Electrophysiological indexes of eyes open and closed resting states conditions following the Quadrato Motor Training: a longitudinal study

[a]S.Lasaponara*, [ab]F.Mauro*, [a]T. Dotan Ben-Soussan, [c]F. Carducci, [d]M. Tombini, [d]C. C. Quattrocchi, [d]Y. Errante, [d]C. A. Mallio, [a]P. Paoletti.

*equal contribution

[a]*Research Institute for Neuroscience, Education and Didactics - Patrizio Paoletti Foundation for Development and Communication*
[b]*Department of Psychology - Sapienza Università di Roma*
[c]*Department of Physiology and Pharmacology - Sapienza University of Rome*
[d]*Unit of Neurology, Neurophysiology, Neurobiology, Department of Medicine - Università Campus Bio-Medico di Roma*

Correspondence: Tal Dotan Ben-Soussan, Research Institute for Neuroscience, Education and Didactics, Patrizio Paoletti Foundation for Development and Communication, via Cristoforo Cecci 2. 06081 - Santa Maria degli Angeli, Assisi (PG), Italy.
e-mail: research@fondazionepatriziopaoletti.org

Abstract. Eyes closed (EC) and eyes open (EO) resting states are generally considered the brain states with the lowest level of arousal. However, recent studies showed that the resting brain activity is not a static phenomenon, but is rather modulated by the incoming stimuli, producing differences in the neural activity. In the past, we showed that dynamic electrophysiological measures, such as coherence and functional connectivity, were modulated by Quadrato Motor Training (QMT) during the rsEEG with closed eyes, while it particularly affects the alpha-power during the rsEEG recorded with open eyes. Here we investigated the differences in the power spectrum between EC and EO following 3 months of QMT. To this purpose, we analyzed separately power spectrum, and the differences in the cortical generators using eLORETA software. We found that QMT lead to an increased differentiation between EC and EO mainly in the beta frequency range, and most importantly a change in cortical generators related to alpha oscillation in the para-hippocampal gyrus and to beta activity bilateral in the frontal areas. These results showed that QMT could positively contributes to sharpen the specialization during the different EC and EO brain states, refining their specific characteristics.

Keywords: Power-spectrum, EEG, Resting state, Quadrato Motor Training, eLORETA

1. Introduction

Eyes closed (EC) and eyes open (EO) resting states are both usually considered as baseline conditions with the lowest level of arousal or activation, useful for experimental comparisons with task demanding conditions. However, it has pointed out that there are consistent quantitative and qualitative differences between these two states, and thus that they represent not equivalent baseline measures of arousal/activation [Barry et al., 2007]. The transition between the two states is traditionally characterized by the suppression of occipital alpha activity related to visual stimulation, also known as "alpha blocking" or "alpha desynchronization" [Pollen and Trachtenberg, 1972; Klimesch et al., 2007], which has been proposed to reflect an idle state of the brain [Ben-Simon et al., 2008]. Moreover, it was also reported as associated with a significant reduction in the average activity in delta, theta and a significant increase in beta activity over frontal regions [Barry et al., 2007].

Together with this, neuroimaging approaches revealed the contribution of specific brain networks in the spontaneous activity of the brain at rest, such as the default mode network (DMN) [Gusnard and Raichle, 2001; Gusnard et al., 2001; Raichle and Snyder, 2007; Raichle et al., 2001], which involves

different brain regions widely distributed [Honey et al., 2009] and is most active during task-free conditions [Biswal et al., 1995; Broyd et al., 2009; De Luca et al., 2006; Fransson, 2006; Lowe et al., 1998; Mantini et al., 2007].

Interestingly, several studies reported that there is a stimulus – interaction, using different kinds of tasks [Lewis et al., 2009; Albert et al., 2009] and indicating that the resting activity level is not static, but modulated by the incoming stimuli, leading to differences in the resting state connectivity between areas involved in the task or, in general, in the neural activity of the DMN.

In line with that, our previous works showed how the Quadrato Motor Training (QMT), a whole-body motor training paradigm which involves cognitive and mental operations with the aim to improve coordination, attention and creativity [Paoletti, 2008; Ben-Soussan et al., 2013; Ben-Soussan et al., 2015], led to significant longitudinal changes in resting state spectral activity recorded in rsEEG with open eyes, and that these changes were related to behavioral measures such as creativity. In particular, in a recent study from our group (under review), successively to 6-weeks of training, an increased left frontal and right posterior alpha power were observed as compared to the baseline resting state condition [Mauro et al., under review].

Conversely, significant enhancement in the inter- and intra-hemispheric alpha (8 - 12 *Hz*) coherence was observed in the rsEEG recorded with closed eyes [Ben-Soussan et al, 2013].

