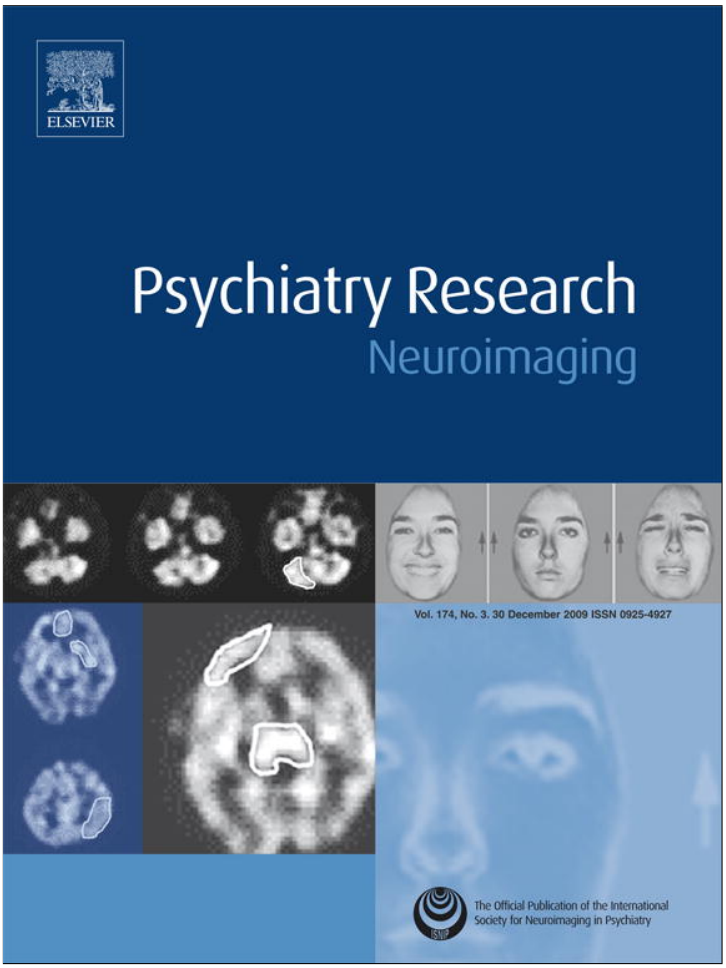

Psychiatry Research: Neuroimaging 174 (2009) 231–239

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Effect of a psychoneurotherapy on brain electromagnetic tomography in individuals with major depressive disorder

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ARTICLE INFO

Article history:
Received 11 March 2008
Received in revised form 27 May 2009
Accepted 4 June 2009

Keywords:
Power spectral analysis (PSA)
Quantitative electroencephalography (EEG)
Brain–computer interface (BCI)
Psychotherapy
Major depressive disorder (MDD)
Low Resolution Brain Tomography (LORETA)
EEG normative database
Psychoneurotherapy
Neurotherapy
Neurofeedback

ABSTRACT

Recent advances in power spectral analysis of electroencephalography (EEG) signals and brain–computer interface (BCI) technology may significantly contribute to the development of psychoneurotherapies. The goal of this study was to measure the effect of a psychoneurotherapy on brain source generators of abnormal EEG activity in individuals with major depressive disorder (MDD). Thirty participants with unipolar MDD were recruited in the community. The proposed psychoneurotherapy was developed based on the relationship between the localization of abnormal EEG activity and depressive symptomatology. Brain electromagnetic abnormalities in MDD were identified with low resolution brain electromagnetic tomography (LORETA) and a normative EEG database. Localization of brain changes after treatment was assessed through the standardized version of LORETA (sLORETA). Before treatment, excessive high-beta (18–30 Hz) activity was noted in several brain regions located in the fronto-temporal regions. After treatment, only participants who successfully normalized EEG activity in cortico-limbic/paralimbic regions could be considered in clinical remission. In these regions, significant correlations were found between the percentage of change of depressive symptoms and the percentage of reduction in high-beta activity. These results suggest that the normalization of high-beta activity in cortico-limbic/paralimbic regions can be associated with a significant reduction of depressive symptoms.

1. Introduction

Recent advances in computerized power spectral analysis (PSA) of electroencephalography (EEG) signals (Hughes and John, 1999; Coburn et al., 2006) and brain–computer interface (BCI) technology (Birbaumer et al., 2006; Scott, 2006; Fetz, 2007) may significantly contribute to the development of brain-based psychotherapies (as we may call psychoneurotherapies) in the context of an evidence-based and personalized medicine. With magnetoencephalography, EEG has the best temporal resolution of all functional neuroimaging techniques (Coburn et al., 2006). Further, EEG is the most practical and accessible neuroimaging technique because it is relatively simple and inexpensive. Given this and the compact nature of the equipment, EEG can readily be accommodated by clinics, hospitals and private offices. In regard to data analysis, visual inspection of the time-domain conventional EEG has been regarded as too nonspecific to investigate selective mental disorders. However, computerized PSA has made it possible to link quantitative descriptions of brain electrical activity with specific mental disorders (Hughes and John, 1999; Coburn et al., 2006). In combination with clinical assessment, computerized PSA is used as an adjunct in differential diagnostic and subtyping of depressive disorders (John et al, 1988; Lieber and Prichep, 1988; Pizzagalli et al., 2002). It is also utilized to predict the most effective pharmacological treatment for a given patient (Suffin and Emory, 1995; Hunter et al., 2007).

