterior insula (BA45/13) (Figure 3A, Table 1).

Three of these clusters (rMFG, rIPL, rvlPFC/anterior insula) in Analysis 2 closely overlapped with the results from Analysis 1. Thus, a post hoc analysis was conducted to better understand the effects of threat/performance in these clusters. Accordingly, analysis 2 betas pulled from a single mask of all three activation clusters garnered from Analysis 1 were decomposed by threat and safe. This analysis revealed that the pattern of stronger deactivation associated with impaired performance during safety was reduced during threat (Figure 3B).

Analysis 3: This third analysis examined the effects of threat *vs* safe on correct NoGo trials. Two brain areas, a midbrain region consistent with the ventral tegmental area (VTA) and the right putamen, showed greater activity in the threat than safe conditions during NoGo trials (Figure 4A). Figure 4B pulls regression betas from these regions and shows significant activation to NoGo trials during threat, but no activation during safe.

A post hoc analysis was also performed with the subjective anxiety measure that followed the imaging runs. We chose three of the observed regions from the threat *vs* safe Go trials analysis (Analysis 1) to pull regression betas for correlations (MFG, vlPFC/anterior insula and IPL). These regions were chosen because they were also observed in Analysis 2. We also created masks in two ways: (i) masks formed from the activation cluster shapes themselves and (ii) spherical masks (8-mm radius) centered on the center of mass of those clusters and therefore not biased by activation cluster size. This created $3 \times 2 = 6$ correlation tests that necessitated Bonferroni correction ($P = 0.05/6 = 0.0083$). There was a robust positive correlation that survived correction ($r = 0.55$, $P = 0.0014$) of right MFG with reported anxiety during the threat of shock condition (see Figure 5).

The check for event-related modeling accuracy confirmed that the left motor network (for a right-handed button-press) was activated in response to all Go trials. The regions involved in this network included the contralateral supplementary motor

Table 1. Peak coordinates for three analyses

Hemisphere	Region	BA	# voxels	x	y	z	μT score
A: Threat *vs* Safe, GO trials							
R	Caudate	–	96	10	2	20	3.89
R	Orbital gyrus	47	51	32	22	−6	4.09
R	Frontal superior gyrus	8	20	8	46	44	3.85
R	MFG	9	16	34	38	32	4.01
R	Parietal inf-Supramar gyrus	40	19	50	−28	32	3.86
R	Parietal inf-Supramar gyrus	40	13	52	−44	36	3.85
B: four GOs before EoC; incorrect *vs* correct							
R	MFG	9	45	35	44	27	−4.08
R	IPL	40	19	47	−47	54	−4.31
R	Inf. frontal gyrus/ant insula	45/13	23	38	29	6	−4.19
L	Insula	13	16	−38	5	9	−4.02
L	IPL	40	15	−62	−35	36	−4.18
C: Threat vs Safe, NOGO trials							
R	Putamen	–	14	26	−4	8	4.12
–	VTA	–	13	2	−20	−10	4.20

A: Analysis1: Threat *vs* Safe, Go trials. B: Analysis2: four trials prior to EoC *vs* four trials prior to correct NoGos. C: Analysis3: Threat *vs* Safe, NoGo trials. Coordinates are in Talairach space and T statistics reported as the mean of each cluster.