Finally, using the exact low-resolution brain electromagnetic tomography (eLORETA), we were able to combine and to evaluate both spatial and EEG functional connectivity estimated through the inverse localization LORETA algorithm [Pascual-Marqui et al., 2002], which has also shown consistence in study of the neuronal resting state networks [e.g. Chen et al., 2012]. In this last study, significant changes were observed for the functional connectivity. In particular, we found that limbic and fronto-temporal alpha connectivity in the open eyes condition increased following 6 weeks, while in the case of closed eyes condition it was enhanced in occipital network only following 12-weeks of daily training [Lasaponara et al., submitted].

These findings seem to show that the QMT may have dissociable long-term effects on the functional connectivity depending on the different ways of recording of the rsEEG. Open eyes recording pointed out a faster onset of Linear Lag Connectivity (LLC) modulations that tend to decay as quickly, while closed eyes recording showed sensible effect only after the complete 3-months training.

Taken together, these results seem to show a coherent pattern in which dynamic electrophysiological measures such as coherence and functional connectivity are particularly affected by our manipulations (QMT) during the rsEEG with closed eyes. In contrast, power spectrum analysis revealed the more interesting and significant results in the rsEEG recorded with open eyes.

In this context, the first aim of the present study was to provide a direct comparison between power spectrum data related to the electrophysiological activity recorded in these two different resting state conditions, in order to provide a complete framework concerning the eventual modulations on the EEG neural activity and deepen the knowledge about the neuroplasticity effects following QMT, as well as their repercussion over different brain states.

Moreover, the second aim was to investigate not only the alpha frequency range that gave the greater results in previous studies, but the complete spectrum of the EEG differences between EC and EO conditions following 3 months of Quadrato Motor Training, using a combination of classic power spectrum analysis performed on the scalp derivation and a different approach, investigating eventual differences in the cortical generators of the oscillations of the various EEG bands, performed with eLORETA software.

2. Material and Methods

2.1. Participants

We investigated 50 healthy volunteers (27 women and 23 men, 35±5 years and 36±6years).

Inclusion criteria were: 1) age between 25 and 45 years; 2) right-handedness; 3) no medical history that might affect the EEG measures (history of traumatic injury, current or past drug or medication addiction/abuse, antidepressant medications use, recent depressive episodes); 4) absence of motor, emotional and cognitive or developmental coordination disorders; 5) negative history of previous practice of the Quadrato Motor Training.

Exclusion criteria were: 1) history of traumatic injury, previous neurosurgery, stroke, inflammatory/infective diseases of the brain; 2) co-morbidity of congenital metabolic diseases or malformations; 3) diagnosis of one histologically proven primary cancer (< 1 years); 4) Vitamin B12 deficiency, positive serology for secondary dementia (RPR/ VDRL, HIV, anti-Borrelia), abnormal

thyroid function considered significant during clinical examination; and 5) clinical evidence of depression (assessed with the Geriatric Depression Scale ≥ 14) or other psychiatric conditions, epilepsy, drugs or alcohol addiction (according to DSM IV-TR); 6) severe impairment of cognition (Mini Mental State Examination ≤ 24); 7) subjects already included in a motor activation program; 8) diagnosis of malnutrition (based on body mass index); 9) chronic inflammatory disease (e.g. Rheumatoid Arthritis) and other diseases in the acute phase; 10) hearing or visual impairment or motor deficits incompatible with the workout (according to the physician opinion); 11) treatment with hormone replacement therapy; 12) current or recent history of smoking (i.e. not smoking during the last year

From the starting number of subjects, we excluded 3 subjects because they were left-handed, 4 subjects because of white matter lesion load, 7 subjects because of MRI/EEG incomplete protocol and 2 subjects because of lack in complying motor exercise. Thus, 34 healthy right-handed subjects were selected for the EEG and behavioral analyses (20 females).

Ethics Statements and study outcomes

The ethical committee of the Università Campus Bio-Medico di Roma, Rome, Italy, approved the study (09/14 PAR ComEt CBM). The experimental protocol was designed as a controlled experimental phase I study. Data were collected in compliance with GCP (Good Clinical Practice) and following the ALCOA (Attributable, Legible, Contemporaneous, Original and Accurate) algorithm. The TREND checklist was accomplished (S1 TREND Checklist).

2.2. Procedure

In the first visit, the participants were introduced to the facilities and all procedures were explained, adequate understanding was tested and written informed consent was obtained from the participants in accordance with the declaration of Helsinki. Then several cognitive tests were assessed. Subsequently, participants underwent an EEG 20-channel EEG recording and finally performed the Quadrato Motor Exercise.

At each time point, every volunteer was also requested to show the accuracy and the completeness of the diary to the researchers as a pre-requisite to undergo next time point measurements. Participants were informed of the option to interrupt the QMT and drop-out from the study at any time for any reason including: change in the clinical status deemed incompatible with the continuation of the study; refusal to continue with the study protocol; personal needs.

