Time-Varying Amygdala Response to Emotional Faces in Generalized Social Phobia

Darren W. Campbell, Jitender Sareen, Martin P. Paulus, Philippe R. Goldin, Murray B. Stein, and Jeffrey P. Reiss

**Background:** Individuals with social phobia (SP) have altered behavioral and neural responses to emotional faces and are hypothesized to have deficits in inhibiting emotion-related amygdala responses. We tested for such amygdala deficits to emotional faces in a sample of individuals with SP.

**Method:** We used functional magnetic resonance imaging (fMRI) to examine the neural substrates of emotional face processing in 14 generalized SP (gSP) and 14 healthy comparison (HC) participants. Analyses focused on the temporal dynamics of the amygdala, prefrontal cortex (PFC), and fusiform face area (FFA) across blocks of neutral, fear, contempt, anger, and happy faces in gSP versus HC participants.

**Results:** Amygdala responses in participants with gSP occurred later than the HC participants to fear, angry, and happy faces. Parallel PFC responses were found for happy and fear faces. There were no group differences in temporal response patterns in the FFA.

**Conclusions:** This finding might reflect a neural correlate of atypical orienting responses among individuals with gSP. Commonly reported SP deficits in habituation might reflect neural regions associated with emotional self-evaluations rather than the amygdala. This study highlights the importance of considering time-varying modulation when examining emotion-related processing in individuals with gSP.

**Key Words:** Amygdala, emotional face, functional magnetic resonance imaging (fMRI), habituation, orienting response, social phobia

Individuals with social phobia (SP) exhibit excessive fear and avoidance of social situations (American Psychiatric Association 2000), and generalized SP (gSP) is the most common and debilitating subtype (Kessler et al 1998), reflecting aversions to most social situations (Boone et al 1999; Heimberg et al 1990). The temporal characteristics of these aversive emotional experiences are not well understood. Evaluating the neural basis of these temporal characteristics is important to understanding the mechanisms underlying psychiatric disorders such as social anxiety (Davidson 2002). To date, no such neuroimaging evaluation has been conducted among individuals with SP (Amir et al 2005; Birbaumer et al 1998; Kilts et al 2006; Lorberbaum et al 2004; Phan et al 2006; Stein et al 2002; Straube et al 2004; Tillfors et al 2001, 2002; Veit et al 2002). With functional magnetic resonance imaging (fMRI), we compared the temporal characteristics of the neural response pattern of individuals with SP with a matched healthy comparison (HC) sample while they viewed emotional faces.

Various cognitive-emotional response mechanisms have been proposed to occur over the time course of an extended emotional response (Bogels and Mansell 2004; Fischer et al 2003; Williams et al 2004). The initial orienting response is an early mechanism (Williams et al 2004). Behavioral studies suggest that individuals with SP are likely to have atypical orienting responses, exhibiting either: 1) hypervigilance-and-then-avoidance, or 2) excessive self-focused attention and reduced attention to external emotional events (Bogels and Mansell 2004). A later cognitive-emotional mechanism is enduring vigilance, actively monitoring for emotionally salient events (Williams et al 2004; Wright et al 2001). Individuals with SP show excessive levels of ongoing vigilance for negative feedback during social situations (Bogels and Mansell 2004). A third cognitive-emotional response mechanism, habituation, reflects a reduced and diminishing response to repeated emotional stimuli over time (Feinstein et al 2002; Fischer et al 2003; Williams et al 2004). Socially anxious individuals show habituation deficits by exhibiting prolonged psychological responses to socially demanding tasks (Beidel et al 1985; Dimberg et al 1986; Eckman and Shean 1997; Mauss et al 2003).

These findings suggest that individuals with SP likely show altered temporal patterns in their neural responses to social-emotional stimuli. In particular, we hypothesized that individuals with SP would show habituation deficits in their neural responses during a social-emotional processing task.

