Neuropsychiatric Disease and Treatment

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ORIGINAL RESEARCH

Preliminary pilot fMRI study of neuropostural optimization with a noninvasive asymmetric radioelectric brain stimulation protocol in functional dysmetria

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment
3 April 2012
Number of times this article has been viewed

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Purpose: This study assessed changes in functional dysmetria (FD) and in brain activation observable by functional magnetic resonance imaging (fMRI) during a leg flexion-extension motor task following brain stimulation with a single radioelectric asymmetric conveyer (REAC) pulse, according to the precisely defined neuropostural optimization (NPO) protocol.

Population and methods: Ten healthy volunteers were assessed using fMRI conducted during a simple motor task before and immediately after delivery of a single REAC-NPO pulse. The motor task consisted of a flexion-extension movement of the legs with the knees bent. FD signs and brain activation patterns were compared before and after REAC-NPO.

Results: A single 250-millisecond REAC-NPO treatment alleviated FD, as evidenced by patellar asymmetry during a sit-up motion, and modulated activity patterns in the brain, particularly in the cerebellum, during the performance of the motor task.

Conclusion: Activity in brain areas involved in motor control and coordination, including the cerebellum, is altered by administration of a REAC-NPO treatment and this effect is accompanied by an alleviation of FD.

Keywords: motor behavior, motor control, cerebellum, dysmetria, functional dysmetria, fluctuating asymmetry

Introduction

Many individuals, in the absence of organic injuries or orthopedic pathology, show a slight misalignment of body segments.[1,2] This misalignment is associated with detectable asymmetries in the tonic and phasic activation of symmetrical muscular groups in the lower limbs that produce a stable misalignment of one's left and right patellar margins[1] during motions that are intended to be symmetrical, such as moving in a sit-up motion from a supine to a sitting position.[2] This phenomenon, which we call functional dysmetria[3] (FD), may be related to the effects of neuropsychomotor attitude on postural control and may be the consequence of an adaptation to environmental stress[4–11] in animals[12–14] as well as humans.[15–19] As for finger-to-nose dysmetria, FD is difficult to evaluate as an absolute measurement.[20] Therefore, the evaluation of FD must be made by medical experts and consists of observation of the presence or absence of FD. In assessing FD, a specific caliper specially designed for this type of evaluation[21] (Dismetrometro, ASMED, Florence Italy) may be used. The radioelectric asymmetric conveyer REAC[22,23] is an innovative medical device originally designed to use the effects produced by the interaction between the electromagnetic field of the human body and those produced

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by the instrument. REAC is an innovative technology for biostimulation and bioenhancement that uses weak radio-electric fields to modulate brain activity. REAC treatment has previously been reported to ameliorate several stress-related disorders,[24–27] depression,[26,28,29] anxiety,[26,29] bipolar disorders,[30] some forms of dementia,[31] and impaired motor control.[32,33] In a recent study, we examined the effects of REAC administered according to a precisely defined neuro-postural optimization[3] (NPO) protocol on brain activation patterns during a finger tapping motor task. We found that changes in activity patterns in motor cerebral and cerebellar regions were evident following the REAC-NPO treatment.[34]

The aim of the present preliminary study was to examine whether the REAC-NPO treatment that was previously shown[34] to affect brain activity patterns in motor regions during the aforementioned finger tapping task would affect FD evident during a lower limb motor task in which subjects are asked to perform a bilateral flexion-extension movement of the legs, bending the legs at the knees. Based on our clinical observations[2,3] of improvements in balance and coordination following REAC-NPO in our patients, we hypothesized that the REAC-NPO treatment would reduce FD signs in the present experimental study group.

Material and methods

Study population

Our study was designed in accordance with the Helsinki Declaration. Each participant gave signed informed consent to participate in the study, which is registered in the Australian New Zealand Clinical Trial Registry (ACTRN12611000366954). Physically active, right-handed students who regularly engaged in running were recruited to ensure a cohort of subjects in good health, particularly with respect to motor performance ability. After screening ten volunteers for FD, a total of ten healthy graduate students (six females, four males), ranging in age from 25–32 years (mean, 28 years), were confirmed by two clinicians to show FD and volunteered to participate in this study without financial compensation. FD was analyzed by two expert clinicians as volunteers moved from a supine to a sitting position on a rigid surface. This action reveals the presence of FD as a misalignment of the patella (red line in Figure 1A).