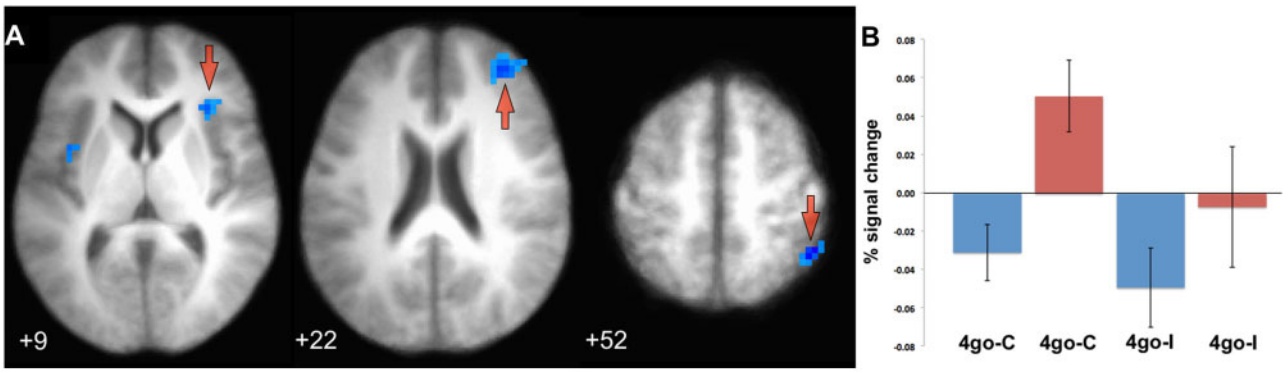

Fig. 3. (A) Four trials prior to EoC *vs* four trials prior to correct NoGos across conditions (safe and threat). From left to right: less activation in right ventrolateral PFC, MFG and right IPL (arrows). See Table 1B for additional regions. $N = 29$. Coloring and thresholding of statistics are the same as in Figure 2. **(B)** Regression coefficients for Go trials just previous to either correct or incorrect NoGos. Beta coefficients are averaged between the three regions highlighted at left, and separated by condition (safe: blue, threat: red) and type of NoGo accuracy they precede. Error bars = s.e.m.

area, hand motor cortex, ventrolateral thalamus and putamen, and ipsilateral cerebellum. On visual inspection, this map was also compared to an automated meta-analysis of imaging studies using the search term "finger" (Yarkoni *et al.*, 2011) and a near identical match was observed (see Supplementary Figure S1).

Discussion

State anxiety, tested here as an experimentally-induced enduring state of apprehension, has been shown to consistently improve performance on the SART, a sustained attention task requiring motor inhibition (Robinson *et al.*, 2013a; Grillon *et al.*, 2015). While replicating the anxiety-related performance improvement, this study provides novel data on the neural correlates of these effects. Predictions were 3-fold. First, anxiety by threat of shock would potentiate activation of regions involved in sustained attention. Second, the activity of these same regions would be altered in trials preceding NoGo errors. Finally, anxiety would reinforce inhibitory processes during NoGo responses.

Threat vs safe of Go trials. In line with predictions, anxiety during Go trials potentiated activation in right-lateralized frontoparietal regions, which are known to be structurally inter-connected (Umarova *et al.*, 2010; Thiebaut de Schotten *et al.*, 2011) and have been consistently associated with sustained attention (Pardo *et al.*, 1991; Sarter *et al.*, 2001; Husain and Rorden, 2003; Langner and Eickhoff, 2013). These regions included right prefrontal areas within MFG/DLPFC and vlPFC/BA47/anterior insula (see Figure 2, upper right), and the IPL (BA40). Similarly threat-related increased activations were found in the right caudate nucleus.

The right prefrontal-parietal network has previously been reported in SART imaging studies (Manly *et al.*, 2003; Grahn and Manly, 2012). For example, Sakai *et al.* (2013) conducted a parametric modulation analysis of fMRI data collected during SART performance using block-based mean Go-RT. They found that right DLPFC and bilateral intraparietal sulcus were positively correlated with Go RT, suggesting that greater activation of the attention network reduced impulsive or automatic responses, indexed by speeded RT. These findings echo the results of this study, i.e. the association of threat-related improved accuracy with enhanced activation in a right frontoparietal network. As

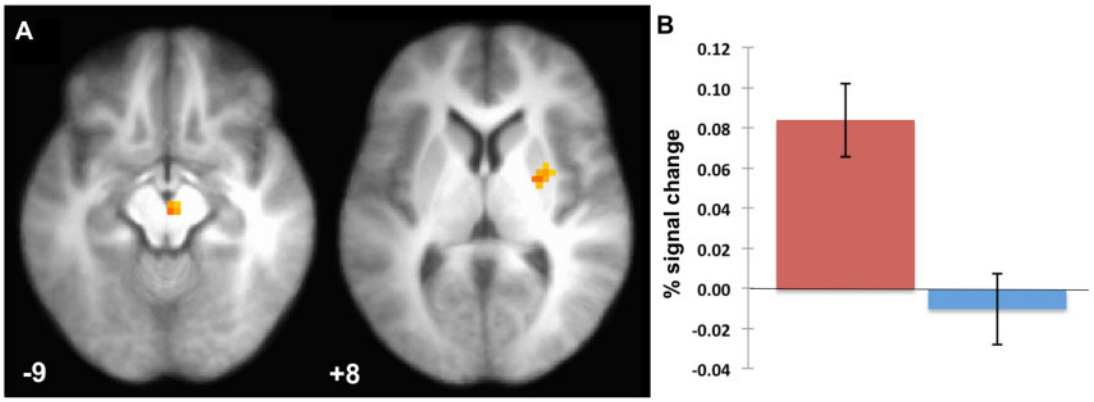

Fig. 4. All correct NoGo trials, in a Threat *vs* Safe contrast. $N = 31$. **(A)** VTA and putamen. **(B)** Betas from regions, red = under threat, blue = safe from threat. See also Table 1C.

