

Anxiety-mediated facilitation of behavioral inhibition: threat processing and defensive reactivity during a go/nogo task

Grillon* C, Robinson# OJ, Krimsky^ M, O'Connell%, K, Alvarez* G., Ernst* M.

*** NIMH, Bethesda, MD, USA**

University College London, Great Britain

^ University of Miami, FL

% Georgetown University, DC

Running title: Anxiety and response inhibition

Correspondence to: Christian Grillon, NIMH, 15K North Drive, Bldg 15k, Bethesda, MD 20892

(301) 594 2894

Christian.grillon@nih.gov

Abstract

Anxiety can be broken down into multiple facets including *behavioral* components, such as defensive reactivity, and *cognitive* components, such as distracting anxious thoughts. In a previous study, we showed that anticipation of unpredictable shocks facilitated response inhibition to infrequent nogo trials during a go/nogo task. The present study extends this work to examine the distinct contribution of defensive reactivity, measures with fear-potentiated startle, and anxious thought, assessed with thought probes, on go and nogo performance. Consistent with our prior findings, shock anticipation facilitated response inhibition (i.e., reduced errors of commission) on the nogo trials. Regression analyses showed that 1) nogo accuracy was positively associated with fear-potentiated startle and negatively associated with threat-related/task-unrelated thoughts and 2) go accuracy correlated negatively with fear-potentiated startle. Thus, while the present findings confirm the influence of anxiety on response inhibition, they also show that such influence reflects the balance between the positive effect of defensive reactivity and the negative effect of distracting anxious thoughts.

Key words: Anxiety, go/nogo task, response inhibition, fear-potentiated startle, distraction

Introduction

Fear and anxiety are adaptive responses to threat but they can also have maladaptive effects that interfere with cognition and behaviors. A better understanding of the boundary between these adaptive and maladaptive effects may help identify malfunction in individuals with anxiety disorders. For example, it is adaptive to rapidly detect threat in dangerous environments (Robinson, Charney, Overstreet, Vytal, & Grillon, 2012; Robinson, Letkiewicz, Overstreet, Ernst, & Grillon 2011), but excessive and chronic attentional bias for threat can lead to pathological anxiety (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van, 2007). While it is now well-established that anxiety facilitates attention and perceptual processing, comparatively little is known about the effect of anxiety on motor processes. Basic research in animals has long associated anxiety with the *behavioral inhibition system* (BIS), a set of neural circuits that trigger various defensive behaviors to potential threat, including the inhibition of prepotent motor responses (Gray & McNaughton, 2000). The present study examined the effect of anxiety induced experimentally by the threat of shock on motor action tendency, specifically on the ability to inhibit a prepotent response.

The inhibition of prepotent motor responses, also termed response inhibition, can be examined using go/nogo tasks (GNG) with frequent go stimuli and infrequent nogo stimuli (Bari & Robbins, 2013). The high frequency of go trials promotes prepotent go responses, leading to elevated errors of commission on nogo trials (i.e., failure to inhibit nogo response). We recently reported that anxiety induced by threat of unpredictable shocks improved nogo accuracy (fewer errors of commission) without affecting go response time (RT) or accuracy, suggesting that anxiety facilitates response inhibition (Robinson, Krinsky, & Grillon, 2013). The present study follows up on these initial findings by examining the differential contributions of cognitive

(distracting thoughts) and behavioral (defensive reactivity) components of anxiety on GNG performance.

Errors of commission during GNG have been linked to two processes, failure to identify nogo stimuli because of distracting thoughts (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997) and failure to inhibit the prepotent go motor response (Head & Helton, 2013; Peebles & Bothell, 2004). We argue that both processes influence GNG performance in opposite directions. Regarding distraction, the monotonous nature of GNG promotes mind wandering, the process of drifting into task-unrelated thoughts (TUTs), which then interferes with performance (J.C. McVay & M.J. Kane, 2012). Because TUTs tend to be about personally-relevant concerns (Klinger, 1999) and are increased by stress and negative mood (Smallwood, Fitzgerald, Miles, & Phillips, 2009; Stawarczyk, Majerus, & D'Argembeau, 2013; Vinski & Watter, 2013), and because attentional resources tend to be preferentially allocated to aversive processing (Löw, Weymar, & Hamm, 2015), one would expect that anxiety induced by shock anticipation increases threat-related TUTs. Increased threat-related TUTs could impair nogo accuracy 1) because of failure to detect nogo trials due to attention lapses and/or 2) because threat-related TUTs divert working memory resources away from goal maintenance (Eysenck & Calvo, 1992; J.C. McVay & M. J. Kane, 2012). The finding that shock threat improves nogo accuracy (Robinson et al., 2013) suggests that another mechanism must counteract the potential negative effect of distraction on performance. We propose this other mechanism is a better efficiency of motor inhibition associated with defensive reactivity.

Defensive reactivity is defined as a defensive motivational state affecting loosely coupled physiological (e.g., heart rate), reflexive (e.g., startle), and behavioral changes (R. Blanchard, Blanchard, Rodgers, & Weiss, 1990; Löw et al., 2015; Zinbarg, 1998). Behaviorally, defensive

reactivity prepares the organism to react adaptively to different types of threats. As indicated above, anxiety is a response to potential threat and is associated with the BIS, which promotes motor inhibition, (Gray & McNaughton, 2000), i.e., the cessation of ongoing behavior and freezing in rodents (D. C. Blanchard, Griebel, Pobbe, & Blanchard, 2011). Cessation of ongoing behavior during potential threat is an adaptive response that facilitates risk assessment and minimizes detection by predators (R. J. Blanchard & Blanchard, 1989). In humans, anxiety to distal or unpredictable threat is associated with bradycardia, freezing-like behavior, and attenuation of the startle probe P3 component of the event-related potentials, indicating increased allocation of attention to the threat context (Facchinetti, Imbiriba, Azevedo, Vargas, & Volchan, 2006; Hagenaaars, Oitzl, & Roelofs, 2014; Löw et al., 2015). This pattern of response accompanying “attentive freezing” is also characterized by potentiation of the startle reflex (Löw et al., 2015). Anxiety, however, must be distinguished from fear, a reaction to an imminent threat (R. J. Blanchard & Blanchard, 1989; Davis, Walker, Miles, & Grillon, 2010). Fear is associated with a different defense strategy, fight-or-flight, and inhibition of the startle reflex when active avoidance is permitted (Löw et al., 2015). Taken together, the inhibition of prepotent motor responses is expected with anxiety, but not with fear. The present study focuses on anxiety induced by sustained periods of unpredictable shock (Davis et al., 2010). We propose that defensive reactivity to unpredictable shock is associated with startle potentiation and with a tonic withholding of action tendency. It is this priming of response inhibition that, we assume, is responsible for the improvement in nogo accuracy.

