Psychological Medicine (2017), **47**, 2502–2512. © Cambridge University Press 2017
doi:10.1017/S0033291717001076

ORIGINAL ARTICLE

Altered activation of the ventral striatum under performance-related observation in social anxiety disorder

M. P. I. Becker[1,2]*†, D. Simon[1,2]†, W. H. R. Miltner[1] and T. Straube[1,2]

[1] *Department of Biological and Clinical Psychology, Friedrich Schiller University, D-07743 Jena, Germany*
[2] *Institute of Medical Psychology and Systems Neuroscience, University Hospital Muenster, D-48149 Muenster, Germany*

Background. Social anxiety disorder (SAD) is characterized by fear of social and performance situations. The consequence of scrutiny by others for the neural processing of performance feedback in SAD is unknown.

Methods. We used event-related functional magnetic resonance imaging to investigate brain activation to positive, negative, and uninformative performance feedback in patients diagnosed with SAD and age-, gender-, and education-matched healthy control subjects who performed a time estimation task during a social observation condition and a non-social control condition: while either being monitored or unmonitored by a body camera, subjects received performance feedback after performing a time estimation that they could not fully evaluate without external feedback.

Results. We found that brain activation in ventral striatum (VS) and midcingulate cortex was modulated by an interaction of social context and feedback type. SAD patients showed a lack of social-context-dependent variation of feedback processing, while control participants showed an enhancement of brain responses specifically to positive feedback in VS during observation.

Conclusions. The present findings emphasize the importance of social-context processing in SAD by showing that scrutiny prevents appropriate reward-processing-related signatures in response to positive performances in SAD.

Received 14 June 2016; Revised 9 March 2017; Accepted 28 March 2017; First published online 3 May 2017

Key words: Feedback, observation, midcingulate cortex, insula, social anxiety disorder, ventral striatum.

Introduction

Individuals suffering from social anxiety disorder (SAD) are characterized by persistent fear responses in social interactions or performance situations (APA, 2013). SAD patients show considerable aversion toward being exposed to scrutiny by others and tend to interpret their role in ambiguous social situations as more negative than healthy controls (HC) (Jensen & Heimberg, 2015). In particular, the clinical picture of SAD frequently comprises severe apprehensiveness about the overt display of performance inadequacy – nervousness, stammering, erythrophobia, tremor, among many others – resulting in public humiliation (Kessler *et al.* 1998; Heimberg *et al.* 2014). It has been suggested that maladaptive appraisals of evaluative social information in patients with SAD promote anxiety, excessive post-event processing (Rachman *et al.* 2000), and subsequent safety and avoidance behaviors (Stangier & Frydrich, 2002).

In search of neural foundations of this disorder, numerous functional imaging studies have investigated the neural correlates of processing negative social stimuli, including negative feedback, in SAD (Freitas-Ferrari *et al.* 2010; Miskovic & Schmidt, 2012; Schulz *et al.* 2013). Research has, for example, pinpointed the role of the amygdala (for an overview see Miskovic & Schmidt, 2012). In accordance with its assumed role as salience detector region, the amygdala might gain its critical role in SAD pathophysiology by a hypersensitivity to evaluative information (Schulz *et al.* 2013). Furthermore, hyper-activation of the anterior insular cortex (AIC) is associated with SAD and has been taken as an indication of biased allocation of attention to bodily signals (Straube *et al.* 2004; Miskovic & Schmidt, 2012). Moreover, activation of midcingulate cortex (MCC), a region frequently co-activated with AIC (Shackman *et al.* 2011; Cieslik *et al.* 2015), has repeatedly been found to be elevated when processing salient cues in SAD (Amir *et al.* 2005; Miskovic & Schmidt, 2012) as well as subclinical social anxiety (Heitmann *et al.* 2014). Investigating

* Address for correspondence: M. P. I. Becker, Institute of Medical Psychology and Systems Neuroscience, University Hospital Muenster, Von-Esmarch-Str. 52, D-48149 Muenster, Germany.
(E-mail: beckermi@uni-muenster.de)
† These authors contributed equally to this work.

neural responses to performance feedback in subclinical social anxiety, Heitmann *et al.* (2014) showed heightened responses of medial prefrontal cortex and anterior insula during receipt of performance feedback independently of its valence. This study also reported decreased medial prefrontal activation (MPFC) during anticipation of negative feedback. However, one widely neglected research field is how social contexts affect the processing of performance-related feedback signals. For example, in healthy individuals, positive performance-feedback is associated with activation of the ventral striatum (VS) (van Veen *et al.* 2004; Nieuwenhuis *et al.* 2005; Carlson *et al.* 2011; Becker *et al.* 2014). Critically, this activation is strongly modulated by social context with increased activation during an observation condition compared with a non-observation control condition (Simon *et al.* 2014). As a central part of the motivational or reward circuit (Haber & Knutson, 2010), VS receives and signals prediction errors (Ruff & Fehr, 2014; Becker *et al.* 2016) and plays a role in initiation of approach behaviors (O'Doherty *et al.* 2017), in humans most often investigated in the context of prosocial behavior (Rilling & Sanfey, 2011). Following this line of research, VS has been suggested to signal the social relevance of feedback and integrate the social context in which feedback is provided. Preliminary evidence in SAD shows decreased differential activation to rewards *v.* punishments in striatal regions during anticipation of social reward (Cremers *et al.* 2014; Richey *et al.* 2014, 2017) and during performance situations (Boehme *et al.* 2014*b*). Further, reduced dopamine D2-receptor and dopamine-transporter availability have been reported in SAD (Tiihonen *et al.* 1997; Schneier *et al.* 2000, 2008), although not unambiguously (Schneier *et al.* 2009). In the VS, presynaptic dopamine levels are associated with increased BOLD activation (Schlagenhauf *et al.* 2013) and dopamine release in this brain region has been associated with music-induced pleasure (Salimpoor *et al.* 2011), as well as signaling of prediction errors (Deserno *et al.* 2015).

Here we asked whether this phenomenon is also observed in SAD or whether patients show an abnormal pattern of performance feedback processing when observed by others. A task commonly used to administer performance feedback is the time estimation task where feedback is needed to infer the adequacy of one's behavioral response in an otherwise underdetermined response situation. We used this task to present participants with correct, incorrect, and ambiguous performance feedback tailored to their individual response accuracy (Miltner *et al.* 1997). We hypothesized that in patients with SAD reward-related activation is reduced during social observation. Specifically, we expected SAD to be associated with diminished BOLD responses in VS to positive relative to negative performance feedback during social observation. To investigate these potential differences between socially anxious and non-anxious individuals we used functional magnetic resonance imaging (fMRI), while SAD patients and healthy participants performed the time estimation task during an observation condition and a non-observation condition. We show that VS activations in patients are not subject to interactions of reward- and observation-condition as they are in HC. In particular, patients do not exhibit an increase of ventral striatal activation to positive feedback relative to negative feedback while observed by others as controls do.

