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Heart rate variability and its neural correlates during emotional face processing in social anxiety disorder

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ABSTRACT

The monitoring and regulation of one's own physiological reactions and cardioregulatory abnormalities are central to the aetiology and maintenance of social anxiety disorder (SAD). We therefore explored the neural correspondences of these heart rate alterations.

21 patients with SAD and 21 matched healthy controls (HCs) underwent 3 T-fMRI scanning. Simultaneously, high-frequency heart rate variability (HF-HRV) was acquired during a short-term resting period and an implicit emotional face-matching task.

Compared to HCs, patients with SAD reported increased self-focused attention while being less accurate in estimating their heartbeats. Physiologically, they showed less HF-HRV at rest and during task. Across groups, HF-HRV at rest correlated positively with activation in visual face-processing areas. The right caudate nucleus showed an interaction of group and cardioregulation: Activation in this region was positively correlated in patients with SAD but negatively in HCs. We conclude that cardioregulation is altered in SAD on the subjective, physiological, and brain level.

1. Introduction

1.1. Social anxiety disorder

Patients with social anxiety disorder (SAD) are extremely afraid of the possible scrutiny by others, of doing or saying something embarrassing, and of showing symptoms of their anxiety. This fear results in the avoidance of social situations or, if unavoidable, their endurance with distress. Consequently, SAD affects the daily functioning in all aspects of professional and private life. SAD is classified as a phobic disorder in both DSM-IV (300.23) and ICD-10 (F40.1). It has a mean age of onset in late childhood/early adolescence and a lifetime prevalence of approximately 5–12%, with higher rates among female individuals (Kessler & Chiu, 2005).

A competence- and performance-oriented model of SAD describes the interaction of cognitive and physiological processes in social situations that, on the backdrop of biological vulnerability factors, personal life history, and social learning/competence, leads to avoidance or safety behaviours (Fydrich, 2002).

Physiological reactions such as blushing, sweating, or trembling play a central role in anxiety disorders in general, albeit mostly secondarily, that is, as an *effect* of the fear. In SAD, bodily symptoms of anxiety during interpersonal interactions and especially their visibility additionally become a central *object* of the fear (Gerlach, Mourlane, & Rist, 2004) and SAD patients exhibit heightened self-focused attention, which in turn is considered central in maintaining the disorder (Clark & Wells, 1995; Spurr & Stopa, 2002). Factual or imagined physiological reactions, their monitoring through processes of interoception, and their regulation are thus fundamental in SAD (A. Wells & Papageorgiou, 2001; Anderson & Hope, 2009).

1.2. Heart rate variability

One important non-invasive parameter assessing the capacity to regulate psychophysiological arousal is heart rate variability (HRV). HRV reflects the subject's ability to adjust physiological arousal on a momentary basis and its measures are derived from the temporal variations between consecutive heartbeats (Thayer, Hansen, Saus-Rose, & Johnsen, 2009). The most prominent frequency domain indices for short-term recordings (Berntson, 1997;

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Task Force, 1996) are spectral power in the high-frequency band between 0.15 and 0.40 Hz (HF-HRV) and in the low-frequency range between 0.04 and 0.15 Hz (LF-HRV).

The heart is dually innervated by the autonomic nervous system with activity of the sympathetic nervous system (SNS) accelerating the heart rate (HR) and increased activity of the parasympathetic nervous system (PSNS) lowering it. While the influences of the SNS are slow, rapid modulation of HR is associated with neural influence of the PSNS, particularly via the vagal nerve (e.g., Eckberg, 2003; Grossman & Taylor, 2007).

The differential time scale of the influences by the SNS (seconds) and the PSNS (milliseconds) enables their respective discrimination after power spectral analysis: while PSNS influences span the whole frequency range of the HR power spectrum, SNS influences only affect frequencies up to 0.15 Hz (Saul, 1990). The low-frequency band between 0.04 and 0.15 Hz is therefore assumed to contain both SNS and PSNS information, while the high-frequency band between 0.15 and 0.4 Hz is thought to represent PSNS and mainly vagal influences. Although mechanical respiratory processes also influence HRV (e.g., Grossman & Taylor, 2007; Song & Lehrer, 2003), HF-HRV is generally taken as an index of vagal tone and of the ability to inhibit SNS-mediated arousal, which, in turn, can be approximated through the ratio between power in the low- and high-frequency bands (LF/HF), indicating sympatho-vagal balance (Task Force, 1996). HF-HRV can be measured both as an individual trait marker when acquired in the absence of experimental stimulation (i.e., at rest) or as a response variable in task settings indexing behavioural flexibility or attentional engagement with the environment (Porges, 2007; Thayer & Lane, 2000, 2009).

HF-HRV as an individual trait marker has recently been shown to also influence task performance as individuals with higher HF-HRV at rest perform better on a test of social cognition and emotion recognition (Quintana, Guastella, Outhred, Hickie, & Kemp, 2012) and inhibit unnecessary processing of affective information more efficiently (Park, Van Bavel, Vasey, & Thayer, 2012). Furthermore, anxiety-reducing breathing exercises significantly increase HF-HRV in highly anxious subjects, while simultaneously reducing LF/HF (Wells, Outhred, Heathers, Quintana, & Kemp, 2012). Taken together, these results suggest a connection between HF-HRV and SAD.

1.3. SAD and HRV

Because heart and brain show complex bidirectional interactions, mental health and autonomic control of cardiovascular processes are inherently intertwined. This is evidenced by the increased risk for and heightened mortality following cardiovascular diseases in patients with affective and anxiety disorders (e.g., Goodwin, Davidson, & Keyes, 2009; Gorman & Sloan, 2000).

Convergently, diminished HRV at rest or during anxiety stressors has been found in subsyndromal anxiety (e.g., Kawachi, Sparrow, Vokonas, & Weiss, 1995; Miu, Heilman, & Miclea, 2009) as well as in a range of anxiety disorders (cf. Cohen & Benjamin, 2006; Friedman, 2007, for reviews). In the case of SAD, mixed results have previously been reported: While studies investigating task-related HRV found no (Gerlach, Wilhelm, & Roth, 2003) or only gender-specific (Grossman, Wilhelm, Kawachi, & Sparrow, 2001) differences, studies that acquired HRV at rest reported diminished HF-HRV in patients with SAD (Licht, De Geus, Van Dyck, & Penninx, 2009; Pittig, Arch, Lam, & Craske, 2012). While Licht et al. (2009) attributed decreased HF-HRV in anxiety disorders solely to the effects of antidepressant medication, a meta-analysis of studies on patients with major depressive disorder (MDD) related the reduction in HRV specifically to the class of tricyclic antidepressants (Kemp et al., 2010). However, a more recent study reported reduced HF-HRV in unmedicated MDD patients with or without comorbid anxiety (Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012) suggesting that the true extent of the mediating effect of antidepressants in earlier studies is currently not quantifiable.