If defensive reactivity promotes a tonic response inhibition tendency, such a tendency could also negatively affect go accuracy. In fact, several studies have reported opposite effects of emotions on go and nogo responses (Crockett, Clark, & Robbins, 2009; S. M. Freeman & Aron,

2015; Scott M. Freeman, Razhas, & Aron, 2014; Guitart-Masip et al., 2012). To stop prepotent responses efficiently on nogo trials (“reactive” inhibition), one needs to be continuously prepared to inhibit the go response (“proactive” inhibition) (Adam R. Aron, 2011). Proactive inhibition should increase during shock threat, possibly impairing go accuracy. This hypothesis is consistent with the finding that aversive cues reduce go accuracy and increase nogo responding (Chiu, Cools, & Aron, 2014).

This study tested the hypothesis that performance during GNG is dependent upon two opposite processes. The first, distraction by TUTs, interferes with the monitoring of nogo trials and impairs nogo accuracy. The second, defensive reactivity, inhibits prepotent responses and improves nogo accuracy. Go response accuracy was expected to be negatively affected by defensive reactivity. To test these hypotheses, subjects performed GNG when safe from shock and when anticipating shock. Distraction was assessed by asking subjects to report their thoughts in terms of task-related thoughts (TRTs), threat-related TUTs, or non-threat-related TUTs. Defensive reactivity was measured with the startle reflex. The startle reflex is a cross-species defensive response to sudden stimuli (e.g., a short-duration burst of noise of high intensity). It is reliably potentiated (i.e., fear-potentiated startle) by threatening stimuli and is an index of fear and anxiety in both humans and animals (Davis et al., 2010). The fear-potentiated startle effect is especially robust during anticipation of shock (Grillon & Baas, 2003). Nogo accuracy was expected to positively correlate with fear-potentiated startle and to negatively correlate with threat-related TUTs. Go accuracy was expected to correlate negatively with fear-potentiated startle.

Method

Subjects

40 healthy volunteers (29 female) were enrolled in the study. Four subjects were excluded because they were outliers or for technical reasons (see below). The final samples consisted of 36 subjects (25 female) with a mean age (SD) of 28.3 (6.47) years. Subjects had no current or past history of any Axis I psychiatric disorder as assessed by SCID-I/NP. Inclusion criteria for all subjects included: no interfering acute or chronic medical condition and negative urine drug screen. All subjects gave written informed consent approved by the NIMH Institutional Review Board and received compensation for participating.

Overview

The task was modeled after our previous study (Robinson et al., 2013) that also investigated the effect of anxiety induced by the threat of shock on GNG performance. In this study, acoustic startle stimuli used to produce a startle response, operationally defined as an eyeblink reflex, were regularly delivered throughout the task to assess subjects' defensive reactivity. Subjects' anxiety during the test was also assessed via retrospective self-reports. The present study added two modifications. First, subjects were probed for their thoughts, and second, a no-task condition was added to permit the evaluation of task performance on anxiety. This resulted in a 2 (task, no task) by 2 (safe, threat) design. A schematic representation of the stimuli is shown in Figure 1.

Procedure

After attachment of the electrodes, nine startle stimuli were delivered every 18–25 s to reduce initial startle reactivity. This was followed by a shock work-up procedure to set the shock

intensity at a level that was uncomfortable but not painful (a 4 on a scale of 1–5, where 1 is barely perceptible and 5 is painful) by gradually increasing the intensity of the shock, after which the experiment started. The experiment proper, which consisted of alternating periods of no task and task (i.e., GNG) in safe and threat (of shock) conditions was then initiated.

Go/nogo (GNG) task and no task

During GNG, subjects were instructed to respond to frequent “go” stimuli (“=”) by pressing the # 2 on the keypad of a computer keyboard and withhold their response to occasional “nogo” stimuli (“O”) presented on a monitor. They were asked to focus on speed and accuracy equally. During the no task condition, frequent “*” and infrequent “#” stimuli were presented and subjects were asked to look passively at the screen. In both the task and the no task conditions, these stimuli were randomly distributed and were presented for 250 ms at a rate of one every 2000 ms. A correct go hit was a response recorded during these 2000 ms to a go trial. Similarly, a correct nogo omission was a no response during the same period to a nogo trial. The four following sequences of stimulus presentation were created with each sequence consisting of eight continuous blocks (i.e., a block was defined as a combination of a condition (safe or threat) and a task (task or no task). All the sequence has the same order of “=” and “O” (or “*” and “#”) and same timing of startle delivery. The four sequences were 1) sequence 1 (Figure 1): no task (threat then safe), task (threat then safe), no task (threat then safe), task (threat then safe); 2) sequence 2 was similar to sequence 1 but no task and task conditions were reversed: 3) Sequence 3 was similar to sequence 1 but threat and safe were reversed: 4) sequence 4 was similar to sequence 1 but no task and task, and safe and threat were reversed. Each subject was presented with one of the following two sequences (1 and 2, 2 and 1, 4 and 3, or 3 and 4) with

approximately equal numbers of subjects per sequence pairs. In each block, the frequent stimuli (“=” or “*”) were presented on 45 occasions while the infrequent stimuli (“O” or “#”) occurred five times for a total of 720 (45 x 8 blocks x 2 sequences) go trials and (5 x 8 x 2) 80 nogo trials over the two sequences. Each block lasted 100 s (50 x 2000 ms).