Methods

Participants

A total of 16 patients with a DSM-IV diagnosis of SAD (11 females) were recruited by public announcements and provided written informed consent to participate in the study. 16 age-, gender-, and education-matched HCs were recruited as a control group (nine females); part of the HC group has previously been reported on in (Simon *et al.* 2014). All participants were right-handed, had normal or corrected-to-normal vision, and were above 18 years of age. The study was approved by the ethics-committee of the University of Jena. Diagnosis was confirmed by the Structured Clinical Interview for DSM-IV Axis I and Axis II disorders (SCID I and II; Wittchen *et al.* 1996). Comorbidities of the SAD sample included major depressive or dysthymic disorder ($n = 5$), obsessive-compulsive disorder ($n = 1$), Binge-eating disorder ($n = 1$), and specific phobia ($n = 1$). Participants had no neurological disorders. HC were free of any psychopathology and reported to not have taken psychotropic medication within the last 3 months. In SAD patients, assessment of medication status is incomplete and precludes the formal categorization of patients according to substance and dosage. Before scanning, all participants completed the LSAS (Liebowitz Social Anxiety Scale, German version; Stangier & Heidenreich, 2005), FNE (Fear of Negative Evaluation, German Version; Vormbrock & Neuser, 1983), and BDI (Beck Depression Inventory, German version; Hautzinger *et al.* 1995) questionnaires. SAD patients scored significantly higher on both LSAS and BDI than the control subjects (Table 1). After the experiment but before being debriefed, subjects were asked if during the course of the experiment they had noticed anything that they wanted to mention. One patient explicitly reported the suspicion that they were not really observed and was excluded from all analyses. No control subject reported any suspicion that they were not actually being observed.

https://doi.org/10.1017/S0033291717001076 Published online by Cambridge University Press

Table 1. *Characteristics of social anxiety disorder (SAD) patients and healthy control (HC) samples*

	SAD ($n = 16$)	HC ($n = 16$)	t-value
Age, mean years (S.D.)	35.3 (±12.7)	38.4 (±12.5)	$t(30) = -0.72$
Gender, male : female	5 : 11	7 : 9	$\chi^2 = 0.53$
Education[a]	9 : 7 : 0	8 : 7 : 1	$U = 0.50$
LSAS, mean (S.D.)	69.4 (±21.2)	28.4 (±14.6)	$t(30) = 6.03$*
FNE, mean (S.D.)	57.5 (±9.2)	38.9 (±8.1)	$t(30) = 6.38$*
BDI, mean (S.D.)	16.8 (±11.3)	6.1 (±5.2)	$t(30) = 3.41$*

Mean scores and standard deviations on Liebowitz Social Anxiety Scales (LSAS), Fear of Negative Evaluation (FNE), and Beck's Depression Inventory (BDI), as well as mean age.

*$p < 0.05$.

[a] Educational period <12 years: 12 years: >12 years.

Experimental procedure

Controls and patients were exposed to two different experimental conditions: in one condition they were informed that they were observed by a video camera mounted inside the scanner bore (observation condition); in the other condition, the camera was not mounted and subjects were informed that no observation was taking place (control condition). Participants were instructed that in the observation condition an observer would focus on visible physiological reactions of the participant's face (e.g. skin perfusion and pupil dilation). Further, participants were informed that blocks with and without a camera were required to optimize recording parameters. The sequence of both conditions was balanced across subjects. Both groups were requested to participate in a time estimation task (Miltner *et al.* 1997; Simon *et al.* 2014) that required estimating the duration of one second in response to an auditory cue by pressing a button as soon as they considered the second elapsed. Subsequently, subjects received positive, negative, or uninformative performance-feedback (the letters A, B, and C assigned pseudo-randomly across subjects to these feedback types) about the accuracy of their response (Becker *et al.* 2014; Simon *et al.* 2014). An adaptive algorithm ensured that all three feedback-types were presented about equally frequently (i.e. ~33% for each feedback type) to both groups in the observation and control conditions. In order to achieve this, the length of a time window around the target time point of 1 s was decreased by 20 ms if the response lay within the window or increased by 20 ms, if the response lay outside the window. The initial value of the time window's length at the start of each block was determined in a training run.

Behavioral data were analyzed using analysis of variance (ANOVA) and independent sample t tests and *post-hoc* t tests using SPSS software (Version 22, IBM Corp., Armonk, NY). A $2 \times 2 \times 3$ level repeated measures ANOVA with group (SAD *v.* HC) as between group factor and observation condition (observation *v.* control) and feedback (positive *v.* negative *v.* uninformative feedback) as within-groups factors were used for reaction times and ratings of valence, arousal, and threat.

We tested for feedback-related accuracy effects in estimation behavior, i.e. whether accuracy on a given trial differed on average for different feedback types presented on the previous trial. We estimated accuracy on a given trial n by calculating the absolute value of the difference between response latency in trial n and 1 s and expressed this as a function of the feedback presented in trial $n-1$. Then we tested whether accuracy differed on average between the feedback conditions.

fMRI data acquisition and analysis

Scanning was performed in a 3-Tesla magnetic resonance scanner (Magnetom Trio, Tim System 3T; Siemens Medical Systems, Erlangen, Germany). After acquisition of a T1-weighted anatomical scan, two runs of T2*-weighted echo planar images consisting of 370 volumes were recorded (TE, 30 ms; TR = 2100 ms, flip angle, 90°; matrix, 64×64; field of view, 192 mm^2). Each volume comprised 35 axial slices (slice thickness 3 mm; interslice gap 0.5 mm; in-plane resolution 3×3 mm^2), which were acquired with a 30° caudally tilted orientation relative to the anterior–posterior commissure line in order to reduce susceptibility artifacts (Deichmann *et al.* 2003). Prior to that, a shimming procedure was performed. To ensure steady-state tissue magnetization the first four volumes were discarded from the analysis.

Functional MRI-data preprocessing and analysis were performed using Brain Voyager QX software (Version 2.4; Brain Innovation, Maastricht,

https://doi.org/10.1017/S0033291717001076 Published online by Cambridge University Press

Netherlands). Data pre-processing comprised correction for slice time errors and temporal (high-pass filter: 10 cycles per run; low-pass filter: 2.8 s; linear trend removal) as well as spatial [8 mm full-width at half-maximum (FWHM) isotropic Gaussian kernel] smoothing. The anatomical and functional images were coregistered and transformed to normalized Talairach-space (Talairach & Tournoux, 1988).

