

## Anxiety & response inhibition

Word count 4581

Number of Figures 3

Number of Tables 2

### **Clinical anxiety promotes excessive response inhibition**

**Grillon\* C, Robinson^ OJ, O'Connell\* K, Davis\* Andrew, Alvarez\* G, Pine&, DS, Ernst\*, M**

\*Section on Neurobiology of Fear and Anxiety, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA

^ Institute of Cognitive Neuroscience, University College London, London, UK

& Section on Development and Affective Neuroscience, NIMH, Bethesda, MD, USA

**Running title:** anxiety and response inhibition

**Key Words:** anxiety, anxiety disorders, behavioral inhibition, go/nogo, threat of shock

Corresponding author:

**Christian Grillon, Ph.D.**

NIMH

15K North Drive

Bldg 15K, Room 203, MSC 2670

Bethesda, MD 20892-2670

Phone: (301) 594 2894

Fax: (301) 594 9959

E-mail: [Christian.grillon@nih.gov](mailto:Christian.grillon@nih.gov)

## **Abstract**

**Background:** Laboratory tasks to delineate anxiety disorder features are used to refine classification and inform our understanding of etiological mechanisms. The present study examines laboratory measures of response inhibition, specifically the inhibition of a prepotent motor response, in clinical anxiety. Data on associations between anxiety and response inhibition remain inconsistent, perhaps because of dissociable effects of clinical anxiety and experimentally-manipulated state anxiety. Few studies directly assess the independent and interacting effects of these two anxiety types (state vs. disorder) on response inhibition. The current study accomplished this goal, by manipulating state anxiety in healthy and clinically anxious individuals while they complete a response inhibition task.

**Methods:** The study employs the threat-of-shock paradigm, one of the best-established manipulations for robustly increasing state anxiety. Participants included 82 adults (41 healthy; 41 patients with an anxiety disorder). A go/nogo task with highly frequent go trials was administered during alternating periods of safety and shock threat. Signal detection theory was used to quantify response bias and signal-detection sensitivity.

**Results:** There were independent effects of anxiety and clinical anxiety on response inhibition. In both groups, heightened anxiety facilitated response inhibition, leading to reduced nogo commission errors. Compared to the healthy group, clinical anxiety was associated with excessive response inhibition and increased go omission errors in both the safe and threat conditions.

**Conclusions:** Response inhibition and its impact on go omission errors appear to be a promising behavioral marker of clinical anxiety. These results have implications for a dimensional view of clinical anxiety.

## Introduction

The National Institute of Mental Health Research Domain Criteria (RDoC) initiative seeks to uncover transdiagnosis, biobehavioral dimensions related to specific neurobiological processes, as quantified with laboratory tasks (Insel *et al.*, 2010). From this perspective, anxiety disorders are conceptualized as extreme variants of normal functioning. A key question therefore is to determine the extent to which adaptive and maladaptive responses to threats vary as a function of clinical and non-clinical variations in anxiety (Robinson *et al.*, 2015). The present study examines the effects of both experimentally-induced and clinical anxiety on one such response, behavioral inhibition or *response inhibition*, operationally defined as the inhibition of prepotent motor responses (Bari and Robbins, 2013) (as opposed to *cognitive inhibition*, the inhibition of thoughts, emotions, and perception, which is impaired in clinical anxiety (Eysenck *et al.*, 2007)).

Works in rodents led Gray to suggest that anxiety activates the behavioral inhibition system, which triggers a set of defensive responses, including inhibition of prepotent responses (i.e., response inhibition) (Gray and McNaughton, 2000). Others proposed that excessive engagement of the behavioral inhibition system in humans contributes to clinical anxiety (Epstein *et al.*, 2001, Gray and McNaughton, 2000, Quay, 1997, Sylwan, 2004). However, few studies have examined how experimentally-induced and clinical anxiety relates to laboratory measures of response inhibition in humans. Moreover, the limited data that do exist are conflicting, with studies finding inconsistent effects of clinical anxiety, trait anxiety, and manipulations in state anxiety (Daugherty *et al.*, 1993, Forster and Lavie, 2014, Geen, 1985, Hagopian and Ollendick, 1994, Karch *et al.*, 2008, Kooijmans *et al.*, 2000, Li *et al.*, 2009, Neo *et*

## Anxiety & response inhibition

*al.*, 2011, Oosterlaan and Sergeant, 1996, Righi *et al.*, 2009, Robinson *et al.*, 2013a, Sehlmeier *et al.*, 2010, Wright *et al.*, 2014).

The Sustained Response to Attention Task is a go/nogo paradigm (GNG) that generates a measure of response inhibition (Helton, 2009, Peebles and Bothell, 2004). This paradigm requires a motor response to frequent ‘go’ target stimuli but not rare ‘nogo’ stimuli, to which a response is withheld. Such withholding of a prepotent response generates a prototypical index of response inhibition (Bari and Robbins, 2013, Helton, 2009). Consistent with Gray’s model, we recently showed that heightened state anxiety induced by threat of shock facilitates response inhibition during GNG, i.e., it reduced nogo commission errors (failure to inhibit the prepotent response) without affecting go response time (Robinson *et al.*, 2013a). We also found, in a recent replication and extension of this finding, a positive correlation between state anxiety and go omission errors; individuals with the highest elevation in state anxiety showed improved nogo accuracy but also impaired go accuracy (Grillon *et al.*, 2016). These results suggest that high state anxiety is associated with an overall inhibition of motor responding, a hypothesis that was confirmed in a subsequent reanalysis of these data using signal detection theory to quantify changes in response bias (McVay and Kane, 2009, Snodgrass and Corwin, 1988).

