

Altered emotion regulation capacity in social phobia as a function of comorbidity

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Social phobia (SP) has been associated with amygdala hyperreactivity to fear-relevant stimuli. However, little is known about the neural basis of SP individuals' capacity to downregulate their responses to such stimuli and how such regulation varies as a function of comorbid depression and anxiety. We completed an functional magnetic resonance imaging (fMRI) study wherein SP participants without comorbidity ($n = 30$), with comorbid depression ($n = 18$) and with comorbid anxiety ($n = 19$) and healthy controls ($n = 15$) were scanned while completing an affect labeling emotion regulation task. Individuals with SP as a whole exhibited a reversal of the pattern observed in healthy controls in that they showed upregulation of amygdala activity during affect labeling. However, subsequent analyses revealed a more complex picture based on comorbidity type. Although none of the SP subgroups showed the normative pattern of amygdala downregulation, it was those with comorbid depression specifically who showed significant upregulation. Effects could not be attributed to differences in task performance, amygdala reactivity or right ventral lateral prefrontal cortex (RVLPFC) engagement, but may stem from dysfunctional communication between amygdala and RVLPFC. Furthermore, the particularly altered emotion regulation seen in those with comorbid depression could not be fully explained by symptom severity or state anxiety. Results reveal altered emotion regulation in SP, especially when comorbid with depression.

Keywords: social anxiety; depression; affect labeling; functional magnetic resonance imaging

INTRODUCTION

Social phobia (SP) is one of the most common and disabling anxiety disorders (Kessler *et al.*, 1999, 2005). At the neural level, SP is often associated with increased activity in the amygdala (Etkin and Wager, 2007), a limbic structure integral to fear processing and emotional arousal (LeDoux, 1995). Such amygdala hyperactivity is theorized to represent a key neural underpinning of the excessive anxiety that defines SP and thereby provides important insights into the neurobiology of anxiety (Rauch *et al.*, 2003; Etkin and Wager, 2007). However, to better use such findings to inform clinical diagnosis, prevention and treatment efforts, additional research is needed to understand the full extent of amygdala hyperactivity in SP.

Amygdala hyperactivity may be the result of either dispositionally high amygdala reactivity and/or a decreased capacity or tendency to effectively downregulate emotional responses once elicited (Berkman and Lieberman, 2009). Although there is an abundance of research on the neural basis of emotion reactivity in SP (i.e. studies in which participants passively view or make simple perceptual ratings or classifications of fear-relevant stimuli; Birbaumer *et al.*, 1998; Stein *et al.*, 2002; Straube *et al.*, 2004, 2005; Phan *et al.*, 2006; Blair *et al.*, 2008; Evans *et al.*, 2008), few studies have explicitly examined the downregulation of emotional responses to such stimuli. Investigations of the latter phenomenon are essential, as the clinical manifestation of anxiety presumably derives from not only elevations in emotional reactivity but also from deficits in emotion regulation (Craske, 2003).

Few studies have specifically examined the neural bases of emotion downregulation in SP. Two studies used fMRI to measure emotion regulation using cognitive reappraisal, which involves intentionally changing the way one thinks about a stimulus to make it seem less threatening, and found alterations in the extent and timing of

activations in prefrontal cortex (PFC) regulatory regions compared with healthy controls (HCs; Goldin *et al.*, 2009a, b). Although results of these studies are informative, they are somewhat confounded by differences across participants in willingness or ability to apply cognitive reappraisal on demand. Therefore, building on this previous research, in this study, we used an implicit emotion regulation task that minimized individual variability in task performance and thereby more effectively isolated activity due to emotion regulatory neural processes. To this end, we scanned participants with SP while they engaged in 'affect labeling', which involves linguistic processing of emotional aspects of stimuli, for example, labeling an emotional facial expression as 'angry' or 'disgusted'.

Although affect labeling is not commonly thought of as an emotion regulation strategy—mainly because it does not involve an explicit and intentional goal of reducing or otherwise changing consciously experienced emotions—several findings suggest that it constitutes an implicit or incidental form of emotion regulation (see Berkman and Lieberman, 2009 or Burklund, *et al.*, 2014 for further discussion). For example, affect labeling has been associated with diminished self-reported distress (Lieberman *et al.*, 2011) and decreased psychophysiological fear responses (Tabibnia *et al.*, 2008; Kircanski *et al.*, 2012). At the neural level, affect labeling of negative images consistently engages lateral PFC regulatory regions and decreases amygdala activity, thereby yielding a similar and even overlapping (Burklund *et al.*, 2014) neural profile relative to intentional emotion regulation in healthy samples (Hariri *et al.*, 2000, 2003; Lieberman *et al.*, 2005, 2007; Ochsner and Gross, 2005; Foland *et al.*, 2008; Berkman and Lieberman, 2009; Payer *et al.*, 2011, 2012; Gee *et al.*, 2012; Burklund *et al.*, 2014). In fact, there is growing appreciation for the idea that not all forms of emotion regulation involve conscious attempts to change felt emotions and may instead sometimes stem from processes set in motion to serve non-regulatory goals (Mauss *et al.*, 2007; Berkman and Lieberman, 2009; Berkman *et al.*, 2009; Koole and Rothermund, 2011). As noted earlier, an added benefit of using a strategy like affect labeling to study emotion regulation is that it does not require an individual to generate an explicit emotional experience or try to reduce that emotional response on demand, processes that may vary widely depending on a

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person's ability and willingness to engage in such a complex task (Lieberman *et al.*, 2011).

SP is also frequently comorbid with other anxiety and depressive disorders (Kessler *et al.*, 1999; Beesdo *et al.*, 2007). However, little emphasis is placed on the contribution of these comorbidities in many fMRI studies of SP, and therefore, little is known about what neural patterns uniquely characterize various types of comorbidity in SP. Therefore, we were particularly interested in whether comorbid depression and anxiety moderated emotion regulation in SP.

