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Resting state Rolandic mu rhythms are related to activity of sympathetic component of autonomic nervous system in healthy humans

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ABSTRACT

We tested the hypothesis of a relationship between heart rate variability (HRV) and Rolandic mu rhythms in relaxed condition of resting state. Resting state eyes-closed electroencephalographic (EEG) and electrocardiographic (ECG) data were recorded (10–20 System) in 42 healthy adults. EEG rhythms of interest were high-frequency alpha (10.5–13 Hz) and low-frequency beta (13–20 Hz), which are supposed to form Rolandic mu rhythms. Rolandic and occipital (control) EEG sources were estimated by LORETA software. Results showed a statistically significant ($p < 0.05$, corrected) negative correlation across all subjects between Rolandic cortical sources of low-frequency beta rhythms and the low-frequency band power (LF, 0.04–0.15 Hz) of tachogram spectrum as an index of HRV. The lower the amplitude of Rolandic sources of low-frequency beta rhythms (as a putative sign of activity of somatomotor cortex), the higher the LF band power of tachogram spectrum (as a putative sign of sympathetic activity). This effect was specific as there was neither a similar correlation between these EEG rhythms and high-frequency band power of tachogram spectrum (as a putative sign of parasympathetic vagal activity) neither between occipital sources of low-frequency beta rhythms (as a putative sign of activity of visual cortex) and LF band power of tachogram spectrum. These results suggest that Rolandic low-frequency beta rhythms are related to sympathetic activity regulating heart rate, as a dynamic neurophysiologic oscillatory mechanism sub-serving the interaction between brain neural populations involved in somatomotor control and brain neural populations regulating ANS signals to heart for on-going homeostatic adaptations.

1. Introduction

It is well known that the autonomic nervous system (ANS) dynamically maintains homeostasis of visceral organs through two major components, namely the parasympathetic and the sympathetic component. The parasympathetic component is associated with vegetative and restorative functions, whereas the sympathetic component causes vegetative changes to support body reactions to psychophysical stress including internal thinking of emotional contents and environmental demands. In this framework, ANS controls heart rate variability (HRV) and cardiac contractility, ensuring the proper cardiac stroke time-by-time.

HRV can be estimated from electrocardiographic (ECG) activity recorded along a period of few minutes (Kim et al., 2005; Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology, 1996; Vaz et al., 2003; Pinna et al., 2007; Vanderlei et al., 2010). A common procedure is fast Fourier transformation (FFT) of time series formed by consecutive R–R intervals of an ECG recording period (i.e., tachogram). The procedure computes the tachogram power density, and the main functional interest is for two frequency bands of the spectrum, namely the low frequency (LF, 0.04 to 0.15 H) and the high frequency (HF, 0.15 to 0.40 Hz) bands. Functional meaning of these bands is still under debate, although most Authors agree that they reflect the activity of parasympathetic (vagal) and sympathetic components on heart sinoatrial node. Specifically, clinical and experimental observations of autonomic maneuvers such as electrical vagal stimulation, muscarinic receptor blockade, and vagotomy showed that parasympathetic (vagal) activity mainly affects HF band of tachogram spectrum as a function of breathing cycles (Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology, 1996). More controversial is the interpretation of the

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LF band of the tachogram spectrum (Hirsch et al., 1991; Montano et al., 2009; Rajendra Acharya et al., 2006; Wu et al., 2008). Some evidence suggests that it mainly reflects sympathetic activity as a function of baroreceptor inputs, especially when expressed in normalized units (Kamath and Fallen, 1993; Rimoldi et al., 1990; Montano et al., 1994), while other evidence supports the idea that it reflects both sympathetic and vagal influences (Appel et al., 1989). This controversy may be due to the fact that absolute power of the LF band decreases in some conditions associated with sympathetic activity. During this activity, tachycardia is usually accompanied by a marked reduction in total power of HRV spectrum, whereas the reverse occurs during vagal activation. When HRV spectral bands are expressed in absolute values such as milliseconds squared, sympathetic activation is associated to reduction of both LF and HF bands, thus preventing the appreciation of the relative different effects on these bands of the tachogram spectrum (Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology, 1996).

An interesting issue is how brain operates to transform the representations of external worlds (i.e., stimuli, events, contingencies) and internal needs and plans (i.e., drives, thinking, etc.) into ANS signals adapting time-by-time cardiac frequency to supply blood to organism during psychophysical stress, especially skeletal muscles, brain, and hearth. Previous studies using brain transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) have demonstrated that human cortex is involved in the causal regulation of ANS inputs to hearth. On one hand, it has been shown that anodal tDCS overlying primary motor cortex increased sympathetic activity as revealed by LF band of tachogram spectrum (Vernieri et al., 2010; Clancy et al., 2014). Furthermore, tDCS overlying left temporal cortex increased parasympathetic activity as revealed by HF band of this spectrum (Montenegro et al., 2011). Moreover, the same effect was observed by tDCS overlying dorsolateral prefrontal cortex during negative images stimuli (Brunoni et al., 2013). On the other hand, inhibitory repetitive TMS (0.2 Hz) overlying vertex affected bilateral motor areas inducing an increase of sympathetic activity as revealed by LF band of tachogram spectrum (Yoshida et al., 2001). Furthermore, inhibitory repetitive TMS (1 Hz) affected left primary motor cortex modulating sympathetic/parasympathetic balance as revealed by LF–HF ratio of tachogram spectrum (Vernieri et al., 2014). Similar effects on HRV were obtained by tDCS and TMS in depressed or schizophrenic subjects (for a complete review see Schestatsky et al., 2013).