1.4. Neural structures associated with SAD and HRV

The empirical literature on disorder-specific alterations in brain activation elicited by affective paradigms in SAD yielded divergent results. While most studies reported increased activation in emotion processing areas such as amygdala and insula (Etkin & Wager, 2007; Freitas-ferrari et al., 2010; Miskovic & Schmidt, 2012), several studies did not find evidence for altered activation of these structures in SAD patients (e.g., Quadflieg, Mohr, Mentzel, Miltner, & Straube, 2008; Sripada et al., 2009; Ziv, Goldin, Jazaieri, Hahn, & Gross, 2013). Hyperactivation of emotion processing areas in SAD thus appears to depend on experimental details such as stimulus type and modality (Quadflieg et al., 2008) or task complexity (e.g., Sripada et al., 2009).

Broader frameworks such as the "Polyvagal Theory" (e.g., Porges, 2007) and the "Neurovisceral Integration Model" (Thayer & Lane, 2000, 2009) relate autonomic, and in particular parasympathetic functioning indexed by HF-HRV, also to regulatory brain regions such as prefrontal and cingulate areas as well as complex feedback circuits involving the hypothalamus and brainstem nuclei. A recent meta-analysis of eight neuroimaging studies on neural correlates of task-related HRV identified several areas, including the ventro-medial prefrontal/anterior cingulate cortex and the extended amygdala/ventral striatum (Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012). In the only previous neuroimaging study in SAD that combined HRV and measures of regional cerebral blood flow (rCBF), 28 patients with SAD executed a stressful, symptom-evoking public speaking task in a PET scanner. In line with the results of the meta-analysis, task-related HRV showed positive correlations with rCBF in several medial and lateral frontal regions, particularly the anterior cingulate cortex and the caudate nucleus (Ahs, Sollers, Furmark, Fredrikson, & Thayer, 2009).

Hypotheses. The aim of our study was to investigate parasympathetic cardioregulatory processes as well as their conscious accessibility and neural underpinnings in patients with SAD. We measured HRV both as a trait marker in a short-term recording at rest and as a response variable upon emotion induction through a widely-used emotional face-matching task (e.g., Hariri, Bookheimer, & Mazziotta, 2000).

Based on previous findings and theoretical models of the disorder, we expected decreased autonomic control of the heart in patients with SAD at rest, manifesting as decreased HF-HRV and an increased LF/HF ratio. Inconsistent results on group differences in task-related HRV in prior studies did not allow us to make directed hypothesis with respect to HF-HRV during emotional processing.

As increased self-focused attention and physiological monitoring are central to the aetiology and maintenance of SAD, the conscious accessibility of cardioregulatory processes carries behavioural relevance. We tested awareness of HR and the accuracy of its perception through an established heartbeat detection task assessing interoceptive sensitivity (Schandry, 1981). To our knowledge, only one clinical study employed the same task and found no differences between patients with SAD and HCs (Antony, Brown, & Craske, 1995), while studies in healthy subjects report positive correlations between interoceptive sensitivity scores and traits of general (Pollatos, Traut-Mattausch, & Schandry, 2009) and social anxiety (Stevens et al., 2011). Although we assumed interoceptive accuracy important for SAD symptomatology, the paucity of prior clinical studies did not allow us to formulate a directed hypothesis concerning group differences.

Table 1
Demographic, diagnostic, and neuropsychological details ($M \pm SD$). All group comparisons as two-sided independent t-tests, either Student's or Welch's (in case of unequal variances).

n	SAD 21 (16f, 5 m)	HC 21 (16f, 5 m)	df	t	p (2-sided)	Cohen's d
Age (yrs)	30.95 ± 7.3	29.14 ± 5.9	40	0.89	0.38	–
EHI	.88 ± .35	.95 ± .12	40	0.88	0.38	–
Weight (kg)	67.3 ± 13.4	67 ± 11.6	40	0.074	0.94	–
Education	Dummy-coded	Dummy-coded	40	1.13	0.27	–
TMT A (s)	29.1 ± 10.6	24.9 ± 7	38	1.48	0.15	–
TMT B (s)	63.2 ± 37.4	54.4 ± 18.3	38	0.95	0.35	–
LSAS	87.4 ± 20.5	18.5 ± 16.7	40	11.9	<0.001***	3.78
STAI-T	57.1 ± 12.2	35.1 ± 11.3	40	6.05	<0.001***	1.92
BDI-II	20.7 ± 17	2.57 ± 3.53	21.7	4.78	<0.001***	1.51
TAS-20	57.8 ± 10.6	46.9 ± 7.83	40	3.81	<0.001***	1.2
CDS-30	31.4 ± 32.8	9.14 ± 11.9	25.2	2.92	0.007**	0.93
CTQ-PhysNegl	7.81 ± 2.6	6 ± 1.61	40	2.71	0.01*	0.86
SPF-IRI_PersDist	13.7 ± 2.67	9.86 ± 3.18	40	4.26	<0.001***	1.32
ERQ-app	3.48 ± 1.11	4.91 ± 1.26	40	3.89	<0.001***	1.22
ERQ-supp	4.05 ± 1.4	2.93 ± 1.29	40	2.69	0.01*	0.85
KIMS	112.9 ± 19.1	141.5 ± 13.4	40	5.61	<0.001***	1.78
DFS	73.6 ± 8.21	65.6 ± 9.5	40	2.92	0.006**	0.92

SAD = social anxiety disorder; HC = healthy controls; df = degrees of freedom. EHI = Edinburgh Handedness Inventory; TMT = Trail-making Test A + B (in seconds); LSAS = Liebowitz Social Anxiety Scale; STAI-T = State-Trait Anxiety Inventory; BDI-II = Beck Depression Inventory; TAS-20 = Toronto Alexithymia Scale; CDS-30 = Cambridge Depersonalization Scale; CTQ-PhysNeg = Childhood Trauma Questionnaire – subscale physical neglect; SPF-IRI_PersDist = Interpersonal Reactivity Index – subscale personal distress; ERQ_app and ERQ_supp = Emotion Regulation Questionnaire – subscales reappraisal and suppression, respectively; KIMS = Kentucky Inventory of Mindfulness Skills; DFS = questionnaire of (dys)functional self-focused attention.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

As previous studies report group differences in the form of increased neural reactivity in brain areas involved in emotional experience, like the amygdala and insula (e.g., Freitas-ferrari et al., 2010), we expected patients with SAD to show heightened BOLD signal (relative to HCs) in these areas during emotional face- compared to geometrical shape-matching. Even though the lack of a healthy control group in the only prior report on a correlation between HF-HRV and brain activation in SAD (Ahs et al., 2009), together with differences in neuroimaging technique and task design, precluded precise hypotheses, we expected HF-HRV to correlate with brain activation in comparable frontal regions.

