Causal brain correlates of autonomic nervous system outflow

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Target Audience: Researchers interested in brain correlates of Heart Rate Variability and its control

Introduction: The study of central correlates of ANS outflow, which can be quantified noninvasively through Heart Rate Variability (HRV), presents considerable difficulties due to limited spatial and temporal resolution of current noninvasive neuroimaging techniques. An additional challenge is posed by the need of a reliable technique for quantifying ANS outflow in a time-resolved manner while differentiating between sympathetic and parasympathetic outflow. Granger causality (GC) is a well established method to analyze the direction of information flow between signals. However, its application to functional MRI (fMRI) [1,2] is controversial, due to the temporal delocalization induced by convolution with the haemodynamic response function (HRF), neuronal delays [3,4] and poor temporal resolution.

Purpose: To investigate the directed, causal interactions between resting state brain activity and ANS outflow by: 1) using high spatial and temporal resolution fMRI acquired with cutting edge technology (7 Tesla scanner, 32 channel receive coil-array, simultaneous multiband EPI and physiological signal acquisition); 2) studying granger causality between dynamical indices of ANS outflow and resting state brain neuronal activity obtained by a recently proposed blind deconvolution method [5].

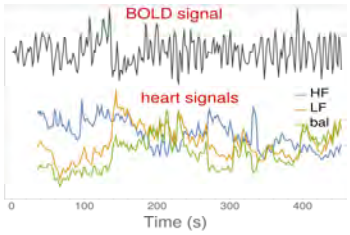

Figure 1 *Example heart and BOLD signals for one healthy volunteer.*

Methods: Nine subjects (age 28 ± 3) underwent 7 Tesla MRI with simultaneous physiological signal acquisition under IRB approval. We employed a common single-shot 2D EPI readout for 1.8 mm isotropic T_2*w axial images, with matrix size/GRAPPA factor/nominal echo-spacing = 136x136/2/0.57 ms and additional parameters N. slices/TE/FA/SMS factor/repetitions = 75/26 ms/40°/3/300, and crucially a TR of 1.5 s for whole brain coverage which minimized aliasing in ANS frequency bands (see below). Slice timing, motion correction, coregistration to MNI space, and physiological noise correction (high pass filtering at 0.01Hz and removal of second order RETROICOR regressors) was applied to fMRI data, after which the average BOLD signal was extracted in 116 regions of interest (ROIs) using the AAL atlas and deconvolved using the approach described in [5]. Cardiac pulsation was recorded by a piezoelectric finger pulse sensor (1 kHz sampling) and used for detecting cardiac peaks from which a peak-to-peak interval series (RR series) was derived. A time-varying probabilistic model [6] for the RR series was employed to estimate instantaneous, time-varying indexes of High Frequency power (HF, 0.15-0.4 Hz, thought to reflect mainly parasympathetic activity), Low Frequency power (LF, 0.04-0.15 Hz, thought to reflect both sympathetic and parasympathetic activity) and simpathovagal balance (Bal=LF/HF). Example signals entering the following analysis are shown in Fig. 1. For each subject, Granger Causality between each of the 116 BOLD signals and HF/LF/Bal was computed through a bivariate autoregressive model (order: 6), and causal links were retained when their pvalue was < 0.05. Anatomical ROIs were grouped according to their involvement in functional networks (Sensory Motor, Default Mode, Left executive, Right executive, Salience) according to the literature and the significant causal links were counted across subjects for visualization.

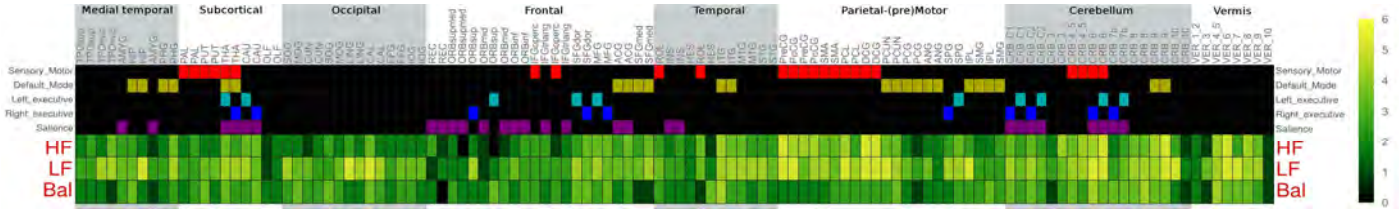

Figure 2. *Average number of subjects in which a significant causal link from a brain region to HF/LF/Bal was detected (green colorscale, bottom pane) and assignment of brain regions to functional networks (color coded in top pane). ROIs are ordered according to Salvador et al [8].*