Computerized PSA has greatly benefited from the development of three-dimensional brain source localization methods such as low

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0925-4927/$ – see front matter © 2009 Published by Elsevier Ireland Ltd.
doi:10.1016/j.pscychresns.2009.06.002

resolution brain electromagnetic tomography (LORETA) (Pascual-Marqui et al., 1994) and standardized LORETA (sLORETA) (Pascual-Marqui, 2002). In LORETA, intracranial generators of brain activity detected on the scalp are mathematically estimated by constraining the inverse solution to an anatomical template of the brain. Using this method, Pizzagalli et al. (2002) found in individuals with major depressive disorder (MDD) abnormally elevated high-beta activity (21–30 Hz) in the right prefrontal cortex (BA 9/10/11), combined with abnormally low high-beta activity in the precuneus/posterior cingulate regions. Importantly, EEG is the only neuroimaging technique that allows statistical comparison of individual recordings with age-matched or age regression life-span normative databases (John et al., 1988; Thatcher et al., 2003, 2005; Gordon et al., 2005; Prichep, 2005). These databases permit the detection of deficient or excessive EEG power and EEG coherence within each patient evaluated without having to create a local control group. With respect to this question, the FDA-approved University of Maryland life-span EEG normative database (Thatcher et al., 2003) permits a comparison of the estimated intracerebral current density distribution with LORETA (Thatcher et al., 2005). It has been previously proposed that LORETA (Saletu et al., 2005) and this normative database (Thatcher et al., 2005) may be useful for the diagnoses and treatment of psychiatric disorders.

There is mounting evidence that emotional dysregulation in MDD is related to a dysfunction of the neural circuitry supporting emotional self-regulation (Drevets, 2000; Mayberg, 2003; Seminowicz et al., 2004; Beauregard et al., 2006). Self-regulation of brain activity through operant control and on-line computerized feedback has been demonstrated a few decades ago with EEG (Fetz, 1969; Rosenfeld et al., 1969; Nowlis and Kamiya, 1970). Previous work conducted by our research team suggests that self-regulation of EEG activity via a BCI was able to functionally normalize the brain systems mediating selective attention and response inhibition in children with attention-deficit hyperactivity disorder (Lévesque and Beauregard, 2006). Recent functional magnetic resonance imaging (fMRI) studies have shown that by receiving continuous feedback about regional blood–oxygen-level dependent (BOLD) signals through a BCI, healthy individuals can learn to increase the magnitude of the BOLD signal responses within and across fMRI sessions (Weiskopf et al., 2003). Regarding this issue, it has been demonstrated that chronic pain patients can decrease their perception of pain by self-regulating BOLD activity in the anterior cingulate cortex (deCharms et al., 2005). As for MDD, the results of a small number of studies indicate that a BCI intervention based on EEG data may be successfully used to reduce depressive symptoms (Rosenfeld, 2000; Hammond, 2005). However, these studies have been done with only a few participants and without measuring whole-brain activity before vs. after treatment. Furthermore, the electrode sites and frequency band to train were determined a priori, based strictly on the literature.

The main goal of this exploratory study was to measure, using a before–after trial design, the effect of a psychoneurotherapy (PNT) on brain source generators of abnormal EEG activity in individuals with MDD. This PNT was developed based on the linkage between the localization of abnormal brain activity and symptoms in the current MDD sample. This brain-based psychotherapy uses a BCI allowing real-time self-regulation of brain activity mediating emotional and cognitive symptoms of depression. To our knowledge, this is the first study measuring the neurobiological and psychological effects of a PNT in MDD. The central aim of this PNT was to help depressed participants to self-regulate the abnormal brain activity via a BCI while learning to decrease their negative thoughts and emotional feelings. We predicted that the post-treatment evaluation (compared with the pre-treatment evaluation) would reveal a significant normalization of EEG abnormalities associated with a substantial decrease of depressive symptoms.

2. Materials and methods

2.1. Subjects

All participants were recruited through Revivre, a Quebec depressive support association. Individuals who had received a diagnosis of current unipolar MDD (as assessed through their physician, psychiatrist or psychologist) and potentially met the study criteria (based on a phone interview) were invited for a diagnostic interview. The Structured Clinical Interview for DSM-IV (First et al., 1997) was used to ensure that depressed participants met the DSM-IV criteria for unipolar MDD. Individuals with any history or current episode of mania, hypomania, psychosis, alcohol or substance abuse, neurological disorders, intellectual deficit or other Axis 1 disorders were excluded, with the exception of comorbid anxiety, which is often present in MDD. Dysthymia was allowed only if occurring in conjunction with current unipolar MDD. Twenty-five females and five males ($n=30$) were recruited in this study. Age ranged from 27 to 58 years ($M=44$, S.D. $=8.7$), years of education ranged from 11 to 23 ($M=16$, S.D. $=3$) and number of depressive episodes ranged from 1 to 20 ($M=4.6$, S.D. $=3.6$). Twenty-two participants had a family history of depression in first degree relatives. Twenty-six of these individuals were taking antidepressant medications at the time of the study but still suffered from unipolar MDD symptoms. The other four participants had stopped taking antidepressant medications long before the study as a result of significant negative side effects. Participants were explicitly requested to refrain from making any change in their medication intakes until the end of the treatment. A written informed consent was obtained for each participant following a complete description of the study. The informed consent form was approved by the Scientific and Ethics Research Committees from the Institut Universitaire de Gériatrie de Montréal.