The mentioned previous studies demonstrated the causal involvement of cerebral cortex, especially primary motor cortex, in the regulation of HRV, but they did not unveil the underlying neurophysiologic mechanism. In this regard, interesting results were obtained by correlation studies using functional magnetic resonance imaging (fMRI) and FDG-positron emission tomography (PET). fMRI evidence during resting state and hand grip tasks showed a correlation between HF band power of the tachogram and BOLD in several brain regions including hypothalamus, cerebellum, parabrachial nucleus/locus ceruleus, periaqueductal gray, amygdala, hippocampus, thalamus, and dorsomedial/dorsolateral prefrontal, posterior insular, and middle temporal cortices (Napadow et al., 2008). Furthermore, fMRI evidence during resting state unveiled a correlation of BOLD among brainstem, thalamus, putamen, and dorsolateral prefrontal cortex, dorsolateral anterior cingulate cortex (dACC) and amygdala when HRV was elevated (Chang et al., 2013). The relationship between this functional brain circuit and HRV differed with HF and LF bands of the tachogram spectrum, thus suggesting a different activity of parasympathetic and sympathetic components (Chang et al., 2013). Moreover, fMRI evidence during a demanding (Stroop) cognitive task indicated that BOLD in pregenual anterior cingulate cortex correlated with HF band power of tachogram spectrum, unveiling the role of this area in parasympathetic (vagal) modulation (Matthews et al., 2004). Finally, fMRI evidence during rectal distension pointed to an increase of BOLD in a complex brain circuit (bilateral insula, putamen, thalamus, midbrain, pons, and cerebellum) in correlation with LF/HF ratio, indicating a prominent role of sympathetic activity (Suzuki et al., 2009).

Two PET studies during stressful conditions showed interesting relationships between HRV indexes and regional cerebral blood flow (rCBF). One PET study pointed to a correlation between HF band of tachogram spectrum and rCBF in medial prefrontal cortex, caudate nucleus, periaqueductal gray and left mid-insula during different emotional states such as happiness, sadness, and disgust, suggesting that a medial visceromotor network is a final common pathway by which emotional and cognitive functions recruit autonomic support (Lane et al., 2009). In the other PET study, subjects with social phobia underwent a stressful public speaking task (Ahs et al., 2009). Stress induced rCBF correlated positively with HF band of tachogram spectrum in supra-genual anterior cingulate cortex, caudate nucleus, medial and dorsolateral prefrontal cortex extending results in healthy subjects (Ahs et al., 2009). On the other hand, a PET study using neutral visual stimuli showed that HF/LF ratio of HRV would be partially interlocked with activity of motor brain regions such as caudate nuclei and motor cortex (Schlindwein et al., 2008).

A modern view on the interaction between brain and ANS for the regulation of hearth rate is grounded upon a general theory about brain–body–mind-integration based on empirical data as well as concepts from physiology, psychology, physics, and philosophy (Başar, 2011). This theory states that a complex and dynamic neurophysiologic oscillatory mechanism might regulate the interaction between brain neural populations representing internal needs and environmental objects/events and those regulating ANS signals to visceral organs for homeostatic adaptations (Başar, 2011). To test such a general theory, electroencephalographic (EEG) techniques are ideal as they capture indexes of oscillatory behavior of large brain neural populations. In this vein, previous studies have shown that two well-validated psychophysiological vulnerability markers of affective style such as interhemispherical asymmetry of frontal EEG power density at about 10 Hz (alpha rhythms) and cardiac vagal tone as revealed by HRV (Miskovic and Schmidt, 2010). In healthy subjects, these psychophysiological indicators were related each other during emotional arousal (Waldstein et al., 2000) and positive/negative mood induction (Kop et al., 2011). Furthermore, they biased early processing of motivationally salient stimuli (Miskovic and Schmidt, 2010). Noteworthy, a study found a negative correlation between frontal EEG power density at beta frequencies (around 20 Hz) and R-wave to pulse interval suggestive of a relationship between higher levels of cortical tone and increased sympathetic and reduced vagal cardiac influences (Duschek et al., 2014). Furthermore, there was an inverse correlation between EEG power density at alpha frequencies (around 10 Hz) and respiratory sinus arrhythmia (RSA) and baroreflex sensitivity (BRS) that may reflect bottom-up modulation of cortical arousal by baroreceptor afferents (Duschek et al., 2014). These EEG and HRV indicators were also correlated each other at rest and during speech anticipation in patients with social anxiety disorder (Schmidt et al., 2012). Another interesting study correlated cortical sources of resting state EEG rhythms with RSA, BRS and R-wave to pulse interval as indices of ANS cardiovascular control in subjects with tinnitus (Vanneste and De Ridder, 2013). The results showed that in these patients, sympathovagal balance might be controlled by anterior cingulate cortex, while right and left insula might control sympathetic and parasympathetic activity, respectively (Vanneste and De Ridder, 2013).

Keeping in mind the above data on the causal effects of stimulation of motor cortex on HRV and the mentioned oscillatory theory about brain–body–mind-integration (Başar, 2011), the present study tested the hypothesis of a relationship between HRV and EEG rhythms of Rolandic cortical areas. These rhythms have a typical arch shape and are called “mu rhythms”. There is consensus that mu rhythms are mainly generated by motor and somatosensory areas. In line with its arch shape, mu rhythms are constituted by two major frequency components when spectrum of EEG power density is computed by fast Fourier transform, namely the alpha and beta components. In the EEG power

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spectrum, alpha does peak at about 10 Hz and is named "mu" or "Rolandic alpha rhythm" (Gastaut et al., 1952; Kuhlman, 1978). Instead, beta does peak at about 20 Hz and is named "central" or "Rolandic beta rhythm" (Pfurtscheller, 1992; Salmelin and Hari, 1994). Here we refer to "Rolandic mu rhythms" to indicate Rolandic EEG rhythms including both alpha and beta components.

