Long-lasting changes in brain activation induced by a single REAC technology pulse in Wi-Fi bands. Randomized double-blind fMRI qualitative study

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The aim of this randomized double-blind study was to evaluate in healthy adult subjects, with functional magnetic resonance imaging (fMRI), long lasting changes in brain activation patterns following administration of a single, 250 milliseconds pulse emitted with radio-electric asymmetric conveyer (REAC) technology in the Wi-Fi bands. The REAC impulse was not administered during the scan, but after this, according to a protocol that has previously been demonstrated to be effective in improving motor control and postural balance, in healthy subjects and patients. The study was conducted on 33 healthy volunteers, performed with a 1.5 T unit while operating a motor block task involving cyclical and alternating flexion and extension of one leg. Subsequently subjects were randomly divided into a treatment and a sham treatment control group. Repeated fMRI examinations were performed following the administration of the REAC pulse or sham treatment. The Treated group showed cerebellar and ponto-mesencephalic activation components that disappeared in the second scan, while these activation components persisted in the Sham group. This study shows that a very weak signal, such as 250 milliseconds Wi-Fi pulse, administered with REAC technology, could lead to lasting effects on brain activity modification.

The Radio electric asymmetric conveyer (REAC) is a new technology for bio and neuro modulation. The REAC technology is based on the production of weak radiofrequency electromagnetic fields in the Wi-Fi bands (2.4–5.8 GHz) in order to generate a flow of electric micro currents in the body of the subject being treated. This current flow can be focused, as required, on specific areas through a probe-conveyor, peculiar of the REAC technology. In previous functional magnetic resonance imaging (fMRI) studies1,2 on healthy subjects, brain activity has been shown to be sensitive to modulation by REAC treatment administered according to a protocol named Neuro Postural Optimization (NPO), which has been proven to be effective in the correction of motor disorders (Fig. 1). In fact REAC-NPO is thought to modulate and optimize motor2 and postural strategies3. Also in patients with advanced Alzheimer’s Disease4, REAC-NPO improved gait and number of steps3. Cumulated experience derived from other studies supports the feasibility, safety and efficacy of this brain neuromodulation technique.

Results

Two subjects, one of NPO-Treated group and one of Sham group, were excluded during statistical analysis due to the presence of artifacts that degraded the functional images. The average patterns of activation areas before treatment were similar in the NPO-Treated and Sham groups in that they were concordant with regard to the topography of the areas activated5. This similarity was expected given that the subjects in the two groups were performing an identical motor task. However, slight variations, statistically non-significant, between the groups with respect to the conspicuity and extent of activation were observed (Fig. 2a vs.2b). Compared to the group-averaged activation patterns before REAC-NPO or sham treatment, those recorded for the two groups after NPO-REAC or sham treatment showed a decrease in the magnitude of activation, a reduction in the conspicuity of the activated areas, and a disappearance of the thalamic activation component6,7 (Figs. 3a vs.3b). These changes were more marked in the NPO-treated group than in the Sham group. Furthermore, the cerebellar and ponto-
mesencephalic activation components that were present in the NPO-
Treated group pretreatment images (Figs. 4a), were completely
absent in the NPO-treated post treatment images7. (Figs. 4b) This
phenomenon was not observed when in the Sham group (Figs. 4c, d).

**Discussion**

The present randomized double-blind fMRI qualitative study,
although it was conducted on 33 patients, could still be considered
as a preliminary study. We chose to perform a double-blind study in
order to avoid any form of conditioning of the experimenters and of
the subjects. Since it was important to verify that the results could be
observed regardless of variables like sex or age, we chose a simple
randomization instead of a stratified randomization sampling.
Consequently we accepted the risk of a numerical imbalance of the
group sizes, since the essential aim of the study was the intra-group
comparison of the pre- and post-procedure fMRI results.