Non-depressed control participants were part of the University of Maryland life-span EEG normative database (Thatcher et al., 1987; 2003). The control sample comprised 625 screened and evaluated normal individuals ranging in age from 2 months to 82 years and stratified into 21 age groups. Detailed descriptions of the methods and sample used in this database are available in several peer-reviewed journals (Thatcher et al., 2003). The University of Maryland life-span EEG normative database has been implemented in the Neuroguide software. This software allows age-dependent digital EEG to be compared under resting state eyes-closed and eyes-opened conditions, for any montage (e.g., linked-ears, average reference, Laplacian) and for 19 electrode sites.

2.2. Self-report questionnaires

Depressive symptoms were assessed with self-report questionnaires administered at baseline and after treatment. The severity of depressive symptoms was evaluated using the Beck Depression Inventory-Second Edition (BDI-II). For the BDI-II, a score of ≤ 13 is considered an indication of a non-clinical level of depression while a score of ≥ 29 is considered an indication of severe clinical depression (Beck et al., 1996). Other self-report questionnaires were used pre- and post-treatment to better characterize the MDD participants and measure the cognitive, affective and behavioral components affected by the proposed PNT. These questionnaires measured the frequency of negative automatic thoughts (ATQn) (Bouvard et al., 1992), frequency of positive automatic thoughts (ATQp) (Ingram and Wisnicki, 1988), frequency of rumination on sadness (RSS) (Conway et al., 2000), dysfunctional attitudes (DAS-A) (Bouvard et al., 1994), and behavioral inhibition and activation (BIS, BAS-rr, BAS-d, and BAS-fun) (Kasch et al., 2002). Given the high comorbidity of anxiety with MDD, the severity of anxiety symptoms (BAI) (Freeston et al., 1994) and frequency of worries (WDQ) (Ladouceur et al., 1999) were also assessed. The results from self-report questionnaires were compared with normative data published for each questionnaire.

2.3. EEG recordings and power spectral analyses

EEG was recorded, before treatment and 1 month following completion, from 19 scalp locations (Electro-cap International, Inc.), based on the International 10/20 System of electrode placement (Jasper, 1958). A linked-ears reference montage was used. We chose the 19 scalp locations that were utilized to create the University of Maryland EEG normative database. EEG data were acquired and amplified within a bandpass of 0.1 to 58 Hz (128 samples/s) with a 60-Hz Notch filter (Deymed Diagnostic, TruScan 32). EEG recordings were acquired in a dimly illuminated room during a 5-min (2×150 s) resting state, eyes-open condition. Data were then imported into the software (Neuroguide 2.4) which carefully calibrated EEG signals coming from the current amplifier. Each participant's EEG samples were plotted, visually examined and then edited to remove artifacts. Non-overlapping, artifact-free 60-s EEG samples were extracted for all participants. Split-half reliability (correlation between the first 30 s and the last 30 s) was examined on the edited EEG segments and only records with >95% average reliability were considered in PSA. This sensitive procedure allows controlling for state changes and drowsiness. Using a linked-ears reference montage, PSA was performed for the 60-s EEG samples with a Fast Fourier Transform (FFT). Overall,

absolute power was computed for seven frequency bands (1–4 Hz, 4–8 Hz, 8–10 Hz, 10–12 Hz, 12–15 Hz, 15–18 Hz, and 18–30 Hz) and 19 electrodes (FP1/FP2, F7/F8, F3/F4, FZ, T3/T4, C3/C4, CZ, P3/P4, T5/T6, PZ, and O1/O2).

2.4. Brain source localization

Intracranial localization of brain regions responsible for generating abnormal activity in our depressive sample was estimated with the LORETA normative EEG database (Thatcher et al., 2005). This *z*-score database has been shown to successfully localize known pathologies to the expected Brodmann areas (BA) as a hypothesis test based on the surface EEG before computing LORETA. Although EEG source localization has some limitations (e.g., infinite possible solutions, varieties of inverse solution models and algorithms, a limited number of electrodes), a review of all published 3D, discrete, distributed, linear EEG/MEG tomography methods for solving the EEG inverse problem has shown that LORETA has the lowest localization error (to within 1 voxel resolution on average) (Pascual-Marqui et al., 2002). Even without using individual MRI anatomical scans, it has been demonstrated that with as few as 16 electrodes, and using the approximate three-shell head model registered to the Talairach human brain atlas (Talairach and Tournoux, 1988), localization accuracy of EEG is 10 mm at worst (Cohen et al., 1990; Pascual-Marqui, 1999). However, by adding localization error due to the head model, the average error is not expected to exceed 2–3 cm. LORETA inverse solutions are a model of the 3D distribution of electric neuronal activity that has maximum similarity (i.e., maximum synchronization) in terms of orientation and strength between neighboring neuronal populations (represented by adjacent voxels) (Pascual-Marqui et al., 2002). LORETA inverse solutions are restricted to 2394 voxels (spatial resolution = 7 mm) within cortical gray matter and hippocampi, as determined by the digitized Talairach and probability atlases of the Brain Imaging Centre, Montreal Neurological Institute (MNI305). EEG electrode coordinates are derived from cross-registrations between spherical and head geometry (Towle et al., 1993). To date, LORETA has received important theoretical and cross-modal validation from studies combining this method with structural and functional MRI, positron emission tomography (PET), visual and auditory event-related potentials, and intracranial recordings (Pascual-Marqui et al., 2002).

