High-frequency heart rate variability and cortico-striatal activity in men and women with social phobia

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A R T I C L E   I N F O
Article history:
Received 27 January 2009
Revised 26 May 2009
Accepted 27 May 2009
Available online 6 June 2009

Keywords:
Heart rate variability
Stress
Anxiety
Regional cerebral blood flow
PET

A B S T R A C T
Identifying brain systems that regulate or modulate autonomic nervous system functions may identify pathways through which psychosocial factors can influence health and disease. Reduced high-frequency heart rate variability (HF-HRV) characterizes anxiety disordered patients and is predictive of adverse myocardial events. Sex differences in the prevalence of anxiety disorders and cardiac diseases implicate the possibility of sex specific neural regulation of HF-HRV. We investigated the correlation between HF-HRV and regional cerebral blood flow (rCBF) in 28 subjects (15 women) with social phobia undergoing a stressful public speaking task. Regional CBF was measured with [15O] water positron emission tomography. Stress induced rCBF correlated positively with HF-HRV in the right supra genual anterior cingulate cortex Brodmann’s area (BA) 32, the right head of the caudate nucleus and bilaterally in the medial prefrontal cortex (BA10), extending into the dorsolateral prefrontal cortex (BA46) in the left hemisphere. Men showed larger positive co-variation in the caudate than women. These findings underscore the importance of the emotional division of the anterior cingulate cortex, the prefrontal cortex and the striatum in cardiovagal activity. The study replicates and extends results from published functional neuroimaging studies on cardio regulatory or modulatory areas in healthy subjects to men and women with social phobia. Moreover, caudate functions, possibly related to dopaminergic neurotransmission, have sexually dimorphic effects on vagal modulation of the heart.

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Introduction
Stressful events may influence health and disease through brain systems that regulate or modulate cardiac activity. One way to index the central control of the heart is the use of heart rate variability (Task Force, 1996; Thayer and Lane, 2009). The heart is dually innervated by the autonomic nervous system such that relative increases in sympathetic activity are associated with heart rate increases and relative increases in parasympathetic activity are associated with heart rate decreases. The parasympathetic (primarily vagal) influences are pervasive over the frequency range of the heart rate power spectrum whereas the sympathetic influences ‘roll-off’ at about 15 Hz (Saul, 1990). Thus, high-frequency HRV (HF-HRV) represents primarily parasympathetic influences with lower frequencies (below about .15 Hz) having a mixture of sympathetic and parasympathetic autonomic influences. The sympathetic effects are relatively slow (on the time scale of seconds) whereas the parasympathetic effects are much faster (on the time scale of milliseconds). Therefore, the parasympathetic influences are the only ones capable of producing rapid changes in the beat-to-beat timing of the heart. This rapid modulation of heart rate is associated with both the mechanical and neural gating of vagal outflow during respiration. Specifically, during inspiration vagal outflow is reduced and heart rate increases whereas during expiration vagal outflow is restored and heart rate decreases. Consequently, heart rate variability largely reflects the respiratory gating of the output of the vagus nerve on the sinoatrial node of the heart (Saul, 1990). A compromised vagal control over heart rate is prospectively associated with adverse cardiac events, especially sudden cardiac death (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996; Thayer and Lane, 2007).

Anxiety symptoms and disorders, as well as depressive symptoms and syndromes, are associated with alterations in autonomic control over cardiac functions (Friedman, 2007; Rottenberg, 2007). For example, our group has consistently found evidence of reduced HRV in anxiety disorders (e.g., Thayer et al., 1996; Melzig et al., 2009) and this has generally been supported by reviews of the literature although there have been some exceptions to this finding (Friedman, 2007). Also, anxious traits and phobic states are associated with an increased rate of adverse cardiac events such as myocardial infarction and stroke (Blumenthal et al., 1979; Frasure-Smith and Lesperance, 2008). It is conceivable that one mechanism mediating the adverse effects of anxiety and phobia may be linked to reduced heart rate...
HF-HRV outside the scanner have been correlated to subsequent brain activity and might suggest a beneficial cardioregulatory mechanism during stress in women. Also, previous studies have been conducted in healthy volunteers during rest or while exposed to mildly emotion-inducing stimuli. Here, subjects with social anxiety disorder were studied under high stress load.