Startle stimuli, shocks, and threat condition

The first block of each sequence was preceded by three startle stimuli presented every 15-20 s. Subsequently, three startle stimuli separated by 22-30 sec were delivered in each block to assess subjects’ anxiety for a total of 27 (3 + (8 x 3)) startle stimuli per sequence. Startle stimuli always occurred always at the same time across sequences. They were delivered between two go trials and go trials that followed a startle stimulus were not included in the analysis. A shock was delivered in two of the four threat blocks in each sequence, just prior to the last go trial, which was not included in the analysis (for a total of 4 shocks). Subjects were informed that shock could be administered only in the threat condition and never in the safe condition. The safe and threat conditions were signaled by a blue and red border on the monitor, respectively.

Subjective anxiety and thought probes

At the end of each block of a sequence, subjects were asked to report their thoughts and their level of anxiety during the preceding block using pencil and paper. A single form contained the following questions repeated 8 times (corresponding to one set of question for each of the 8 blocks of a sequence): 1) what were you thinking about just now? a) About the task you are doing at that exact moment, b) anxious thoughts, c) thinking about something unrelated and 2) on a scale of 1-10 how anxious were you?

Prior to starting the test, subjects were informed that they would have to report their dominant thoughts according to three categories: task-related thoughts, threat-related task-unrelated thoughts, or threat-unrelated task-unrelated thoughts. They were told that a task-related thought (TRT) was thinking about performing the task (choice a) above), a threat-related thought (threatTUTs) was thinking about the threat during the experiment (choice b) above). And a task-unrelated and threat-unrelated thought (nonthreatTUTs) was thinking about something else other than the task or the threat of shock (choice c) above). They were asked to make a single selection among the three choices. They were also informed that when rating their level of anxiety, 1 would mean “not at all anxious” and 10 “extremely anxious”.

Stimulation and Physiological Responses

Stimulation and recording were controlled by a commercial system (Contact Precision Instruments, UK). Presentation of the visual stimuli was controlled by E-Prime. The acoustic startle stimulus was a 40-ms duration 103-dB (A) white noise presented via headphones. The eyeblink reflex was recorded with two electrodes placed under the left eye and a ground electrode placed on the left arm. The electromyographic eyeblink signal was amplified with bandwidth set to 30–500 Hz and digitized at a rate of 1000 Hz. The shock was administered either on the left wrist or on the left middle and ring fingers, depending on where the desired intensity was reached.

Dependent measures and data analysis

The analysis of performance data was conducted on the percentage of correct responses to go and nogo trials. For go trials, a correct response was a go trial followed by a response. For nogo trials, a correct response was a nogo trial not followed by a response. Performance was

determined for each condition (threat, safe) and trial type (go, nogo) by dividing the number of correct trials by the total number of each trial type. The one trial following a shock was excluded from analyses. Mean response time (RT) was also calculated for correct-go, to evaluate speed-accuracy trade-off. Three subjects were excluded from all analyses because their nogo performance in the safe condition differed from the group mean by more than 3 SD.

The three types of thought probes (TRTs, nonthreatTUTs, threatTUTs) were averaged separately within Task (no task, task) and Condition (safe, threat). One subject did not answer the thought probe questions and was excluded from the analysis. Because of multicollinearity issues (the total thought scores equal 1 in each condition), the thoughts were analyzed in two steps. The first focused on the TRTs and the second compared nonthreatTUTs and threatTUTs. The reason for the first analysis is that analyzing TRTs alone provides an index of subject's attention to the task but also the calculation of subjects' attention lapses because the total rate of TUTs = 1 – TRTs (e.g., if TRTs increased during task performance, then TUTs decreased).

After full-wave rectification and smoothing the electromyographic eyeblink signal, peak startle/eyeblink reflex magnitude was determined in the 20–100-ms timeframe following the onset of the acoustic startle stimulus relative to a 50-ms pre-stimulus baseline. Subsequently, the raw scores were standardized into T-scores for each subject in order to control for inter-individual differences in startle reactivity. The startle responses were then averaged separately within Task (no task, task) and Condition (safe, threat).

The retrospective anxiety scores and thought scores were similarly averaged within each condition. Data were analyzed with repeated measures analyses of variance (ANOVAs) and t-tests. To examine the influence of defensive reactivity and cognitive anxiety, correlation and

regression analyses were employed. Cohen's d and partial eta-squared (η_p^2) are reported as measures of effect size for t-tests and ANOVAs, respectively.

Results

Performance

The performance scores are shown in Table 1. The results were analyzed separately for go and nogo trials using paired t-tests. Consistent with our prior findings (Robinson et al., 2013), nogo accuracy improved during threat ($t(35)=3.1$, $p=.004$, $d=.52$) without change in go accuracy ($t(35)=1.2$, ns, $d=.18$) or go RT ($t(35)=1.8$, ns, $d=.31$).

Startle

The startle magnitude scores are shown in Table 2. The results were analyzed using a Condition (safe, threat) x Task (task, no task) repeated ANOVA. The Condition ($F(1,35)=108.8$, $p<.0009$, $\eta_p^2=.75$) and Task ($F(1,35)=5.9$, $p=.02$, $\eta_p^2=.14$) main effects were significant, reflecting that startle magnitude increased from the safe to the threat condition (fear-potentiated startle) but decreased from the no task to the task condition. The Condition x Task interaction was not significant ($F(1,35)=1.3$, ns), indicating that the effect of threat on startle magnitude was the same in the task and no-task conditions.

Subjective anxiety

The anxiety data are shown in Table 2. They were analyzed using a Condition (safe, threat) x Task (task, no task) repeated ANOVA. The only significant finding was the main condition, with a significant increase in subjective anxiety from the safe to the threat condition ($F(1,35)=48.5$, $p<.0009$, $\eta_p^2=.58$).

Thought probes

The thought scores are shown in Figure 2. The TRTs were analyzed using a 2-way Condition (safe, threat) x Task (task, no task) repeated ANOVAs. The rate of TRTs increased from the no-task to the task condition ($F(35)=38.7$, $p<.0009$, $\eta_p^2=.53$). No other effects were significant (all $p>.7$).