Within-subject comparisons (pre- vs. post-treatment) of EEG activity were made using standardized LORETA (sLORETA) (Pascual-Marqui, 2002). This relatively new method yields images of standardized EEG current density and demonstrates the lowest localization errors in noisy simulations (Pascual-Marqui, 2002). sLORETA was selected because of two important innovations that contribute to increase the accuracy of localization (relatively to LORETA). First, realistic electrode coordinates are made from a 10/5 system (Oostenveld and Praamstra, 2001) and are registered to the MNI152 (Mazziotta et al., 2001) scalp, with a 12-parameter affine transformation followed by a spline that projects the electrodes onto the scalp with minimum distortion (Jurcak et al., 2007). This provides a much more realistic head–surface-based positioning system. Second, the transformation matrix for the inverse solution uses the electric potential lead field computed with the boundary element method applied to the MNI152 digitized structural MRI template (Fuchs et al., 2002). sLORETA inverse solutions are constrained to this template composed of 6239 cortical gray matter voxels at 5 mm.

2.5. Psychoneurotherapy (PNT)

At baseline, abnormal absolute power within specific frequency bands was noted for specific electrode sites and for each participant. Based on group average abnormalities, we decided which frequency band to train and in which location in order to develop a group treatment protocol. During PNT, real-time abnormal activity recorded from all participants was translated into a graphic displayed on a computer monitor screen. As for the EEG montage, nose reference was selected because it is midline, probably less active than CZ, and far enough from the active electrodes (T3/T4 and AF3/AF4 see further) compared to a linked-ears montage. In addition, the nose reference gives some kind of bipolar derivation that emphasizes sources between the four active and reference electrodes.

Each session was composed of 8 to 10 blocks of 3 to 4 min of training with eyes, without moving and in silence within blocks. Eyes-opened training was adopted since MDD participants would rapidly fall asleep with eyes closed (due to sleep disturbances). During the first 10 sessions of the PNT, participants were first asked to relax and quiet their mind as much as possible while doing breathing exercises. Then they were instructed to focus visual attention on the computer screen in order to associate specific mental states with variations in their brain activity displayed on that screen. Within this self-reflexive mode, participants were asked to self-regulate the abnormal brain activity while learning to decrease their negative thoughts and emotional feelings. In the last 10 sessions of PNT, the capacity of participants to successfully self-regulate brain activity and mood was challenged by gradually exposing participants to situations usually triggering depressed mood and thoughts (e.g., the therapist read aloud such sentences as "Imagine that your boss is unhappy about your performance at work"). At the end of each block (see below), participants were encouraged to discuss with the therapist or write down any strategies they used as well as any emotionally charged memories, thoughts or images that came to mind. The therapist helped participants to reframe any negatively evoked mental content. Strategies most commonly utilized by participants were changing thought contents (from negative to positive) and thought processes (from self-focused/past or future-oriented, reverberating ruminations or worries to external-focused/present-oriented goal-directed thoughts guiding action), practicing mindful awareness (mindfulness) and letting go with their thoughts and emotions, allowing to feel and name their emotions in order to understand their meanings, maintaining emotionally positive memories, and visually imagining positive outcomes. Participants met the therapist (VP) two times per week for 20 1-h sessions that lasted 10 weeks.

2.6. Statistical analyses

Statistical analyses were conducted only on those subjects who completed all 20 sessions. Dropouts were excluded from these analyses. BDI-II scores were used at the end of treatment to distinguish Responders from Non-Responders. Changes in more specific cognitive, affective and behavioral symptoms associated with depression and anxiety were assessed by means of multivariate analysis of variance (MANOVA, using SPSS version 15.0; SPSS Inc., Chicago, Ill) performed on all self-reported questionnaires, with repeated measures on Treatment (pre- vs. post-treatment). Independent *t*-tests were also performed between Responders and Non-Responders to test any difference at baseline or after treatment.

