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ORIGINAL RESEARCH

# Self-referential and anxiety-relevant information processing in subclinical social anxiety: an fMRI study

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**Abstract** The fear of negative evaluation is one of the hallmark features of social anxiety. Behavioral evidence thus far largely supports cognitive models which postulate that information processing biases in the face of socially relevant information are a key factor underlying this widespread phobia. So far only one neuroimaging study has explicitly focused on the fear of negative evaluation in social anxiety where the brain responses of social phobics were compared to healthy participants during the processing of self-referential relative to other-referential criticism, praise or neutral information. Only self-referential criticism led to stronger activations in emotion-relevant regions of the brain, such as the amygdala and medial prefrontal cortices (mPFC), in the social phobics. The objective of the current study was to determine whether these findings could be extended to subclinical social anxiety. In doing so, the specificity of this self-referential bias was also examined by including both social and non-social (physical illness-related) threat information as well as a highly health anxious control group in the experimental paradigm. The fMRI findings indicated that the processing of emotional stimuli was accompanied by activations in the amygdala and the ventral mPFC, while self-referential processing was associated with activity in regions such as the mPFC, posterior cingulate and temporal poles. Despite the validation of the paradigm, the results revealed that the previously reported behavioral and brain biases associated with social phobia could not be unequivocally extended to subclinical social anxiety. The divergence between the findings is explored in detail with reference to paradigm differences and conceptual issues.

**Keywords** Social anxiety · Social cognition · Neuroimaging · Self-referential processing · Emotion processing · Fear of negative evaluation

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## Introduction

Social phobia is characterized by an intense fear and the consequent avoidance of social situations that may involve scrutiny by other people (DSM-IV-TR: American Psychiatric Association 2000). This irrational fear of being negatively evaluated by others is the core feature of social phobia and causes considerable disruption in the lives of those affected by it.

A great deal of research has been directed at understanding the psychological and neurobiological underpinnings of this highly prevalent phobia which, according to cognitive-behavioral models of social phobia, arise from information processing biases (Clark and Wells 1995). One of the more consistent findings is that the attentional processing of emotional stimuli, such as angry facial expressions, is aberrant in clinical and sub-clinical social anxiety (Machado-de-Sousa et al. 2010; Staugaard 2010). For instance, using a dot-probe

task where the stimuli were presented for 175 ms, patients with social phobia displayed an attentional bias towards angry but not happy or neutral faces compared to a healthy control group (Stevens et al. 2009).

Furthermore, neuroimaging studies have complemented such findings by showing heightened involvement of emotion-relevant structures in the brain, such as the amygdala, insula, anterior cingulate, medial prefrontal and orbitofrontal cortices (Canteras et al. 2010; Lamm and Singer 2010; Ochsner 2008; Salzman and Fusi 2010) in socially anxious individuals relative to control groups when presented with threatening facial stimuli (Etkin and Wager 2007; Freitas-Ferrari et al. 2010; Shin and Liberzon 2010). For instance, patients with social anxiety disorder relative to a healthy control group revealed greater responsiveness in the amygdala for angry compared to neutral schematic faces (Evans et al. 2008).

Despite being commonly employed in behavioral research (Heinrichs and Hofmann 2001), the neural processing of verbal stimuli in social phobia has received considerably less attention than that of faces. A recent study employed tasks that either directly or indirectly involved the processing of verbal threat-related stimuli that were phobia-related or phobia-unrelated (Schmidt et al. 2010). Direct processing involved attending to the social meaning of the words whereas indirect processing involved attending to the grammatical category of the words. While no differences were found between the groups on the direct processing task, social phobics compared to the healthy control group showed elevated responses in the amygdala and the orbitofrontal cortex when indirectly processing phobia-related versus phobia-unrelated words.

So far only one fMRI study has explicitly focused on assessing the brain responses associated with the fear of negative evaluation in social phobia (Blair et al. 2008). The neural response of patients with social phobia were compared to that of a healthy control group while processing self-referential versus other-referential criticism (e.g., You're an idiot, She's an idiot), praise (e.g., You're a genius, She's a genius) or neutral information (e.g., You're a human, She's a human). Processing self-referential criticism compared to any other kind of information led to stronger activations in emotion-relevant regions of the brain such as the bilateral amygdala and medial prefrontal cortices in the social phobics relative to the control group. This was complemented by the behavioral data which indicated that the social phobics rated the self-referential criticism to be significantly more unpleasant than the control group. These are consequential findings as they bring together the defining criteria of social phobia together with evidence of information processing biases in terms of its associated behavioral and neural indices. Moreover, these results are also consistent with previous work where social phobics were shown to be prone to interpretation biases exclusively when social information was processed from the self-perspective, but not the other-perspective (Amir et al. 1998). What remains unknown is whether this enhanced affective response to self-referential threat is specific for social cues or whether it represents a generalized response to all self-threatening information that need not necessarily be social in nature. An example of the latter would be self-referential physical illness-related information.

The current study was developed in view of the findings by Blair et al. (2008) in order to explore the extent to which such biases in social phobia are also present in sub-clinical social anxiety. We sought to verify whether the behavioral biases as well as the special role attributed to the amygdala and the medial prefrontal cortex in the processing of self-referential socially negative stimuli in social phobia could also be found in healthy individuals who demonstrate high levels of social anxiety.

In order to determine the specificity of such biases, we examined whether they would be exclusively associated with negatively evaluative social stimuli or also with non-social threat stimuli. For instance, if the response in these brain regions was modulated by one's type and level of anxiety, it would be expected that highly socially anxious individuals would exhibit stronger responses when processing negative social stimuli (e.g., You are worthless) but not when processing negative non-social stimuli (e.g., You have cramps). Similarly, we also explored whether "hyperactivity" (Blair et al. 2008) in these brain areas as well as the polarized behavioral assessment of the stimuli is particular to social anxiety in response to negative social information, or whether parallel findings would be associated with other types of anxiety, such as health anxiety[1] in response to illness information (Marcus et al. 2007). Indeed, cognitive models have proposed that health anxiety arises when benign bodily sensations are misinterpreted based on selective attention to illness-related information which is referred to oneself (Warwick and Salkovskis 1990; Williams 2004).

The current event-related functional magnetic resonance imaging (fMRI) paradigm was developed in line with these objectives. Self-referential relative to other-referential processing was examined in relation to social negative, health negative and neutral information in highly social anxious individuals (HSA), highly health anxious individuals (HHA) and in a non-high anxious control group (NC).

[1] It should be noted that health anxiety or hypochondriasis belongs to the generic classification of somatoform disorders and not anxiety disorders (DSM-IV-TR). Health anxiety was nevertheless chosen as the control variable in this study as it offered a good parallel to social anxiety in several respects. With few other disorders is it possible, for instance, to generate the variety of salient verbal stimuli necessary for such a paradigm that can be sensibly adapted to test self-referentiality versus other-referentiality. Moreover, as the symptom of anxiety or worry is a core feature of hypochondriasis, the hypotheses regarding the brain structures involved would be expected to be similar when it comes to the processing of anxiety-relevant stimuli. In fact, there is evidence that some facets of information processing-related brain differences in hypochondriasis are comparable to that of other anxiety disorders, such as panic disorders (van den Heuvel et al. 2005).