The clinical results from previous studies on healthy subjects1,2,
neurological patients3 and subjects with advanced Alzheimer’s dis-
ase4 seem to suggest the implementation of the same mechanism
that we observe with fMRI after REAC-NPO to improve balance and
gait. In this study, in both groups the post-treatment phase fMRI
scans showed a reduction in the extension and in degree of activation
in those areas activated during the leg motor task with respect to the
first, pre-treatment phase scans.

As regards the sham group, one possible explanation of the
decrease and change of activation in the parietal cortex and thalamus
at the second scan, compared to the first scan, may be related to
motor learning.

These reductions in activation were more pronounced in the
REAC-NPO-treated group than in the Sham group. The most salient
qualitative difference observed between the groups was that the
REAC-NPO-treated group showed a disappearance of cerebellar

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**Figure 1** | Study design overview. (a) Initial assessment of functional dysmetria (FD). (b) Pre REAC-NPO/Sham scans during performance of the motor
task. (c) Administration of REAC-NPO/Sham. (d) Post REAC-NPO/Sham scans during performance of the motor task. (e) Post-REAC-NPO
assessment of FD. (f) Post-Sham assessment of FD. A.C. prepared figure 1.

**Figure 2** | The average patterns of activation areas before treatment were similar in the NPO-Treated (a) and Sham (b) groups. Slight variations
observed are statistically non-significant between the groups with respect to the conspicuity and extent of activation.
and ponto-mesencephalic activation components following REAC-NPO, while these activation components persisted in the Sham group. These findings show that after REAC-NPO treatment, we obtain a reduction of the brain areas involved in the movement motor control. These results can be interpreted as a functional optimization of the brain structures that govern the coordination of motor control and balance. It is still unclear what are the mechanisms that make the effects of a single REAC-NPO treatment very stable over time, as verified in several clinical trials. Indeed, it is precisely this characteristic of long duration of the effect of REAC-NPO, which allowed us to carry out the administration of the treatment not during the fMRI scanning phase, as it happens in all other studies, conducted with different techniques, but after this. Thanks precisely to the long duration of the effects of REAC-NPO, which greatly exceed the fMRI temporal resolution, we could then capture the effects of REAC-NPO treatment here showed. Probably the single REAC-NPO treatment could induce a neuromodulation of brain electrical activity and metabolism. Of course, as this study investigates a new phenomenology in the induction of neurological mechanisms in motor control and balance improvement, further studies will be needed.

Methods
Study cohort and study design. A total of 33 healthy, unpaid volunteers (19 females, 14 males), ranging in age from 19 to 54 years old (mean, 32.4 years) were recruited to participate in this double-blind randomized study. We chose to perform a double-blind study in order to avoid any form of conditioning of the experimenters and of the subjects, as the double blind tests are designed primarily to eliminate all the parameters conditioning the results.

We chose the simple randomization, since we believed the results should not be influenced by either the sex or age. We accepted the risk of a numerical imbalance of the group sizes, since the essential aim of the study was the intra-group comparison of the pre- and post-procedure fMRI results.

Before being subjected to the pre-treatment fMRI assessment, all subjects were investigated for the presence of functional dysmetria (Fig. 1a), so that at the end of fMRI examinations we could verify the clinical response to treatment in subjects treated compared to sham (Fig. 1c–f).

All subjects underwent a pre-treatment brain fMRI examination while performing a motor task already used in a previous study (Fig. 1b). After the pre-treatment fMRI assessment of all the patients enrolled, a staff member allocated each patient by coin-tossing randomization, assigning subjects to the REAC-NPO treatment (NPO-Treated) group or to the sham treatment control group (Sham). The randomization procedure placed 20 subjects (15 females, 5 males) in the NPO-Treated group and 13 subjects (4 females, 9 males) in the Sham group. Then a different staff member administered the therapy, unaware if he was performing the treatment or sham. Subjects belonging to the NPO-Treated group were treated with our previously validated NPO-REAC procedure (Fig. 1c), and Sham group subjects received a sham treatment. For the sham treatment, we followed the same procedures that were followed for the NPO-Treated subjects, except that the REAC device was not active. After the treatment phase, all subjects, after centering sequences, received a second fMRI examination while performing the same motor task (Fig. 1d). Neither the subjects nor the radiologist nor those who have examined the data were aware of which subjects were REAC treated and which ones were Sham treated. The timing between the REAC treatment and the post-treatment fMRI scan was 20 minutes.