Neuroelectrical differences between our current MDD sample and healthy individuals were estimated by contrasting EEG samples with the University of Maryland normative EEG database (Thatcher et al., 2003; 2005). Before treatment, a *z*-score was computed with regard to the absolute power of each of the seven frequency bands for the 19 electrode sites. The frequency bands showing the most abnormal *z*-score ($z \leq -1.5$ or $z \geq 1.5$) were retained for source localization. Planned comparisons were then performed before launching *z*-score LORETA in order to generate a priori data-driven hypotheses about the corresponding 3D volume of interests (VOIs). LORETA VOIs were selected based on the estimation of the most probable BA underlying the electrode sites that showed the highest band abnormalities. Only one BA per electrode site was retained for subsequent analyses (i.e., the BA with the most abnormal *z*-score). Three other VOIs (insula, amygdala/parahippocampal cortex and subgenual cingulate cortex) were included in data analyses given the evidence indicating an involvement of these brain regions in the mediation of the cognitive, physiological, and experiential aspects of emotional responses (Beauregard, 2004; Beauregard et al., 2006). One month after termination, *z*-scores were measured once again for each of the LORETA VOIs in order to assess any significant change in absolute power.

PSA changes following treatment were measured by using sLORETA and comparing with paired *t*-tests absolute power of the selected bands within electrode sites and corresponding BAs. sLORETA VOIs were created by selecting only voxels corresponding to BAs identified by *z*-score LORETA in the between-subject analyses. Before contrasting pre- vs. post-treatment sLORETA VOIs, a subject-wise normalization was performed for every participant in the selected band. This procedure consisted in multiplying the value of every single voxel by the inverse of the total activity over all voxels, as an attempt to control for a potential global effect over all voxels due to treatment or the passage of time. Normalized data were then log transformed, without smoothing. Statistically significant voxels were identified based on a nonparametric approach using a randomization strategy (Nichols and Holmes, 2002). This method determined the critical probability threshold values for the observed *t* values with correction for multiple testing. After each iteration, the largest *t* value was kept. Following 5000 iterations, the *t* value associated with the most extreme 5% of the distribution was identified for the selected band. A one-tailed test was used ($P<0.05$). Finally, a mean *t* value was computed for each voxel and the largest *t* value among voxels which belong to the same VOI was retained for the final analyses. The structure-probability maps atlas (Lancaster et al., 2000) implemented in sLORETA was used to determine the brain regions and BAs closest to the significant locations identified with the MNI coordinates. To specifically test whether changes in abnormal activity in brain areas were related to changes in symptoms severity, we correlated changes in sLORETA normalized, log-transformed BAs (i.e., *t*-values from the post- vs. pre-comparison) with percentage change ((Post-Pre)/(Pre)*100) in BDI-II score. Degrees of freedom were defined as the number of participants who completed the treatment ($df = 27 - 2 = 25$, $P<0.05$, uncorrected, threshold for significance: $r>0.36$).

3. Results

Twenty-seven participants (22 females and 5 males) completed all 20 sessions and were included in data analyses. Their ages ranged from 27 to 58 years ($M = 44$, S.D. = 9). Three participants did not pursue PNT for varied reasons (i.e., personality problems, extreme fatigue or very low level of energy).

3.1. Pre-treatment

3.1.1. Self-report symptoms

As shown in Table 1, self-report questionnaires confirmed that our current MDD sample was characterized by severe depressive

symptoms, high frequency of negative automatic thoughts, low frequency of positive automatic thoughts, and high levels of dysfunctional attitudes and rumination on sadness. There was also a high comorbidity with anxiety, especially associated with high frequency of worries. In addition, participants scored high on the behavioral inhibition scale and low on behavioral activation subscales.

3.1.2. Brain electrical abnormalities

Compared to the University of Maryland EEG normative database, PSA revealed that high-beta (18–30 Hz) activity was the frequency band involving the highest number of electrode sites with an abnormal *z*-score. No abnormal theta and alpha activity was detected at any site. Electrode sites showing excessive high-beta activity were noted at FP2 ($z=2.4$), FP1 ($z=2.3$), F4 ($z=1.7$), F8 ($z=1.7$), F3 ($z=1.6$), F7 ($z=1.5$) and T4 ($z=1.5$). *z*-Score LORETA solutions estimated the corresponding BAs with the highest *z*-score (see Table 2). A clear pattern of excessive high-beta activity was uncovered (see Table 2) in the right hemisphere compared to the homologous regions in the left hemisphere.

3.2. Treatment protocol

Based on these PSA data, the treatment protocol was designed to ask depressed participants to reduce high-beta (18–30 Hz) activity in cortico-limbic/paralimbic regions via a BCI while learning to decrease their negative thoughts and emotional feelings. During treatment, EEG activity was filtered in an 18–30 Hz band from four electrodes positioned at AF3, AF4, T3 and T4, referenced to nose. AF3 and AF4 (Oostenveld and Praamstra, 2001) were selected because of their middle position between FP1–F3–F7 and FP2–F4–F8, respectively. Real-time activity within each electrode was translated into one of the four bar graphs displayed on a computer monitor screen. Height variations of the bar graph corresponded to real-time variations of amplitude (in microvolts [mV]) in the selected band for each of the four electrodes. Cumulative mean amplitude for each electrode was shown above each bar graph. No auditory feedback was given.