Statistical analyses were performed by multiple linear regression of the signal time course at each voxel. Expected blood oxygenation level-dependent (BOLD) signal change for each predictor was modeled by a 2-gamma hemodynamic response function. On the first level, predictor estimates based on *z*-standardized time course data were generated for each subject using a random-effects model with adjustment for autocorrelation following a global AR(2) model. On the second level, predictor estimates were analyzed across subjects for the relevant contrasts. We investigated brain responses in regions of interest relevant for feedback processing and/ or SAD symptomatology. Thus, we performed small-volume correction for VS, because the structure plays a major role in reward processing (Haber & Knutson, 2010), as well as insula, anterior cingulate cortex (ACC), MPFC, amygdala, dorsal striatum, and MCC because these regions' have repeatedly been shown to be involved in SAD (Amir *et al.* 2005; Miskovic & Schmidt, 2012; Schulz *et al.* 2013). Masks for these regions were extracted from the AAL atlas included in WFU PickAtlas software (Tzourio-Mazoyer *et al.* 2002; Maldjian *et al.* 2003) after dilating them by 1 mm. Using in-house MATLAB (Version 7.8; MathWorks, Natick, MA) scripts based on ICBM2tal (Lancaster *et al.* 2007) all maps were transformed into BrainVoyager-compatible Talairach coordinates. A cluster-size threshold estimation procedure was used (Goebel *et al.* 2006) to correct for multiple comparisons. Significant clusters of contiguously activated voxels were determined by a Monte Carlo simulation based on 2000 iterations. After setting the voxel-level threshold to $p < 0.005$ (uncorrected) and specifying the FWHM of the spatial filter, the simulation resulted in a minimum cluster size of 6 contiguously activated functional voxels (162 mm^3) corresponding to a false positive rate of 5%. We refer to this false positive rate as $p_{corrected}$. The watershed-algorithm of Neuroelf (v0.9c; http://neuroelf.net/; i.e. the splitclustercoords function) was used to assess local maxima of clusters.

Results

Behavioral data

Immediately after the experiment, subjects separately rated valence, arousal, and threat induced by each feedback category and each observation condition. One patient's rating data had to be excluded from analyses due to a misconception of the scale format.

Across both groups and observation conditions, a 2 (*group: SAD, HC*) × 2(*observation condition: observation, control*) × 3(*feedback: positive, negative, ambiguous*) *repeated measures ANOVA* showed significant main effects for arousal [$F(2,58) = 13.74$, $p < 0.05$] and valence [$F(2,58) = 46.46$, $p < 0.05$], both of which resulted from positive feedback being rated as more pleasant than negative [$t(30) = 7.13$, $p < 0.05$] and uninformative feedback [$t(30) = 8.64$, $p < 0.05$], and more arousing than negative [$t(30) = 3.65$, $p < 0.05$] and uninformative feedback [$t(30) = 4.39$, $p < 0.05$]. Furthermore, negative feedback was rated less pleasant than uninformative feedback [$t(30) = 2.18$, $p < 0.05$] but not less arousing [$t(30) = 1.40$, $p > 0.05$].

Furthermore, the repeated-measures ANOVA yielded an observation × group interaction for ratings of threat [$F(1,29) = 4.58$, $p < 0.05$]. Post-hoc comparison revealed that SAD subjects rated feedback as significantly more threatening than HC subjects if it was received during the observation condition [$t(29) = 2.23$, $p < 0.05$] but not if it was received during the control condition [$t(29) = 1.33$, $p = 0.20$]. While an observation × group interaction of valence ratings was marginally significant [$F(1,29) = 3.57$; $p < 0.07$], no further significant main effects or interactions involving the group factor were found for ratings of valence and arousal (all p values $\geqslant 0.11$).

As revealed by a significant main effect [$F(2,60) = 57.96$; $p < 0.05$], reaction time data indicated that subjects' estimations were more accurate in trials after positive feedback than in trials after negative [$t(31) = 9.98$, $p < 0.05$] or uninformative feedback [$t(31) = 5.39$, $p < 0.05$]. However, no significant group differences were found for any reaction time measure (all p values >0.05).

A robust behavioral finding in the time estimation task is the increased estimation accuracy after presentation of positive feedback. This is indicated by increased accuracy in trials that succeed a positive feedback trial as compared to trials that succeed negative or uninformative feedback trials. We analyzed whether on average accuracy in estimation differed for positive, negative, and ambiguous feedback in these subsequent trials. First, we calculated the absolute deviation of response latencies from the target time point (1 s after auditory cue onset) for every trial n. Then, we averaged the absolute deviation from the target time point across all trials that follow positive feedback in position $n-1$ and repeated this step for all trials that follow negative feedback and uninformative feedback in position $n-1$, respectively (Simon *et al.* 2014). Entering this data into the repeated-measures

https://doi.org/10.1017/S0033291717001076 Published online by Cambridge University Press

ANOVA, we found that estimations were significantly more accurate in trials after positive feedback [$F(2,60) = 18.43$; $p < 0.05$; after positive: M = 158 ms (±67 S.D.); after negative: M = 197 ms (±85 S.D.); after uninformative: M = 181 ms (±82 S.D.)]. This effect did not differ significantly between groups [$F(1,30) = 0.98$; $p = 0.33$], neither did the interaction of observation and group [$F(1,30) = 3.50$; $p = 0.07$].

fMRI data

Elevated responses in patients

Across both groups and observation conditions, activation in VS [left peak *x,y,z*: −12,8,−2, $t(31) = 6.63$, $p_{corrected} < 0.05$, cluster size 11 988 mm^3; right peak *x,y,z*: 12,11,−2, $t(31) = 5.51$, $p_{corrected} < 0.05$, cluster size 1485 mm^3] and ACC [peak *x,y,z*: 04,47, $t(31) = 4.75$, $p_{corrected} < 0.05$, cluster size 13 959 mm^3] was detected for positive relative to negative feedback. Across both groups, differential processing of positive and negative performance-feedback in VS was elevated in the observation condition relative to the control condition [peak *x,y,z*: −3,11,−2, $t(31) = 3.31$, $p_{corrected} < 0.05$, cluster size 216 mm^3], which, however, was mainly driven by healthy participants (Fig. 1). Critically, there was a significant difference between groups for the interaction contrast of observation condition and feedback valence (positive *v.* negative) in left VS [peak *x,y,z*: −6,14,−5, $t(31) = 3.67$, $p_{corrected} < 0.05$, cluster size 324 mm^3] (Fig. 1). This effect was due to enhanced responses to positive feedback in the observation *v.* control condition in HC subjects as compared with SAD subjects [$t(30) = 4.06$, $p_{corrected} < 0.05$]. There were no differences between groups for negative [$t(30) = -0.46$, $p_{corrected} = 0.65$] or uninformative feedback [$t(30) = 0.57$, $p_{corrected} = 0.57$]. Thus, the observation condition only significantly changed processing of positive feedback in SAD subjects compared to HC subjects with diminished enhancement of observation driven VS activation in SAD subjects.

There was also a significant difference between groups for the interaction contrast of observation condition and feedback valence (positive *v.* negative) in MCC [peak *x,y,z*: −6,23,37, $t(31) = 3.85$, $p_{corrected} < 0.05$, cluster size 270 mm^3] (Fig. 2). Further analyses revealed that SAD and HC subjects showed a significant difference between observation and control conditions for positive feedback [$t(30) = 4.69$, $p_{corrected} < 0.05$], but not for negative [$t(30) = -0.06$, $p_{corrected} > 0.05$] or uninformative feedback [$t(30) = -0.62$, $p_{corrected} > 0.05$]. This significant difference resulted from MCC being more activated by positive feedback during the control condition in SAD than in HC subjects (Fig. 2).