The Quadrato Motor Training (QMT)

The QMT requires standing at one corner of 0.5 m × 0.5 m square and making movements in response to verbal instructions given by an audio tape recording (See Fig. 2). In the QMT there are 3 optional directions of movement. The instructions direct participants to keep the eyes focused straight ahead and hands loose at the side of the body. They were also instructed to immediately continue with the next instruction and not to stop in the case of mistakes. At each corner, there are three possible directions to move. The training thus consists of 12 possible movements (3 directions × 4 corners): 2 forward, 2 backward, 2 left, 2 right and 4 diagonals. For example, if the sequence required is 1, 2, 1, 2, 1, 2, 3, 2, 4, 3, 1…. this means moving to the first corner, then to the second, then back to the first, and so on. See Figure 1 for a graphical illustration. In this longitudinal experimental protocol, the daily training consisted of a sequence of 69 commands lasting 7 minutes. We used a movement sequence paced at a rate of an average of 0.5 Hz (similar to a slow walking rate) and instructed the participants to begin all movements with the leg closest to the center of the square.
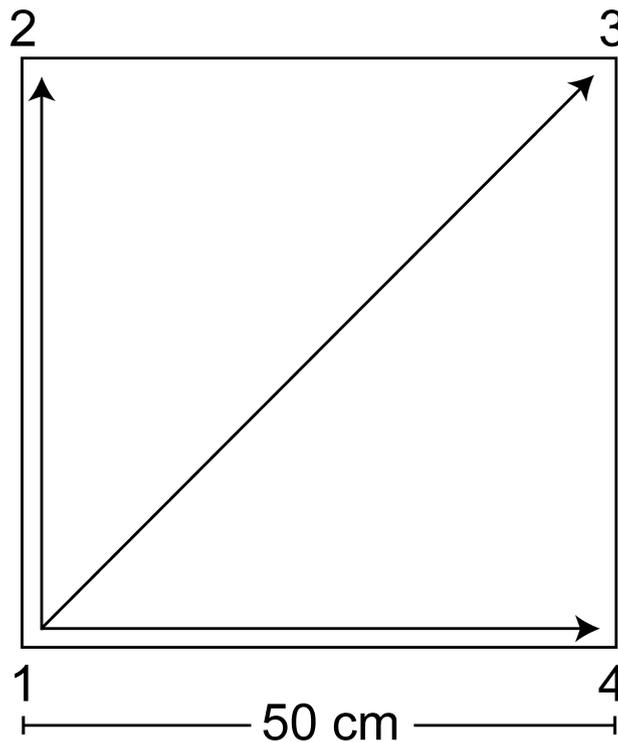
Figure 1. Graphical illustration of the Quadrato Motor training.

2.3. EEG recording and analysis

EEG was recorded in wake rest state (five minutes with eyes-closed and five minutes with eyes open) in late morning hours from 19 electrodes positioned according to the International 10–20 System (i.e., Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2) with common average reference (time constant of 0.3 s., 0.3–70 Hz filtering bandpass, MICROMED Brain Quick System). To monitor eye movements, the vertical electro-oculogram was simultaneously recorded. All data were digitized in continuous recording mode (256 Hz sampling rate). Impedances of all electrodes were kept below 5 kΩ. In order to keep constant the level of vigilance, an operator controlled on-line the subject and the EEG traces, alerting the subject any time there were signs of behavioral and ∕ or EEG drowsiness.

The EEG data pre-processing was performed via the EEGLAB [Delorme and Makeig, 2004] toolbox for MATLAB. Data were re-referenced to the average reference, low-pass filtered (cut off 45 Hz) and high-pass filtered (cut off 0.5 Hz) and then divided in 1s epochs. All trials were visually inspected for artefacts and eye movements and potentially rejected. Moreover, they were subjected to an algorithm that automatically rejected epochs when the signal exceeded by abnormal spectra (±50 dB in the 0-2 Hz band for eye movements and ±25-100 Hz in the 20-40 Hz for muscular activity), by probability (± 3 standard deviations from the mean distribution of occurrence of each trial) and by extreme values (± 70 μV).

In order to evaluate the differences in brain oscillations between the Eyes Closed (EC) and the Eyes Open (EO) conditions along the QMT, the EEG power spectra recorded at each derivation was compared statistically across subjects using a paired t test at each experimental time point (T0, T1; 33 degrees of freedom; FDR Alpha = 0,1 and 0,05 corrected for multiple comparisons, and uncorrected). This procedure led to the individuation of cortical regions of interest specifically involved in the dynamic changes induced by the QMT over time, for each band of frequency taken into consideration (δ: 1.5–6.0 Hz, θ: 6.5–8.0 Hz, α1: 8.5–10.0 Hz, α2: 10.5–12.0 Hz, β1: 12.5–18.0 Hz, β2:18.5–21.0 Hz, β3: 21.5–30.0 Hz and Ω: > 30).