3.3. Post-treatment

3.3.1. Changes in self-report symptoms

Following treatment, there was a statistically significant reduction of the mean BDI-II score ($P<0.001$), and 20 out of 27 participants (74%) did not meet DSM-IV criteria for MDD (Confidence interval [95%] = [55% to 87%]) (see Table 1). Independent *t*-tests revealed no difference between Responders (R) and Non Responders (NR) on the following demographic variables: age, years of education and medication intake. Consequently, it was unnecessary to control for these variables in the R vs. NR analyses. Only four Responders and two Non-Responders were not on medication. There was no male participant in the Non-Responders group. The only self-report questionnaire that showed a statistically significant difference between R and NR at baseline was the BAS-rr ($t^{26}=11.17$, $P=0.02$), which suggests that a high pre-treatment score on the BAS-rr is a good predictor of treatment outcome. Since a comparison of symptom change between R and NR could only be adequately interpreted for variables on which the two groups had an equivalent baseline, this subscale was eliminated from further analyses. A MANOVA with repeated measures on Treatment (Pre- vs. Post-treatment) was performed on the 10 self-report questionnaires for the whole MDD sample (see Table 1). Wilk's criterion showed a statistically significant main effect of Treatment [$F(10,17)=14.24$, $P<0.001$]. Univariate tests indicated statistically significant post- vs. pre-treatment differences of scores for all these questionnaires except the BASd ($P=0.45$) and BASfun ($P=0.27$) (see Table 1). For Non-Responders, a MANOVA showed no main effect of Treatment [$F(10,10)=0.47$, $P<0.80$]. Only the BASd ($P=0.32$) and BASfun ($P=0.08$) showed no statistical difference between R and NR after treatment.

3.3.2. Brain electrical changes

One month after the end of treatment, absolute power of high-beta (18–30 Hz) activity showed a significant reduction in the orbitofrontal cortex (BA 11/47), insula (BA 13), amygdala/parahippocampal cortex (BA 36/37), temporal pole (BA 38), lateral prefrontal cortex (BA 10 and BA 6/8), and subgenual cingulate cortex (BA 25) (see Fig. 1 and Table 3). Further, *z*-score LORETA indicated that high-beta activity in VOIs after treatment fell within normal range ($z<2$) for Responders but not for Non-Responders (see Table 2), which means that the reduction in high-beta activity was associated to the reduction in symptoms. Interestingly, in Responders a statistically significant reduction of cortico-limbic/paralimbic activity was measured in the right hemisphere whereas in Non-Responders, a significant increase of cortico-limbic/paralimbic activity was evidenced in the left hemisphere (see Fig. 1).

The percentage of reduction of high-beta activity in the right orbitofrontal (BA 11/47, $r=0.46$, $P<0.05$), right medial prefrontal cortex/dorsal anterior cingulate cortex (BA 9/32, $r=0.45$, $P<0.05$,

Table 1
Mean score and standard deviation of self-report questionnaires.

Questionnaires	Norms	Total ($n=27$)				Responders ($n=20$)				Non Responders ($n=7$)			
		Pre	Post	%	*t*	Pre	Post	%	*t*	Pre	Post	%	*t*
BDI-II	7.7 (5.9)[1]	37.3 (9.0)	10.1 (9.2)	−72.9**	11.83**	36.7 (8.2)	5.3 (3.7)	−85.7**	15.82**	39.0 (11.4)	24.0 (4.3)	−38.5*	3.42*
BAI	9.9 (10.5)[2]	18.5 (9.3)	7.6 (7.7)	−58.9**	6.71**	17.0 (8.7)	5.0 (4.9)	−70.8**	7.85**	22.9 (10.1)	15.4 (9.3)	−32.5	1.67
WDQ	21.1 (16.1)[3]	62.6 (27.4)	28.7 (19.5)	−54.2**	5.72**	65.5 (27.8)	19.7 (10.4)	−69.9**	8.19**	54.4 (26.9)	54.4 (15.8)	0.0	0.00
ATQn	46.2 (12.0)[4]	91.3 (24.1)	49.2 (19.9)	−46.1**	8.86**	89.3 (22.0)	39.6 (6.6)	−55.7**	10.07**	97.0 (30.4)	76.9 (19.3)	−20.8	2.91*
RSS	35.4 (10.6)[5]	40.6 (10.7)	21.9 (8.3)	−46.0**	7.13**	41.7 (9.5)	18.6 (5.0)	−55.5**	10.10**	37.4 (13.7)	31.6 (8.7)	−15.7	1.07
ATQp	107.2 (18.6)[6]	69.9 (16.2)	91.0 (23.2)	30.2**	−4.47**	72.7 (16.6)	100.6 (17.0)	38.4**	−5.07**	61.9 (12.4)	63.6 (15.0)	2.8	−0.47
DAS-A	115.8 (25.9)[7]	146.0 (38.1)	107.2 (36.8)	−26.6**	4.63**	149.7 (39.8)	99.0 (35.7)	−33.8**	5.21**	135.4 (33.4)	130.6 (30.9)	−3.6	0.63
BIS/BAS (BIS)	20 (3.8)[8]	23.3 (3.1)	19.1 (3.84)	−18.0**	6.56**	23.1 (3.3)	18.1 (3.4)	−21.6**	6.98**	23.9 (2.6)	22.1 (3.5)	−7.2	2.05
BIS/BAS (BAS-fun)	12.6 (2.0)[8]	11.0 (3.2)	11.5 (2.4)	4.5	1.12	11.5 (3.1)	12.0 (2.3)	4.3	−0.85	9.6 (3.3)	10.1 (2.1)	6.0	−0.88
BIS/BAS (BAS-d)	11.9 (2.9)[8]	10.7 (2.2)	11.1 (2.1)	3.7	−0.76	10.5 (2.3)	11.4 (2.1)	8.6	−1.33	11.3 (1.8)	10.4 (2.0)	−7.6	1.00
BIS/BAS (BAS-rr)	17.7 (2.3)[8]	15.7 (2.7)	15.7 (2.6)	0	0.11	16.5 (2.5)	15.9 (2.8)	−3.3	0.73	13.7 (2.1)	15.1 (2.3)	10.4	−1.70