The nonthreatTUTs and threatTUTs were compared using a 3-way ANOVA of Condition (safe, threat) x Task (task, no task) x Thought Type (nonthreatTUTs, threatTUTs). The Condition x Thought Type interaction was significant ($F(35)=24.1$, $p<.0009$, $\eta_p^2=.41$), reflecting decreased nonthreatTUTs and increased threatTUTs from the safe to the threat condition. The Task x Thought Type interaction was also significant ($F(35)=13.9$, $p=.001$, $\eta_p^2=.28$), reflecting greater reduction in nonthreatTUTs compared to threatTUTs from the no task to the task condition. The main effects of Thought Type (more nonthreatTUTs compared to threatTUTs): $F(35)=44.4$, $p<.0009$, $\eta_p^2=.59$) and Task (more total TUTs in no-task compared to task: $F(35)=38.7$, $p<.0009$, $\eta_p^2=.51$) were also significant.

In order to establish the validity of the thought probe methodology, the threatTUTs were correlated with retrospective anxiety scores in the threat condition. ThreatTUTs correlated positively with subjective anxiety in both the no task ($r=.68$, $p<.0009$) and the task ($r=.57$, $p<.0009$) conditions.

Correlation and regression

Fear-potentiated startle was defined as the increased startle reactivity from the safe to threat condition (i.e., difference startle threat minus safe). In order to correlate each relevant variable with fear-potentiated startle we calculated difference scores of threat minus safe in the

task condition for go accuracy (difference % correct go hit threat minus safe), nogo accuracy (difference % correct nogo omission threat minus safe), and threatTUTs (difference proportion threatTUTs threat minus safe). Table 3 shows the correlation matrix. The delta go accuracy was *negatively* correlated with fear-potentiated startle (Figure. 3, right), i.e., as fear-potentiated startle increased, go accuracy decreased during threat. The delta nogo accuracy correlated *positively* with fear-potentiated startle and *negatively* with the delta threatTUT (and positively with TRTs) (Figure. 3, left). In other words, nogo performance improved as fear-potentiated startle increased and delta threatTUTs decreased. Finally, the delta threatTUT correlated positively with the delta of retrospective anxiety (Figure. 3, middle).

Multiple regression analyses were conducted to examine the unique contribution of defensive reactivity (fear-potentiated startle) and anxious cognition (both threatTUTs, retrospective anxiety) to go and nogo changes in accuracy from safe to threat. The delta go accuracy and delta nogo accuracy were used as dependent variables, while fear-potentiated startle, the delta threatTUTs, and delta retrospective anxiety were used as predictors. For delta go accuracy, the only predictor was fear-potentiated startle (see Table 3). For delta nogo accuracy the final model comprised two predictors, fear-potentiated startle and delta threat, explaining 32% of the variance ($F(2,33)=7.8, p=.002$). Delta nogo accuracy was positively associated with fear-potentiated startle ($\beta = .36, p=.02$), and negatively associated with delta threatTUT ($\beta = -.37, p=.01$). Thus, while delta go accuracy was uniquely and negatively associated with fear-potentiated startle, delta nogo accuracy was predicted independently and in the opposite direction by two measures of anxiety, positively with fear-potentiated startle and negatively with delta threatTUT.

Discussion

This study replicates previous findings that, at the group level, shock threat improves nogo accuracy without sacrificing go response accuracy. The new findings were 1) nogo accuracy correlated positively with fear-potentiated startle and negatively with threat-related off task thoughts (threatTUTs), and 2) go accuracy correlated negatively with fear-potentiated startle. We propose that when subjects are anxious nogo response accuracy depends on two opposite mechanisms, defensive reactivity, which improves response inhibition, and threat-related thoughts, which increases attention lapses and automatic motor responses.

As expected, startle magnitude, subjective reports of anxiety, and the rate of threat-related thoughts increased from the safe to the threat condition, confirming that the shock effectively increased subjects' anxiety and subjects' threat-related thoughts. The positive correlation between the rate of threatTUTs and subjective anxiety in the threat condition provides validity to the thought probe methodology. In addition, reports of TRTs and TUTs varied systematically with the experimental manipulation in the expected directions: TRTs increased (TUTs decreased) from the no task to the task condition, and, among TUTs, threatTUTs increased (nonthreatTUTs decreased) from the safe to the threat condition.

The regression analysis indicated that fear-potentiated startle and delta threatTUTs were both associated with delta nogo accuracy, but in an opposite fashion with greater fear-potentiated startle and smaller delta threatTUT being associated with better performance. Fear-potentiated startle is part of a large coordinated set of defensive responses activated by threats. The pattern of activation of these defensive responses is loosely coupled with and depends on the nature of the threat (R. Blanchard et al., 1990). While an imminent threat prompts fight-or-flight, and under some circumstance startle inhibition (Davis & Astrachan, 1978; Lang, Bradley, &

Cuthbert, 1997), a distal and uncertain threat is associated with a more hypervigilant state, characterized by risk-assessment, behavioral inhibition, and a priming of fast escape behavior (with increased startle). We propose that, in the present study, the anticipation of unpredictable shocks primed both startle (fear-potentiated startle) and response inhibition (nogo accuracy), resulting in a positive correlation between these two responses.

The negative association between delta threatTUTs and delta nogo accuracy likely reflects the causal influence of threatTUTs on nogo errors. TUTs may lead to momentary attentional lapses that are detrimental to performance during laboratory tasks, e.g., GNG (McVay & Kane, 2009), and during daily activity (McVay, Kane, & Kwapil, 2009). The increase in threatTUTs during shock anticipation probably results in failure to detect nogo trials and/or in the rapid triggering of the motor response to stimulus onset prior to full analysis of the stimulus (Robertson et al., 1997).

Taken together, the result of the regression analysis suggests that nogo accuracy is partly determined by the balance between the positive influence of defensive reactivity (fear-potentiated startle) and the negative influence of distraction by threat-related thoughts (threatTUTs). In this study, the overall nogo accuracy improved during threat, suggesting greater influence of defensive reactivity over threat-related thoughts. In fact, the rate of threatTUTs in the threat condition during GNG was relatively low (Figure 3, threat/task: 15%), probably because subjects were able to substantially reduce the rate of threatTUTs during task as compared to no task (Figure 3, Threat/no task: 25%).

