Modeling Heart Beat Dynamics and fMRI Signals during Carotid Stimulation by Neck Suction

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Abstract—**Central autonomic control on the cardiovascular system has been widely investigated in the last decades. More recently, with the advent of brain imaging techniques, considerable effort is being spent on defining the role of specific brain areas, and their dynamic network, acting on autonomic efferents. A way to assess autonomic modulation is offered by carotid stimulation. In this work, we propose a methodology to investigate autonomic control in carotid stimulation experiments using heartbeat series in combination with fMRI imaging. We modeled cardiovascular signals using the point process model, and processed fMRI data in order to estimate independent components of correlated information. Using cross-correlation and surrogate analysis, we assessed the responsiveness of subjects to neck suction stimuli and identified stimulus-related fMRI independent components.**

I. Introduction

The autonomic nervous system (ANS) is the part of peripheral nervous system responsible for the control of visceral functions, e.g. heart beating, breathing, swallowing. Focusing on cardiovascular control, several studies have shown specific functions of the brainstem and other areas [1]. Functional magnetic resonance imaging (fMRI) is an established technique, and it is claimed to be the best tool for gaining insights into brain function and formulating interesting and eventually testable hypotheses. The success in testing such hypotheses critically depends on a wide range of factors, e.g. the specific magnetic resonance technology, the experimental protocols, the statistical analysis tools, and the modeling approach chosen for each undertaken study [2]. Combining fMRI with autonomic monitoring has permitted new insight into brain-heart interaction and the integration of autonomic cardiovascular and cognitive processes [3],[1]. A way to perform autonomic perturbation, in order to investigate the cardiovascular control focusing on the baroreflex mechanism, is the non-invasive carotid stimulation technique by neck suction [4], that has proven to be an efficacious method to alter heart beat dynamics (HBD) [5] and heart rate variability (HRV) as quantitative markers of cardiovascular regulation by the ANS.

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The combination of neck suction, HBD and fMRI analysis requires a tailored modeling of the time series involved, since the original data have specific and distinctive time courses and representations.

In this paper, we propose a signal modeling framework to investigate the baroreflex central processing and responses elicide at higher cortical centers, based on both a point process model of heartbeat dynamics and a data-driven approach to fMRI analysis. Care was paid to model the different dynamics of the various signals involved, from few milliseconds in the case of the ECG signal to several seconds in the case of the Blood Oxygenation Level Dependent (BOLD) signal.

Since standard time varying techniques do not really overcome the stationarity constraint and do not give instantaneous measures of HBD using a statistical physiologically-based model framework, Barbieri et al. proposed a statistical model of the human heart beat based on a inhomogeneous history-dependent probability density that may be used to compute instantaneous estimates of heart rate and heart rate variability from electrocardiogram recordings [6]. Maximum local likelihood and adaptive filtering methods are used to estimate the model parameters. The point process statistical model is defined by an inverse Gaussian density function. It has been shown that the inverse Gaussian framework gives an excellent model to describe interval data.

Furthermore, in order to avoid any a priori hypothesis and to perform the analysis on the entire brain, we chose a data-oriented strategy to find features directly from the data. A common method used in cognitive and clinical studies in the last years is given by the independent component analysis (ICA), which has proven to be a powerful tool to identify task-related brain regions [7]. However, no attempt has been made before to use this technique so as to analyze autonomic data. This is due to the issue of describing a stimulation signal as in the motor or cognitive task-related protocols. Since carotid stimulation offer a suitable way to thoroughly describe cardiovagal stimuli, ICA becomes a viable tool for studying ANS.

In order to assess the relationship between independent components of BOLD signals and neck suction stimuli, we performed cross-correlation analysis and then evaluated its significance.

