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ANXIETY, A BENEFIT AND DETRIMENT TO COGNITION: BEHAVIORAL AND MAGNETOENCEPHALOGRAPHIC EVIDENCE FROM A MIXED-SACCADE TASK

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Abstract

Anxiety is typically considered an impediment to cognition. We propose anxiety-related impairments in cognitive-behavioral performance are the consequences of enhanced stimulus-driven attention. Accordingly, reflexive, habitual behaviors that rely on stimulus-driven mechanisms should be facilitated in an anxious state, while novel, flexible behaviors that compete with the former should be impaired. To test these predictions, healthy adults ($N=17$) performed a mixed-saccade task, which pits habitual actions (pro-saccades) against atypical ones (anti-saccades), under anxiety-inducing threat of shock and safe conditions. Whole-head magnetoencephalography (MEG) captured oscillatory responses in the preparatory interval preceding target onset and saccade execution. Results showed threat-induced anxiety differentially impacted response times based on the type of saccade initiated, slowing anti-saccades but facilitating erroneous pro-saccades on anti-saccade trials. MEG source analyses revealed that successful suppression of reflexive pro-saccades and correct initiation of anti-saccades during threat was marked by increased theta power in right ventrolateral prefrontal cortical and midbrain regions (superior colliculi) implicated in stimulus-driven attention. Theta activity may delay stimulus-driven processes to enable generation of an anti-saccade. Moreover, compared to safety, threat reduced beta desynchronization in inferior parietal cortices during anti-saccade preparation but increased it during pro-saccade preparation. Differential effects in inferior parietal cortices indicate a greater readiness to execute anti-saccades during safety and to execute pro-saccades during threat. These findings suggest that, in an anxiety state, reduced cognitive-behavioral flexibility may stem from enhanced stimulus-driven attention, which may serve the adaptive function of optimizing threat detection.

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Keywords

anxiety; beta oscillation; magnetoencephalography; saccade; stimulus-driven attention; theta oscillation

1. Introduction

Cognitive models of anxiety emphasize anxiety's detrimental effects on cognitive-behavioral performance (Bishop, 2007; Eysenck & Calvo, 1992; Eysenck et al., 2007). High-anxious participants show disturbances in prefrontally-mediated processes such as goal-directed control of attention (Bishop et al., 2007). These attention control disturbances may stem directly from inherent executive dysfunction and underlying abnormalities in prefrontal cortices (Bishop, 2008). An alternative view emphasizes adaptive functions of anxiety, defined as heightened action readiness in the face of ambiguous, unpredictable threat. Anxiety may constrain goal-directed attention mechanisms, but only secondarily as priorities are shifted to monitoring the environment and being maximally receptive to potential threat signals, irrespective of competing task demands (Cornwell et al., 2011). Two hypotheses emerge from this latter standpoint, and promote a broader view of anxiety's effects – positive and negative – on cognition (see also Eysenck et al., 2007; Pessoa, 2009). First and foremost, anxiety facilitates reflexive and habitual, over-learned behaviors that rely on stimulus-driven attention mechanisms. Second and as a consequence, anxiety hinders novel, flexible behavior, particularly that which competes with the former.

The mixed-saccade task – which pits habitual actions (pro-saccades) against atypical actions (anti-saccades) – provides an ideal platform to test these hypotheses. Despite both being volitional responses in this task, pro-saccades are congruent with, while anti-saccades compete with and demand suppression of, the habitual tendency to target the eyes toward a suddenly appearing object. This task has figured prominently in research on various psychopathological conditions such as schizophrenia and attention-deficit/hyperactivity disorder (for a review, see Hutton & Ettinger, 2006). Recent work has shown that anxiety is associated with impaired anti-saccade performance, further linking anxiety with poor cognitive-behavioral performance (Ansari et al., 2008; Derakshan et al., 2009; Jazbec et al., 2005; Wieser et al., 2009; but see Ettinger et al., 2005). However, no evidence was provided for anxiety-related improvements in pro-saccade performance. Such evidence would bolster the hypothesis that anxiety facilitates stimulus-driven actions, which, in turn, hinder competing actions. In these studies, participants were grouped by pre-existing anxiety characteristics (e.g., trait anxiety). Anxiety was not manipulated, leaving open the possibility that group differences were driven by dispositional attributes other than anxiety.

Experimentally manipulating anxiety, as we did here, allows direct attribution of changes in cognitive-behavioral performance to concurrent anxiety states and may provide a more sensitive means to study the broader impact of anxiety on cognition (Lavric et al., 2003; Shackman et al., 2006; Vytal et al., manuscript under review). Healthy volunteers performed visually-elicited pro-saccades and anti-saccades under two conditions: (1) during periods of risk of receiving aversive electric shocks and (2) during periods of safety. Threat of shock is a robust method for inducing sustained anxiety in healthy individuals (Cornwell et al., 2007; Grillon, 2002). Threat-induced anxiety sensitizes sensory-perceptual processing as evidenced by increased cortical and midbrain responses to innocuous stimuli when participants anticipate shock (Baas et al., 2006; Cornwell et al., 2007). Arguably, this leads to increased stimulus-driven attention capture (Cornwell et al., 2008b; Grillon & Davis, 1997), which, in the present context, should be beneficial to performing pro-saccades but detrimental to performing anti-saccades. Accordingly, we hypothesized greater divergence

(opposite effects) in pro- vs. anti-saccade performance (i.e., onset latency) under threat-induced anxiety relative to safe, non-anxious conditions. This divergence was expected to reflect a combination of a facilitating effect on initiating pro-saccades and a hindering effect on initiating anti-saccades under threat.