These data show that heightened state anxiety induced by threat of shock drives a transient response inhibition tendency with beneficial and detrimental effects depending on the nature of the response (i.e., improved nogo responses, impaired go responses). However, these data emerged only from variations in normal anxiety. This raises questions on the relationships among variations in response inhibition, threat-induced state anxiety, and clinical levels of anxiety. Although data in children find some evidence of associations between response inhibition and clinical anxiety (Daugherty *et al.*, 1993, Kooijmans *et al.*, 2000, Oosterlaan and

## Anxiety & response inhibition

Sergeant, 1996), little is known about this link in adults (Beutel *et al.*, 2010, Thomas *et al.*, 2016).

Investigations of the effect of trait anxiety on response inhibition can inform predictions. Most studies found no behavioral effect of trait anxiety in GNG (Karch *et al.*, 2008, Righi *et al.*, 2009, Sehlmeier *et al.*, 2010) or stop-signal tasks (Li *et al.*, 2009, Neo *et al.*, 2011). However, there is indirect evidence that when state anxiety is elevated, high trait anxiety is also associated with increased nogo accuracy, but at the expense of go accuracy (Geen, 1985, Hagopian and Ollendick, 1994). These results suggest that state and trait anxiety drive a response inhibition tendency along a continuum from “normal” to “abnormal”. Given that clinical anxiety is characterized by both high state and trait anxiety, one could then hypothesize that response inhibition would be excessive in clinical anxiety.

To test this possibility, we compared the effect of threat of shock during GNG performance in individuals with clinical anxiety and in healthy participants. We focused on generalized anxiety disorder and social anxiety disorder, two conditions with an overly sensitive behavioral inhibition system (Gray and McNaughton, 2000, Maack *et al.*, 2012, Morgan *et al.*, 2009, Roelofs *et al.*, 2009, Rosenbaum *et al.*, 1991). We expected both heightened state anxiety and clinical anxiety to shift response bias (McVay and Kane, 2009, Snodgrass and Corwin, 1988) away from the prepotent go response (towards nogo response, i.e., response inhibition tendency), but to a greater extent in clinical anxiety. Excessive response inhibition in clinical anxiety could be a disease characteristic. One would then expect increased response inhibition in the patients compared to the healthy participants in both the safe and the threat conditions. Alternatively, excessive response inhibition in the patients could be state-dependent, i.e., arising from elevated

## Anxiety & response inhibition

state anxiety during threat processing. If so, excessive response inhibition in the patients vs. healthy participants would be seen only during shock anticipation.

Because heightened state anxiety facilitates perceptual processes (Baas *et al.*, 2006, Cornwell *et al.*, 2007), we also expected signal detection to be facilitated by the threat of shock. Tasks such as GNG, usually promote a speed-accuracy trade-off with slower reaction time (RT) being correlated with better nogo accuracy (Peebles and Bothell, 2004). However, our previous results showed that heightened state anxiety improved nogo accuracy without affecting go RT, i.e., independently of a speed-accuracy trade-off (Robinson *et al.*, 2013b). To control for individual differences in RT, a skill index was also computed (nogo accuracy/go-trial RT) (Saucedo Marquez *et al.*, 2013, Seli, 2016, Seli *et al.*, 2016). This index provides a measure of efficiency by accounting for both response speed and accuracy.

## Method

### Participants

Participants included 41 medication-free patients (34 female) and 41 healthy participants (34 female). Following an initial telephone screen, participants visited the NIH for comprehensive screening by a clinician. The patients had a diagnosis of generalized anxiety disorders (GAD, N=14), social anxiety disorder (SAD, N=7), or GAD and comorbid SAD (N=20) and no other current Axis I psychiatric disorders, or past psychosis as assessed by the SCID-I/P (First *et al.*, 2002). The healthy participants had no current or past history of any Axis I psychiatric disorders as assessed by SCID-I/NP. Exclusion criteria for all participants consisted of any interfering acute or chronic medical conditions and positive urine drug screen. All participants gave written informed consent approved by the NIMH Combined Neuroscience Institutional Review Board. The study was registered at clinical-trials.gov (no. NCT00055224).

## Overview

We used a procedure modeled after one of our previous studies (Grillon *et al.*, 2016), as described in Figure 1. Briefly, subjects participated in a task (GNG) and no-task (see below) condition during periods of threat of shocks and periods of safety when no shock could be administered. This resulted in a 2 (healthy participants, anxiety patients) x 2 (task, no task) x 2 (safe, threat) design. Acoustic startle stimuli used to produce a startle response, operationally defined as an eyeblink reflex, were regularly delivered throughout testing to assess subjects' defensive reactivity. Subjects' anxiety was assessed via retrospective reports.

## Procedure

Shortly after participants' arrival on the testing day, a startle habituation procedure was conducted. For this, two electrodes were attached under the left eye to record the eyeblink/startle reflex. Nine startle stimuli were then delivered every 18–25 s to reduce initial startle reactivity. This was followed by a shock work-up procedure that set the shock intensity at a level that was uncomfortable but not painful. Shock levels (Table 1) did not differ significantly between the two groups ( $t(80)=.8$ , ns,  $d=.2$ ). The GNG task was then initiated.

### *Go/nogo (GNG) and control task*

During the GNG and the control tasks, stimuli were presented on a monitor. In the GNG task, participants were asked to respond to frequent (91%) “go” stimuli (“=”) by pressing the “2” on the keypad of a computer keyboard and to withhold their response to infrequent (9%) “nogo” stimuli (“O”). They were asked to focus on speed and accuracy equally. In the control task, frequent “\*” (91%) and infrequent “#” (9%) stimuli were presented and participants were asked to look passively at the screen. In both the GNG and control tasks, these stimuli were randomly

## Anxiety & response inhibition

distributed and were presented for 250 ms at a rate of one every 2000 ms. Stimuli were presented on a blank screen and were not followed by a mask. 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.

Four sequences of stimulus presentation, with each sequence consisting of 8 blocks, were created: 1) sequence 1 (Fig. 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 participant 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 to further reduce initial startle reactivity. Subsequently, three startle stimuli separated by 22-30 sec were delivered in each block to assess participants’ anxiety. Startle stimuli always occurred 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). Participants 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.