Several studies have correlated HF-HRV with regional cerebral blood flow (rCBF) or blood oxygen level dependent (BOLD) signal changes during imaging of cognitive, emotional and motor functions (Critchley et al., 2003; Gianaros et al., 2004; Matthews et al., 2004; Neumann et al., 2006; Lane et al., 2009; O'Connor et al., 2007; Napadow et al., 2008). However, none of these studies have reported on sex differences in brain activity as related to cardiovascular activity. Women are less susceptible to cardiac disease than men, even though they are more prone to anxiety disorders. This could be due to sex differences in the central nervous system’s role in vagal modulation of the heart and might suggest a beneficial cardioregulatory mechanism during stress in women. Also, previous studies have been conducted in healthy volunteers during rest or while exposed to mildly emotion-inducing stimuli. Here, subjects with social anxiety disorder were studied under high stress load.

Studies vary with respect to whether cardiovascular recordings have been performed during imaging or whether baseline measures of HF-HRV outside the scanner have been correlated to subsequent brain imaging data. However, two studies have used PET and online measurements of R–R intervals to allow determination of HF-HRV. Gianaros et al. (2004) found that regional cerebral blood flow co-varied positively with HF-HRV in the anterior cingulate, the insula and in the amygdala/hippocampal complex. A negative correlation was observed in the cerebellum. Lane et al. (2009) reported positive correlations in the superior prefrontal cortex (Brodmann’s area [BA] 8/9), the anterior cingulate cortex (BA24/32), the dorsolateral prefrontal cortex (BA46) and the parietal cortex (BA40). The study design included both neutral and emotional film clips and emotion-specific positive co-variations were observed in the caudate, midbrain, the insula and the medial prefrontal cortex (BA10). An additional negative correlation was found in the cuneus (BA19). Two studies have measured BOLD signal changes in response to a cognitive task and a handgrip task with simultaneous recordings of the R–R interval (Critchley et al., 2003; Napadow et al., 2008). Critchley et al. (2003) reported positive correlations between HF-HRV in the cerebellum, the supplementary motor area, the anterior cingulate and the somatosensory cortex. Napadow et al. (2008) demonstrated correlations between HF-HRV and BOLD signal changes in the hypothalamus, cerebellum, parabrachial nucleus/locus ceruleus, periaqueductal gray (PAG), amygdala, hippocampus, thalamus, and dorsomedial/dorsolateral prefrontal, posterior insular, and middle temporal cortices. In summary, studies have revealed a consistent pattern of brain areas involved in the regulation of HF-HRV including limbic/striatal, medial and dorsolateral prefrontal together with cerebellar cortices. Importantly these areas overlap with areas involved in stress and anxiety (Rauch et al., 2003; Etkin and Wager, 2007) forming a possible link between anxiety and heart disease. A recent paper (Goldin et al., 2009) suggests that SAD is related to altered activation in a brain circuitry implicated in self control including medial and lateral prefrontal cortices. This network is composed of frontal and temporal cortices and might be involved not only in emotional control, but also in autonomic modulation (Goldin et al., 2009).

In order to study the co-variation between HF-HRV and rCBF during negative affect, we recorded R–R intervals in men and women with social anxiety disorder undergoing a stressful speaking task. The analyses here are focused on two research questions: 1) Do brain areas previously associated with vagal modulation of the heart also regulate vagally mediated heart activity during social stress? 2) Are these areas differentially involved in vagal modulation of the heart in men and women? We used a region of interest (ROI) approach targeting regions that were previously implicated in the two PET-studies that measured rCBF and R–R intervals simultaneously (Gianaros et al., 2004; Lane et al., 2009).