The first step in the analyses would be to determine whether the experimental paradigm is valid in accordance with prerequisite behavioral and neural criteria. This includes evidence showing that the HSA have the highest degree of social anxiety whereas the HHA have the highest degree of health anxiety relative to the other groups (sample characterization), and that the social and health negative stimuli are rated to be more unpleasant than the neutral stimuli by all participants (stimuli characterization). In addition, the fMRI findings across all participants should reveal that self-referential relative to other-referential processing would be accompanied by activations in the medial prefrontal cortex, posterior cingulate cortex, inferior parietal lobule and temporal poles as these brain regions are active during self-referential thinking (Lou et al. 2004; Northoff et al. 2006; Schmitz and Johnson 2007). Also, in line with the emotion processing literature, negative (social and health) relative to neutral information processing should be associated with greater activity in the medial prefrontal cortex and amygdala across all participants (Bishop 2007; Canteras et al. 2010; Etkin 2010; Salzman and Fusi 2010).

Following the validation of the experimental paradigm, group based differences will be explored to test whether the findings from Blair et al. (2008) can be extended to subclinical social anxiety. To ensure a comprehensive comparison of the findings from both studies, region-of-interest analyses will also be conducted alongside whole brain analyses within the bilateral medial prefrontal cortex and amygdala as these regions were reported to be more strongly engaged in social phobics compared to controls during the processing of self-referential social negative stimuli relative to self-referential social positive stimuli, self-referential social neutral stimuli or any other-referential stimuli. As previous work on diverse anxiety disorders has also implicated the involvement of these regions in the processing of anxiety-specific emotional stimuli (Etkin 2010; Etkin and Wager 2007; Shin and Liberzon 2010), it is expected that the processing of anxiety-relevant compared to anxiety-irrelevant information would lead to stronger activations in these regions. Highest activations would be expected from the HSA during the processing of self-referential social negative information and from the HHA during the processing of self-referential health negative information. Corresponding behavioral differences are also expected such that, relative to the other groups, the HSA rate the social negative stimuli to be the most unpleasant stimuli type whereas the HHA rate the health negative stimuli to be the most unpleasant stimuli type.

## Methods

### Participants

The sample was selected based on the screening of 280 undergraduate volunteers who completed the German Fear of Negative Evaluation Scale (FNE) (Vormbrock and Neuser 1983; Watson and Friend 1969) (Mean=45.26, SD=10.01) and the German Health Anxiety Inventory (HAI) (Bailer and Witthöft 2006; Salkovskis et al. 2002) (Mean=34.63, SD=11.27). The FNE assesses the extent of one's fear of criticism (e.g., "I often worry that I will say or do the wrong things"), whereas the HAI assesses the degree to which one is excessively concerned about one's health (e.g., "If I hear about an illness I always think I have it myself").

On the basis of their scores on the FNE and HAI, 60 participants were randomly selected from this pool of volunteers and assigned to one of three groups. The non-high anxious control group (NC) included participants ($n$=20) who obtained a score between Mean±1 standard deviation (SD) on both the FNE and the HAI. The high social anxiety group (HSA) ($n$=20) included participants who obtained a score greater than the Mean+1 SD on the FNE but between Mean±1 SD on the HAI. The high health anxiety group (HHA) ($n$=20) consisted of participants who obtained scores greater than Mean+1 SD on the HAI but between Mean ±1 SD on the FNE. The descriptive data for all groups over each of the self-report measures are given in Table 1. All participants were native German speakers with no reported history of neurological or psychiatric illness (as indicated within a telephone screening prior to recruitment for the study). None were taking medication at the time of measurement. All gave informed consent before participation and received either payment (EUR 20) or course credits for their participation. The experimental standards of the study were approved by the Local Ethics Commission of the Justus Liebig University of Giessen in Germany.

After excluding participants who exhibited movement artefacts in their fMRI data (more than 3 mm head motion), the final sample whose data was analyzed included 55 participants (41 females, 14 males) within three subgroups: HSA ($n$=19; 14 females, 5 males; mean age=23.42), HHA ($n$=18; 14 females, 4 males; mean age=22.89) and NC ($n$=18; 13 females, 5 males; mean age=23.42). These three groups did not differ from one another with regard to age, gender or depressiveness as assessed by the German version of the CES-D (Center for Epidemiological Studies Depression Scale) (all $p$>0.5).

### Experimental design

A 2×3×3 factorial design was employed with reference type (self, other), information type (social-negative, health-negative, neutral), and group (HSA, HHA, NC) as the factors. There were 30 trials per condition (social-self, social-other, health-self, health-other, neutral-self, neutral-other) as well as 30 catch trials (explained below) and 18 resting baseline trials (empty screen which was presented every 9–12 trials). All stimuli were presented visually in a pseudo-randomized order (e.g., all trial transition types were counterbalanced). With a

**Table 1** Descriptive data of all the behavioral dependent measures (CES-D = Center for Epidemiological Studies Depression Scale; FNE = Fear of Negative Evaluation Scale; HAI = Health Anxiety Inventory, HHA = high health anxiety group, HSA = high social anxiety group, NC = normal anxiety control group, SAM = Self-Assessment Manikin Valence Ratings, SIAS = Social Interaction Anxiety Scale, SPS = Social Phobia Scale, WI = Whiteley Index)

| | HSA | | HHA | | NC | |
|---|---|---|---|---|---|---|
| | Mean | Std Dev | Mean | Std Dev | Mean | Std Dev |
| Age | 23.42 | 2.61 | 22.89 | 2.95 | 22.33 | 2.81 |
| N | 19 | - | 18 | - | 18 | - |
| Female : Male | 14:5 | - | 14:4 | - | 13:5 | - |
| FNE | 61.53 | 4.18 | 47.39 | 5.09 | 45.78 | 6.86 |
| SPS | 24.63 | 8.77 | 17.22 | 12.27 | 11.00 | 8.43 |
| SIAS | 32.32 | 7.89 | 20.89 | 11.80 | 16.78 | 9.64 |
| HAI | 31.26 | 5.93 | 49.00 | 5.29 | 25.28 | 5.14 |
| WI | 1.42 | 1.46 | 5.61 | 3.24 | 1.00 | 1.14 |
| CES-D | 18.79 | 7.84 | 17.71 | 8.73 | 15.13 | 11.33 |
| SAM social-self | 7.26 | 0.53 | 6.87 | 1.02 | 6.26 | 0.74 |
| SAM health-self | 6.76 | 0.75 | 6.72 | 1.00 | 5.89 | 0.74 |
| SAM neutral-self | 4.26 | 0.45 | 4.00 | 0.88 | 4.33 | 0.36 |
| SAM social-other | 5.78 | 0.56 | 5.71 | 0.75 | 5.33 | 0.85 |
| SAM health-other | 6.04 | 0.79 | 5.93 | 0.99 | 5.51 | 0.52 |
| SAM neutral-other | 4.68 | 0.35 | 4.69 | 0.61 | 4.65 | 0.58 |