This study was performed in accordance with the Helsinki Declaration. The work has been approved by the appropriate ethical committees related to the institution in which it was performed and subjects gave informed consent to the work. The clinical trial has been registered at Primary Registry Australian New Zealand Clinical Trials Registry with the Trials ID number ACTRN12611000366954 (Registration Title:...
Effect of a single REAC pulse on brain activity in healthy volunteers: fMRI double blind randomized pilot study.

REAC technology and treatment. It is known that electromagnetic fields interacting with tissues can induce currents in them, which may also generate therapeutic effects. In neurological ambit, TMS is the most widely used technology7. TMS involves the administration to the scalp of a short (~200 ms) and powerful (0.2 to 4.0 T) magnetic pulse through a coil. This magnetic pulse induces in the cortical surface below the coil an electric transient current, which causes the depolarization of the cell membranes and the transinaptic depolarization of the population of cortical neurons.

The effects of TMS single pulse on the neural activity are short-term, up to about 200 ms. TMS may also be administered with pulse trains. This mode of administration is called repetitive TMS (rTMS). The effects of rTMS persist longer than the single-TMS pulse, up to a few minutes1,2.

TMS and REAC technology have in common only the fact that both induce currents in brain tissue, but the differences between these technologies are substantial. In fact, the operating diagram of the REAC technology can be summarized as follows.

The REAC technology generates an emission of microwaves (2.4 or 5.8 GHz) of very weak intensity (about 2 mW at the emitter). Solely thanks to the converter (asymmetric probe) of the REAC technology, this emission interacts with the biological tissues of the human body. This interaction generates, also in deep tissues, radiofrequency micro-currents, variables oriented upon the molecular characteristics of the tissues. The sum of these radiofrequency micro-currents gives rise to a resulting micro current which, concentrated by the converter-probe of the device, exerts its therapeutic effect.

In the brain, the REAC technology has no limits in the degree of action, unlike TMS. Preliminary works and a diagnostic clinical experience show that single pulse REAC-NPO determines long-term effects. The persistence of these effects can be easily controlled by the stability of correction of the functional dynamics.

The REAC technology has two main fields of application, neuromodulation and biomodulation. In the context of neuromodulation specific REAC treatments have proven to be effective in treating various neuropsychiatric disorders10-13.

Motor task. Given the physical constraints of fMRI examination, and according to the aim of evaluating the brain areas involved in the complex movements in walking, we used a motor task which simulates walking. The validity of this motor task has already been tested in a preliminary study6. The subjects performed a simple block design consisting of a 30-s-long knee movement task alternating with a 30-s-long rest, with the subject lying in a supine position (Fig. 1b and 1d). Each subject performed 30 motor task blocks during each scan. We specifically instructed the participants to execute the motor task in a slow but fluid motion such that the moving foot remained in contact with the MR scanner bed.

Image acquisition, Image processing and statistical analysis. Because the purpose of this randomized double blind study is to verify the data obtained in the preliminary study6, we used the same procedures of image acquisition, image processing and statistical analysis.

Brain fMRI was performed with a 1.5 T unit (Philips Intera NT, The Netherlands), shown in Figure 1B. The survey was obtained with sequences of centering axial, sagittal, and coronal planes. Volumetric sequences with T1-weighted and T2-weighted gradient echo sequence were oriented upon these planes. The total duration of the fMRI acquisition, conducted while the subject performed the motor task, was about 40 minutes. Two radiologists who were not present for the REAC-NPO treatments performed the scans.