II. Methods

A. Data Acquisition

All data were collected at the Neuroimaging Laboratory of Santa Lucia Foundation in Rome (Italy). Participants consisted of fourteen healthy right-handed subjects, all men. The protocol was approved by the local ethics committee. During a two sessions fMRI scan, each subject was

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stimulated with a MRI compliant neck suction device, consisted of a two chambers collar and a vacuum source [8], [9]. In order to set the pressure, a feedback system was built using the pressure signal of the pump and a reference signal generated by a National Instruments acquisition card: in this way the aspiration level of the source was controlled. The vacuum source and the related controlling unit were placed in the MRI control room. A 5-m length silicon tube connected the pump with the neck collar, passing through a waveguide of the Faraday cage. Furthermore, the actual pressure of the collar was continuously recorded by a pressure transducer. Since two cuffs were used, the pressure line was split in two parallel arms, and the pressures were monitored and recorded independently in both cuffs in order to avoid asymmetric pressure losses. During each session, two different pressures were applied as efficacious and non-efficacious stimuli, the lowest pressure inducing autonomic response (-60 mmHg), and the highest one not inducing response (-10 mmHg). These values were preliminary defined in another study [10]. In the first session, an event-related design was used: 50 efficacious and 30 non-efficacious stimuli were randomly arranged, where each stimulus had a duration of 8 seconds. The subjects were instructed to just lie in the scanner with their eyes closed. In the second session, the stimulation followed a block design: there were eight 60-seconds blocks of efficacious stimuli interchanged with eight ones of non-efficacious stimuli, and each block included five stimuli. Each single stimulus had a duration of eight seconds. In this session, the subjects had to perform a two-part spatial attention task: in the first part, they were required to respond by key-press when presented with items showing a symmetry and not to press in case of non-symmetry; in the second part, they had to respond by key-press to items presented in yellow and not to respond to items presented in other colors. Outside the scanner, the autonomic tone was proved not to be altered by this task. [9] During each scan, the ECG signal was recorded using a BIOPAC MRI compliant system, with a sampling rate of 200 Hz. The functional brain imaging was carried out with a head-only 3 Tesla MRI Scanner (Siemens Magnetom Allegra), equipped with a circularly polarized transmit-receive coil. Functional images were collected using echo-planar T2* sequence with blood oxygenation level-dependent contrast. Each acquiring volume consisted of 32 axial slices covering the whole brain, with a repetition time of 2.08 s, for a total duration of 20 minutes for each session. In both sessions, the first four volumes were discharged to allow for T1 equilibration effects. The fMRI data were then preprocessed using the software SPM5 (Statistical Parametrical Mapping, http://www.fil.ion.ucl.ac.uk), in order to realign the images, to normalize them and finally to smooth and filter them.

B. Point-Process Model of Heart Beat Dynamics

The R events series were first obtained from the ECG signal using a threshold algorithm developed in MATLAB. Then, each series was visually searched and manually corrected for artifacts and detection errors. The resulting data were processed with an algorithm developed by Barbieri et al. in order to automatically detect and correct further erroneous and ectopic heartbeats [11]. The final heartbeat intervals were modelled as a history-dependent inverse Gaussian process using the point-process algorithms developed in MATLAB by Barbieri et al. as well [5]. No hypothesis on the stationarity of the signal was made, so the parameters retrieved from the software were time-varying. As a result of using a point-process approach, the agreement between heartbeat series and the model could be assessed using the Kolmogorov-Smirnov (KS) test and the correlation between the RR interval values: in this way the best order for the model was determined. Furthermore, we assessed the response of heart rate to the neck suction stimuli performing cross-correlation between the point-process time course and the pressure signal generated by the neck suction device.

C. fMRI Independent Component Analysis

The independent component analysis of the fMRI data was performed with GIFT 2.0a (Group ICA of fMRI Toolbox, http://mialab.mrn.org) [7]. Since the study included also an event-related design with stimuli randomly given to each subject, we performed single-subject instead of group analysis. For each subject and each session, the number of independent components was estimated using minimum description length criterion. Then the independent components were calculated using the Infomax algorithm. For each component, the correlation with the pressure stimulation signal was computed, and then the maximum value with the related lag was used. Due to the higher sampling frequency of the pressure signal, the components were low-pass filtered and resampled at the same frequency of the MRI scanner.

