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Regional cerebral blood flow correlates with heart period and high-frequency heart period variability during working-memory tasks: Implications for the cortical and subcortical regulation of cardiac autonomic activity

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Abstract

The aim of the present study was to characterize the functional relationships between behaviorally evoked regional brain activation and cardiac autonomic activity in humans. Concurrent estimates of regional cerebral blood flow (rCBF; obtained by positron emission tomography), heart period, and high-frequency heart period variability (HFHPV; an indicator of cardiac parasympathetic activity) were examined in 93 adults (aged 50–70 years) who performed a series of increasingly difficult working-memory tasks. Increased task difficulty resulted in decreased heart period (indicating cardioacceleration) and decreased HF-HPV (indicating decreased cardiac parasympathetic activity). Task-induced decreases in heart period and HF-HPV were associated with concurrent increases and decreases in rCBF to cortical and subcortical brain regions that are speculated to regulate cardiac autonomic activity during behavioral processes: the medial-prefrontal, insular, and anterior cingulate cortices, the amygdala–hippocampal complex, and the cerebellum. These findings replicate and extend a small number of functional neuroimaging studies that suggest an important role for both cortical and subcortical brain systems in human cardiac autonomic regulation.

Keywords

Central cardiac autonomic regulation; Heart period; High-frequency heart period variability; Positron emission tomography

The cortical and subcortical brain systems that regulate cardiac autonomic activity during behavior have been detailed by extensive research in nonhuman animals (reviewed by Bennarroch, 1997; Buchanan & Powell, 1993; Loewy & Spyer, 1990; Neafsey, Terreberry,

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Hurley, Ruit, & Frysztak, 1993). An open question is whether similar brain systems regulate behaviorally integrated cardiac autonomic activity in humans. Answering this question is important because the brain's regulation of cardiac autonomic activity is purported to influence a range of behavioral processes: attending to novel stimuli (Porges, 1995), processing environmental information (Lacey & Lacey, 1974), making decisions (Damasio, 1994), experiencing fear and anxiety (Berntson, Sarter, & Cacioppo, 1998), perceiving pain (Dworkin et al., 1994; Rosen et al., 1996), and reacting to stressors (Lovallo & Gerin, 2003) are examples of such processes.

Drawing on the support of nonhuman animal research, the cortical brain systems that are hypothesized to regulate cardiac autonomic activity during behavior include the medial-prefrontal (Brodmann Areas 10 and 11), insular, and anterior cingulate (Brodmann Areas 24, 25, and 32) regions of the cortex. A prevailing view is that these cortical systems act as a network with subcortical systems to initiate and represent cardiac autonomic adjustments that support behavioral responses to environmental, psychological, and social stimuli (Bennarroch, 1997; Cechetto, 1994; Groenewegen & Uylings, 2000; Loewy & Spyer, 1990; Thayer & Lane, 2000). Subcortical regions that are thought to regulate behaviorally integrated cardiac autonomic activity include the amygdala, hypothalamus, and nuclei in the midbrain (e.g., periaqueductal gray), cerebellum (e.g., cerebellar vermis), and brain stem (e.g., solitary tract nucleus; nucleus ambiguous; dorsal motor nucleus; and rostral ventrolateral medulla; Bennarroch, 1997; Loewy & Spyer, 1990). By coordinating changes in cardiac autonomic activity with ongoing behavior, these subcortical brain systems are thought to support such processes as gauging the emotional significance of a stimulus (LeDoux, 2000), mobilizing aggressive and defensive responses (Paredes, Winters, Schneiderman, & McCabe, 2000), and relaying afferent visceral information that modulates cortical activity (Berntson et al., 1998). Yet despite the putative roles of the above cortical and subcortical systems in cardiac autonomic regulation, very few human functional neuroimaging studies have investigated whether and how measures of activity in these brain regions relate to measures of cardiac autonomic activity during cognitive or emotional behaviors—and the results of the few existing studies are mixed.

For example, two studies reported mixed results regarding the relationships between regional brain activation and high-frequency heart period variability (HF-HPV), which is an indicator of cardiac parasympathetic activity (Berntson et al., 1997). In the first study, Lane, Reiman, Ahern, and Thayer (2001) used positron emission tomography to examine the relationships between regional cerebral blood flow (rCBF) and HF-HPV in participants who viewed emotional films and recalled emotional experiences. The authors reported that during these emotional tasks, increased rCBF to the medial-prefrontal and insular cortical regions correlated with increased HF-HPV. These particular findings were compatible with prior speculations (e.g., Oppenheimer, 1993; Thayer & Lane, 2000) and research in individuals with epilepsy (Ahern et al., 2001; Oppenheimer, Gelb, Girvin, & Hachinski, 1992) and cerebral infarctions (Tokgözoglu et al., 1999) that suggested that these cortical systems contribute to both long- and short-term changes in human cardiac parasympathetic activity. But the findings of Lane et al. (2001) were inconsistent with those reported by Shapiro et al. (2000). In that study, no statistically significant correlations were found between rCBF (estimated by single-photon emission computed tomography) and HF-HPV

in participants who completed a stressful mental arithmetic task. Together, these two studies leave unclear which human brain systems regulate cardiac parasympathetic activity (as indexed by HF-HPV) during different behaviors.

Two other studies that investigated the relationships between measures of rCBF and cardiac hemodynamic activity (heart rate and blood pressure) during mental arithmetic tasks yielded similarly mixed results. In the first study, Critchley, Corfield, Chandler, Mathias, and Dolan (2000) found that increases in heart rate and mean arterial pressure during a mental arithmetic task and an isometric exercise correlated with changes in rCBF to both cortical (including the medial-prefrontal, insular, and cingulate areas) and subcortical (including the amygdala, cerebellum, and brain stem) regions. Overall, these correlations were on par with the assumption that activation and deactivation in these cortical and subcortical brain systems initiate and represent changes in cardiac hemodynamic activity that provide metabolic support for behavioral action (e.g., Bennarroch, 1997); however, these results contrasted with those reported by Soufer et al. (1998). The results from that study were that changes in cardiac hemodynamic activity (the product of heart rate and mean arterial pressure), which were elicited by a mental arithmetic task, did not correlate with rCBF in a sample of otherwise healthy individuals; but, in a matched sample of individuals with coronary artery disease, greater rCBF to the medial-prefrontal and inferior frontal cortex, the periaqueductal gray, and the cerebellum did correlate with task-induced increases in the product of heart rate and mean arterial pressure.

Thus, although a small number of functional neuroimaging studies are beginning to characterize the human brain systems that may regulate cardiac autonomic activity during cognitive and emotional behaviors, the results of these studies are discrepant. A salient discrepancy of these studies is that some have found correlations between cardiac autonomic activity and regional brain activation whereas others have not. Possible reasons for these mixed findings include the use of different (a) neuroimaging techniques, (b) data analytical approaches, (c) measures of cardiac autonomic and hemodynamic activity, and (d) experimental tasks. Furthermore, the above studies may also have been limited by the use of samples that were relatively small: the ns ranged from 5 to 12. Importantly, the use of these small samples may have reduced the statistical power with which to detect correlations between measures of regional brain activation and cardiac autonomic activity. Partly as a result of these study differences and limitations, we consequently have an insufficient understanding of the human brain systems that regulate cardiac autonomic activity during cognitive and emotional behaviors.