2.4. Standardized Low-Resolution Brain Electromagnetic Tomography (eLORETA)

We used standardized low resolution brain electromagnetic tomography (eLORETA) to localize the generators of the scalp EEG power spectra. The eLORETA solution space is restricted to the cortical gray matter in the digitized MNI atlas with a total of 6239 voxels at 5 mm spatial resolution [Pascual-Marqui et al., 2002]. The fundamental assumption of LORETA directly relies on the neurophysiological observation of coherent firing of neighbouring cortical neurons. Cross-validation studies using simultaneous functional magnetic resonance imaging have provided evidence for a high validity of LORETA localization findings [Mulert et al., 2004 & 2005]. The eLORETA assumes that the smoothest of all activity distributions is the most plausible, and it is based on images of standardized current density. The unique property of eLORETA in contrast to the former LORETA version is that under ideal conditions, eLORETA has zero localization error [Pascual_Marqui, 2002]. One downfall of the method is that eLORETA has very low spatial resolution, and spatial resolution decreases with depth. Furthermore, it does not filter noisy measurements, so its usage is constrained to artefact-free data. We calculated tomographic eLORETA images corresponding to the estimated neuronal generators of brain activity within a given frequency range: δ (1.5–6.0 Hz), θ (6.5–8.0 Hz), $\alpha 1$ (8.5–10.0 Hz), $\alpha 2$ (10.5–12.0 Hz), $\beta 1$ (12.5–18.0 Hz), $\beta 2$ (18.5–21.0 Hz), $\beta 3$ (21.5–30.0 Hz) and Ω (> 30 Hz). A spatial over-smoothing with signal-to-noise ratio 10 was chosen for the eLORETA transformation matrix. An eLORETA image for a given subject, for some given oscillation (i.e., frequency band), is displaying the actual cortical neuronal oscillators.

Whole brain analyses were performed through the statistical tools included in the LORETA software package. Worth noticing, at variance from conventional power-spectrum analysis, statistical tests were performed on the generators, not on scalp power spectra.

The methodology used is non-parametric. It is based on estimating, via randomization, the empirical probability distribution for the max-statistic (e.g. the maximum of a t or an F statistic), under the null hypothesis. This methodology corrects for multiple testing (i.e., for the collection of tests performed for all voxels, and for all discrete frequencies). Due to the non-parametric nature of the method, its validity need not rely on any assumption of Gaussianity. The next step consists of computing the corresponding 3D cortical distribution of the electric neuronal generators (with eLORETA). eLORETA were computed for each subject, for each frequency band.

In this case, we ran a series of paired T-test with frequency scale normalization and smoothing 1, comparing the current density value in each voxel between all the experimental conditions. More specific, in each time points (i.e. T0 and T1) we performed the sequent CE > OE contrast. The significance threshold was based on a permutation test with 5000 permutations. The t-values of the comparisons between log of F-ratios, not standardized current density were plotted onto a MRI template with a scale bar indicating statistical power and color scale.

3. Results

3.1. Power spectrum results

For both the conditions (T0 and T1), the differences in EEG spectral activity between the EC and the EO conditions showed different effects according on the range of frequency considered.
Significant differences were found in the range between late Delta and Beta 2, with higher spectral activity in the EC condition, especially in the ranges Alpha 1 and 2, globally distributed all over the derivations.

Moving toward Beta 1 and Beta 2 ranges, the higher spectral activity for the EC condition was still significantly present, with a posterior and bilateral distribution of the effect, which, in the T1 condition, also involved more central derivations.