Methods and materials

A detailed description of the procedure is given in Furmark et al. (2005). Briefly, 28 patients (all individuals with artifact free R–R interval recordings; 15 women; mean age ± SD: 31.3 ± 7.3 years) of the original 36 were included in the present analyses. Subjects were recruited through newspaper advertisements. After an initial screening interview performed over the telephone social anxiety questionnaires were sent and returned by mail. The structured clinical diagnostic interview (SCID; First et al., 1998) was performed, and the MINI-interview (Sheehan et al., 1998) was administrated to exclude other serious psychiatric disorders. In addition, medical examinations were performed. All participants met the DSM-IV criteria for social phobia, exhibited marked public speaking anxiety and were free of somatic diseases.

Exclusion criteria were: treatment of social anxiety in the past six months; current serious or dominant psychiatric disorder other than social phobia (e.g. psychosis, major depressive or bipolar disorder); neurological disorders; somatic disease; chronic use of prescribed medication; abuse of alcohol/narcotics; pregnancy; menopause; left-handedness; previous PET-examination; and positive family history of cancer. Approvals were obtained from the Uppsala University Medical Faculty Ethical Review Board and the Uppsala University Isotope Committee. Written informed consent was obtained from all participants.

PET-assessments

Investigations were performed with a 32-ring ECAT Exact HR+ scanner (Siemens/CTI, Knoxville, USA). The scanner enables acquisition of 63 contiguous planes of data with a distance of 2.46 mm resulting in a total axial field of view of 155 mm. Subjects were positioned in the scanner, had the head gently fixated and venous catheter inserted for tracer injections. Patients prepared a 2 1/2-minute speech about a vacation or travel experience roughly 20 min before the emission scan. A 10-minute transmission scan was performed using three retractable 58/Ge rotating line sources. Thereafter the 15O-water tracer, approximately 10 MBq/kg body weight, was injected intravenously. Emission scans started automatically in the 3D mode when the bolus reached the brain (50,000 counts/s), and consisted of three 30-s frames.

Directly following tracer injection patients were instructed to start speaking and continue until they were asked to stop 2 1/2 min later. A silently observing audience of 6–8 persons was present during the speech. Patients were instructed to observe the audience, and the subject was recorded from a close distance using a video camera to increase observational anxiety and document verbal performance. One scan per subject was obtained during which heart rate was simultaneously recorded using Psylab (Contact Precision Instruments, London).

Emission scans were reconstructed with a filter back projection using a 8 mm Hanning filter, resulting in a spatial resolution of about 5 mm in the field of view. The matrix included 128 × 128 pixels. Data were corrected for photon attenuation, decay, scattered radiation and random coincidences. After reconstruction, a summation image of the three frames was made in order to obtain a better statistical reference for realignment and subsequent analyses.

Participants fasted 3 h, and refrained from tobacco, alcohol and caffeine for 12 h prior to PET-investigations.

Heart rate variability analysis

ECG was recorded using Psylab (Contact Precision Instruments, London, UK) and three leads. Psylab was equipped with an interval
and Tournoux, 1988. Symptom severity and motor activity during the speech
Symptom severity was assessed with the Liebowitz Social Anxiety Scale (LSAS) (Liebowitz, 1987). Motor activity during the speech was defined as the number of words spoken during a 10 s time window.

PET-data analyses
PET-images were realigned to correct for different positions between scans and normalized to the Montreal Neurological Institute's (MNI) stereotactic template (ICBM 152), using the SPM99 software (Wellcome Department of Cognitive Neurology, London, UK). Images were then smoothed using a 12 mm Gaussian kernel. PET-data were statistically evaluated using SPM2 with rCBF-data fitted to the general linear model (Friston et al., 1994). Differences in global blood flow were corrected for using the proportional scaling method within SPM2. Locations of areas with peak correlations are described as xyz coordinates in the Talairach space, obtained by non-linear transformation of the MNI coordinates obtained from SPM2 (www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html). Anatomical localization was supported by searches in the Talairach atlas (Talairach and Tournoux, 1988) and the Talairach Daemon (Lancaster et al., 2000).

