Is heart rate variability a hidden factor in resting-state functional connectivity?

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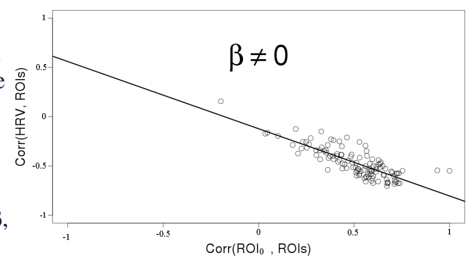
TARGET AUDIENCE – Researchers involved in resting-state functional connectivity MRI (rs-fcMRI).

PURPOSE – In resting-state functional connectivity analysis, the connectivity relies on the measures of cross-correlation between pairs of regions (or voxels). However, if a hidden factor is correlated to two regions, the consequence will be an artificial cross-correlation between these two regions. Recent reports state that resting-state activity can reflect a complex combination of neural, neurovascular or other physiological factors[1,2]. Since the parasympathetic and sympathetic components of the autonomic nervous system (ANS) control physiological processes, the signals arising from the ANS might be a hidden factor in rs-fcMRI. Heart rate variability (HRV), defined as changes in the beat-to-beat intervals, is a widely-used marker of autonomic activity[3]. Interestingly, its frequency band [0.004 Hz-0.4 Hz] covers the frequency band currently used in rs-fcMRI analysis. Here, we investigated if HRV acted as a hidden factor in rs-fcMRI.

METHODS – Resting-state fcMRI data were acquired simultaneously with ECG signals and photoplethysmography in sixteen healthy volunteers (male/female ratio: 0.4; age ranges: 22-43) with a T2* BOLD-weighted sequence (TR=2s, 400 volumes) on a 3T Philips Achieva scanner equiped with a 32-channel head coil. Standard preprocessing pipeline was applied on rs-fcMRI[4] to extract raw MR time-series in ROIs defined by the AAL template. These raw time-series were decomposed in 4 sub-bands using wavelets: [0.015-0.03 Hz], [0.03-0.06 Hz], [0.06-0.125 Hz] and [0.125-0.25 Hz]. HRVs were subsampled and time-decomposed in the same 4 sub-bands using the same wavelet decomposition. The 3 main components of the HRV relate to these 4 sub-bands: the [0.015-0.03 Hz] band is included in the VLF band of the HRV ; the [0.03-0.06 Hz] and [0.06-0.125 Hz] correspond to the lower and upper parts of the LF band of HRV and will be referred as LF- and LF+ ; and [0.125-0.25 Hz] corresponds to the lower part of the HF component of HRV. In order to assess the impact of HRV on connectivity, we performed two kinds of measurement: the first one quantified the correlation between each ROI and HRV in each sub-band; the second one quantified the HRV impact on the correlation between regions in the following manner. Given an interest ROI_0, if HRV does not impact, the correlation with all other regions ROI_i, implies that the correlation between ROI_0 and ROI_i (=corr(ROI_0, ROI_i), are independent of the correlation between $R0I_i$ and HRV (= corr(HRV, ROI_i)). Thus the plot for all ROI_i between corr(HRV, ROI_i) and corr(ROI_0, ROI_i) either can be regressed by an horizontal line (no influence of HRV) or by a line different from 0 (influence of HRV). Thus for each ROI_0, we computed the coefficient of the regression line, β, between corr(HRV, ROI_i) vs. corr(ROI_0, ROI_i). The β value indicates the degree to which HRV influences the correlation between ROI_0 and all other ROIs.



RESULTS – First, the histogram of correlations between the four different components of HRV and ROIs indicates a clear bias in the correlations towards lower correlation values (figure 1). Second, the HRV biases the correlation values of most regions with the rest of the regions at LF- (figure 2) and LF+ components, in areas such as the thalamus, cingulate cortex (posterior and anterior) or precuneus.

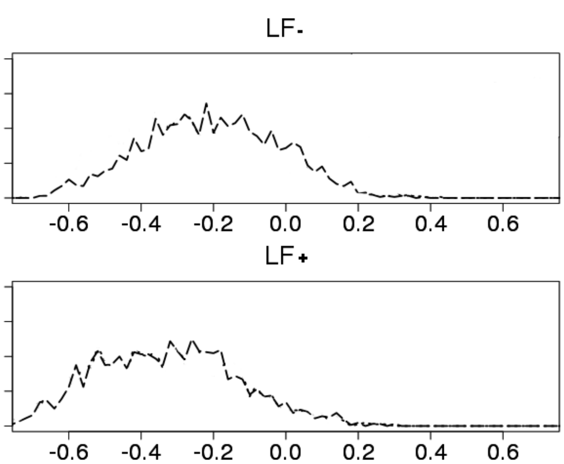


Fig. 1 : Histogram of the correlations of HRV components with all ROI time-series for the 16 healthy subjects

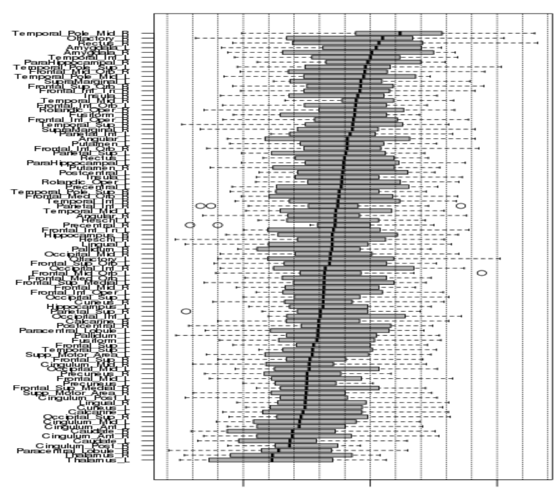


Fig. 2 : Boxplots of the β values per region among the 16 healthy subjects

DISCUSSION – These results indicate that HRV, a marker of the ANS, impacts the correlation analysis in most of the brain regions by biasing differently the correlations according to the location in the brain. The correlations with the rest of the brain are biased in regions belonging to the DMN and other networks.

CONCLUSION – As a first consequence, since numerous pathologies or drug treatments may affect the ANS, as currently reported in the litterature, it is not possible to disentangle whether correlation differences observed in rs-fcMRI between patients and controls relate to true connectivity changes or to HRV changes. As a second consequence, we suggest that rs-fcMRI sequences should be acquired together with ECG so that HRV could systematically be taken into account in the analysis.

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