Strong empirical support exists for the importance of the amygdala in negative and positive social-emotional processing (Davis and Whalen 2001; Fitzgerald et al 2006; Hamann and Mao 2002; Kalin and Shelton 2003; LeDoux 2000; Phan et al 2002; Phillips et al 2003b; Winston et al 2005; Zald 2003). With regard to the temporal characteristics of amygdala responses, healthy samples exhibit rapid amygdala habituation to emotional stimuli (Breiter and Rauch 1996; Fischer et al 2000, 2003; Phan et al 2003; Strauss et al 2005; Whalen et al 1998; Williams et al 2004; Wright et al 2001). Among SP samples, only overall amygdala responses have been evaluated. Most SP studies have identified an exaggerated amygdala response to emotional stimuli, including: neutral or negative faces (Birbaumer et al 1998; Lorberbaum et al 2004; Stein et al 2002; Straube et al 2004, 2005), aversive conditioning (Schneider et al 1999; Veit et al 2002), and public-speaking symptom-provocation (Tillfors et al 2001, 2002) with some exceptions (Amir et al 2005; Kilts et al 2006; Van Ameringen et al 2004). The SP-related amygdala differences to positive (happy) faces are limited and mixed (Phan et al 2006; Straube et
al 2005). Furthermore, the importance of the amygdala in SP was shown in a study in which successful treatment was associated with reduced amygdala responses to a public-speaking task (Furmak et al 2002).

Selected regions of the prefrontal cortex (PFC) also are considered important to the duration of emotion-related neural reactions (Davidson 2002; Ochsner and Gross 2005). Studies of healthy control subjects have associated PFC and anterior cingulate cortex (ACC) responses with decreased emotional states (Hariri et al 2000, 2003; Ochsner et al 2002, 2004; Phan et al 2003, 2005; Urry et al 2006). The SP samples show both hyperactivity (Adolphs 2006; Amir et al 2005; Kilts et al 2006; Phan et al 2006; Stein et al 2002; Veit et al 2002) and hypoactivity (Lorberbaum et al 2004; Tillfors et al 2001) to emotional stimuli within the medial PFC/ACC.

The specific PFC/ACC region and the valence of its response depend on the nature of the cognitive-emotional task performed, such as: self versus situational evaluation (Kelley et al 2002), distraction versus reappraisal (Kalisch et al 2006), or up-regulation versus down-regulation (Ochsner et al 2004). Given the various functions that PFC responses might reflect, in this study we will focus on PFC responses that parallel those of the amygdala to understand better amygdala-related emotional processing.

The fusiform face area (FFA) is implicated in perceptual processing of the structural features of faces (Kanwisher et al 1997). Thus, we also examined the temporal characteristics of the FFA to compare them with those found in the amygdala. The FFA neural results will help us interpret the amygdala findings. If the FFA findings parallel the amygdala findings, this would suggest that group differences in temporal response patterns reflect temporal differences in general perceptual face processing. Alternatively, if the amygdala response is unique, this would suggest that the group differences in temporal response patterns reflect differences in emotional processing.

To examine the temporal characteristics of emotion-related neural responses in SP, we analyzed data from a previously published SP fMRI study (Stein et al 2002). This study reported greater average responses to harsh faces (fear, anger, and contempt) versus accepting faces (happy) in the SP group compared with the HC group, but unexamined issues remain. Like other extant SP studies, Stein et al (2002) did not examine the temporal pattern of neural responses, the central focus of this paper. Secondly, Stein et al (2002) examined the neural response to harsh faces with happy faces as the reference condition. This approach precludes identifying group differences common to both harsh and accepting faces, because common responses would be subtracted out. General face processing alterations in amygdala response are expected on the basis of behavioral studies showing altered interpretations of facial expressions (Bogels and Mansell 2004; Hirsch and Clark 2004) to both negative (Mogg et al 2004) and positive emotional faces (Coles and Heimberg 2004) among individuals with SP. In the current analysis, we evaluated the duration of neural responses separately for positive, negative, and neutral facial expressions against a low-level fixation baseline.

The study hypothesis was that participants with gSP, relative to HC participants, would show prolonged emotion-related amygdala responses when exposed to emotional faces. We also tested for PFC responses that paralleled those of the amygdala and examined the temporal characteristics of the FFA as a perceptual processing control region.
Stimulus Timing

During each face trial, participants made a gender decision by pressing one of two buttons on a response pad held in the right hand (accuracy and latency of responses for each trial were not available, owing to computer backup failure (Stein et al 2002). Each face was presented for 2.5 sec followed by a 0.5-sec blank screen interstimulus interval, resulting in a trial duration of 3 sec and a block duration of 12 sec (four faces/block). Each half-run included 18 blocks (Figure 1) for a total duration of 216 sec/half-run. Participants completed six half-runs or three full runs. Each full run was separated by a pause of approximately 3 min.