Delta go accuracy was associated negatively with fear-potentiated startle and was not associated with TUTs. This latter result suggests that occasional attention lapses does not interfere with the identification of go trials. The negative association between delta go accuracy

and fear-potentiated startle suggests that anxiety promoted more inhibition of responses to go trials (errors of omission), perhaps because of proactive inhibition. Given that anxiety also facilitated nogo responses (see above), these results suggest that anxiety causes a behavioral shift that facilitated the action of stopping. A key question concerns the nature of this behavioral shift. Various mechanisms could improve response inhibition. The most obvious one is relying on a more “cautious” decision-making approach to the task, reflected in a speed-accuracy trade-off (Peebles & Bothell, 2004). Clearly, given that go RT did not slow down during the threat of shock, anxiety did not improve nogo accuracy via such a mechanism. Other possibilities include faster decision-making and better ability to withdraw a motor response. For example, several studies have established that action tendencies are primed differently by negative and positive emotional states such that withdrawal and nogo responses are facilitated by negative emotion and, conversely, approach and go responses are facilitated by positive emotions (Crockett et al., 2009; S. M. Freeman & Aron, 2015; Scott M. Freeman et al., 2014; Guitart-Masip et al., 2012). Action tendencies generated by these emotional states can exert their effect directly at the motor system levels (Chiu et al., 2014; S. M. Freeman & Aron, 2015; Guitart-Masip et al., 2012). Neuroimaging studies could help better understand the nature of the processes responsible for the effect of threat of shock on go and nogo responses by examining network associated with decision-making and response inhibition (A. R. Aron, Behrens, S., J., & A., 2007; A. R. Aron, Robbins, & Poldrack, 2004; Bari & Robbins, 2013). The present results may improve our understanding of inter-individual differences in the effect of anxiety on cognitive performance. Given that defensive reactivity and distraction by threatTUTs influence nogo accuracy an opposite fashion, variables that mitigate defensive reactivity or TUTs probably also affect nogo accuracy. For example, because lower working memory capacity predicts greater vulnerability

to TUTs (McVay & Kane, 2010), one could expect low working memory capacity to be associated with increased threatTUTs and increased nogo errors during shock threat.

This study has strengths and limitations. Among the strengths, the study relied on a within-subject design with well-established methods of fear induction and measurement (Grillon & Baas, 2003). Limitations include the difficulty associated with probing the content of thoughts. Importantly, the threatTUTs probes correlated with subjective reports. It could be argued that the improved nogo accuracy during shock threat merely reflects a non-specific increase in arousal. This is unlikely. First, arousal cannot explain the positive and negative effect of shock threat on nogo and go accuracy, respectively. Second, caffeine is arousing and improves not only nogo accuracy but also go accuracy (Foxy et al., 2012). Finally, the valence of arousal also determines of performance. For example, aversive cues improve and appetitive cues impair nogo accuracy (Chiu et al., 2014). These findings cannot be interpreted solely in term of non-specific arousal.

To summarize, this study found that shock threat improved nogo accuracy, an effect that was not caused by a more cautious approach to the task, as indicated by the lack of speed-accuracy trade off (Peebles & Bothell, 2004). Rather, results suggest that nogo accuracy depended on two factors, the magnitude of defensive reactivity (as measured with fear-potentiated startle) and the rate of threat-related task-irrelevant thoughts (threatTUTs), the former factor having a positive impact and the latter a negative impact on nogo accuracy. Because nogo accuracy was negatively impacted by defensive reactivity, these results suggest that anxiety shifts motor action tendency towards more response inhibition.

Disclosure/conflict of interest: The authors report no conflicts of interest. Financial support of this study was provided by the Intramural Research Program of the National Institute of Mental Health, ZIAMH002798 (ClinicalTrials.gov Identifier: NCT00026559; Protocol ID 01-M-0185).

References

- Aron, A. R. (2011). From Reactive to Proactive and Selective Control: Developing a Richer Model for Stopping Inappropriate Responses. *Biological Psychiatry*, *69*(12), e55-e68. doi: <http://dx.doi.org/10.1016/j.biopsych.2010.07.024>
- Aron, A. R., Behrens, T. E., S., S., J., F. M., & A., P. R. (2007). Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. *J. Neurosci.*, *27*, 3743–3752
- Aron, A. R., Robbins, T. W., & Poldrack, R. A. (2004). Inhibition and the right inferior frontal cortex. *Trends Cogn Sci*, *8*, 170-177.
- Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J., & van, I. M. H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychol Bull*, *133*(1), 1-24. doi: 10.1037/0033-2909.133.1.1
- Bari, A., & Robbins, T. W. (2013). Inhibition and impulsivity: Behavioral and neural basis of response control. *Progress in Neurobiology*, *108*(0), 44-79. doi: <http://dx.doi.org/10.1016/j.pneurobio.2013.06.005>
- Blanchard, D. C., Griebel, G., Pobbe, R., & Blanchard, R. J. (2011). Risk assessment as an evolved threat detection and analysis process. *Neuroscience & Biobehavioral Reviews*, *35*(4), 991-998. doi: <http://dx.doi.org/10.1016/j.neubiorev.2010.10.016>
- Blanchard, R., Blanchard, D., Rodgers, J., & Weiss, S. (1990). The characterization and modelling of antipredator defensive behavior. *Neuroscience & Biobehavioral Reviews*, *14*, 463-472.
- Blanchard, R. J., & Blanchard, D. C. (1989). Antipredator defensive behaviors in a visible burrow system. *Journal of comparative psychology*, *103*(1), 70-82.
- Chiu, Y.-C., Cools, R., & Aron, A. R. (2014). Opposing effects of appetitive and aversive cues on go/no-go behavior and motor excitability. *Journal of Cognitive Neuroscience*, *26*(8), 1851-1860. doi: 10.1162/jocn_a_00585
- Crockett, M. J., Clark, L., & Robbins, T. W. (2009). Reconciling the Role of Serotonin in Behavioral Inhibition and Aversion: Acute Tryptophan Depletion Abolishes Punishment-Induced Inhibition in Humans. *The journal of neuroscience*, *29*(38), 11993-11999. doi: 10.1523/jneurosci.2513-09.2009
- Davis, M., & Astrachan, D. I. (1978). Conditioned fear and startle magnitude: effects of different footshock or backshock intensities used during training. *Journal of Experimental Psychology: Animal Behavior Processes*, *4*, 95-103.
- Davis, M., Walker, D. L., Miles, L., & Grillon, C. (2010). Phasic vs sustained fear in rats and humans: role of the extended amygdala in fear vs. anxiety. *Neuropsychopharmacol*, *35*, 105-135.
- Eysenck, M. W., & Calvo, M. G. (1992). Anxiety and performance: the processing efficiency theory. *Cognition and Emotion*, *6*, 409-434.