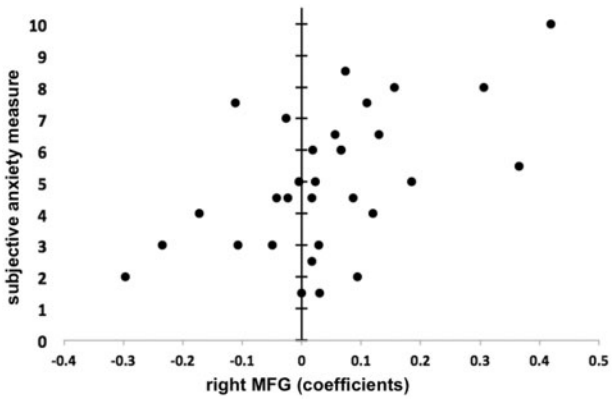

Fig. 5. Right MFG beta coefficients from correct Go trials in Threat *vs* Safe contrast and correlated with subjective report of anxiety during threat blocks. $r = 0.55$, $P = 0.0014$.

such, anxiety would facilitate sustained attention by strengthening the attention network. In support of this interpretation, the activation of the corresponding MFG/DLPFC region tracked self-reported anxiety during threat (Figure 5).

Furthermore, a meta-analysis of insula function found that the anterior insula peak shown connected to vlPFC/BA47 in Figure 2 plays a robust role in the attentional domain as well (Kurth *et al.*, 2010). In fact, the three frontoparietal regions shown in Figure 2, but further investigated in Figure 3B (vlPFC, MFG and IPL), may also constitute the largely right-lateralized ventral attention network (VAN) (Corbetta and Shulman, 2002; Corbetta *et al.*, 2008). To further explore this notion, we compared, in a post hoc manner, their peak coordinates to the corresponding peaks of regions reported in a large resting state study (Thomas Yeo *et al.*, 2011). The current SART peak coordinates were found to be between 7 and 17 mm Euclidian distance away from the Thomas Yeo *et al.*'s VAN node peak coordinates. The VAN typically responds to conditions of target detection and reorientation to behaviorally-relevant oddballs and unpredictable events (Corbetta and Shulman, 2002; Kim, 2013). This type of response is consistent with the behavioral responses to SART's NoGo trials. However, more recent research has broadened the conceptualization of the VAN response profile to include rare event expectation (Corbetta *et al.*, 2008; Vossel *et al.*, 2014). Our findings of an enhanced right-lateralized group of regions during Go trials give further support to this broadened definition of the VAN, and is especially appropriate in our shock paradigm given this network's alleged involvement in anxiety disorders (Sylvester *et al.*, 2012).

Besides an attention-related interpretation, inhibitory processes are also invoked by the SART. Anxiety can facilitate a sustained state of readiness to inhibit motor responses to the rare and unpredictable NoGo trials. This state of readiness might also be conceptualized as proactive inhibitory control (Aron, 2011; Sakai *et al.*, 2013). The right inferior prefrontal cortex together with right parietal areas have also been consistently implicated in response inhibition (see review, Aron *et al.*, 2014). Unfortunately, this study does not permit us to behaviorally dissociate sustained attention from proactive inhibition. However, the strong potentiation of the caudate during the threat condition is consistent with a strengthening of inhibitory mechanisms. Indeed, the striatum has been shown to play a critical role supporting anticipation of response withdrawing, suggesting that anxiety might recruit striatal function to maintain a state of readiness to inhibit (Chikazoe *et al.*, 2007; Zandbelt and Vink, 2010; Jahfari and Waldorp, 2011). This consideration also fits with the propensity for anxious individuals to withdraw from novel or uncertain stimuli (Fox *et al.*, 2005; Clauss *et al.*, 2014). Taken together, these findings call for future work that could dissociate the effects of anxiety on proactive inhibitory processes from sustained attention.