MRI Acquisition

In each functional run, 146 T2* volumes were acquired with 20 interleaved 7-mm-thick axial slices covering the whole brain. Gradient echo, echo-planar images (repetition time/echo time/flip angle/field-of-view/matrix = 3000 msec/40 msec/90°/22 cm/64 × 64 matrix) with a voxel size = 3.44 × 3.44 × 7 mm were acquired with a Siemens 1.5-T magnet (Siemens AG, Erlangen, Germany) with an actively shielded magnet. These voxels were resampled into 3.5-mm³ voxels. A high-resolution 1-mm³ anatomical volume also was acquired with a magnetization prepared rapid acquisition with gradient echo sequence.

Preprocessing

All MRI data were preprocessed and analyzed with Analysis of Functional Neuroimaging (AFNI) software (Cox 1996). Echo-planar images were co-registered to the image that minimized image translation and rotation relative to all other images within each run. As well, any volumes with visually detectable movements or obvious MRI abnormalities were excluded. Data linear detrending and normalization steps are described within the regression analysis steps in the following text.

Individual fMRI Analyses

A separate reference function for each face type (neutral, fear, angry, contempt, and happy) in each half of each functional run versus the asterisk was created. To account for the delay in the hemodynamic response function (HRF), each reference function was convolved with the default AFNI HRF model. Each face was presented for 2.5 sec followed by a 0.5-sec blank screen interstimulus interval, resulting in a trial duration of 3 sec and a block duration of 12 sec (four faces/block). Each half-run included 18 blocks (Figure 1) for a total duration of 216 sec/half-run. Participants completed six half-runs or three full runs. Each half run was separated by a pause of approximately 3 min.

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Thus, gSP participants’ state-based anxiety levels decreased significantly over the course of the experiment.

**Amygdala**

**Group × Time Responses.** For fear faces, right and left amygdala Group × Time interactions were found (Figure 2) $F(5,130) = 3.2, p < .01$, and $F(5,130) = 3.2, p < .01$, respectively. For happy faces, right and left amygdala Group × Time interactions were found (Figure 3) $F(5,130) = 3.3, p < .008$, and $F(5,130) = 3.2, p < .01$, respectively. For angry faces, a right amygdala Group × Time interaction was found (Figure 4) $F(5,130) = 4.5, p < .001$. Trend level Group × Time effects were found in the left amygdala for angry faces $F(5,130) = 3.2, p < .01$ and neutral faces $F(5,130) = 3.2, p < .01$ in clusters smaller than the a priori minimum of 214 mm$^3$. Even at a trend level, contempt faces failed to show reliable evidence of a Group × Time interaction.

**Contempt Re-Examined.** Given the expected salience of contempt to a gSP population, supplementary testing of the contempt data was conducted. Specifically, contempt responses were extracted from each of the three amygdala clusters showing a significant Group × Time effect to a negative face: right amygdala for anger, and left and right amygdala clusters for fear (Supplementary Figure 1 example). No significant Group × Time effect was found, $p_s > .05$.

All subsequent amygdala and PFC analyses focused on the significant fear, happy, and anger effects. For the FFA control region, all five faces were examined.

**The Temporal Pattern.** The temporal response patterns of the amygdala were not simple linear decreases, all $p_s > .10$.

Figures 2, 3, and 4 illustrate that the peak amygdala response occurred at Time 1 in the HC group but at Time 2 in the gSP group. Follow-up analyses restricted to the first two time points (Group × Times 1 vs. 2) confirmed that the timing of these peak responses differed significantly between the two groups in four (left-fear, left-happy, right-happy, right-anger) of the five clusters and was borderline in the fifth (right-fear) cluster (Supplementary Table 1).

**Healthy Comparison Amygdala Peak Response.** One-sample $t$-tests confirmed that the HC group’s Time 1 amygdala response was significantly different from zero in four (left-happy, left-fear, right-happy, right-anger) of the five amygdala clusters and borderline higher in the fifth (right-fear) amygdala cluster (Table 2). Furthermore, the decrease after this peak response (Time 1 vs. Time 2 contrasts) was significant in three (left-fear, left-happy, and right-happy) of the five clusters and was borderline lower in a fourth (right-fear) cluster (Table 2). No other one-sample $t$-test time point contrasts were consistently significant across the different clusters.