- Facchinetti, L. D., Imbiriba, L. A., Azevedo, T. M., Vargas, C. D., & Volchan, E. (2006). Postural modulation induced by pictures depicting prosocial or dangerous contexts. *Neuroscience letters*, *410*(1), 52-56. doi: <http://dx.doi.org/10.1016/j.neulet.2006.09.063>
- Foxe, J., Morie, K., Laud, P., Rowson, M., de Bruin, E., & Kelly, S. (2012). Assessing the effects of caffeine and theanine on the maintenance of vigilance during a sustained attention task. *Neuropharmacology*, *62*(7), 2320-2327.
- Freeman, S. M., & Aron, A. R. (2015). Withholding a Reward-driven Action: Studies of the Rise and Fall of Motor Activation and the Effect of Cognitive Depletion. *J Cogn Neurosci*.
- Freeman, Scott M., Razhas, I., & Aron, Adam R. (2014). Top-Down Response Suppression Mitigates Action Tendencies Triggered by a Motivating Stimulus. *Current Biology*, *24*(2), 212-216. doi: <http://dx.doi.org/10.1016/j.cub.2013.12.019>
- Gray, J. A., & McNaughton, N. (2000). *The Neuropsychology of Anxiety: An Inquiry into the function of the Septo-Hippocampal System* (2nd ed.). Oxford: Oxford University Press.
- Grillon, C., & Baas, J. M. (2003). A review of the modulation of the startle reflex by affective states and its application to psychiatry. *Clinical Neurophysiology*, *114*, 1557-1579. doi: 10.1016/S1388-2457(03)00202-5
- Guitart-Masip, M., Huys, Q. J. M., Fuentemilla, L., Dayan, P., Duzel, E., & Dolan, R. J. (2012). Go and no-go learning in reward and punishment: Interactions between affect and effect. *Neuroimage*, *62*(1), 154-166. doi: <http://dx.doi.org/10.1016/j.neuroimage.2012.04.024>
- Hagenaars, M. A., Oitzl, M., & Roelofs, K. (2014). Updating freeze: Aligning animal and human research. *Neuroscience & Biobehavioral Reviews*, *47*(0), 165-176. doi: <http://dx.doi.org/10.1016/j.neubiorev.2014.07.021>
- Head, J., & Helton, W. S. (2013). Perceptual decoupling or motor decoupling? *Consciousness and Cognition*, *22*(3), 913-919. doi: <http://dx.doi.org/10.1016/j.concog.2013.06.003>
- Klinger, E. C. (1999). At play in the fields of consciousness: Essays in the honour of Jerome L. Singer. In J. A. Singer & P. Salovey (Eds.), *Thought flow: Properties and mechanisms underlying shifts in content* (pp. 29-50). Mahwah, NJ Erlbaum.
- Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1997). Motivated attention: Affect, activation and action. In P. J. Lang, R. F. Simons, & M. F. Balaban (Eds.), *Attention and Orienting: Sensory and Motivational Processes* (in files ed., pp. 97-135). Hillsdale, NJ: Lawrence Erlbaum Associates.
- Löw, A., Weymar, M., & Hamm, A. O. (2015). When Threat Is Near, Get Out of Here: Dynamics of Defensive Behavior During Freezing and Active Avoidance. *Psychological science*. doi: 10.1177/0956797615597332
- McVay, J. C., Kane, J. M., & Kwapil, T. R. (2009). Tracking the train of thought from the laboratory into everyday life: an experience-sampling study of mind wandering across controlled and ecological contexts. *Psychon Bull Rev*, *16*, 857-863. doi: 10.3758/PBR.16.5.857
- McVay, J. C., & Kane, M. J. (2009). Conducting the train of thought: Working memory capacity, goal neglect, and mind wandering in an executive-control task. *Journal of experimental psychology. Learning, memory, and cognition*, *35*(1), 196-204. doi: 10.1037/a0014104

- McVay, J. C., & Kane, M. J. (2010). Does mind wandering reflect executive function or executive failure? Comment on Smallwood and Schooler (2006) and Watkins (2008). *Psychological Bulletin*, *136*(2), 188-197. doi: 10.1037/a0018298
- McVay, J. C., & Kane, M. J. (2012). Drifting from slow to "D'oh!": working memory capacity and mind wandering predict extreme reaction times and executive control errors. *Journal of experimental psychology. Learning, memory, and cognition*, *38*(3), 525-549. doi: 10.1037/a0025896
- McVay, J. C., & Kane, M. J. (2012). Why does working memory capacity predict variation in reading comprehension? On the influence of mind wandering and executive attention. *Journal of Experimental Psychology: General*, *141*(2), 302-320. doi: 10.1037/a0025250
- Peebles, D., & Bothell, D. (Eds.). (2004). *Modelling performance in the Sustained Attention to Response Task*. Pittsburgh, PA: Carnegie Mellon University/University of Pittsburgh.
- Robertson, I. H., Manly, T., Andrade, J., Baddeley, B. T., & Yiend, J. (1997). `Oops!': Performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. *Neuropsychologia*, *35*(6), 747-758.
- Robinson, O. J., Charney, D. R., Overstreet, C., Vytal, K., & Grillon, C. (2012). The adaptive threat bias in anxiety: amygdala-dorsomedial prefrontal cortex coupling and aversive amplification. *Neuroimage*, *60*, 523-529.
- Robinson, O. J., Krimsky, M., & Grillon, C. (2013). The impact of induced anxiety on response inhibition. *Front Hum Neurosci*, *7*:69. doi: 10.3389/fnhum.2013.00069
- Robinson, O. J., Letkiewicz, A. M., Overstreet, C., Ernst, M., & Grillon, C. (2011). The effect of induced anxiety on cognition: threat of shock enhances aversive processing in healthy individuals. *Cogn Affect Behav Neurosci*, *11*, 217-227.
- Smallwood, J., Fitzgerald, A., Miles, L., & Phillips, L. (2009). Shifting moods, wandering minds: negative moods lead the mind to wander. *Emotion*, *9*(2), 271-276.
- Stawarczyk, D., Majerus, S., & D'Argembeau, A. (2013). Concern-induced negative affect is associated with the occurrence and content of mind-wandering. *Consciousness and Cognition*, *22*(2), 442-448.
- Vinski, M. T., & Watter, S. (2013). Being a grump only makes things worse: a transactional account of acute stress on mind wandering. *Frontiers in Psychology*, *4*. doi: 10.3389/fpsyg.2013.00730
- Zinbarg, R. E. (1998). Concordance and synchrony in measures of anxiety and panic reconsidered: a hierarchical model of anxiety and panic. *Behavior Therapy*, *29*, 301-323.