trial length of 7.5 s and a total of 228 trials, the experimental session lasted around 30 minutes. The participants were given instructions and a 10-minute practice session with stimuli that were not used in the experiment on a laptop prior to the imaging session. The imaging session was followed by a feedback session where participants were required to complete the German Whiteley Index (WI) (Pilowsky 1967; Rief et al. 1994), the Social Phobia Scale (SPS) and Social Interaction Anxiety Scale (SIAS) (Mattick and Clarke 1998; Stangier et al. 1999). The WI measures hypochondriacal beliefs (e.g., "Do you feel like others do not take your illnesses seriously enough"), whereas the SPS/SIAS assesses the fear of being observed during general social interaction (e.g., "I have difficulty talking with other people."). Following the fMRI session, participants rated the stimuli from the 6 experimental conditions using the 9-point Self-Assessment Manikin Scale (SAM) (Bradley and Lang 1994) in terms of how they experienced each of the 180 statements to be ranging from 1 ("extremely pleasant") to 9 ("extremely unpleasant").

## Experimental task

Following a variable jitter period (0–1500 ms), each trial began with a fixation cross (300 ms) which was followed by a brief pause (200 ms) and then the presentation of the sentence stimuli in the middle of the screen (2000 ms) (Fig. 1). Responses were accepted up to 1000 ms after the stimuli disappeared from the screen. German sentences were used as stimuli in all conditions. The participant's first and last names were used for all trials which were self-referential (e.g., Jane Doe …) whereas all sentences that were other-referential began with the word "Steffi Graf". Steffi Graf was chosen as the other-reference based on the results of a pilot study (unpublished) which indicated that she was the German celebrity with the most neutral associated valence. Sentences contained either socially negative (e.g., Jane Doe is worthless), health negative (e.g., Jane Doe feels dizzy), or neutral information (e.g., Jane Doe is female). Catch trials were defined as those trials where the presented sentences contained a spelling mistake (e.g., Jane Doe is tirepd). The participants were required to read the sentence and to indicate with a left button press ("read-button") once they had finished reading it. However, if the sentence contained a spelling mistake, the participants were required to indicate this with a right button press ("mistake-button"). Such "catch trials" were included to ensure that the subjects were actually performing the task while they were in the scanner. Anyone who did not reach the behavioral criterion of 75 % accuracy on the catch trials were to be excluded from the final sample. The data revealed that all participants showed a high response accuracy (over 90 %) which indicated that they were performing the task as instructed.

## MRI scanning procedure

Functional and anatomical imaging was carried out using a 1.5 Tesla whole-body tomography system (Siemens Symphony) with a standard head coil. The structural image acquisition consisted of 160 T1-weighted sagittal images (MPRAGE, 1 mm slice thickness). One functional run was

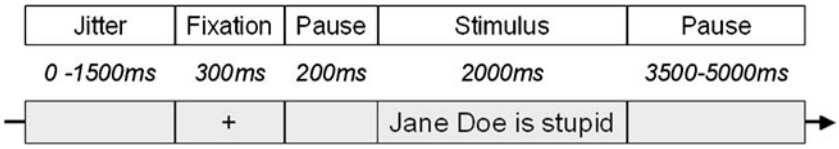


**Fig. 1** The trial events were the same across all conditions. Each trial began with a jitter period (blank screen) that varied from trial to trial (0–1500 ms). This was directly followed by a fixation cross for 300 ms which indicated the commencement of the task. Following a brief pause (200 ms), the sentence was presented for 2000 ms to which the participants responded with button presses. This was followed by a longer pause (3500–5000 ms). The total trial duration was 7.5 s

carried out with a total of 902 volumes recorded using a T2*-weighted gradient echo-planar imaging sequence (EPI) with 25 slices covering the whole brain (slice thickness= 5 mm; gap=1 mm; descending slice order; TA=100 ms; TE=55 ms; TR=2.5 s; flip angle=90°; field of view= 192 mm×192 mm; matrix size=64×64). The orientation of the axial slices was tilted to parallel the OFC tissue–bone transition to minimize susceptibility artefacts. The stimuli were visually projected onto a screen which was viewed through a mirror mounted on the head coil.

## fMRI data analysis

The fMRI data were processed using the LIPSIA software package (Lohmann et al. 2001) .[2] This freeware contains tools for preprocessing, registration, statistical evaluation and presentation of fMRI data. Functional data were motion-corrected using a matching metric based on linear correlation. To correct for the temporal offset between the slices acquired in one scan, a sinc-interpolation based on the Nyquist-Shannon-Theorem was applied. Low-frequency signal changes and baseline drifts were removed using a temporal high pass filter with a cut-off frequency of 1/100 Hz. Spatial smoothing was performed with a Gaussian filter of 10 mm FWHM. The functional data were registered to the anatomical data via a rigid linear registration with 6 degrees of freedom (3 rotational, 3 translational) and were then normalized to the Talairach standard space. The normalized parameters were then used to transform the functional slices using trilinear interpolation, thus generating output data with a spatial resolution of 3×3×3 mm (voxel size: 27 cubic mm).

The statistical evaluation was based on a least-squares estimation using the general linear model for serially autocorrelated observations (Friston et al. 1994; Worsley and Friston 1995). The design matrix used to model the data consisted of onset vectors for each of the six conditions with two additional onset vectors for the catch trials and null events. The design matrix was generated with a box-car function, convolved with the hemodynamic response function. The hemodynamic modelling was done using a gamma function and two derivatives (temporal, dispersion). Brain activations were analyzed in an event-related design, time-locked to the presentation of the stimulus. The model equation, including the observation data, the design matrix, and the error term, was convolved with a Gaussian kernel dispersion of 5 s FWHM to account for the temporal autocorrelation. Contrast images or beta value estimates of the raw-score differences between specified conditions were generated for each participant. As all individual functional data sets were aligned to the same stereotactic reference space, the single-subject contrast images were entered into a second-level Bayesian statistical analysis for each of the contrasts (Neumann and Lohmann 2003). The single subject parameter estimates obtained from the general linear model are used to calculate posterior probability maps and maps of the effect size for the contrasts of interest. This Bayesian statistical method, in comparison to conventional analyses based on t statistics, has been shown to be more robust against outliers. It provides estimates for the size of an effect of interest and the probability for that effect to occur in the population. It even overcomes some of the common problems of null hypothesis significance tests such as the need to correct for multiple comparisons. The output of the Bayesian second-level analysis is a probability map which shows the probability that the contrast is greater than zero. There are no "thresholds" that indicate the significance of a result within the framework of Bayesian statistics.[3] As values of over 99 % are generally held to indicate a high probability of activation, a threshold of 99 % was applied in the current study with a minimum cluster size of 5 voxels (135 cubic mm). To determine which brain regions were commonly activated across contrasts as a function of a particular process of interest, conjunction analyses were carried out from these direct contrasts.