**gSP Peak Amygdala Response.** Among the gSP group, Time 1 amygdala responses were not significantly different from zero ($p_s > .25$), whereas Time 2 amygdala responses were significantly different from zero in all five amygdala clusters (Table 2). Furthermore, the decrease after this peak response (Time 2 vs. Time 3 contrasts) was significant in four (left-fear, left-happy, right-happy, right-anger) of the five clusters and was borderline lower in a fifth (right-fear) cluster (Table 2). No other one-sample $t$-test time point contrasts were consistently significant across the different clusters.

**Figure 2.** Temporal pattern of the blood oxygen level dependent (BOLD) signal response in the amygdala to fear faces for the healthy comparison (HC) and generalized social phobia (gSP) groups.

**Figure 3.** Temporal pattern of the blood oxygen level dependent (BOLD) signal response in the amygdala to happy faces for the healthy comparison (HC) and generalized social phobia (gSP) groups.
Prefrontal Cortex

Group × Time Responses. Within the PFC, three regions showed significant Group × Time interactions that paralleled those of the amygdala: left lateral PFC (inferior frontal gyrus, Brodmann area [BA] 9, 44, and 45) for fear faces, and both right dorsolateral-medial PFC (middle and superior frontal gyrus and dorsal ACC, BA 6, 8, and 32) and left dorsolateral PFC (middle frontal gyrus, BA 6, 8, and 9) for happy faces (Table 3). For the HC group, a significant peak response at Time 1 dropped significantly by Time 2 for all three clusters (Table 4). For the gSP group, the peak responses were significant at Time 2 but only decreased significantly by Time 3 for fear faces (Table 4).

Fusiform Face Area

Within the FFA search region, no significant Group × Time interactions in BOLD responses were found for any of the different facial expressions, all ps > .05. An analysis of Time effects ignoring group revealed that FFA BOLD responses were relatively stable but particularly high in the first Time period for both groups. These results indicate that the groups did not differ in basic perceptual processing of the faces.

Discussion

The goal of this fMRI study was to examine the temporal characteristics of the amygdala and related-PFC responses to emotional faces among individuals with gSP. Within the amygdala, the peak response occurred later among the gSP participants than the HC participants. The delayed amygdala response does not support our hypothesis that gSP participants would show more sustained emotion-related amygdala BOLD responses. Rather, this delay might be a neural correlate of altered orienting responses in SP and linked to the deficits in emotional face processing previously reported in behavioral studies of individuals with SP (Bogels and Mansell 2004; Coles and Heimberg 2005; Horley et al 2004).

Behavioral studies suggest that gSP individuals show prolonged emotional responses to social stimuli (Beidel et al 1985; Bogels and Mansell 2004; Dimberg et al 1986; Eckman and Shean 1997; Mauss et al 2003). But, evidence for prolonged autonomic responses (e.g., changes in heart rate or skin conductance) is less consistent across SP samples. Some studies find extended physiological responses (i.e., habituation deficits: Beidel et al 1985; Dimberg et al 1986; Eckman and Shean 1997), whereas other studies do not (Gerlach et al 2003; Mauss et al 2003). This current study does not find evidence for amygdala habituation deficits in a gSP sample. Evaluations of internal feelings do not depend on amygdala function (Anderson and Phelps 2002; Zald 2003). Brain regions other than the amygdala might account for prolonged psychological responses individuals with SP exhibit. To speculate, the medial PFC might be associated with prolonged psychological responses involving negative self-reflections (Kelley et al 2002).

Altered Orienting Response

The atypical emotional face processing tendencies of individuals with SP might account for the delayed amygdala response found in this study. Individuals with SP show reduced task-related attention and more self-focused attention during emotional face processing (see reviews by Bogels and Mansell 2004; 2005; Horley et al 2004).