Results: A large number of brain regions, unevenly distributed across functional networks, were found to significantly Granger-cause (para)sympathetic activity and sympathovagal balance (Fig. 2), with a maximum concordance across subjects of 6/9 for LF and Bal and 5/9 for HF (Table 1). An estimate of the % (0-100%) involvement of different networks in Granger-causing ANS-related heart signals was obtained in every subject as the number of significant causal links between regions belonging to a network divided by the number of regions which constitute the network. The distributions of % network involvement across subjects are summarized in Fig. 3.

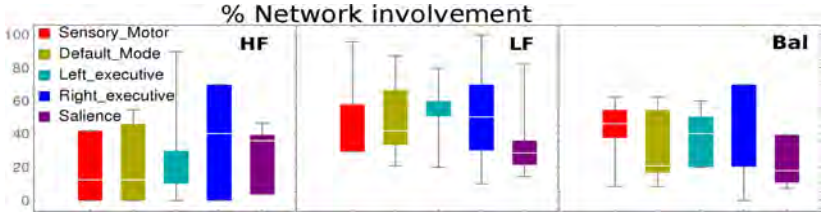

Figure 3. *Box-whisker plots of distributions (across subjects) of the involvement (0-100%) of each functional network in Granger causing parasympathetic outflow (HF, left), mixed parasympathetic and sympathetic outflow (LF, middle) and sympathovagal balance (right)). Box-whisker plots of (0.25,0.4,0.6,0.75) quantiles and median values.*

Brain regions G-causing HF

ROI	Network	# of sub.
Cerebelum_6_L		5
Cerebelum_8_R		5
Temporal_Inf_L		5
Vermis_4_5		5

Brain regions G-causing Bal

ROI	Network	# of sub.
Cerebelum_6_R		6
Cerebelum_9_R		6
Cingulum_Mid_L		6
Cingulum_Mid_R		6
Precentral_L		6
Vermis_6		6

Brain regions G-causing LF

ROI	Network	# of sub.
Calcarine_L		6
Cerebelum_10_L		6
Cerebelum_6_L		6
Cerebelum_6_R		6
Cerebelum_9_R		6
Cingulum_Mid_L		6
Cingulum_Mid_R		6
Hippocampus_R		6
Lingual_L		6
Paracentral_Lobule_L		6
Parietal_Inf_L		6
Postcentral_L		6
Precentral_L		6
Precuneus_L		6
Vermis_6		6
Vermis_7		6

Table 1 *Brain regions which showed the maximum concordance across subjects (9 total subjects) in causing parasympathetic outflow (HF, top left), mixed parasympathetic and sympathetic outflow (LF, top right) and sympathovagal balance (bottom left)). See legend in Fig. 3*

Discussion and Conclusion: Traditional, correlation-based (i.e. non-causal) fMRI studies at 3T and longer TRs [6,7] have provided important initial insight into the human brain correlates of ANS modulation. Using superior spatial and temporal resolution, we demostrate the existence of significant causal links between additional cortical as well as subcortical brain regions and ANS outflow for all three heart-related signals. Cerebellar regions were consistently involved in modulating ANS activity**.** For all but the salience network the LF signal was consistently caused by the largest percentage of the network, ranging from 29% (salience) to 58% (sensory motor). The cingulum was found to be significantly involved in modulating both sympathetic and parasympathetic activity, while the hippocampus scored "highly" only in modulating LF (mixture of sympathetic and parasympathetic activity). In summary, 7T functional imaging coupled with Granger causality estimates is able to quantify directed brain-heart interaction which can be interpreted in terms of central modulation of ANS outflow.

References: [1] Roebroeck et al, Neuroimage 25.1 (2005). [2] Bressler, Steven et al. Neuroimage 58.2 (2011). [3] Deshpande et al. Neuroimage 52.3 (2010). [4] Schippers et al. Neuroimage 57.1 (2011). [5] Wu et al. Medical image analysis 17.3 (2013). [6] Napadow et al. Neuroimage 42, no. 1 (2008). [7] Napadow et al, Human brain mapping 34(10) (2013) [8]. Salvador et al. Cerebral cortex 15.9 (2005).