For the explorative ROI analyses, the single-subject contrast images were entered into a second-level random-effects analysis for each of the contrasts. ROI analyses (a peak voxel coordinate with a 3-voxel radius sphere) were carried out by pre-selecting regions of interest reported by Blair et al. (2008) in the left mPFC (peak coordinate: X: -26, Y: 35, Z: 38), right mPFC (peak coordinate: X: 16, Y: 35, Z: 48), left amygdala

[2] For more information, refer to: http://www.cbs.mpg.de/institute/software/lipsia/index.html)

[3] For more information, refer to: http://static.cbs.mpg.de/lipsia/vbayes/index.html

(peak coordinate: X: -23, Y: -3, Z: -22), and right amygdala (peak coordinate: X: 24, Y: -2, Z: -22). One-sample t tests were employed for the group analyses across the contrast images of all subjects which indicated whether observed differences between conditions were significantly distinct from zero. t values were subsequently transformed into z scores. The results were uncorrected with the minimum threshold set at $p<0.05$, which is an extremely lenient threshold to adopt in order to detect effects.

## Results

### Sample characterization

The descriptive data are presented in Table 1. Statistical analyses of the questionnaire data revealed that the HSA was more socially anxious and the HHA was more health anxious relative to the other groups. The HSA had significantly higher scores than the HHA and NC on all the social anxiety measures such as the FNE, SPS and SIAS (all $p<0.05$, all d>0.6) whereas the HHA displayed significantly higher scores than the HSA and NC on both the measures of heath anxiety, namely the HAI and the WI (all $p<0.001$, all d>1.6). While the HHA were no different from the NC on all three measures of social anxiety, the HSA showed elevated responses compared to the NC on one of the health anxiety measures (HAI: $p<0.005$, d=1.08).

### Stimuli characterization

In order to assess the stimuli, a 2×3×3 repeated measures ANOVA was carried out on the SAM valence ratings of the stimuli with the factors reference type (self, other), information type (social, health, neutral) and group (HSA, HHA, NC). The results revealed all three main effects to be significant (all $p<0.005$; all $h_p^2 > 0.2$). While the interaction effects *reference x group* and *reference x information type x group* did not reach significance, the interaction effects *reference x information type* ($p<0.001$; $h_p^2 = 0.62$) and *information type x group* ($p=0.051$; $h_p^2 = 0.1$) reached or approached significance. Details pertaining to these analyses are presented in the Supplementary Material.

Further analyses to explore the *reference x information type* interaction revealed that regardless of reference, neutral stimuli were judged to be more pleasant than health and social stimuli (all $p<0.001$; all $h_p^2 > 0.4$). Within the emotional stimuli, self-referential social and health stimuli were both judged to be more unpleasant than the other-referential social and health stimuli respectively (all $p<0.001$; all $h_p^2 > 0.5$). The findings thus indicate that while social and health stimuli were rated as more unpleasant compared to the neutral stimuli, this effect was even stronger for self-referential relative to other referential stimuli.

Additional analyses to explore the *information type x group* interaction revealed that the HSA rated both social and health stimuli as being more unpleasant than the NC (all $p<0.02$; all $h_p^2 > 0.15$). A similar pattern, albeit less strong, was also found in the HHA group as they also rated health stimuli ($p=0.04$; $h_p^2 = 0.11$) and social stimuli ($p=0.075$; $h_p^2 = 0.9$) to be more unpleasant than the NC group. However, there were no significant differences between the three groups in their pleasantness ratings of the social versus health stimuli (all $p>0.5$). These findings thus indicate that although the HSA and HHA rated the social and health stimuli to be more unpleasant than did the NC, there was no clear indication of significant anxiety-specific differences between the groups in their stimulus ratings as the HSA did not rate the social stimuli as being more negative than the health stimuli and the HHA did not rate the health stimuli as being more negative than the social stimuli.

In order to rule out that important effects were being overlooked due to power issues that result from such an omnibus analysis, we carried two further analyses. The first was w 3×3 ANOVA on the SAM valence ratings of the stimuli with the factors information type (social, health, neutral) and group (HSA, HHA, NC) using only the self-referential stimuli, which resulted in a significant interaction effect *information type x group* ($p=0.004$; $h_p^2 = 0.14$). *T*-test analyses to explore this interaction revealed that the HSA rated the self-referential social stimuli to be significantly more unpleasant than the self-referential health stimuli ($p<0.01$, d=0.5) but there were no such differences between HHA's ratings of the self-referential health versus social stimuli. Moreover, although there were no significant differences between the HSA and HHA groups on their ratings of the self-referential health or neutral stimuli, a medium effect size was found when exploring the differences between the HSA and HHA ratings of the self-referential social stimuli ($p=0.15$, d=0.5).

Taken together, the findings indicated that the expected pattern of greater unpleasantness ratings for the self-referential social stimuli by the HSA compared to the other groups was partially confirmed. When the information is self-referential, HSA rated the social stimuli more negatively than the other stimuli compared to the comparison groups. The predictions with reference to the stimulus ratings for the HHA, however, were not supported by the findings.

### fMRI findings (whole brain analyses): paradigm validation

To assess the efficacy of paradigm, it was vital to demonstrate that self-referential and emotional information processing led to activations across all participants in a network of regions commonly found to be involved during these kinds of information processing. Self-referential thinking, for instance, is usually accompanied by activations in the dorsal and ventral aspects of the medial prefrontal cortex (mPFC), posterior

cingulate cortices (PCC), temporoparietal junction (TPJ) and the temporal poles (TP). In line with predictions, the comparison of self-referential relative to other-referential information processing (direct contrast: self > other) revealed activations in the aforementioned brain regions (Fig. 2) as well as in the inferior frontal and the middle temporal gyri (Table S1 in Supplementary Material).

The processing of emotional stimuli was expected to lead to activations in structures known to be relevant for information processing of emotional material such as the amygdala, insula, anterior cingulate, ventral medial PFC and orbitofrontal cortex (OFC). The findings from this comparison using a conjunction analysis (direct contrast: social > neutral ∩ direct contrast: health > neutral) revealed that, in line with predictions, the processing of both types of emotional stimuli (social and health stimuli) relative to neutral stimuli resulted in common activations in the ventral medial PFC and the amygdala (Fig. 2) (Table S2 in Supplementary Material).

In summary, the findings validate the efficacy of the current paradigm in that emotional and self-referential processing led to activations in relevant brain structures that have been widely implicated in the literature.