Given that SP is characterized by dysfunctional emotion processing, we hypothesized that all individuals with SP, regardless of comorbidity type, would exhibit a neural pattern reflecting less successful emotion regulation capacity, as indexed by increased amygdala activity, decreased lateral prefrontal activity and reduced amygdala-lateral prefrontal inverse correlation during affect labeling relative to HCs. Because individuals with SP and comorbid anxiety and depression tend to have increased disorder severity, increased functional impairments (Erwin *et al.*, 2002), worse quality of life (Dalrymple and Zimmerman, 2007) and decreased treatment success than SP alone (Bruce *et al.*, 2005; Ledley *et al.*, 2005), we also predicted that SP individuals with comorbid anxiety and depressive disorders would exhibit less successful emotion regulation compared with those with SP alone. For completeness, we also examined emotion reactivity using a non-emotion regulatory task and, based on previous findings (Birbaumer *et al.*, 1998; Stein *et al.*, 2002; Straube *et al.*, 2004, 2005; Phan *et al.*, 2006; Blair *et al.*, 2008; Evans *et al.*, 2008), expected to see increased amygdala activity (Lieberman *et al.*, 2007) in all SP participants relative to HCs, reflecting greater emotion reactivity in SP. To enhance the generalizability of our findings, we did not specifically match SP comorbid groups on specific variables and instead examined neural differences across these groups as they naturally exist.

METHODS

Participant recruitment and screening

Participants were recruited through the University of California, Los Angeles (UCLA) Anxiety Disorders Research Center, flyers posted throughout the UCLA community and newspaper and internet advertisements. Participants completed a diagnostic evaluation using the Anxiety Disorders Interview Schedule-IV (ADIS-IV; Brown *et al.*, 1994). Trained ADIS-IV interviewers assigned each participant a clinical severity rating (CSR) for each current diagnosis on a scale of 0–8, where a CSR of 4 or higher indicates clinically significant severity, distress or impairment, a CSR of 2 or lower indicates the absence of clinical significance and a CSR of 3 indicates probable but borderline clinical significance. All participants provided informed consent before completing the ADIS-IV. Our research protocol was approved by the UCLA Office for the Protection of Human Research Subjects.

Inclusion and exclusion criteria

Inclusion criteria for all participants were 18–45 years old, English speaking and right-handed. Exclusion criteria were pregnancy, claustrophobia, non-removable metallic objects, serious medical conditions or brain damage, bipolar disorders, substance-related disorders, suicidality, psychosis, psychiatric hospitalization, recent modifications to psychotropic medication (i.e. within the last month for benzodiazepines and 3 months for SSRIs and SNRIs) and recent modifications to psychotherapy (i.e. within the last 6 months). Owing to issues of generalizability and feasibility, we did not exclude participants with stabilized psychotropic medication use, although the majority of participants were medication-free, as shown in Table 1.

Additionally, SP participants had to meet DSM-IV criteria for a current (i.e. at the time of study participation) principal or coprincipal

diagnosis of SP with a CSR of 4 or higher. Participants in the 'SP_{only}' group must not have had any other current psychiatric diagnoses. Participants in the 'SP_{Anx}' group must have had at least one current comorbid anxiety disorder with a CSR of 3 or higher and no current depressive disorders. Participants in the 'SP_{Depr}' group must have had at least one current comorbid unipolar depressive disorder (i.e. major depressive disorder, dysthymia) with a CSR of 3 or higher and may or may not have had additional current comorbid anxiety disorders. We allowed additional comorbid anxiety disorders in the SP_{Depr} group because previous research has suggested that individuals with SP and comorbid depression are similar on many factors, including severity and treatment outcomes, regardless of whether they had additional comorbid anxiety disorders (Erwin *et al.*, 2002). Additionally, as described in more detail below, few individuals presented with SP and comorbid depression only ($n=7$), and therefore, we were not able to separately examine moderation by comorbid depression only vs comorbid depression and anxiety. The notation 'SP_{All}' refers to the entire sample of SP participants, collapsing across comorbidity types. HC participants must not have had any current or past psychiatric disorders.

Participants

Fifteen HCs and 67 SPs participated in the study. Of the 67 SP participants, 30 met criteria for SP_{only}, 19 for SP_{Anx} and 18 for SP_{Depr}. As shown in Table 1, the groups were similar on demographic variables except that the SP_{Depr} group was slightly older than the SP_{only} group [$t(45) = -2.167, P < 0.05$]. As shown in Table 2, there was a pattern of increasing SP CSRs from SP_{only} to SP_{Anx} to SP_{Depr}; however, the only significant difference was between SP_{only} and SP_{Depr}. There was also more widespread comorbidity in SP_{Depr} compared with SP_{Anx} such that SP_{Anx} individuals generally had SP plus a single comorbid anxiety disorder, whereas SP_{Depr} individuals generally had SP plus both a comorbid unipolar depressive disorder and at least one additional anxiety disorder (see Table 1). The difference in the extent of comorbidities between the SP_{only}, SP_{Anx} and SP_{Depr} groups is, of course, partially a function of how we defined the groups. Nevertheless, it is noteworthy that the presence of a comorbid depressive disorder was much more likely to involve additional comorbidities than the presence of a comorbid anxiety disorder. To address this issue, we created an index of all disorder clinical severity by summing all CSR scores for each diagnosis for each participant (see Table 2) and examined its moderating effect on neural activity, as described in more detail later. It should be noted that the goal of the present study was not to examine neural differences in matched groups of SP participants with and without comorbid anxiety and depressive disorders, but rather to examine the neural differences across these groups as they naturally exist.

Questionnaires

SP severity was assessed using the Liebowitz Social Anxiety Scale–Self Report Version (LSAS-SR; Fresco *et al.*, 2001). Participants also completed the Mood and Anxiety Symptom Questionnaire (MASQ; Watson *et al.*, 1995) to provide indices of general anxiety and depression symptoms. State anxiety was assessed via the short State-Trait Anxiety Inventory (STAI; Marteau and Bekker, 1992).

Procedures

Participants completed the LSAS and MASQ during a laboratory session 1–2 weeks before an fMRI session. Immediately before being scanned, participants were given a chance to practice the fMRI labeling and reactivity task (described below) and asked to complete the short STAI.