Therefore, our aim was to better characterize the human brain systems that regulate behaviorally evoked changes in cardiac autonomic activity. To this end, we used positron emission tomography to examine the correlations between rCBF and heart period and HF-HPV in a relatively large sample (n = 93) of men and women who completed a series of increasingly difficult working-memory tasks. This approach allowed us to determine how both activation (assessed by increased rCBF) and deactivation (assessed by decreased rCBF) in cortical and subcortical brain regions relate to changes in cardiac autonomic activity while individuals engage in cognitive tasks.

Difficult cognitive tasks have been shown in numerous studies to elicit cardioacceleration (increased heart rate or reduced heart period), which is often mediated by increased sympathetic and decreased parasympathetic cardiac activity (e.g., Berntson et al., 1994; Cacioppo, Uchino, & Berntson, 1994). Thus, we expected that increased task difficulty (greater working-memory demand) would decrease both heart period and HF-HPV. Based on available human and nonhuman animal research, we also expected that these changes in heart period and HF-HPV would correlate with activation and deactivation in cortical and subcortical areas that are hypothesized to integrate cardiac autonomic activity with cognitive and emotional behavioral processes. Establishing such correlations in a relatively large sample would thus extend prior research by identifying the specific human brain regions that may regulate behaviorally integrated cardiac autonomic activity.

Method

Participants

Participants were ninety-three 50–70-year-old men (n = 54) and women (n = 39). Of these participants, 2 were left-handed and 32 had untreated hypertension, defined as a resting blood pressure above 140 mmHg systolic or 90 mmHg diastolic. The data reported here were collected as part of the Hypertension and Positron Emission Tomography study at the University of Pittsburgh. The primary aim of this study was to compare normotensive to untreated hypertensive individuals in their rCBF responses to working-memory tasks; sample size calculations were based on testing this aim and preliminary results were reported by Jennings (2003).

Exclusion criteria included secondary hypertension; current use of antihypertensive, cardiovascular-active, or psychotropic medication; lifetime antihypertensive treatment exceeding 2 years; a prior stroke or myocardial infarction; prior vascular surgery; congestive heart failure or pulmonary disease; diabetes; obesity (>30% overweight by Metropolitan Life Insurance tables); cancer; renal failure (serum creatinine above 2.0 mg/dl); hepatitis; cirrhosis; alcoholism; a psychiatric disorder; and less than eighth-grade reading skills. Female participants were postmenopausal and were not receiving hormone replacement therapy. All participants provided informed consent and the University of Pittsburgh's Institutional Review Board granted study approval.

Study Design

Participants completed four initial experimental sessions prior to the positron emission tomography imaging session. In these initial sessions, the study was described and informed consent was provided by each participant, two assessments of seated resting blood pressure were made, a structural image of each participant's brain was acquired using a 1.5-Tesla GE Signa Scanner (Milwaukee, WI), and a neuropsychological battery was administered (battery results were reported in Jennings, 2003). After these initial sessions (and within 2 weeks of the first experimental session) participants completed a positron emission tomography scanning session in which they completed a series of working-memory tasks while simultaneous estimates of rCBF, heart period, and HF-HPV were obtained.

Working-Memory Tasks

In the positron emission tomography scanning session, participants completed a series of five tasks: a perceptual-motor control task and two increasingly difficult levels each of a verbal working-memory task and a spatial working-memory task. These working-memory tasks were adapted from those described by Smith, Jonides, and Koeppe (1996). The five tasks were 5 min in length, were presented in a random order, and were completed twice. Thus, a total of 10 experimental epochs were available to correlate rCBF with cardiac autonomic activity for each participant (see Statistical Analyses section below).

For each trial of each experimental task, the participant was presented with a visual display that was comprised of a permanently visible central fixation point and a single letter. Each letter was presented once every 2 s, was visible for 1 s, and was presented around the fixation point at one of eight possible equidistant positions. When a target or nontarget stimulus appeared on the visual display, the participant used her or his dominant hand to push one of two buttons on a response box with her or his index finger (for target responses) or middle finger (for nontarget responses). The participant's response was followed by an auditory tone, which indicated whether the response was correct or incorrect.

In the perceptual-motor control task, the participant pushed the left response button when a letter appeared on the left side of the fixation point and a right button when a letter appeared on the right side. In the first level of the verbal working-memory task, the participant maintained three target letters in memory. More specifically, the participant responded with her or his index finger when one of three target letters appeared on the visual display; the participant responded with her or his middle finger when a nontarget letter appeared. In the second level of the verbal working-memory task, the participant was presented with a series of individual letters; the task of the participant was to make a target response if the same letter had been presented two trials ago. That is, if the letter series "*a v a*" was presented, the participant would make a target response indicating that "*a*" had occurred two trials ago; but if the letter series "*r v a*" was shown, the participant made a nontarget response with her or his middle finger. In the first level of the spatial working-memory task, the participant maintained three target positions in memory. Like the first level of the verbal working-memory task, the participant responded with her or his index finger when a letter appeared in one of three target positions, but responded with her or his middle finger when a letter appeared in a nontarget position. In the second level of the spatial working-memory task, the participant was required to make a target response if a letter had appeared in a target position two trials prior; a nontarget response was required if a letter had not appeared in a target position two trials prior.

Assessment of rCBF

During each task, a Siemens 951R/31 positron emission tomography scanner (Knoxville, TN) was used to acquire 31 simultaneous axial images of rCBF. These 31 functional images covered 11 cm of the brain at a resolution of approximately 6 mm full-width half-maximum (FWHM). Prior to functional imaging, each participant was positioned in the scanner to align the axis of the scanner so that it was parallel to the glabellar-inion line. Each participant was then fitted with a short 21-gauge catheter in her or his radial artery and an

intravenous line to inject ^{15}O water. Following catheterization, a 10-min transmission scan was performed using rotating rods of $^{68}Ge/^{68}Ga$ for attenuation calculations. During the experiment, estimates of rCBF were measured during each task by recording the cerebral-radioactivity distribution of a 7-mCi bolus of freely diffusible ^{15}O water, which was injected 30 s after the initiation of each task. Beginning with each bolus injection, a 180-s scan was obtained during each task, and this scan was divided into 20 sequential frames. Each scan was followed by a 7-min rest period for a total of 10 min between injections, which allowed for the decay of background radiation. For each task, voxel-by-voxel images of rCBF were generated using a weighted least-squares approach (Alpert et al., 1984) and motion artifacts in these functional images were corrected using Automated Image Registration (Woods, Cherry, & Mazziotta, 1992).