## Anxiety & response inhibition

### ***Subjective anxiety & Thought probes***

At the end of each safe and threat block of a sequence, subjects were asked to report their level of anxiety during the preceding block on an analog scale ranging from 1 “not at all anxious” to 10 “extremely anxious”.

Tasks such as GNG are also used to explore task-related thoughts and task-unrelated thoughts (Seli, 2016). At the end of each block, just prior to assessing subjective anxiety, participants were asked to indicate whether they were focused on the task (task-related thoughts) or whether they were mind-wandering with task-unrelated, whether threat-related or threat-unrelated, thoughts. In this study, as in our past study (Robinson *et al.*, 2013a), we found no reliable correlations between task-unrelated thoughts and GNG performance. Consequently, the thought probe methodology and the results are presented in Supplementary Materials.

### **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. Finally, the shock was administered on the left wrist.

## **Data Analysis**

### ***Performance***

Correct go responses were go trials followed by button press. Correct nogo responses were nogo trials followed by no button press. Performance was determined for each condition (threat, safe) and trial type (go, nogo) by dividing the number of correct response by the total number of each trial type. The trial following a shock was excluded from analyses. Mean RT was calculated for correct-go to evaluate speed-accuracy trade-off (Peebles and Bothell, 2004). In addition, go RT variability (standard error) and RT coefficient of variation (standard deviation/mean RT) were also calculated as these measures reflect the ability to sustain attention across trials (Stuss *et al.*, 1995).

Signal-detection sensitivity ( $d_L$ ) and response bias ( $C_L$ ) scores were calculated for each participant as done by others (McVay and Kane, 2009) using the formulas for logistic distributions (Snodgrass and Corwin, 1988) (see details in Supplemental Materials).

The skill index was calculated as:

Skill index =  $1000 * (\text{mean nogo accuracy ratio} / \text{mean go-trial RT})$  (Saucedo Marquez *et al.*, 2013, Seli, 2016, Seli *et al.*, 2016). (The index is multiplied by 1000 to reduce the number of decimals (Seli, 2016)).

### ***Startle reflex***

After full-wave rectification and smoothing the EMG signal, peak startle/eyeblink magnitude was determined in the 20–100-ms timeframe following stimulus onset relative to a 50-ms pre-stimulus baseline. The startle responses from each participant were converted to t-scores.

## Anxiety & response inhibition

Data were analyzed with mixed-model repeated measures analyses of variance (ANOVAs) and t-tests. Cohen's d and partial eta-squared ( $\eta_p^2$ ) are reported for effect sizes. Preliminary analyses showed no significant order effects of the sequence of stimulus presentation on the key variables.

## Results

### Demographic

The demographic data are presented in Table 1. The two groups did not differ in age ( $t(80)=1.2$ , ns). As expected, the patients had higher scores of state anxiety ( $t(80)=8.3$ ,  $p<.0009$ ,  $d = 1.8$ ), trait anxiety ( $t(80)=12.6$ ,  $p<.0009$ ,  $d=2.6$ ), and BDI ( $t(79)=5.9$ ,  $p<.0009$ ,  $d=1.3$ ) compared to the healthy participants. Note that BDI of one subject was missing in the patient group.

### Performance

Each performance score ( $C_L$ ,  $d_L$ , nogo accuracy, go accuracy, go RT, go RT-coefficient of variation, and skill index) was analyzed using analyses of variance (ANOVAs) with group (healthy participants, anxiety patients) as a between-subject factor and condition (safe, threat) as a within-subject factor.

As expected given the nature of the task, the response bias index ( $C_L$ ) was negative (Fig. 2, left), reflecting a "go" bias (McVay *et al.*, 2013). Consistent with our hypothesis, the go bias was reduced (i.e., increased nogo bias) in the threat compared to the safe condition ( $F(1,80)=6.5$ ,  $p=.01$ ,  $\eta_p^2=.075$ ), and in the patients compared to the healthy participants ( $F(1,80)=4.4$ ,  $p=.04$ ,  $\eta_p^2=.052$ ). However, these effects did not interact with one another (condition x group:  $F(1,80)=1.4$ , ns,  $\eta_p^2=.017$ ). The group difference remained unchanged when BDI was used as a

## Anxiety & response inhibition

covariate (group main effect:  $F(1,78)=5.8$ ,  $p=.02$ ,  $\eta_p^2=.069$ ). Thus, both heightened state anxiety and clinical anxiety independently resulted in greater nogo biases, leading the nogo response bias to be lowest in the controls/safe condition and greatest in the patients/threat condition (Fig. 2, left)..

The signal-detection sensitivity index ( $d_L$ ) was higher in the threat compared to the safe condition (condition:  $F(1,80)=14.1$ ,  $p<.001$ ,  $\eta_p^2=.149$ ), reflecting better perceptual discrimination during heightened state anxiety (Fig. 2, right). There was also a trend for larger  $d_L$  in the healthy participants compared to the patients (group:  $F(1,80)=3.5$ ,  $p=.066$ ,  $\eta_p^2=.041$ ), but this trend disappeared when BDI was used as a covariate ( $F(1,78)=1.9$ , ns,  $\eta_p^2=.023$ ). The condition x group effect was not significant ( $p>.1$ ).

Nogo accuracy, go accuracy, skill index, go RT and go RT-variability are presented in Table 2. Nogo accuracy did not differ significantly among the healthy participants and patients ( $F(1,80)=.04$ , ns,  $\eta_p^2=.0005$ ), but it was higher (less commission errors) in the threat compared to the safe condition, with a similar threat effect in both groups (condition:  $F(1,80)=12.5$ ,  $p=.001$ ,  $\eta_p^2=.135$ ; condition x group:  $F(1,80)=.03$ , ns,  $\eta_p^2=.0004$ ). Go accuracy was lower (i.e., increased omission errors) in the patients compared to the healthy participants ( $F(1,80)=4.5$ ,  $p=.04$ ,  $\eta_p^2=.054$ ), but it was not affected by threat (condition:  $F(1,80)=.05$ , ns,  $\eta_p^2=.0006$ ; condition x group:  $F(1,80)=.4$ , ns,  $\eta_p^2=.004$ ). The Go accuracy group difference remained significant after controlling for depression symptoms ( $F(1,78)=5.4$ ,  $p=.02$ ,  $\eta_p^2=.064$ ).

