Journal of Affective Disorders 209 (2017) 23–29

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Altered time course of amygdala activation during speech anticipation in social anxiety disorder

Carolyn D. Davies[a], Katherine Young[a], Jared B. Torre[a], Lisa J. Burklund[a,b], Philippe R. Goldin[c], Lily A. Brown[a], Andrea N. Niles[a], Matthew D. Lieberman[a], Michelle G. Craske[a,*]

[a] Department of Psychology, University of California, Los Angeles (UCLA), Los Angeles, CA, USA
[b] Defense Group Inc, USA
[c] Betty Irene Moore School of Nursing, University of California, Davis, USA

ARTICLE INFO

Keywords:
Social anxiety disorder
Anticipation
fMRI
Amygdala
Public speaking

ABSTRACT

Background: Exaggerated anticipatory anxiety is common in social anxiety disorder (SAD). Neuroimaging studies have revealed altered neural activity in response to social stimuli in SAD, but fewer studies have examined neural activity during anticipation of feared social stimuli in SAD. The current study examined the time course and magnitude of activity in threat processing brain regions during speech anticipation in socially anxious individuals and healthy controls (HC).

Method: Participants (SAD n=58; HC n=16) underwent functional magnetic resonance imaging (fMRI) during which they completed a 90 s control anticipation task and 90 s speech anticipation task. Repeated measures multi-level modeling analyses were used to examine group differences in time course activity during speech vs. control anticipation for regions of interest, including bilateral amygdala, insula, ventral striatum, and dorsal anterior cingulate cortex.

Results: The time course of amygdala activity was more prolonged and less variable throughout speech anticipation in SAD participants compared to HCs, whereas the overall magnitude of amygdala response did not differ between groups. Magnitude and time course of activity was largely similar between groups across other regions of interest.

Limitations: Analyses were restricted to regions of interest and task order was the same across participants due to the nature of deception instructions.

Conclusions: Sustained amygdala time course during anticipation may uniquely reflect heightened detection of threat or deficits in emotion regulation in socially anxious individuals. Findings highlight the importance of examining temporal dynamics of amygdala responding.

1. Introduction

Excessive anxiety in both the presence and anticipation of social situations is a central feature of social anxiety disorder (SAD). Exaggerated anticipatory anxiety can lead socially anxious individuals to avoid social situations or engage in safety behaviors, thus maintaining SAD symptoms by preventing new learning and reinforcing the maladaptive belief that social apprehension is warranted (Hofmann, 2007; Wells et al., 1995). Cognitive models of SAD posit that socially anxious individuals engage in negatively biased anticipatory processing prior to entering social situations (e.g., expecting a negative outcome from an interaction), which enhances anxiety and increases avoidance behaviors (Clark and Wells, 1995; Hinrichsen and Clark, 2003). Given the role of anticipatory anxiety as a maintenance factor for SAD, it is important to better understand the neural bases of anticipatory processing in social anxiety.

Studies of the functional neuroanatomy of anxiety and emotional reactivity in SAD have revealed altered neural activity in response to social stimuli, including heightened amygdala responses to harsh (e.g., angry, disgusted) faces compared to happy faces (Phan et al., 2006; Stein et al., 2002), exaggerated amygdala reactivity to harsh faces compared to healthy controls (e.g., Klumpp et al., 2010), and greater amygdala and insula activity in response to faces with angry expressions compared to neutral ones (Straube et al., 2004). Indeed, amygdala and insula regions frequently show hyperactivation across provocation and affective processing study designs in individuals with anxiety disorders, including SAD (Etkin and Wager, 2007; Miskovic and Schmidt, 2012). In addition to amygdala and insula, anterior

* Corresponding author.
E-mail address: craske@psych.ucla.edu (M.G. Craske).

http://dx.doi.org/10.1016/j.jad.2016.11.014
Received 26 June 2016; Accepted 14 November 2016
Available online 16 November 2016
0165-0327/

cingulate cortex and medial prefrontal cortex regions are also implicated in fear and anxiety neural circuitry (Etkin, 2012), and SAD individuals exhibit altered functioning in these areas in response to threatening or negative stimuli (Brühl et al., 2014). Specifically, studies largely show increased activity in anterior cingulate regions (e.g., Amir et al., 2005; Labuschagne et al., 2012; Phan et al., 2006; but see Pujol et al., 2013) and medial prefrontal cortex areas (e.g., Stein et al., 2002; Straube et al., 2004; Labuschagne et al., 2012) compared to controls, consistent with evidence for these regions in identifying and expressing negative emotion (Etkin et al., 2011).