Finally, in the range from Beta 3 to Gamma, significantly higher spectral power was found in the EO condition (with higher rates of significance in the Gamma band) with a frontal distribution, left lateralized in T0 and then gradually expanding bilaterally along the second time points. See Figure 2.
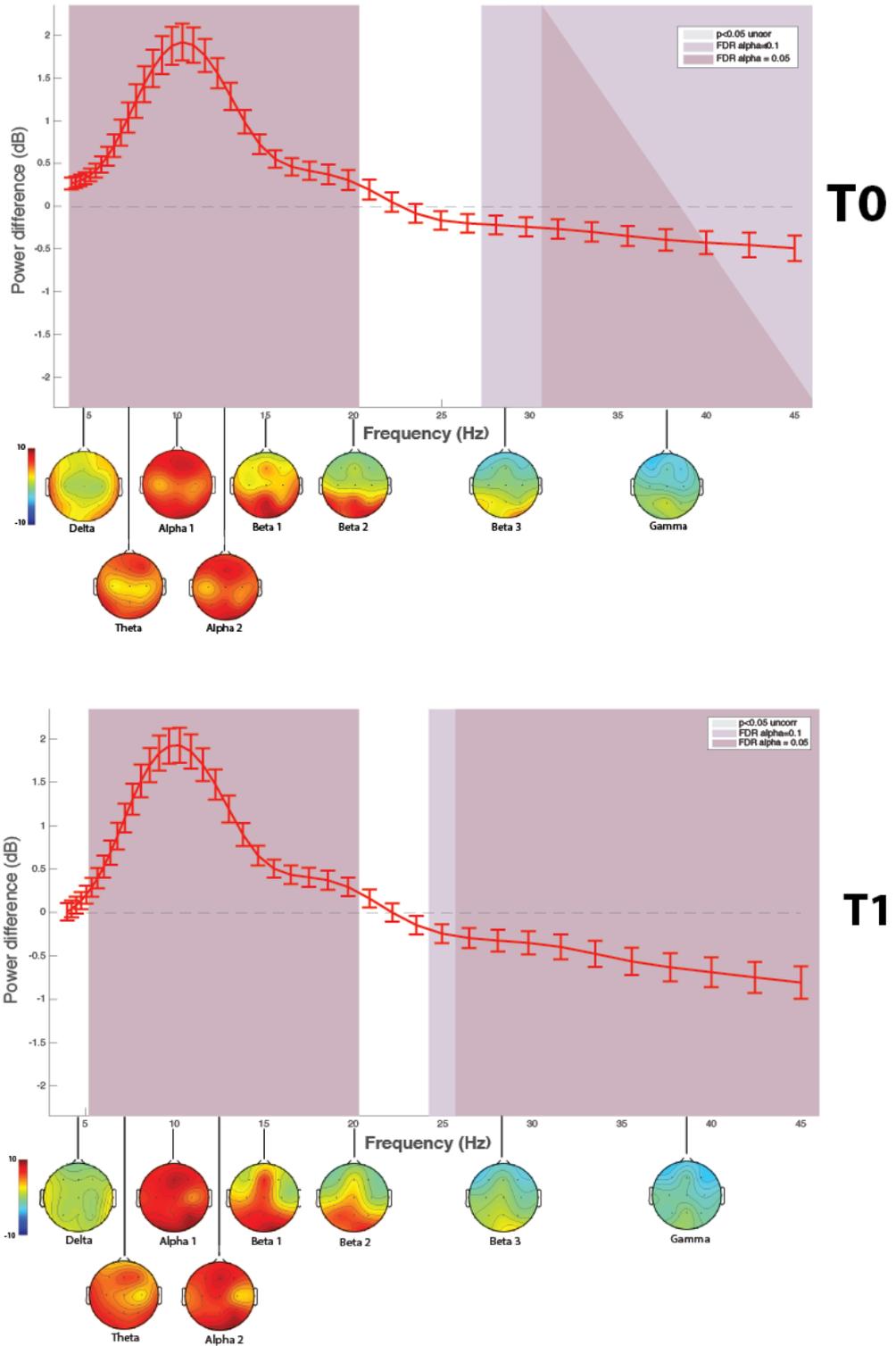
Figure 2. *Power spectrum differences between EC and EO for each frequency band, at different time points (T0, T1). Distribution of FDR corrections for spectral power t test comparisons between Eyes Closed (positive values) and Eyes Open (negative values) conditions, for both T0 (upper panel) and T1 (lower panel). In the lower section of the panels is depicted the topografic distribution of t values for the comparisons (positive values in red for EC, negative values in blue for EO), for each frequency band considered.*

3.2. eLORETA results

A cross-spectrum eLORETA analysis between log of F-ratios, not standardized current density related to EO and EC EEG bands oscillations was performed before and after a three months of daily QMT.

In the T0, this comparison pointed out a significant (see Table 1 for all T-values and p) stronger oscillation with eyes open (or equivalently, a larger number of synchronously oscillating neurons) in the β2 (18.5–21.0 Hz) and the β3 (21.5–30.0 Hz) bands respectively in the right precentral gyrus (B.A. 6; MNI coord: 10, 65 and 0) and in the right medial frontal gyrus (B.A. 10; MNI coord: 35, 40 and 15).

A different pattern of results was observed in T1, β3 shown a larger oscillation with eyes open in the superior frontal gyrus bilaterally (B.A. 10; MNI coord: -9, 65 and 20; 65 and -15) while a stronger α1 oscillation with EC as compared to the EO in the right para-hippocampal gyrus (B.A. 19; MNI coord: 25 -50 and -5) was observed.

Notably the increased α1 oscillation with closed eyes was selectively present only after three months training. See Figure 3.