Regions of interests
We based our regions of interests (ROIs) on the two papers that also used PET and measures of rCBF collected simultaneously with heart rate recordings (Gianaros et al., 2004; Lane et al., 2009). Gianaros et al. (2004) reported positive correlations in the ventromedial prefrontal cortex (anterior cingulate cortex, BA 32, reported coordinates as mapped in the Talairach atlas), the insula and the amygdala hippocampal complex. A negative correlation was observed in the cerebellum. Lane et al. (2009) reported positive correlations in the superior prefrontal cortex (BA 8/9), the anterior cingulate cortex (BA 24/32), the dorsolateral prefrontal cortex (BA 46) and the parietal cortex (BA 40). Emotion-specific positive co-variations were observed in the caudate, midbrain (including PAG), the insula and the medial prefrontal cortex (BA 10). An additional negative correlation was found in the cuneus (BA 19). ROIs were defined in MNI space using WFU-pickatlas (Maldjian et al., 2003). ROIs of Brodmann areas were dilated by 3 mm to include all tissue circumscribed by the original ROI.

Statistical analyses
To test for differences in mean HF-HRV between men and women, independent t-tests were performed using SPSS version 16.0. Within the SPM2 software, co-variations between HF-HRV and rCBF were evaluated at the voxel level by examining voxels showing p-values <.05. Family wise error correction (FWE) for multiple comparisons was used within the defined ROI's. Cluster size is the number of voxels surviving an uncorrected threshold of p <.01. Contrasts were generated to test for positive and negative co-variation between HF-HRV and rCBF. Sex differences in HF-HRV co-variation with rCBF were evaluated using psychophysiological interaction analysis (Friston et al., 1997). In addition, exploratory analyses were performed evaluating correlations exceeding p <.001 uncorrected for multiple comparisons within each ROI.

Finally, Pearson's correlation coefficients were used to test for associations between symptom severity as indexed by LSAS and rCBF in areas displaying significant co-variation with HF-HRV. Regional CBF in these areas was also correlated with the number of words pronounced during the first 10 s of the speech to control for the possible confound that rCBF reflected motor activity. Voxel values were extracted from SPM2 and correlations were performed in SPSS version 16.0.

Results
Physiological parameters
As previously reported, the public speaking task was experienced as highly distressing (Furmark et al., 2005). Men and women did not differ in HF-HRV (t(26) = 1.48; n.s.) with means (±SD) being 13.25 (±10.61) and 21.64 (±17.72) for men and women respectively.

Brain–body relations
Positive correlations
Fig. 1 and Table 1 display significant findings within the a priori ROIs. There were positive correlations between HF-HRV and rCBF in right genual anterior cingulate cortex (BA32), in the right head of the caudate voxel that exhibited a sex-dependent co-variation with HF-HRV. Sex differences in rCBF were evaluated using psychophysiological interaction analysis (Friston et al., 1997). Differences in global blood flow were corrected for using the proportional scaling method within SPM2. Locations of areas with peak correlations are described as xyz coordinates in the Talairach space, obtained by non-linear transformation of the MNI coordinates obtained from SPM2 (www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html). Anatomical localization was supported by searches in the Talairach atlas (Talairach and Tournoux, 1988) and the Talairach Daemon (Lancaster et al., 2000).

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same voxels was uncorrelated with motor activity as indicated by word count (all $p$’s > .1).

**Discussion**

Anxiety disorders have been associated with increased risk for cardiovascular disease. One possible mechanism that has been proposed is altered autonomic balance and decreased HRV (Roy-Byrne et al., 2008). However, little is known about the neural concomitants of this possible mechanism. We assessed rCBF in individuals with social phobia undergoing a stressful public speaking task while simultaneously recording R–R intervals to determine HF-HRV as an index of parasympathetic drive. We observed positive correlations between HF-HRV and rCBF in the anterior cingulate cortex, the medial and dorsolateral prefrontal cortex as well as in the head of the caudate nucleus. Men showed a larger positive covariation in the caudate than did women. The study replicates and extends results from previous functional neuroimaging studies on cardiorégulatory and modulatory areas in healthy subjects (Critchley et al., 2003; Gianaros et al., 2004; Matthews et al., 2004; Neumann et al., 2006; O’Connor et al., 2007; Napadow et al., 2008; Lane et al., 2009). It extends these findings to men and women with social phobia and suggests that caudate functions have sexually dimorphic effects on vagal modulation of the heart. These present findings provide some of the first data aimed at understanding the neural underpinnings of the link between anxiety and cardioregulatory mechanisms.