Neural correlates of anxiety's effects on pro-saccade or anti-saccade performance have not received much attention, heretofore (Ansari & Derakshan, 2011). To fill this gap, we recorded brain oscillations with whole-head magnetoencephalography (MEG). Specifically, we examined spectral power during saccade preparation (i.e., before saccade execution) in the interval between the instruction cue (pro- or anti-saccade) and target presentation. This time window was selected for analysis because electrophysiological data in humans and nonhuman primates point to an important role of neuronal activity during saccade preparation in tuning saccade pathways for optimal execution of an upcoming pro-saccade or anti-saccade (Dorris et al., 1997; Everling et al., 1998; Mueller et al., 2009; Munoz & Everling, 2004). It has also been recently shown that neural activity preceding anti-saccades differs between high and low anxious participants (Ansari & Derakshan, 2011). MEG, unlike other neuroimaging techniques such as functional MRI, has the prerequisite temporal resolution to isolate this preparatory activity from activity mediating visual target detection and saccade execution (Herdmann & Ryan, 2007; Hinkley et al., 2011; Sestieri et al., 2008). Adaptive MEG beamformer analyses (i.e., synthetic aperture magnetometry, SAM, Vrba & Robinson, 2001) were performed to estimate oscillatory power in key regions involved in controlling saccades and/or attention: frontal eye fields, supplementary eye fields, dorsolateral prefrontal cortices, dorsal anterior cingulate, inferior parietal cortices and superior colliculi (Chikazoe et al., 2008; Corbetta et al., 2008; Luna et al., 1998; Munoz & Everling, 2004).

The dorsal fronto-parietal cortical network mediating volitional saccades has also been implicated, more generally, in goal-directed attention control (Corbetta et al., 2008, Corbetta & Shulman, 2002). This dorsal attention system, as argued by Corbetta and colleagues, can be partially dissociated from a right-lateralized ventral fronto-parietal cortical system – comprised of right ventrolateral prefrontal and temporoparietal cortices – that mediates stimulus-driven attention. It is this ventral attention system that we hypothesize must be down-regulated for participants to effectively suppress reflexive pro-saccades to correctly execute anti-saccades under threat-induced anxiety, when sensory-perceptual systems are sensitized and stimulus-driven attention capture is likely optimized (Vuilleumier & Driver, 2007). Thus, ventral cortical structures involved in stimulus-driven attention should be distinctly modulated on anti-saccade trials under threat. Threat-related modulation of activity in dorsal cortical structures mediating goal-directed attention and volitional control of saccades was also anticipated, but no specific predictions were made. We focused on theta (4–8 Hz), alpha (8–12 Hz), and beta (14–30 Hz) oscillatory activity within these regions of interest.

2. Materials and Methods

2.1 Participants

Twenty healthy adult volunteers participated in both a MEG testing session and a separate session to obtain an anatomical MRI for source analysis. Data from three participants were discarded due to either excessive head movement during the MEG scan or significant eye movement artifacts recordings, leaving a final sample of 17 participants (10 men, 7 women, mean age = 27 yr, range = 22–34 yr). Exclusion criteria included: (1) past or current psychiatric disorders as per the Structured Clinical Interview for DSM-IV (First et al., 1995), (2) current use of psychoactive medications as per self-report, and (3) current use of illicit drugs determined by urine analysis. Participants were screened for metallic objects

that might cause significant artifacts in the MEG (or pose safety concerns in the MRI environment). The study was approved by the Combined Neuroscience Institutional Review Board of the National Institutes of Health. All participants gave informed consent prior to participation and were monetarily compensated for their time.

2.2 Electrode set-up

Two surface electrodes were attached to the wrist for shock administration by a Grass S88 constant voltage stimulator (Astro-Med, Inc., RI, USA). A third surface electrode attached to the forearm served as ground. Two final surface electrodes were attached to the left and right thoracic region to record cardiac activity. At each site, skin was cleaned with a mildly abrasive substance and electrodes were prepared with conductive gel. Before participants were placed in the MEG scanner, shock intensity was set individually for each participant to a level reported to be moderately uncomfortable during a shock work-up procedure. This resulted in a range of physical intensities between 3–5 mA. Participants were informed that they could receive 5–15 shocks during the recordings.

2.3 Anxiety induction

Participants performed a mixed-saccade task under threatening conditions and under safe conditions. Threat and safe contexts each lasted approximately 70 s and alternated in predictable fashion. Two runs of neuromagnetic, eye-tracking and electrocardiographic data were collected. In each run, participants cycled five times through threat and safe contexts, beginning with the threat context in one run and the safe context in the other, and with no temporal gap between contexts. This was counterbalanced across participants. During the threat context, participants were at risk of receiving moderately-uncomfortable electric shocks to the wrist without warning. A total of 8 shocks (4 per run) were administered, and were equally distributed during fixation on pro-saccade and anti-saccade trials. There was no risk of shocks during the safe context. The start of each context was marked with a written message appearing on the screen for 5 s before the first saccade trial; it read either “Shocks can come at any time” or “You are completely safe” (Figure 1a). Cardiac activity (i.e., heart rate) was analyzed during this 5-s period when no shocks were administered and saccades were not performed. Participants were asked at the end of each run to quantify their anxiety level for each context, using a 0–10 scale (0 = “Not anxious”, 10 = “Highly anxious”).

2.4 Mixed-saccade task

Participants performed a total of 160 saccades in each context (16 trials per iteration of each context): 80 pro-saccades and 80 anti-saccades in fixed pseudo-random order. The fixed pseudo-random order of pro- and anti-saccade trials was designed so that participants switched or repeated the same type of saccade from trial to trial in roughly equal numbers; thus, task switching or trial carryover effects were modeled in our analyses of saccade performance. Each trial began with the presentation of a centrally-located stimulus, which participants were instructed to fixate (Figure 1b). The fixation stimulus (white “+” sign) appeared for a variable duration (range = 1800–2200 ms, mean = 2000 ms) upon which it was replaced by a centrally-located instruction cue in one of two colors (blue or red “+” sign), indicating whether to make a pro-saccade or anti-saccade upon appearance of the peripheral stimulus. The instruction cue was presented for a fixed duration of 1000 ms. The peripheral target stimulus (white “+” sign) appeared immediately following the offset of the instruction cue (i.e., no-gap). It was presented for a fixed duration of 800 ms to the left or right of central fixation (8 cm or 12.2 degrees of visual angle) with equal probability in a fixed, pseudo-random order. Once the peripheral target stimulus disappeared, the central fixation stimulus for the next trial immediately followed. All “+” signs were 1.5×1.5 cm, presented against a gray background.

Participants were instructed to rapidly move their eyes to the peripheral target stimulus on pro-saccade trials or to the mirror (unmarked) location on the opposite side on anti-saccade trials; in both cases they were asked to hold the position until the target disappeared. Participants completed a set of practice trials before the MEG recordings to ensure familiarity with the instruction cues and pace of the task.