	T0		T1	
	T-value	p	T-value	p
β2	1.92	< .0001	/	/
β3	2.11	< .0001	1.56	< .0001
α1	/	/	-1.7	< .0001

Table 1. *T-values and probabilities for the significant EEG bands of the comparison EC > EO in each of the two time points*
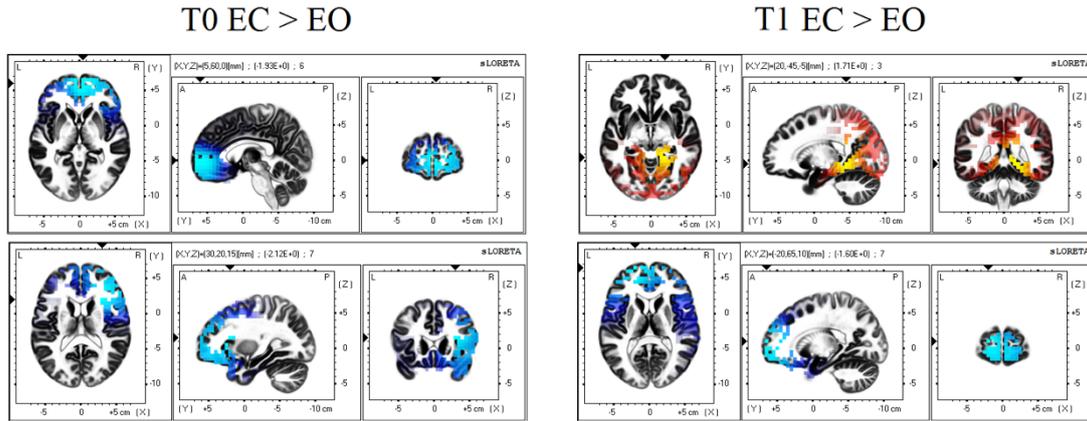

Figure 3. *Significant eLORETA T-values for the T0 and T1 time points. MNI coordinates indicates peaks of T-values, corresponding with the probabilities threshold reported in Table 1.*

4. Discussion

In the present work we investigated if the classic pattern of differences observed between rsEEG recorded with closed and open eyes could be eventually modulated by external activities and tasks able to influence the externally as well the internally oriented thoughts and attention [Harrison et al., 2008; Schneider et al., 2008].

For this reason, we choose the QMT, a recently introduced specifically-structured motor training which required dividing attention between the different motor response for producing the correct sequences of movement and the current location of the body within the Quadrato Space [Ben-Soussan et al., 2013].

The main aims of the QMT are to improve coordination, attention, and creativity [Ben-Soussan et al., 2013; Ben-Soussan et al., 2015], but most important it was also recently demonstrated that QMT increases reflectivity and reduces impulsivity and automatic responses, as requires the ability to wait for the coming command in an attentive way [Ben-Soussan et al., 2015].

At the electrophysiological level, a series of studies investigating the neural correlates of the QMT effects, revealed that QMT enhance inter- and intra-hemispheric alpha (8 - 12 Hz) coherence [Ben-Soussan et al., 2014], as well as increase left frontal and right posterior alpha power [Mauro et al., under review] in healthy participants. All together, these results showed that dynamic electrophysiological measures such as coherence and functional connectivity are particularly affected by QMT during the rsEEG with closed eyes, while power spectrum effects induced by QMT seems to be more sensitive during the rsEEG recorded with open eyes.

For this reason, we decided to compare power-spectrum, electrophysiological effects in open and closed eyes rsEEG, induced after a 12-weeks QMT training.

To this aim, we adopted two different approach: (I) in the first analysis, we performed a classic power-spectrum analysis on the entire frequency range across the 19 derivation using to record the EEG. (II) Successively, we investigated whether the significant effects found in the power-spectrum analysis were reflected in significant changes in their cortical generators estimated using the eLORETA software.

The results of the power-spectrum analysis pointed out that in both T0 and T1 the two conditions EC and EO were characterized by different patterns of activation. Specifically, higher spectral activity was reported in EC for the entire frequency band with specific topographical patterns (except for the Alpha range), together with a decrement in frontal Beta and Gamma spectral power. Moreover, QMT led to a decrease of Delta spectral power and to an expansion of the increase of Beta 1 and 2 over central derivations in the EC condition, along with an increase and bilateral expansion of Beta 3 and Gamma activity over frontal and bilateral derivations in the EO condition.

Interestingly, these results appear to be in line with what reported by Barry et al. [2007], supporting the idea that topographical changes between EC and EO indicate a processing-related activation in the eyes open condition. In particular, in agreement with previous works, here we report an enhancement of the shift from posterior to frontal Beta/Gamma from EC to EC after QMT (T1 condition), which has been usually related to activation in higher order processing, compatible with changes reported during increased mental efforts [Ray and Cole, 1985].

In general, the activity of brain networks engaged during rest has been related to introspective thoughts or planning of future responses [Raichle and Snyder, 2007] or to the active selection of the brain over previous experiences [Miall and Robertson, 2006]. In this framework, the present results can be added to our previous results indicating alpha and creativity enhancement after QMT [Mauro et al., under review] and to those indicating how tasks, in particular motor tasks, can modulate the subsequent activity within fronto-parietal resting networks, usually active during visuo-motor adaptation [Albert et al., 2009], offering a closer view over the functional differences in EO and EC conditions looking at the effects of a structured whole-body cognitive and motor training.