Table 1

Mean (confidence interval) go and nogo accuracy (%) and go RT (ms) in the safe and threat conditions

	Safe	Threat
Go accuracy	90.9 (88.6-93.1)	91.6 (89.2-94.0)
Nogo accuracy	74.4 (70.8-78.6)	81.2 (76.7-85.7)*
Go RT	358.5 (339.1- 377.9)	349.3 (331.0- 367.5)

* for significant ($p < .05$) difference between the safe and threat condition

Table 2

Mean (confidence interval) startle magnitude expressed in T-scores and subjective anxiety as a function of task (task, no task) and condition (safe, threat)

	No Task		Task	
	Safe	Threat	Safe	Threat
Startle	44.2 (41.9-46.4)	57.2 (55.0-59.5)	42.4 (41.0-43.9)	53.0 (50.4-55.5)
Subjective anxiety	1.6 (1.2-1.8)	3.4 (2.7-4.2)	1.6 (1.4-1.9)	3.6 (2.9-4.3)

Table 3

Correlation among the changes from safe to threat (delta scores) in startle magnitude (fear-potentiated startle), go and nogo accuracy, and threatTUTs.

	FPS	Delta go Accuracy	Delta nogo accuracy
Delta go Accuracy	-.36 (p=.03)	.	.
Delta nogo accuracy	.42 (p=.009)	-.45 (p=.007)	.
Delta ThreatTUTs	-.18	.20	-.44 (p=.007)

Note. FPS = fear-potentiated startle; Delta = difference threat minus safe

Figure captions

Figure 1. Schematic description of stimulus presentation (sequence 1). There were four sequences of predetermined order of stimulus presentation (see text). Each sequence consisted of eight blocks with alternating blocks of safe and threat conditions. Sequences started with either two task blocks or two no task block followed by two blocks of the alternating task condition (i.e., task -> no task -> task -> no task or no task -> task -> no task -> task). Each subject was presented with two sequences of stimulus order. Each block consisted of 45 go, 5 no go, and 3 acoustic startle stimuli. In addition, one shock was given in two out of the four threat blocks per sequence. Finally, at the end of each block, subjects had to retrospectively rate their anxiety and to select one type of thought with choices of task-related thoughts (TRTs), task-unrelated/threat-unrelated thoughts (nonthreatTUTs), and threat-related thoughts (threatTUTs).

Figure 2. Mean rates of task-related thoughts (TRTs), task-unrelated/threat-unrelated thoughts (nonthreatTUTs), and threat-related thoughts (threatTUTs) as a function of task (task, no task) and condition (safe, threat).

Figure 3. Scatter plots of the correlation of fear-potentiated startle with delta nogo accuracy (left) and delta go accuracy (right), and delta threatTUTs with delta nogo accuracy (middle).