Table 1 SP and HC participant demographics and clinical characteristics

Measure	HC	SP _{All}	SP _{Only}	SP _{Anx}	SP _{Depr}	Stat HC × SP _{All}	Stat HC × SP _{only} × SP _{Anx} × SP _{Depr}
<i>N</i>	15	67	30	19	18		
Age mean (s.d.)	27.94 (6.80)	28.35 (7.25)	26.31* (6.50)	29.06 (7.20)	30.90* (7.89)		
Age range (years)	19–39	18–44	18–43	20–44	19–44		
Gender (male/female)	6/9	35/32	14/16	10/9	11/7	$\chi^2(1) = 0.73$, n.s.	$\chi^2(3) = 0.17$, n.s.
Ethnicity						$\chi^2(5) = 6.75$, n.s.	$\chi^2(15) = 20.55$, n.s.
Asian	6	12	7	3	2		
Hispanic	0	14	6	4	4		
White	8	29	12	11	6		
African American	0	3	1	0	2		
Other	0	9	4	1	4		
Mixed	1	0	0	0	0		
Education						$\chi^2(7) = 11.58$, n.s.	$\chi^2(21) = 26.53$, n.s.
Less than high school	0	1	0	0	1		
High school	0	17	11	1	5		
Some college/2-year degree	2	15	7	5	3		
4-year degree	6	24	9	8	7		
Post-grad work or degree	1	9	3	4	2		
Unknown	6	1	0	1	0		
Medication						$\chi^2(3) = 7.11$, n.s.	$\chi^2(9) = 13.33$, n.s.
None	15 (100%)	55 (82%)	25 (83%)	15 (79%)	15 (83%)		
Current daily	0	8	4	2	2		
Current prn	0	2	1	1	0		
Unknown	0	2	0	1	1		
Total number of comorbid disorders	0		0	1.11 (0.32)	1.94 (0.94)		
Comorbid disorders							
Specific phobia (e.g. heights, animals)	0	13	0	7	6		
Panic disorder with or without agoraphobia	0	7	0	4	3		
Obsessive compulsive disorder	0	1	0	0	1		
Hypochondriasis	0	1	0	1	0		
Generalized anxiety disorder	0	16	0	10	6		
Dysthymia	0	7	0	0	7		
Major depressive disorder	0	12	0	0	12		

*Denotes significant difference, $P < 0.05$.

Table 2 Self- and clinician-reported questionnaire data

Measure	HC	SP _{All}	SP _{Only}	SP _{Anx}	SP _{Depr}	SP _{All} vs HC	SP _{Only} vs HC	SP _{Anx} vs HC	SP _{Depr} vs HC	SP _{Only} vs SP _{Anx}	SP _{Only} vs SP _{Depr}	SP _{Anx} vs SP _{Depr}
SP CSR	0 (0)	5.66 (0.96)	5.37 (0.85)	5.68 (0.89)	6.11 (1.08)	*	*	*	*	ns	**	ns
All disorder severity	0 (0)	8.87 (4.33)	5.37 (0.85)	9.74 (2.56)	13.78 (4.07)	*	*	*	*	*	*	*
LSAS—anxiety	9.30 (4.57)	44.13 (9.63)	40.76 (8.44)	46.44 (9.65)	47.32 (10.16)	*	*	*	*	**	**	ns
LSAS—avoidance	8.20 (5.40)	38.28 (10.47)	36.33 (9.46)	38.01 (10.60)	41.72 (11.60)	*	*	*	*	ns	***	ns
LSAS—total	17.50 (7.48)	82.41 (19.05)	77.09 (17.02)	84.54 (18.95)	89.05 (20.80)	*	*	*	*	ns	**	ns
MASQ—general anxiety	13.53 (2.07)	25.41 (8.26)	20.83 (5.84)	29.11 (6.49)	29.32 (9.72)	*	*	*	*	*	*	ns
MASQ—general depression	16.87 (6.27)	32.69 (11.62)	25.79 (8.72)	36.13 (9.59)	40.79 (11.46)	*	*	*	*	*	*	ns
STAI (short)—state anxiety	1.54 (0.38)	2.26 (0.59)	1.98 (0.50)	2.54 (0.51)	2.42 (0.61)	*	*	*	*	*	**	ns

Note. Means with standard deviations in parentheses. All measures are self-report except for the CSRs and Total Disorder Severity.

Abbreviations: CSR, clinical severity rating; LSAS, Liebowitz Social Anxiety Scale; MASQ, Mood and Anxiety Symptom Questionnaire; STAI, State-Trait Anxiety Inventory.

*** $P < 0.005$; ** $P < 0.05$; * $P < 0.1$.

fMRI affect labeling and reactivity task

While being scanned, participants observed blocks of photographs of emotional facial expressions and geometric shapes and were instructed to complete simple labeling and matching tasks. There were four conditions (i.e. types of trials): affect label, gender label, affect match and shape match. For each condition, participants chose one of two response options at the bottom of the screen that labeled/matched the top target face/shape (see Figure 1). Emotion regulation capacity was indexed by the contrast of affect label vs gender label, which isolates activity specific to emotion-based linguistic processing of emotional stimuli and controls for neural activity associated with the perception of emotional stimuli, response selection, motor processing and verbal

processing in general (Lieberman *et al*, 2007). Emotion reactivity was indexed by the contrast of affect matching vs shape matching, consistent with previous studies (Hariri *et al*, 2000, 2003). This contrast isolates activity specific to the perception and matching of emotional stimuli, while only controlling for basic task attention, response selection and motor processes.

Stimuli were presented in a blocked design, with four blocks of each condition type and six trials per block. Each trial was 5 s long, with the stimuli presented for the entire trial length. Each block was preceded by a 10 s fixation crosshair and a 3 s instruction cue. Condition order was counterbalanced across participants. Facial stimuli were taken from the NimStim Face Stimulus set (Tottenham *et al*, 2009) and

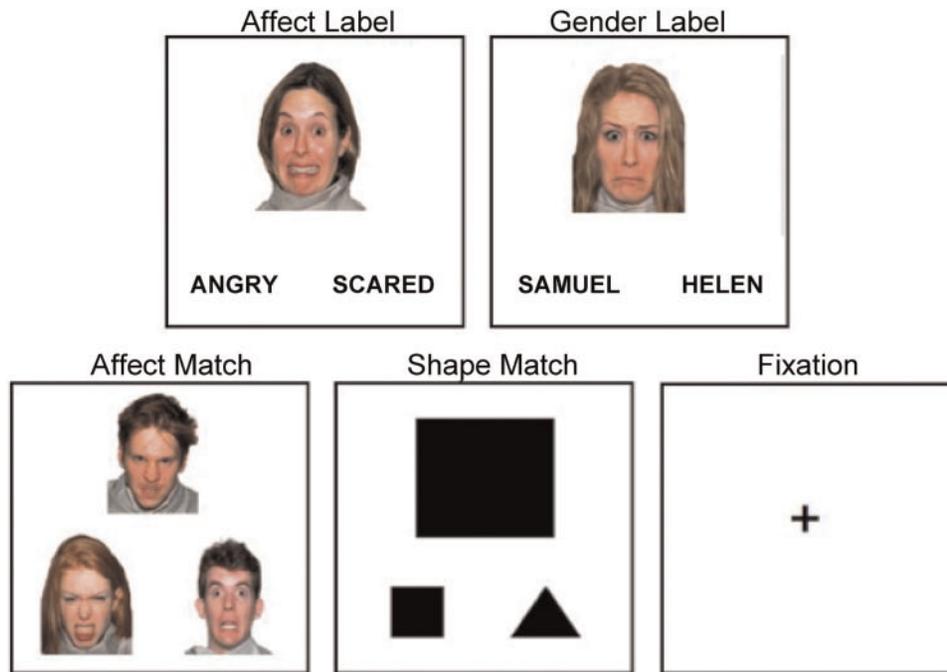


Fig. 1 Sample screens of each condition, plus the fixation crosshair.