Similar to most other studies in non-anxious populations, we observed a positive co-variation between neural activity in the

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>Brodmann area</th>
<th>Talairach coordinates</th>
<th>$z$</th>
<th>$p$ (corrected)</th>
<th>Cluster size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cingulate cortex</td>
<td>32</td>
<td>16, 49, 10</td>
<td>3.47</td>
<td>.037</td>
<td>135</td>
</tr>
<tr>
<td>Medial prefrontal cortex</td>
<td>10</td>
<td>18, 51, 7</td>
<td>3.98</td>
<td>.027</td>
<td>239</td>
</tr>
<tr>
<td>Dorsolateral prefrontal cortex</td>
<td>46</td>
<td>−36, 51, 16</td>
<td>4.38</td>
<td>.003</td>
<td>99</td>
</tr>
<tr>
<td>Caudate (head)</td>
<td>-</td>
<td>10, 17, −6</td>
<td>3.57</td>
<td>.022</td>
<td>315</td>
</tr>
</tbody>
</table>

Fig. 1. Positive correlations between stress-induced rCBF and HF-HRV. Pictures are presented using neurological convention with the right hemisphere to the right. The color bar represents $t$-scores.
anterior cingulate cortex and the parasympathetically linked high-frequency component of heart rate variability. This reflects a functional relationship that also may correspond to structural alterations, as right ACC volume is positively correlated with respiratory sinus arrhythmia (Woodward et al., 2008). It has been suggested that the ACC can be divided into two separate areas involved predominantly with cognitive and emotional processes respectively (Bush et al., 2000). We observed, like in previous studies (Critchley et al., 2003; Gianaros et al., 2004; Matthews et al., 2004; Neumann et al., 2006; O’Connor et al., 2007; Lane et al., 2009) that the emotional part of the anterior cingulate seems to be involved in cardiovagal control. Intriguingly, we have previously reported data that suggested a negative association between anterior cingulate activity and cortisol excretion during public speaking in individuals with social anxiety disorder (Åhs et al., 2006). A similar negative regulation of cortisol by the anterior cingulate cortex has also been found in subjects with PTSD (Bonne et al., 2003). Collectively, this would suggest that enhanced ACC activity may be associated with reductions in stress related endocrine activity and increased cardiovagal activity in the context of negative affect. It has been argued that automatic control of negative affective states is associated with increased activity in the anterior cingulate (Phillips et al., 2008). If correct, our results predict that the ACC involvement in controlling negative affect may be paralleled by beneficial effects for both cardiac and endocrine functions.

Napadow et al. (2008) studied the relation between cardiac vagal drive and BOLD signal changes during a handgrip task and observed that areas previously implicated in animal research reflecting activity of a central autonomic network were altered also in humans. The relations of cortical and limbic brain regions with vagal drive were held to be unique for humans. One of those areas included the prefrontal cortex. Other studies by Critchley et al. (2003), Gianaros et al. (2004) and Lane et al. (2009) have also implicated the prefrontal cortex as being involved in cardiovagal control. Because the prefrontal cortex performs many functions, such as cognitive processes related to emotional regulation (Davidson et al., 2000; Ochsner and Gross, 2005), it is likely that some of these cognitive processes are linked to control of vagal modulation of the heart.