2.5 MEG and MRI acquisition

Neuromagnetic activity was measured with a CTF-OMEGA 275-channel (first-order gradiometers) whole-head magnetometer (VSM MedTech, Ltd., Canada) in a magnetically-shielded room (Vacuumschmelze, Germany) using synthetic third gradient balancing for active noise cancellation. Magnetic flux density was digitized at a 1200 Hz rate with a bandwidth of 0–300 Hz and notch filter at 60 Hz. Fiducial coils were attached to the nasion and right and left preauricular sites. Digital photographs were taken of each coil's position. Coils were energized continuously to provide real-time head position in the dewar for later co-registration with the anatomical MRI. Participants who deviated more than 5 mm from their initial head position were excluded. One run of one participant was discarded for this reason. MRIs were obtained in a separate session using a 3-Tesla whole-body scanner (GE Signa, WI, USA). A high resolution T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) anatomical image (162 sagittal slices, slice thickness = 1 mm, TR = 7.24 ms, TE = 2.7 ms, matrix = 256×256) was obtained from each participant with radiological markers (IZI Medical Products Corp, MD, USA) attached to the same three fiducial sites indicated by the digital photographs. Relative distances among the MEG coils and those among the fiducial MRI markers did not deviate more than 5 mm.

2.6 Eye-tracking and scoring

We aimed a charge-coupled device (CCD) camera (Hitachi KP-M2RN, Japan), equipped with a 60–300 mm lens (Soligor, Japan) and infrared light filter, at the left eye. Eye tracking was digitized at 60 Hz using commercial software (iView X 1.03, SensoMotorics Instruments, Germany); this sampling rate is sufficient for accurate calculation of saccade peak velocity (Wierds et al., 2008) and simple metrics such as onset latency. An automated 9-point calibration procedure was performed before initial head localization to ensure eye movement accuracy at the beginning of each run. For this standard calibration, nine evenly distributed points on the screen are presented sequentially. The calibration proceeds after accurate fixation of each point.

Saccades were scored manually off-line using Matlab 7 (Mathworks Inc, MA, USA) by one experimenter (SCM) who was blind to the experimental conditions (for similar methods, see Jackson et al., 2007; Mueller et al., 2009). A saccade was scored as incorrect if it started off in the wrong direction and was subsequently self-corrected or if it was executed in the wrong direction and fixation maintained there until the end of the trial. Trials with saccade onset latencies less than 80 ms were considered anticipatory responses, and trials with onset latencies of more than 600 ms were considered delayed responses. Both were removed from analysis. In addition, trials with eye blinks before the critical saccade, trials with no saccades, or trials in which gazes were directed off the screen were excluded from analysis (13.1% total). Finally, one run of two participants was discarded due to significant ocular artifacts, and analyses for these two participants were carried out on the one run of remaining data. Mean saccade onset latency data were $\log_{10}$ -transformed to reduce moderate positive skew in the raw mean data. Preliminary analyses did not reveal gender differences in saccade performance; thus, gender is not considered further.

2.7 Heart-rate analysis

Electrocardiographic (ECG) recordings were taken continuously. We extracted the first 5 s of each context (and 250 ms before context onset) to calculate change in heart rate to the context onset before the first saccades were performed. The ECG was converted by linear interpolation to instantaneous inter-beat interval values with a 4 Hz sampling rate.

2.8 Time-frequency analyses

The Stockwell transform, a generalization of the Fourier transform (Stockwell et al., 1996), was applied to raw MEG sensor data to determine the dominant spectral changes occurring in the 1-s interval between the onset of the instruction cue and the onset of the target. Custom software (freely available at <http://kurage.nimh.nih.gov>) was used for Stockwell analyses and plotting. For plotting, these data were normalized to a 1-s baseline window immediately preceding instruction cue onset.

2.9 Synthetic Aperture Magnetometry (SAM)

SAM is a minimum-variance adaptive beamformer algorithm for estimating source power within specific time and frequency windows across the brain with no *a priori* assumptions about the number of active sources or their spatial locations (Hillebrand et al., 2005; Robinson & Vrba, 1999; Vrba & Robinson, 2001). In general, source space is parsed into a 3-dimensional grid with an optimum spatial filter specified at each grid point from the signal covariance of unaveraged sensor data. Interfering sources, neural as well as artifactual ones of ocular and muscular origin, are suppressed by minimizing the output of the spatial filter. Signal from the target location is, however, retained by constraining the lower bound of minimization to unity gain for a current dipolar source. This is obtained by calculating the biomagnetic forward solution, using the normalized vector formulation of Sekihara et al. (2001), with a multiple-sphere source-space model (derived from the anatomical MRIs). SAM source activations and functional MRI activations have been demonstrated to be highly spatially congruent within the same experimental paradigms (Singh et al., 2002; Schultz et al., 2004). Adaptive beamformer methods also reliably detect signals from deeper brain structures such as the amygdala (Cornwell et al., 2008a; Hung et al., 2010; Maratos et al., 2009), hippocampus (Cornwell et al., 2008c; Quraan et al., 2011) and cerebellum (Hashimoto et al., 2003).

SAM analyses were carried out on trials in which a correct pro-saccade or correct anti-saccade was executed. Trials containing shocks were excluded from analysis. Error trial counts were too low to perform SAM analyses (mean < 15 trials) and were consequently not investigated further. There were also too few trials to perform SAM analyses separately for switch vs. repeat trials. Raw data were filtered in the relevant frequency band (4–8 Hz for theta, 8–12 Hz for alpha, and 14–30 Hz for beta) and signal covariance was calculated from and power was integrated over the whole 1 s fixed interval between instruction cue onset and peripheral target onset, as participants kept a central fixation. Contrasts were made between power during this preparatory time window and power during a 1-s pre-instruction cue baseline window, when participants were also fixated centrally but had not yet received trial instructions. This dual-state (active-vs-control) analysis yields a metric of relative power (pseudo-F ratio) in which noise is factored out under the assumption that the beamformer projects the same level of noise for active and control windows. Each individual SAM source image consisted of a volume of pseudo-F power ratios with a spatial sampling or grid-spacing of 5 mm (voxel size = 5 mm³).