Study design

As summarized in Figure 1, the volunteers were subjected to two FD assessments and two functional magnetic resonance imaging (fMRI) scans. Before REAC-NPO, each subject was assessed for FD as described above (Figure 1A) and then scanned while performing the alternating leg flexion-extension motor task described below (Figure 1B). Immediately following the scan, the subject was brought to a designated treatment room for delivery of the REAC pulse (Figure 1C). Forty minutes after the REAC-NPO, the subject was brought back to the magnet room and scanned while performing the alternating leg flexion-extension motor task, as described below (Figure 1D). Following the second scan, a post REAC-NPO assessment was performed (Figure 1E).

Motor task

The motor task consisted of a simple "block" of leg-bending movements with alternating flexion and extension of the knee with the subject lying in a supine position (Figure 1B). Within each block, there was 30 seconds of cyclical movement followed by a 30-second rest period. Each subject performed 30 blocks of the motor task during each scan.

REAC-NPO

A Convogliatore di Radianza Modulante REAC instrument (ASMED, Florence, Italy) specific for noninvasive brain stimulation techniques was used in this study. The REAC-NPO protocol used consisted of a single 250-millisecond radiofrequency burst administered at 5.8 GHz. The REAC probe is placed at the level of the scapha[28,32] when the radiofrequency pulse is delivered (Figure 1C). The REAC procedure is painless, and no adverse effects from its use have been reported. The density of the radio-electric current flowing to the subject (150 cm from the emitter) during the single radiofrequency burst is 7 $\mu A/cm^2$ and the electromagnetic field surrounding the device is approximately 20 $\mu W/m^2$.

Image acquisition

Brain fMRI was performed with a high-field unit (1.5 T 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 gradient echo T1 (3D TFE; TR = 13, TE = 3, FA = 30) and T2 (EPI-FFE; TR = 3000, TE = 50, FA = 90)) were oriented upon these planes. The total duration of the fMRI acquisition, conducted while the subject performed the alternating leg flexion-extension motor task, was about 40 minutes. Two radiologists who were not present for the REAC-NPO treatments performed the scans.

Image processing

Acquired DICOM images were sent to a computer running on a LINUX operating system and then exported as com-

