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Brief Report

Perceptual load modulates anterior cingulate cortex response to threat distractors in generalized social anxiety disorder

Michael G. Wheaton[a], Daniel A. Fitzgerald[a,b], K. Luan Phan[a,b,c], Heide Klumpp[a,*]

[a] Mood and Anxiety Disorders Research Program, Department of Psychiatry (MGW, DAF, KLP, HK), University of Illinois at Chicago, Chicago, IL, USA
[b] Neuropsychiatric Research Program (DAF, KLP), Mental Health Service, Jesse Brown VA Medical Center, Chicago, IL, USA
[c] Departments of Psychology and Anatomy and Cell Biology, University of Illinois at Chicago, Chicago, IL, USA

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ABSTRACT

Generalized social anxiety disorder (gSAD) is associated with impoverished anterior cingulate cortex (ACC) engagement during attentional control. Attentional Control Theory proposes such deficiencies may be offset when demands on resources are increased to execute goals. To test the hypothesis attentional demands affect ACC response 23 patients with gSAD and 24 matched controls performed an fMRI task involving a target letter in a string of identical targets (low load) or a target letter in a mixed letter string (high load) superimposed on fearful, angry, and neutral face distractors. Regardless of load condition, groups were similar in accuracy and reaction time. Under low load gSAD patients showed deficient rostral ACC recruitment to fearful (vs. neutral) distractors. For high load, increased activation to fearful (vs. neutral) distractors was observed in gSAD suggesting a compensatory function. Results remained after controlling for group differences in depression level. Findings indicate perceptual demand modulates ACC in gSAD.

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1. Introduction

Generalized social anxiety disorder (gSAD) is characterized by pervasive fears of negative evaluation (APA, 2000) and attentional bias toward threat-relevant stimuli (Bögels & Mansell, 2004) making it difficult to ignore such stimuli even in the context of cognitively demanding tasks (Hope, Rapee, Heimberg, & Dombeck, 1990; Mattia, Heimberg, & Hope, 1993; Spector, Pecknold, & Libman, 2003). According to biased competition models of attention, sensory-driven emotional signals compete with task-relevant demands for resources in a limited-capacity processing system (Desimone & Duncan, 1995; Pessoa, McKenna, Gutierrez, & Ungerleider, 2002). What prevails, even if incongruent to cognitive aims, subsequently interacts with emotion-generating regions; therefore, prefrontal areas that modulate attentional deployment such as the anterior cingulate cortex (ACC) (Bush, Luu, & Posner, 2000; Etkin, Egner, & Kalisch, 2011) play a role in emotion generation and regulation (Ochsner, Silvres, & Buhle, 2012). Attentional bias is a proposed causal mechanism in maintaining anxiety that

is excessive (e.g., Mathews & MacLeod, 1994; Williams, Watts, MacLeod, & Mathews, 1997); consequently, it is important to elucidate mechanisms associated with bias to threat in gSAD.

When attending to threat faces, gSAD relative to healthy controls (HC), exhibit exaggerated activation in rostral ACC (rACC) (Amir et al., 2005; Blair et al., 2008) and subgenual ACC (Goldin, Manber, Hakimi, Canli, & Gross, 2009) indicative of aberrant emotion regulation (Etkin et al., 2011); exaggerated dorsal ACC (dACC) (Phan, Fitzgerald, Nathan, & Tancer, 2006) signifying heightened appraisal or reactivity to threat (Etkin et al., 2011); as well as hyperactivation in key limbic emotion regions (e.g., amygdala, anterior insula; Freitas-Ferrari et al., 2010).

Regarding attentional control, we found less rACC engagement in gSAD relative to HC when attention was directed to shapes in a simple task comprising images of face distractors alongside shapes, but no limbic-related group effects (Klumpp, Post, Angstadt, Fitzgerald, & Phan, 2013). Results suggest a failure to optimally resolve emotional interference in gSAD. Similarly, Blair et al. (2012) observed hypo-activation in the dACC in gSAD participants during an attentional control task also without accompanying differential limbic activation. The dACC is involved in conflict monitoring and action initiation to cognitive demands (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Bush et al., 2000; Srinivasan et al., 2013). Thus, a lack of dACC engagement in gSAD indicates a deficiency in controlled cognitive processes.

