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Association between heart rate variability and fluctuations in resting-state functional connectivity

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ABSTRACT

Functional connectivity has been observed to fluctuate across the course of a resting state scan, though the origins and functional relevance of this phenomenon remain to be shown. The present study explores the link between endogenous dynamics of functional connectivity and autonomic state in an eyes-closed resting condition. Using a sliding window analysis on resting state fMRI data from 35 young, healthy male subjects, we examined how heart rate variability (HRV) covaries with temporal changes in whole-brain functional connectivity with seed regions previously described to mediate effects of vigilance and arousal (amygdala and dorsal anterior cingulate cortex; dACC). We identified a set of regions, including brainstem, thalamus, putamen, and dorsolateral prefrontal cortex, that became more strongly coupled with the dACC and amygdala seeds during states of elevated HRV. Effects differed between high and low frequency components of HRV, suggesting specific contributions of parasympathetic and sympathetic tone on individual connections. Furthermore, dynamics of functional connectivity could be separated from those primarily related to BOLD signal fluctuations. The present results contribute novel information about the neural basis of transient changes of autonomic nervous system states, and suggest physiological and psychological components of the recently observed non-stationarity in resting state functional connectivity.

Introduction

Functional magnetic resonance imaging (fMRI) studies have demonstrated that distributed regions of the brain exhibit temporally correlated blood-oxygen-level-dependent (BOLD) signal fluctuations, even in the absence of tasks or stimuli ("resting state"; (Biswal et al., 1995)). Quantifying functional connectivity in both task and resting states has provided critical advances in the understanding of large-scale neural organization (see (Fox and Raichle, 2007)). While a number of functional networks can be identified quite reliably across individuals and sessions, fluctuations in connectivity on shorter scales within the same individual have been reported, such as in relation to sleep stages (Horovitz et al., 2009), previous history of activation (Grigg and Grady, 2010; Waites et al., 2005), and in resting state, as seen with fMRI (Chang and Glover, 2010; Kiviniemi et al., 2011; Sakoglu et al., 2010) and MEG (de Pasquale et al., 2010). Determining the basis of "spontaneous" connectivity variation is challenging, since there is a limited number of state-related measurements that one can acquire under typical resting-state conditions. Yet certain physiological processes, such as the cardiac and respiratory cycles, are readily monitored during fMRI, offering a potential window into physiological changes that may be associated with fluctuations in brain connectivity.

Heart rate variability (HRV), defined as *changes* in the beat-to-beat interval or in the instantaneous heart rate, is a widely-used marker of autonomic activity (Task Force, 1996). HRV results from the interaction between parasympathetic (vagal) and sympathetic nervous system influences on the sinoatrial node (reviewed by (Berntson et al., 1997)). The high frequency (HF) component of HRV, spanning approximately the range 0.15–0.4 Hz, is attributed to respiration-induced heart rate modulation and is mediated

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primarily by parasympathetic outflow. A lower-frequency (LF) component of HRV, typically defined as 0.05–0.15 Hz, is not fully understood but believed to rather reflect a mixture of sympathetic and parasympathetic activities.

The relative balance of parasympathetic and sympathetic influences can be modulated by breathing, physical activity (Bernardi et al., 1990), arousal, drug intake (Elghozi and Julien, 2007; Elghozi et al., 2001; Penttila et al., 2005) and more stable states such as mood or diseases involving the autonomous nervous system (ANS), such as cardiac ischemia (reviewed in Montano et al., 2009). HRV is an important predictor of mortality (Huikuri et al., 2009), and decreased HRV is also one well-described symptom of ANS dysregulation in depression (Kemp et al., 2010; Licht et al., 2008). States of different HRV levels can be readily connected to distinct states of ANS activity; e.g., HRV is modulated by emotionally salient contexts, with subsequent changes in sympathetic tone (Jonsson and Sonnby-Borgstrom, 2003; Wallentin et al., 2011). Whether such state changes during resting state would also be reflected by changes in the low frequency dynamics of brain connectivity is, so far, unknown.

Previous fMRI and PET studies have examined the neural basis of HRV changes by measuring BOLD activity (Critchley et al., 2003; Napadow et al., 2008) and regional cerebral blood flow (rCBF; Gianaros et al., 2004; Lane et al., 2009) in relation to task-induced emotional, physical, and cognitive changes in HRV. Results of a task-based study relating HRV to brain activation might be affected by the specific task, causing a coincidence of brain activation and changes in HRV. As such, a task-free approach of resting state fMRI might offer new insights into brain heart interactions, examining spontaneous variations in brain activity and HRV that are not constrained by the activation and functional network connectivity representative of the functional state imposed by the task manipulation.