depicted a negative emotion (i.e. fear, anger, disgust). Analyses collapsed responses across the different emotions because our goal was to examine responses to negative social stimuli in general rather than responses to different types of negative social stimuli. Stimuli were presented on a Macintosh MacBookPro computer using MacStim software (WhiteAnt Occasional Publishing, www.brainmapping.org/WhiteAnt) and high-resolution goggles (Resonance Technology, Inc). Button press responses were collected using a fMRI-compatible button box connected to the Macintosh via a custom USB interface.

fMRI image acquisition

Magnetic resonance images were acquired using a Trio 3.0 Tesla MRI scanner at the UCLA Ahmanson-Lovelace Brainmapping Center. For each participant, a high-resolution structural T2-weighted echo-planar imaging volume (spin-echo, TR = 5000 ms, TE = 34 ms, matrix size = 128×128 , resolution $1.6 \text{ mm} \times 1.6 \text{ mm} \times 3 \text{ mm}$, FOV = 200 mm, 36 slices, 3 mm thick, flip angle = 90° , bandwidth = 1302 Hz/Px) was acquired coplanar with the functional scans. Four functional scans were acquired (gradient-echo, TR = 3000 ms, TE = 25 ms, flip angle = 90° , matrix size = 64×64 , resolution $3.1 \text{ mm} \times 3.1 \text{ mm} \times 3.0 \text{ mm}$, FOV = 200 mm, 36 axial slices, 3 mm thick, bandwidth = 2604 Hz/Px).

fMRI data analysis

The imaging data were analyzed using SPM5 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). Functional images for each participant were realigned to correct for head motion, coregistered to the high-resolution structural images, normalized into a standard stereotactic space as defined by the Montreal Neurological Institute and smoothed with an 8 mm Gaussian kernel, full width at half maximum. Experimental blocks were modeled using a boxcar function convolved with the canonical hemodynamic response. Linear contrasts of affect label vs gender label and affect match vs shape match were computed for each participant using a fixed-effects model. For second-level group analyses, the

contrast images were pooled together in random-effects analyses, described in more detail later.

Numerous studies with HCs have demonstrated that affect labeling particularly involves increased right ventral lateral PFC (RVLPFC) activity coupled with diminished amygdala activity (Hariri *et al.*, 2000, 2003; Lieberman *et al.*, 2005, 2007; Herwig *et al.*, 2010; Burklund *et al.*, 2014). Therefore, given our strong a priori hypotheses regarding activity in amygdala and RVLPFC, our analyses focused on these regions of interest (ROIs), defined using an anatomical atlas (Tzourio-Mazoyer *et al.*, 2002). For affect labeling analyses, we restricted our results search area to bilateral amygdala (97 voxels total) and RVLPFC (composed of right-sided pars orbitalis, pars triangularis and pars opercularis; 1094 voxels total), correcting for multiple comparisons using a significance threshold of a *P*-value of 0.005 combined with extent thresholds of 4 and 15 contiguous voxels for the amygdala and RVLPFC, respectively, corresponding to a false-positive discovery rate of 5% in each ROI as estimated by 10 000 Monte Carlo simulations using AlphaSim (http://afni.nimh.nih.gov/pub/dist/doc/program_help/AlphaSim.html). For affect match vs shape match, we restricted our results search area to bilateral amygdala, using the threshold described above. For completeness, a Supplementary Table shows significant activations from whole-brain main effects labeling analyses (see Supplementary Table S1); however, these results will not be discussed in detail.

To investigate the neural bases of affect labeling, the following analyses were completed using the contrast affect label vs gender label. We first completed an omnibus *F*-test in SPM5 including all four groups of participants (i.e. HC, SP_{Only}, SP_{Amx}, SP_{Depr}) to examine possible differences within and between groups. Subsequently, main effects analyses were completed using a series of one-sample *t*-tests. These main effects analyses provided a manipulation check in that they allowed an examination of whether the observed neural pattern in HCs generally resembled that seen in several previous studies of affect labeling in healthy samples, and also provided a means for qualitative comparison with previous studies of SP involving various types of comorbidities. To directly compare neural activity between groups, we used the

analysis of variance (ANOVA) function in SPM5 to complete a series of planned follow-up pairwise 2×2 group (e.g. HC, SP_{Only}, SP_{Anx}, SP_{Depr}) vs condition (i.e. affect label, gender label) analyses, including comparing HCs with all SPs regardless of comorbidity, comparing HCs with each type of SP comorbidity, and comparing each type of SP comorbidity with each other. Given our particular interest in how neural patterns may vary as a function of comorbidity type, we further examined whether RVLPC activity was differentially correlated with amygdala activity between the HCs and each of the SP groups by completing a series of planned pairwise analyses using the regression function in SPM5, entering both average values of parameter estimates from the anatomically defined amygdala seed region and group membership as regressors, and examining results within the anatomical constraints of RVLPC. This type of analysis yields an activation map showing voxels that are significantly differentially correlated with activity in the amygdala between the two compared groups, providing a measure of how the relationship between amygdala and RVLPC activity differs between two groups of participants.

While our primary analyses compared groups defined categorically based on DSM-IV diagnostic criteria (i.e. HC vs SP_{Only} vs SP_{Anx} vs SP_{Depr}), we also examined whether several individual differences, including SP severity, state anxiety, general anxiety and depression symptoms, and all disorder severity, moderated neural activity in the amygdala and/or RVLPC during affect labeling in a linear fashion across all SP participants. To this end, we completed a series of regression analyses, entering scores of the LSAS, STAI, MASQ general anxiety subscale, MASQ general depression subscale, and all disorder severity into separate group-level regression analyses using the regression function in SPM5, collapsing across all SP groups.

Finally, we examined emotion reactivity by completing an analogous omnibus *F*-test followed by a series of pairwise group analyses using the ANOVA function in SPM5 for the contrast of affect match vs shape match.