Go RT was faster in the patients compared to the healthy participants ( $F(1,80)=6.0$ ,  $p=.02$ ,  $\eta_p^2=.07$ ). No other go RT effects were significant (all  $p>.05$ ). Go RT-variability was smaller in the patients compared to the healthy participants ( $F(1,80)=4.9$ ,  $p=.03$ ,  $\eta_p^2=.058$ ), and in the threat compared to the safe condition across both groups ( $F(1,80)=10.3$ ,  $p=.002$ ,  $\eta_p^2=.114$ ). The

## Anxiety & response inhibition

difference between the threat and safe condition remained significant after controlling for individual differences in RT (coefficient of variation) ( $F(1,80)=8.7$ ,  $p=.004$ ,  $\eta_p^2=.099$ ), but the group difference did not (Group:  $F(1,80)=1.8$ , ns,  $\eta_p^2=.23$ ; Group x Condition:  $F(1,80)=.6$ , ns,  $\eta_p^2=.006$ ). The group differences in go RT and go RT variability remained significant when BDI was used as a covariate ( $F(1,78)=6.4$ ,  $.01$ ,  $\eta_p^2=.07$  and  $F(1,78)=6.8$ ,  $.01$ ,  $\eta_p^2=.08$ , respectively).

The skill index was larger in the patient group compared to the control group ( $F(1,80)=5.9$ ,  $p=.017$ ,  $\eta_p^2=.068$ ) and in the threat compared to the safe condition ( $F(1,80)=16.5$ ,  $p<.0009$ ,  $\eta_p^2=.171$ ) without significant group x condition interaction ( $F(1,80)=.1$ , ns,  $\eta_p^2=.00004$ ). The group difference in skill index remained significant when BDI was used as a covariate ( $F(1,78)=9.3$ ,  $p=.003$ ,  $\eta_p^2=.10$ ).

## Startle reflex & subjective anxiety

Analysis of the startle data with raw scores and T-score led to similar results. The raw scores are presented here (Fig 3, top) and the t-scores in Supplementary Materials (Fig. 1s). These data were analyzed with a group (healthy participants, anxiety patients) x task (control task, GNG) x condition (safe, threat) ANOVA. Startle magnitude was larger in the threat compared to the safe condition (i.e., fear-potentiated startle:  $F(1,80)=77.1$ ,  $p<.0009$ ,  $\eta_p^2=.49$ ) and in the no task compared to the GNG task condition ( $F(1,80)=19.9$ ,  $p<.0009$ ,  $\eta_p^2=.19$ ), but these effects were qualified by 1) a group x condition interaction ( $F(1,80)=4.6$ ,  $p=.03$ ,  $\eta_p^2=.05$ ), reflecting greater fear-potentiated startle in the patients compared to the healthy participants, and 2) a task x condition interaction ( $F(1,80)=4.2$ ,  $p=.04$ ,  $\eta_p^2=.05$ ), due to reduced fear-potentiated startle in the GNG task compared to the no task. The group x condition interaction remained significant when BDI was used as a covariate ( $F(1,78)=12.2$ ,  $p=.001$ ,  $\eta_p^2=.13$ ),

## Anxiety & response inhibition

Subjective anxiety (Fig 3, bottom) was higher overall in the patients compared to the healthy participants ( $F(1,80)=9.0$ ,  $p=.003$ ,  $\eta_p^2=.102$ ) (including after controlling for BDI, ( $F(1,78)=4.7$ ,  $p=.03$ ,  $\eta_p^2=.12$ ), in the threat compared to the safe condition ( $F(1,80)=76.2$ ,  $p<.0009$ ,  $\eta_p^2=.488$ ), and (at trend) in the control task compared to the GNG task ( $F(1,80)=3.7$ ,  $p=.057$ ,  $\eta_p^2=.446$ ). No interaction was significant (all  $p>.1$ ).

## Discussion

This study examined the interacting effects of state and clinical anxiety on response inhibition. As predicted, clinical anxiety was associated with excessive response inhibition, as measured by the signal-detection response bias index ( $C_L$ ), leading to decreased go accuracy. This effect was independent of the threat manipulation. These findings suggest that clinical anxiety is associated with over activation of an adaptive defense mechanism (i.e., the behavioral inhibition system) that promotes an excessive response inhibition tendency, leading to a maladaptive behavioral effect (i.e., impaired go performance). This maladaptive behavior is a marker of the disease rather than the result of excessive state anxiety arising from an actual threat.

The finding that threat of shock in the healthy participants improved nogo accuracy without affecting go accuracy or go RT replicates and extends our original study (Robinson *et al.*, 2013a). The signal-detection analysis suggests that two factors contributed to this improvement. First, the response bias index  $C_L$  indicated that heightened state anxiety decreased go tendency (i.e., increased nogo tendency), aligning behavior preferentially with the task of stopping the motor response on nogo trials. Second, heightened state anxiety improved signal-detection sensitivity ( $d_L$ ), probably leading to better target discrimination. This latter effect is consistent with findings that heightened state anxiety facilitates early perceptual and sensory

## Anxiety & response inhibition

processing (Baas *et al.*, 2006, Cornwell *et al.*, 2007, Pessoa *et al.*, 2012, Vuilleumier, 2005). These sensory effects may have facilitated stimulus detection, also contributing to improved nogo accuracy (Smallwood, 2013).