2. Methods

2.1. Participants

Twenty-two patients with SAD were recruited through self-help groups, online forums, and advertisements in local out-patient treatment facilities. Twenty-two healthy controls (HCs) were found through ads in public spaces and through university mailing lists. Groups were matched for sex, age, handedness (as assessed by the Edinburgh Handedness Inventory; Oldfield, 1971), education, and body weight (see Table 1). After an initial screening assessing MRI compatibility and SAD symptomatology, both patients and controls were invited for an extensive diagnostic session encompassing the structured clinical diagnostic interviews for DSM-IV Axis I disorders (SCID-I, First, Spitzer, Gibbon, & Williams, 2002; Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997) and dissociative disorders (SCID-D, Gast, Oswald, Zündorf, & Hofmann, 2000; Steinberg, Cicchetti, Buchanan, Hall, & Rounsaville, 1993) as well as the International Personality Disorder Examination (IPDE, Loranger, Janca, & Sartorius, 1997; Mombour et al., 1996) to assess Axis II disorders. All included patients met DSM-IV criteria (American Psychiatric Association, 1994) for current SAD. The SAD group exhibited current DSM-IV comorbid diagnoses (2 × major depression, 3 × dysthymia, 2 × panic disorder, 1 × obsessive-compulsive disorder). Four patients were medicated with antidepressants (2 × SSRI, 1 × SNRI, 1 × tricyclicum).

Exclusion criteria were all current psychiatric disorders (other than dysthymia, major depression or other anxiety disorders), lifetime psychotic, bipolar, or neurological disorders, MRI exclusion criteria (e.g., magnetic or electronic implants), psychopharmacological treatment (other than antidepressants), current or past abuse of alcohol/narcotics, pregnancy, claustrophobia, insufficient proficiency in German, noise sensitivity or tinnitus. Approval was obtained by the local ethics committee and all participants gave their written informed consent. One participant of each group had to be excluded due to corrupted pulse data acquisition. All further analyses were therefore conducted on the data of 42 participants in total, 21 per group. Because data was missing from four HCs for the task-related HR recordings, group comparisons in this modality include 17 HCs and 21 patients with SAD. Resting-state ratings were not available for one subject with SAD.

2.2. Instruments

Symptom severity for social phobia was assessed with the German version (Stangier & Heidenreich, 2003; Cronbach's $\alpha = .982$) of the self-report Liebowitz Social Anxiety Scale (LSAS, Liebowitz, 1987). For this questionnaire, 24 items are scored independently for frequency and duration on 4-point Likert-type scales. For further diagnostic and neuropsychological assessment participants completed German versions of the Beck Depression Inventory (BDI-II, Beck, Steer, Ball, & Ranieri, 1996; Hautzinger, Keller, & Kühner, 2006), the trait version of the State-Trait Anxiety Inventory (STAI-T, Laux, Glanzmann, Schaffner, & Spielberger, 1981; Spielberger, 1970), the Toronto Alexithymia Scale (TAS-20, Bagby, Parker, & Taylor, 1994; Franz, Schneider, Schäfer, Schmitz, & Zweyer, 2001), the Cambridge Depersonalization Scale (CDS-30, Michal et al., 2004; Sierra & Berrios, 2000), and the Childhood Trauma Questionnaire (CTQ, Bernstein & Fink, 1994; Wingenfeld et al., 2010). Neuropsychological characteristics were assessed using the Trail-making Test (TMT, Reitan, 1955), the questionnaire for functional and dysfunctional self-focused attention (DFS, Hoyer, 2000), the Kentucky Inventory of Mindfulness Skills (KIMS, Baer, Smith, & Allen, 2004; Ströhle, Nachtigall, Michalak, & Heidenreich, 2010), the Emotion Regulation Questionnaire (ERQ, Abler & Kessler, 2009; Gross & John, 2003), and the Interpersonal Reactivity Index (SPF-IRI, Davis, 1983; Paulus, 2009).

2.3. Procedures

2.3.1. Resting session

In order to get acquainted with the scanner environment, participants were laying in the fMRI scanner in supine position for at least 5 min before resting-state data acquisition started. The pulse clip was attached to the ring finger of the left hand and optimally adjusted until signal and peak detection were clean upon visual inspection. Five minutes of continuous heartbeat were recorded during the simultaneous acquisition of resting-state fMRI (the data is currently under analysis and will be reported elsewhere). Participants were asked to "relax and let their thoughts wander" (translated from German) and to fixate the cross in the middle of the screen. The first minute of the resting HR data was not analyzed as we consider it the adaptation phase of the participants to the scanner noise. At the end of the recording, participants were asked to answer three unannounced questions by button press: How much time on a 7-point Likert-type scale (1 = "not at all"; 7 = "the whole time") they (1) "let their mind wander", (2) "ruminated over something" or (3) "internally worked on a topic" (translated from German; original wording available upon request).

2.4. Interoceptive sensitivity task

While participants were in the scanner, we conducted a variant of an established task assessing interoceptive sensitivity (Schandry, 1981): Participants were

asked to count or guess the number of heartbeats during three intervals of 25, 35, and 45 s length. The three intervals were indicated by acoustic commands of "start" and "stop", they were presented in randomized order, and participants were instructed to perceive their heartbeats by "listening into [hineinhorchen] their body" and without the use of auxiliaries.

2.5. Emotional face-matching task

For the widely used emotional face-matching task (e.g., Hariri et al., 2000), participants received printed task instructions outside of the scanner. Inside the magnet, participants completed 4 blocks of geometrical shape comparison and 4 intermittent blocks comparing faces in black and white from the Ekman Faces set (Ekman & Friesen, 1971). For triplets of emotional faces or geometrical shapes participants had to decide which of the two items presented in the lower quadrants of the screen was identical with the item presented centrally in the upper half of the screen. Answers were given by button press with either the index or the middle finger of the right and dominant hand. Each block lasted 32 s and started with an instruction screen of 2 s before 6 item triplets were presented for 5 s each. Face blocks contained alternating triplets of either female or male faces. The experiment was programmed and presented using Presentation software 14.9 (Neurobehavioral Systems, http://www.neurobs.com) and responses were collected using a button box (Current Designs, Inc., Philadelphia, PA). We chose angry and fearful faces as particularly threat-conveying stimuli in SAD: angry as signalling negative evaluation from conspecifics and fearful as generally indicating proximity of danger. Matching faces were identical so that the emotionality of the face was irrelevant for task completion and affective face processing was thus rendered implicit.

2.6. FMRI data acquisition

The study was performed on a Siemens Tim Trio 3 T MRI scanner (Siemens, Erlangen, Germany) with a 12-channel head coil at the Berlin Center for Advanced Neuroimaging. High-resolution T1-weighted anatomical images were acquired at the beginning of each session using a 3D-MPRAGE sequence with 192 sagittal slices of 1 mm thickness, repetition time (TR) 1900 ms, echo time (TE) 2.52 ms, flip angle 9 degrees, field of view (FoV) 256 mm. During the emotional faces task, 118 functional T2*-weighted volumes were recorded with an echo-planar gradient echo pulse sequence to measure blood-oxygen-level-dependent (BOLD) signal changes. TR was 2250 ms, TE 25 ms, flip angle 80 degrees, FoV 192 mm and 37 slices of 3 mm thickness with 20% distance factor were acquired in descending order. Cushions were used to minimize head motion during scanning.