As described earlier, all analyses used a restricted ROI search volume thresholded at $P < 0.005$ with 4 or 15 voxels for the amygdala and RVLPC, respectively.

RESULTS

Behavioral data

Comparing HCs with SP_{All} (collapsing across comorbidity types), there were no significant differences in response times for the affect label [$F(1,180) = 0.04$, $P = 0.97$], gender label [$F(1,180) = 1.30$, $P = 0.28$], affect match [$F(1,180) = 0.05$, $P = 0.95$] or shape match [$F(1,180) = 0.52$, $P = 0.60$] conditions. Additionally, HCs and SP_{All} did not have significantly different error rates on the affect label [$F(1,180) = 2.13$, $P = 0.13$], gender label [$F(1,180) = 1.04$, $P = 0.36$] or affect match [$F(1,180) = 1.84$, $P = 0.17$] trials, or on the task as a whole [$F(1,180) = 2.73$, $P = 0.07$]. There was, however, a significant difference in error rates on the shape match task [$F(1,180) = 6.58$, $P = 0.002$]. We then examined specific differences between all four groups (HC, SP_{Only}, SP_{Anx}, SP_{Depr}). The four groups did not show significantly different response times for the affect label [$F(3,78) = 0.26$, $P = 0.90$], gender label [$F(3,78) = 0.83$, $P = 0.51$], affect match [$F(3,78) = 0.59$, $P = 0.68$] or shape match [$F(3,78) = 0.35$, $P = 0.84$] conditions. Additionally, the four groups did not have significantly different error rates on the affect label [$F(3,78) = 1.17$, $P = 0.33$], gender label [$F(3,78) = 1.54$, $P = 0.20$] or affect match [$F(3,78) = 2.08$, $P = 0.09$]¹ trials, or on the task as a

whole [$F(3,78) = 1.75$, $P = 0.15$]. There was, however, a significant difference in error rates on the shape match task [$F(3,78) = 3.30$, $P = 0.02$] that was driven by a greater number of errors in the HC group compared with SP_{only} [$t(43) = 2.62$, $P = 0.01$].

Clinician- and self-reported data

As expected and shown in Table 2, all three SP comorbid groups, as well as the entire sample of SPs as a whole (SP_{All}) reported significant higher SP symptoms (LSAS), general anxiety and depression symptoms (MASQ), and state anxiety (STAI) compared with HCs. Comparing the three SP groups, we found that SP_{Anx} and SP_{Depr} exhibited significantly or marginally significantly higher SP symptoms, general anxiety, depression symptoms and state anxiety than SP_{only}, whereas there were no significant differences in any of these measures between SP_{Anx} and SP_{Depr}. Finally, as expected, we found that disorder severity was significantly different across all groups, with scores escalating from HCs to SP_{only} to SP_{Anx} to SP_{Depr}.

Neural differences between and within all groups during affect labeling

We first completed an omnibus *F*-test to test for significant activations within and between each of the four groups during affect labeling. This analysis yielded a large activation cluster spanning RVLPC (51, 30, 9; $t = 6.82$; 187 voxels) as well as significant activation in the right amygdala (21, -3, -18; $t = 4.85$; 10 voxels). We then completed a series of follow-up analyses to further explore these effects.

Neural main effects for affect labeling

Using a one-sample *t*-test, as expected, and replicating previous studies with healthy participants, the HC group exhibited increased RVLPC (48, 30, 3; $t = 3.19$ and 48, 24, 12; $t = 3.77$; 17 voxels, $P < 0.005$; see Figure 2) as well as decreased amygdala activation (21, -6, -21; $t = 3.85$; 4 voxels, $P < 0.005$) during affect labeling relative to gender labeling. Collapsing across comorbidity types, a one-sample *t*-test of SP_{All} also yielded increased RVLPC activation (54, 36, 6; $t = 4.92$; 266 voxels) during affect labeling relative to gender labeling (see Figure 2). However, the SP_{All} participants also exhibited increased amygdala activity during affect labeling relative to gender labeling (18, 0, -18, $t = 3.15$; 10 voxels; -27, -6, -18; $t = 3.71$; 6 voxels), reflecting a complete reversal of the amygdala pattern typically seen in HCs. We then examined each SP group separately to examine how neural patterns varied based on comorbidity type. In separate one-sample *t*-tests, each of the three SP groups also exhibited increased RVLPC activation during affect labeling relative to gender labeling (SP_{only}: 54, 36, 6; $t = 4.37$; 23 voxels; SP_{Anx}: 42, 27, -3; $t = 4.29$ and 42, 30, 3; $t = 3.33$; 66 voxels; SP_{Depr}: 51, 36, 3; $t = 3.50$ and 48, 42, -6; $t = 4.20$; 66 voxels; $P < 0.005$ for all; see Figure 2). However, there was no difference in amygdala activation between affect labeling and gender labeling for SP_{only} and SP_{Anx}, and there was greater amygdala activation during affect labeling compared with gender labeling for SP_{Depr} (21, 0, -18; $t = 3.59$; 18 voxels).

Neural differences between SP and HC groups during affect labeling

We then performed several direct comparisons. First, comparing HCs with SP_{All}, collapsing across all types of comorbidity, we found no differences in RVLPC activation; however, SP_{All} exhibited significantly greater amygdala activity than HCs (21, -6, -21; $t = 3.79$; 19 voxels; see Figure 3). We then examined how each SP comorbid group compared with HCs. There were no differences in RVLPC activation comparing HCs with any of the SP groups. The

¹ This marginal significance reflects the SP_{only} group showing a pattern of approximately one fewer error than the other groups during affect matching [Mean (s.d.) for each group: HC = 2.40(2.26); SP_{only} = 1.53(1.33); SP_{Anx} = 2.53(1.68); SP_{Depr} = 2.22(1.80)]; however, no pairwise comparisons were significant (all $P > 0.2$).