2.10 Group Statistical Analyses

Using AFNI (Cox, 1996), anatomical MRIs were manually spatially warped to a Talairach brain template. Individual SAM images for each condition and frequency were similarly warped using the same warping parameters and within-volume normalized by the standard deviation of pseudo-F values. The latter procedure was performed to limit the influence of global power on local power in a particular brain region. SAM source images for each run were averaged within participants. Spherical masks with 8-mm radii were centered at Talairach coordinates obtained from previous studies to estimate theta, alpha and beta power within regions of interest (ROIs). We also used spherical masks with 12-mm and 16-mm radii centered at the same coordinates in order to account for MRI-MEG coregistration errors and anatomical variability between participants that might exceed 8 mm. These larger masks yielded the same pattern of significant activations as the 8-mm masks, and are therefore not reported.

One set of ROIs, comprising the primary dorsal cortical network mediating volitional control of saccades, was obtained from an fMRI study of visually-guided saccades (Luna et al., 1998): bilateral frontal eye fields (inferior FEF, center for left: -52, 0, 37; center for right: 48, -5, 44; superior FEF, center for left: -25, -12, 53; center for right: 38, -9, 55), supplementary eye fields (SEF, center: 0, 0, 51) and bilateral inferior parietal cortices (IPC, center for left: -31, -41, 40; center for right: 50, -42, 46). A second set, which included additional cortical structures implicated in anti-saccade execution, was obtained from an fMRI study that used a modified anti-saccade task that placed greater demand on inhibitory processes (Chikazoe et al., 2008): bilateral dorsolateral prefrontal cortices (DLPFC, center: $\pm 38, 36, 26$) and right dorsal anterior cingulate (dACC, center: 10, 32, 28). We also used coordinates from Chikazoe et al. (2008) to define two right-lateralized ventral cortical structures mediating stimulus-driven attention (Corbetta et al., 2008): right ventrolateral prefrontal cortex (VLPFC, center: 36, 18 -4) and right temporo-parietal junction (TPJ, center: 58, -44, 20). Finally, a single mask encompassing the superior colliculi was defined by coordinates from a high-resolution fMRI study of the human superior colliculi (Schneider & Kastner, 2005; center: 0, -28, 1).

Theta, alpha and beta power for each ROI was averaged across the mask and extracted for group-level analyses in SPSS. For bilateral dorsal cortical ROIs (FEF, IPC, DLPFC), three-way repeated-measures ANOVAs were performed, with Context (safe, threat), Saccade type (pro-saccade, anti-saccade) and Hemisphere (left, right) as factors. There was no Hemisphere factor for ventral cortical ROIs (right IFG, right TPJ) and midline ROIs (SEF, right dACC, superior colliculi).

2.11 Virtual sensor time-frequency analyses

For ROIs showing contextually-modulated power, we explored its stability over the 1-s preparatory interval by projecting their virtual sensor time series and performing Stockwell time-frequency analyses on these data. Virtual sensor time series were created from the weighted sum of sensor data using the SAM beamformer weights for voxels of interest. The standardized spatial coordinates of each voxel contained in each ROI (16–18 voxels for 8-mm radii spheres) were reversed-transformed to individual-subject space. One set of beamformer weights, derived from a 1–50 Hz frequency window for covariance estimation, was used for reconstruction at each spatial location. The use of a broad-band for covariance estimation avoids possible bias introduced by narrow-band filtering in reconstructing the frequency characteristics of a signal. Time-frequency data were averaged for voxels within an ROI and normalized to the 1-s baseline window immediately preceding the 1-s preparatory interval. Signal power was compared for threat and safe contexts using nonparametric Wilcoxon signed-ranked tests.

2.12 Single-state baseline SAM analyses

For the main analyses, ROI activations were defined by power changes during the 1-s preparatory interval relative to the pre-instruction cue baseline interval (i.e., pseudo-F ratio). Because the magnitude of frequency-specific power during this baseline interval may differ between threat and safe contexts, we performed single-state SAM analyses on the pre-instruction cue baseline interval. Using the same filtering for covariance estimation (4–8 Hz, 8–12 Hz, and 14–30 Hz), voxel-wise power was estimated for each condition without noise normalization (i.e., neural activity index). The same ROI extraction procedures were used, except that we restricted group analyses to only those ROIs showing contextually-modulated power from the main SAM analyses. Baseline power for threat and safe contexts were compared with paired *t* tests.

2.13 Secondary SAMerf analyses

In an effort to establish that contextually-modulated theta activity was induced or non-phase-locked to the instruction cue, we performed secondary analyses with a variant of the SAM algorithm (SAMerf, Robinson, 2004). Like traditional SAM, SAMerf also uses covariance over unaveraged epochs for source reconstruction. The difference is that before estimating source power with SAMerf, a virtual sensor time series is projected from a given source, from beamformer weights derived from the same normalized vector formulation (Sekihara et al., 2001), and then averaged in the time domain. From this last step, non-phase-locked activity is attenuated and source power reflects the phase-locked evoked response (for a similar approach, see Cornwell et al., 2008a). We used the same filtering parameters (4–8 Hz) and temporal windows for covariance calculations as in the main SAM analyses, contrasting phase-locked theta power in the 1-s preparatory interval to phase-locked theta power in a 1-s baseline window before instruction cue onset. These ratios were $\log_{10}$ transformed, and then within-volume normalized by the standard deviation. The same ROI extraction procedures were used, but we restricted group analyses to only those ROIs showing contextually-modulated theta activity from the main SAM analyses.

3. Results

3.1 Subjective and physiological arousal

Higher mean subjective anxiety was reported for Threat (Mean $\pm$ SD, 4.96 ± 1.84 AU) relative to Safe (1.87 ± 1.36 AU), $t_{(16)} = 6.99$, $p < .001$. In addition, there was a greater mean change in heart rate following onset of Threat (2.89 ± 2.18 bpm) compared to Safe (1.90 ± 2.84 bpm), $t_{(16)} = 2.21$, $p = .04$.

3.2 Saccade performance

Mean raw onset latencies and error rate data are presented in Table 1. For $\log_{10}$ -transformed mean (correct) saccade onset latencies, a $2 \times 2 \times 2$ repeated-measures ANOVA, with Context (safe, threat), Saccade (pro-saccade, anti-saccade) and Switch (switch, repeat) as factors revealed significant two-way interactions between Context and Saccade, $F_{(1,16)} = 11.54$, $p = .004$, and between Saccade and Switch, $F_{(1,16)} = 8.29$, $p = .01$. No other interactions, including a three-way interaction, were significant, $F_s < 1$. Main effects were found for Saccade, $F_{(1,16)} = 106.68$, $p < .001$, and Switch, $F_{(1,16)} = 7.53$, $p = .01$, but not for Context, $F < 1$.