Blunted responses in patients

We found a cluster in right ventral AIC to reflect an interaction between observation and group [peak *x,y,z*: 39,8,−11, $t(31) = -3.21$, $p_{corrected} < 0.05$, cluster size 216 mm^3]. However, AIC did not show the same pattern of activation differences between SAD and HC subjects that VS and MCC showed (Fig. 3). In HC subjects as compared with SAD subjects AIC was stronger activated by positive relative to negative feedback in the control condition than in the observation condition [$t(30) = -2.62$, $p_{corrected} < 0.05$]. Further, negative feedback did not elicit a differential response between the observation and control conditions in SAD subjects, while in HC subjects it did [$t(30) = 1.75$, $p_{corrected} < 0.05$].

Controlling for BDI scores

As BDI scores differed between groups, we tested whether group differences in beta estimates were maintained after controlling for depression levels. A univariate ANCOVA (analysis of covariance) with BDI scores as covariate revealed that neither in VS [$F(1,29) = 0.372$; $p = 0.547$], nor in AIC [$F(1,29) = 0.018$; $p = 0.893$] nor in MCC [$F(1,29) = 0.003$; $p = 0.956$] depression levels accounted for group differences in beta estimates.

Discussion

The data presented here demonstrate the importance of considering aberrant processing of positive performance-feedback when addressing the neural correlates of SAD. Compared with healthy age- and gender-matched controls, we found blunted activation in the VS of individuals with a diagnosis of SAD during reward processing under observation. By shifting the focus of research toward the human reward circuit this approach complements longstanding traditions in the clinical investigation of SAD-associated neurobiology.

While heightened sensitivity in amygdala and medial prefrontal cortex to self-referential negative feedback in SAD has been reported (Blair *et al.* 2008), very few fMRI studies have investigated alterations in the processing of performance-relevant feedback albeit either not in a clinical sample (Heitmann *et al.* 2014) or by using facial stimuli as feedback (Cremers *et al.* 2014; Richey *et al.* 2014). The present study investigated feedback-processing in a clinical sample of SAD subjects using a design that reliably modulated reward-related responses in the VS of HC subjects by manipulating the presence/absence of public observation (Simon *et al.* 2014). Other studies in healthy subjects have shown that gaining a good reputation activates VS (e.g. Izuma *et al.* 2008). Further, shared representation of reward value in VS across domains

https://doi.org/10.1017/S0033291717001076 Published online by Cambridge University Press

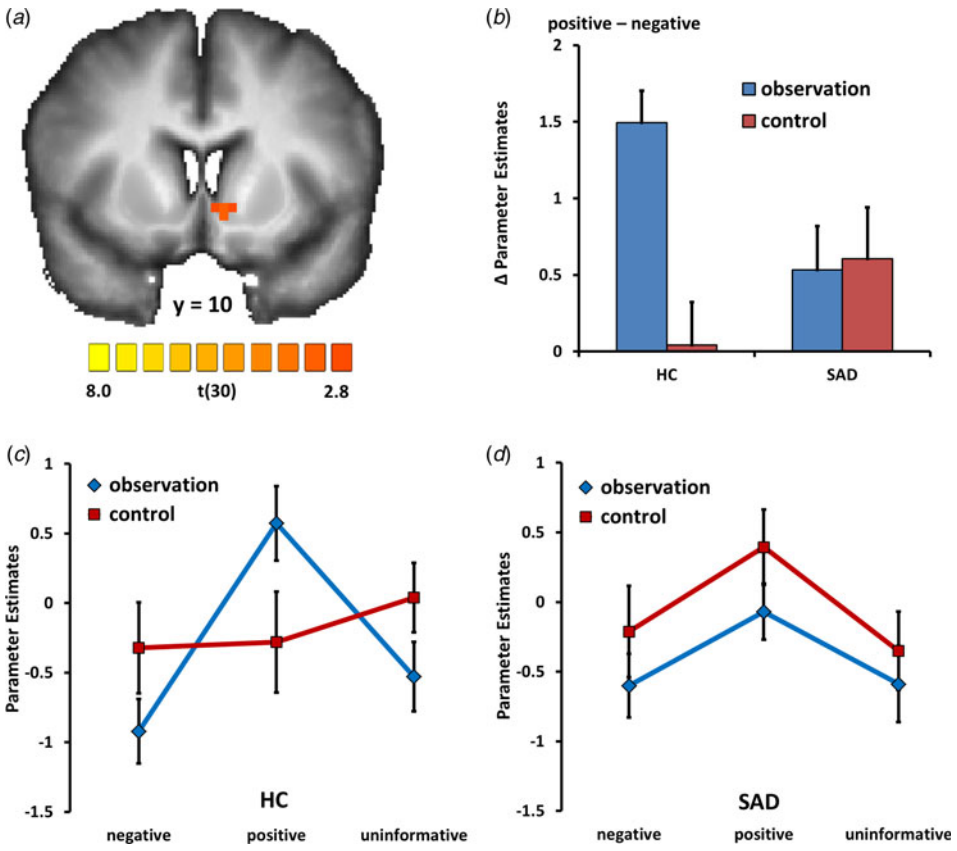

Fig. 1. Group-differences between patients with social anxiety disorder (SAD) and healthy controls (HC) in the camera-enhancement effect in ventral striatum (VS). (*a*) In HC, VS shows higher activation to the camera-enhancement effect than in SAD (contrast reflects higher difference between positive > negative feedback in the observation condition than in the control condition). (*b*) Differences in parameter estimates between observation and control conditions in left VS (peak *x*,*y*,*z*: −6,14, −5) shown separately for HC and SAD. In HC, valence-coding (positive > negative feedback) in VS is stronger in the observation condition than in the control condition, while in SAD this difference is absent. (*c*, *d*) Parameter estimates from the cluster in (*a*) and (*b*) shown condition-wise for the HC (*c*) and SAD (*d*) groups (observation condition in blue, control condition in red) reveal that the differences in (*a*) and (*b*) are due to enhanced responses to positive feedback in the observation *v*. control condition in HC subjects as compared with SAD subjects.

(money, social reward, and cognitive feedback) has been established (Lin *et al.* 2012; Daniel & Pollmann, 2014) and VS can be assumed to be a key region for processing social motivation (Le Bouc & Pessiglione, 2013; Ruff & Fehr, 2014).

In healthy participants, the mere presence of an observer is sufficient to increase VS activation to positive feedback. Accordingly, if HC subjects master a task successfully while being observed by others, VS seems to encode positive performance-feedback more strongly in comparison to being successful while acting alone. For SAD patients, performance situations that include observation by others induce or amplify apprehensiveness and often result in avoidance behavior. Presence of a social performance context appears to counteract the enhancing effect of observation on VS activation in SAD subjects. Specifically, processing of positive performance-feedback was *reduced* during observation in the SAD group. Thus, our findings strongly suggest defective use of social context information in reward processing in SAD subjects.

