34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

Cerebral cortex and sub-cortex lateralization in cardiovascular regulation: Correlations of BOLD fMRI and heart rate variability

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Abstract— **The role of cerebral cortex in cardiovascular regulation has not yet been mapped in detail. Especially the lateralization of different regions that are connected to cardiovascular modulation is still unknown. In this study we used simultaneously measured electrocardiography (ECG) and blood oxygen level dependent (BOLD) fMRI to examine the correlation of cerebral cortex and sub-cortex activation and heart rate variability parameters. Correlations were calculated for 11 subjects. Regions of interest (ROIs) were predefined from observations made in previous studies. Lateralization was studied by forming ratios of left and right hemisphere activations in ROIs and calculating correlations of these to heart rate variability (HRV) parameters. Statistically significant correlations were found in every ROI.**

I. Introduction

It has been long known that there is a two-way connection between heart and brain. The role of brainstem in controlling of cardiac output through autonomic nervous system (ANS) has been well established. However, there is still a lot of uncertainty on what kind of roles the different parts of cerebral cortex have on the regulation of cardiac system.

Studying the activation of brain is possible with constantly developing functional imaging methods, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Previous studies have used these methods with heart rate variability (HRV) to study the connection between brain activation and ANS function. Most studies have used heart rate (HR) or high frequency (HF) power of RR time series as the HRV parameter [1], [2], [3], [4], [5], [6], [7], [8]. Only few studies have used other HRV parameters like low frequency (LF) power of RR time series or root mean square of successive RR interval differences (RMSSD) [9], [10]. Also, brain lateralization on controlling of cardiovascular system has not been studied extensively [7].

In this study, predefined brain regions were used to examine the correlation between blood oxygen level dependent (BOLD) fMRI and standard HRV parameters. Changes in these parameters can be used to study sympathetic and parasympathetic regulation of heart rate [11]. Also, ratios of activation changes in different hemispheres were used to explore how the ANS regulation of cardiovascular output is lateralized in different parts of brain cortex (Broca's and Wernicke's areas, prefrontal and insular cortices) and parts of sub-cortex (amygdala and hippocampus).

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II. Materials and Methods

A. Measurement protocol

Simultaneous BOLD fMRI and electrocardiography (ECG) signals were measured from 20 subjects (11 females, 16 right-handed) while performing multiple language related tasks. Subjects were scanned with 1.5-T MRI scanner (Siemens Magnetom Avanto, Siemens AG, Germany) and ECG was recorded with one channel of MRI compatible EEG measuring device (Brainamp MR+, Brain Products GmbH, Germany). From the multiple tasks the task with longest active blocks (responsive naming) was chosen to be analyzed for the HRV values to have enough time to change while performing the task. In this task the subjects were given visually a text description of a noun (e.g. "a long yellow fruit"). They were instructed to read the description and answer it covertly ("a banana"). Between active blocks were passive control blocks where the subjects were shown just a row of hashes ("#######"). Each block had 10 descriptions and lasted 14 scans (49.42 s). There were totally 5 active and 6 passive blocks. Passive blocks lasted the same time. For a more specific description of the measurement protocol see Niskanen et al. [12].

B. HRV analysis

The MRI gradient artefacts in ECG signals were removed with moving window principal component analysis (PCA) method [13]. Nine subjects were discarded because unsuccessful artefact removal from ECG. RR time series were formed from the detected R-peaks. They were interpolated to 4 Hz for equidistant sampling. Trend was removed from the RR time series with smoothness priors method [14] to make the time series zero mean for spectral estimation.

Different time- and frequency-domain HRV parameters (HR, SDNN, RMSSD, HF, LF, LF nu and total power) were calculated for each block (active and passive). Frequency-domain parameters were calculated for each block with discrete Fourier transform with 50 second window. These HRV parameters are listed and described in Table I. The mean differences of HRV values in active blocks to previous passive blocks were compared to mean changes in fMRI signals from specific regions of interest (ROIs).