Rolandic mu rhythms can be easily observed in EEG, its magnetic counterpart (magnetoencephalogram, MEG), and electrocorticogram (ECoG) in the condition of muscle relaxation and immobility (i.e., no muscle tension or movement). In that condition, high-amplitude EEG oscillations at around 10 and 20 Hz are often referred to as "synchronized" EEG activity, to remark that they are produced by large cortical neural populations whose activity is synchronized at about 10 Hz and 20 Hz (Pfurtscheller and Lopes da Silva, 1999). During passive and active movements or isometric muscle tension, both alpha and beta components of Rolandic mu rhythm disappear (i.e., "block") or are markedly reduced in amplitude (Crone et al., 1998; Del Percio et al., 2010; Kumar et al., 2013; Pfurtscheller et al., 2000). In these active conditions, Rolandic EEG rhythms without the components at around 10 Hz and 20 Hz are often referred to as "desynchronized" EEG activity, to remark that they are produced by cortical neural populations whose activity is no longer or minimally synchronized at about 10 and 20 Hz (Pfurtscheller and Lopes da Silva, 1999). MEG and scalp EEG recordings showed that both alpha and beta components of mu rhythms substantially increase in amplitude 1–2 s post-movement, with the beta component being about 300 ms faster (Salmelin and Hari, 1994; Pfurtscheller and Lopes da Silva, 1999). A fine spatial analysis of mu rhythms was performed by subdural ECoG recordings in epilepsy patients during their pre-surgical assessment for the localization of epileptic foci (Crone et al., 1998; Miller et al., 2007). It was shown that alpha and beta desynchronization accompanying motor tasks was mapped on the surface of both primary motor and somatosensory areas, confirming the composite nature of human mu rhythms (Crone et al., 1998; Miller et al., 2007).

The present exploratory study tested the hypothesis of a correlation between HRV, as a marker of ANS activity, and alpha and beta components of Rolandic mu rhythms in the relaxed condition of resting state, when fluctuations of mu rhythms and HRV can be reliably recorded by non-invasive EEG and ECG recordings in healthy subjects.

2. Methods

2.1. Subjects

We recruited 42 healthy subjects (14 men) aged between 18 and 31 years. They presented neither heart diseases nor psychiatric/neurological symptoms, as revealed by medical, neurological and psychiatric assessments. All subjects received Mini Mental State Evaluation (MMSE; Folstein et al., 1975), State Trait Anxiety Inventory (STAI Y-1, STAI Y-2; Spielberger, 1983), and Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). Furthermore, they had not to assume psychoactive medications or substances interfering with EEG recordings.

The study was approved by the local Ethics Committee. Furthermore, all subjects signed a written informed consent to participate in the present study.

2.2. EEG, EOG, and ECG recordings

The experimental recordings were performed in the afternoon in relaxing and quiet environment. EEG, electrooculographic (EOG) and ECG data were recorded while subjects were seated in an armchair in resting state eyes-closed condition. The EEG recordings were performed (bandpass: 0.01–100 Hz; EB-Neuro Be-light©, Firenze, Italy) from 19 scalp electrodes positioned over the whole head according to the 10–20 System (i.e., Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2; see Fig. 1). Electrical reference was the earlobe, and the ground electrode was located between the AFz and Fz electrodes.

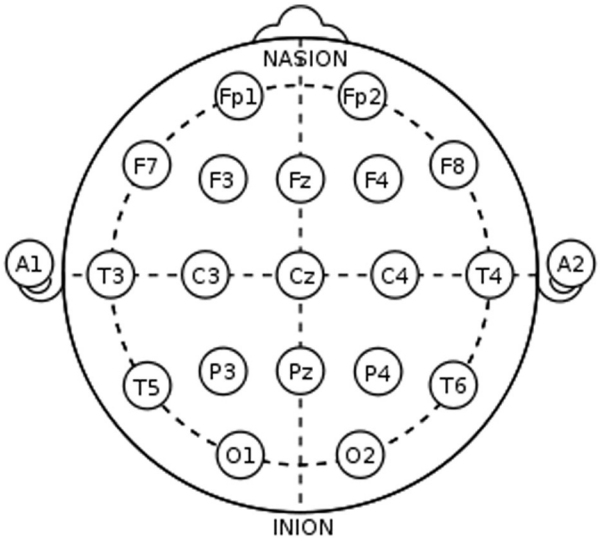

Fig. 1. Standard 10–20 System electroencephalographic (EEG) electrode montage.

Electrode impedance was kept below 5 kΩ. To monitor eye movements, bipolar horizontal and vertical EOGs (0.3–70 Hz band-pass) were collected. In parallel, we recorded an ECG channel with two electrodes on the chest. All data were digitized in continuous recording mode (5 min; 256 Hz sampling rate). All subjects were instructed not to move or talk and stay relaxed during EEG and ECG recordings. They experienced no problem to follow the instructions.