The present study investigates the dynamic association between functional connectivity and HRV in the resting state. We apply a sliding-window analysis of functional connectivity seeded from regions implicated in salience and autonomic processing, the dorsal anterior cingulate cortex (dACC) and amygdala (Critchley et al., 2003; Dalton et al., 2005; Seeley et al., 2007), and ask whether there are regions whose temporal variation in connectivity strength with these nodes significantly correlates with variations in HRV across the scan. While there are a number of brain regions involved in autonomic control, the dACC and amygdala are among the most important (Critchley, 2005; Critchley et al., 2003; Lane et al., 2009; Thayer et al., 2012). In addition, the dACC is a key node of the salience network (Seeley et al., 2007), and exhibits robust resting-state functional connectivity with other regions related to HRV – notably, including the insula (Critchley et al., 2003; Medford and Critchley, 2010) – and may therefore be regarded as a representative node for such a network of regions. The amygdala was highlighted as having a significant relationship with HRV across multiple studies in a recent meta-analysis (Thayer et al., 2012). It was also observed that emotional films evoked dynamic, sadness-correlated fluctuations in HRV as well as in the functional connectivity within a network of limbic regions that included the amygdala (Raz et al., 2012). Both the dACC and the amygdala have been used as regions of interest (ROIs) for functional connectivity analysis in previous studies of autonomic control and salience processing (e.g. Gianaros et al., 2008; Pannekoek et al., in press).

The finding of a significant correlation between functional connectivity and HRV may illuminate potential factors underlying dynamic changes in resting-state connectivity. In turn, delineating the brain regions exhibiting such connectivity modulation may bring further insight into neural mechanisms underlying autonomic control mechanisms. With regard to the latter, this work differs from and extends previous neuroimaging literature (reviewed in Thayer et al., 2012) by considering fluctuations of HRV under resting-state conditions rather than external manipulations, and by examining functional connectivity in addition to (and in comparison with) the BOLD signal time series itself.

Methods

Subjects

Participants included 36 healthy volunteers, who were recruited by study advertisements. All volunteers completed the mini-international neuropsychiatric interview (MINI), specifically to ensure the absence of any ICD-10 psychiatric disorders (Sheehan et al., 1998). Exclusion criteria consisted of self-reported psychiatric, neurological or medical illness, as well as common exclusion criteria for MRI. The study was approved by the institutional review board of the University of Magdeburg, Germany, and all subjects provided written informed consent. Data from one subject was omitted due to corruption of cardiac data, so a total of 35 subjects were included in all analyses described below.

fMRI acquisition

Magnetic resonance imaging was performed at 3 T using a Siemens MAGNETOM Trio scanner (Siemens, Erlangen, Germany) with an 8-channel phased-array head coil. Subjects underwent a resting-state scan of duration 610 s, during which they were instructed to lie still with their eyes closed. Functional MRI time series of 488 volumes were acquired with an echo-planar imaging sequence and the following acquisition parameters: TR = 1250 ms, TE = 25 ms, flip angle = 70°, FOV = 22 cm, acquisition matrix = 44 × 44 (voxel size = 5 × 5 × 5 mm^3). Each volume comprised 26 contiguous axial slices covering the entire brain. High resolution T1-weighted structural MRI scans of the brain were acquired for anatomic reference using a 3D-MPRAGE sequence (TE = 4.77 ms, TR = 2500 ms, T1 = 1100 ms, flip angle = 7°, bandwidth = 40 Hz/pixel, acquisition matrix = 256 × 256 × 192, isometric voxel size = 1.0 mm^3). Cushions were used to minimize head motion during the scan.

Physiological recordings

Cardiac and respiratory data were acquired concurrently with fMRI using the scanner's built-in equipment. The cardiac cycle was monitored using a photoplethysmograph placed on the right index finger, and respiration was monitored using a bellows strapped around the upper thorax. The sampling rate of the Siemens built-in equipment for both signals was 49.82 Hz, and a time stamp on the output permitted temporal registration to the BOLD functional images.

fMRI pre-processing

The first 5 time frames were discarded to allow the MR signal to achieve T1 equilibrium. RETROICOR was performed in order to reduce artifacts due to cyclic cardiac and respiratory noise (Glover et al., 2000). Our implementation of RETROICOR is an in-house C program that performs slice-wise corrections in native acquisition space and uses a 2nd-order Fourier expansion for both cardiac and respiratory regressors (Glover et al., 2000). Subsequent pre-processing included slice-timing correction with sinc interpolation, motion coregistration with FSL (MCFLIRT; Jenkinson et al., 2002) and nuisance regression of the following time series: linear and quadratic temporal trends, 6 affine motion parameters, and the time series of one region of interest (ROI) in the white matter (3-mm-radius sphere centered at x = 26, y = −12, z = 35) and one ROI in the cerebrospinal fluid (CSF; 3-mm-radius sphere centered at x = 9, y = −33, z = 18). The white and CSF ROIs are identical to those used in our previous studies (Chang and Glover, 2009, 2010). Also included in the nuisance regression were two signals designed to model the causal, non-neural influence of low-frequency respiratory volume (RV) and heart rate (HR) changes on the BOLD signal, and were formed by convolving RV and HR with the impulse response functions described in our previous study (Chang and Glover, 2009). No other temporal filtering was performed.