D. Surrogate Data Analysis

In order to estimate the significance of the correlation for the point-process model and the independent components with the pressure stimulation signal, we considered surrogate data analysis as a bootstrap method [12]: the correlation between time-shuffled versions of target data, i.e. independent components and point process signal, and the reference signal, i.e. the pressure stimulus, was calculated. In this way, we canceled almost any kind of information contained in the signal, and we could assess the significance of correlation by checking the difference between the original correlation and the surrogate ones, without making any assumption on the distribution. The results of surrogate data analysis were evaluated in two ways. The first measure of significance was calculated as:

$$S = \frac{| Q^{*}_{surrogate} - Q_{original} |}{\sigma_{surrogate}} \tag{1}$$

where $Q_{original}$ is the maximum of cross-correlation for the original data set and $Q^{*}_{surrogate}$ and $\sigma_{surrogate}$ are the mean and the standard deviation, respectively, of the maximum of cross-correlation for the surrogate data set. The second way to assess the significance is the α-level defined as

$$\alpha = \frac{n_i}{n_s} \tag{2}$$

where n_i is the number of surrogate signals with a higher correlation than the original one, and n_s is the total number of surrogate signals. In order to obtain reliable estimates, we chose the number of shuffled signals computed equal to 10000 [13].

III. Results

A. HBD model goodness-of-fit

For the point-process model, we initially chose the standard parameters for the framework (time resolution: 5 ms, regressive order: 9, forgetting factor: 0.98) and then assessed the model goodness-of-fit using the KS test and the autocorrelation. Fig. 1 illustrates these results for a representative subject: the KS plots showed a good agreement between the heartbeat interval time series and the model for all the subjects, and the autocorrelation function was indistinguishable from zero. Variations of the model order showed no significant improvement in the model goodness-of-fit, while increasing the model order caused worse KS plots, so the standard parameters were considered appropriate for the data.

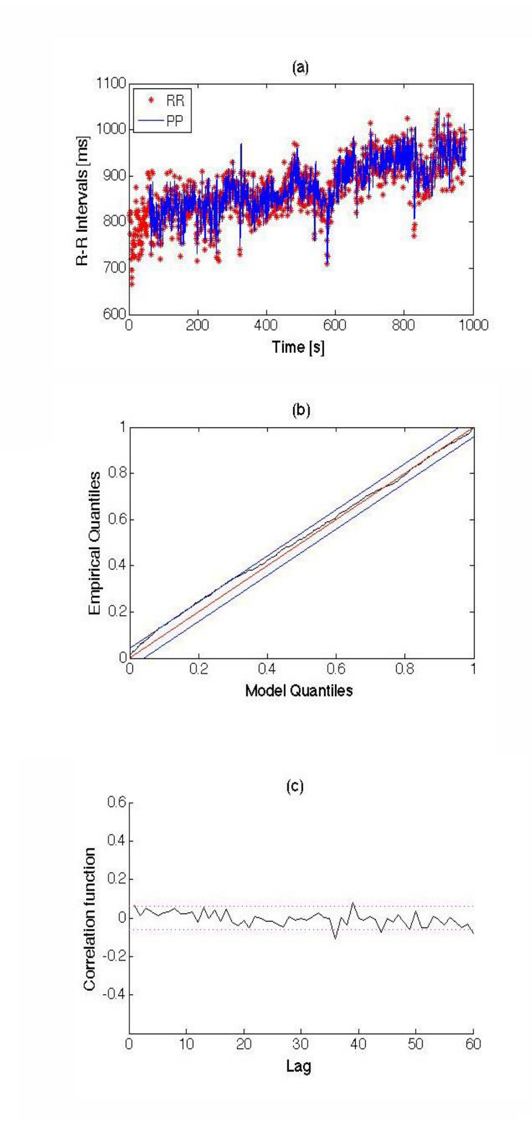

Figure 1 - Point process estimate of heart beat dynamics of a representative subject. (a) Point process model time course (continuous blue line) compared with the R-R interval series (red dots); (b) KS plot and (c) autocorrelation of the estimated R-R interval series.