## fMRI whole brain findings: between-groups contrasts (Interaction: Group x Information type)

In line with predictions concerning stimulus-specific brain activation differences in relation to social anxiety, it was expected that the medial PFC as well as the amygdala would be more strongly involved in the HSA compared to the HHA and NC when processing social relative to neutral information as well as when processing social relative to health information. This was not supported by the findings of the conjunction analyses of the social versus neutral contrast (HSA versus NC: social versus neutral ∩ HSA versus HHA: social versus neutral) nor the social versus health contrast (HSA versus NC: social versus health ∩ HSA versus HHA: social versus health) (Table 2). In fact, neither of these regions was found to be significantly activated even in the direct contrast between the HSA and NC in the processing of social versus neutral information. Only one relevant region for emotional information processing, the right insula, was activated as a function of this interaction effect (Fig. 3, $p<0.05$). However, the pattern of findings was not in the expected direction as stronger activations in the insula were associated with the HSA when presented with neutral compared to social conditions, whereas the opposite was true for the NC.

Similar predictions were made concerning health anxiety related stimulus-specific brain activation differences, where it was expected that the medial PFC as well as the amygdala would be more strongly involved in the HHA compared to the NC and HSA when processing health relative to neutral information as well as when processing health relative to social information. These hypotheses were neither supported by the findings of the conjunction analyses (Table 2) nor the direct contrast between the HHA and NC when processing health versus neutral information.

In accordance with the previous findings on the role of referentiality in modulating the activation patterns in specific brain regions, it was also expected that the medial PFC and amygdala would be more strongly involved in the HSA compared to the other groups when processing self-referential relative to other-referential social information. By extension, it was also expected that the same regions would be more strongly involved in the HHA compared to the other groups when processing self-referential relative to other-referential health information. The results from the conjunction analyses that were carried out to this effect do not support these hypotheses as only regions in the inferior frontal, middle temporal and inferior temporal gyri were significantly more involved in anxiety-specific self-referential information processing in each of the groups (Table 3).

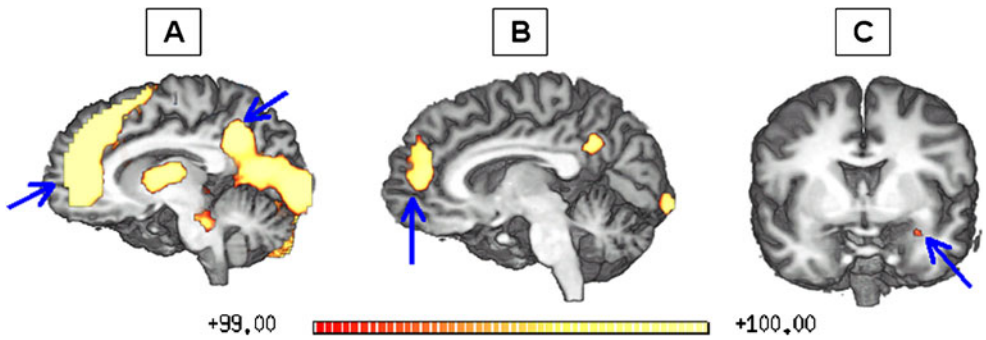


**Fig. 2** (**A**) Self-referential > Other-referential thinking was associated with greater activations in the medial prefrontal and the posterior cingulate cortices; (**B**) Emotional > Neutral information processing was associated with activation in the medial prefrontal cortex, (**C**) Emotional > Neutral information processing was associated with activation in the amygdala. Blue arrows indicate the location of all these brain regions

**Table 2** Group-based differences in brain regions activated when processing social emotional stimuli and health emotional stimuli relative to neutral stimuli. The minimum threshold for the findings was set at 99 % probability (Bayesian). The results associated with all four conjunction analyses are given below in terms of anatomical specification, Talairach coordinates, maximum probability (Prob) and volume (mm3) of the significantly activated areas. [HHA: high health anxiety group; HSA: high social anxiety group, NC: normal-anxious control group; ∩: logical 'AND' conjunction]

| Area | x | y | z | BA | mm3 | Prob |
|---|---|---|---|---|---|---|
| HSA vs NC (social vs neutral) ∩ HSA vs HHA (social vs neutral) | | | | | | |
| Insula | 25 | 14 | 15 | | 3375 | 99.98 |
| Caudate Nucleus | 19 | -16 | 27 | | 243 | 99.68 |
| Cerebellum | 1 | -82 | -18 | | 297 | 99.67 |
| Cerebellum | -23 | -88 | -27 | | 162 | 99.68 |
| Cerebellum | -41 | -70 | -30 | | 486 | 99.84 |
| Cerebellum | 43 | -70 | -33 | | 270 | 99.31 |
| HSA vs NC (social vs health) ∩ HSA vs HHA (social vs health) | | | | | | |
| Cerebellum | 1 | -88 | -33 | | 594 | 99.75 |
| HHA vs NC (health vs neutral) ∩ HHA vs HSA (health vs neutral) | | | | | | |
| (no significant findings) | | | | | | |
| HHA vs NC (health vs social) ∩ HHA vs HSA (health vs social) | | | | | | |
| (no significant findings) | | | | | | |

## fMRI findings (ROI analyses): between-groups contrasts

As a final step, region-of-interest (ROI) analyses in the bilateral amygdala and mPFC were carried out to explore the comparability between the results of the current study with that of Blair et al. (2008). All of the previously mentioned between-groups contrasts were carried out on these four functional ROIs (direct contrasts uncorrected at $p<0.05$). Despite such lenient