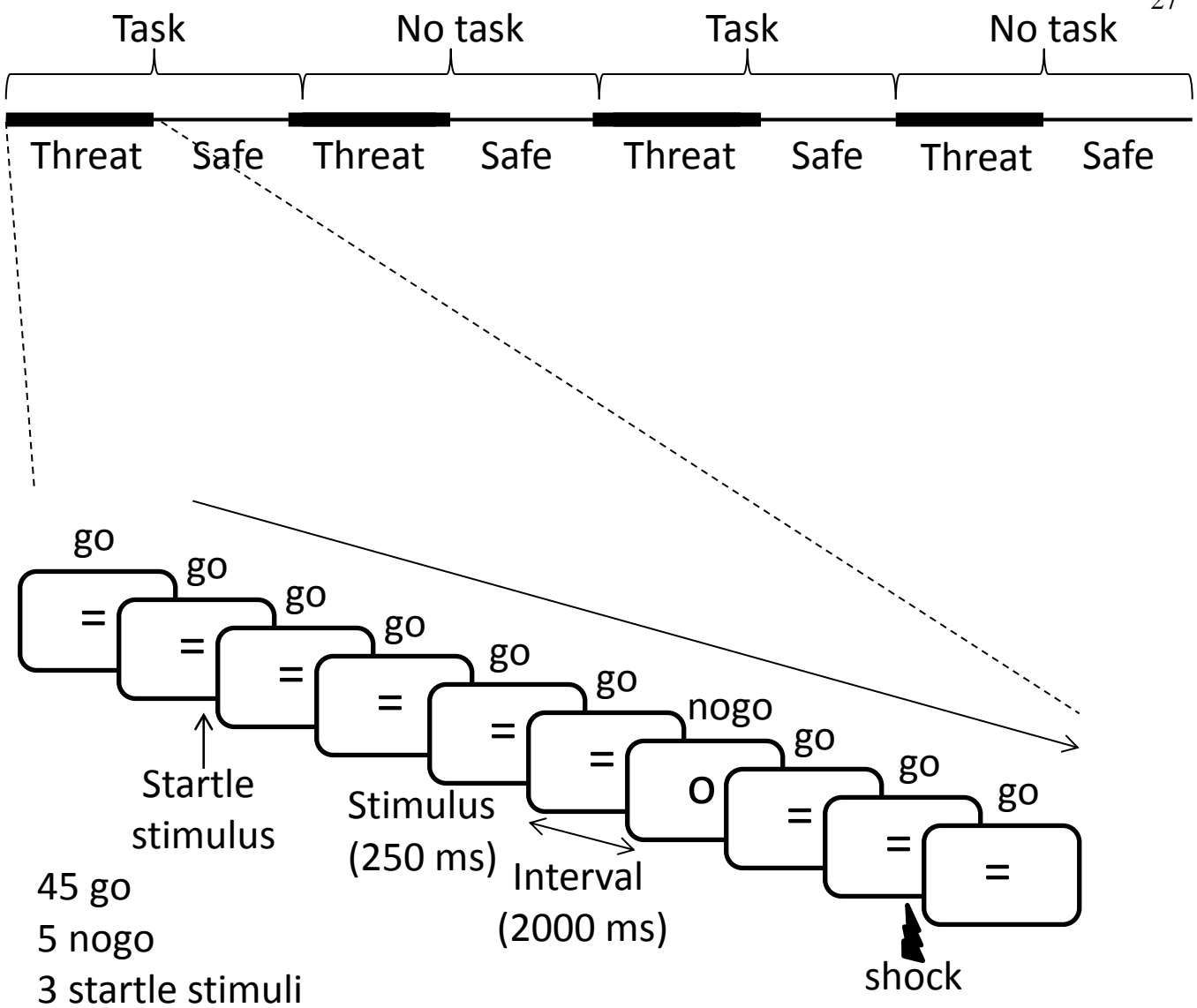


Figure 1

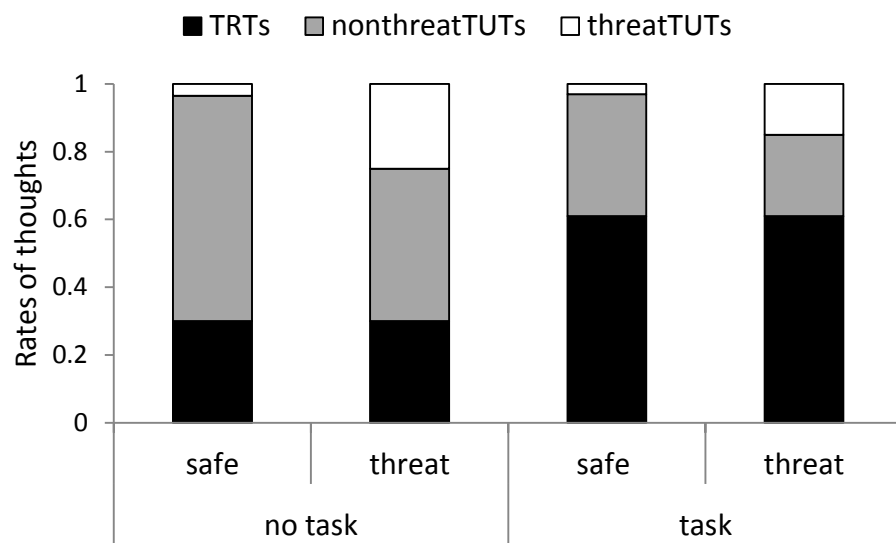
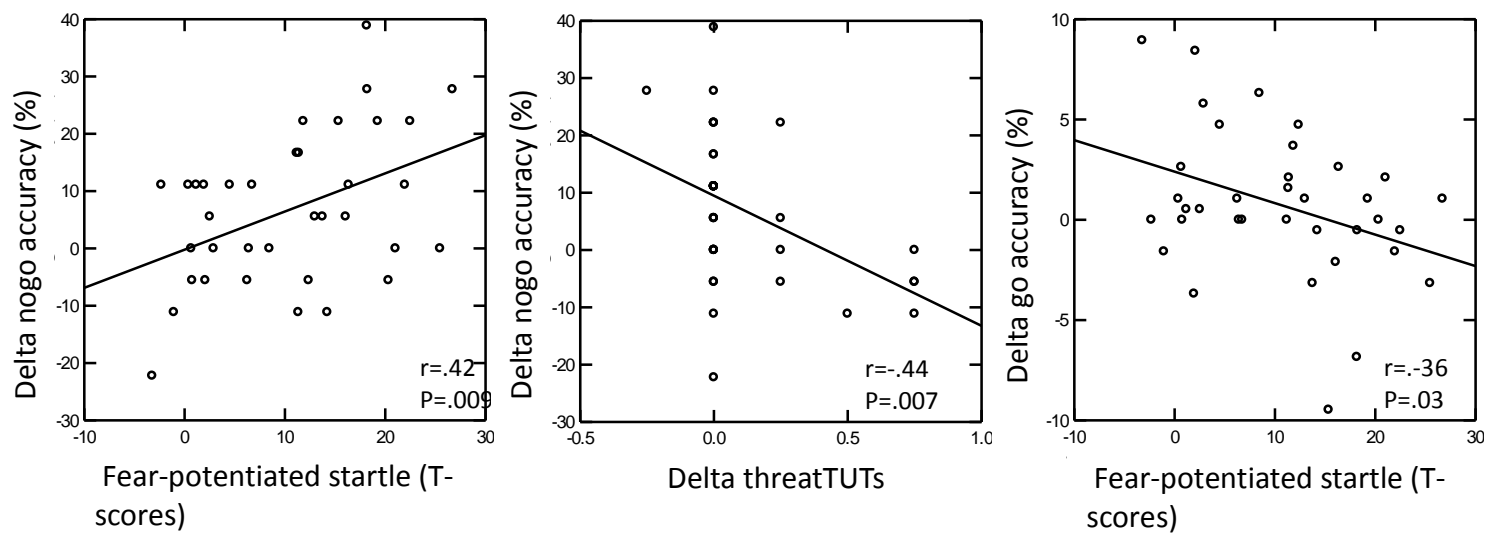


Figure 2

**Figure 3**