**Two-tailed, $P<0.001$, *Two-tailed, $P<0.05$. % = % Change = (Post − Pre) / (Pre) * 100. [1]Beck et al. (1996). Non-depressed control subjects ($n=44$). Score of 0–13 = non-depressed; 14–19 = mild; 20–28 = moderate; 29–63 = severe. [2]Freeston et al. (1994). Non-depressed control group ($n=332$); [3]Ladouceur et al. (1999). Non-depressed control group ($n=20$); [4]Bouvard et al. (1992). Non-depressed control subjects ($n=93$); [5]Conway et al. (2000). Non-depressed control group ($n=220$); [6]Ingram and Wisnicki (1988). Non-depressed control group ($n=480$); [7]Bouvard et al. (1994). Non-depressed control subjects ($n=93$); [8]Kasch et al. (2002). Non-depressed control group ($n=27$).

Table 2
z-Score absolute power of high-beta activity (18–30 Hz).

z-Score LORETA VOI (BA)	TAL coord.			Total ($n=27$)				Responders ($n=20$)				Non Responders ($n=7$)			
	x	*y*	*z*	Pre	Post	%	*t*	Pre	Post	%	*t*	Pre	Post	%	*t*
R middle frontal cortex (BA 10)	39	45	24	3.14	2.21	−29.5	−1.89*	3.13	1.61	−48.6	−2.62**	3.15	3.92	24.4	1.32
L middle frontal cortex (BA 10)	−38	45	24	2.81	2.09	−25.6	−1.53	2.89	1.51	−47.8	−2.69**	2.59	3.73	44.0	1.53
R middle frontal cortex (BA 6/8)	46	12	45	3.06	2.15	−29.7	−1.80*	3.01	1.56	−48.2	−2.66**	3.22	3.83	18.9	0.98
L middle frontal cortex (BA 6/8)	−51	5	39	2.73	1.97	−27.8	−1.61	2.80	1.43	−48.9	−2.74**	2.52	3.51	39.3	1.20
R orbitofrontal cortex (BA 11/47)	18	29	−18	2.89	2.08	−28.0	−1.91*	2.94	1.54	−47.6	−2.88**	2.76	3.63	31.5	1.70
L orbitofrontal cortex (BA 11/47)	−17	22	−18	2.67	2.02	−24.3	−1.48	2.71	1.44	−46.9	−2.67**	2.53	3.67	45.1	1.72
R temporal pole (BA 38)	32	2	−11	2.31	1.49	−35.5	−2.15*	2.30	0.99	−57.0	−2.91**	2.32	2.89	24.6	1.47
L temporal pole (BA 38)	−31	2	−11	2.13	1.53	−28.2	−1.34	2.20	1.13	−48.6	−2.62**	1.95	3.05	56.4	1.88
R amygdala/parahippocampal complex (BA 36/37)	4	−11	−5	2.70	1.96	−27.4	−1.59	2.70	1.36	−49.6	−2.57**	2.71	3.69	36.16	1.45
L amygdala/parahippocampal complex (BA 36/37)	−17	−4	−11	2.32	1.78	−23.3	−1.27	2.36	1.24	−47.5	−2.47*	2.20	3.35	52.3	1.71
R insula (BA 13)	32	23	0	2.58	1.75	−32.2	−2.09*	2.60	1.26	−51.5	−2.87**	2.53	3.17	25.30	1.61
L insula (BA 13)	−31	17	7	2.38	1.82	−23.5	−1.36	2.47	1.29	−47.8	−2.68**	2.12	3.32	56.6	1.87
C subgenual cingulate cortex (BA 25)	4	16	−12	2.92	2.14	−26.7	−1.72*	2.95	1.54	−47.8	−2.74**	2.85	3.83	34.39	1.58

Abbreviations: MDD, major depressive disorder; VOI, volume of interest; LORETA, low-resolution brain electromagnetic tomography; BA, Brodmann area; R, right; L, left; C, central; TAL, Talairach. %, % Change = (Post − Pre) / (Pre) * 100. **One-tailed, $P<0.01$ corrected; *One-tailed, $P<0.05$ corrected.

uncorrected), right subgenual cingulate cortex (BA 25, $r=0.45$, $P<0.05$) and right temporal pole (BA 38, $r=0.45$, $P<0.05$) was positively correlated with the percentage of reduction of depressive symptoms (as measured with the BDI-II) (see Fig. 2). A positive correlation ($r=0.48$, $P<0.05$) was also found between an increase of high-beta activity in bilateral precuneus/posterior cingulate cortex (BA 40/31) and the percentage of reduction of depressive symptoms (see Fig. 2).