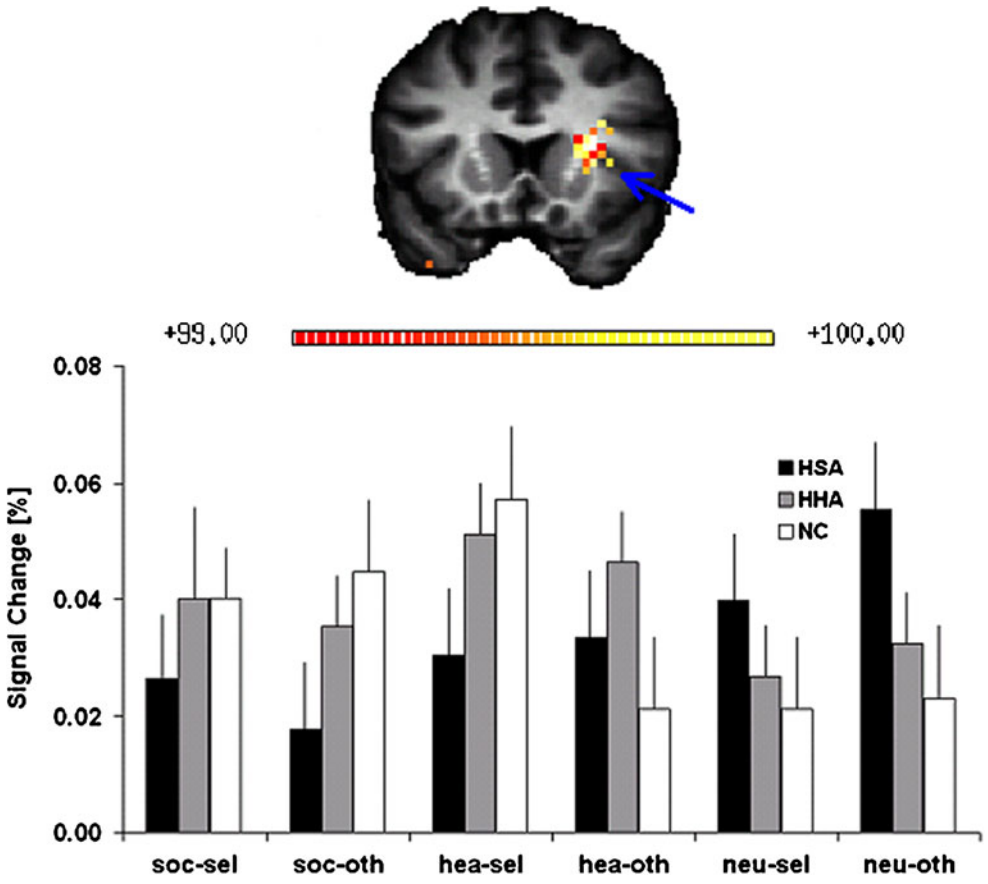


**Fig. 3** A significant interaction effect (Group x Information type) was found in the insula for the social versus neutral conjunction contrast (HSA versus NC: social versus neutral ∩ HSA versus HHA: social versus neutral). However, this was not in the expected direction as higher BOLD responses in this region surfaced within the HSA when presented with neutral compared to social conditions whereas the opposite was true for the NC. The graph shows the average percentage signal change (PSC) response (Mean+ SE) associated with all conditions within a peak voxel and its 26 adjacent neighboring voxels in the insula (peak coordinate: X=25, Y=14, Z= 15). (Abbreviations: soc = social, neu = neutral, hea = health, sel = self, oth=other)

**Table 3** Group-based differences in brain regions involved when processing stimulus-specific self-emotional stimuli relative to other-emotional stimuli. The minimum threshold for the findings was set at 99 % probability (Bayesian). The results associated with all the conjunction analyses are given below in terms of anatomical specification, Talairach coordinates, maximum probability (Prob) and volume (mm3) of the significantly activated areas. [HHA: high health anxiety group; HSA: high social anxiety group, NC: normal-anxious control group; ∩: logical 'AND' conjunction]

| Area | x | y | z | BA | mm3 | Prob |
|---|---|---|---|---|---|---|
| HSA vs NC (social-self vs social-other) ∩ HSA vs HHA (social-self vs social-other) | | | | | | |
| Inferior frontal gyrus | -47 | 26 | -3 | 47/45 | 135 | 99.57 |
| Middle temporal gyrus | -56 | -34 | 0 | 21 | 189 | 99.72 |
| HHA vs NC (health-self vs health-other) ∩ HHA vs HSA (health-self vs health-other) | | | | | | |
| Middle temporal gyrus | 46 | -49 | 3 | 21 | 189 | 99.74 |
| Inferior temporal gyrus | 52 | -22 | -15 | 20 | 378 | 99.73 |

criteria, only one interaction effect, Group x Information type (HSA versus NC: social versus neutral), was found to be significant ($p$=0.035) in the left amygdala. However, the activation differences were not in the expected direction as the interaction effect was driven by weaker BOLD responses in the neutral conditions compared to the social condition on the part of the NC relative to the HSA. The activations across all conditions in each of the ROIs (Figs. 4, 5, 6 and 7) clearly illustrate that the pattern of findings in each area is contrary to the expected direction of highest activations in HSA for self-referential social stimuli and highest activations in HHA for self-referential health stimuli.

## Discussion

The objective of the current study was to validate and extend the findings reported by Blair and colleagues (2008) on the processing of self-referential versus other-referential information of praise and criticism in social phobia. We examined whether the specific role attributed by the authors to the amygdala and the medial prefrontal cortex in the processing of self-referential socially negative stimuli in social phobia as well as the behavioral biases exhibited by the social phobics in their ratings of the criticism stimuli would also be observed in individuals who are highly socially anxious. In order to investigate this question, it was essential to also examine the specificity of the claim such as whether the "hyperactivity" of these brain regions and the behavioral bias as a function of social anxiety was limited to socially evaluative negative stimuli. If these regions were reacting in a anxiety-specific manner in accordance with one's type and level of anxiety, it would be expected that highly socially anxious individuals would show stronger brain responses in these regions when processing self-referential socially negative stimuli (e.g., You are worthless) but not when processing self-referential non-social negative stimuli (e.g., You have cramps). We also took the opportunity to explore whether the enhanced activity in these regions is specific to social anxiety in response to negative social information or whether the similar patterns of activity in the same regions would also be associated with other types of anxiety, such as health anxiety in response to physical illness-related information.

The experimental paradigm employed in the current study was developed in line with these ideas. Self-referential relative to other-referential information processing was assessed in relation to social negative, health negative and neutral

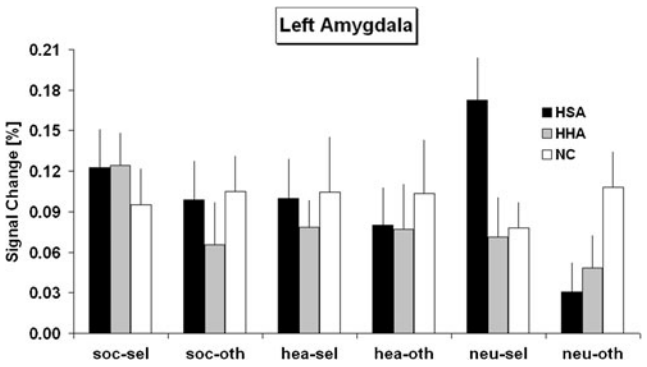


**Fig. 4** The graph shows the average PSC response (Mean+SE) associated with all experimental conditions within a peak voxel and its 26 adjacent neighboring voxels in an ROI within the left amygdala (peak coordinate: X=-23, Y=-3, Z=-22)

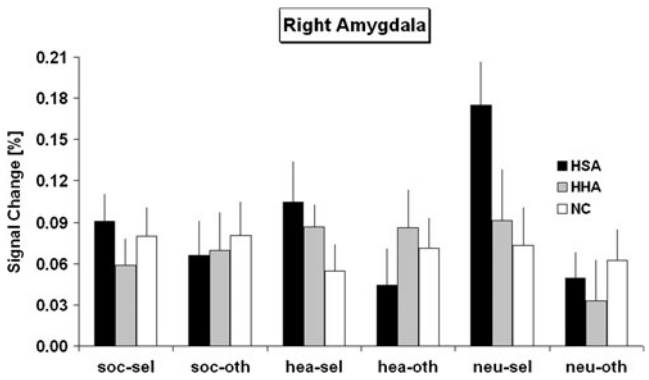


**Fig. 5** The graph shows the average PSC response (Mean+SE) associated with all experimental conditions within a peak voxel and its 26 adjacent neighboring voxels in an ROI within the right amygdala (peak coordinate: X=24, Y=-2, Z=-22)