Table 2. Post Hoc t-Tests of Amygdala BOLD Response Peaks and Drop from Peaks for Fear, Happy, and Angry

<table>
<thead>
<tr>
<th>Face</th>
<th>Side</th>
<th>HC Time 1 vs. 0</th>
<th>HC Drop From Peak (T1 − T2)</th>
<th>SP Time 2 vs. 0</th>
<th>SP Drop from Peak (T2 − T3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear</td>
<td>L</td>
<td>2.5, ( p &lt; .03 )</td>
<td>1.9, ( p &lt; .045 )</td>
<td>3.3, ( p &lt; .006 )</td>
<td>4.6, ( p &lt; .001 )</td>
</tr>
<tr>
<td>Fear</td>
<td>R</td>
<td>1.9, ( p &lt; .08 )</td>
<td>1.2, ( p &lt; .13 )</td>
<td>2.4, ( p &lt; .035 )</td>
<td>2.5, ( p &lt; .015 )</td>
</tr>
<tr>
<td>Happy</td>
<td>L</td>
<td>2.3, ( p &lt; .04 )</td>
<td>1.6, ( p &lt; .07 )</td>
<td>4.1, ( p &lt; .002 )</td>
<td>4.9, ( p &lt; .001 )</td>
</tr>
<tr>
<td>Happy</td>
<td>R</td>
<td>2.9, ( p &lt; .015 )</td>
<td>2.3, ( p &lt; .03 )</td>
<td>3.7, ( p &lt; .003 )</td>
<td>2.9, ( p &lt; .01 )</td>
</tr>
<tr>
<td>Anger</td>
<td>R</td>
<td>2.2, ( p &lt; .05 )</td>
<td>2.7, ( p &lt; .01 )</td>
<td>2.4, ( p &lt; .032 )</td>
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\( t \)-value degrees of freedom = 1, 13. Drop from Peak \( t \)-tests are one-tailed. Side, amygdala cluster side; SP, social phobia; HC, healthy comparison subjects; L, left; R, right. T1 − T2 = Time 1 − Time 2 blood oxygen level dependent (BOLD) response; T2 − T3 = Time 2 − Time 3 BOLD response.

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Figure 4. Temporal pattern of the blood oxygen level dependent (BOLD) signal response in the amygdala to angry faces for the healthy comparison (HC) and generalized social phobia (gSP) groups.
Hirsch and Clark 2004). As well, SP participants engage in less scanning of the eyes and mouth and more scattered face scanning than the visual scan paths of healthy individuals (Horley et al. 2004). These tendencies could interfere with the initial development of a coherent emotional face orienting response and account for the delay in amygdala BOLD responses. The aforementioned behavioral studies and other neuroimaging studies of orienting responses (Williams et al. 2005) typically rely on event-related designs with finer temporal resolution than scanning of the eyes and mouth and more scattered face scanning than the visual scan paths of healthy individuals (Baas et al. 2004; Zald 2003). More systematic studies of anger-related amygdala lateralization are needed before any firm conclusions can be drawn.

Fear. The fear face findings are noteworthy in their association with left inferior frontal gyrus response. Fearful faces reliably engage amygdala responses among healthy samples (Phan et al. 2002; Zald, 2003). But, only Stein et al. (2002) have reported on fear-specific amygdala responses that were relatively weak when averaged across all three runs (these results were based on the same fMRI dataset as the current study). In this study, the early left inferior frontal gyrus response to fear faces might have reduced the overall amygdala’s BOLD response to fear (Stein et al. 2002). The inferior frontal gyrus can provide a semantic representation of emotional responses (e.g., labeling) that can reduce the strength of an emotional response (e.g., Ochsner et al. 2004; Phan et al. 2005). Thus, in this gSP sample, the amygdala response seems to reflect a delayed-orienting response rather than an enduring impairment in processing fear faces.

Contempt. Contempt would seem to be a particularly relevant social-emotional expression to individuals with gSP. No temporal group differences to contempt were found in the amygdala. Other SP neuroimaging studies (aside from Stein et al. 2002) have not evaluated contempt faces. Contempt might be more difficult to label and less commonly experienced (Matsuzawa and Ekman 2004). Labeling emotional expressions has been shown to reduce amygdala responses (Hariri et al. 2000). If contempt is more difficult to recognize and label, then associated emotional responses might be more enduring and less susceptible to change over time. This interpretation is consistent with the greater mean response reported in the earlier paper (Stein et al. 2002).