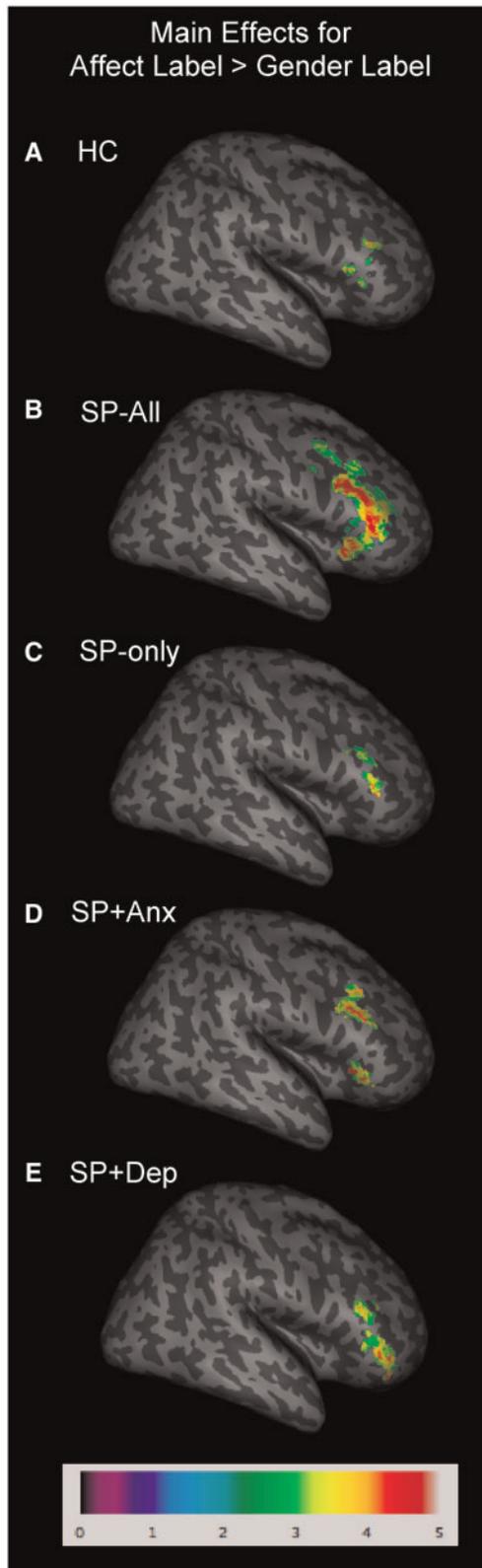


Fig. 2 Rendering of statistical activation maps showing main effects of activity in RVLPPFC during affect label vs gender label for (A) HCs, (B) SP_{All}, (C) SP_{only}, (D) SP_{Anx} and (E) SP_{Dep}.

SP_{only} and SP_{Anx} groups did not show different amygdala activation compared with HCs during affect labeling. However, SP_{Dep} exhibited greater amygdala activity than HCs (21, 0, -18; $t=4.04$; 29 voxels) during affect labeling (see Figure 3).

Neural differences between the SP groups during affect labeling

We completed additional pairwise comparisons to examine how each SP group compared with the others. Both SP_{Anx} and SP_{Dep} exhibited greater RVLPPFC activity compared with SP_{only} during affect labeling (SP_{Anx}: 45, 27, -6; $t=3.59$; 15 voxels; SP_{Dep}: 48, 48, -9; $t=3.37$; 32 voxels) and there were no differences in RVLPPFC activity between SP_{Anx} and SP_{Dep}. However, there were no differences in amygdala activity between any of the three SP groups.

Figure 4 shows right amygdala activity during affect labeling vs gender labeling for each group, as extracted from the significant omnibus F -test activation cluster, illustrating the normative pattern of reduced amygdala activity seen in the HC group during affect labeling and the divergence from this pattern seen in the SP groups.

Regions differentially correlated with amygdala activity between the SP groups and HCs for affect labeling

Past research with HCs has typically observed a negative correlation between RVLPPFC activity and amygdala during affect labeling, consistent with the notion that RVLPPFC is serving to functionally reduce amygdala responses to emotionally evocative stimuli (Lieberman et al., 2007). Given the different patterns of amygdala activity across SP groups, we investigated potential differences in the functional relationship between the amygdala and RVLPPFC by completing pairwise regression analyses between HCs and each of the three SP groups. We found a significant interaction for activity in RVLPPFC for all three pairwise analyses, indicating that clusters of RVLPPFC activity were differentially correlated with amygdala activity for HCs relative to each of the SP groups (SP_{only}: 48, 39, -3, $t=4.13$, 55 voxels; SP_{Anx}: 45, 48, -9, $t=3.76$; 45, 51, -3, $t=3.88$; 57 voxels; and SP_{Dep}: 48, 36, -3, $t=3.60$; 42, 54, 0, $t=3.98$; 87 voxels; see Figure 5). Specifically, we found that amygdala activity was positively correlated with RVLPPFC activity for each SP group (SP_{only}: $r=0.56$, $P=0.001$; SP_{Anx}: $r=0.68$, $P=0.001$; and SP_{Dep}: $r=0.87$, $P<0.001$), and was not significantly correlated with RVLPPFC activity for HCs (vs SP_{only}: $r=-0.275$, $P=0.32$; vs SP_{Anx}: $r=-0.347$, $P=0.21$; vs SP_{Dep}: $r=0.029$, $P=0.91$). Figure 5 shows RVLPPFC activity correlating positively with the amygdala for each SP group.

Correlations with self-report measures for affect labeling

Collapsing across all SP groups, we did not find amygdala or RVLPPFC activity to be correlated with SP severity, state anxiety, anxiety symptoms, depression symptoms or all disorder severity ($P>0.005$).

Neural differences between all groups for affect matching

Using an omnibus F -test to test for significant amygdala activations within and between each of the four groups during affect matching relative to shape matching, we found significant activations in bilateral amygdala. However, these activations were driven by main effects for each group individually (as shown in Supplementary Table S1) as follow-up pairwise direct comparisons showed that there were no amygdala reactivity differences between any of the groups, or between HCs and SP_{All} collapsing across comorbidities, using the a priori defined significance threshold of $P<0.005$, 4 voxels. Given the unexpectedness of these pairwise comparison null findings, we then repeated these analyses, lowering the threshold to $P<0.01$, 1 voxel to search for subsignificant findings. Even with this liberal threshold, we found only a two-voxel cluster was activated in the comparison of SP_{All}>HC, and a single amygdala voxel was activated for the comparison of SP_{Dep}>HC. We did not find any amygdala activations comparing SP_{only} and SP_{Anx} with the HCs.