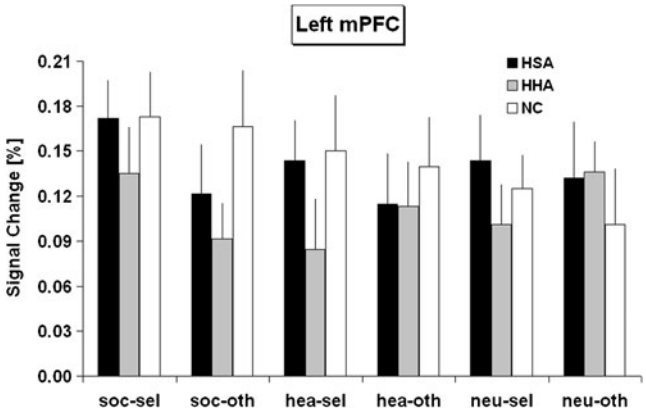


**Fig. 6** The graph shows the average PSC response (Mean+SE) associated with all experimental conditions within a peak voxel and its 26 adjacent neighboring voxels in the ROI within the left medial prefrontal cortex (peak coordinate: X=-26, Y=35, Z=38)

information in highly social anxious individuals (HSA), highly health anxious individuals (HHA) and in a non-high anxious control group (NC). The analyses of the sample characterization, stimuli characterization and the paradigm validation revealed a satisfactory implementation of all three factors. The HSA group were significantly more socially anxious than the other groups and that the HHA were significantly more health anxious than the other groups. All participants also rated the social and health stimuli to be more unpleasant than the neutral stimuli and this effect was even more pronounced for self-referential versus other referential stimuli, which is in line with the findings of Blair et al. (2008). Moreover, the fMRI analyses across all participants revealed that self-referential processing in contrast to other-referential processing was accompanied by activations in regions such as the ventral and dorsal medial prefrontal cortex, posterior cingulate cortex, inferior parietal lobule and temporal poles. These brain regions have been extensively implicated in self-referential thinking using a variety of different paradigms (Legrand and Ruby 2009; Lou et al. 2004; Northoff et al. 2006; Schmitz and Johnson 2007; Zysset et al. 2002). Finally, the processing of negative valence information (social and health) relative to neutral information was associated with activity in the ventral medial PFC and the amygdala which fits well with the bulk of previous literature on emotional information processing (Canteras et al. 2010; Etkin 2010; Lamm and Singer 2010; Morrison and Salzman 2010; Salzman and Fusi 2010; Shin and Liberzon 2010; Singer et al. 2009). Together these findings indicate a successful implementation of the experimental paradigm which was a pre-requisite to allow sound interpretations of the group-based differences in the behavioral and fMRI data.

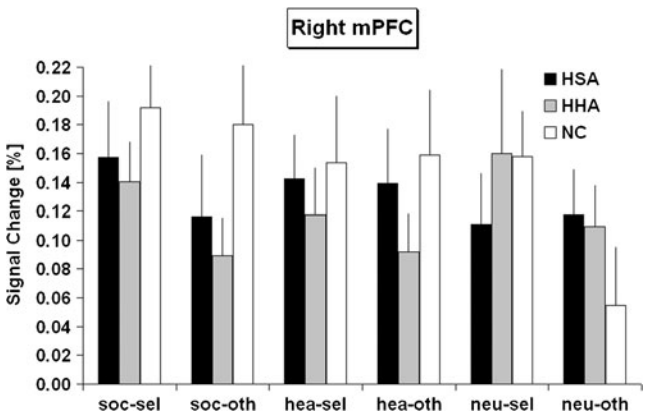


**Fig. 7** The graph shows the average PSC response (Mean+SE) associated with all experimental conditions within a peak voxel and its 26 adjacent neighboring voxels in an ROI within the right medial prefrontal cortex (peak coordinate: X=16, Y=35, Z=48)

## Group differences: behavioral findings

Information processing biases as a function of social anxiety when faced with socially relevant negative stimuli have been widely reported in the literature in both social phobics and in highly socially anxious individuals (for competing views, see Straube et al. 2005). Similar information processing biases when faced with health relevant stimuli have been reported in hypochondriacs and highly health anxious individuals (Marcus et al. 2007). Although such findings appear to speak for the stimulus-relevant nature of such biases, the reality is that the specificity of such biases has seldom been tested beyond the issue of valence. It is rare to find studies where non-specific or more than one negative valence stimulus is employed as a comparison to neutral and/or positive valence stimuli (Brühl et al. 2011; Goldin et al. 2009). The current study has gone beyond the customarily adopted approach in that an additional variable was included in the experimental design to assess stimulus specificity and its modulatory effect on the behavioral and brain data. The findings revealed that although both the HSA and HHA perceive stimuli of negative valence to be more unpleasant than neutral stimuli in comparison to the NC, this bias is unaffected (in the case of the HHA) or only partially affected (in the case of the HSA) by the relevance of the stimuli vis-à-vis their own anxieties.

The social stimuli was rated to be more unpleasant than the health stimuli by the HSA compared to the other groups, but only in selective contexts, such as when the information was self-referential. The HHA, on the other hand, did not rate the health stimuli (self-referential or other-referential) to be significantly more unpleasant than the social stimuli. This was unexpected given that the self-report questionnaire measures indicated that the HHA were significantly more health anxious than the other groups. The absence of the predicted information processing bias for health stimuli in association with the HHA compromises our ability to interpret the brain imaging related findings resulting from the HHA-related health stimuli comparisons. The fMRI findings associated with the HHA group will therefore not be discussed further.

An important point to bear in mind at this juncture is that had the current study only focused on the processing of socially negative versus neutral stimuli in HSA relative to NC, the logical conclusion would have been that the participants behaved as predicted given that, compared to the NC, the behavioral findings indicate that the HSA had indeed experienced the social stimuli to be overwhelmingly more negative than the neutral stimuli. And this would be in line with the findings of Blair et al. (2008). The present more complex findings have resulted from including both non-social stimuli as well as a subclinical control group within the paradigm in an effort to more comprehensively test the specificity of such biases. These results indicate that caution needs to be exercized when generalizing the implications of findings based on seemingly straightforward designs.

## Group differences: fMRI findings

With regard to the fMRI findings, it was expected that the results of the current study would constitute an extension of the findings from Blair et al. (2008) in that the amygdala and medial PFC would be involved during the processing of salient stimulus-specific information as a function of social anxiety. The findings, however, did not show any involvement of these brain structures during the processing of social negative information relative to health negative or neutral information in the HSA group compared to the other groups. Further analyses were also carried out to assess whether the self-referentiality of the salient information modulated the responsivity in these brain regions such that they would be more strongly involved during self-referential relative to other-referential information processing of social stimuli in the case of the HSA compared to the other groups. Although such a pattern was also predicted from the behavioral findings of the current study, these expectations were not supported by the imaging data. In order to ensure that this lack of significant results was not attributable to a Type II error, functional data-based region of interest (ROI) analyses were carried out on the same peak coordinates in the amygdala and mPFC as reported by Blair et al. (2008). Despite adopting a liberal threshold for establishing significance, the ROI findings were not in line with, and were partly even contrary to, predictions. The current study was thus unable extend the findings of Blair et al. (2008) in the predicted fashion.