Acquired DICOM images were sent to a computer running on a LINUX operating system and then exported as compressed neuroimaging informatics technology initiative (NIFTI) files. The NIFTI files were then processed using fMRI expert analysis tool (FEAT) software in the functional MRI of the brain (FMRIB) software library (FSL). Two radiologists performed the first-level statistical analysis concurrently.

Brain tissue was isolated from surrounding tissues using the Brain Extraction Tool (BET) in the FSL. The MCFLIRT Motion Correction tool was used for excluding “activations” caused by head movements.

The output was then processed with FMRIB’s Improved Linear Modeling (FILM) tool in accordance with the block diagram of the study and taking into account the spatial parameters of the head motion detected by the MCFLIRT tool. A high-pass filter was used to adding the temporal derivative of the paradigm to the model. Spatial smoothing using a Gaussian kernel of FWHM 8.0 mm was applied. The results were registered with FMRIB’s Linear Image Registration Tool (FLIRT).

Activation images were superimposed onto template image from the Montreal Neurological Institute provided with FSL (MN1152).

1. Rinaldi, S., Fontani, V. & Castagna, A. Brain activity modification produced by a single radioelectric asymmetric brain stimulation pulse a new tool for neuropsychiatric treatments. Preliminary fMRI study. Neurophysiopath Dis Treat 7, 649–654, doi:10.2147/NDT.S26123 (2011).

2. Mura, M., Castagna, A., Fontani, V. & Rinaldi, S. Preliminary fMRI study of neuropsychological optimization with a noninvasive asymmetric radioelectric brain stimulation protocol in functional dysmetria. Neuropsychiatric Disease and Treatment 8, 149–154, doi:10.2147/NDT.S29971 (2012).

3. Fontani, V., Rinaldi, S., Castagna, A. & Margotti, M. L. Noninvasive asymmetric voice transmission brain stimulation treatment improves balance in individuals up to 65 suffering from neurological diseases: pilot study. Ther Clin Risk Manag 8, 73–78, doi:10.2147/TCRM.S28812 (2012).

4. Olazaran, J. et al. Motor Effects of REAC in Advanced Alzheimer’s Disease: Results From a Pilot Trial. J Alzheimers Dis 10, doi:10.3233/JAD-130077 (2013).

5. Deber, M. P., Ibanez, V., Sadato, N. & Hallett, M. Cerebral structures participating in motor preparation in humans: a positron emission tomography study. J Neurophysiol 75, 221–247 (1996).

6. Delia-Maggiore, V., Malfait, N., Ostry, D. J. & Pau, T. Stimulation of the posterior parietal cortex interferes with arm trajectory adjustments during the learning of new dynamics. J Neurosci 24, 9971–9976, doi:10.1523/jneurosci.24-44-9971 (2004).

7. Jueptner, M. & Weiller, C. A review of differences between basal ganglia and cerebellar control of movements as revealed by functional imaging studies. Brain 121 (Pt 8), 1437–1449 (1998).

8. Bohning, D. E. et al. BOLD-f MRI response to single-pulse transcranial magnetic stimulation (TMS). J Mag Reson Imaging 11, 569–574 (2000).

9. Thut, G. et al. Effects of single-pulse transcranial magnetic stimulation (TMS) on functional brain activity: a combined event-related TMS and evoked potential study. Clin Neurophysiol 114, 2073–2080 (2003).

10. Wagner, T., Rushmore, J., Eden, U. & Valero-Cabre, A. Biophysical foundations underlying TMS: setting the stage for an effective use of neurostimulation in the cognitive neurosciences. Cortex 45, 1025–1034, doi:10.1016/j.cortex.2008.10.002 (2009).

11. d’Alfonso, A. A., van Honk, J., Hermans, E., Postma, A. & de Haan, E. H. Laterality effects in selective attention to threat after repetitive transcranial magnetic stimulation at the prefrontal cortex in female subjects. Neurosci Lett 280, 190–195 (2000).

