# Dynamics of resting-state functional connectivity associated with heart rate variability

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**Introduction:** Analysis of resting-state data typically aims to estimate a single, static functional connectivity pattern from all available fMRI time points, thereby highlighting functional connections that are most temporally stable. Yet, connectivity has been observed to fluctuate across the course of a resting state scan [1,2], raising the prospect that dynamic information may provide a richer characterization of spontaneous activity. The origins and functional significance of these more rapid (seconds to minutes) and apparently spontaneous connectivity changes, however, are not clear. Understanding factors that modulate resting-state functional connectivity (rsFC), both on shorter "dynamic" and longer "static" time scales, will allow one to maximize the potential of resting-state fMRI for understanding neural interactions.

Difficulty arises from the limited number of state-related measurements that can be acquired under typical resting-state conditions. Yet certain physiological processes (cardiac, respiration) are routinely monitored during fMRI, offering a potential window into physiological and psychological changes that underlie fluctuations in brain connectivity. Here, we examine the association between rsFC dynamics and heart rate variability (HRV), a well-established marker of autonomic nervous system activity [3]. While previous neuroimaging studies have used emotional and physical tasks to modulate HRV across a scan[e.g. [4,5]], here we examine whether naturally-occurring changes in HRV during resting state may account for variations in functional connectivity. Specifically, using a sliding-window analysis, we identify regions for which rsFC with the salience network tracks changes in HRV across the scan. A significant association between rsFC and HRV may illuminate potential factors underlying modulation of resting-state connectivity, and might in turn contribute information about brain connectivity patterns involved in autonomic activity.

**Methods:** Eyes-closed resting-state fMRI data were acquired from 35 healthy volunteers at 3T (TR=1.25s, 488 volumes, voxel size 5mm isotropic) with concurrent respiratory and cardiac monitoring. The first 5 volumes were discarded for $T_1$ equilibration, and the remaining images underwent slice-timing correction, motion coregistration, and nuisance regression of low-order trends, physiological noise [6,7], and signals from two spherical (6-mm diameter) regions in the white matter and CSF as in [1]. Two nodes of the salience network, dorsal ACC (dACC) and right amygdala, were chosen as seed regions for the rsFC analysis. For each subject and seed ROI, a whole-brain sliding-window analysis of seed-based functional connectivity was performed (45-sec windows, 50% overlap between consecutive windows, yielding 25 windows per scan). Each voxel's sequence of sliding-window correlation coefficients was then transformed to a sequence of Fisher $z$ values, and was subsequently compared to the sequence of sliding-window HRV measurements (performed in identical time windows) using linear regression (Fig. 1). The HRV within a sliding window $w_t$ was defined as the root mean square successive deviations (RMSSD [3]) of the segment of the heart rate (inverse beat-to-beat interval) time



**Fig. 1.** Analysis of temporal relationship between functional connectivity and heart rate variability.

series lying within $w_t$. The RMSSD metric captures the high frequency component of HRV, which is primarily attributed to parasympathetic activity[8]. To examine results at the group level, the single-subject regression (beta) maps were normalized to MNI space and entered into a one-sample t-test using SPM5[9]. In addition to quantifying the temporal relationship between rsFC and HRV within a scan, we also performed a between-subject correlation analysis of rsFC and HRV, where values were averaged across each subject's entire scan rather than computed on a sliding basis.