2.3. Analysis of HRV

ECG signals were filtered by a band pass filter set at 0.5–35 Hz, so that QRS complex was not altered for automatic recognition (Berntson et al., 1997; Ruha et al., 1997; Hejjel and Kellenyi, 2005). Afterward, an experimenter (T.I.A.) visually inspected the ECG signals to control that they did not contain artifacts due to movements or others. QRS complexes including R-waves were automatically recognized, and the time series with intervals between two consecutive peaks (RR intervals) were formed, namely the tachogram. No single beat was missed, and no interpolation was used to correct the tachograms. The tachogram was analyzed in frequency domain by HRV Analysis Software 1.1 for windows developed by the Biomedical Signal Analysis Group, Department of Applied Physics at University of Kuopio, Finland (Niskanen et al, 2004; http://kubios.uku.fi/). This procedure served to compute low frequency (LF, 0.05–0.15 Hz) and high frequency (HF, 0.15–0.40 Hz). In addition, the LF/HF-ratio was calculated.

2.4. EEG data analysis

The recorded EEG data were analyzed and fragmented off-line in consecutive epochs of 2 s. The EEG epochs with ocular, muscular, and other types of artifact were preliminarily identified by a computerized automatic procedure. EEG epochs with sporadic blinking artifacts (less than 10% of the total) were corrected by an autoregressive method (Moretti et al., 2003). Two independent experimenters, blind to the diagnosis, manually confirmed the EEG segments accepted for further analysis. Special attention was given to avoid the inclusion of EEG segments and individual data sets with EEG signs of drowsiness or pre-sleep stages. Finally, we re-referenced off-line artifact free EEG data to a common average for further analysis.

A digital FFT-based power spectrum analysis (Welch technique, Hanning windowing function, no phase shift) computed power density of the EEG rhythms with 0.5 Hz frequency resolution. We computed the following standard band powers: delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–10.5 Hz), alpha 2 (10.5–13 Hz), beta 1 (13–20 Hz), beta 2 (20–30 Hz)

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and gamma (30–40 Hz). These band frequencies were chosen averaging those used in previous relevant EEG studies (Babiloni et al., 2005, 2006b, 2011, 2013; Besthorn et al., 1997; Chiaramonti et al., 1997) with the sharing of a frequency bin by two contiguous bands, a widely accepted procedure (Besthorn et al., 1997; Jelic et al., 1996) that fits the theoretical consideration that near EEG rhythms may overlap at their frequency borders (Babiloni et al., 2005, 2010; Klimesch, 1996, 1999).

Low resolution electromagnetic source tomography (LORETA) was used for EEG source estimation (http://www.unizh.ch/keyinst/NewLORETA/LORETA01.htm; Pascual-Marqui et al., 1994). LORETA is a functional imaging technique that provides a linear inverse solution for distributions of EEG cortical sources (Pascual-Marqui et al., 2002). LORETA computes 3D linear solutions (LORETA solutions) for the EEG inverse problem within a 3-shell spherical head model including scalp, skull, and brain compartments. The brain compartment is restricted to the cortical gray matter/hippocampus of a head model co-registered to the Talairach probability brain atlas and digitized at the Brain Imaging Center of the Montreal Neurological Institute (Talairach and Tournoux, 1988). This compartment includes 2394 voxels (7 mm resolution), each voxel containing an equivalent current dipole. It has been shown that LORETA was quite efficient when compared to other linear inverse algorithms like minimum norm solution, weighted minimum norm solution or weighted resolution optimization (Pascual-Marqui et al., 1999; Yao and He, 2001). LORETA solutions consisted of voxel current density values able to predict EEG spectral power density at scalp electrodes. Noteworthy, resting state eyes-closed EEG rhythms can be properly sampled with a relatively low amount of electrodes of the present study (i.e., 19 electrodes placed according to the 10–20 System), as opposed to the higher spatial sampling required to take into account to the detailed functional topography of event-related EEG activity. This relatively low-spatial sampling of EEG rhythms is consistent with the fact that LORETA solutions are intrinsically maximally smoothed at source space, due to its regularization procedure (Pascual-Marqui et al., 1994).

LORETA is a reference-free method of EEG analysis, in that one obtains the same LORETA source distribution for EEG data referenced to any reference electrode including common average. A normalization of the data was obtained by normalizing the LORETA current density at each voxel with the power density averaged across all frequencies (0.5–45 Hz) and 2394 voxels of the LORETA brain volume. After the normalization, the solutions lost the original physical dimension and were represented by an arbitrary unit scale. The general procedure reduced inter-subject variability of LORETA solutions (Leuchter et al., 1993). Of note, we focused on normalized (relative) rather than absolute EEG power at source level since the absolute EEG power mainly depends on electrical resistance of individual skull and scalp, which is affected by water and fat in the tissues intervening between scalp electrodes and cortical generators of EEG activity. Such electrical resistance does not reflect functional properties of the central nervous system, and influences the EEG voltage and inter-subject variability of EEG activity.

For the specific hypotheses of the present study, two cortical regions of interest were considered. The first region was called “Rolandic or central” and included all LORETA voxels of the Brodmann areas 1, 2, 3, 4, and 6. This is a cortical region supposed to generate Rolandic mu rhythms (specifically, central cortical sources of alpha 2 and beta 1 rhythms were assumed to form the Rolandic mu rhythm). The second region was called “occipital” and included all LORETA voxels of the Brodmann areas 17, 18, and 19. This is a control cortical region supposed to be a main source of “visual” alpha rhythms.

2.5. Statistical analysis

R package software was used for statistical analysis. Normality of each variable was evaluated by Shapiro–Wilk test ($p < 0.05$). Since alpha 2 and beta 1 cortical sources of interest (central, occipital) and HRV indexes were found to be non-Gaussian ($p > 0.05$), they were square-root transformed.