12. Thut, G., Niestel, A. & Pascual-Leone, A. Dorsal posterior parietal rTMS affects voluntary orienting of visuospatial attention. Cereb Cortex 15, 628–638, doi:10.1093/cercor/bhh164 (2005).

13. Rinaldi, S., Fontani, V., Aravagl, L. & Mannu, P. Psychometric evaluation of a radio electric auricular treatment for stress related disorders: a double-blind, placebo-controlled clinical pilot study. Health and Quality of Life Outcomes 8, doi:10.1186/1477-7525-8-31 (2010).

14. Rinaldi, S. et al. A new approach on stress-related depression & anxiety: Neuro-Psycho-Physical-Optimization with Radio Electric Asymmetric-Convoyer. Indian J Med Res 132, 189–194 (2010).

15. Fontani, V., Mannu, P., Castagna, A. & Rinaldi, S. Social anxiety disorder: radio electric asymmetric conveyor brain stimulation versus sertraline. Patient Prefer Adherence 5, 581–586, doi:10.2147/PPA.S27409 (2011).

16. Fontani, V. et al. Noninvasive radioelectric asymmetric brain stimulation in the treatment of stress-related pain and physical problems: psychometric evaluation in a randomized, single-blind placebo-controlled, naturalistic study. Int J Gen Med 4, 681–686, doi:10.2147/IJGM.S24628 (2011).

17. Mannu, P., Rinaldi, S., Fontani, V. & Castagna, A. Radio electric asymmetric brain stimulation in the treatment of behavioral and psychiatric symptoms in Alzheimer disease. Clin Interv Ageing 6, 207–211, doi:10.2147/CIA.S23394 cia-6-207 (2011).

18. Mannu, P., Rinaldi, S., Fontani, V. & Castagna, A. Long-term treatment of bipolar disorder with a radioelectric asymmetric conveyor. Neuropsychiatr Dis Treat 7, 373–379, doi:10.2147/NDT.S22007 ndt-7-373 (2011).

19. Mannu, P., Rinaldi, S., Fontani, V., Castagna, A. & Margotti, M. L. Noninvasive brain stimulation by radioelectric asymmetric conveyor in the treatment of agoraphobia: open-label, naturalistic study. Patient Prefer Adherence 5, 575–580, doi:10.2147/PPA.S26594 (2011).

20. Oliveri, E. B. et al. Radioelectric brain stimulation in the treatment of generalized anxiety disorder with comorbid major depression in a psychiatric hospital: a pilot study. Neuropsychiatr Dis Treat 7, 449–455, doi:10.2147/NDT.S23420 ndt-7-449 (2011).

21. Rinaldi, S. et al. Stress-related psycho-physiological disorders: randomized single blind placebo controlled naturalistic study of psychometric evaluation using a radio electric asymmetric treatment. Health and Quality of Life Outcomes 9, 54, doi:10.1186/1477-7525-9-54 (2011).

Acknowledgments
We would like to thank the technical staff of Diagnostic Imaging Service at Azienda Ospedaliero Universitaria in Cagliari for their assistance.

Author contributions
S.R. and V.F. invented REAC, developed the experimental design and wrote the manuscript, M.M., conceived and executed most of the experimental plan, wrote the manuscript and
prepared figures 2–4. A.C. performed the experiments and prepared figures 1. All authors reviewed the manuscript.

Additional information
Competing financial interests: Yes there is potential Competing Interest as SR and VF are the inventors of the Radio Electric Asymmetric Convener technology.

How to cite this article: Rinaldi, S., Mura, M., Castagna, A. & Fontani, V. Long-lasting changes in brain activation induced by a single REAC technology pulse in Wi-Fi bands. Randomized double-blind fMRI qualitative study. Sci. Rep. 4, 5668; DOI:10.1038/srep05668 (2014).

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