It has been demonstrated that SAD subjects tend to overemphasize the emotional impact of negative social outcomes relative to positive social outcomes (Gilboa-Schechtman *et al.* 2000). Further, individuals diagnosed with SAD even show negative affective reactions to successful social interactions (Wallace & Alden, 1997), possibly because they anticipate a positive social outcome to subsequently result in heightened standards for what is considered adequate, which might blunt the experience of positive emotions. Most importantly, a reduced bias to interpret ambiguous social information as benign and positive has been demonstrated in individuals with SAD (Amir *et al.* 2012).

Our results further support the assumption that SAD pathophysiology is also characterized by alterations of

https://doi.org/10.1017/S0033291717001076 Published online by Cambridge University Press

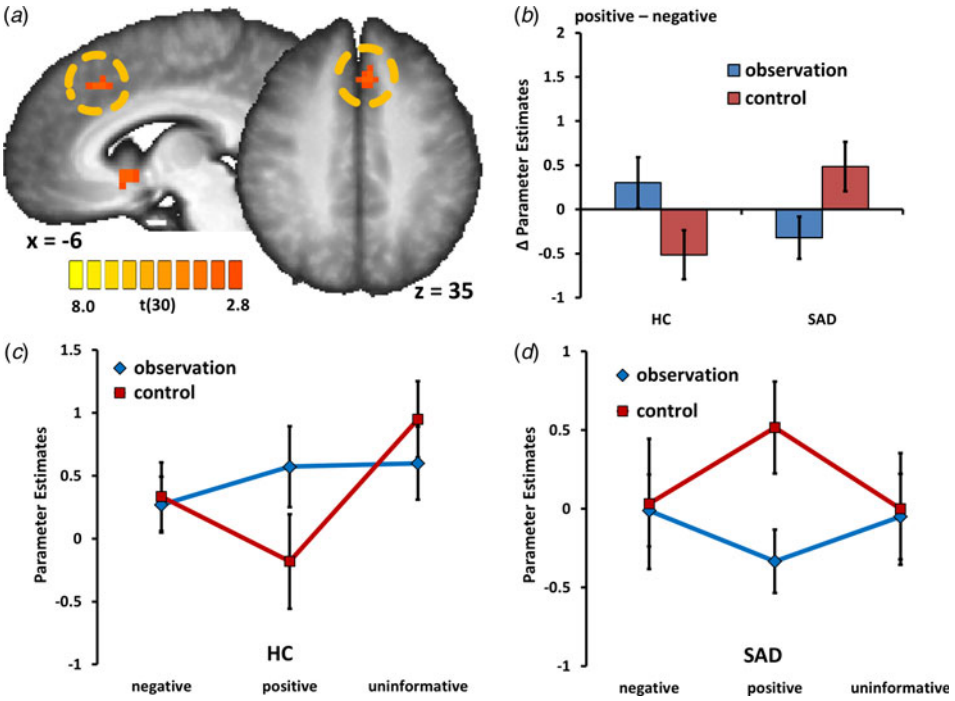

Fig. 2. Group-differences between patients with social anxiety disorder (SAD) and healthy controls (HC) in the camera-enhancement effect in midcingulate cortex (MCC). (*a*) In HC, MCC shows higher activation to the camera-enhancement effect than in SAD (contrast reflects higher difference between positive > negative feedback in the observation condition than in the control condition). (*b*) Differences in parameter estimates between observation and control conditions in MCC (peak *x*,*y*,*z*: −6,23,37) shown separately for HC and SAD. In HC, valence-coding (positive > negative feedback) in MCC is stronger in the observation condition than in the control condition, while in SAD this pattern reverses: valence-coding is stronger in control condition than in the observation condition. (*c*, *d*) Parameter estimates from the cluster in (*a*) and (*b*) shown condition-wise for the HC (*c*) and SAD (*d*) groups (observation condition in blue, control condition in red).

the system that generates positive social motivational signals. While biases for threatening and negative social information rightfully play an important role in current models of the disorder (Clark & Wells, 1995; Rachman *et al.* 2000), the cognitive dynamics of SAD might not be fully characterized without considering alterations in processing of positive social feedback. It is therefore necessary that future studies further investigate the alteration of this network in individuals diagnosed with SAD.

It has been proposed that in patients with SAD diminished activity of the behavioral approach system might contribute to genesis and maintenance of the disorder (Kimbrel, 2008). Classically, behavioral approach and the experience of positive emotions have been associated with the mesolimbic dopamine pathway connecting midbrain regions with the VS. Previously, changed striatal function in social anxiety has been suggested by [^{11}C]-PET and SPECT studies and decreased VS activity was shown to be linked to avoidance behaviors and reduced motivation (Schneier *et al.* 2009; Boehme *et al.* 2014*b*). Yet, these studies reported inconsistent findings regarding dopamine availability and utilization in striatal regions in SAD patients (Tiihonen *et al.* 1997; van der Wee *et al.* 2008; Schneier *et al.* 2009). Furthermore, differential VS activation to cooperative *v.* uncooperative partners during social decision making is absent in patients with SAD (Sripada *et al.* 2013). Recently, reduced activation of VS in SAD patients during anticipation of a public speech has been reported (Boehme *et al.* 2014*b*), suggesting that, in SAD patients, alterations of the brain system for positive motivational signals contribute to anticipatory anxiety in performance-related situations. As these situations are important for many social activities and in particular occupational and academic functioning, it is necessary to gain a deeper understanding of this phenomenon's behavioral and neural mechanisms.

Another region crucial for social motivation is the ACC, which often shows co-activation with VS. We found ACC to reliably code the difference between positive and negative feedback. However, in the paradigm we used, ACC activation does not distinguish between the observation and control conditions (see also Simon *et al.* 2014). Analogously, we did not find differences

https://doi.org/10.1017/S0033291717001076 Published online by Cambridge University Press