Pearson's test was used to test the correlation between HRV indexes (LF, HF) and central cortical (LORETA) sources of alpha 2 and beta 1 rhythms ($p < 0.05$). Bonferroni correction for 4 repeated measures was applied ($p < 0.0125$ for $p < 0.05$ corrected).

Control analyses were computed using occipital cortical (LORETA) sources of alpha 2 and beta 1 rhythms (Pearson's test, $p < 0.05$; see Results section).

3. Results

Fig. 2 plots mean and standard error (SE) across subjects of cortical (LORETA) sources of resting state EEG rhythms in two regions of interest (central, occipital) at all frequency bands such as delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–10.5 Hz), alpha 2 (10.5–13 Hz), beta 1 (13–20 Hz), beta 2 (20–30 Hz) and gamma (30–40 Hz). It is noted that alpha 1 sources show maximum amplitude in both regions of interest. Delta, theta, and alpha 2 sources had moderate amplitude values when compared to alpha 1 sources. Finally, beta 1, beta 2, and gamma sources were characterized by lowest amplitude values. Compared to the (Rolandic) central region, the occipital region is characterized by higher amplitude of alpha 1 and alpha 2 sources. These results are in line with well-known features of Rolandic mu rhythms and occipital “visual” alpha rhythms.

Table 1 reports mean (± standard error, SE) and range across all subjects of HRV and EEG indexes of interest used in the present study. The HRV indexes are represented by LF and HF band powers of tachogram spectrum. The EEG indexes are represented by central cortical sources of high-frequency alpha rhythms (Central Alpha 2, 10.5–13 Hz) and of low-frequency beta rhythms (Central Beta 2, 20–30 Hz), which typically form Rolandic mu rhythms. It is observed that the dispersion of the HRV and EEG indexes is relatively low. Furthermore, the mean values of LF and HF band powers are similar, as expected during a condition of resting state. Finally, (Rolandic) central sources show higher mean amplitude at alpha 2 than at beta 1 frequencies, as expected in such a condition. These results confirmed the good global quality of the EEG and ECG recordings in the present experimental conditions. Of note, the values reported in Table 1 refer to the root square transformation of the HRV and EEG indexes, in order to make them Gaussian for Pearson's correlation analysis whose results are reported in Table 2.

Pearson's test ($p < 0.05$, corrected) evaluated correlations across all subjects of Central Alpha 2 sources with LF and HF band powers of tachogram spectrum as well as of Central Beta 1 sources with LF and HF band powers. Results showed that the only statistically significant correlation was observed between Central Beta 1 sources and LF band power ($p < 0.05$, corrected; see Fig. 3 for the scatterplot of the two variables). It was negative, namely the lower the amplitude of Central Beta 1 sources, the higher the LF band power of tachogram spectrum. Table 2 reports the r and p values of this session of correlation analysis.

To corroborate the above finding, two control analyses were performed. In the first control analysis, Pearson's test ($p < 0.05$) was used to evaluate the possible influence of the factor age, although the subjects' age range was relatively short in the present study. Results showed statistically significant correlations neither between Central Beta 1 sources and age nor between LF band power (tachogram spectrum) and age ($p > 0.05$), thus it is improbable that the factor age explains the main finding.

In the second control analysis, Pearson's test ($p < 0.05$) was used to evaluate the specificity of the correlation between Central Beta 1 sources and LF band power of tachogram spectrum. Results showed no statistically significant correlation between Occipital Beta 1 sources and LF band power ($p > 0.05$ see Fig. 4 for the scatterplot of the two variables), thus suggesting the cortical regional specificity of the correlation between Central Beta 1 sources and LF band power of tachogram spectrum.

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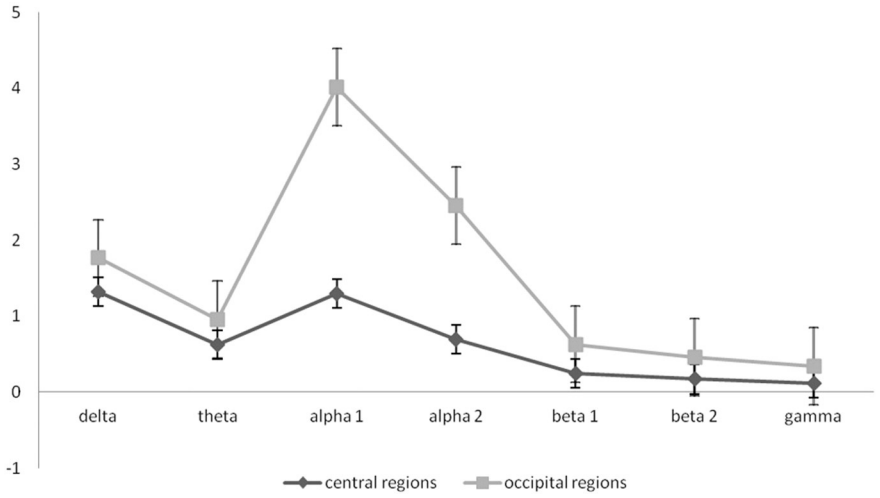

Fig. 2. Mean ± and standard error (SE, vertical bars) across subjects of EEG indexes of interest used in the present study. They are represented by central and occipital cortical sources of EEG rhythms recorded in the condition of resting state eyes closed in all subjects. These sources were estimated by the popular freeware called low-resolution brain electromagnetic tomography (LORETA). The frequency bands of these EEG rhythms are reported in the following: delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–10.5 Hz), alpha 2 (10.5–13 Hz), beta 1 (13–20 Hz), beta 2 (20–30 Hz) and gamma (>30 Hz). LORETA sources are expressed as normalized current density averaged across all voxels of the cortical regions of interest.