Heart rate data were acquired using the built-in Siemens MRI-compatible photoplethysmograph (PPG) with an acquisition rate of 50 Hz, online visualization, and automated peak detection. For the technique of pulse-oximetry, (near-)infrared light at two different wavelengths is passed through tissue to a sensitive photo detector and changes in absorbance are measured to monitor oxygen saturation and detect the pulse. Studies simultaneously acquiring electrocardiographic (ECG) and PPG data found extremely high correlations with coefficients around .96–.99 between both data sources (Lu et al., 2008; Selvaraj, Jaryal, Santhosh, Deepak, & Anand, 2008), so that PPG recordings can be assumed to sensitively acquire HR data. Visual stimulation inside the MRI scanner was accomplished through a goggle system (VisualSystem by Nordic NeuroLab, Bergen, Norway), which was carefully adjusted for the individual participant and had a resolution of 800 × 600 pixels.

3. Data analysis

Statistical analyses were conducted using SPSS version 20.0 (IBM, http://www-01.ibm.com/software/analytics/spss/) and R (R Core Team, http://www.R-project.org/) applying a statistical threshold of $p < .05$. For group comparisons we used two-sided independent Student's or Welch's t-tests in case that Levene's test indicated a violation of the homoscedasticity assumption.

3.1. Heart rate variability

For both the HR data at rest and during the emotional faces task, peak-to-peak intervals were extracted using Matlab R2012a (MathWorks, Natick, MA, USA) and resulting tachograms (for the task, concatenated peak-to-peak intervals from 4 blocks à 30 s per condition) were imported into Kubios (version 2.0, 2008, Biosignal Analysis and Medical Imaging Group, University of Koupio, Finland, http://kubios.uef.fi/). Samples were filtered with the medium automatic filter, that is, faulty intervals were cubic spline interpolated and de-trended with a 1st-order filter.

For most participants, HR data at rest existed from two sessions which were approximately two weeks apart. For further analyses, the resting session with fewer corrected artefacts was chosen. Correlation between the measurements from the subjects for which both sessions existed was reasonably high (HC: $r(15) = .52$, $p = .049$; SAD: $r(17) = .71$; $p = .002$) but lower than previously reported (Schmidt et al., 2012). For both groups, the same number of session 1 and session 2 data sets was used for further analysis ($\chi^2(1) = .1$, $p = .75$).

Data quality was high (2 per mil corrected peaks) and the number of artefacts did not differ between groups ($T(40) = 1.1$, $p = .3$). Power spectral analysis was conducted in Kubios to extract spectral power in the low (LF) and high frequency (HF) band (0.04–0.15 Hz and 0.15–0.4 Hz, respectively) using Fast Fourier transform (Welch's periodogram method) with a sliding window of 256 s and 50% overlap. To account for non-normality and unequal variances between groups, HF-HRV values were log10-transformed, successfully achieving normally distributed and homoscedastic data. The ratio of LF and HF power (LF/HF) did not require data transformation as it was normally distributed. Two-sided independent t-tests were conducted to extract group differences on measures of HRV at rest, a 2×2 mixed-design ANOVA with "group" as between-subject and "condition" (faces vs shapes) as within-subject factor was used to analyze HR and HRV during task, and two-sided bivariate correlations were calculated to connect these measures to demographic and neuropsychological factors. As a meta-analysis by Kemp et al. (2010) specifically reported tricyclic antidepressants to reduce HRV, the central analyses were repeated with the exclusion of the one patient taking a tricyclicum.

3.2. Interoceptive sensitivity task

An individual heartbeat (HB) perception score was calculated according to the formula $1/3 \sum 1 - (|\text{recorded HB} - \text{counted HB}|/\text{recorded HB})$. This often-used derivation disregards the direction of estimation error and yields an index of interoceptive sensitivity between 0 and 1, with 1 indicating perfect performance (e.g., Pollatos, Schandry, Auer, & Kaufmann, 2007).

3.3. FMRI data analysis

FMRI data analysis was conducted using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm/) on Matlab R2012a (MathWorks, Natick, MA, USA). Data were checked for signal dropout and excessive head movements using ArtRepair visualization (http://www.nitrc.org/projects/art_repair/) and preprocessed in the following sequence: Realign to the first image and unwarp using the acquired fieldmap, coregistration of structural T1 image onto mean EPI, segmentation into tissue classes (using "New Segment"), creation of an anatomical group template (from the segmented grey matter, white matter, and cerebrospinal fluid), normalization using individual flow fields, and smoothing with a Gaussian kernel of 6 mm FWHM using DARTEL. For each subject, temporal information of the two conditions (faces, shapes) were convolved with a canonical haemodynamic response function to model the acquired BOLD signal. Similarly, instruction periods and the six affine motion parameters were included in the model as regressors of no interest. The target contrast (faces >shapes) was created for each subject on the first level and transferred to the second level, where a two-sample t-test was conducted to extract group differences in BOLD signal. For correlation analyses, this two-sample t-test included resting HF-HRV as covariate as well as its interaction with the group factor. Individual parameter estimates for a significant activation cluster in the correlation of BOLD signal with HF-HRV were extracted using MarsBaR 0.43 (Brett, Anton, Valabregue, & Poline, 2002; http://marsbar.sourceforge.net/). Unless

otherwise specified, fMRI results were thresholded at $p = .005$ with a minimal cluster extent that ensured whole-brain correction at $p < .05$ (Lieberman & Cunningham, 2009). Individual extent thresholds were determined using the calculated intrinsic smoothness of the individual *T*-value image, a cluster connection radius of 3 mm, and a 1000-iteration Monte Carlo simulation (AlphaSim) as implemented in the REST Toolbox v1.8 (Song et al., 2011, http://www.restfmri.net/).

4. Results

4.1. Self-report results

Self-reported symptom severity was significantly higher in the SAD group than in the HCs and patients with SAD selectively reported significantly higher personal distress on the respective subscale of the SPF-IRI, significantly higher trait anxiety (STAI-T), depressive (BDI-II), alexithymic (TAS-20), and depersonalization–derealization (CDS-30) tendencies. In addition, they gave accounts of significantly more physical neglect, but not any other form of childhood trauma, resulting in no significant group difference for the sum score of the CTQ (cf. Table 1). Neuropsychological questionnaires indicated that groups did not differ in general information processing speed as measured by the TMT but individuals with SAD exhibited more functional and dysfunctional self-focused attention (DFS) and, convergently, less mindfulness skills (KIMS). In addition, patients with SAD reported habitual use of other emotion regulation strategies than HCs (ERQ): they more commonly suppress emotional expression and less often regulate their emotional experience through re-appraisal (cf. Table 1 for details).

Correlation analyses of the unannounced questions about the participants' mental occupation during the resting-state measurement showed a connection to scores on self-report questionnaires in that spontaneous rumination during the resting period was positively correlated with the DFS-D subscale ($r(41) = .465$, $p = .002$), the STAI-T ($r(41) = .445$, $p = .004$), and the BDI-II score ($r(41) = .477$, $p = .002$).