B. HBD response

In order to assess the response of heart rate to the neck suction stimuli, we performed cross-correlation between the point-process time course and the pressure signal generated by the neck suction device. The results are shown in table 1. Although every subject shows a high correlation value, not all show significance: surrogate data analysis showed that for the block design session 6 subjects out of 14 showed an α-level lower than 0.05 and a S value equal at least to 3, used as a threshold in another study [12], while for the event-related session 5 subjects showed values in that range.

C. Stimulation-related fMRI Independent Components

The results of the cross-correlation between the independent components and the pressure signal are summarized in table 2: for each subject we report the correlation and the relative lag of the most correlated component, together with the results of surrogate data analysis. The block design session results show that for each subject there is at least one component with a moderate correlation value. Regarding surrogate data analysis, every subject shows a very low α-level but only 7 subjects exhibit a S value equal at least to 3, regardless of the significance of the correlation between HBD and stimulation. The event-related design session results present a similar situation, with the exception of three subjects showing correlated components with a very high lag value.

IV. Discussions and Conclusion

We have presented a modeling framework for analyzing fMRI and cardiovascular data during autonomic nervous system perturbation in normal subjects. Because the novelty of the experiments and the peculiarity of the neck suction stimulation prevented assumptions related to specific temporal or regional pattern of activation in the brain, the main tool of this framework was identified in the data-driven approach given by ICA. The cross-correlation between stimuli and independent components has led to identify stimulus-related components.

Moreover, we were able to apply the point-process model used in defining heartbeat dynamics to represent further induced responses. This is the first attempt to model the neck suction induced heart beat dynamics suitable for a joint analysis with fMRI data. Such modeling provides HBD time series suitable to be used for cross-correlation and independent component analysis. By using cross-correlation between point process HBD and stimuli, it has also been possible to classify subjects in terms of responsiveness to stimuli. In most of the subjects, indeed, a component correlated with the neck suction signal was found. Surrogate data analysis allowed to evaluate the statistical significance of the observed correlation.

The next step could be isolating the brain regions involved and then studying the activation timing to complete the tracking of the baroceptors response. Finally, relevant inter-individual differences were observed. Such differences need further analysis and eventually group analysis.

TABLE I. RESULTS OF THE CORRELATION BETWEEN POINT-PROCESS TIME COURSE AND PRESSURE STIMULATION SIGNAL

Subject	Block design session				Event-related design session			
	Correlation	*Lag*	*α*	*S*	*Correlation*	*Lag*	*α*	*S*
1	-0.666	0	0.004	2.977	-0.711	1	0.002	3.276
2	-0.680	0	0.170	0.944	-0.689	5	0.795	0.839
3	-0.657	2	0.400	0.177	-0.667	5	0.023	2.135
4	-0.672	0	0.084	1.462	-0.713	0	0.031	1.988
5	-0.673	-1	0.828	0.954	-0.679	3	0.945	1.500
6	-0.680	4	0.084	1.389	-0.708	0	0.998	2.860
7	-0.680	0	0.000	7.633	-0.635	1	0.000	7.827
8	-0.683	0	0.001	3.368	-0.696	0	0.071	1.522
9	-0.695	-1	0.229	0.728	-0.732	0	0.006	2.725
10	-0.659	-1	0.543	0.130	-0.693	1	0.774	0.770
11	-0.698	0	0.000	7.651	-0.728	0	0.000	4.355
12	-0.702	0	0.000	4.547	-0.721	0	0.003	3.243
13	-0.697	0	0.000	8.552	-0.726	-1	0.000	8.755
14	-0.677	-1	0.046	1.734	-0.713	1	0.019	2.333