Successful performance during GNG tasks did not depend solely on response inhibition. For example, it also involves changes in response strategy. However, the result that RT was not affected by heightened state anxiety indicates two points: participants (including the anxiety patients) did not adopt a more deliberate, cautious and controlled response strategy (Gold and Shadlen, 2007) and improved nogo performance did not come at the expense of efficiency (Eysenck *et al.*, 2007), which would be reflected in a speed-accuracy trade-off (i.e., slower RT) (Peebles and Bothell, 2004). Rather, the skill index indicated superior nogo performance efficiency during the threat condition when RT was taken into account to evaluate nogo performance.

Clinical anxiety, like heightened state anxiety, increased response inhibition based on response bias index (Fig 2, left). In healthy participants, the GNG task promoted a strong go prepotency in innocuous context (safe condition), which resulted in a low response inhibition tendency that increased the likelihood of nogo commission errors. As state anxiety was heightened in the healthy participants (threat condition) and in the anxiety patients (safe and threat conditions), response inhibition increased. This facilitated stopping on nogo trials in both groups, but increased go omission errors in the patients. Thus, consistent with Gray's models (Epstein *et al.*, 2001, Gray and McNaughton, 2000, Quay, 1997, Sylwan, 2004), a transient increase in response inhibition under threat is normative, but excessive response inhibition characterizes clinical anxiety. This excessive behavioral inhibition in anxiety patients has beneficial effects such as superior nogo performance (based on the skill index scores), but it is

## Anxiety & response inhibition

also detrimental for go accuracy, compared to the healthy participants. The exact implication of these findings remains to be determined. A key question is how increased response inhibition relates to maladaptive behaviors, such as avoidance and fearful inhibited temperament, which is characterized by a behavioral inhibition phenotype (Buss *et al.*, 2004, Kagan *et al.*, 1988)? Indeed it is likely context dependent, increased inhibition could be adaptive in the face of threat, but it could be maladaptive in the face of positive outcomes. Future work should explore the impact of inhibitory processes across valenced outcomes.

During go trials, a balance is established between prepotent go responses and the need to adjust motor readiness in anticipation of stopping the response on nogo trials (i.e., proactive response inhibition) (Aron, 2011). The go results point to excessive proactive response inhibition in clinical anxiety. However, one could alternatively argue that the anxiety patients failed to develop prepotent go responses. This explanation is unlikely given that 1) RT was faster in the patients compared to the healthy participants and 2) it is inconsistent with the literature that show no detrimental effect of anxiety on prepotent responses. For example, eye movement studies show no impairment in pro-saccade, a prepotent response, in trait anxious individuals (Ansari and Derakshan, 2011, Ansari *et al.*, 2008). In addition, acute and chronic stress promote rather than impair the development of habit behaviors and prepotent responses in humans and in animals (Kim *et al.*, 2001, Schwabe *et al.*, 2008, Schwabe and Wolf, 2009).

The present findings have several implications. First, organisms need to react adaptively to threat with a set of behavioral adjustments including attentional bias towards threat, increased arousal and negative affect, and behavioral inhibition. Clinical anxiety has long been associated with attentional bias for threat and excessive arousal (Robinson *et al.*, 2013b). We now show that it is also marked by excessive behavioral inhibition, which has previously been suggested as an



## Anxiety & response inhibition

underlying cause of anxiety disorders (Quay, 1988). Second, one of the objectives of RDoC is to identify neurobiological dimensions of dysfunction that characterize psychiatric disorders. We propose that response inhibition is an important behavioral component that can inform our understanding of clinical anxiety. Future studies should examine whether response inhibition is an enduring feature of clinical anxiety or a pre-existing vulnerability and whether strong response inhibition tendencies are associated with passive or avoidant behaviors as it has been proposed (Kooijmans *et al.*, 2000).

The present results seem to contradict the prominent view that anxiety impaired a host of cognitive functions, including cognitive control and inhibition (Ansari *et al.*, 2008, Derakshan *et al.*, 2009, Eysenck *et al.*, 2007). However, this view needs to be revisited. First, inhibition reflects an umbrella of concepts (Bari and Robbins, 2013). Inhibiting a premotor response and inhibiting intrusion from task-irrelevant thought or stimuli (e.g., Stroop effect) relies on distinct mechanisms. There is no reason to assume that anxiety would affect these two types of inhibition similarly. In addition, in most inhibition studies, anxiety refers to trait anxiety, but trait anxiety is different from state anxiety or clinical anxiety. It is important to distinguish among the expression of these different forms of anxiety as they may present commonalities but also important differences (Bijsterbosch *et al.*, 2015). In fact, most studies do not show a detrimental effect of trait anxiety in GNG tasks (Righi *et al.*, 2009, Sehlmeier *et al.*, 2010).

This study had strengths and limitations. Among the strengths, the study relied on a within-subject design with well-established methods of fear induction and measurement (Grillon and Baas, 2003, Kaye *et al.*, 2016). In addition, the study was based on strong a priori hypotheses from prior studies, and replicated the effect of heightened state anxiety on response inhibition. Finally, the anxiety patients were off medication. A limitation was that the safe condition is not

## Anxiety & response inhibition

fully affectively neutral. Participation in a study where shocks are administered raises the level of state anxiety even when shocks are not imminent. It is therefore possible, that anxiety caused by the threatening context was responsible for the group difference in performance observed in this study. However, one could argue that if this contextual anxiety was responsible for the performance difference between the controls and the patients in the safe condition, the patients should have been even more affected by the much greater anxiety evoked by the actual shock threat in the threat condition. We could have then expected the two groups to show differential performance over the safe and threat conditions, a result which was not obtained. Nevertheless, future studies should examine response inhibition in anxiety patients in a non-threatening context. Another limitation was that the anxiety patients were not homogeneous with regard to diagnosis. However, our approach was consistent with current conceptualization of mental disorders (Insel *et al.*, 2010). In addition, there was no performance difference among the anxiety groups (Supplementary Materials, Table 1s). Finally, the small number of males, reflective of the clinical prevalence - prevented us from testing for sex differences.