4.2. HR and HRV at rest

While there was no group difference in HR, individuals with SAD showed different HRV than HCs in the form of significantly decreased HF-HRV and significantly increased LF/HF at rest (cf. Fig. 1 and Table 2). Analysis of LF/HF was conducted removing an outlier of more than 3 standard deviations above the group mean in the patient group. While the measures of HF-HRV and LF/HF at rest were significantly negatively correlated in HCs ($r(21) = -.55$, $p = .009$), no such correlation was present in patients with SAD ($r(20) = -.12$, $p = .61$).

HF-HRV at rest correlated negatively with self-reported rumination in HCs ($r(21) = -.51$, $p = .017$) and with the TMT parts A (SAD: $r(20) = -.51$, $p = .023$; HC: $r(20) = -.52$, $p = .018$; ALL: $r(40) = -.54$, $p < .001$) and B (SAD: $r(20) = -.53$, $p = .015$; HC: $r(20) = -.51$, $p = .023$; ALL: $r(40) = -.51$, $p = .001$).

4.3. Task-related HRV

The mixed-design ANOVA showed a trend towards increased HR in individuals with SAD compared to HCs ($F(1, 36) = 4.03$, $p = .052$, $\eta_p^2 = .1$) while there was no main effect of condition ($F(1, 36) = 1.36$, $p = .25$) and no interaction between these two factors ($F(1, 36) = 0.7$, $p = .41$).

For HF-HRV during the task, a significant condition by group interaction emerged ($F(1, 1) = 5.66$, $p = .023$, $\eta_p^2 = .14$; cf. Fig. 1C). Post hoc paired t-tests within each group indicated that HF-HRV power during the blocks of emotional faces was significantly higher than during blocks of geometrical shapes for HCs ($T(16) = 3.21$, $p = .006$, $d = .43$), but not for patients with SAD ($T(20) = .37$, $p = .72$). Furthermore, compared to HCs, patients with SAD showed significantly less HF-HRV during the emotional faces condition but not during the matching geometrical shapes condition (cf. Table 2 and Fig. 1).

4.4. Interoceptive sensitivity

Patients with SAD exhibited significantly lower interoceptive sensitivity than HCs ($T(40) = 3.06$, $p = .004$, $d = .97$). This effect remained significant after exclusion of participants that reported having objectively sensed their pulse in fingers or other body parts (4 healthy controls) and an outlier more than 3 standard deviations below the mean in the patient group ($T(35) = 2.31$, $p = .027$, $d = .78$; cf. Fig. 1B).

Importantly, interoceptive sensitivity was not correlated with HR or any of the HRV measures.

4.5. Brain activation and correlation

Across all subjects, emotional faces evoked significantly stronger activation in bilateral visual and frontal cortices, the thalamus, and bilateral amygdala compared to geometric shapes (at the level of $p < .05$, whole-brain FWE-corrected; cf. Supplementary Table 1).

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.biopsycho.2013.06.009.

As there were no significant group differences for the contrast faces >shapes (at a voxel threshold of $p < .005$ with a cluster extent threshold of $k = 77$), correlation analyses with HF-HRV were conducted across the sample as a whole.

For HF-HRV as a task-related response variable, there were no significant correlations found on a whole-brain level.

For HRV as a trait marker, positive correlations (cluster extent thresholded at $k = 75$) between HF-HRV at rest and the BOLD signal during the target contrast (faces >shapes) appeared in left-hemispheric temporo-occipital cortex, extending from fusiform gyrus into inferior and middle occipital cortex (cf. Table 3).

A significant interaction between HF-HRV at rest and group (with $k > 84$) emerged in the right caudate nucleus (cf. Table 3). While HF-HRV at rest showed a significant positive correlation with activation in this cluster in patients with SAD ($r(21) = .8$, $p < .001$), the correlation was significantly negative in HCs ($r(21) = -.61$, $p = .004$; Fisher's *z*-transform: $z = 5.42$, $p < .001$).

Across groups, no significant negative correlations were observed between HF-HRV and BOLD signal.

5. Discussion

Our study in patients with social anxiety disorder (SAD) investigated interoception as well as cardioregulation and its relation to brain activation during an emotional face-matching task. Our main findings were that patients with SAD were less accurate in estimating their heartbeat, showed decreased cardiovagal control as indexed by diminished HF-HRV during rest and task, and that these cardioregulatory measures were positively correlated with activation in the right caudate nucleus during the task condition.

5.1. Self-report, HRV, and interoceptive sensitivity

Patients with SAD reported increased self-focused attention and habitual emotional suppression compared to HCs, while, at the same time, being less accurate in estimating their heartbeats, an