TABLE II. RESULTS OF THE CORRELATION BETWEEN FMRI INDEPENDENT COMPONENTS AND PRESSURE STIMULATION SIGNAL

Subject	Block design session				Event-related design session			
	Correlation	*Lag*	*α*	*S*	*Correlation*	*Lag*	*α*	*S*
1	0.211	-2	0.000	2.259	-0.148	-1	0.001	1.452
2	-0.377	-1	0.000	3.962	0.302	-1	0.000	3.172
3	0.225	5	0.000	2.594	-0.196	-1	0.000	2.150
4	0.227	-1	0.000	2.609	0.195	-1	0.000	2.086
5	-0.269	-1	0.000	2.772	0.188	-1	0.000	1.959
6	0.252	3	0.000	2.519	-0.298	-1	0.000	3.086
7	-0.327	-1	0.000	3.497	-0.179	0	0.000	1.891
8	0.364	-2	0.000	3.820	0.479	-1	0.000	4.946
9	-0.496	0	0.000	5.084	0.484	-1	0.000	5.018
10	0.420	-1	0.000	4.467	-0.352	-1	0.000	3.682
11	-0.535	-1	0.000	5.523	-0.531	-1	0.000	5.447
12	0.196	4	0.000	2.089	-0.108	1	0.001	1.463
13	0.226	1	0.000	2.340	-0.365	5	0.000	3.679
14	-0.521	-1	0.000	5.380	-0.334	0	0.000	3.468

The correlation values and the related statistics refer to the most correlated independent component for each subject.

REFERENCES

[1] V. Napadow, R. Dhond, G. Conti, N. Makris, E.N. Brown, R.Barbieri, "Brain correlates of autonomic modulation: combining heart rate variability with fMRI", *Neuroimage*, vol. 42, no. 1, pp. 169-77, Aug. 2008.

[2] N.K. Logothetis, "What we can do and what we cannot do with fMRI", *Nature*, vol. 453, no. 7197, pp. 869-78, June 2008.

[3] H.D. Critchley, "Psychophysiology of neural, cognitive and affective integration: fMRI and autonomic indicants", *Int. J. Psychophy.*, vol. 73, no. 2, pp. 88-94, 2009.

[4] V.L. Cooper, R. Hainsworth, "Carotid baroreflex testing using the neck collar device", *Clin. Auton. Res*, vol. 19, no. 2, pp: 102-12, Apr. 2009.

[5] R. Barbieri, E.N. Brown, "Analysis of heartbeat dynamics by point-process adaptive filtering", *IEEE Trans. Biomed. Eng.*, vol. 53, no.1, 2006.

[6] R. Barbieri, E.C. Matten, A.A. Alabi, E.N. Brown, "A point process model of human heart rate intervals: new definition of heart rate and heart rate variability", *Am. J. Physiol. Heart Circ. Physiol.*, vol. 288, no. 1, pp. 424-35, Jan. 2005.

[7] V.D. Calhoun, T. Adali, "Unmixing fMRI with independent component analysis", *IEEE Eng. Med. Biol. Mag.*, vol. 25, no. 2, pp. 79-90, 2006.

[8] G. Calcagnini, E. Mattei, M. Triventi, B. Basile, A. Bassi, M. Bozzali, S. Strano, P. Bartolini, "Investigation of the autonomic nervous system control of cardiovascular variables using fMRI and carotid stimulation", *Comp. Card.*, pp. 529-32, Sept. 2010.

[9] B. Basile, A. Bassi, G. Calcagnini, S. Strano, C. Caltagirone, E. Macaluso, P. Cortelli, M. Bozzali, "Direct stimulation of the autonomic nervous system modulates activity of the brain at rest and when engaged in a cognitive task", *Hum. Brain Mapp.*, vol. 34, no. 7, pp. 1605-14, Jul. 2013.

[10] R.G. Querry, S.A. Smith, M. Strømstad, K. Ide, N.H. Secher, P.B. Raven, "Anatomical and functional charateristics of carotid sinus stimulation in humans", *Am. J. Physiol. Heart Circ. Physiol.*, vol. 280, no. 5, pp. 2390-8, May 2001.

[11] L. Citi, E.N. Brown, R. Barbieri, "A real-time automated point-process method for the detection and correction of erroneous and ectopic heartbeats", *IEEE Trans. Biomed. Eng.*, vol. 59, no. 10, pp. 2828-37, 2012.

[12] J. Theiler, S. Eubank, "Don't bleach caothic data", *Chaos*, vol. 3, pp. 1-11, 1993.

[13] G.A. Churchill, R.W. Doerge, "Empirical threshold values for quantitative trait mapping", *Genetics*, vol. 138, pp. 963-71, 1994.