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TABLE I

HRV PARAMETERS USED TO CALCULATE CORRELATIONS WITH BOLD CHANGES

parameter	description
HR	Heart rate
SDNN	Standard deviation of normal to normal RR intervals
RMSSD	Root mean square of successive RR interval differences
HF	Power of high frequency band 0.15-0.40 Hz
LF	Power of low frequency band 0.04-0.15 Hz
LF nu	LF power in normalized units, LF/(LF+HF) $\times$ 100
TP	Total spectral power

C. BOLD fMRI and ROIs

The fMRI scans were pre-processed and normalized to standard ICBM152-space with SPM5 (the Wellcome Trust Center for Neuroimaging, UCL, London, UK, www.fil.ion.ucl.ac.uk/spm/). The ROIs were chosen by observations made in previous studies [8], [6]. Areas included in the present study were prefrontal cortex (PFC), amygdala, hippocampus and insular cortex. These have been shown to possibly have some connection to regulation of heart. Also language and speech related Broca's and Wernicke's areas were studied due to the type of the task. The areas were defined with WFU Pickatlas masks [15], [16] and they were defined separately for left and right hemispheres. Brodmann areas were used for Broca's (BA44, BA45), Wernicke's (BA21, BA22) and PFC (BA10, BA11). Insular cortex, amygdala and hippocampus were defined with corresponding masks from Automated anatomical labeling atlas [17]. All the masks were dilated twice in 2D and then exported from WFU Pickatlas. The rest of the analysis was done with Matlab R2010a (The MathWorks, Inc.). Illustration of the masks used and sample measurements are shown in Fig. 1.

The fMRI BOLD signals were averaged spatially for each ROI and over time for each block. Furthermore, differences in BOLD signal strength between active block and previous passive block were calculated. These changes were also averaged over every active-passive block pair.

To study brain lateralization in autonomic control of heart, we formed three different values to compare the changes in left and right hemispheres. These laterality values were dR-dL, dR/dL and (dR-dL)/(dR+dL), where dR and dL are the calculated BOLD signal changes in a specific ROI between active and passive blocks in right and left hemispheres, respectively.

This resulted in each subject to have one averaged value to describe the change from passive block to active block. These values were calculated for each HRV parameter and for each BOLD parameter in every ROI separately. Correlations between changes in HRV parameters and BOLD values over all subjects were then calculated.

III. RESULTS

Correlations of every HRV parameter change and BOLD signal change for each ROI were calculated by dividing covariance of the two variables with the square root of the multiplication of their variances. P-values for correlations were calculated with t statistic and normally distributed confidence levels. Statistically significant correlations are presented in Table II. Correlations are organized by area and statistical significance is indicated for three different levels ($p<0.05$, $p<0.01$ and $p<0.001$). Values from which the correlations are calculated are presented in Fig. 2 for selected correlations, that are discussed in the next section.

TABLE II

CORRELATIONS BETWEEN BOLD VALUE CHANGES AND HRV PARAMETER VALUE CHANGES IN DIFFERENT BRAIN AREAS OVER ALL SUBJECTS

Brain area	BOLD parameter	HRV parameter	r
Broca's area	dR	HF	-0.63*
	dR/dL	HF	-0.70*
	(dR-dL)/(dR+dL)	RMSSD	-0.62*
	(dR-dL)/(dR+dL)	HF	-0.75**
	(dR-dL)/(dR+dL)	LF nu	0.62*
Wernicke's area	dL	RMSSD	-0.63*
	dL	HF	-0.70*
	(dR-dL)/(dR+dL)	RMSSD	-0.69*
Prefrontal cortex	dR	HR	0.62*
	(dR-dL)/(dR+dL)	RMSSD	-0.71*
Insular cortex	dR	SDNN	-0.67*
	dR	HF	-0.68*
	dR	TP	-0.74**
	dR-dL	HF	-0.61*
	dR-dL	TP	-0.71*
	dR/dL	HF	-0.61*
	dR/dL	LF	-0.68*
	dR/dL	TP	-0.78**
	(dR-dL)/(dR+dL)	SDNN	-0.67*
	(dR-dL)/(dR+dL)	HF	-0.66*
	(dR-dL)/(dR+dL)	LF	-0.90***
	(dR-dL)/(dR+dL)	TP	-0.94***
Amygdala	dR	LF	-0.60*
	dL	HR	0.61*
	dR/dL	HR	0.74**
Hippocampus	dR	LF nu	-0.81**
	(dR-dL)/(dR+dL)	LF nu	-0.63*

* $p<0.05$ ** $p<0.01$ *** $p<0.001$

IV. DISCUSSION

The HRV parameters used in this study can be divided in two groups: 1) those presenting mainly parasympathetic activity (SDNN, RMSSD, HF and TP) and 2) those presenting mainly sympathetic activity (HR and LF nu) of ANS. LF power has been shown to present both parasympathetic and sympathetic activity of ANS.