Moreover, eLORETA results nicely expands and complete the general pattern of results of the power spectrum, providing important information as regard to the cortical generators subtending the differential values observed in the power analysis related to EC and EO. In particular, successively to QMT, in T1 was confirmed the expansion of of Beta 3 activity moving from the right frontal areas (precentral and middle frontal gyrus, respectively) to a more diffused, bilateral cortical activity placed in the superior frontal gyrus of both right and left hemisphere. Moreover, at T1 a greater oscillation of the alpha 1 band for the EC was observed in the posterior cortex with a peak placed in the para-hippocampal gyrus. This results in particular, seems to show that both peculiar EEG bands characterizing EC (alpha synchronization) and EO (Beta activity) were positively modulated and increased after QMT. This may suggest a contribution in order to sharpen the specialization during the different EC and EO brain states, refining their specific electrophysiological characteristics [Pollen and Trachtenberg, 1972; Klimesch et al., 2000; Barry et al., 2007] and more important, their cortical generators. Worth noticing, the same source localization specifically related to EO and EC were previously reported in another study using the same software [Pascual-Marqui et al., 2014] and demonstrating a specific role of the Posterior Cingulate (PC, including also the para-hippocampal gyrus) that sends alpha activity to all other regions during EC. The increased oscillation in this specific area following QMT could be addressed as one of the main cause of the increased alpha-power observed during this condition.

Functional interactions in the brain are often studied at rest, when the activity is not biased by tasks-directed goals, showing, on the other hand, that oscillatory activity in distributed brain networks is fundamental for task representation [Ganzetti & Martini, 2013], reflecting the "off-line" processing of information after learning and short term memories consolidation [Albert et al., 2009].

In conclusion, the present results provide interesting new information about the intrinsic modulation of the electrophysiological activity of the brain and its implication for stimulus processing, looking specifically at the stimulus-rest interaction and at its variation over different kinds of resting state conditions, using a whole-body training paradigm, the QMT, which already consistently showed to elicit longitudinal effects over brain activity and behavioral indexes [Ben Soussan et al., 2013; 2015].

References

1. Albert, N. B., Robertson, E. M., & Miall, R. C. (2009). The Resting Human Brain and Motor Learning. *Current Biology*, *19*(12), 1023–1027. http://doi.org/10.1016/j.cub.2009.04.028

2. Anderson FA. Impedance plethysmography, in Encyclopedia of Medical Devices and Instrumentation. Webster JG, Editor. John Wiley & Sons, New York, 1988, 111-122.

3. Barry, R. J., Clarke, A. R., Johnstone, S. J., Magee, C. A., & Rushby, J. A. (2007). EEG differences between eyes-closed and eyes-open resting conditions. Clinical Neurophysiology, 118(12), 2765-2773.

4. Ben-Soussan T.D., Berkovich-Ohana A., & Glicksohn J., (2015). Attentional Effort, Mindfulness and Altered States of Consciousness experiences following Quadrato Motor Training. Mindfulness. DOI: 10.1007/s12671-015-0469-5.

5. Ben-Soussan, T. D., Glicksohn, J., Goldstein, A., Berkovich-Ohana, A., & Donchin, O. (2013). Into the square and out of the box: the effects of Quadrato Motor Training on creativity and alpha coherence. *PloS one, 8*(1), e55023.

6. Biswal, B., Zerrin Yetkin, F., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magnetic resonance in medicine*, *34*(4), 537-541.

7. Broyd, S. J., Demanuele, C., Debener, S., Helps, S. K., James, C. J., & Sonuga-Barke, E. J. (2009). Default-mode brain dysfunction in mental disorders: a systematic review. *Neuroscience & biobehavioral reviews*, *33*(3), 279-296.

8. Castor G, Simon J, Pilz A, Niedermark I, Klocke RK. The second derivation of the bioimpedance signal as index for successful systemic lysis of a coronary artery thrombus. In proceedins of the 14th Annual International Conference of the IEEE/EMBS, 1992, 1746-1747.

9. Chen, C., Liu, C., Huang, R., Cheng, D., Wu, H., Xu, P., ... & Luo, Y. J. (2012). Suppression of aversive memories associates with changes in early and late stages of neurocognitive processing. Neuropsychologia, 50(12), 2839-2848.

10. De Luca, M., Beckmann, C. F., De Stefano, N., Matthews, P. M., & Smith, S. M. (2006). fMRI resting state networks define distinct modes of long-distance interactions in the human brain. *Neuroimage*, *29*(4), 1359-1367.

11. Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of neuroscience methods*, *134*(1), 9-21.

12. Fransson, P. (2006). How default is the default mode of brain function?: Further evidence from intrinsic BOLD signal fluctuations. *Neuropsychologia*, *44*(14), 2836-2845.

13. Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nature Reviews Neuroscience*, *2*(10), 685-694.

14. Gusnard, D. A., Akbudak, E., Shulman, G. L., & Raichle, M. E. (2001). Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proceedings of the National Academy of Sciences*, *98*(7), 4259-4264.