4. Discussion

In the present exploratory study, we tested the hypothesis of a relationship between Rolandic (central) EEG mu rhythms and HRV in healthy subjects during a behaviorally relaxed condition of resting state eyes-closed. The basic idea was that a dynamic neurophysiologic oscillatory mechanism might regulate the interaction between brain neural populations representing somatomotor control and brain neural populations regulating ANS signals to heart for on-going homeostatic adaptations (Başar, 2011). In the resting state eyes-closed condition, fluctuations of these EEG rhythms and HRV can be easily recorded by non-invasive EEG and ECG recordings even in neurologic and psychiatric patients, as an important aspect for future clinical applications (Gastaut et al., 1952; Kuhlman, 1978). Furthermore, resting state EEG and ECG recordings are cost effective, diffuse, and unaffected by learning or repetition effects. In this condition, EEG recordings of Rolandic mu rhythms probe neurophysiologic oscillatory mechanisms of spontaneous cortical neural synchronization and desynchronization occurring during fluctuation of cortical arousal and control of posture and muscular tone (Pfurtscheller and Lopes da Silva, 1999). On the other hand, ECG recordings probe HRV, which reflects spontaneous fluctuations of ANS parasympathetic (vagal) and sympathetic regulation of heart beats and contractility (Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology, 1996).

Table 1
Mean ± standard error (SE) and range across all subjects of heart rate variability (HRV) and electroencephalographic (EEG) indexes of interest used in the present study.

	Mean ± SE	Range
LF	24.26 ± 1.18	11.33–42.96
HF	22.92 ± 1.48	10.57–45.27
Central Alpha 2	0.79 ± 0.03	0.38–1.48
Central Beta 1	0.47 ± 0.02	0.2–0.83

HRV and EEG indexes refer to a condition of resting state eyes closed. HRV indexes are represented by low- (LF) and high-frequency (HF) band powers of the time series (tachogram) of consecutive R–R intervals recorded by electrocardiogram (ECG). Unit measurement of the FL and HF bands of the tachogram spectrum is expressed as area under curve of power density (i.e., ms^2). EEG indexes are represented by central cortical sources of high-frequency alpha rhythms (Central Alpha 2, 10.5–13 Hz) and of low-frequency beta rhythms (Central Beta 2, 20–30 Hz). These sources were estimated by the popular freeware called low-resolution brain electromagnetic tomography (LORETA). LORETA solutions are expressed as normalized current density averaged across all voxels of the cortical regions of interest. To make it Gaussian the above HRV and EEG indexes for the Pearson's correlation analysis whose results are reported in Table 2, root square transformation was used.

As a main and novel finding of the present study, we found a statistically significant ($p < 0.05$, corrected) negative correlation across all subjects between the Rolandic (central) cortical sources of low-frequency beta rhythms (13–20 Hz) and the LF band power (0.04–0.15 Hz) of tachogram spectrum as an index of HRV. The lower the amplitude of Rolandic sources of low-frequency beta rhythms (as a putative sign of activity of somatomotor cortex), the higher the LF band power of tachogram spectrum (as a putative sign of sympathetic activity). Specificity of this correlation was indicated by the lack of similar correlation between these EEG rhythms and HF band power of tachogram spectrum (as a putative sign of parasympathetic – vagal – activity). Moreover, there was no correlation between occipital sources of low-frequency beta rhythms (as a putative sign of activity of visual cortex) and LF band power of tachogram spectrum.

The present study using physiological measurements of Rolandic cortical activity complements previous tDCS and TMS studies showing that Rolandic cortex is involved in the causal regulation of ANS inputs to hearth. Those previous studies have reported that anodal tDCS overlying primary motor cortex increased sympathetic activity as revealed by LF band power of tachogram spectrum (Vernieri et al., 2010; Clancy et al., 2014), while cathodal tDCS applied over the primary motor cortex decreased LF band power reactivity (Vernieri et al., 2010). Furthermore, inhibitory repetitive TMS (0.2 Hz) affecting bilateral motor areas induced the same effect on LF band power of tachogram spectrum (Yoshida et al., 2001). Finally, inhibitory repetitive TMS (1 Hz) affecting left primary motor cortex modulated sympathetic/parasympathetic (vagal) balance as revealed by LF–HF ratio of band power tachogram spectrum (Vernieri et al., 2014).

Why did the present study unveil a correlation between LF band power of tachogram spectrum and Rolandic beta but not alpha rhythms? Why did not this correlation regard HF band power of tachogram spectrum? At this early stage of the research, conclusive explanations of these issues cannot be provided. In the following, we

Table 2
Pearson correlation coefficients between HRV (LF, HF) and EEG indexes (Central Alpha 2, Central Beta 1) of interest in all subjects.

	Central Alpha 2	Central Beta 1
LF	0.004	−0.411*
HF	0.072	−0.195

There was a statistically significant negative correlation ($r = -0.42$, * $p < 0.05$, corrected) between Central Beta 1 sources and values of LF band power of the tachogram spectrum. See legend of Table 1 for more methodological details.