Assessment of Heart Period and High-Frequency Heart Period Variability

Throughout each task, electrocardiographic (ECG) signals were obtained from two disposable Ag/AgCl electrodes that were positioned in a modified Lead II configuration. The digitized (12 bit) ECG signal was sampled at 1000 Hz and was stored for a two-stage off-line processing sequence. In the first stage, R-waves in the ECG signal were identified with a locally developed peak-detection software algorithm; in the second stage, R-wave markers were reviewed visually and corrected manually if necessary (<1% of the R-waves were corrected).

Heart period was derived from the ECG signal and was defined as the interval in milliseconds between sequential R-waves. Average heart period for each 5-min task was calculated by dividing the sum of these time intervals by the total number of intervals in a given task. The PSPAT software program (Weber, Molenaar, & van der Molen, 1992) was used to determine the spectral power in high-frequency (0.15 to 0.30 Hz) heart period variability (HF-HPV) during each task. Specifically, the 5-min heart-period time series from each task was submitted to PSPAT, which linearly detrended, mean centered, and tapered the time series with a Hamming window. Then, spectral-power estimates in 0.15- to 0.30-Hz heart period variations were determined (in ms^2/Hz) with a point process algorithm (de Boer, Karemaker, & Strackee, 1984). Because of distributional violations, these spectral-power estimates were natural-log transformed prior to statistical analyses; natural-logged spectral-power HF-HPV estimates were then taken as an indicator of cardiac parasym-pathetic activity.

Statistical Analyses

We first evaluated changes in heart period and HF-HPV across the tasks using multivariate analyses of variance (MANOVAs) with Task as a repeated measure. For these multivariate analyses, we averaged heart period and HF-HPV separately over both replications of each task; this yielded five values of heart period and HF-HPV: one each for the perceptual motor-control task, the first level of the verbal and spatial working-memory tasks, and the second level of these two working-memory tasks. The Wilks–Lambda MANOVA test statistic was used to determine whether heart period and HF-HPV changed across the tasks. Statistically significant ($\alpha \leq .05$) task-induced changes were then followed with post hoc

comparisons of each level of the working-memory tasks to the perceptual motor-control task.

We evaluated the relationships between rCBF and heart period and HF-HPV using random-effects regression analyses with Statistical Parametric Mapping software (SPM99; University College, London, Wellcome Department of Imaging Neuro-science; described by Friston et al., 1995). Prior to these regression analyses, we spatially transformed (cross-registered) each functional rCBF image into the standard stereotaxic template of the Montreal Neurological Institute; we also increased the signal-to-noise ratio of each functional image in the *x*, *y*, and *z* dimensions with a Gaussian smoothing filter of 10 mm FWHM.

After image standardization and smoothing, we performed single-subject regression analyses (with covariate-only SPM design matrices) that evaluated the linear relationships between the 10 task estimates of rCBF and the corresponding 10 estimates of heart period and HF-HPV. In these single-subject regression analyses, rCBF to each brain voxel was first regressed on the global change in CBF associated with each scan. After controlling for global CBF, rCBF was then regressed separately on heart period and HF-HPV. From these single-subject analyses, we retained the voxel-by-voxel regression slopes that reflected the positive and negative relationships between rCBF and cardiac autonomic activity (heart period and HF-HPV) across the tasks. These voxel-by-voxel slopes were then aggregated across individuals and were subjected to a second-level, one-sample *t* test.

This *t* test tested the null hypothesis that the aggregated slopes did not differ from zero. The results from these second-level analyses were visualized (and are presented) as statistical parametric maps (SPMs), which illustrate the brain regions where increased or decreased rCBF correlated with heart period or HF-HPVacross the tasks. We specifically present the results of second-level analyses on the aggregated regression slopes that revealed a correlation of heart period and HF-HPV to rCBF in brain regions having both (a) 15 contiguous (clustered) voxels in spatial extent and (b) an entire-brain-voxel (196, 954 total voxels) corrected-statistical-significance level of $p<.05$ (Worsley, Evans, Marrett, & Neelin, 1992).

We further present the results from second-level region-of-interest analyses (ROIs) that used bilateral small-volume anatomical masks. These masks were used to examine the relationships between rCBF and heart period and HF-HPV (at a statistical threshold of $p<.05$, corrected for tests over fewer brain voxels) in the insular cortex (20,786 voxels), the anterior cingulate cortex (3,614 voxels), the amygdala–hippocampus complex (4,803 voxels), and the cerebellum (30,922 voxels). These small-volume analyses were used to decrease the probability of making Type II errors that may result from conducting statistical tests that are corrected for the entire brain volume, and they were motivated by prior functional neuroimaging research implicating these ROIs in cardiac autonomic control (Critchley et al., 2000; Lane et al., 2001; Soufer et al., 1998).

Results

Task Effects on Heart Period and High-Frequency Heart Period Variability

Consistent with our expectation that greater working-memory demands would decrease heart period, we found that heart period was lower across the verbal and spatial working-memory tasks compared to the perceptual motor-control task, $F(4,87) = 15.69$, $p<.001$, Wilks–Lambda = .58 (see Table 1). In particular, post hoc comparisons showed that, compared to the perceptual-motor control task, heart period decreased during the first, $t(92) = 6.99$, $p<.001$, and second, $t(92) = 6.88$, $p<.001$, levels of the verbal working memory-task and during the first, $t(92) = 4.71$, $p<.001$, and second, $t(92) = 6.90$, $p<.001$, levels of the spatial working-memory task.

Also as expected, the verbal and spatial working-memory tasks decreased HF-HPV, $F(4,87) = 2.83$, $p<.05$, Wilks-Lambda = .89 (see Table 1). Compared to the perceptual motor-control task, HF-HPV decreased during the first, $t(92) = 2.23$, $p = .03$, and second, $t(92) = 3.30$, $p = .01$, levels of the verbal working-memory task and also decreased during the first, $t(92) = 2.52$, $p = .01$, and second, $t(92) = 2.72$, $p = .008$, levels of the spatial working-memory task. The results of these comparisons suggest that the working-memory tasks decreased cardiac parasympathetic activity.

No interactions between Task and blood pressure status (hypertensive, normotensive) or gender (men, women) were observed for heart period or for HF-HPV, $Fs<1$, which indicated that these groups did not differentially respond to the tasks.

Associations between rCBF and Heart Period and High-Frequency Heart Period Variability

Task-induced decreases in heart period were associated with increased rCBF (reflecting increased activation) in the left insula, the right anterior cingulate cortex (Brodmann Area 32), the left inferior parietal cortex (Brodmann Area 40), and the medial and bilateral sectors of the cerebellum. Task-induced decreases in heart period were also associated with decreased rCBF (reflecting decreased activation) in the bilateral medial-prefrontal cortex (including Brodmann Areas 10 and 11), in the bilateral ventromedial sectors of the anterior cingulate cortex (covering Brod-mann Areas 24, 25, and 32), and to the bilateral insula; decreases in heart period were also associated with decreased rCBF in the bilateral amygdala–hippocampal complex. Table 2 and Figure 1 summarize and illustrate these heart period–rCBF correlations, respectively.