Trials preceding NoGo errors (4go-I) vs correct NoGo trials (4go-C). To determine which regions might specifically be related to task performance errors, we compared, in a second analysis, Go trials before correct *vs* incorrect NoGo trials, i.e. during compromised sustained attention. In line with expectations, across threat and safe conditions, significantly less activation of the right frontoparietal attention network was observed during the Go trials that preceded EoCs (incorrect NoGo trials) compared with those that preceded correct NoGo trials. Critically, these regions largely overlapped with the frontoparietal regions identified in the first analysis (see also Figure 3B). Therefore, these results suggest that threat improves performance through the same group of brain regions (vlPFC, MFG, IPL) that disengage when performing the task incorrectly.

In addition, the caudate nucleus was not differentially affected in the 4go-I *vs* 4go-C contrast. This suggests that the recruitment of the caudate nucleus in the first analysis (threat-go *vs* safe-go) was specific to the effects of threat, rather than purely performance modulation. The third analysis may help

distinguish the effects of threat on sustained attention from those interacting with response inhibition.

Threat vs safe of NoGo trials. The contrast of threat *vs* safe during correct NoGo trials revealed greater activation to threat *vs* safe only in two subcortical clusters, the right putamen and a midbrain region consistent with the VTA (D'Ardenne *et al.*, 2008; Murty *et al.*, 2014). These findings depart from our prediction that threat would strengthen inhibitory prefrontal control regions, including right IFG and dACC when having to inhibit pre-potent responses (Aron *et al.*, 2014). Of note, the right IFG was strongly activated in response to correct NoGo trials (results of main effect of NoGo trials not shown). However, it was not potentiated by threat, which may likely be because only correct NoGo trials were included in the analysis. Nonetheless, the findings from Threat *vs* Safe of NoGo trials suggests that striatal subcomponents such as the putamen contribute to both proactive (Go) and reactive (NoGo) inhibition (Aron, 2006; Zandbelt and Vink, 2010).

While this study informs the cognitive effects of state anxiety, it is important to contrast these findings with previous work on trait anxiety for two reasons. First, it is important to recognize the difference between these two expressions of anxiety, because their clinical implications can lead to different interventions. Second, the neural mechanisms underlying trait anxiety is dissociable from those underlying state anxiety, although they present commonalities (Bijsterbosch *et al.*, 2015).

Indeed, the extent to which findings based on state anxiety could overlap with findings on trait anxiety is an important question. Sehlmeyer *et al.* (2010) reported findings consistent with ours, that is, high trait anxiety was associated with better response inhibition reflected in reduced NoGo EoCs. These authors' conclusion that anxiety trait was related to enhanced response inhibition was in line with our current finding. Sehlmeyer *et al.*'s study is significant given that we (submitted for publication) recently found excessive response inhibition in individuals with anxiety disorders, suggesting that response inhibition could be a vulnerability factor for such conditions.

However, others failed to find that trait anxiety improved response inhibition (commission errors). Righi *et al.* (2009) found no effect of trait anxiety on SART performance, but reported increased (interpreted as inefficient) cortical activity associated with NoGo trials. Forster *et al.* (2015) reported that trait anxiety was associated with slower Go RT in the context of unimpaired NoGo performance. Concurrently, high trait anxiety was associated with reduced recruitment of cognitive control areas during NoGo trials. These findings, opposite to our results, support the argument that high state anxiety and high trait anxiety are not identical and could be dissociated (Bijsterbosch *et al.*, 2015). This is further exemplified by other work which links anxiety to impoverished attentional function (Bishop *et al.*, 2004; Ansari and Derakshan, 2011; Kalanthroff *et al.*, 2016). In the case of the work by Derakshan *et al.*, for example, these authors primarily examine trait anxiety without manipulating state anxiety (Derakshan *et al.*, 2009) and when they manipulate emotional states they use punctual affective stimuli that capture attention and compete for attentional resources over a short period of time (Bishop *et al.*, 2004; Kalanthroff *et al.*, 2016), as opposed to the induction of sustained anxiety during threat of shock. Therefore, future research is needed to disambiguate the nuanced relationship of state *vs* trait anxiety to brain function and performance.