Separately, we also determined by procedures described by Keppel and Wickens (2004) that there was a significant main effect of practice, $F_{(1,16)} = 5.76$, $p = .03$. Direct comparisons between contexts were therefore adjusted for practice effects. Regarding the Context-by-Saccade interaction, simple effect analyses showed that *anti-saccades were initiated more slowly* during Threat than Safe, $F_{(1,15)} = 4.52$, $p = .05$, but there was no difference in

initiating pro-saccades, $F_{(1,15)} = 2.50$, *ns*. Medium effect sizes were obtained in both cases: for correct anti-saccade latencies, Cohen's $d = .53$ and for correct pro-saccade latencies, Cohen's $d = -.40$. Regarding the Saccade-by-Switch interaction, simple effect analyses revealed that anti-saccades were faster after a pro-saccade trial than after an anti-saccade trial, $F_{(1,16)} = 15.31$, $p = .001$; there was no difference in pro-saccade latencies on switch vs. repeat trials, $F < 1$.

For mean error rates, a $2 \times 2 \times 2$ repeated-measures ANOVA revealed a main effect of Saccade, $F_{(1, 16)} = 26.55$, $p < .001$. No other main effects or interactions were found. Although an interaction between Context and Saccade on mean error rates did not emerge, sample means showed a similar pattern to mean saccade onset latencies (Table 1). A speed-accuracy tradeoff between contexts is not evident based on this similar pattern.

We also determined whether *erroneously* executed pro-saccades on trials calling for an anti-saccade were initiated faster during Threat relative to Safe. This is important in that erroneous pro-saccades are stimulus-driven actions like volitional pro-saccades, and should also be facilitated under threat-induced anxiety. A paired t test of $\log_{10}$ -transformed mean saccade onset latencies revealed that erroneous pro-saccades were initiated faster during Threat (raw mean $\pm$ SD, 244 ± 29 ms) than Safe (raw mean $\pm$ SD, 261 ± 35 ms), $t_{(16)} = -3.08$, $p = .007$, Cohen's $d = -.75$. An insufficient number of *erroneously* executed anti-saccades occurred on trials calling for a pro-saccade and were therefore not analyzed.

3.3 Exploratory correlations among anxiety and performance variables

Exploratory nonparametric correlation analyses were conducted on differential (Threat – Safe) values for subjective anxiety, heart rate and saccade performance variables. A step-down modified-Bonferroni approach was used to control familywise alpha at .05 (Rom, 1990). Two significant correlations were observed. First, differential heart rate was negatively correlated with differential onset latency for correct pro-saccades, $r_{s(15)} = -.61$, $p = .01$, indicating that greater differential change in heart rate at threat onset was associated with faster correct pro-saccades under threat. Second, differential onset latency for correct anti-saccades was negatively correlated with differential onset latency for erroneous pro-saccades, $r_{s(15)} = -.55$, $p = .022$, indicating that, on trials calling for anti-saccades, faster erroneous pro-saccades were associated with slower correct anti-saccades.

3.4 Time-frequency analyses of raw sensor data

Stockwell time-frequency plots are presented in Figure 2, averaged across sensors (i.e., axial gradiometers) positioned approximately over frontal, temporal, central, parietal and occipital cortical regions. Spectral changes associated with instruction cue onset on correct trials during Safe and Threat were observed in theta (~6Hz), alpha (~9Hz) and beta bands (~18Hz). These changes were broadly distributed across the sensor array, but appear particularly prominent over the right hemisphere. Whereas theta power increased during this interval, most notably in temporal and central sensors, alpha and beta power predominantly decreased. Alpha and beta power decreases were particularly prominent in central, parietal and occipital sensors, and appear more sustained across the 1-s preparatory interval on anti-saccade compared to pro-saccade trials. There were, however, instances of increased alpha and beta power, particularly in frontal sensors. From these plots, we defined our frequency bands of interest for source analyses: 4–8 Hz for theta, 8–12 Hz for alpha and 14–30 Hz for beta.

3.5 ROI-based theta activity (4–8Hz)

Two ROIs exhibited contextually-modulated theta activity. In the *right VLPFC* ROI, there was a significant Context-by-Saccade interaction, $F_{(1,16)} = 9.12$, $p = .008$, with greater theta

power increases preceding anti-saccades during Threat compared to Safe, $F_{(1,16)} = 15.08$, $p = .001$, but no difference in theta activity preceding pro-saccades, $F < 1$ (Figure 3). In the *superior colliculi* ROI, there was a significant Context-by-Saccade interaction, $F_{(1,16)} = 15.20$, $p = .001$, with greater theta power increases preceding anti-saccades during THREAT compared to SAFE, $F_{(1,16)} = 10.80$, $p = .005$, but no difference in theta power preceding pro-saccades, $F < 1$ (Figure 3). Single-state SAM analyses of baseline theta power did not reveal differences between Threat and Safe in either the right VLPFC or superior colliculi ROIs. No other regions that were explored – including bilateral superior FEF, bilateral inferior FEF, bilateral IPC, bilateral DLPFC, SEF, right TPJ, and right dACC – exhibited contextually-modulated theta differences.

For the right VLPFC and superior colliculi ROIs in which contextually-modulated theta was observed selectively on anti-saccade trials, we also looked secondarily at differences in phase-locked theta power using SAMerf analyses (Robinson, 2004). Two-way ANOVAs for each ROI on phase-locked theta power did not reveal any significant effects. The lack of differences in phase-locked power suggest that theta increases in right VLPFC and superior colliculi ROIs were induced or non-phase-locked to the instruction cue.

3.6 ROI-based alpha activity (8–12Hz)

One ROI exhibited contextually-modulated alpha activity. In the *bilateral inferior FEF* ROI, there was a significant Context-by-Saccade-by-Hemisphere interaction, $F_{(1,16)} = 5.89$, $p = .03$. Follow-up two-way ANOVAs for each hemisphere revealed a marginally significant Context-by-Saccade interaction in the left inferior FEF, $F_{(1,16)} = 3.61$, $p = .08$, but not in the right inferior FEF, $F < 1$. Simple effect analyses for the left inferior FEF did not reveal a difference in alpha power between contexts on anti-saccade trials, $F_{(1,16)} = 2.68$, *ns*, nor on pro-saccade trials, $F_{(1,16)} = 1.26$, *ns*. Single-state SAM analyses did not reveal differences in alpha power during the pre-instruction cue baseline period between Threat and Safe in the bilateral inferior FEF. No other regions that were explored exhibited contextually-modulated differences in alpha power.