Task-induced decreases in HF-HPV were associated with increased rCBF in the right cerebellum and with decreased rCBF in the right ventromedial prefrontal cortex (Brodmann Area 10), the left insula, and the left amygdala–hippocampal complex (see Table 3 and Figure 2 for summary of HF-HPV–rCBF correlations).

We found no differences between hypertensive and norm-otensive individuals or between men and women in the patterns of association between rCBF and heart period and HF-HPV. First, when each group was analyzed separately, we found that rCBF correlated with both heart period and HF-HPV in the same lateral and bilateral brain regions that are described above. Second, specific comparisons in SPM between genders and blood pressure groups

revealed no differences in the magnitude of the positive or negative slopes relating rCBF to heart period and HFHPV. In these SPM comparisons, each group was given a different weight (SPM contrast −1, 1) when conducting the second-level *t* tests on the aggregated regression slopes. This differential weighting allowed us to test whether the groups differed in the strength of the relationships between rCBF and cardiac autonomic activity. However, none of these SPM analyses yielded statistically significant differences between groups in the magnitude of any correlation when either corrected or uncorrected statistical significance thresholds were applied.

Discussion

The present results show that behaviorally evoked decreases in heart period and HF-HPV correlate with concurrent changes in rCBF to the ventral and medial regions of the prefrontal and anterior cingulate cortex, the insula, the amygdala–hippocampal complex, and the cerebellum. As such, these results (a) agree with prior research that indicates that these brain regions regulate cardiac autonomic activity in nonhuman animals (for reviews, see Bennarroch, 1997; Buchanan & Powell, 1993; Loewy & Spyer, 1990; Neafsey, 1990; Neafsey et al., 1993) and (b) support speculations that these brain regions integrate cardiac autonomic activity with cognitive and emotional behavioral processes (e.g., Bennarroch, 1997; Cechetto, 1994; Groenewegen & Uylings, 2000; Loewy & Spyer, 1990; Thayer & Lane, 2000; Verberne & Owens, 1997).

Extensive research in nonhuman animals has established a relatively detailed working knowledge of the cortical and subcortical brain systems that regulate cardiac autonomic activity during behavior. It is widely assumed that similar brain systems regulate human cardiac autonomic activity; however, empirical support for this assumption has been limited. Moreover, because of mixed findings from the few existing functional neuroimaging studies on central cardiac autonomic control, it has been unclear how different patterns of behaviorally evoked activity (e.g., activation or deactivation) in these brain systems relate to ongoing changes in cardiac autonomic activity. The present results show that patterns of both increased and decreased activation in cortical and subcortical brain systems are functionally related to ongoing changes in cardiac autonomic activity. This suggestion is supported by the findings that task-induced decreases in heart period correlated with increased rCBF to the caudal portion of the anterior cingulate cortex (Brodmann Area 32) and to the medial and bilateral cerebellum. Conversely, task-induced decreases in heart period correlated with decreased rCBF to medial and ventral regions of the prefrontal cortex (encompassing Brodmann Areas 10, 11, 24, and 25), the bilateral insula, and the bilateral amygdala–hippocampal complex.

Overall, these patterns of correlation for heart period are in line with those reported by Critchley et al. (2000). In that study, changes in heart rate (the reciprocal of heart period), which were elicited by engaging in a mental arithmetic task and an isometric hand-grip exercise, correlated negatively with rCBF to the ventral and dorsal medial prefrontal cortex, the cingulate cortex, the insula, the amygdala, and the cerebellum; heart rate changes also correlated positively with rCBF to the insula, the cerebellum, and the pons. The present heart-period correlations also parallel those reported in an fMRI study by Porro, Cettolo,

Francescato, and Baraldi (2003). Specifically, increases in heart rate during the anticipation of a painful stimulus were found in that study to correlate with decreased activation of the ventromedial prefrontal and cingulate cortex and with increased activation of the dorsal medial prefrontal cortex, the mid- and posterior cingulate cortex, the parietal cortex, and the thalamus. Thus, our findings and those from prior functional neuroimaging research indicate that in humans, both increased and decreased activation in cortical and subcortical brain systems are functionally related to cardiac activity, specifically cardioacceleration, across a range of behavioral states. The present findings also suggest that this conclusion applies to behaviorally evoked changes in cardiac parasympathetic activity.

In particular, we found that task-induced decreases in HF-HPVcorrelated with increased rCBF to the cerebellum and with decreased rCBF to the ventromedial prefrontal cortex, the left insula, and the left amygdala–hippocampal complex. These particular findings agree with the results of Lane et al. (2001). More specifically, Lane et al. showed that increased rCBF to the ventromedial prefrontal cortex and insula correlated with increased HF-HPVacross a series of emotionally evocative tasks (emotional film clip viewing and emotion recollection). Collectively, our results and those of Lane et al. are thus in line with clinical evidence suggesting that the ventromedial prefrontal cortex and insula participate in human cardiac parasympathetic regulation. For example, studies in stroke victims and individuals with epilepsy have shown that insular cortex infarctions are associated with decreased HF-HPV (Tokgözoglu et al., 1999), that left insular cortex stimulation slows heart rate, possibly through increased cardiac parasympathetic activation (Oppenheimer et al., 1992), that intracarotid sodium amobarbital injections, which suppress medial prefrontal cortex activity, increase heart rate and decrease HF-HPV (Geoffrey et al., 2001), and that vagal nerve stimulation, which increases afferent cardiac parasympathetic activity, activates the medial prefrontal cortex and the insula (e.g., Ko et al., 1996; Narayanan et al., 2002).

However, we are not aware of other functional neuroimaging studies that have documented a relationship between HF-HPV and functional activity in the amygdala or the cerebellum. In nonhuman animals, the amygdala and the cerebellum have been shown to support cardiac autonomic regulation and a range of emotional and behavioral processes. The amygdala, for example, supports the emotional processing of sensory information by integrating external and internal (visceral) input from cortical, thalamic, and brain stem afferent relays (for review, see LeDoux, 2000). After integrating this sensory input, the amygdala can influence cardiac autonomic activity via direct projections to other subcortical (e.g., the hypothalamus and brain stem autonomic network) and cortical (ventromedial prefrontal, insular, and anterior cingulate) regions (Loewy & Spyer, 1990). Cerebellar influences on cardiac autonomic activity have also been studied in the context of motor control, balance, and conditioned fear (e.g., Balaban, & Porter, 1998; Dietrichs, Haines, Roste, & Roste, 1994; Maschke et al., 2002). Thus, it is possible that the correlations that we observed between heart period and HF-HPVand rCBF changes in the amygdala and the cerebellum could be related to the emotional- or motor-related contextual aspects of the working-memory tasks (e.g., the distress elicited by completing demanding cognitive tasks or the motor demands of responding to each trial). Nevertheless, these correlations do suggest that in humans the amygdala and the cerebellum are involved in regulating cardiac autonomic activity during cognitive or emotional behaviors.