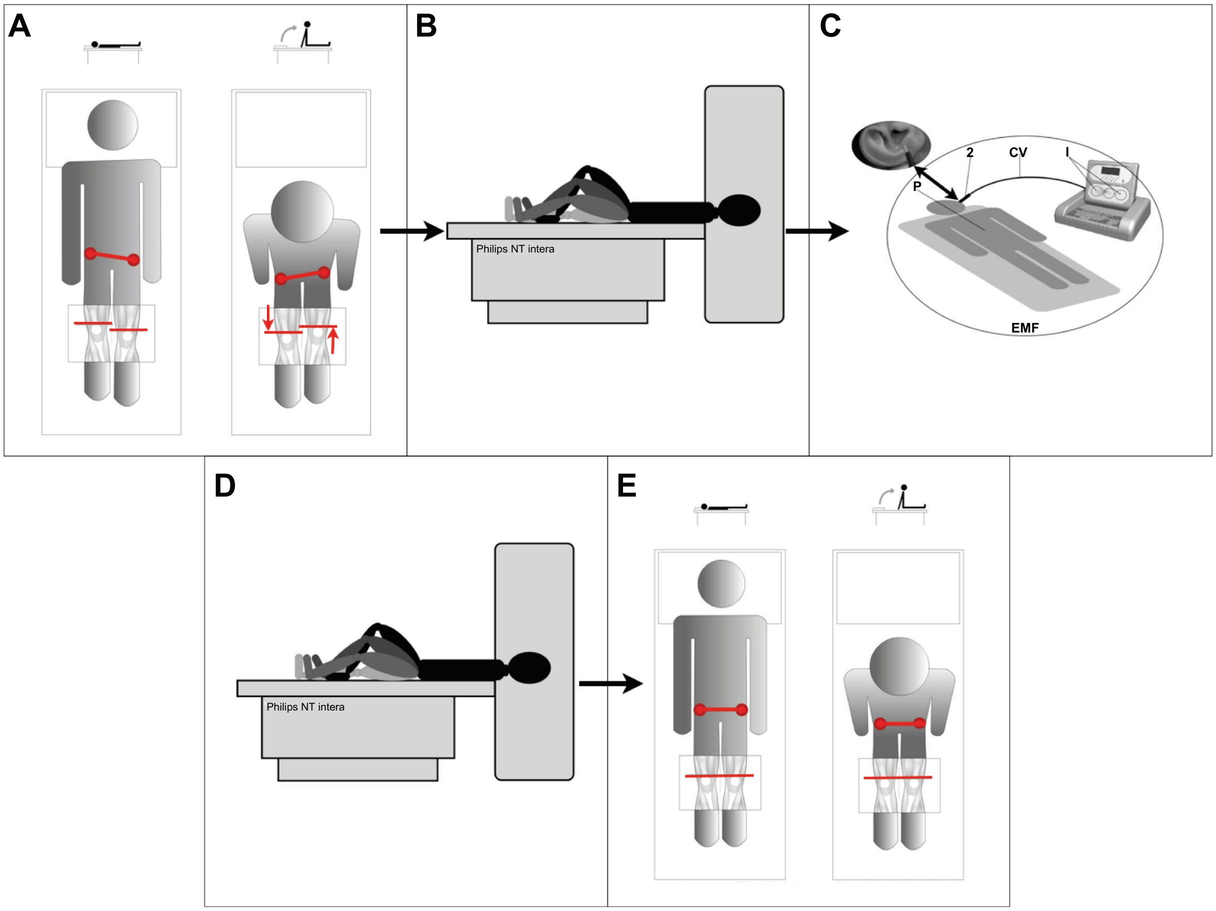

Figure 1 Study design overview. (**A**) Initial assessment of functional dysmetria (FD). (**B**) Pre radio-electric asymmetric conveyer neuro-postural optimization (REAC-NPO) scans during performance of the motor task. (**C**) Administration of REAC-NPO. (**D**) Post REAC-NPO scans during performance of the motor task. (**E**) Post-REAC-NPO assessment of FD.

pressed NIFTI files. The NIFTI files were then processed using FEAT (fMRI Expert Analysis Tool) software in the 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 to correct for misalignment due to subjects' inadvertent movements using an algorithm based on the FLIRT technique of intra- and intermodal brain image registration. 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 remove low-frequency artifacts. The results were coregistered (ie, the different sessions were registered to each other with FLIRT).

Statistical analysis

A t-test was performed for the statistical analysis. The relative Z statistic image was designated with a Z-threshold of 4.6 to show which clusters were activated significantly ($P = 0.05$). The activation images were rendered with a pseudocolor scale (Z value range, 4.6–9) and then superimposed onto a standard brain template. To assess inter-subject and inter-group variance and average activation within each phase of the experiment (before and after REAC-NPO), the output of the first-level statistical analysis was processed using FMRIB's Local Analysis of Mixed Effects algorithm, which eliminates outlier data. An arbitrary Z-threshold of 2.3 was set to enable rendering in a pseudocolor scale using a contiguous-clusters technique (significance level $P = 0.05$). Activation images were superimposed onto MN 1–152 standard brain atlas template images.

Results

The FD (evidenced by misalignment of the patellae during a sit-up movement) observed before REAC-NPO treatment was alleviated in all ten subjects at the time of the second, post REAC-NPO fMRI scan. That is, two expert clinicians reported that the subjects showed proper alignment of the patellae at the second scan (see Figure 1E). Due to the presence of artifacts that degraded the functional images, one subject was excluded from our second-level statistical analysis. The averaged fMRI datasets from the remaining nine subjects before and after REAC-NPO are illustrated in Figure 2. In particular, note that there was markedly less activation in motor cortical areas, disappearance of right thalamic activation, and reduced activation in the cerebellar vermis and pontomesencephalic regions in the post REAC-NPO averaged images (Figure 2A) relative to the pre REAC-NPO averaged images (Figure 2B).

Discussion

The current study showed that a 250-millisecond REAC-NPO pulse was able to produce changes in brain activity that were apparent 40 minutes after delivery of the REAC stimulation. This observation implies there are stable changes in brain activation patterns, including activation of brain areas involved in motor control. Additionally, following the REAC-NPO treatment, we observed improved patellar symmetry when subjects were asked to perform a sit-up motion, indicating they experienced a concomitant amelioration of FD. We suggest that the presently observed reduction in FD may be due to brain activity changes enabling a more efficient motor control and motor strategy,[35] similar to that described following other brain stimulation techniques.[36] The modulation of cerebellar function is the most important finding of this study, considering the importance of the cerebellum in motor control.[37–40] Moreover, there is growing evidence implicating the cerebellum in stress-influenced affective[41] and cognitive[42–44] functions.