To conclude, heightened state anxiety shifts motor action tendencies towards increased response inhibition, improving individuals' ability to stop motor responses. Clinical anxiety is characterized by excessive response inhibition tendencies, which lead to inappropriate stopping. These results have clinical implications. Discovery of clinical biological phenotypes is a key step in improving clinical classification and identifying pathophysiological mechanisms that could be targeted for treatment development. This study suggests that increased response inhibition may be a clinical phenotype of anxiety disorders. The study of response inhibition in anxiety as a state (Hagenaars *et al.*, 2014, Wright *et al.*, 2014) or a disorder is in its infancy. However, there is substantial knowledge of the underlying mechanisms of response inhibition in healthy

## Anxiety & response inhibition

individuals. This knowledge provides a benchmark to identify underlying dysfunction associated with pathological anxiety.

Anxiety & response inhibition

**Acknowledgement:** This research was supported by the Intramural Research Program of the National Institute of Mental Health [ZIAMH002798] (Protocol 03-M-0093; NCT00055224).

### **DISCLOSURE/CONFLICT OF INTEREST**

The author(s) declare that, except for income received from the primary employer, no financial support or compensation has been received from any individual or corporate entity for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest. Further, the authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

## References

- Ansari, T. L. & Derakshan, N.** (2011). The neural correlates of impaired inhibitory control in anxiety. *Neuropsychologia* **49**, 1146-1153.
- Ansari, T. L., Derakshan, N. & Richards, A.** (2008). Effects of anxiety on task switching: Evidence from the mixed antisaccade task. *Cognitive, Affective, & Behavioral Neuroscience* **8**, 229-238.
- Aron, A.** (2011). From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. *Biological Psychiatry* **69**, 55-68.
- Baas, J. M. P., Milstein, J., Donlevy, M. & Grillon, C.** (2006). Brainstem correlates of defensive states in humans. *Biological Psychiatry* **59**, 588-593.
- Bari, A. & Robbins, T. W.** (2013). Inhibition and impulsivity: Behavioral and neural basis of response control. *Progress in Neurobiology* **108**, 44-79.
- Beck, A. T. & Steer, R. A.** (1987). *BDI: Beck Depression Inventory*. The Psychological Corporation, Harcourt Brace Jovanovich, Inc.: New York.
- Beutel, M. E., Stark, R., Pan, H., Silbersweig, D. & Dietrich, S.** (2010). Changes of brain activation pre- post short-term psychodynamic inpatient psychotherapy: An fMRI study of panic disorder patients. *Psychiatry Research: Neuroimaging* **184**, 96-104.
- Bijsterbosch, J., Smith, S. & Bishop, S. J.** (2015). Functional connectivity under anticipation of shock: correlates of trait anxious affect versus induced anxiety. *Journal of Cognitive Neuroscience*, 1-14.
- Buss, K. A., Davidson, R. J., Kalin, N. H. & Goldsmith, H. H.** (2004). Context-specific freezing and associated physiological reactivity as a dysregulated fear response. *Developmental Psychology* **40**, 583-594.
- Cornwell, B. R., Baas, J. M. P., Johnson, L., Holroyd, T., Carver, F. W., Lissek, S. & Grillon, C.** (2007). Neural responses to auditory stimulus deviance under threat of electric shock revealed by spatially-filtered magnetoencephalography. *Neuroimage* **37**, 282-289.
- Daugherty, T. K., Quay, H. C. & Ramos, L.** (1993). Response perseveration, inhibitory control, and central dopaminergic activity in childhood behavior disorders. *Journal of Genetic Psychology* **154**, 177-188.
- Derakshan, N., Ansari, T. L., Hansard, M., Shoker, L. & Eysenck, M. W.** (2009). Anxiety, Inhibition, Efficiency, and Effectiveness. *Experimental Psychology (formerly "Zeitschrift für Experimentelle Psychologie")* **56**, 48-55.
- Epstein, J., Johnson, D., Varia, I. & Conners, C. K.** (2001). Neuropsychological Assessment of Response Inhibition in Adults With ADHD. *Journal of Clinical and Experimental Neuropsychology* **23**, 362-371.
- Eysenck, M. W., Derakshan, N., Santos, R. & Calvo, M. G.** (2007). Anxiety and cognitive performance: attentional control theory. *Emotion* **7**, 336-53.

- First, M. B., Spitzer, R. L., Gibbon, M. & Williams, J. B. W.** (2002). *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition. (SCID-I/NP)* New York: Biometrics Research, New York State Psychiatric Institute.
- Forster, S. & Lavie, N.** (2014). Distracted by Your Mind? Individual Differences in Distractibility Predict Mind Wandering. *Journal of Experimental Psychology-Learning Memory and Cognition* **40**, 251-260.
- Geen, R. G.** (1985). Test anxiety and visual vigilance. *Journal of Personality and Social Psychology* **49**, 963-970.
- Gold, J. I. & Shadlen, M. N.** (2007). The Neural Basis of Decision Making. *Annual Review of Neuroscience* **30**, 535-574.
- Gray, J. A. & McNaughton, N.** (2000). *The Neuropsychology of Anxiety: An Inquiry into the function of the Septo-Hippocampal System.* Oxford University Press: Oxford.
- 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.
- Grillon, C., Robinson, O., Krimsky, M., O'Connell, Alvarez, G. & Ernst, M.** (2016). Anxiety-mediated facilitation of behavioral inhibition: threat processing and defensive reactivity during a go/nogo task. *Emotion*.
- Hagenaars, M. A., Oitzl, M. & Roelofs, K.** (2014). Updating freeze: Aligning animal and human research. *Neuroscience & Biobehavioral Reviews* **47**, 165-176.
- Hagopian, L. P. & Ollendick, T. H.** (1994). Behavioral inhibition and test anxiety: An empirical investigation of Gray's theory. *Personality and Individual Differences* **16**, 597-604.
- Helton, W. S.** (2009). Impulsive responding and the sustained attention to response task. *Journal of Clinical and Experimental Neuropsychology* **31**, 39-47.
- Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., Sanislow, C. & Wang, P.** (2010). Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders. *American Journal of Psychiatry* **167**, 748-751.
- Kagan, J., Reznick, J. S. & Snidman, N.** (1988). Biological basis of childhood shyness. *Science* **240**, 167-171.
- Karch, S., Jäger, L., Karamatskos, E., Graz, C., Stammel, A., Flatz, W., Lutz, J., Holschmidt-Täschner, B., Genius, J., Leicht, G., Pogarell, O., Born, C., Möller, H.-J., Hegerl, U., Reiser, M., Soyka, M. & Mulert, C.** (2008). Influence of trait anxiety on inhibitory control in alcohol-dependent patients: Simultaneous acquisition of ERPs and BOLD responses. *Journal of Psychiatric Research* **42**, 734-745.
- Kaye, J. T., Bradford, D. E. & Curtin, J. J.** (2016). Psychometric properties of startle and corrugator response in NPU, affective picture viewing, and resting state tasks. *Psychophysiology* **53**, 1241-1255.
- Kim, J. J., Lee, H. J., Han, J. S. & Packard, M. G.** (2001). Amygdala is critical for stress-induced modulation of hippocampal long-term potentiation and learning. *Journal of Neuroscience* **21**, 5222-8.