* Corresponding author at: Department of Psychiatry, University of Illinois at Chicago, 1747 W. Roosevelt Rd, Chicago, IL 60608, USA. Tel.: +1 312 996 0416; fax: +1 312 413 1703.
E-mail address: hklumpp@psych.uic.edu (H. Klumpp).

The general finding of impoverished ACC recruitment in gSAD when top-down control is required is consistent with Attentional Control Theory (ACT), in which the failure of anxious individuals to inhibit task-irrelevant stimuli is due to cognitive efficiency deficits (Eysenck, Derakshan, Santos, & Calvo, 2007). Yet, ACT also proposes anxiety-related impairment can be counteracted when a task is particularly challenging to execute, though at the cost of recruiting more resources. For example, in an emotional Stroop task, high-trait anxious individuals have shown greater dACC activity than low-trait anxious individuals during high-conflict incongruent trials, relative to congruent trials (Krug & Carter, 2010). However, Stroop-related dACC recruitment reflects a late-stage selection process (Silton et al., 2010) and attentional bias to threat in anxious individuals is thought to be somewhat involuntary (Mathews & MacLeod, 1994; Williams et al., 1997) as evinced by the fact that paradigms commonly employed are low in cognitive load (Freitas-Ferrari et al., 2010).

Early stages of attention are modulated by load on attentional resources (O'Connor, Fukui, Pinsk, & Kastner, 2002); thus, varying perceptual load in gSAD may capture ACC responses according to ACT. In a study by Bishop, Jenkins, & Lawrence (2007), load was manipulated to place varying (high/low) demands on attention resources. Anxiety level and dACC activity to fearful face distractors were inversely related in high-trait anxious individuals *but only* under low load (with a non-significant trend towards the same finding in rACC). Furthermore, state anxiety positively correlated with amygdala response under low, but not high load. In spider-phobia, phobic individuals showed greater amygdala reactivity to distracting spider images than HC regardless of load but no ACC group effects were found (Straube, Lipka, Sauer, Mothes-Lasch, & Miltner, 2011). These mixed results may be due in part to a subclinical sample (Bishop, 2007) and perceptual differences when supplanting fearful faces with spider images (Straube et al., 2011).

To our knowledge the modulation of varied perceptual load on ACC in gSAD is not known despite its potential to expand our understanding of attentional bias mechanisms that may not be detected with behavioral measures (e.g., accuracy, reaction time) particularly when compensatory functions occur. Therefore, we employed a paradigm similar to Bishop et al. (2007). Under low perceptual load, we hypothesized that relative to HC, gSAD would show less rACC recruitment and under high load, greater dACC activation. We also explored whether amygdala and/or anterior insula activation to threat distractors would be greater in gSAD to HC.

2. Method

2.1. Participants

All participants provided written informed consent as approved by the local Institutional Review Board. The gSAD group encompassed 23 individuals (69.6% female) with a mean age of 26.1 ± 6.7 years who met criteria for gSAD as determined by the Structured Clinical Interview for DSM-IV (First, Spitzer, Williams, & Gibbon, 1995). Co-morbidities were specific phobia ($n = 3$), generalized anxiety disorder ($n = 2$), and obsessive-compulsive disorder ($n = 1$). Exclusionary criteria included current or recent (within last 6 months) major depressive disorder or substance abuse. The HC group comprised 24 individuals (54.2% female) with an average age of 25.0 ± 5.6 years. The Liebowitz Social Anxiety Scale, which comprises a total score derived by adding fear and avoidance sub-scores (Liebowitz, 1987), Spielberger State-Trait Anxiety Inventory (Spielberger, 1983) and Beck Depression Inventory (Beck, Steer, & Brown, 1996) were used to evaluate symptom severity, trait anxiety, and depression levels, respectively. Greater symptom severity was evident in the gSAD ($M = 70.7 \pm 15.1$) than HC group