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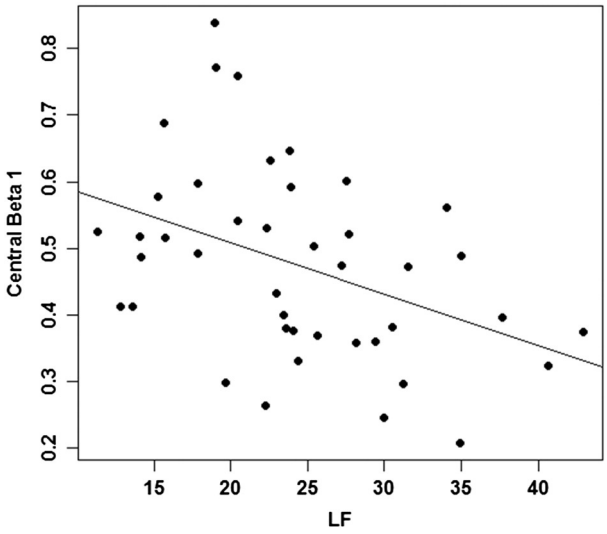

Fig. 3. Scatterplot of (Rolandic) central cortical sources of low-frequency beta rhythms (Central Beta 1, 13–20 Hz) and low-frequency (LF) band power of tachogram spectrum of heart rate variability (HRV) in all subjects. Data refer to resting state eyes-closed condition. These sources were estimated by LORETA. There was a statistically significant negative correlation ($r = -0.42$, $p < 0.05$, corrected) between these central cortical sources and values of LF band power. LORETA sources are expressed as normalized current density averaged across all voxels of the cortical regions of interest. Unit measurement of the LF and HF of the tachogram spectrum is expressed as area under curve of power density (i.e., ms^2). To make it Gaussian the above HRV and EEG indexes, root square transformation was used.

posit a tentative explanation based on a well-known theoretical framework about neural mechanisms underlying the generation of Rolandic mu rhythms and of LF/HF band powers of tachogram spectrum.

There is consensus that resting state eyes-closed EEG rhythms reflect a condition of relative behavioral relaxation and inhibition of brain mechanisms sub-serving the interaction with external world. These rhythms are generated by a complex pattern of parallel cortico-cortical and cortico-subcortico(thalamic)-cortical neural networks in which integrative activity of neurons, which is mainly expressed by

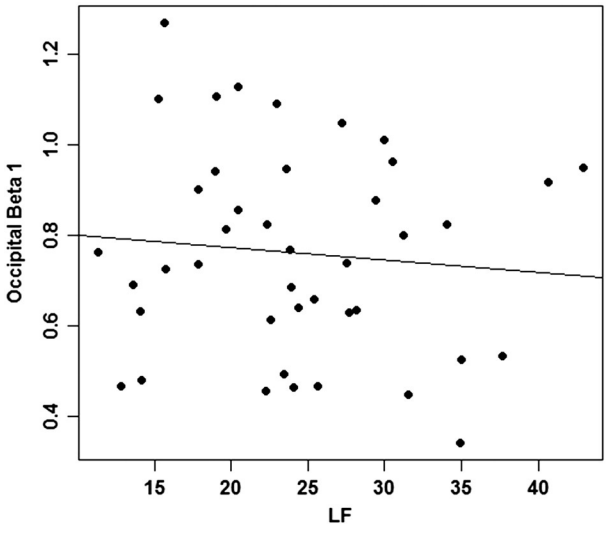

Fig. 4. Scatterplot of occipital cortical sources of low-frequency beta rhythms (Occipital Beta 1, 13–20 Hz) and LF band power of tachogram spectrum of HRV in all subjects. Data refer to resting state eyes-closed condition. These sources were estimated by LORETA. This control analysis was performed to test the specificity of the correlation between central beta 1 sources and LF band power of tachogram spectrum ($p < 0.05$, corrected). Correlation between these occipital cortical sources and values of LF band power showed no statistically significant effect ($r = -0.1$, $p > 0.05$, corrected). For the measurement units of the EEG and HRV variables, see the legend of Fig. 3.

synaptic currents, is characterized by synchronous oscillatory mode across neural assemblies (Başar, 2011). These neural networks modulate the activity of cortical pyramidal neurons, which provide the output of cortical modules. These neurons play a major role in the generation of scalp recorded EEG signals, due to an adequate orientation of their main dendrites for spatial summation of synaptic currents and diffusion of these currents towards scalp electrodes (Pfurtscheller and Lopes da Silva, 1999). In this theoretical framework, topographically widespread low-frequency alpha rhythms (8–10 Hz) would reflect global cortical arousal and tonic alertness (Klimesch, 1999), whereas Rolandic high-frequency alpha (10–13 Hz) and low-frequency beta (13–20 Hz) rhythms would reflect activation of somatomotor neural circuits subserving postural and motor control (Pfurtscheller and Lopes da Silva, 1999). The higher the amplitude of cortical alpha rhythms, the lower the cortical activation as demonstrated by the co-registration of resting state EEG rhythms and functional magnetic resonance imaging (MRI; Mantini et al., 2007). Such co-registration also unveiled the relationship between global alpha and beta rhythms and BOLD signals in the so-called default mode network (DMN), a set of parietal (including angular gyrus) and medial fronto-temporal regions metabolically active during resting state and consistently suppressed during goal-driven behavior (Shulman et al., 1997). Notably, DMN showed a competitive relationship both at rest (Fox et al., 2009) and during attention and memory tasks with the so-called dorsal attention network (DAN; Corbetta and Shulman, 2011), a set of frontoparietal regions involved in the selection of behaviorally relevant sensory-motor information. In previous fMRI and EEG co-registrations, some correlations were found between fluctuations of the BOLD signals in the DMN and alpha power fluctuations (Laufs et al., 2003; Gonçalves et al., 2006; Mantini et al., 2007; Wu et al., 2010; Knyazev et al., 2011). The same was true between BOLD signals and beta power fluctuations (Laufs et al., 2003; Mantini et al., 2007). Of note, amplitude of Rolandic alpha and beta EEG rhythms was inversely related to BOLD signals in primary somatosensory and motor cortex (Ritter et al., 2009). With another multi-modal methodological approach, inhibitory repetitive TMS (1 Hz) affecting angular gyrus of DMN enhanced global alpha rhythms in the resting state condition (Capotosto et al., 2014).