We will discuss the results of the present study (Table II) for each ROI and how they compare to results from previous studies. The values in the table are referred in (BOLD parameter, HRV parameter, r-value)-format.

Broca's and Wernicke's areas have not been linked to autonomic control of cardiovascular system but they were included in the study because the task that subjects performed was language related. These areas have been shown to have important role on understanding and producing language.

The negative correlation with HF was expected because these areas were more active during the task and parasympathetic activity is known to decrease during different kind

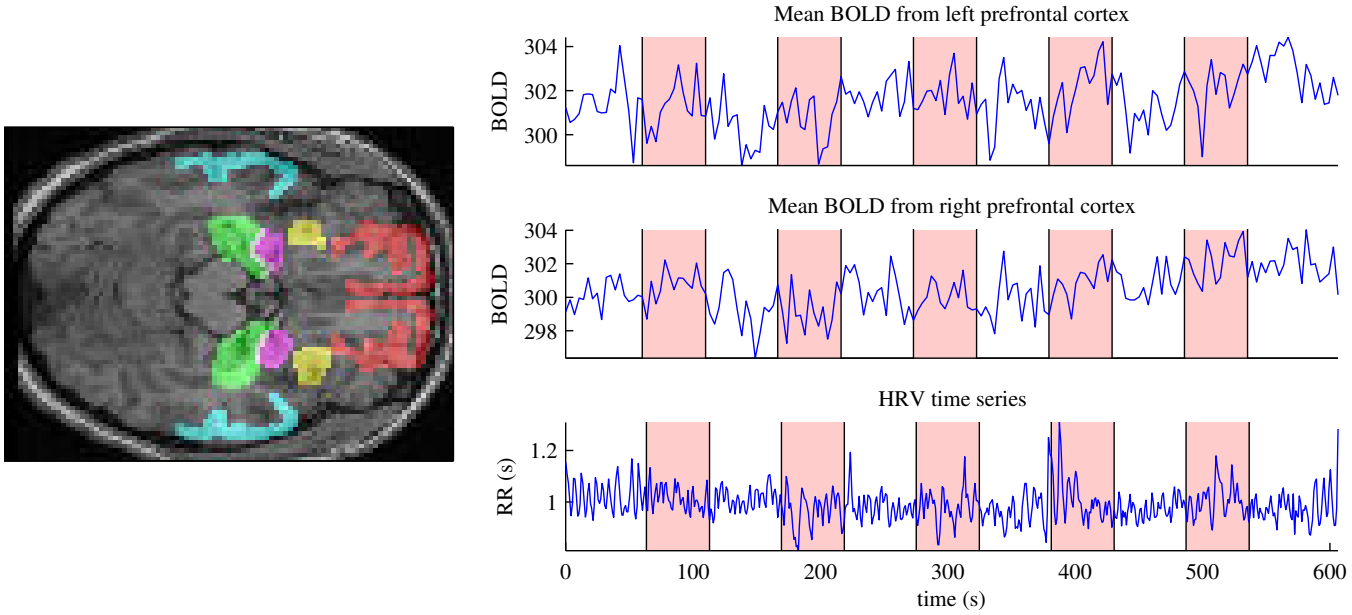

Fig. 1. On left side: sample of the masks used for different ROIs on transverse slice of anatomical MRI scan, red is prefrontal cortex, yellow is insular cortex, magenta is amygdala, green is hippocampus and cyan is Wernicke's area. Broca's area is not show on this slice. On right side: mean BOLD signals from prefrontal cortices of both hemispheres and simultaneous RR time series. Task periods are marked with red background.

of work loads. But it should be noted that in Broca's area there is statistically significant correlation only with right hemisphere and in Wernicke's area with left hemisphere. This might indicate that these sides of the ROIs are more connected to sympathetic activity than their opposite sides.