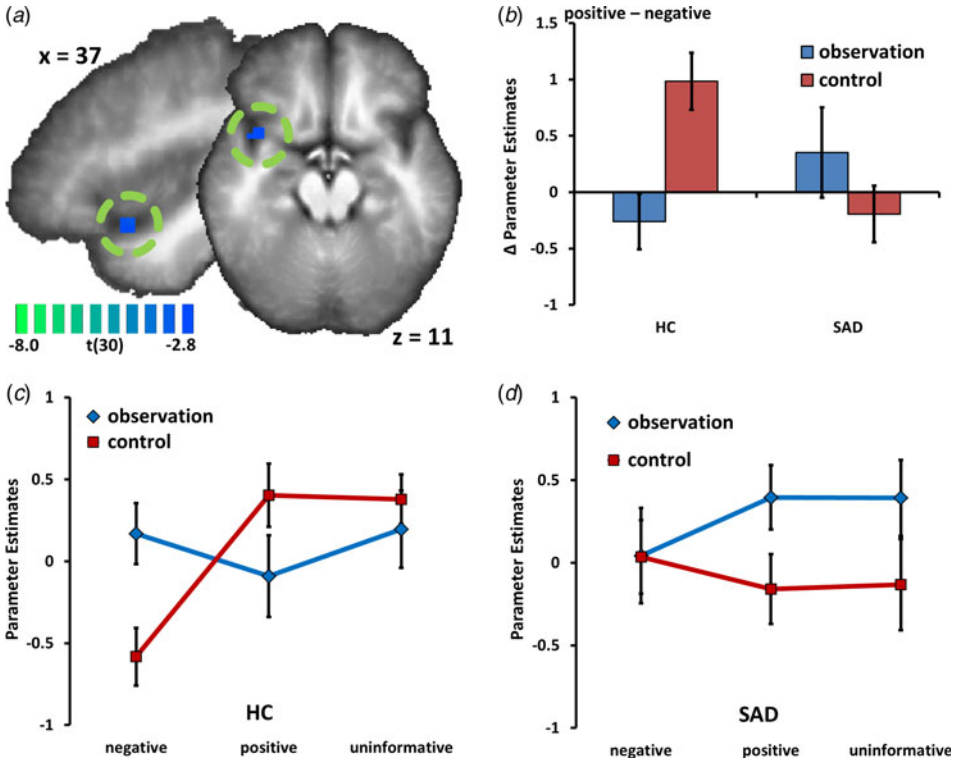

Fig. 3. Group-differences between patients with social anxiety disorder (SAD) and healthy controls (HC) in the camera-enhancement effect in anterior insula (AIC). (*a*) In HC, AIC shows higher activation to the camera-enhancement effect than in SAD (contrast reflects higher difference between positive > negative feedback in the observation condition than in the control condition). (*b*) Differences in parameter estimates between observation and control conditions in AIC (peak *x*,*y*,*z*: 39,8, −11) shown separately for HC and SAD. In HC, valence-coding (positive > negative feedback) in AIC is stronger in the control condition than in the observation condition, while in SAD this difference is absent. (*c*, *d*) Parameter estimates from the cluster in (*a*) and (*b*) shown condition-wise for the HC (*c*) and SAD (*d*) groups (observation condition in blue, control condition in red). See 'Results' for details.

between the SAD and HC groups in ACC activation. Evidence indicates that ACC activation is central for the computation of value in the human brain (Clithero & Rangel, 2014). Accordingly, we interpret the lack of a group difference in ACC activation to indicate that value computations in individuals with SAD are intact to a degree similar to HC subjects.

We also investigated the functional responses of MCC and AIC – two regions that are often co-activated within a network that tracks salient cues during tasks requiring context-based action-policy selection (Menon, 2011). Functional alterations in both regions have also been implicated in SAD (e.g. Straube *et al.* 2004; Amir *et al.* 2005; Boehme *et al.* 2014*a*). We found that MCC activation tracks differences in the processing of positive feedback between the groups, with SAD patients showing higher MCC responses to positive feedback than HC in the control condition. In past studies, MCC activation has most often been reported in the context of threatening stimuli (e.g. Straube *et al.* 2004; Amir *et al.* 2005; Boehme *et al.* 2014*a*). However, as positive performance feedback is unlikely to be perceived as threatening, the response pattern found here implies that MCC activation in SAD patients does not indicate the processing of threatening information *per se*. In healthy individuals, it has been repeatedly demonstrated that MCC encodes positive as well as negative feedback if both signal the same value of internally generated response selection processes (Walton *et al.* 2004; Jessup *et al.* 2010; Becker *et al.* 2014). The present findings suggest that positive feedback in the control condition has particular relevance for SAD patients compared to HC subjects. In the latter, MCC is significantly less active during positive feedback in the control condition; while in SAD there is no significant difference between MCC activation in any condition. Therefore, we would like to speculate that the group difference in MCC activation reflects differences in attribution of feedback relevance.

Interestingly, AIC activation does not precisely follow MCC activation. Both regions are often co-activated. But our results indicate that AIC of HC subjects also tracks differences in negative feedback between observation and control. In contrast, AIC of

https://doi.org/10.1017/S0033291717001076 Published online by Cambridge University Press

SAD patients does not show any significant differences in processing negative feedback between observation and control. In accordance with the literature, it is to assume that AIC activation reflects differences in attention to bodily states between the groups with SAD patients exhibiting generally elevated activation across all observation and feedback conditions. This finding concurs with the frequently reported observation of insular hyperactivation in SAD subjects.

Taken together, there is evidence that the neural pathophysiology of SAD should be investigated beyond the fear-related circuits traditionally implicated in the disorder. Blunted processing of positive feedback during observation is likely to prevent positive reinforcement of social approval and might even promote avoidance behaviors in the long run.

Limitations

We would like to report some important limitations of our study. An important limitation of the present results is the lack of concordance between neural and behavioral results, i.e. feedback ratings did not reflect the observation × feedback interaction found in VS. The neural effects not being accompanied by overt behavioral changes in ratings could imply that the interactions on the neural level are not primarily associated with evaluative behavioral responses such as valence, arousal, and threat ratings. Alternatively, this association might exist during the experiment but is not conserved in post-experimental ratings. Data from trial-by-trial ratings acquiring during the experiment proper might help solving this issue.

Another important limitation of the present results is the lack of detailed information regarding the medication status in patients. While there is evidence to suggest that the neural correlates of performance monitoring are not affected by Selective Serotonin Reuptake Inhibitors (SSRIs) at least in healthy volunteers (Fischer *et al.* 2015), it is not possible to statistically control for the influence of SSRIs or other psychotropic medication in this patient sample.

Another caveat of the present study is the lack of a formal measure for potential differences in intelligence between the groups, which might have interfered with processing of performance feedback. It must also be noted that the sample size of the present study is relatively small and cluster significance has been assessed by a cluster-size threshold procedure. Potentially owing to both limitations the dimensions of the identified regions were rather small (343 and 270 mm^3). However, it has been exemplified several times that activation of VS is reduced (Boehme *et al.* 2014*b*; Cremers *et al.* 2014; Richey *et al.* 2014, 2017) and activation of MCC is elevated (Amir *et al.* 2005; Miskovic & Schmidt, 2012) in SAD and these results were clearly predicted by theory. Further, an omnibus approach would theoretically decrease the potential for type I error. However, our contrasts have been derived from explicit hypotheses as well as prior work and reflect basic tenets of the reward-processing literature. Nonetheless, future studies are needed to replicate the effects.

Conclusions

SAD patients do not exhibit an increase of VS activation to positive feedback relative to negative feedback under observation as is the case in controls. Hence, this finding might prove fruitful in elucidating the neurocognitive basis of a crucial aspect of social anxiety symptomatology: the abnormal processing of positive reinforcement during social observation might be related to SAD patients' diminished responsiveness of the brain system that generates positive social motivational signals.

Acknowledgements

This research was supported by grants from the German Research Foundation (DFG project numbers: STR 987/3-1, & SFB/TRR-58, C06, C07).