The present results also suggest that the functional relationships between regional brain activation and cardiac autonomic activity do not differ between hypertensives and normotensives. There is some evidence that hypertension is associated with altered cardiac autonomic function. For example, individuals with hypertension and borderline hypertension have been shown to display altered heart-period-variability responses to laboratory challenges (e.g., Grossman, Brinkman, & de Vries, 1992; Langewitz, Rüddel, & Schächinger, 1994). However, we did not observe differences between blood pressure groups in either heart period or HF-HPV responses to the working-memory tasks; nor did we find differences between these groups in the magnitude or pattern of correlations between rCBF and cardiac autonomic activity. One possible explanation of these null findings is that our working-memory tasks were not evocative enough to elicit cardiac autonomic reactivity differences between the blood pressure groups. By extension, comparable patterns of reactivity in these groups could have resulted in similar patterns of rCBF–cardiac autonomic correlations. Alternatively, our results may indicate that the central regulation of cardiac autonomic activity is similar among normotensives and untreated hypertensives. To test this alternative explanation, future research could employ more evocative laboratory tasks (or stressors) in a functional neuroimaging paradigm.

Two limitations of the present study should be noted. First, with the present design, it is difficult to dissociate the cognitive from the emotional effects of the working-memory tasks on regional brain activation and related cardiac autonomic responses. Indeed, the verbal and spatial memory tasks likely engaged regional brain activity that was related to the cognitive demands of attention and working memory, the emotional demands of maintaining accurate performance with increasing task difficulty, and the behavioral demands of making motor responses on each task trial. As a result, these conflated demands may have increased or decreased activity in those brain regions where rCBF correlated with heart period and HF-HPV: the ventral and medial prefrontal cortex, the anterior cingulate cortex, the insula, the amygdala–hippocampal complex, and the cerebellum. Indeed, these brain systems are thought to act as a network to support a broad range of emotional and cognitive processes (e.g., motivation, attention, working memory, response selection, and error monitoring), and they are thought to integrate somatosensory and visceral afferent (e.g., autonomic and cardiovascular) information with these processes (e.g., Bennarroch, 1997; Cechetto, 1994; Groenewegen & Uylings, 2000; Loewy & Spyer, 1990; Thayer & Lane, 2000; Verberne & Owens, 1997). Thus, future research may be better able to isolate the brain activity that may independently support the cognitive and emotional contributions to cardiac autonomic activity by separately manipulating the cognitive and emotional demands of different behavioral tasks.

A second limitation of the present study is that the observed patterns of positive and negative correlations between rCBF and cardiac autonomic activity are unclear with regard to underlying patterns of activation, inhibition, and disinhibition within and between brain areas. Thus, the issue of how these cortical and subcortical brain systems work in concert to regulate cardiac autonomic activity cannot be addressed by the present data. Future work employing different behavioral tasks or analysis strategies may, therefore, be useful in evaluating the functional relationships between these regions during varying behavioral states that elicit cardiac and autonomic adjustments. For example, functional neuroimaging

paradigms (e.g., event-related fMRI designs) that differently manipulate and examine the timing of activation in different brain areas and the onset of cardiac autonomic responses may help to resolve this issue.

To summarize, the current results show that behaviorally evoked changes in heart period and HF-HPV correlate with rCBF to the ventral and medial prefrontal cortex, the anterior cingulate cortex, the insula, the amygdala–hippocampal complex, and the cerebellum. These results thus suggest that these brain systems are involved in regulating (generating and representing) changes cardiac autonomic activity. To our knowledge, this study employed the largest sample size to date to study the relationship between behaviorally evoked changes in brain activity and corresponding changes in peripheral cardiac autonomic activity in humans. Given that the areas of correlation between rCBF and cardiac autonomic activity observed in the present study agree strongly with the areas that have been identified in prior human and nonhuman animal work, the present results underscore the importance of these areas in cardiac and autonomic regulation during behavior.

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REFERENCES

Ahern GL, Sollers JJ, Lane RD, Labiner DM, Herring AM, Weiland ME, Hultzer R, Thayer JF. Heart rate and heart rate variability changes in the intracarotid sodium amobarbital test. Epilepsia. 2001; 42:912–921. [PubMed: 11488892]

Alpert NM, Eriksson L, Chang JY, Bergstrom M, Litton JE, Correia JA, Bohm C, Ackerman RH, Taveras JM. Strategy for the measurement of regional cerebral blood flow using short-lived tracers and emission tomography. Journal of Cerebral Blood Flow and Metabolism. 1984; 4:28–34. [PubMed: 6607259]

Balaban CD, Porter JD. Neuroanatomic substrates for vestibulo-autonomic interactions. Journal of Vestibular Research. 1998; 8:7–16. [PubMed: 9416584]

Bennarroch, EE. Central autonomic network: Functional organization and clinical correlations. Futura Publishing Company; Armonk, NY: 1997.

Berntson GG, Bigger JT Jr. Eckberg DL, Grossman P, Kaufmann PG, Malik M, Nagaraja HN, Porges SW, Saul JP, Stone PH, van der Molen MW. Heart rate variability: Origins, methods, and interpretive caveats. Psychophysiology. 1997; 34:623–648. [PubMed: 9401419]

Berntson GG, Cacioppo JT, Binkley PF, Uchino BN, Quigley KS, Fieldstone A. Autonomic cardiac control III: Psychological stress and cardiac response in autonomic space as revealed by pharmacological blockades. Psychophysiology. 1994; 31:599–608. [PubMed: 7846220]

Berntson GG, Sarter M, Cacioppo JT. Anxiety and cardiovascular reactivity: The basal forebrain cholinergic link. Behavioural Brain Research. 1998; 94:225–248. [PubMed: 9722275]

Buchanan, SL.; Powell, DA. Cingulothalamic and prefrontal control of autonomic function.. In: Vogt, BA.; Gabriel, M., editors. Neurobiology of cingulate cortex and limbic thalamus: A comprehensive handbook. Birkhäuser; Boston, MA: 1993. p. 381-414.

Cacioppo JT, Uchino BN, Berntson GG. Individual differences in the autonomic origins of heart rate reactivity: The psychometrics of respiratory sinus arrhythmia and preejection period. Psychophysiology. 1994; 31:412–419. [PubMed: 10690921]

Cechetto DF. Identification of a cortical site for stress-induced cardiovascular dysfunction. Integrative Physiological and Behavioral Sciences. 1994; 29:362–373.