The correlation of right side PFC and heart rate (dR, HR, 0.62) suggests that activation of this ROI increases sympathetic effects of ANS. This is in line with a previous finding [7]. Also, the negative correlation of (dR-dL)/(dR+dL) and RMSSD supports the observation that left side of PFC more actively affects parasympathetic modulation and right side the sympathetic modulation of ANS. However, some studies have had conflicting results of positive correlation with right side PFC activity and HF [3], [6].

Left insular cortex has been shown to have connection to both parasympathetic [10] and sympathetic [6] regulation of ANS. Our results for right insular cortex (dR, SDNN, -0.67), (dR, HF, -0.68) and (dR, TP, -0.74) suggest that it might have connection to sympathetic regulation of ANS by overall decreasing HRV.

Our result for left amygdala (dL, HR, 0.61) suggests that this brain region is connected to sympathetic part of ANS. However, this is in contradiction with many previous results [3], [6], [10]. Right amygdala has also been shown to correlate with parasympathetic activity [10] and our result of (dR, LF, -0.60) is more consistent with that, since change in LF can be from either parasympathetic or sympathetic activity.

Hippocampus has been correlated with HF in few studies. One showed positive correlation of HF and left amygdala-hippocampal complex [3] and one showed both positive and negative correlation with HF and right hippocampus [6]. The positive correaltion with HF is in line with our result (dR, LF nu, -0.81) which suggests that sympatho-vagal balance is decreased when right hippocampus is activated. This could be because increase in HF. However, there was no significant correlation between activation of right hippocampus and HF.

The limitations of this study were the small number of subjects whose ECG could be cleared from artefacts and the task, which resulted in relatively small changes in HRV parameters. That is, the task could have been more "demanding". Also the masks for some ROIs might be too large and should be divided into smaller ones. This is because in some studies there have been opposite correlations inside one anatomical structure, e.g. in anterior and posterior parts of hippocampus [6]. With our method these opposite correlations in one ROI are not detected because they are averaged away.

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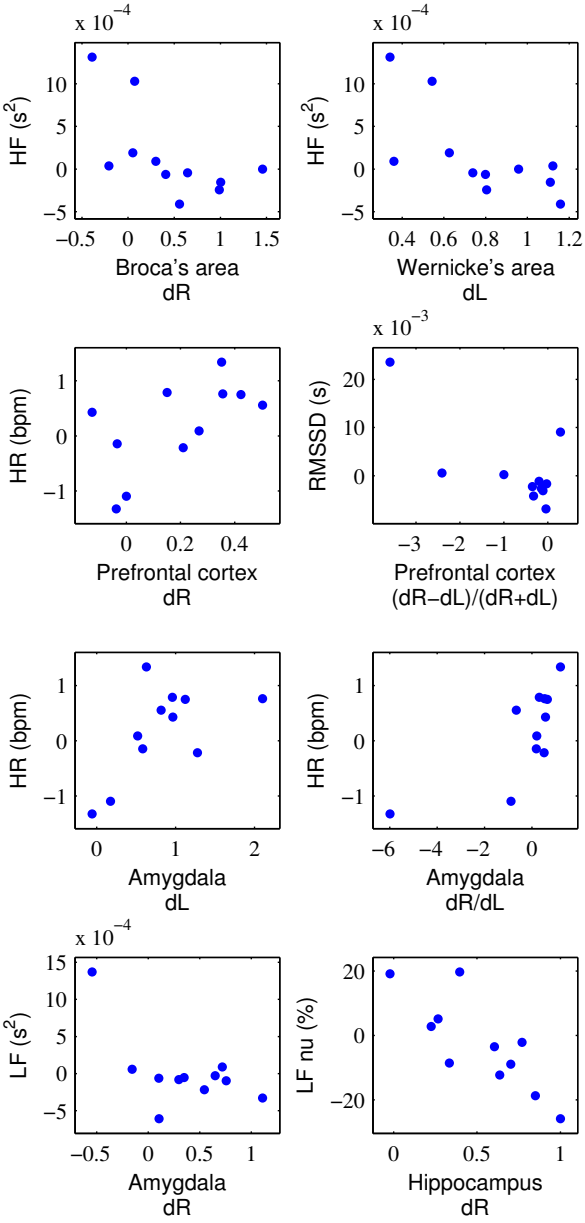

Fig. 2. Selected correlations between BOLD parameter and HRV parameter changes from baseline to active block.