Interestingly, numerous studies have related stress to various forms of dysmetria, including motor dysmetria and behavioral and cognitive dysmetria phenomena such as cognitive dysmetria,[45,46] dysmetria of thought,[47–50] and cerebellar cognitive affective syndrome.[48,51–53] These forms of dysmetria do not appear to result from any anatomical or physiological lesion, but rather seem to reflect a cerebellar dysfunction.[47,50] Hence, FD may be the result of dysfunctional adaptive phenomena that involve the complex interrelationships between cerebellar, cerebral motor, cognitive, emotional, and behavioral functions. Since in our clinical experience the positive effects of REAC-NPO on coordination and FD tend to persist for long periods of time, even years,[3] we have an interest in examining the potential of REAC-NPO for remodeling cerebellar activation related to coordination and precision of movement. Additional research is needed to delineate the physiological mechanisms underlying the establishment and alleviation of FD. Furthermore, longer-term controlled studies are needed to elucidate the long-term stability of changes in the brain activation pattern and FD alleviation observed following REAC-NPO.

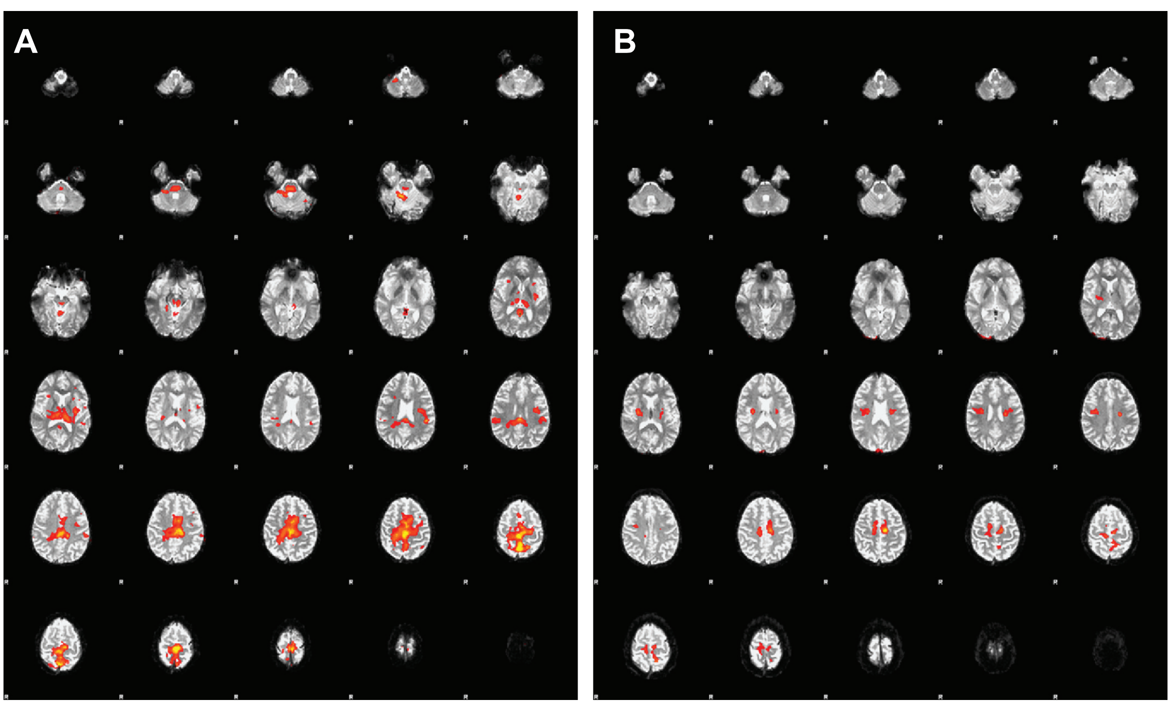

Figure 2 Average of functional magnetic resonance imaging (fMRI) scans from nine subjects before (**A**) and after (**B**) radioelectric asymmetric conveyer neuro-postural optimization (REAC-NPO).

Conclusions

REAC-NPO may be useful to correct FD. Correction of FD may be particularly helpful in the rehabilitation of patients showing FD in addition to a motor physiological pathology, as improved coordination may facilitate recovery. Additional studies to compare the brain activities of an experimental stimulation group with those of a sham stimulation group are needed.

Acknowledgments

We would like to thank the technical staff of Diagnostic Imaging Service at Azienda Ospedaliero Universitaria in Cagliari for their assistance and Dr Francesco Sias, MD for his collaboration. The Italian Society of Neuro Psycho Physical Optimization financially supported this study.

Disclosure

Salvatore Rinaldi and Vania Fontani are the inventors of the Radio-Electric Asymmetric Conveyer.

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