Critchley HD, Corfield DR, Chandler MP, Mathias CJ, Dolan RJ. Cerebral correlates of autonomic cardiovascular arousal: A functional neuroimaging investigation in humans. Journal of Physiology. 2000; 523:259–270. [PubMed: 10673560]

Damasio, AR. Descartes' error: Emotion, reason, and the human brain. G.P. Putnam; New York: 1994.

de Boer RW, Karemaker JM, Strackee J. Comparing spectra of a series of point events, particularly for heart-rate variability spectra. IEEE Transactions in Biomedical Engineering. 1984; 31:384–387.

Dietrichs E, Haines DE, Roste GK, Roste LS. Hypothalamocerebellar and cerebellohypothalamic projections: Circuits for regulating nonsomatic cerebellar activity? Histology and Histopathology. 1994; 9:603–614. [PubMed: 7981506]

Dworkin BR, Elbert T, Rau H, Birbaumer N, Pauli P, Droste C, Brunia CH. Central effects of baroreceptor activation in humans: Attenuation of skeletal reflexes and pain perception. Proceedings of the National Acadamy of Sciences, USA. 1994; 91:6329–6333.

Friston KJ, Holmes AP, Worsely KJ, Poline JP, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: A general approach. Human Brain Mapping. 1995; 2:189–210.

Geoffrey A, Sollers J, Lane RD, Labiner DM, Herring AM, Weinand ME, Hutzler R, Thayer JF. Heart rate and heart rate variability changes in the intracarotid sodium amobarbital test. Epilepsia. 2001; 42:912–921. [PubMed: 11488892]

Groenewegen HJ, Uylings HB. The prefrontal cortex and the integration of sensory, limbic and autonomic information. Progress in Brain Research. 2000; 126:3–28. [PubMed: 11105636]

Grossman P, Brinkman A, de Vries J. Cardiac autonomic mechanisms associated with borderline hypertension under varying behavioral demands: Evidence for attenuated parasympathetic tone but not for enhanced beta-adrenergic activity. Psychophysiology. 1992; 29:698–711. [PubMed: 1334272]

Jennings JR. Autoregulation of blood pressure and thought: Preliminary results of an application of brain imaging to psychosomatic medicine. Psychosomatic Medicine. 2003; 65:384–395. [PubMed: 12764211]

Ko D, Heck C, Grafton S, Apuzzo ML, Couldwell WT, Chen T, Day JD, Zelman V, Smith T, DeGiorgio CM. Vagus nerve stimulation activates central nervous system structures in epileptic patients during PET H2(15)O blood flow imaging. Neurosurgery. 1996; 39:426–430. [PubMed: 8832691]

Lacey, BC.; Lacey, JI. Studies of heart rate and other bodily proceses in sensorimotor behavior.. In: Obrist, PA.; Black, AH.; Brener, J.; DiCara, LV., editors. Cardiovascular psychophysiology: Current issues in response, mechanisms, biofeedback, and methodology. Aldine; Chicago, IL: 1974. p. 538-564.

Lane RD, Reiman EM, Ahern GL, Thayer JF. Activity in medial prefrontal cortex correlates with vagal component of heart rate variability during emotion. Brain and Cognition. 2001; 47:97–100.

Langewitz W, Rüddel H, Schächinger H. Reduced parasympathetic cardiac control in patients with hypertension at rest and under mental stress. American Heart Journal. 1994; 127:122–128. [PubMed: 8273730]

LeDoux JE. Emotion circuits in the brain. Annual Review of Neuroscience. 2000; 23:155–184.

Loewy, AD.; Spyer, KM. Central regulation of autonomic function. Oxford University Press; New York: 1990.

Lovallo WR, Gerin W. Psychophysiological reactivity: Mechanisms and pathways to cardiovascular disease. Psychosomatic Medicine. 2003; 65:36–45. [PubMed: 12554814]

Maschke M, Schugens M, Kindsvater K, Drepper J, Kolb FP, Diener HC, Daum I, Timmann D. Fear conditioned changes of heart rate in patients with medial cerebellar lesions. Journal of Neurology, Neurosurgery, & Psychiatry. 2002; 72:116–118.

Narayanan JT, Watts R, Haddad N, Labar DR, Li PM, Filippi CG. Cerebral activation during vagus nerve stimulation: A functional MR study. Epilepsia. 2002; 43:1509–1514. [PubMed: 12460253]

Neafsey EJ. Prefrontal cortical control of the autonomic nervous system: Anatomical and physiological observations. Progress in Brain Research. 1990; 85:147–166. [PubMed: 2094892]

Neafsey, EJ.; Terreberry, RR.; Hurley, KM.; Ruit, KG.; Frysztak, RJ. Anterior cingulate in rodents: Connections, visceral control functions, and implications for emotion.. In: Vogt, BA.; Gabriel, M.,

editors. Neurobiology of cingulate cortex and limbic thalamus: A comprehensive handbook. Birkhäuser; Boston, MA: 1993. p. 206-223.

Oppenheimer S. The anatomy and physiology of cortical mechanisms of cardiac control. Stroke. 1993; 24:I3–I5. [PubMed: 8249017]

Oppenheimer S, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology. 1992; 42:1727–1732. [PubMed: 1513461]

Paredes J, Winters RW, Schneiderman N, McCabe PM. Afferents to the central nucleus of the amygdala and functional subdivisions of the periaqueductal gray: Neuroanatomical substrates for affective behavior. Brain Research. 2000; 887:157–173. [PubMed: 11134600]

Porges SW. Orienting in a defensive world: Mammalian modifications of our evolutionary heritage. A polyvagal theory. Psychophysiology. 1995; 32:301–318. [PubMed: 7652107]

Porro CA, Cettolo V, Francescato MP, Baraldi P. Functional activity mapping of the mesial hemispheric wall during anticipation of pain. NeuroImage. 2003; 19:1738–1747. [PubMed: 12948728]

Rosen SD, Paulesu E, Nihoyannopoulos P, Tousoulis D, Frackowiak RSJ, Frith CD, Jones T, Camici PG. Silent ischemia as a central problem: Regional brain activation compared in silent and painful myocardial ischemia. Annals of Internal Medicine. 1996; 124:939–949. [PubMed: 8624061]

Shapiro PA, Sloan RP, Bagiella E, Kuhl JP, Anjilvel S, Mann JJ. Cerebral activation, hostility, and cardiovascular control during mental stress. Journal of Psychosomatic Research. 2000; 48:485–491. [PubMed: 10880670]

Smith EE, Jonides J, Koeppe RA. Dissociating verbal and spatial working memory using PET. Cerebral Cortex. 1996; 6:11–20. [PubMed: 8670634]

Soufer R, Bremner JD, Arrighi JA, Cohen I, Zaret BL, Burg MM, Goldman-Rakic P. Cerebral cortical hyperactivation in response to mental stress in patients with coronary artery disease. Proceedings of the National Academy of Sciences, USA. 1998; 95:6454–6459.

Talairach, J.; Tournoux, P. Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system: An approach to cerebral imaging. Thieme Medical Publishers; New York: 1988.

Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. Journal of Affective Disorders. 2000; 61:201–216. [PubMed: 11163422]

Tokgözoglu SL, Batur MK, Topuoglu MA, Saribas O, Kes S, Oto A. Effects of stroke localization on cardiac autonomic balance and sudden death. Stroke. 1999; 30:1307–1311. [PubMed: 10390300]

Verberne AJM, Owens NC. Cortical modulation of the cardiovascular system. Progress in Neurobiology. 1997; 54:149–168. [PubMed: 9481796]

Weber EJM, Molenaar PCM, van der Molen MW. A nonstationarity test for the spectral analysis of physiological time series with an application to respiratory sinus arrhythmia. Psychophysiology. 1992; 29:55–65. [PubMed: 1609027]

Woods RP, Cherry SR, Mazziotta JC. A rapid automated algorithm for accurately aligning and reslicing positron emission tomography images. Journal of Computer Assisted Tomography. 1992; 16:620–633. [PubMed: 1629424]

Worsley KJ, Evans AC, Marrett S, Neelin P. A three-dimensional statistical analysis for CBF activation studies in human brain. Journal of Cerebral Blood Flow and Metabolism. 1992; 12:900–918. [PubMed: 1400644]

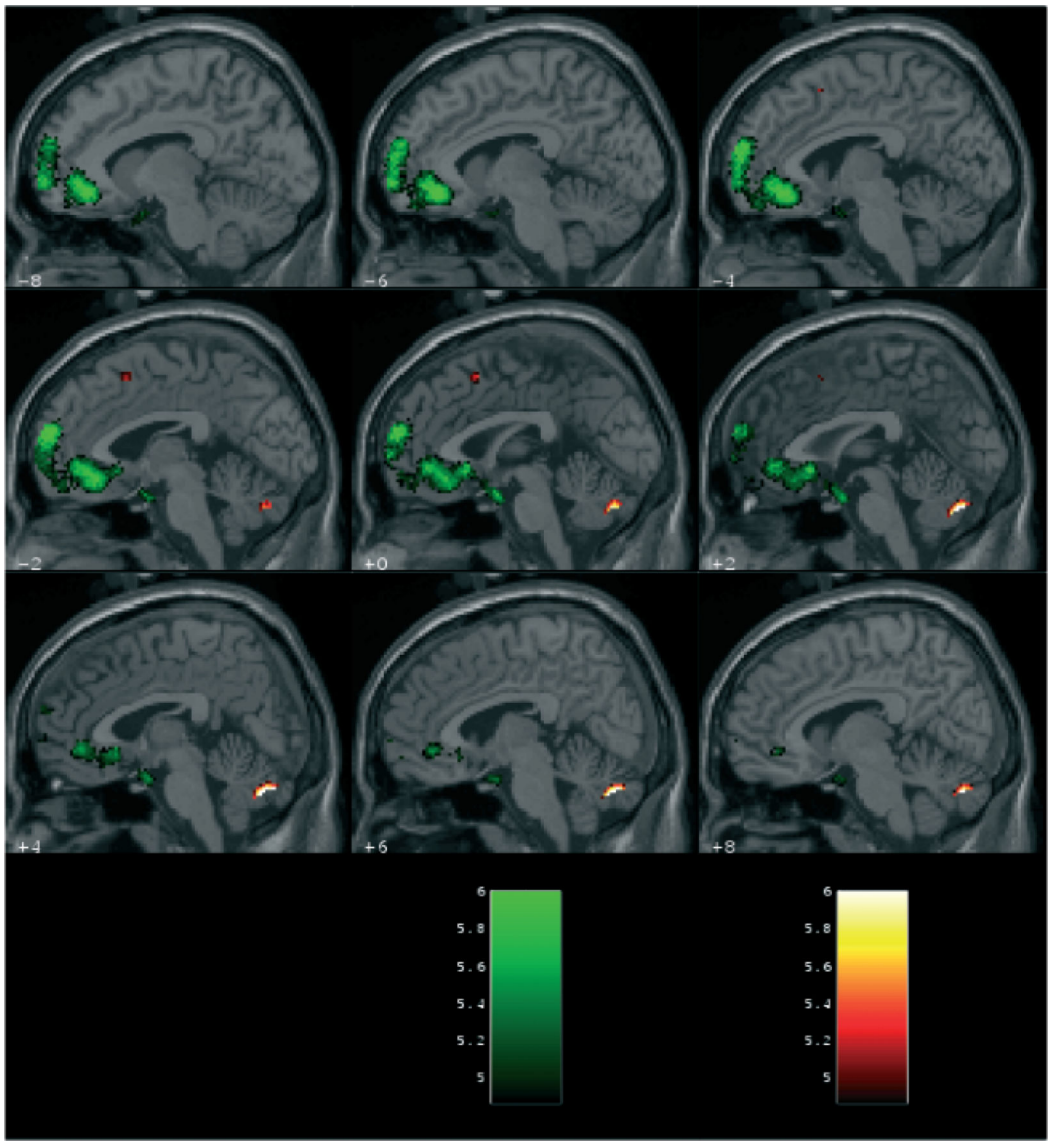

Figure 1.

Sagittal images of brain regions where regional cerebral blood flow (rCBF) correlated with heart period across a series of working-memory tasks. Red regions are brain areas where increased rCBF correlated with decreased heart period; green regions are brain areas where decreased rCBF correlated with decreased heart period. Regions of correlation are coded with *t* values that correspond to the statistical significance of regression slopes relating rCBF to heart period. For illustration, *t* values range from 4 to 6, and they are scaled to the color bars in the lower right. Coordinate values in the lower left of each image refer to the relative distance (in millimeters) from the midline of the brain; positive values indicate that the image is from the right side of the midline, negative values are from the left of the midline.