Financial Disclosure

The authors reported no biomedical financial interests or potential conflicts of interest.

References

Amir N, Klumpp H, Elias J, Bedwell JS, Yanasak N, Miller LS (2005). Increased activation of the anterior cingulate cortex during processing of disgust faces in individuals with social phobia. *Biological Psychiatry* **57**, 975–981.

Amir N, Prouvost C, Kuckertz JM (2012). Lack of a benign interpretation bias in social anxiety disorder. *Cognitive Behaviour Therapy* **41**, 119–129.

APA (2013). *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. American Psychiatric Association: Washington, DC.

Becker MPI, Nitsch AM, Hewig J, Miltner WHR, Straube T (2016). Parametric modulation of reward sequences during a reversal task in ACC and VMPFC but not amygdala and striatum. *Neuroimage* **143**, 50–57.

Becker MP, Nitsch AM, Miltner WH, Straube T (2014). A single-trial estimation of the feedback-related negativity and its relation to BOLD responses in a time-estimation task. *Journal of Neuroscience* **34**, 3005–3012.

Blair K, Geraci M, Devido J, McCaffrey D, Chen G, Vythilingam M, Ng P, Hollon N, Jones M, Blair RJ, Pine

https://doi.org/10.1017/S0033291717001076 Published online by Cambridge University Press

DS (2008). Neural response to self- and other referential praise and criticism in generalized social phobia. *Archives of General Psychiatry* **65**, 1176–1184.

Boehme S, Mohr A, Becker MP, Miltner WH, Straube T (2014*a*). Area-dependent time courses of brain activation during video-induced symptom provocation in social anxiety disorder. *Biology of Mood and Anxiety Disorders* **4**, 6.

Boehme S, Ritter V, Tefikow S, Stangier U, Strauss B, Miltner WH, Straube T (2014*b*). Brain activation during anticipatory anxiety in social anxiety disorder. *Social Cognitive and Affective Neuroscience* **9**, 1413–1418.

Carlson JM, Foti D, Mujica-Parodi LR, Harmon-Jones E, Hajcak G (2011). Ventral striatal and medial prefrontal BOLD activation is correlated with reward-related electrocortical activity: a combined ERP and fMRI study. *Neuroimage* **57**, 1608–1616.

Cieslik EC, Mueller VI, Eickhoff CR, Langner R, Eickhoff SB (2015). Three key regions for supervisory attentional control: evidence from neuroimaging meta-analyses. *Neuroscience and Biobehavioral Reviews* **48**, 22–34.

Clark DM, Wells AA (1995). A cognitive model of social phobia. In *Social Phobia: Diagnossi, Assessment, and Treatment* (ed. R. G. Heimberg, M. R. Liebowitz, D. A. Hope and F. R. Schneider). pp. 69–93. Guilford Press: New York.

Clithero JA, Rangel A (2014). Informatic parcellation of the network involved in the computation of subjective value. *Social Cognitive and Affective Neuroscience* **9**, 1289–1302.

Cremers HR, Veer IM, Spinhoven P, Rombouts SA, Roelofs K (2014). Neural sensitivity to social reward and punishment anticipation in social anxiety disorder. *Frontiers in Behavioral Neuroscience* **8**, 439.

Daniel R, Pollmann S (2014). A universal role of the ventral striatum in reward-based learning: evidence from human studies. *Neurobiology of Learning and Memory* **114**, 90–100.

Deichmann R, Gottfried JA, Hutton C, Turner R (2003). Optimized EPI for fMRI studies of the orbitofrontal cortex. *Neuroimage* **19**, 430–441.

Deserno L, Huys QJ, Boehme R, Buchert R, Heinze HJ, Grace AA, Dolan RJ, Heinz A, Schlagenhauf F (2015). Ventral striatal dopamine reflects behavioral and neural signatures of model-based control during sequential decision making. *Proceedings of the National Academy of Science of the Unites States of America* **112**, 1595–1600.

Fischer AG, Endrass T, Reuter M, Kubisch C, Ullsperger M (2015). Serotonin Reuptake inhibitors and serotonin transporter genotype modulate performance monitoring functions but not their electrophysiological correlates. *Journal of Neuroscience* **35**, 8181–8190.

Freitas-Ferrari MC, Hallak JE, Trzesniak C, Filho AS, Machado-de-Sousa JP, Chagas MH, Nardi AE, Crippa JA (2010). Neuroimaging in social anxiety disorder: a systematic review of the literature. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **34**, 565–580.

Gilboa-Schechtman E, Franklin ME, Foa EB (2000). Anticipated reactions to social events: differences among individuals with generalized social phobia, obsessive compulsive disorder, and nonanxious controls. *Cognitive Therapy and Research* **24**, 731–746.

Goebel R, Esposito F, Formisano E (2006). Analysis of functional image analysis contest (FIAC) data with brainvoyager QX: from single-subject to cortically aligned group general linear model analysis and self-organizing group independent component analysis. *Human Brain Mapping* **27**, 392–401.

Haber SN, Knutson B (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology* **35**, 4–26.

Hautzinger M, Bailer M, Worall H, Keller F (1995). *Beck-Depressions-Inventar (BDI) [Beck Depression Inventory (BDI)]*. Hans Huber: Bern.

Heimberg RG, Hofmann SG, Liebowitz MR, Schneier FR, Smits JA, Stein MB, Hinton DE, Craske MG (2014). Social anxiety disorder in DSM-5. *Depression and Anxiety* **31**, 472–479.

Heitmann CY, Peterburs J, Mothes-Lasch M, Hallfarth MC, Bohme S, Miltner WH, Straube T (2014). Neural correlates of anticipation and processing of performance feedback in social anxiety. *Human Brain Mapping* **35**, 6023–6031.

Izuma K, Saito DN, Sadato N (2008). Processing of social and monetary rewards in the human striatum. *Neuron* **58**, 284–294.

Jensen D, Heimberg RG (2015). Domain-specific intolerance of uncertainty in socially anxious and contamination-focused obsessive-compulsive individuals. *Cognitive Behaviour Therapy* **44**, 54–62.

Jessup RK, Busemeyer JR, Brown JW (2010). Error effects in Anterior Cingulate cortex reverse when error likelihood is high. *Journal of Neuroscience* **30**, 3467–3472.

Kessler RC, Stein MB, Berglund P (1998). Social phobia subtypes in the National Comorbidity Survey. *The American Journal of Psychiatry* **155**, 613–619.

Kimbrel NA (2008). A model of the development and maintenance of generalized social phobia. *Clinical Psychology Review* **28**, 592–612.

Lancaster JL, Tordesillas-Gutierrez D, Martinez M, Salinas F, Evans A, Zilles K, Mazziotta JC, Fox PT (2007). Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. *Human Brain Mapping* **28**, 1194–1205.

Le Bouc R, Pessiglione M (2013). Imaging social motivation: distinct brain mechanisms drive effort production during collaboration versus competition. *Journal of Neuroscience* **33**, 15894–15902.