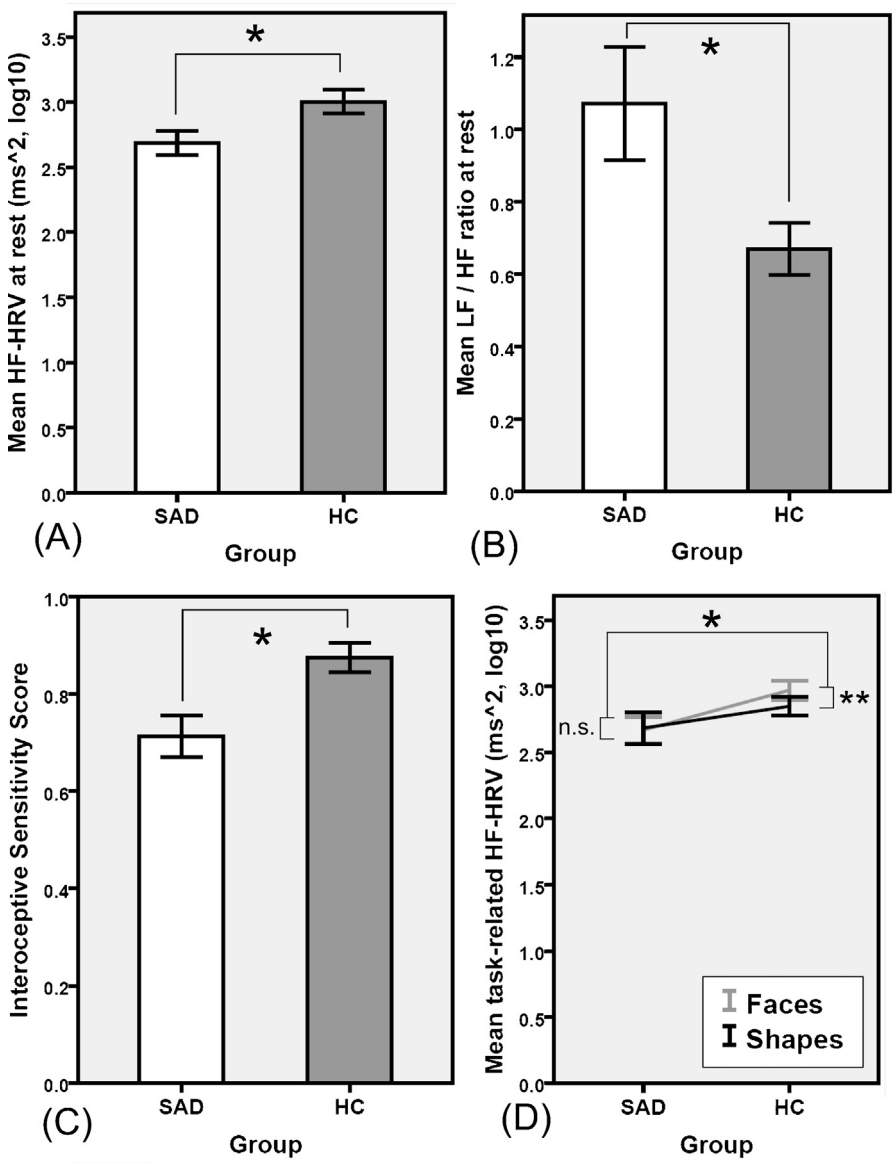

Fig. 1. Group differences in heart rate variability and interoceptive sensitivity between healthy controls (HCs) and patients with social anxiety disorder (SAD). Compared to HCs, patients with SAD show (A) reduced power in the high-frequency band between 0.15 and 0.4 Hz (HF-HRV) during a 5-min resting-state recording (21 SAD vs. 21 HCs; $T(40) = 2.4$, $p = .023$, Cohen's $d = .76$), (B) increased ratio between low-frequency (0.04–0.15 Hz) power (LF) and HF-HRV (LF/HF ratio) during the same period (20 SAD vs. 21 HC; $T(26.8) = 2.33$; $p = .028$, $d = .76$), (C) reduced interoceptive sensitivity as measured with an established heartbeat detection task (20 SAD vs. 17 HCs; $T(35) = 2.31$, $p < .027$, $d = .78$), and (D) absence of a selective increase in task-related HF-HRV during emotional face-matching compared to neutral shape-matching as indicated by a significant group by condition interaction ($F(1,1) = 5.66$, $p = .023$, $\eta_p^2 = .14$) with HCs showing a selective increase in HF-HRV for faces compared to shapes ($T(16) = 3.2$, $p = .006$, $d = .43$), not present in patients with SAD ($T(20) = .37$, $p = .72$). Error bars: *SEM*. Also cf. Table 2.

important physiological signal of arousal and anxiety. The patient group also exhibited significantly diminished spectral power in the high-frequency band of HR recordings (HF-HRV) both at rest and during emotion induction through an emotional face-matching task, indicating decreased cardiovagal control in SAD. Convergently, a significantly increased LF/HF ratio indicated heightened sympathetic activation during rest.

While heightened self-focused attention is a commonly observed symptom in SAD and considered important in maintaining the disorder (Clark & Wells, 1995; Spurr & Stopa, 2002), the habitual inhibition of emotional expression replicates previous findings (Brühl et al., 2011) and corresponds with reports that patients with SAD worry about displaying bodily anxiety symptoms (Gerlach et al., 2004). Both characteristics are also central features in the competence- and performance-oriented model of SAD by Fydrich (2002).

Our results of decreased HF-HRV demonstrate that patients with SAD exhibit decreased parasympathetic cardioregulatory flexibility upon emotional processing as well as spontaneously at rest. Previous studies have similarly reported decreased HF-HRV in subsyndromal anxiety and in a range of anxiety disorders including social anxiety (e.g., Pittig et al., 2012; Cohen & Benjamin, 2006; Friedman, 2007, for reviews). Additionally, a significantly increased LF/HF ratio at rest suggests heightened sympathetic arousal. Importantly, the significant inverse correlation of HF-HRV and LF/HF observed in HCs was not present individuals with SAD, implying less vagal control over sympatho-excitatory activation in the patients.

HCs showed a selective increase in HF-HRV during the condition of emotional face-matching that was not present in patients with SAD. As emotional processing was task-irrelevant for successful

Table 2
Heart rate data and interoceptive sensitivity scores from patients with social anxiety disorder (SAD) and healthy controls (HC).

	SAD ($n = 21$)	HC ($n = 21$)	df	t	p (2-sided)	Cohen's d
HR rest	74.5 ± 10.9	68.6 ± 12.3	40	1.63	0.11	–
HF-HRV rest (ms^2, log10)	2.68 ± .44	3 ± .42	40	2.41	0.021*	0.76
	SAD ($n = 20$)	HC ($n = 21$)				
LF/HF rest	1.07 ± .7	.67 ± .33	26.8	2.33	0.028*	0.76
	SAD ($n = 21$)	HC ($n = 17$)				
HR faces	75.4 ± 11.1	68.3 ± 11.3	36	1.94	0.061	0.65
HR shapes	75.8 ± 10.8	68.3 ± 11.3	36	2.07	0.045*	0.7
HF-HRV faces (ms^2, log10)	2.67 ± 46	2.97 ± .3	36	2.31	0.027*	0.77
HF-HRV shapes (ms^2, log10)	2.68 ± .55	2.85 ± .28	31.2	1.19	0.24	–
	SAD ($n = 21$)	HC ($n = 21$)				
Interoceptive sensitivity	.71 ± .2	.87 ± .14	40	3.06	0.004**	0.97
	SAD ($n = 20$)	HC ($n = 17$)				
Interoceptive sensitivity	.75 ± .12	.85 ± .14	35	2.31	0.027*	0.78

Heart rate (HR) values during a 5-min resting period (HR rest), heart rate variability as power in the high-frequency (HF) band (0.15–0.4 Hz) during the same period (HF-HRV rest) as well as the ratio between low-frequency (0.04–0.15 Hz) and HF-HRV (LF/HF rest). In addition, HR and HF-HRV data during matching of emotional faces (HR/HF-HRV faces) or geometrical shapes (HR/HF-HRV shapes) are presented. Interoceptive sensitivity was assessed through an established heartbeat detection paradigm (Schandry, 1981) with a score of 1 indicating perfect accuracy. All values: $M \pm SD$. Also cf. Fig. 1.

* $p < .05$.