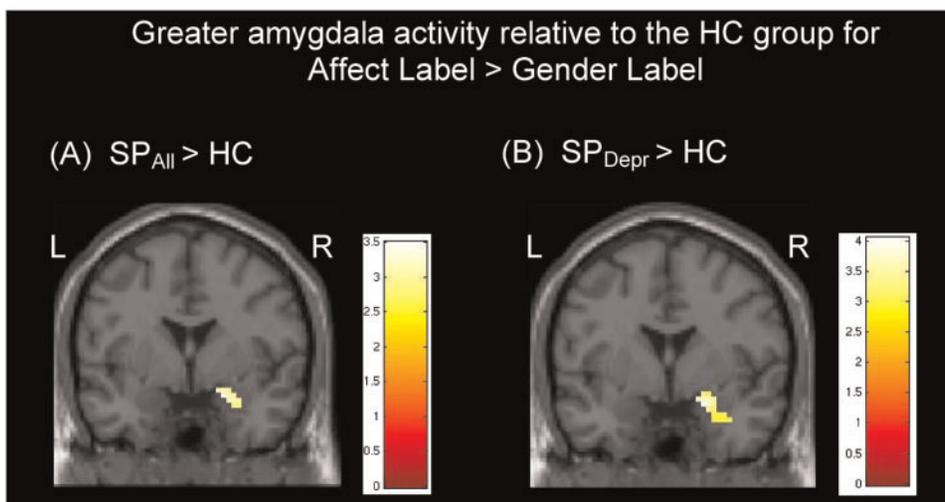


Fig. 3 Magnetic resonance images showing significantly greater amygdala activity during affect label vs gender label relative to the HC group for (A) SP_{All} (collapsing across comorbidities) and (B) SP_{Depr} specifically, both on a coronal slice at $y=0$ at $P < 0.005$.

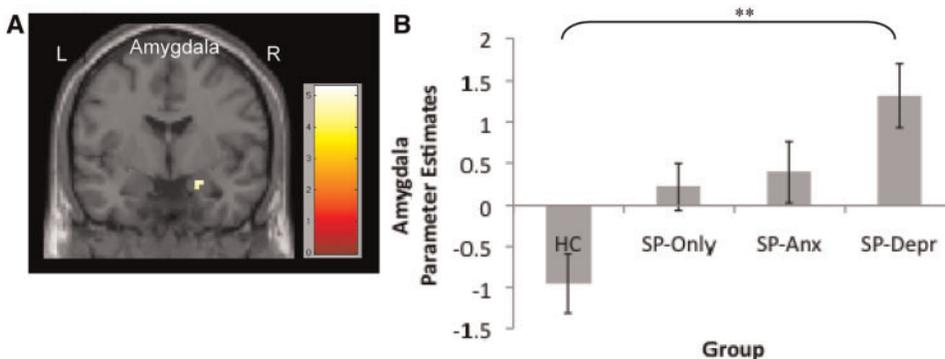


Fig. 4 (A) Magnetic resonance image showing significant amygdala activation from the omnibus F-test examining differences across all four groups of participants and (B) parameter estimates extracted from this cluster. Error bars represent standard errors within each group. Group differences between SP_{Depr} and HCs were significant at $P < 0.005$.

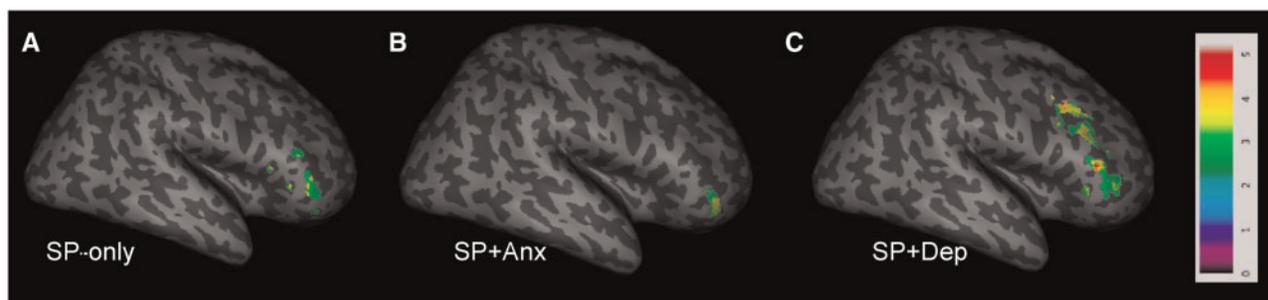


Fig. 5 Rendering of statistical activation maps showing activity in RVLPC that was significantly differentially correlated with activity in the amygdala compared with the HC group for (A) SP_{only} (55 voxels), (B) SP_{Anx} (57 voxels) and (C) SP_{Depr} (87 voxels). In each case, these RVLPC activations were significantly positively correlated with amygdala activity (SP_{only}: $r = 0.56$, $P = 0.001$; SP_{Anx}: $r = 0.68$, $P = 0.001$; SP_{Depr}: $r = 0.87$, $P < 0.001$). In contrast, RVLPC activity was not significantly correlated with amygdala activity (either negatively or positively) for the HC group.

DISCUSSION

Using fMRI, we found evidence for altered emotion regulation capacity in SP. Individuals with SP as a whole (collapsing across all comorbidity types) exhibited a reversal of the pattern observed in HCs here and in previous studies (Hariri *et al.*, 2000, 2003; Lieberman *et al.*, 2007) in that they showed an upregulation of

amygdala activity during affect labeling. However, additional analyses revealed important insights into how neural patterns actually varied as a function of distinct types of SP comorbidity. Specifically, while none of the SP groups showed downregulation of amygdala responses as did the HCs, it was those with comorbid depression specifically who showed increased amygdala activity. Such results

emphasize the significant impact of comorbid conditions within a common primary disorder and therefore underscore the importance of recognizing heterogeneity within disorders.

We also examined RVL PFC activation as well as amygdala-RVL PFC correlations to gain additional insights into the ineffective amygdala downregulation seen during affect labeling in SP. First, we found that each SP group showed increased RVL PFC activation during affect labeling that was not significantly different than that seen in HCs. Thus, the key regulatory and inhibitory mechanism (i.e. RVL PFC) was equally engaged during this task for those with and without SP. Yet, in contrast to HCs, RVL PFC activity in the SP groups was insufficient and/or ineffective in dampening amygdala responses. Given that individuals with SP and comorbid depression had significantly more amygdala activity during affect labeling compared with HCs, it is possible that these individuals may require 'extra' regulatory control from the PFC (e.g. greater RVL PFC activity) to dampen higher levels of amygdala reactivity. However, the lack of any group differences in amygdala activity observed during a task indexing simple emotional reactivity (i.e. affect matching) suggests that this is not the case here. Interestingly, we did find greater RVL PFC activity with similar amygdala activity for SP comorbid with anxiety and depression compared with those with no comorbidities, suggesting that even this 'extra' activation of RVL PFC was insufficient to downregulate amygdala responses.