**Results:** Regions for which sliding-window connectivity with the dACC had significant positive correlation with sliding-window fluctuations in HRV are illustrated in Fig. 2 (top row). Corresponding results for the amygdala seed appear in the bottom row. Significant (p<0.05 corrected) regions included midbrain, thalamus, basal ganglia, and insula. No voxels had functional connectivity fluctuations with either seed that were negatively correlated with changes in HRV at any statistical threshold. Inter-subject correlations between mean HRV and mean rsFC were much weaker than the within-subject temporal relationship, but relaxing the statistical threshold to p<0.05 uncorrected in the latter, for exploratory purposes, revealed clusters that overlap to some extent with the intra-subject analysis (Fig. 3).
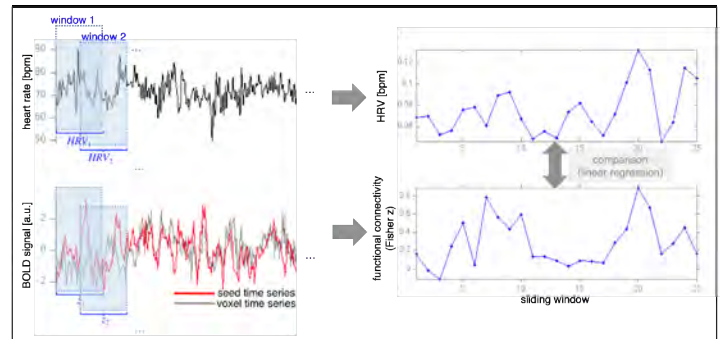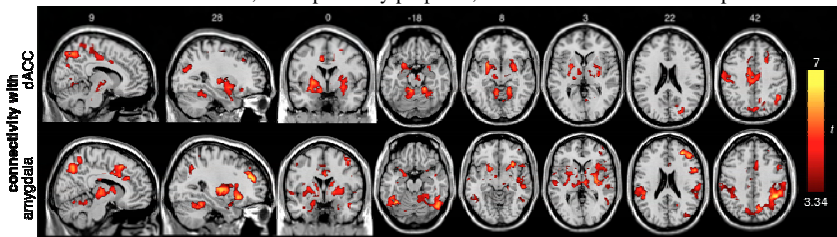


**Fig. 2.** Regions whose functional connectivity with the dACC (upper) and amygdala (lower) significantly covaried with temporal changes in HRV in resting state (p<0.05 corrected).
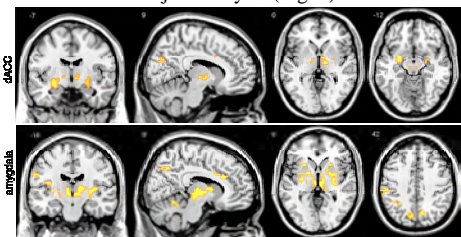


**Fig. 3.** Overlap between intra-subject (p<0.05 corrected) and inter-subject (p<0.05 uncorrected) group-level t maps.

**Conclusions:** The present study examined how functional connectivity dynamics of the salience network relate to heart rate variability, a marker of physiological and psychological state. Increases in connectivity strength between multiple brain regions and the dACC/amygdala seeds were found to co-vary with increases in HRV across the course of a resting-state fMRI scan. For both dACC and amygdala, HRV-related connectivity changes were observed with regions related to autonomic processing, including the midbrain (which is a termination field of parasympathetic afferents), periaqueductal gray (related to autonomic control), and the ventromedial nucleus of the thalamus (integrating sympathetic and parasympathetic afferent information)[10]. The cerebellar vermis has been reported to show HRV-dependent changes in blood flow during a task [11], the caudate nucleus has been implicated in mediating HRV responses to social stress [12], and the insula is broadly implicated in autonomic control and internal awareness. The fact that the statistically significant regions were confined to focal anatomic structures with ties to autonomic monitoring and control suggests that we are not observing an artifactual inflation of connectivity with systemic processes that may co-occur with changes in HRV, but more likely effects of neural origin. While the association between network connectivity and HRV was robust at the within-subject level, the between-subject associations were weaker, possibly owing to inter-subject variability in age, gender, caffeine intake, and other factors that are known to affect baseline HRV[8].

**References:** [1]Chang et al, Neuroimage 50:81-98(2010). [2]Kiviniemi et al, Brain Connectivity 1(4): 339-347(2011). [3]Task Force, Circulation 92:1043-1065(1996). [4] Lane et al, Neuroimage 44(1):213-22(2009) [5] Critchley et al, Brain 126(Pt 10):2139-52(2003) . [6] Glover et al, MRM 44:162-167(2000). [7] Chang et al, Neuroimage 44:857-869(2009). [8] Berntson et al, Psychophysiology (34)623-648. [9] http://www.fil.ion.ucl.ac.uk/spm [10] Craig, Trends Cogn Sci 9(12):566-71(2005). [11] Critchley et al, J Physiol 523(1):259-70(2000). [12] Wager et al, Neuroimage 47(3):836-51(2009).