15. Harrison, B. J., Pujol, J., Ortiz, H., Fornito, A., Pantelis, C., & Yücel, M. (2008). Modulation of brain resting-state networks by sad mood induction. PLoS One, 3(3), e1794.

16. Honey, C. J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J. P., Meuli, R., & Hagmann, P. (2009). Predicting human resting-state functional connectivity from structural connectivity. *Proceedings of the National Academy of Sciences*, *106*(6), 2035-2040.

17. Kauppinen PK, Hyttinen JAK, Kööbi T, Malmivuo J. Multiple lead recordings improve accuracy of bio-impedance plethysmographic technique. *Medical Engineering & Physics*, 21(5): 371-375, 1999.

18. Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: the inhibition–timing hypothesis. *Brain research reviews*, *53*(1), 63-88.

19. Lasaponara, S., Mauro, F., Paoletti, P., Carducci, F., Tombini, M., Quattrocchi, C. C., Mallio, C. A., Errante, Y., Dotan Ben-Soussan, T. (submitted). Increased alpha band functional connectivity following the Quadrato Motor Training: a longitudinal study.

20. Lewis, C. M., Baldassarre, A., Committeri, G., Romani, G. L., & Corbetta, M. (2009). Learning sculpts the spontaneous activity of the resting human brain. *Proceedings of the National Academy of Sciences*, *106*(41), 17558-17563.

21. Lowe, M. J., Mock, B. J., & Sorenson, J. A. (1998). Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. *Neuroimage*, *7*(2), 119-132.

22. Malmivuo J, Plonsey R. Bioelectromagnetism: Principles and Application of Bioelectric and Biomagnetic Fields. Oxford University Press, New York, 1995.
23. Mauro, F., Carducci, F., Tombini, M., Quattrocchi, C.C., Errante, Y., Mallio, C.A., Scarciolla, L., Ben-Soussan, T.D., Paoletti, P. Effect of the Quadrato Motor Training on creativity and EEG creativity markers: a longitudinal study. (under review).
24. Mantini, D., Perrucci, M. G., Del Gratta, C., Romani, G. L., & Corbetta, M. (2007). Electrophysiological signatures of resting state networks in the human brain. *Proceedings of the National Academy of Sciences*, *104*(32), 13170-13175.
25. Miall, R. C., & Robertson, E. M. (2006). Functional imaging: is the resting brain resting?. *Current Biology*, *16*(23), R998-R1000.
26. Mulert, C., Jäger, L., Propp, S., Karch, S., Störmann, S., Pogarell, O., ... & Hegerl, U. (2005). Sound level dependence of the primary auditory cortex: simultaneous measurement with 61-channel EEG and fMRI. Neuroimage, 28(1), 49-58.
27. Mulert, C., Jäger, L., Schmitt, R., Bussfeld, P., Pogarell, O., Möller, H. J., ... & Hegerl, U. (2004). Integration of fMRI and simultaneous EEG: towards a comprehensive understanding of localization and time-course of brain activity in target detection. Neuroimage, 22(1), 83-94.
28. Paoletti, P. (2008) Crescere nell'eccellenza. Rome: Armando Publishing.
29. Pollen, D. A., & Trachtenberg, M. C. (1972). Some problems of occipital alpha block in man. Brain Research, 41(2), 303-314.
30. Pascual-Marqui, R. D., Biscay, R. J., Bosch-Bayard, J., Lehmann, D., Kochi, K., Kinoshita, T., ... & Sadato, N. (2014). Assessing direct paths of intracortical causal information flow of oscillatory activity with the isolated effective coherence (iCoh). Frontiers in human neuroscience, 8.
31. Pascual-Marqui, R. D. (2007). Discrete, 3D distributed, linear imaging methods of electric neuronal activity. Part 1: exact, zero error localization. arXiv preprint arXiv:0710.3341.
32. Pascual-Marqui, R. D., Esslen, M., Kochi, K., & Lehmann, D. (2002). Functional mapping of electric neuronal activity with zero localization error: standardized low resolution brain electromagnetic tomography (sloreta). Methods Findings Exp Clin Pharmacol D, 24, 5-12.
33. Pascual-Marqui, R. D. (2002). Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. Methods Find Exp Clin Pharmacol, 24(Suppl D), 5-12.
34. Raichle, M. E., & Snyder, A. Z. (2007). A default mode of brain function: a brief history of an evolving idea. *Neuroimage*, *37*(4), 1083-1090.
35. Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences*, *98*(2), 676-682.
36. Ray, W. J., & Cole, H. W. (1985). EEG activity during cognitive processing: influence of attentional factors. *International Journal of Psychophysiology*, *3*(1), 43-48.
37. Schneider, F., Bermpohl, F., Heinzel, A., Rotte, M., Walter, M., Tempelmann, C., ... & Northoff, G. (2008). The resting brain and our self: self-relatedness modulates resting state neural activity in cortical midline structures. *Neuroscience*, *157*(1), 120-131.