Neuroimaging studies examining anticipatory anxiety in SAD are more limited, but fear and emotion processing regions have been similarly implicated. In a positron emission tomography study comparing SAD individuals speaking privately prior to giving a public speech (the anticipation group) to those speaking privately after giving a speech (the comparison group), anticipatory anxiety was associated with enhanced regional cerebral blood flow in the left amygdaloid-hippocampal region and right dorsolateral prefrontal and left inferior temporal cortices, suggesting altered fear network activity (Tillfors et al., 2002). However, this study was limited by its small sample size (n=9), lack of control group, and presence of speaking during the anticipation phase. A second small (n=8) fMRI study examining neural activity during speech anticipation compared to rest (a counting-breathing relaxation task) showed increased activation in temporal lobe and limbic regions, including amygdala, during anticipation in SAD individuals compared to healthy individuals, and decreased activation in left dorsal anterior cingulate and medial prefrontal cortex areas (Lorberbaum et al., 2004). However, this paradigm was limited by its use of a rest phase as a control condition. Boehme et al. (2013) improved upon this fMRI paradigm by including a novel control anticipation task in which participants anticipated reading a word aloud so that experimenters could ostensibly "test" their equipment, compared to a 40s speech anticipation task. Compared to controls, SAD participants exhibited increased right insula and decreased left ventral striatum activity during speech versus control anticipation, as well as heightened right amygdala activity during the first half of speech anticipation (but not in the second half), suggesting a variation in the association of amygdala activity with anticipation over time in SAD participants.

The current study aimed to examine neural activity during speech anticipation in SAD individuals, expanding upon previous findings in two main ways. First, we aimed to better distinguish between neural processing during anticipation of a non-threatening versus threatening task. In previous studies, participants were informed prior to entering the scanner that they would be delivering a speech or series of speeches (e.g., Boehme et al., 2013). While this design allows for multiple trials of control and speech anticipation, it may have the unintended consequence of eliciting speech anticipatory anxiety and related neural patterns well before neural scanning of speech anticipation begins and during control anticipation, in effect "contaminating" the control condition. In the current paradigm, we informed participants of an upcoming speech only after they completed the control anticipation task and immediately prior to the speech anticipation task in the scanner.

Second, we examined the time course, or change in brain activity over time, during anticipation. Previous studies have largely focused on the magnitude or amplitude of neural reactivity rather than variability or time course of neural responses, despite the fact that timing is an important element of anticipatory anxiety (Grillon et al., 1993; Straube et al., 2009). We chose to focus on the temporal neural dynamics in a small set of *a priori* regions of interest (ROIs) that have been implicated in previous studies of anticipatory anxiety and threat processing in social anxiety (Boehme et al., 2013; Miskovic and Schmidt, 2012), namely, bilateral amygdala, insula, ventral striatum, and dorsal anterior cingulate cortex (dACC).

The time course of amygdala activity may be of particular importance for anxious populations. A previous study found that SAD individuals exhibit altered amygdala temporal response patterns to negative and positive emotional faces, such that amygdala responses occurred later in SAD versus control participants (Campbell et al., 2007). In another fMRI study of 120 participants, heightened trait neuroticism was associated with more prolonged amygdala activation following the presentation of negative images, but was not associated with initial amygdala reactivity (Schuyler et al., 2012). In other words, slower amygdala "recovery" rather than elevated amygdala reactivity to negative images correlated with trait neuroticism. Based on these findings, we expected that SAD individuals would have not only more elevated but also more sustained or prolonged amygdala activation to threat during speech anticipation compared to healthy controls. Additionally, we expected that heightened and more sustained amygdala activity would be associated with more severe social anxiety symptoms. For other ROIs, we hypothesized that SAD individuals would show heightened insula activity and reduced ventral striatum activity compared to controls. We also examined whether dACC activation in SAD was reduced (replicating Lorberbaum et al. [2004] results) or elevated (e.g., Phan et al., 2006) compared to controls. Beyond main effects of group, hypotheses regarding the time course of activity in non-amygdala regions were largely exploratory.

2. Methods

2.1. Participants

Participants were recruited as part of a study comparing two behavioral treatments for SAD (see Craske et al., 2014). SAD participants met DSM-IV criteria for principal or co-principal SAD with a clinical severity rating (CSR) of 4 or higher according to the Anxiety Disorders Interview Schedule (Brown et al., 1994). HC participants could not meet DSM-IV criteria for any Axis I disorder. All participants were between 18 and 45 years of age, either medication free or stabilized on medication, not undergoing behavioral therapy, English-speaking, and right-handed. Exclusion criteria included active suicidal ideation or severe depression (CSR > 6), psychiatric hospitalization within the past five years, serious medical conditions or pregnancy, history of psychosis or bipolar disorder, substance abuse or dependence within the past 6 months, claustrophobia, and non-removable metal in body.

Seventeen HC participants and 71 SAD participants entered the study and completed the fMRI scan. Of these, 1 HC and 11 SAD participants did not complete the speech anticipation task due to technical errors; thus 16 HC and 60 SAD participants were included in the present study. Participants were 50% female with a mean age of 27.8 years (SD=6.6) and were 49.3% Caucasian, 24.0% Asian/Pacific Islander, 14.7% Hispanic/Latino, 2.7% Black/African American, and 9.3% other race. HC and SAD participants did not differ by gender, age, or ethnicity ($ps > .26$). The majority (82.5%) of SAD participants were unmedicated.

2.2. Procedure

Participants completed the ADIS-IV and a battery of questionnaires, including the Liebowitz Social Anxiety Scale (Liebowitz, 1987). Eligible participants then completed a laboratory assessment, which included a computer dot probe task and public speaking task, followed by an fMRI scan approximately one week later. During the fMRI, participants completed several tasks to assess emotional reactivity and emotion regulation, including the control and speech anticipation tasks below.

2.3. Control anticipation task

Prior to entering the scanner, participants were told that they would