## Wider implications of the findings

There are a number of factors to consider when interpreting the findings of the current study in relation to that of Blair and colleagues (2008). It is possible, for instance, that the expected effects in the amygdala and the mPFC were too subtle to be detected in a sub-clinical population like highly social anxious individuals compared to people with social phobia. This argument cannot be fully ruled out especially given that different measures of social anxiety were employed in both studies. However, it should be noted that the HSA displayed levels of social anxiety that are consistent with that of other studies where altered processing of social threat has been reported in relation to social anxiety (Amir et al. 2005; Amir et al. 2008; Bögels and Lamers 2002; Stevens et al. 2010, 2011). In addition, performance on the the Liebowitz Social Anxiety Scale (LSAS), which was employed by Blair et al. (2008) to assess social anxiety symptoms, correlates very highly with performance on other social anxiety measures such as the FNE, SIAS and SPS, which were used in the current study (Heimberg et al. 1999). Most importantly, the findings in the brain areas of interest were not even in the hypothesized direction. Indeed, in some cases, the pattern of activation within these brain regions were most strongly seen in the HSA group when processing neutral stimuli compared to emotional stimuli. While the findings of Blair et al. (2008) cannot be refuted on the basis of the current study, what certainly is apparent is that replication studies are necessary to clarify several issues.

It is imperative, for instance, to assess whether the negative biases (behavioral and neural) associated with anxiety disorders such as social phobia are truly anxiety-specific or simply valence-general. Such an endeavour would involve incorporating both social and non-social stimuli into an experimental design when assessing information processing biases in social phobia. Previous work has indeed shown that patients with social anxiety disorder exhibited stronger activation in emotional arousal brain regions even when presented with non-specific general emotional stimuli (Brühl et al. 2011). Moreover, brain areas such as the amygdala have been also found to be more active during emotional face processing in generally anxiety-prone subjects, as determined by measures of trait anxiety (Stein et al. 2007).

Another factor that could account for the divergence of the findings of the current study with that of Blair et al. (2008) is that, unlike in the original study, we did not employ positive stimuli. Given what is known about the ambiguity that is sometimes associated with the processing of neutral stimuli in social anxiety (Cooney et al. 2006; Hermann et al. 2004) as well as the current findings of heightened activation of the insula and the amygdala within the HSA group in response to neutral information, it is possible that including positive stimuli in the experiment design is necessary so that the participants experience enough divergence between the valences of the stimuli during the experiment. Positive stimuli could not be incorporated in the current experimental design because of issues related to stimuli construction. Unlike in the case of social anxiety where stimuli invoking "praise" are positive alternatives to negative stimuli that invoke "criticism", there are very few positive alternatives to health anxiety negative stimuli that invoke "physical illness".

Other differences between the experimental designs include that the current study used an event-related design whereas Blair et al. (2008) employed a block design. Both design types are associated with particular advantages and disadvantages over the other (Amaro and Barker 2006; Arja et al. 2010). The robust

findings associated with the whole group analyses on self-referential thinking and emotional information processing argue strongly against the possibility that the event-related design employed in the current study was suboptimal. A further important difference between the paradigms was the "other-referentiality" factor. Blair and colleagues (2008) did not exert control over who the participants chose as their "other-reference" which meant that the other-reference factor in their case was associated with more variability than that of the "self-reference". As the importance of the choice of the other-reference has been addressed in the study of the self-reference effect (Symons and Johnson 1997) and the fact that fMRI investigations of self-referential thinking customarily employ explicit other-references (Lou et al. 2004), the current study chose a fixed other-reference for all participants. In addition, the inclusion of "catch trials" in the current paradigm enabled us to ensure that participants were genuinely attending to the task at hand. The male-to-female ratio between the two studies was also different as the current study included 13–14 women and 4–5 men across all groups whereas the study by Blair et al. (2008) included 11 men: 6 women in the patient group and 8 men: 9 women in the control group. While neither study reported differences between the groups in terms of gender, the gender proportion in the present study is highly consistent with the data on the prevalence of social phobia in the general population.

The chief limitation of the current study was the sample size especially given that the between-subjects and multifactorial nature of the experimental design. This may have resulted in low power and as a consequence a reduced ability to detect subtle differences between the groups. To deal with this issue, we conducted Bayesian analyses as opposed to conventional t-tests as this approach is more robust against outliers. ROI analyses on the key regions specified by Blair et al. (2008) were also carried out using a liberal uncorrected threshold to ensure whether at least the general expectations of the direction of differences between the groups could be confirmed. This was not found to be the case.

A further limitation was that the psychiatric history screening of participants was only done via self-report. Conducting a more systematic clinical or structured interview for DSM-IV disorders, for instance, would have enabled higher homogeneity of the samples under study. Such procedures, however, can be logistically complex as well as time and cost intensive, which is why they are not always feasible. Another concern was that the HSA also showed higher scores on one measure of health anxiety compared to the NC. While it could be argued that this may have led to the clouding of some results, this is unlikely to have been the case as the HSA was the most socially anxious group and the HHA was the most health anxious group. In addition, the level of health anxiety in the HSA was comparable to that previously reported for control or student samples on the HAI (Salkovskis et al. 2002), and the HSA group did not show higher responses on the second measure of health anxiety (Whiteley Index). Moreover, the patterns of results in the brain regions of interest are not explained by such differences.

## Conclusions

The current study was designed to extend the findings reported by Blair and colleagues (2008) of behavioral biases as well as "hyperactivity" in the amygdala and the medial prefrontal cortices of social phobics when faced with emotional stimuli conveying self-referential criticism in comparison to praise or neutral information. Although the presented behavioral evidence was at least partially in line with their findings, the imaging evidence demonstrated that the pattern of brain activity associated with social phobia cannot be generalized to individuals with a high degree of subclinical social anxiety. The findings therefore highlight the need to replicate the original study in terms of the specificity of the claims regarding the stimulus relevance associated with the brain response in relation to social anxiety. It is especially necessary to ascertain the degree to which the "socialness" of the stimuli have an impact on the information processing bias associated with social phobia, as well as whether such effects are limited to social anxiety or can be generalized to other anxiety disorders. Related lines of investigation could include assessing the correlation between degree of symptom severity in social phobia and the strength of activation in pertinent brain regions when performing such experiments. Such investigations are necessary if the objective is to uncover the neurocognitive mechanisms underlying the biases associated with the information processing of emotional stimuli in anxiety disorders.

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