** $p < .01$.

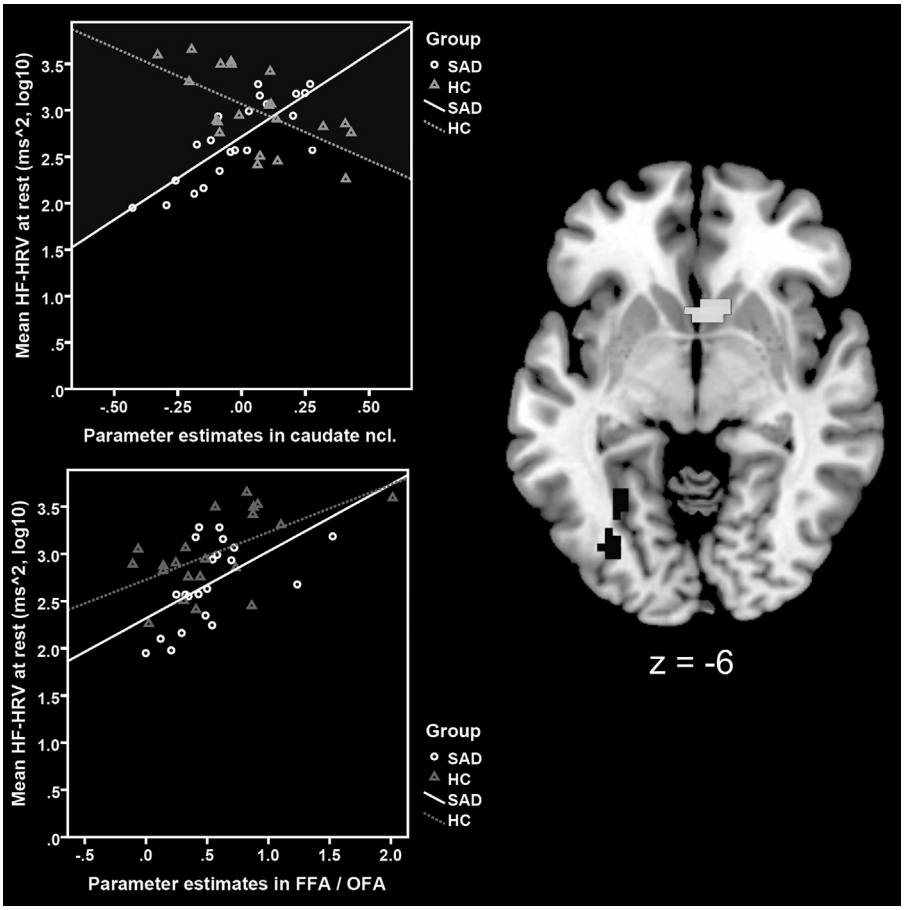

Fig. 2. BOLD contrast correlations of high-frequency heart rate variability (HF-HRV) at rest. Brain activations for the contrast emotional faces minus geometrical shapes showing a positive correlation across groups with trait HF-HRV acquired in an independent 5-min resting period (dark shading) in a left-hemispheric temporo-occipital cluster encompassing fusiform (FFA) and occipital face areas (OFA) (for details cf. Table 3). A significant interaction between HF-HRV at rest and group emerged in right-hemispheric caudate nucleus (light shading; for details cf. Table 3). While HF-HRV at rest showed a significant positive correlation with activation in this cluster in patients with SAD ($r(21) = .8$, $p < .001$), the correlation was significantly negative in HCs ($r(21) = -.61$, $p = .004$; Fisher's z-transform: $z = 5.42$, $p < .001$). Coordinates of slices in MNI space.

Table 3
Details of correlations between BOLD contrast during the emotional face-matching task with spectral power in the high-frequency band (HF-HRV) during an independent 5-min resting-state recording. Threshold: $p < .005$, uncorrected at the voxel level with an individually calculated cluster extent threshold to achieve whole-brain correction (using AlphaSim; Song et al., 2011). For anatomical labelling, AAL was used (Tzourio-Mazoyer et al., 2002). Also cf. Fig. 2.

Positive correlation with HF-HRV at rest (across subjects)						Anatomical label (AAL)	Hemisphere
MNI coordinates (mm)				p (unc)	Cluster extent k		
x	y	z	T				
−30	−57	−9	3.86	<0.001	113	Fusiform	Left
−33	−90	15	3.55	0.001		Middle occipital	Left
−33	−75	−6	3.49	0.001		Inferior occipital	Left
Interaction HF-HRV at rest by group (SAD + 1, HC − 1)						Anatomical label (AAL)	Hemisphere
MNI coordinates (mm)				p (unc)	Cluster extent k		
x	y	z	T				
3	21	9	4.4	<0.001	104	Caudate	Right
12	24	12	4.21	<0.001		Caudate	Right
3	15	−6	3.74	<0.001		Olfactory	Right

performance, and even detrimental to it (Pessoa, 2005; Vuilleumier, 2005), increased cardiovagal control may indicate uninstructed emotion regulation in HCs (cf. Thayer et al., 2012; Park et al., 2012) that was not present in individuals with SAD. In a similar vein, we observed that across groups individuals with higher HF-HRV at rest were faster in completing the Trail-making Test, which is in line with findings that higher vagal tone is associated with better performance on tasks of executive functioning (Hansen, Johnsen, & Thayer, 2003).

Our finding that patients with SAD are less accurate at guessing their heartbeats than HCs is in contrast to earlier studies that employed the same task and that found a positive correlation between interoceptive sensitivity scores and traits of general (Pollatos et al., 2007, 2009) and social anxiety (Stevens et al., 2011) in non-clinical samples. The only clinical study using a similar task in SAD, however, found no differences in interoceptive sensitivity between patients and HCs (Antony et al., 1995). It remains to be determined to which degree heightened but inaccurate physiological self-monitoring contribute to SAD symptomatology.

5.2. FMRI results

Although across both groups the emotional face-matching task elicited activation patterns that have been commonly found in similar tasks (for meta-analyses cf. Fusar-poli et al., 2009; Staugaard, 2010), we did not observe significant group differences on the whole-brain level shown in previous studies. In particular, we did not find amygdala hyperactivation in SAD in response to emotional faces. However, recent neuropsychological evidence suggests that fear and panic can occur without involvement of the amygdala (Feinstein, Adolphs, Damasio, & Tranel, 2011) and several studies in SAD did not find group differences in the amygdala (e.g., Quadflieg et al., 2008; Sripada et al., 2009), even not during emotional face processing (e.g., Ziv et al., 2013). A particularity of our task design was that emotional face-processing was implicit. Even though amygdala activation was observable across groups, congruent with the automaticity of affective processing (Pessoa, 2005), differences in implicit compared to explicit emotional face processing may have interacted with potential group differences in our design (Fusar-poli et al., 2009). Furthermore, experimental blocks in our task mixed angry (social threat) and fearful (physical threat) faces to increase emotive impact. Although overlapping in their brain aetiology and consequences, social threat and physical threat may be qualitatively different, particularly in SAD (Doehrmann et al., 2012; Goldin, Manber, Hakimi, Canli, & Gross, 2009). Further studies should include "socialness" as experimental factor to test its specificity.

However, we observed significant associations of HF-HRV at rest with the BOLD signal during the emotional face-matching task.

Across groups, we found category-specific effects on neurovisceral integration in the form of an engagement of regions in occipito-temporal cortex during an emotional face-matching task as a function of resting-state HF-HRV.

These extrastriate visual areas have been implied in the perception of facial features (Haxby, Hoffman, & Gobbini, 2000; Nichols, Betts, & Wilson, 2010), particularly during implicit affective processing (Bayle & Taylor, 2010), and they include the fusiform and the occipital face area (FFA and OFA; cf. Kanwisher & Yovel, 2006; Pitcher, Walsh, & Duchaine, 2011, respectively, for reviews).