- Kooijmans, R., Scheres, A. & Oosterlaan, J.** (2000). Response Inhibition and Measures of Psychopathology: A Dimensional Analysis. *Child Neuropsychology* **6**, 175-184.
- Li, C.-s. R., Chao, H. H.-A. & Lee, T.-W.** (2009). Neural Correlates of Speeded as Compared with Delayed Responses in a Stop Signal Task: An Indirect Analog of Risk Taking and Association with an Anxiety Trait. *Cerebral Cortex* **19**, 839-848.
- Maack, D. J., Tull, M. T. & Gratz, K. L.** (2012). Examining the incremental contribution of behavioral inhibition to generalized anxiety disorder relative to other Axis I disorders and cognitive-emotional vulnerabilities. *Journal of Anxiety Disorders* **26**, 689-695.
- 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**, 196-204.
- McVay, J. C., Meier, M. E., Touron, D. R. & Kane, M. J.** (2013). Aging ebbs the flow of thought: Adult age differences in mind wandering, executive control, and self-evaluation. *Acta Psychologica* **142**, 136-147.
- Morgan, B. E., van Honk, J., Hermans, E. J., Scholten, M. R. M., Stein, D. J. & Kahn, R. S.** (2009). Gray's BIS/BAS dimensions in non-comorbid, non-medicated social anxiety disorder. *The World Journal of Biological Psychiatry* **10**, 925-928.
- Neo, P. S. H., Thurlow, J. & McNaughton, N.** (2011). Stopping, goal-conflict, trait anxiety and frontal rhythmic power in the stop-signal task. *Cognitive, Affective & Behavioral Neuroscience* **11**, 485-493.
- Oosterlaan, J. & Sergeant, J. A.** (1996). Inhibition in ADHD, aggressive, and anxious children: a biologically based model of child psychopathology. *Journal of Abnormal Child Psychology* **24**, 19-36.
- Peebles, D. & Bothell, D. eds.** (2004). *Modelling performance in the Sustained Attention to Response Task*. Carnegie Mellon University/University of Pittsburgh: Pittsburgh, PA.
- Pessoa, L., Padmala, S., Kenzer, A. & Bauer, A.** (2012). Interactions between cognition and emotion during response inhibition. *Emotion* **12**, 192-197.
- Quay, H.** (1988). The behavioral reward and inhibition system in childhood behavior disorder. In *Attention Deficit Disorder* (ed. L. M. Bloomingdale), pp. 176-186. Pergamon Press: Oxford, England.
- Quay, H. C.** (1997). Inhibition and attention deficit hyperactivity disorder. *Journal of Abnormal Child Psychology* **25**, 7-13.
- Righi, S., Mecacci, L. & Viggiano, M.** (2009). Anxiety, cognitive self-evaluation and performance: ERP correlates. *Journal of Anxiety Disorders* **23**, 1132-1138.
- Robinson, O. J., Krimsky, M. & Grillon, C.** (2013a). The impact of induced anxiety on response inhibition. *Frontier in Human Neuroscience* **7:69**.
- Robinson, O. J., Lieberman, L., Allen, P., Vytal, K. & Grillon, C.** (2015). The dorsal medial prefrontal-amygdala 'aversive amplification' circuit in unmedicated generalized and social anxiety disorders. *The Lancet Psychiatry* **1**, 294-302.