3.7 ROI-based beta activity (14–30Hz)

Two ROIs exhibited contextually-modulated beta power. In the *bilateral inferior FEF* ROI, there was a main effect of Context, $F_{(1,16)} = 4.55$, $p = .05$, with greater beta power decreases during Safe compared to Threat (Figure 4). No other effects approached significance. Single-state SAM analyses did reveal significantly greater beta power during the pre-instruction cue baseline period during Safe compared to Threat, $t_{16} = 2.12$, $p = .05$. In the *bilateral IPC* ROI, the Context-by-Saccade interaction on beta activity was significant, $F_{(1,16)} = 6.38$, $p = .02$, with statistical trends toward greater beta power decreases during Threat compared to safe on pro-saccade trials, $F_{(1,16)} = 4.10$, $p = .06$, and toward greater beta power decreases during SAFE on anti-saccade trials, $F_{(1,16)} = 3.79$, $p = .07$ (Figure 4). In addition, left IPC showed greater beta power decreases than right IPC, $F_{(1,16)} = 5.46$, $p = .03$. No other effects approached significance, and single-state SAM analyses of baseline beta power did not reveal differences between Threat and Safe in the bilateral IPC ROI. No other regions that were explored – including bilateral DLPFC, bilateral superior FEF, SEF, dACC, right VLPFC, right TPJ and superior colliculi – exhibited contextually-modulated differences in beta power.

4. Discussion

Our results confirm that threat of shock reliably elicits sustained anxiety, and they support its use as a means to examine the effects of state anxiety on neurocognitive processes. As expected, participants reported increased anxiety and showed increased heart rate under

threat relative to safety. Within this threat-induced anxiety state, both saccade performance and neural oscillatory activity preceding saccades were affected. Although threat of shock loomed equally large over all trials, saccade performance was not singularly impaired by anxiety. Flexible responding (correct anti-saccades) was impaired, but stimulus-driven responding (i.e., erroneous pro-saccades on anti-saccade trials) was enhanced. These behavioral data highlight the detrimental as well as potential beneficial effects of anxiety on cognitive-behavioral performance. Anxiety-related changes in neuromagnetic activity on anti-saccade trials emerged primarily in ventral brain structures involved in stimulus-driven attention. These findings suggest that reduced cognitive-behavioral flexibility related to anxiety may stem from increased stimulus-driven attention capture and the need to buffer against sensitized sensory-perceptual processes under threat (Baas et al., 2006; Cornwell et al., 2007; Vuilleumier & Dolan, 2007).

Saccade performance between contexts strongly depended on the type of saccade initiated, but the results are somewhat ambiguous regarding whether this interaction was driven only by a hindering effect of anxiety on anti-saccade performance, or also a facilitating effect of anxiety on pro-saccade performance (Table 1). Slower initiation of correct anti-saccades under threat is consistent with previous studies associating individual differences in high trait anxiety with poorer anti-saccade performance (Ansari et al., 2008; Derakshan et al., 2009; Jazbec et al., 2005; Wieser et al., 2009; but see Ettinger et al., 2005). Lacking is clear evidence for faster volitional initiation of correct pro-saccades under threat; greater cardiac responses at threat onset were associated with faster onset latencies, indicating a possible link between anxious arousal and enhanced stimulus-driven responding. Notably, an analysis of error trials revealed that pro-saccades on trials calling for an anti-saccade were initiated faster under threat. Given that these erroneous pro-saccades are thought to be reflexive (Munoz & Everling, 2004), faster responding here directly supports the hypothesis that stimulus-driven actions are facilitated under anxiety. Altogether, the data appear to support the presence of both negative and positive effects of anxiety on saccade performance. It should be recognized that because saccade performance was not *generally* disrupted under threat (also see Cornwell et al., 2011; Shackman et al., 2006), it is unlikely that these results are better explained by participants' dividing their attention more during threat than safety. Thus, threat-induced anxiety may therefore impede novel, flexible actions as a consequence of enhancing habitual, stimulus-driven actions; that this latter effect is primary is supported by its large effect size (Cohen's $d = -.75$).

In exploratory correlation analyses, we observed that individual differences in the effects of threat-induced anxiety on erroneous pro-saccade latencies and correct anti-saccade latencies were inversely correlated, contrary to the dissociation, noted previously, between these variables under non-threatening conditions (Klein, 2001). That is, faster erroneous pro-saccades under threat (relative to safety) were associated with slower correct anti-saccades under threat across individuals. This relationship may have important theoretical implications. Recent cognitive models of anti-saccade performance emphasize parallel response programming without the need for active inhibitory control over the stimulus-driven pro-saccade to successfully execute an anti-saccade (Massen, 2004; for a review see Hutton, 2008). These race models posit that suppression of an erroneous pro-saccade is achieved by local competitive integration processes (i.e., lateral inhibition) in the superior colliculus (Cutsuridis et al., 2007). Framed in this perspective, threat-induced anxiety introduces biased competition toward habitual responding, which should increase anti-saccade error rates but not necessarily slow correct anti-saccade onset latency. Yet, these effects are linked in the present data, indicating that in the process of dampening stimulus-driven processes to neutralize the facilitating effect of threat-induced anxiety, anti-saccades are also slowed. Whether this increased need of suppressing erroneous pro-saccades entails positing a supervisory (top-down) active inhibitory mechanism for anti-saccade performance

in the context of heightened stimulus-driven responding will need to be considered in future work.

As a final note on the behavioral data, we also examined task switching effects on performance to determine any further impact of threat-induced anxiety on cognitive-behavioral flexibility. Task switching effects on anti-saccade performance were indeed present, with faster initiation of correct anti-saccades following pro-saccade trials (switch) compared to correct anti-saccades following anti-saccade trials (repeat). No such task-switching effects on pro-saccade performance were observed. This paradoxical improvement in anti-saccade performance following a switch has been reported previously (Ansari et al., 2008; Cherkasova et al., 2002; Manoach et al., 2002). Still, this benefit of task switching did not increase or decrease under threat. Given that shifting between tasks is considered a core executive function for maintaining cognitive-behavioral flexibility (Miyake et al., 2000), we can speculate from the absence of greater (or lesser) task switching effects under threat that threat-induced anxiety has limited consequences for prefrontal-mediated processes, as opposed to producing global dysfunction. The pattern of oscillatory activity associated with these cognitive-behavioral changes under threat of shock bolsters this conclusion.