A previous study (Lane et al., 2009) that also used emotion-inducing techniques reported a positive relation between activity in the head of the caudate nucleus and HF-HRV. Lane et al. (2009) interpreted this as suggesting that behavioral inhibition would result in greater sympathetic activity in the caudate nucleus, reflecting a close link between cardiovagal and somatomotor activity in the context of emotional arousal. In the present study, the positive relation between HF-HRV and caudate activity was replicated, but no relation was found between motor activity and the regions associated with vagal control. Taken together with the sex differences observed here, this may suggest an alternative interpretation of the present data. There was a higher positive co-variation in the caudate between rCBF and HF-HRV in men than women. The caudate is richly innervated by dopamine; it is conceivable that the differential relation between neural activity in the caudate and vagal control of heart rate in men and women reflect differences in the dopaminergic striatal system. For example, Yeh et al. (2006) demonstrated that increased dopamine D2/D3 receptor availability was positively associated with parasympathetic control over heart rate, reflected in the cardiac vagal index and by a positive correlation with HF-HRV. At the same time, Munro et al. (2006) demonstrated that the striatal dopamine system was more active to amphetamine challenge in men than women. Collectively, these findings suggest that enhanced dopaminergic striatal drive in men as compared to women may underlie sex differences in brain cardiac couplings. This would imply that individual differences in dopaminergic functions in other studies in part may account for the relationship between enhanced synaptic activity in the caudate and increased cardiac vagal activity. Thus, these findings may imply a role for dopaminergic mechanisms in explaining less susceptibility for cardiac disease in women.

Negative correlations were also observed between activity in the anterior insula and HF-HRV at a sub-threshold level (p < 0.10) corrected for multiple comparisons. Both Gianaros et al. (2004) and Napadow et al. (2008) reported negative correlations between blood flow in the cerebellum and HF-HRV. Enhanced activity in the cerebellum may be linked to the fight/flight response and associated with motor processes. On the other hand, the cerebellum has been implicated in modulation of autonomic functions through its connections with the hypothalamus and this is also a plausible route for the observed relations. The anterior insula is involved in viscerosensory control and interoceptive awareness (Paulus and Stein, 2006) and also responds to negative affect (Calder et al., 2001). Lane et al. (2009) reported a positive correlation between HF-HRV and insula activity when using moderate to high intensity stimuli with both a positive and a negative emotional impact. The negative relationship observed here possibly reflects the impact of a highly aversive and stressful public speaking event associated with an insula-related decrease in cardiovagal activity.

Social phobia is associated with reduced ACC activity relative to healthy controls during emotion regulation (Goldin et al., 2009). However, the present study demonstrates that the relation of activity in this area to HF-HRV seems to be the same as in healthy controls (e.g. Lane et al., 2009). Similarly, during social threat, dorsolateral prefrontal cortex activity appears reduced in social phobia compared to controls (Goldin et al., 2009), whereas the functional relationship between HF-HRV and rCBF in this area appears the same as in healthy controls. It could be that the mean levels of activity in these brain areas differ in social phobia, but that the functional relationship between neural activity and HF-HRV does not differ between groups. This predicts that subjects with social phobia would show decreased mean levels of rCBF in anterior cingulate and dorsolateral prefrontal cortices and possibly decreased HF-HRV compared to controls, whereas the correlation between rCBF and HF-HRV could be expected to be equivalent in both groups. Taken together, this suggests that individuals with social phobia might be less able to implement cognitive emotional regulation strategies to social threat which in turn could have effects on the vagal modulation of the heart.

There are some limitations to the present study. First, we did not include non-anxious controls to directly compare the brain vagal relationships in patients to healthy controls. This may also limit the generalizability of the observed sex difference, possibly being restricted to anxiety disordered patients. It should, however, be noted that there was no association between symptom severity and brain regions involved in the vagal modulation of the heart, suggesting that results were not directly linked to the severity of social phobia. Second, we did not measure rCBF and HF-HRV during baseline or a control task making it impossible to determine if our findings mirror state or trait effects. Thus, our design captures individual differences in brain vagal couplings but we cannot determine if differences reflect trait differences present at rest or state differences induced by emotional stress. However, it should be noted that most other brain imaging studies comparing activity and reactivity suggest that the task-related increase is most influential (e.g. Furmark et al., 2004, 2008) and we hold it likely that this is the case here too.

In conclusion, vagal modulation of the heart is associated with activity in striatal as well as medial and lateral prefrontal areas in men and women with social phobia. Moreover, striatal functions, possibly related to dopaminergic neurotransmission, have sexually dimorphic effects on vagal modulation of the heart. This sex difference in central cardiac control might be of importance for understanding differences between men and women in cardiovascular health and disease.
References