- Robinson, O. J., Vytal, K., Cornwell, B. R. & Grillon, C.** (2013b). The impact of anxiety upon cognition: perspectives from human threat of shock studies. *Frontier in Human Neuroscience* **7**:203.
- Roelofs, K., van Peer, J., Berretty, E., Jong, P. d., Spinhoven, P. & Elzinga, B. M.** (2009). Hypothalamus–Pituitary–Adrenal Axis Hyperresponsiveness Is Associated with Increased Social Avoidance Behavior in Social Phobia. *Biological Psychiatry* **65**, 336-343.
- Rosenbaum, J. F., Biederman, J., Hirshfeld, D. R., Bolduc, E. A., Faraone, S. V., Kagan, J., Snidman, N. & Reznick, J. S.** (1991). Further Evidence of an Association Between Behavioral Inhibition and Anxiety Disorders - Results from a Family Study of Children from a Non-Clinical Sample. *Journal of Psychiatry Research* **25**, 49-65.
- Saucedo Marquez, C. M., Zhang, X., Swinnen, S. P., Meesen, R. & Wenderoth, N.** (2013). Task-specific effect of transcranial direct current stimulation on motor learning. *Frontiers in Human Neuroscience* **7**.
- Schwabe, L., Dalm, S., Schächinger, H. & Oitzl, M. S.** (2008). Chronic stress modulates the use of spatial and stimulus-response learning strategies in mice and man. *Neurobiology of Learning and Memory* **90**, 495-503.
- Schwabe, L. & Wolf, O. T.** (2009). Stress prompts habit behavior in humans. *Journal of Neuroscience* **29**, 7191-7198.
- Sehmeyer, C., Konrad, C., Zwitterlood, P., Arolt, V., Falkenstein, M. & Beste, C.** (2010). ERP indices for response inhibition are related to anxiety-related personality traits. *Neuropsychologia* **48**, 2488-2495.
- Seli, P.** (2016). The Attention-Lapse and Motor Decoupling accounts of SART performance are not mutually exclusive. *Consciousness and Cognition* **41**, 189-198.
- Seli, P., Risko, E. F. & Smilek, D.** (2016). On the Necessity of Distinguishing Between Unintentional and Intentional Mind Wandering. *Psychological Science* **27**, 685-691.
- Smallwood, J.** (2013). Penetrating the fog of the decoupled mind: The effects of visual salience in the sustained attention to response task. *Canadian journal of experimental psychology* **67**, 32-40.
- Snodgrass, J. G. & Corwin, J.** (1988). Pragmatics of measuring recognition memory: Applications to dementia and amnesia. *Journal of Experimental Psychology: General* **117**, 34–50.
- Spielberger, C. D.** (1983). *Manual for the State-Trait Anxiety Inventory*. Consulting Psychologist Press.: Palo Alto, CA.
- Stuss, D. T., Shallice, T., Alexander, M. P. & Picton, T. W.** (1995). A Multidisciplinary Approach to Anterior Attentional Functions. *Annals of the New York Academy of Sciences* **769**, 191-212.
- Sylwan, R. P.** (2004). The control of deliberate waiting strategies in a stop-signal task. *Brazilian Journal of Medical and Biological Research* **37**, 853-862.
- Thomas, S. J., Gonsalvez, C. J. & Johnstone, S. J.** (2016). Electrophysiology of facilitation priming in obsessive–compulsive and panic disorders. *Clinical Neurophysiology* **127**, 464-478.



## Anxiety & response inhibition

**Vuilleumier, P.** (2005). How brains beware: neural mechanisms of emotional attention. *Trends in Cognitive Science* **9**, 585-94.

**Wright, L., Lipszyc, J., Dupuis, A., Thayapararajah, S. & Schachar, R.** (2014). Response inhibition and psychopathology: A meta-analysis of Go/No-Go task performance. *Journal of Abnormal Psychology* **123**, 429-439.

Anxiety & response inhibition

**Table 1**

**Demographic information and shock intensity**

	<b>Age</b>	<b>State anxiety<sup>a</sup></b>	<b>Trait anxiety<sup>b</sup></b>	<b>BDI<sup>c</sup></b>	<b>Shock Intensity<sup>d</sup></b>
<b>Healthy participants</b>	30.0 (1.2)	25.9 (1.1)	28.8 (1.1)	.8 (.3)	2.9 (.2)
<b>Anxiety patients</b>	28.1 (1.2)	43.6 (1.8)	52.3 (1.5)	8.7 (1.3)	2.8 (.1)

<sup>a</sup> State portion and <sup>b</sup> trait portion of the State-Trait Anxiety Inventory (Spielberger, 1983) and <sup>c</sup> Beck Depression Inventory<sup>#</sup> (Beck and Steer, 1987); <sup>a</sup> in mA.

**Table 2**

Mean (sem) performance scores

	Healthy participants		Anxiety patients	
	Safe	Threat	Safe	Threat
<b>nogo correct omission<sup>a</sup></b>	.76 (.02)	.80 (.02)	.76 (.01)	.81 (.02)
<b>go correct hit<sup>b</sup></b>	.91 (.01)	.90 (.01)	.87 (.01)	.87 (.02)
<b>go RT (msec)<sup>c</sup></b>	387.8 (16.2)	377.4 (14.7)	337.3 (10.7)	332.2 (10.9)
<b>Skill index<sup>d</sup></b>	2.1 (.07)	2.3 (.08)	2.3 (.07)	2.5 (.08)
<b>go RT variability<sup>e</sup></b>	148.4 (10.0)	133.4 (9.8)	124.9 (8.8)	105.1 (7.3)
<b>go RT coefficient of variation<sup>f</sup></b>	.38 (.02)	.35 (.02)	.36 (.02)	.31 (.02)

<sup>a</sup> Nogo trials followed by no button press; <sup>b</sup> Go trials followed by button press; <sup>c</sup> RT to correct button press to go trials; <sup>d</sup>  $1000 * (\text{mean nogo accuracy ratio} / \text{mean go-trial RT})$  (Saucedo Marquez *et al.*, 2013, Seli, 2016, Seli *et al.*, 2016). <sup>e</sup> Go RT standard error. <sup>f</sup> standard deviation/mean RT to go trials.

### Figure captions

**Figure 1.** Schematic description of stimulus presentation (sequence 2). 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 nogo, 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 select one type of thought with choices of task-related thoughts (TRTs), task-unrelated/threat unrelated thoughts (nonthreatTUTs), and threat-related thoughts (threatTUTs) (see Supplementary Materials).

**Figure 2.** Signal-detection sensitivity ( $d_L$ ) and response bias ( $C_L$ ) scores in the two groups in the safe and threat conditions. Error bars are sem. \* for significant ( $p < .05$ ) overall group difference; # for significant ( $p = .001$ ) difference between the safe and threat conditions across groups.

**Figure 3.** Startle magnitude (top) and subjective anxiety (bottom) in each condition in the two groups. Difference is difference scores threat minus safe (fear-potentiated startle). Error bars are sem. \* for a significant ( $p < .05$ ) greater fear-potentiated startle in the patients compared to the control group; # for a significant ( $p < .05$ ) greater fear-potentiated startle in no task compared to GNG task; ^ for significant ( $p < .05$ ) greater overall subjective anxiety in the patients compared to the control group.