Two regions exhibited greater theta (4–8Hz) activity preceding successful execution of anti-saccades during threat relative to safety: right VLPFC and superior colliculi (Figure 3). Right VLPFC has been implicated in executive control – specifically in response inhibition (Aron et al., 2004) – and found to be active in a modified anti-saccade task that increased demand on inhibitory processes (Chikazoe et al., 2008). A specific role for right VLPFC in response inhibition, however, is a matter of significant debate (Dodds et al., 2010; Hampshire et al., 2010; Sharp et al., 2010). Rather, this structure shows a response profile consistent with a general role in stimulus-driven attention (Asplund et al., 2010; Ettinger et al., 2008; Shulman et al., 2009). Likened to a ‘circuit breaker,’ the right VLPFC is thought to work in concert with the right TPJ to interrupt current attention for redirection to salient, behaviorally relevant stimuli (Corbetta & Shulman, 2002; Corbetta et al., 2008). Here we find that, under threat, theta activity increases while anti-saccades are being prepared, before stimulus presentation and before a specific response can be targeted for suppression. Altered right VLPFC activity may constrain stimulus-driven processes long enough to enable generation of an anti-saccade, without participating directly in the actual suppression of a reflexive pro-saccade. The fact that contextual modulation of theta was not observed on trials calling for pro-saccades supports this interpretation insofar as stimulus-driven processes are beneficial to executing pro-saccades, and therefore do not need to be dampened.

Increased theta activity preceding anti-saccades during threat was also evident in the superior colliculi, a central hub for saccade execution (Krebs et al., 2010; Munoz & Everling, 2004). Because of the relatively deep location of the superior colliculi, the plausibility of this finding merits consideration. Theta oscillations have been observed in collicular local field potentials in rodents (Routtenberg & Taub, 1973), suggesting that this structure displays coherent population activity at theta frequencies that could yield a net current vector large enough to be detectable by our whole-head array. Moreover, the MEG source reconstruction algorithm used here has captured theta activity in other deep brain structures, such as the amygdala and hippocampus, in their expected behavioral contexts (i.e., threatening faces for the amygdala vs. virtual spatial navigation for the hippocampus, Cornwell et al., 2008a; 2008c; Maratos et al., 2009; Quraan et al., 2010). Most importantly, spatially-selective differences in theta activity can be seen in the superior colliculi in several individual whole-brain maps as well as at the group level (Figure 5). Based on these considerations, we suggest that theta activity in the superior colliculi during saccade

preparation may, along with the right VLPFC, constrain stimulus-driven processes during threat. This interpretation is supported by evidence that low-frequency stimulation of collicular neurons delays saccades (Munoz & Wurtz, 1993), and, again, by the lack of modulation of theta on trials calling for pro-saccades when dampening stimulus-driven processes is not necessary.

Beyond its association with slower (correct) initiation of anti-saccades under threat, potential functional significance of *theta synchronization* can only be speculated. Neural oscillations can be conceptualized as alternating low and high neuronal excitability states (Schroeder & Lakatos, 2008). Neuronal populations embedded in this cyclical process are minimally receptive to and not likely perturbed by afferent (bottom-up) signals when in a low excitability state. This refractory period is quite protracted in the case of theta (half cycle = 63–125 ms for 4–8 Hz oscillations), and could therefore have significant consequences for executing rapid shifts of attention to a target stimulus. One potential clue comes from secondary source analyses, using a variant of the SAM algorithm (SAMerf, Robinson, 2004), that showed no effects of threat-induced anxiety on phase-locked theta power in this interval. This implies that theta synchronization in these structures was primarily induced or non-phase-locked to the instruction cue. Thus, induced theta may preset stimulus-driven mechanisms to a state of low excitability, the timing of which will vary across trials with respect to target onset because of its non-phase-locked nature. This could buffer against potentiated sensory-perceptual responses during threat-induced anxiety states. An analysis of instantaneous phase at target onset with a larger set of trials could test the hypothesis that theta phase variability in right VLPFC, for instance, correlates with error probability and/or predicts onset latency of correct anti-saccades.

Aside from theta synchronization, the other prominent oscillatory change preceding saccades that varied by context was beta (14–30Hz) activity in dorsal cortical regions, specifically bilateral FEF and bilateral IPC (Figure 4). The left FEF also evidenced contextually-modulated alpha activity, but the results are ambiguous in that effects are not apparent on pro-saccade or anti-saccade trials; the significance of alpha activity is not discussed further. Bilateral FEF exhibited greater beta desynchronization (i.e., more pronounced decreases in power) during safety compared to threat on pro- and anti-saccade trials rather than being selective for one type of saccade. However, it should be noted that bilateral FEF exhibited greater baseline beta activity during safety compared to threat. Thus, greater desynchronization in these structures during safe following the instruction cue may be influenced by these greater baseline values and should be interpreted cautiously.

In the case of bilateral IPC, relative beta power mirrored the pattern of saccade performance, with greater desynchronization preceding pro-saccades during threat and a trend toward greater desynchronization preceding anti-saccades during safety. Engel and Fries (2010) have recently proposed that the function of beta oscillations is to maintain the current sensorimotor or cognitive state. From this perspective, beta synchronization reflects active maintenance of the current state, while beta desynchronization reflects transition between states. In the present context, stronger beta desynchronization on trials calling for a task switch would support this hypothesis, but too few trials allowed us to consider this variable in our source analyses and test this prediction. Nevertheless, beta desynchronization within bilateral FEF and IPC – critical nodes mediating volitional saccades (Munoz & Everling, 2004) and goal-directed attention (Corbetta et al., 2008) – could also reflect the transition from actively maintaining fixation to a readiness to trigger a saccade (or covert attention shift).