($M = 6.8 \pm 5.6$), $t(44) = 19.4$, $p < 0.001$. Similarly, the gSAD group had greater trait anxiety ($M = 52.3 \pm 9.9$) and depression ($M = 11.8 \pm 8.1$) levels than the HC group ($M = 26.2 \pm 4.5$; $M = 0.8 \pm 1.1$); $t(44) = 11.6$, $p < 0.001$, $t(44) = 6.6$, $p < .001$, respectively. The groups were similar in age, years of education, ethnicity, and gender (all $p_s > 0.2$). All participants were right-handed and free of major medical or neurologic illness.

2.2. Task

During fMRI, participants completed a task modeled on Bishop et al. (2007), which also included angry face distractors, as anger and fear have been shown to differentially perturb emotion processing circuitry (Whalen et al., 2001). Participants viewed a string of six letters superimposed on a task-irrelevant face distractor and had to identify target letters (N or X). In *low perceptual load* trials, the string was comprised entirely of target letters; under *high perceptual load*, the string included a single target letter and five non-target letters (H, K, M, W, Z) arranged in randomized order. Distractor faces were from a standardized set of photographs and consisted of fearful, angry, and neutral expressions from 8 different individuals (Ekman & Friesen, 1976). The experiment involved two image acquisition runs, each comprising 12 blocks of 5 trials. A mixed block/event-related design was employed whereby perceptual load (low vs. high) varied across blocks and facial expression (fearful, angry, neutral) varied within blocks on a trial-by-trial basis. Images were presented for 200 ms followed by a fixation cross presented for 1800 ms; participants were asked to respond by button press as quickly and accurately as possible. Within blocks, trials were separated by a jittered interstimulus interval lasting 2–6 s; trials between blocks were separated by 4–8 s.

2.3. Functional imaging

Imaging was performed with blood-oxygen level-dependent (BOLD) sensitive whole-brain fMRI on a 3.0 Tesla GE Signa System (General Electric; Milwaukee, WI) using a standard radio frequency coil. Images were acquired with 30 axial, 5-mm-thick slices using a standard T2*-sensitive gradient echo reverse spiral acquisition sequence (2000 ms TR; 25 ms TE; 64×64 matrix; 24 cm FOV; 77° flip angle). For anatomical localization, a high-resolution, T1-weighted volumetric anatomical scan was acquired. Data were analyzed using the Statistical Parametric Mapping (SPM8) software package (Wellcome Trust Centre for Neuroimaging, London; www.fil.ion.ucl.ac.uk/spm) using standard preprocessing steps. Briefly, images were temporally corrected to account for differences in slice time collection, spatially realigned to the first image of the first run, normalized to a Montreal Neurological Institute (MNI) template, resampled to $2\,mm \times 2\,mm \times 2\,mm$ voxels, and smoothed with an 8 mm isotropic Gaussian kernel.

A general linear model was applied to the time series, convolved with the canonical hemodynamic response function and with a 128 s high-pass filter. Blocks of low and high perceptual load were modeled separately based on task-irrelevant face type (fearful, angry, neutral) resulting in six regressors (fearful low, fearful high, angry low, angry high, neutral low, neutral high), the effects of which were estimated for each voxel for each participant and taken to the second level for random effects analysis.

In SPM8, we performed separate 2 (Group: gSAD, HC) $\times$ 2 (Face Type: threat, neutral) $\times$ 2 (Load: low, high) ANOVAs for fearful (vs. neutral) and angry (vs. neutral) faces. To test hypotheses, anatomically derived regions of interest (ROI) from the Automated Anatomical Labeling (AAL) toolbox based on the atlas of Tzourio-Mazoyer et al. (2002) were used to examine group effects in ACC, amygdala, and anterior insula. To examine ACC and insula sub-regions, the rostral ACC was created by taking the AAL ACC below