A final critical issue is the potential contribution of increased arousal to our findings. Conceivably, our findings may reflect a non-specific increase in arousal during the threat condition, which would counteract an under-arousal supposedly generated by the typical SART performance. Under-arousal would lead to absentmindedness, perceptual decoupling, and ultimately attention lapses (Robertson *et al.*, 1997). Threat, by increasing arousal, would prevent the deleterious effects of under-arousal on SART performance. However, this proposition would be invalidated by another view of SART, which does not rest on arousal levels. According to this view, NoGo EoCs are not caused by attention lapses, but actually reflect response inhibition errors (Helton and Warm, 2008; Helton, 2009; Helton *et al.*, 2009). Along with this argument, five other reasons mitigate the arousal interpretation of our findings. First, SART does not typically induce under-arousal. In fact, SART was designed to be of short-duration (Robertson *et al.*, 1997), and is relatively cognitively demanding and accordingly requires a high level of arousal (Helton *et al.*, 2009). Second, emotions, including anxiety, are arousing and motivate specific action tendencies, such as inhibitory tendencies in anxiety (Chiu *et al.*, 2014). Accordingly, consistent with our results, a recent study reported that aversive cues improved NoGo accuracy and appetitive cues improve Go accuracy (Chiu *et al.*, 2014). These findings cannot be interpreted in terms of general non-specific arousal. Third, we showed that high levels of state anxiety, as measured with fear-potentiated startle (Grillon and Baas, 2003), were associated with improved NoGo accuracy, but at the expense of Go accuracy, suggesting that anxiety promoted a cautious action tendency, rather than non-specific increased arousal (Grillon *et al.*, in preparation). Fourth, vigilance tasks are not necessarily improved by increased arousal. Helton's group showed that increasing arousal with negative pictures impaired rather than improved performance on a vigilance tasks (Helton and Russell, 2011; Ossowski *et al.*, 2011) and van Steenbergen *et al.* (2011) demonstrated a dissociation of attentional effects between threat and arousal. Finally, the brain regions most implicated in general arousal (e.g. reticular formation, basal forebrain, locus coeruleus, raphe nuclei or central thalamus) were not detected in the Go trials contrast of Threat *vs* Safe. However, despite these arguments, it would be important to design an experiment that manipulates arousal and threat orthogonally to prove or disprove the unspecific hyper-arousal theory.

This study presents a number of strengths and limitations. With regard to strengths, anxiety was manipulated in a within-subject design using well-established methods of anxiety induction and measurement (Grillon and Baas, 2003). Secondly, this study uses SART, a cognitive paradigm that has shown to be modulated in a consistent fashion by anxiety, a finding replicated here. Thirdly, this study uses separate analyses to show that a collection of lateralized regions are involved in both anxiety and performance in a way that complement each other. In other words, we show that this set of regions is involved in response to anxiety, which putatively reduces performance errors. With regard to limitations, the design of this study did not permit to fully dissociate the effects of anxiety on the cortical correlates of sustained attention *vs* inhibitory control. Another drawback concerns our inability to identify with high spatial precision the midbrain structure activated in the third analysis. Finally, although we took the same approach of many other investigators, the second analysis probing Go trials prior to EoCs may have been underpowered because it was based on subjects' variable performance, and relatively small number of trials. Therefore, the results of this analysis should be interpreted with caution.

In conclusion, this study brings novel insights into the neural mechanisms underlying the interaction of anxiety, defined here as an enduring state of apprehension, with cognitive and behavioral processes, and particularly those involved in anxiety-related performance improvement on a sustained attention task. Threat of shock strengthens the recruitment of the right frontoparietal attention network, which, conversely, becomes less engaged before incorrect performance. The insula follows the same pattern of activation, and may play a role in increasing sustained attention. Finally, threat of shock recruits striatal structures, which might more specifically support a motor inhibitory function, during both proactive control (Go trials) and reactive control (NoGo trials). The present findings open important questions for future studies, particularly about the nature of cognition impacted by anxiety (i.e. sustained attention *vs* inhibitory control) and about the role of midbrain regions in these processes. Ultimately, understanding how anxiety modulates cognitive performance can have critical implications for understanding individuals with pathological anxiety, and how the mechanisms identified herein contribute to the symptoms of anxiety disorders.

Supplementary data

Supplementary data are available at *SCAN* online.

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Conflict of interest

The authors declare that, except for income received from the primary employer, no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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