Considering bilateral FEF and bilateral IPC activity together, a potentially meaningful pattern of beta desynchronization emerges (Figure 4). Both regions show the same

differential pattern of beta desynchronization between contexts on anti-saccade trials (safe > threat); however, on pro-saccade trials, only the bilateral IPC shows greater beta desynchronization during threat than safety. This is important in light of evidence that the relative timing of frontal and parietal cortical neuronal activity is linked to goal-directed (or top-down) attention vs. stimulus-driven (or bottom-up) attention. Buschmann and Miller (2007) showed that goal-directed attention is associated with changes in frontal activity before parietal activity, while stimulus-driven attention is associated with changes in parietal activity before frontal activity. Beta desynchronization in bilateral IPC during pro-saccade preparation, and its relative absence in bilateral FEF, is therefore consistent with a bias toward stimulus-driven attention during threat. At the same time, these data also reflect a lack of recruitment of goal-directed attention mechanisms during threat compared to safety, particularly for anti-saccade preparation. Nevertheless, this could be merely a consequence of enhanced stimulus-driven attention mechanisms, and not necessarily indicative of inherent executive dysfunction. More research is needed to substantiate this claim.

4.1 Conclusion

It is clear from these data that anxiety has multifaceted effects on cognition and underlying brain processes. Threat-induced anxiety impaired flexible responding (anti-saccades) but enhanced stimulus-driven responding (pro-saccades), at least the kind thought to be reflexive (erroneous pro-saccades). Instead of pointing to inherent dysfunction of prefrontal-based executive mechanisms, evidence from MEG source analyses emphasizes the need to constrain stimulus-driven mechanisms – perhaps by presetting ventral cortical (right VLPFC) and midbrain structures (superior colliculi) to a low excitability state at target onset – in order to execute anti-saccades correctly. We contend that the preponderance of negative effects of anxiety on cognition recorded in the literature may be skewed by the kinds of cognitive-behavioral tasks that have been administered in the laboratory – typically those requiring atypical, arbitrary responses like the anti-saccade – rather than because of any fundamental conflict between anxiety and cognition. In the context of ambiguous, unpredictable threat, behavioral priorities are shifted to monitoring the environment for signs of imminent danger (Cornwell et al., submitted; Cornwell et al., 2008b; Grillon & Davis, 1997). For tasks that exploit this mode of attention, like executing pro-saccades or other habitual, reflexive actions, cognitive-behavioral performance will be improved. We suggest that a greater appreciation and characterization of functionally-adaptive changes that define anxiety, such as sensory-perceptual sensitization and enhanced stimulus-driven attention, will provide solid bedrock for understanding its pathological manifestations.

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Highlights

- Subjects performed a mixed-saccade task under anxiety-provoking conditions.
- Threat of shock impeded anti-saccades, but facilitated reflexive pro-saccades.
- Enhanced lateral frontal cortical theta preceded correct anti-saccades under threat.
- Parietal beta desynchronization preceded efficient saccade execution.
- Anxiety may reduce cognitive flexibility by promoting stimulus-driven responding.

Figure 1.

Representation of the experimental procedure. (a) Contexts defined by messages displayed at their onset for 5 s before the first saccade trial. Participants cycled between contexts 5x per run (2 runs) and performed 16 saccade trials (8 pro- and 8 anti-saccades) per iteration. (b) A schematic of two trials showing the progression from fixation stimulus to instruction cue to peripheral target stimulus. The instruction cue appeared in one of two colors indicating the type of saccade required when the target appears.

Figure 2.

Stockwell time-frequency plots of raw sensor data in the 1-s preparatory interval between instruction cue onset (time = 0) and target presentation (time = 1), as a function of Context (Threat vs. Safe) and Saccade (Pro- vs. Anti-saccade). Spectral data (1–50Hz) are averaged across sensors overlying frontal, temporal, central, parietal and occipital cortical regions for left and right hemispheres. Data in each plot are normalized to a 1-s baseline period (not shown) preceding the instruction cue and $\log_{10}$ transformed. Hot colors indicate increased power and cold colors indicate decreased power.

Figure 3.

Theta power preceding target presentation. Spherical masks (in red) depicting the right ventrolateral prefrontal cortical (VLPFC) and superior colliculi ROIs are overlaid on a standardized brain template. Bar graphs show normalized theta power (4–8Hz) as function of both Context and Saccade. Error bars represent SEMs. Stockwell time-frequency plots of reconstructed time series data from each ROI show the temporal course of theta power differences over the 1-s preparatory interval between Threat and Safe. Plots are thresholded at a nominal $p = .05$ based on nonparametric Wilcoxon signed-rank tests. Pro = pro-saccade, Anti = anti-saccade.

Figure 4.

Beta power preceding target presentation. Spherical masks (in red) depicting bilateral frontal eye fields (FEF) and bilateral inferior parietal cortices (IPC) ROIs are overlaid on a standardized brain template. Bar graphs show normalized beta power (14–30 Hz) as function of both Context and Saccade. Error bars represent SEMs. Stockwell time-frequency plots of reconstructed time series data from each ROI show the temporal course of beta power differences over the 1-s preparatory interval between Threat and Safe. Plots are thresholded at a nominal $p = .05$ based on nonparametric Wilcoxon signed-rank tests. Pro = pro-saccade, Anti = anti-saccade.

Figure 5.

Localization of superior collicular theta activity in whole-brain analyses. Single- subject images (S1–S4), overlaid on a standardized brain template along with the 8-mm spherical ROI used in the main analysis (blue ring), show local maxima in the left or right superior colliculus in the comparison of theta power between Threat and Safe on anti-saccade trials (normalized pseudo-F ratio difference). Each single-subject image is thresholded arbitrarily for visualization of local maxima. The group-level image ($N=17$) displays the Threat minus Safe contrast for anti-saccade trials (Student's t) thresholded at a nominal $p = .001$. Anti = anti-saccade.

Table 1

Mean ($\pm$ standard deviation) raw error rates, and saccade onset latencies for correct pro-saccades and anti-saccades.

Condition	Pro-saccade		Anti-saccade	
	Switch	Repeat	Switch	Repeat
<i>Onset latency (ms)</i>				
Safe	256 $\pm$ 33	254 $\pm$ 26	305 $\pm$ 31	318 $\pm$ 36
Threat	253 $\pm$ 28	249 $\pm$ 22	309 $\pm$ 26	322 $\pm$ 28
<i>Error rate (%)</i>				
Safe	11 $\pm$ 9	5 $\pm$ 8	21 $\pm$ 9	20 $\pm$ 15
Threat	9 $\pm$ 8	5 $\pm$ 8	22 $\pm$ 13	24 $\pm$ 16