Lin A, Adolphs R, Rangel A (2012). Social and monetary reward learning engage overlapping neural substrates. *Social Cognitive and Affective Neuroscience* **7**, 274–281.

Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* **19**, 1233–1239.

Menon V (2011). Large-scale brain networks and psychopathology: a unifying triple network model. *Trends in Cognitive Sciences* **15**, 483–506.

Miltner WHR, Braun CH, Coles MGH (1997). Event-related brain potentials following incorrect feedback in a time-estimation task: evidence for a "generic" neural system for error detection. *Journal of Cognitive Neuroscience* **9**, 788–798.

Miskovic V, Schmidt LA (2012). Social fearfulness in the human brain. *Neuroscience and Biobehavioral Reviews* **36**, 459–478.

Nieuwenhuis S, Slagter HA, von Geusau NJ, Heslenfeld DJ, Holroyd CB (2005). Knowing good from bad: differential activation of human cortical areas by positive and negative outcomes. *European Journal of Neuroscience* **21**, 3161–3168.

O'Doherty JP, Cockburn J, Pauli Wm (2017). Learning, reward, and decision making. *Annual Review of Psychology* **68**, 73–100.

Rachman S, Gruter-Andrew J, Shafran R (2000). Post-event processing in social anxiety. *Behaviour Research and Therapy* **38**, 611–617.

Richey JA, Ghane M, Valdespino A, Coffman MC, Strege MV, White SW, Ollendick TH (2017). Spatiotemporal dissociation of brain activity underlying threat and reward in social anxiety disorder. *Social Cognitive and Affective Neuroscience* **12**, 81–94.

Richey JA, Rittenberg A, Hughes L, Damiano CR, Sabatino A, Miller S, Hanna E, Bodfish JW, Dichter GS (2014). Common and distinct neural features of social and non-social reward processing in autism and social anxiety disorder. *Social Cognitive and Affective Neuroscience* **9**, 367–377.

Rilling JK, Sanfey AG (2011). The neuroscience of social decision-making. *Annual Review of Psychology* **62**, 23–48.

Ruff CC, Fehr E (2014). The neurobiology of rewards and values in social decision making. *Nature Reviews Neuroscience* **15**, 549–562.

Salimpoor VN, Benovoy M, Larcher K, Dagher A, Zatorre RJ (2011). Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. *Nature Neuroscience* **14**, 257–262.

Schlagenhauf F, Rapp MA, Huys QJ, Beck A, Wustenberg T, Deserno L, Buchholz HG, Kalbitzer J, Buchert R, Bauer M, Kienast T, Cumming P, Plotkin M, Kumakura Y, Grace AA, Dolan RJ, Heinz A (2013). Ventral striatal prediction error signaling is associated with dopamine synthesis capacity and fluid intelligence. *Human Brain Mapping* **34**, 1490–1499.

Schneier FR, Abi-Dargham A, Martinez D, Slifstein M, Hwang DR, Liebowitz MR, Laruelle M (2009). Dopamine transporters, D2 receptors, and dopamine release in generalized social anxiety disorder. *Depression and Anxiety* **26**, 411–418.

Schneier FR, Liebowitz MR, Abi-Dargham A, Zea-Ponce Y, Lin SH, Laruelle M (2000). Low dopamine D(2) receptor binding potential in social phobia. *American Journal of Psychiatry* **157**, 457–459.

Schneier FR, Martinez D, Abi-Dargham A, Zea-Ponce Y, Simpson HB, Liebowitz MR, Laruelle M (2008). Striatal dopamine D(2) receptor availability in OCD with and without comorbid social anxiety disorder: preliminary findings. *Depression and Anxiety* **25**, 1–7.

Schulz C, Mothes-Lasch M, Straube T (2013). Automatic neural processing of disorder-related stimuli in social anxiety disorder: faces and more. *Frontiers in Psychology* **4**, 282.

Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ, Davidson RJ (2011). The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nature Reviews Neuroscience* **12**, 154–167.

Simon D, Becker MP, Mothes-Lasch M, Miltner WH, Straube T (2014). Effects of social context on feedback-related activity in the human ventral striatum. *Neuroimage* **99**, 1–6.

Sripada C, Angstadt M, Liberzon I, McCabe K, Phan KL (2013). Aberrant reward center response to partner reputation during a social exchange game in generalized social phobia. *Depression and Anxiety* **30**, 353–361.

Stangier U, Frydrich T (2002). *Soziale Phobie und Soziale Angststoerung: Psychologische Grundlagen, Diagnostik und Therapie [Social Phobia and Social Anxiety Disorder: Psychological Principals, Diagnosis and Therapy]*. Beltz: Göttingen, Germany.

Stangier U, Heidenreich T (2005). Liebowitz Soziale Angst Skala [Liebowitz social anxiety scale]. In *Internationale Skalen für Psychiatrie* (ed. C.I.P. Scalarum), pp. 299–307. Beltz Test: Göttingen.

Straube T, Kolassa IT, Glauer M, Mentzel HJ, Miltner WH (2004). Effect of task conditions on brain responses to threatening faces in social phobics: an event-related functional magnetic resonance imaging study. *Biological Psychiatry* **56**, 921–930.

Talairach J, Tournoux P (1988). *Co-Planar Stereotaxic Atlas of the Human Brain*. Thieme: Stuttgart.

Tiihonen J, Kuikka J, Bergstrom K, Lepola U, Koponen H, Leinonen E (1997). Dopamine reuptake site densities in patients with social phobia. *American Journal of Psychiatry* **154**, 239–242.

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* **15**, 273–289.

van der Wee NJ, van Veen JF, Stevens H, van Vliet IM, van Rijk PP, Westenberg HG (2008). Increased serotonin and dopamine transporter binding in psychotropic medication-naive patients with generalized social anxiety disorder shown by 123I-beta-(4-iodophenyl)-tropane SPECT. *Journal of Nuclear Medicine* **49**, 757–763.

van Veen V, Holroyd CB, Cohen JD, Stenger VA, Carter CS (2004). Errors without conflict: implications for performance monitoring theories of anterior cingulate cortex. *Brain and Cognition* **56**, 267–276.

Vormbrock F, Neuser J (1983). Konstruktion zweier spezifischer Trait-Fragebogen zur Erfassung von Angst in sozialen Situationen (SANB und SVSS) [Construction of two specific trait questionnaires for assesment of fear in social situations (SANB and SVSS)]. *Diagnostica* **29**, 165–182.

Wallace ST, Alden LE (1997). Social phobia and positive social events: the price of success. *Journal of Abnormal Psychology* **106**, 416–424.

Walton ME, Devlin JT, Rushworth MF (2004). Interactions between decision making and performance monitoring within prefrontal cortex. *Nature Neuroscience* **7**, 1259–1265.

Wittchen HU, Wunderlich U, Gruschwitz S, Zaudig M (1996) *Strukturiertes Klinisches Interview für DSM-IV (SKID) [Structured Clinical Interview for DSM-IV (SCID)]*. Beltz-Test: Göttingen, Germany.