Second, we found evidence for possible impaired communication between amygdala and RVL PFC in SP such that these regions were positively correlated during affect labeling for all SP comorbidity groups. This is in contrast to the typical inverse relationship seen in healthy individuals (Lieberman *et al.*, 2007),² and consistent with previous research showing fewer PFC regulatory regions inversely correlated with amygdala activity during cognitive reappraisal of negative self-statements in individuals with SP compared with HCs (Goldin *et al.*, 2009b).

Although all SP groups showed evidence of possible emotion regulation dysfunction, those with comorbid depression exhibited clear and significant dysfunction. The emotion dysregulation associated with comorbid depression in particular could not be attributed to differences in task performance (response time or errors), or linear differences in state anxiety, social phobia severity, all disorder severity, or depression symptoms. Thus, some aspect associated with the categorical diagnosis of depression—whether it is the categorical difference itself or some as-yet-unknown individual difference measure—appears to be driving the observed effect.

Overall, results suggest that individuals with SP, and especially those with comorbid depression, do not downregulate neural emotion responses to negative social stimuli as effectively or automatically as non-anxious individuals. As such, the results suggest a potential neural mechanism of the excessive anxiety that defines SP as well as the relatively more severe impairments seen with comorbid depression (e.g. Erwin *et al.*, 2002; Kessler *et al.*, 2005; Ledley *et al.*, 2005; Dalrymple and Zimmerman, 2007). Importantly, given our use of a task that minimized intersubject variability in task application, results suggest that the observed deficits are more likely to pertain to emotional regulation capacity; that is, the problem appears to lie in the operation of the underlying neural structures rather than in how the strategy was implemented by participants. More specifically, the problem may lie in the underlying structures and processes themselves or in other unintentional or automatic factors controlling such structures. This would suggest that even when attempting to appropriately use an emotion downregulation strategy to deal with aversive social situations,

individuals with SP may not experience corresponding reductions in their emotional responding. As such, treatment approaches that can enhance the capacity of prefrontal regions such as RVL PFC to dampen amygdala responses or otherwise compensate for such impairment would appear to be most helpful. One possible approach is affect labeling practice itself; spider phobic participants who engaged in affect labeling of fear-relevant stimuli, ostensibly engaging RVL PFC activity, evidenced reduced fear responses on subsequent testing (Tabibnia *et al.*, 2008; Kircanski *et al.*, 2012), possibly reflecting the idea that practicing an under-used strategy may increase its efficacy. In fact, affect labeling is central to the cognitive restructuring component of cognitive behavioral therapies (e.g. 'I'm anxious, but my anxiety is not harmful'), and thus, results also suggest a potential neural mechanism underlying existing treatment approaches.

It should be noted, however, that participants may have exhibited differential emotion regulation tendencies despite our use of a task that minimized intersubject variability in task utilization. For example, during each stimulus, social phobic participants may have engaged in additional cognitive processing that interfered with otherwise normal PFC downregulation of amygdala responses via affect labeling. However, there were no differences among the groups in task performance (reaction time or errors). This suggests similar overall effective processing across the groups, as one would expect that extraneous and interfering thoughts would somehow affect response speed or accuracy. However, it does remain a possibility that social phobic participants may have had different task tendencies immediately following each response selection that would not be reflected by task performance or reaction time. For example, social phobic participants may have continued to focus on the negative facial expressions after choosing a label, while HC participants may have moved on to more benign thoughts. Futures studies that use shorter trial times can investigate this possibility.

It is also worth noting that, as mentioned above, we did not find that any of the social phobic groups exhibited greater amygdala activity than the HC group during the emotion reactivity affect matching task. We did find main effects of significant amygdala activation during affect matching for all groups when examined separately, as shown in Supplementary Table S1, which suggests that the task was valid (e.g. Hariri *et al.*, 2000). Nevertheless, we did not find any group differences. While this runs counter to our predictions and some previous studies, a closer examination of the literature reveals additional previous studies that have similarly failed to find differences in amygdala activity between social phobic and HCs during certain comparisons. For example, a handful of studies have failed to find differences in response to angry faces (Straube *et al.*, 2004; Blair *et al.*, 2008; Evans *et al.*, 2008), neutral faces (Straube *et al.*, 2005; Phan *et al.*, 2006) and even fearful faces (Stein *et al.*, 2002). These studies used different paradigms including gender identification, emotion identification or passive observation paradigms, and a variety of comparison conditions including neutral faces, mildly happy faces, happy faces or fixation. While it is unclear why we failed to find significant amygdala differences between social phobic and healthy participants during affect matching, it may be due to the type of emotional facial expressions used, the control condition, the task instructions and/or interactions between these factors. In particular, one key distinction of our study is that we collapsed neural responses across multiple types of negative facial expressions rather than focusing on responses to specific emotions, as is common in previous studies. If amygdala differences are more robust for some emotions (e.g. fear) than others (e.g. anger), collapsing across emotions may have muted results. Future studies may be able to determine the precise conditions under which social phobic and healthy participants show similar *vs* distinct amygdala reactivity.

² It is unclear why we did not find an inverse correlation between RVL PFC and amygdala during affect labeling in the HC group as in previous research (Lieberman *et al.*, 2007).

The present study does have limitations. As mentioned above, given that we collapsed our analyses across multiple expression types (anger, fear, disgust), it is not possible to examine how affect labeling of specific emotional faces may differentially moderate neural activity. Our analyses comparing RVLPPFC and amygdala activity were correlational and do not provide a direct measure of functional connectivity. Although only a minority of social phobic participants (10 of 67) endorsed medication use, and such medication use was evenly distributed across the SP groups, this may have nonetheless influenced the results. We did not assess nicotine use, and this may have affected neural functioning as well. Results may also have been influenced by unequal sample sizes in the groups, particularly for analyses comparing HCs with all social phobics, collapsing across comorbidities. And finally, this study is limited in that we focused on only two brain regions, at a somewhat macro level. Investigations of different brain regions, subregions of key structures (e.g. subnuclei of the amygdala) and the functional connectivity between regions will likely provide additional insights into the neural bases of SP.

Future research should further explore the neural bases of emotion regulation in the development and maintenance of SP and other anxiety and depressive disorders. Such research may examine the contribution of neural regions beyond the amygdala and RVLPPFC ROIs that we have focused on here to examine the likely possibility of a wider system of dysfunction in emotion regulation capacity in SP, as well as take a longitudinal approach to explore the possible causal role of differences in neural functioning, such as those seen here, in the development of SP and depression comorbidity.

SUPPLEMENTARY DATA

Supplementary data are available at SCAN online.

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