Keeping in mind this general theoretical framework, resting state Rolandic high-frequency alpha and low-frequency beta rhythms might reflect the fluctuation of synchronization (i.e., cortical inhibition) and desynchronization (i.e., cortical dis-inhibition) of diffuse neural networks regulating the excitability in human somatomotor cortex. In this theoretical framework, the correlation of Rolandic beta (but not alpha) rhythms with LF band power of tachogram spectrum leads support to previous MEG and EEG findings showing that source estimation of Rolandic alpha and beta rhythms did not coincide in primary somatosensory and motor cortical areas (Pfurtscheller and Lopes da Silva, 1999; Stancák and Pfurtscheller, 1995), with a possible pivotal role of somatosensory cortex and motor cortex in the generation of Rolandic alpha and beta rhythms, respectively (Salmelin and Hari, 1994; Ritter et al., 2009). As a novelty, the present results unveiled the composite nature of Rolandic mu rhythms with respect to their relationship with HRV. Activity of motor (but not somatosensory) cortex, as reflected by Rolandic low-frequency beta rhythms, may play a major role in the causal regulation of ANS inputs to heart, affecting LF band power of tachogram spectrum as a sign of sympathetic activity. This tentative explanation captures the seminal findings of previous tDCS and TMS studies demonstrating that Rolandic cortex is involved in the causal regulation of sympathetic inputs reflected by LF band power of tachogram spectrum (Vernieri et al., 2010, 2014; Clancy et al., 2014; Yoshida et al., 2001). It can be speculated that motor cortex implements parallel commands to pyramidal and extra-pyramidal neural networks for the control of peripheral motoneurons and to brain neural networks controlling ANS sympathetic inputs to sinoatrial node for the regulation of heart rate and contractility. It can be also speculated that this is true not only during resting state condition but also during motor events. During

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these events, Rolandic high-frequency alpha and low-frequency beta rhythms desynchronize and are replaced by high-frequency beta (about 20–30 Hz) and gamma (>30 Hz) rhythms (Crone et al., 1998; Pfurtscheller and Lopes da Silva, 1999; Babiloni et al., 2006a, 1999; Del Percio et al., 2010). Furthermore, Rolandic low-frequency beta rhythms would reflect activity of motor cortex to modulate ANS sympathetic inputs to sinoatrial node for the regulation of heart rate and contractility.

Unfortunately, resting state EEG recordings do not have the sufficient spatial resolution to enlighten the functional connectivity between brain neural networks generating Rolandic mu rhythms and central autonomic network (CAN) supposed to adapt the activity of visceral organs according to animal data (Arthur and Loewy, 1990; Benarroch, 1993; Friedman and Thayer, 1998; Napadow et al., 2008; Saper, 2002; Ida and Llewellyn-Smith, 2011). It is supposed that CAN receives sensory afferents in medulla and integrate them in pons, thalamus, hypothalamus, amygdala, and insula. Its efferent regions include rostral ventrolateral medulla, dorsal motor nucleus of the vagus and nucleus ambiguous, which receive modulating signals from rostral ventromedial medulla, midbrain periaqueductal gray, hypothalamus, amygdala, dorsomedial prefrontal and anterior cingulate regions. Future studies combining fMRI–EEG–ECG and TMS–EEG–ECG should unveil the neurophysiologic mechanisms and functional connectivity between DMN, DAN, and CAN in the resting state condition and during cognitive–motor tasks.

As a final consideration, it should be remarked that this is an exploratory study on the relationship between Rolandic (central) EEG mu rhythms and HRV in healthy subjects during resting state condition. The results encourage a conclusive cross-validation study using multiple measurements to index activity of sympathetic and parasympathetic (vagal) activity such as respiratory sinus arrhythmia and baroreflex sensitivity (Vanneste and De Ridder, 2013). However, it is not expected that the present results are affected by changes in respiratory sinus arrhythmia or in baroceptive input CAN. Indeed, we recorded EEG and ECG during resting state eyes closed in behaviorally relaxed and comfortable stationary condition.

5. Conclusions

The present study tested the hypothesis of a correlation between HRV, as a marker of ANS activity, and Rolandic mu rhythms in the relaxed condition of resting state. Results showed a statistically significant ($p < 0.05$, corrected) negative correlation across all subjects between the Rolandic (central) cortical sources of low-frequency beta rhythms (13–20 Hz) and the LF band power (0.04–0.15 Hz) of tachogram spectrum as an index of HRV. The lower the amplitude of Rolandic sources of low-frequency beta rhythms (as a putative sign of activity of somatomotor cortex), the higher the LF band power of tachogram spectrum (as a putative sign of sympathetic activity). This effect was specific as there was neither a similar correlation between these EEG rhythms and HF band power of tachogram spectrum (as a putative sign of parasympathetic – vagal – activity) nor between occipital sources of low-frequency beta rhythms (as a putative sign of activity of visual cortex) and LF band power of tachogram spectrum. These results suggest that Rolandic low-frequency beta rhythms are related to HRV index of sympathetic activity regulating heart rate, as a dynamic neurophysiologic oscillatory mechanism sub-serving the interaction between brain neural populations involved in somatomotor control and brain neural populations regulating ANS signals to heart for on-going homeostatic adaptations.

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