Neutral. An early neuroimaging study showed that neutral faces might be viewed as negative by individuals with SP and associated with exaggerated amygdala responses (Birbaumer et al. 1998). More recent SP neuroimaging studies report that emotional faces are associated with significantly greater amygdala responses compared with neutral faces (Straube et al. 2004, 2005) with some exceptions (Amir et al. 2005). In summary, SP participants appear to rely on event-related designs with finer temporal resolution than scanning than the visual scan paths of healthy individuals (Williams et al. 2005) typically rely on event-related designs with finer temporal resolution than scanning of the eyes and mouth and more scattered face scanning than the visual scan paths of healthy individuals (Baas et al. 2004; Zald 2003). More systematic studies of anger-related amygdala lateralization are needed before any firm conclusions can be drawn.

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Fear. The fear face findings are noteworthy in their association with left inferior frontal gyrus response. Fearful faces reliably engage amygdala responses among healthy samples (Phan et al. 2002; Zald, 2003). But, only Stein et al. (2002) have reported on fear-specific amygdala responses that were relatively weak when averaged across all three runs (these results were based on the same fMRI dataset as the current study). In this study, the early left inferior frontal gyrus response to fear faces might have reduced the overall amygdala’s BOLD response to fear (Stein et al. 2002). The inferior frontal gyrus can provide a semantic representation of emotional responses (e.g., labeling) that can reduce the strength of an emotional response (e.g., Ochsner et al. 2004; Phan et al. 2005). Thus, in this gSP sample, the amygdala response seems to reflect a delayed-orienting response rather than an enduring impairment in processing fear faces.

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neutral faces are less emotionally evocative and less consistently associated with robust amygdala responses among SP samples, thus consistent with our findings.

**Happy.** The temporal group differences in amygdala responses to happy faces were noteworthy. Previous SP-neuroimaging studies of happy faces are inconsistent. One study reported an exaggerated amygdala response to happy (Stratube et al 2005), whereas another reported no difference (Phan et al 2006). Behavioral face processing studies report that individuals with SP experience greater negative reactions to positive emotional stimuli than do healthy individuals (Alden et al 2004; Coles and Heimberg 2005; D’Argembeau et al 2003; Hirsch and Clark 2004). The right dorsolateral-dorsomedial PFC response to happy faces in this study might reflect greater self-reflection (Kelley et al 2002; Schmitz and Johnson 2006) associated with viewing happy faces. Individuals with SP might view positive faces as “mocking me” or setting social expectations so high they lead to inevitable future social failures (Alden et al 2004; Coles and Heimberg 2005; Hirsch and Clark 2004). These SP-specific aversive interpretations might account for their altered orienting responses and delayed amygdala and PFC responses to happy faces. The left dorsolateral PFC BOLD responses to happy faces might reflect greater cognitive processing demands (Steele and Lawrie 2004) associated with more intensive interpretations of happy faces.

**Fusiform Face Area**

Our findings are not consistent with a general face processing deficit among this gSP sample. The gSP group shows FFA neural responses comparable to those of the HC group and previously showed similar gender identification accuracy (Stein et al 2002). This suggests that both groups were processing general face features similarly. If the delay in amygdala response reflects initial face processing deficits, the deficits are likely specific to the emotional characteristics of the faces.

**Study Limitations**

These results might only be applicable to the gSP subtype examined in the current study. This group experiences the most severe SP symptoms (Kessler et al 1998). However, the SP neuroimaging literature shows no consistent differences in amygdala responses between gSP and unspecified SP samples. A second limitation is the restricted focus on the amygdala, PFC, and the FFA as a control region. A variety of brain regions are typically involved in emotional processing (Damasio 1996; Phan et al 2006). These SP-specific aversive interpretations might account for their altered orienting responses and delayed amygdala and PFC responses to happy faces. The left dorsolateral PFC BOLD responses to happy faces might reflect greater cognitive processing demands (Steele and Lawrie 2004) associated with more intensive interpretations of happy faces.

**Conclusions**

This investigation found that individuals with SP have altered temporal response patterns to negative and positive emotional faces in the amygdala. This finding seems to reflect a neural correlate of an atypical orienting response to emotional faces among individuals with SP. Commonly reported SP deficits in habituation might reflect neural regions more directly associated with emotional self-evaluation than the amygdala. More generally, the study findings highlight the importance of examining the timing and duration of neural responses to acquire a complete understanding of the neural basis of SP-related emotional processing.

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