Our results thus suggest that parasympathetic cardioregulation as individual marker shows a connection to early sensory cortices. A recent study in healthy subjects, also using an implicit affective face-processing task, found that individuals with high HF-HRV at rest were better at inhibiting attention to task-irrelevant fearful and neutral faces and the authors proposed that this ability was cortically mediated (Park et al., 2012). Our findings on differential cortical activation in face-processing areas as a function of HF-HRV at rest support and specify this suggestion. It can be assumed that heightened attentional inhibition of affective faces already occurs at early stages during (feature) processing of facial stimuli in OFA and FFA compared to full-blown emotional processing for example in the amygdala (Orlov, Makin, & Zohary, 2010; Pujol et al., 2009).

Differential group effects of HF-HRV at rest on brain activation during emotional face-matching were found in the caudate nucleus. While activation in this cluster was positively correlated with HF-HRV at rest in patients with SAD, the inverse correlation was found in HCs. This region has previously been identified as a neural correlate of task-related HRV both in individuals with SAD (Ahs et al., 2009) and in healthy subjects (Critchley et al., 2005; Lane et al., 2009). The caudate nucleus, which forms part of the dorsal striatum in the basal ganglia, has been associated with learning, selection and initiation of actions that lead to reward and it thus subserves decision-making (e.g., Balleine, Delgado, & Hikosaka, 2007). It is also closely related to emotional processing–particularly if one understands emotions as including "action tendencies" (Frijda, 1986) or "action programmes" (Damasio & Carvalho, 2013).

The caudate nucleus has also been implied in subliminal face processing (e.g., Phillips et al., 2004) and it has been found active together with a subcortical "alarm" system for fear signals (Liddell et al., 2005). Our results suggest that the more flexible the cardiovagal control in HCs, the more active were extrastriate areas of

facial feature processing and the less active a subcortical "alarm" system during a task in which emotional processing was irrelevant for performance. While activation in visual face-processing areas during face-matching was also positively associated with HF-HRV at rest in patients with SAD, so was activation in the caudate nucleus, indicating that the emotional information, albeit task-irrelevant, still activated areas involved in fear processing. Alternatively, activation in caudate nucleus could indicate a compensatory mechanism.

Behavioural flexibility, as indexed by HF-HRV (cf. Porges, 2007; Thayer & Lane, 2000, 2009), can therefore be related to the caudate nucleus. Further support for this connection comes from the finding that binding of dopamine type 2/3 ($D_{2/3}$) in the striatum was shown to correlate positively with HF-HRV (Yeh et al., 2006). A relation between altered activation in caudate nucleus and SAD is suggested by the finding that striatal D_2 receptor binding potential is both significantly decreased in patients with SAD (Schneier et al., 2000; but cf. Schneier, Kent, Star, & Hirsch, 2009) and correlates with clinical symptoms in SAD (mentioned in Li, Chokka, & Tibbo, 2001).

Although the positive correlation between HF-HRV and BOLD signal in temporo-occipital cortex was found across groups, the significant HF-HRV decrease observed in the individuals with SAD both during emotional face-processing and at rest suggests these areas may be implied in SAD symptomatology. Importantly, a recent study reports that activation of visual cortices adjacent to or overlapping with the OFA in reaction to angry compared to neutral faces before treatment with cognitive behavioural therapy was selectively predictive of treatment success as indexed by differential LSAS scores (Doehrmann et al., 2012).

5.3. Limitations

In order to ensure ecological validity, we opted not to exclude patients with concurrent anxiety or affective disorders (other than bipolar depression). However, we cannot rule out that these comorbidities might have contributed to the observed effects. We equally allowed inclusion of medicated patients. Control analyses excluding the one patient taking a tricyclicum did not significantly alter the results of our study. In contrast to previous studies our measurements of interoceptive sensitivity took place with the distraction of the rhythmic noise produced by the MRI's helium pump. The significantly lower interoceptive sensitivity scores we observed could thus also indicate that patients with SAD are more easily distracted in reading out interoceptive signals or more easily deceived by false feedback than HCs. The latter hypothesis is supported by a study that provided eight patients suffering from SAD with false feedback about HR, observing that believed changes in HR had a significant effect on anxiety symptoms (Wells & Papageorgiou, 2000). Studies directly manipulating the veracity of online physiological feedback comparing patients with SAD to HCs (cf. e.g., Gray, Harrison, Wiens, & Critchley, 2007) could follow-up on this assumption. Both decreased interoceptive sensitivity and facilitated distraction fit with interoception models of anxiety, which assume altered bodily prediction errors and posit a mechanism of noisy amplification of interoceptive afferences (Paulus & Stein, 2006).

Furthermore, given the complex interplay between SNS and PSNS, analysis of independently acquired SNS activation would complement the findings. While during resting-state SNS arousal could be approximated through the LF/HF ratio (but cf. Billman, 2013), suggesting complementary modulation in SNS and PSNS, task-related HR data was not long enough to meaningfully calculate the LF component in order to estimate sympathetic activation during emotional face-matching. Furthermore, a baseline of HR data acquired outside the scanner or immediately before task completion would have allowed the assessment of inter-individual and short-term variability, respectively.

5.4. Implications for treatment

Interoceptive sensitivity can be considered an acquired skill as parental factors have been shown to influence the perception of bodily symptoms (Mechanic, 1979; Whitehead, Busch, Heller, & Costa, 1986). Thus, interoceptive accuracy provides a starting point for therapeutic intervention (cf. e.g. Arntz, 2002 for treatment of panic disorder).

Upon the finding of diminished HF-HRV in SAD, specialized biofeedback intervention to increase HF-HRV may be indicated. Such therapies have previously shown to be successful in alleviating anxiety symptoms in healthy subjects (Wells et al., 2012) and in patients with post-traumatic stress disorder (Tan, Dao, Farmer, Sutherland, & Gevirtz, 2011; Zucker, Samuelson, Muench, Greenberg, & Gevirtz, 2009). In addition, mindfulness-based stress therapy has previously been demonstrated to decrease social anxiety symptoms (Bögels & Mansell, 2004; Goldin, Ramel, & Gross, 2009). However, as no heart rate measures were acquired in these studies, a concomitant increase in HF-HRV can only be hypothesized.

6. Conclusion

Our findings extend previous reports of decreased cardiovagal control in SAD, acquired at rest, by the observation of diminished HF-HRV selectively during emotional face-matching. Aberrant cardioregulation in individuals with SAD was accompanied by heightened but inaccurate physiological self-monitoring.

Parasympathetic flexibility as a trait marker correlated positively with BOLD signal in temporo-occipital areas, suggesting that heightened attentional inhibition of emotional faces occurs at early stages of visual face-processing.

The caudate nucleus, implied in processing of subliminal fear faces, showed differential group effects: While in patients with SAD, HF-HRV correlated positively with activation in this region, the inverse correlation was observed in HCs.

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