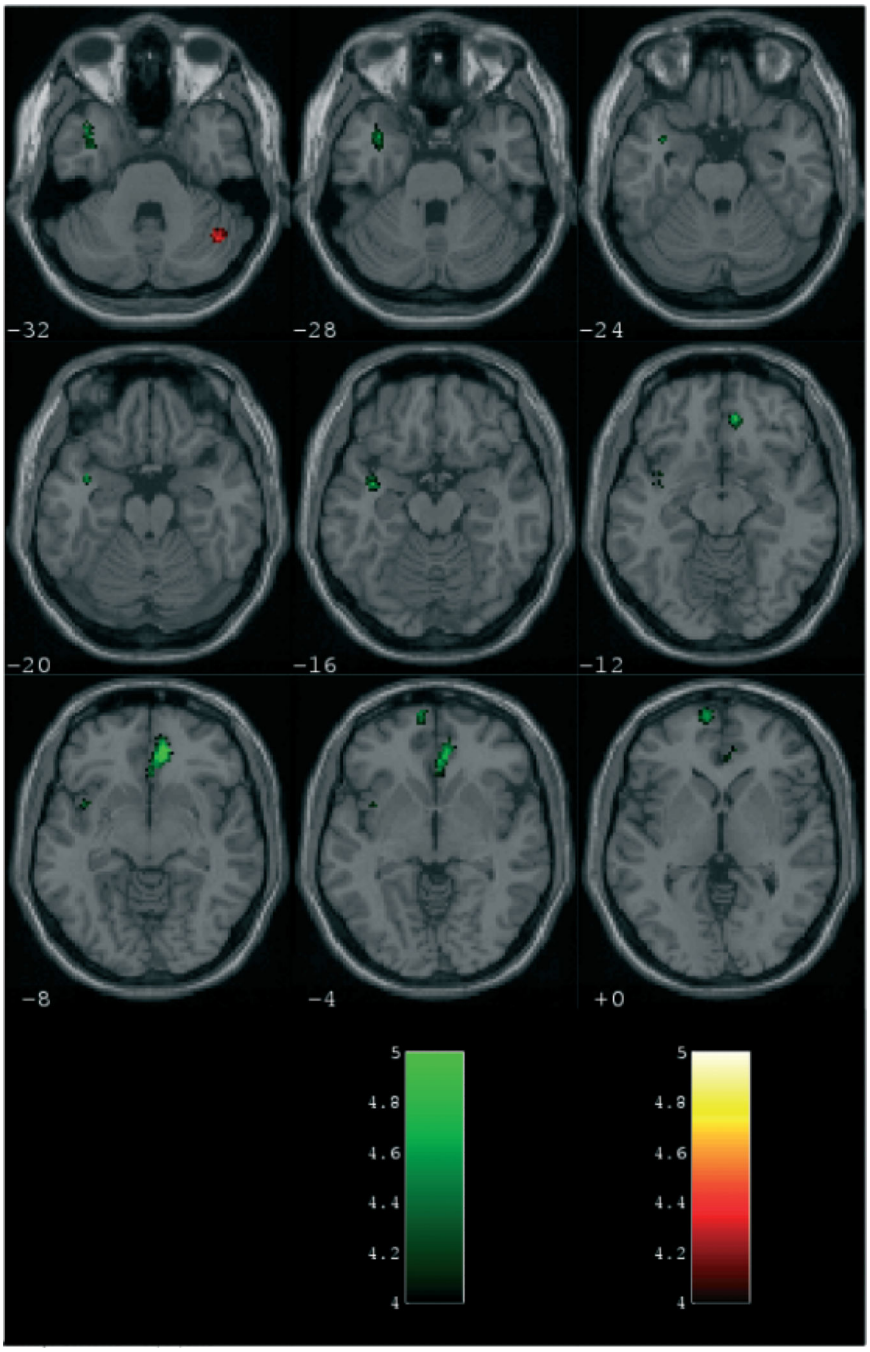

Figure 2.

Axial images of brain regions where regional cerebral blood flow (rCBF) correlated with 0.15–0.30-Hz high-frequency heart period variability (HF-HPV) across a series of working-memory tasks. Red regions are brain areas where increased rCBF correlated with decreased HF-HPV; green regions are brain areas where decreased rCBF correlated with decreased HF-HPV. Regions of correlation are coded with *t* values that correspond to the statistical significance of regression slopes relating rCBF to HFHPV. For illustration, *t* values range from 4 to 6, and they are scaled to the color bars in the lower right. Coordinate values in the

lower left of each image refer to the relative distance (in millimeters) from the plane of the anterior–posterior (AC-PC) commissure; positive values indicate that the image is above the AC-PC plane and negative values indicate the image is below the AC-PC plane.

Table 1

Mean Change in Heart Period and High-Frequency Heart Period Variability (HF-HPV) from a Control Task to Two Increasingly Difficult Levels of a Verbal and Spatial Working-Memory Task

	Working-memory task and level			
Measure	**Verbal memory level 1**	**Verbal memory level 2**	**Spatial memory level 1**	**Spatial memory level 2**
Heart period change (ms)	–27.7 (4.0)	–35.6 (5.2)	–20.2 (4.3)	–28.4 (4.1)
HF-HPV change (ln units)	–0.21 (0.10)	–0.28 (0.08)	–0.21 (0.08)	–0.20 (0.07)

Values in parentheses indicate standard error of the mean.

Table 2

Brain Areas where rCBF Correlated with Heart Period across Working-Memory Tasks

Area	Side	Tal. (*x*, *y*, *z*)	No. Voxels	*t*	*p*
A. Areas of positive correlation between rCBF and heart period (decreased rCBF, decreased heart period)					
Ventromedial prefrontal cortex	L	–6, 36, –10	2,169	6.45	.001
Anterior cingulate cortex*	R	12, 40, –6	1,154	5.08	.001
Insula	R	36, –4,8	22	5.20	.016
Insula*	L	–18, 10, –26	4	4.51	.019
Amygdala-hippocampal complex*	L	–14, 2, –24	192	5.61	.001
Amygdala-hippocampal Complex*	R	20, –6, –22	152	3.91	.030
B. Areas of negative correlation between rCBF and heart period (increased rCBF, decreased heart period)					
Anterior cingulate cortex	—	0, 12, 54	22	5.30	.010
Inferior parietal cortex	L	–34, –52, 40	59	5.31	.011
Cerebellum	R	4, –72, –32	102	6.72	.001
Cerebellum	R	56, –56, –26	21	5.69	.003
Cerebellum	L	–42, –56, –30	131	5.50	.005

Note: Results are presented at an entire-brain-volume corrected threshold of $p < .05$, except for those areas followed by an asterisk, for which small-volume corrections were applied. L: left; R: right. Tal.: *x*, *y*, and *z* Talairach and Tournoux (1988) coordinates for the voxel with the lowest *p* value within a given cluster; No. Voxels: the number of contiguous voxels associated with the region of correlation.

Table 3

Brain Areas where rCBF Correlated with High-Frequency Heart Period Variability (HF-HPV) across Working-Memory Tasks

Area (Brodmann Area)	Side	Tal. (*x*, *y*, *z*)	No. Voxels	*t*	*p*
A. Areas of positive correlations between rCBF and HF-HPV (decreased rCBF, decreased HF-HPV)					
Ventromedial prefrontal cortex	R	8, 40, –8	199	5.14	0.021
Insula	L	–38, –3, –13	147	4.72	0.010
Amygdala–hippocampal complex	L	–34, –4, –16	10	4.30	0.009
B. Areas of negative correlations between rCBF and HF-HPV (increased rCBF, decreased HF-HPV)					
Cerebellum	R	46, –58, –34	111	4.61	0.020

Note: Results are presented at small-volume corrected thresholds of $p < .05$. L: left; R: right. Tal.: *x*, *y*, and *z* Talairach and Tournoux (1988) coordinates for the voxel with the lowest *p* value within a given cluster. No. Voxels: the number of contiguous (clustered) voxels associated with the region of correlation.