4. Discussion

In agreement with what has been previously reported by Pizzagalli et al. (2002), EEG spectral analyses and brain source localization revealed, in MDD participants, excessive high-beta activity in cortico-limbic/paralimbic regions. Based on this finding, a novel PNT was developed. The main objective of this treatment was to ask depressed participants to reduce high-beta activity in cortico-limbic/paralimbic regions via a BCI while learning to decrease their negative thoughts and emotional feelings. Results demonstrated that only participants who successfully normalized cortico-limbic/paralimbic EEG activity could be considered in clinical remission (i.e., BDI-II score ≤13) after the treatment. These results strongly suggest a relationship between the decrease of high-beta activity within cortico-limbic/paralimbic regions and the reduced frequency of ruminative processes. Moreover, following treatment, Responders reported being less overwhelmed

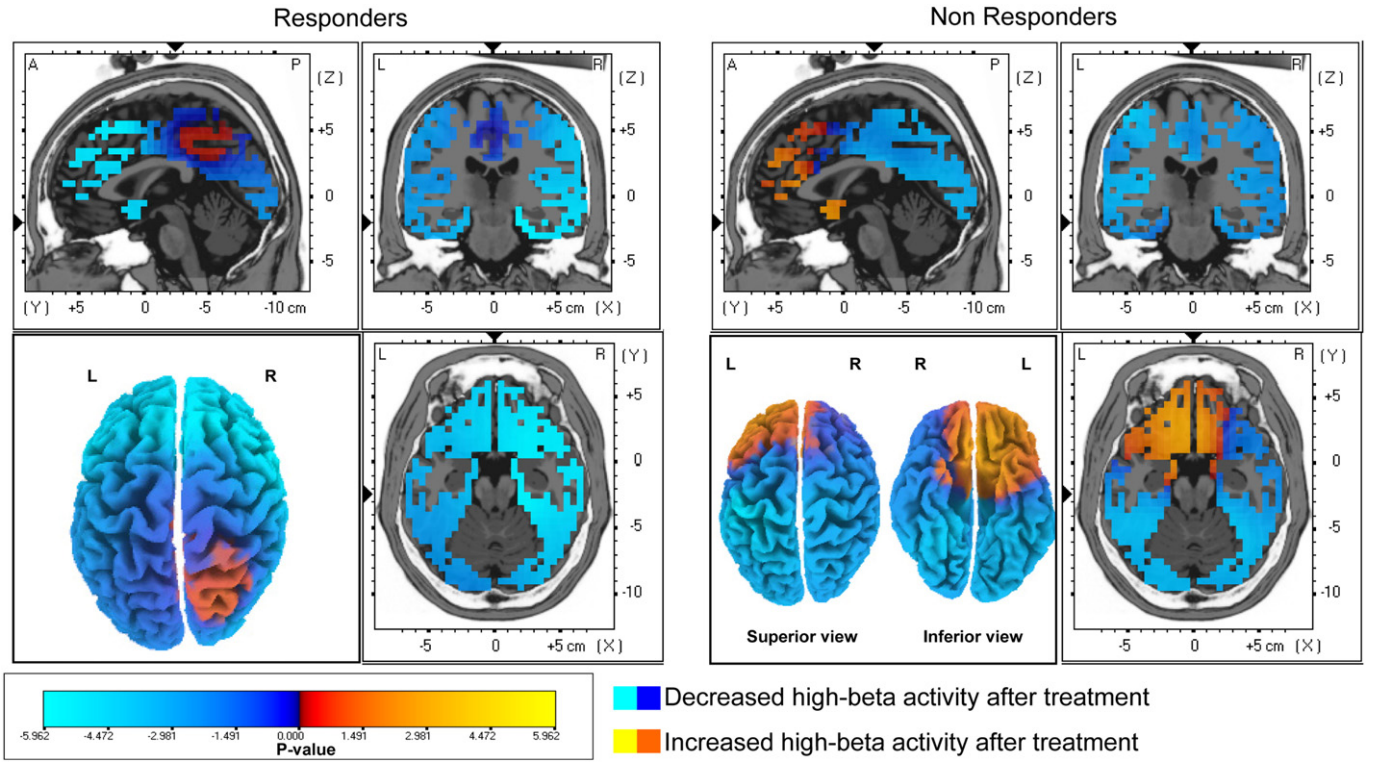

Fig. 1. Whole-brain sLORETA direction of changes in absolute power of high-beta (18–30 Hz) activity after PNT. L, left; R, right; A, anterior; P, posterior; PNT, psychoneurotherapy.

Table 3
Raw sLORETA values of high-beta activity (18–30 Hz).

sLORETA VOI (BA)	TAL coord.			Total ($n=27$)				Responders ($n=20$)				Non Responders ($n=7$)			
	x	*y*	*z*	Pre	Post	%	*t*	Pre	Post	%	*t*	Pre	Post	%	*t*
R Middle Frontal Cortex (BA 10)	45	53	−7	368.2	284.4	−22.8	−3.99**	344.2	152.9	−55.6	−4.46**	436.8	660.2	51.1	−0.45
L Middle Frontal Cortex (BA 10)	−45	48	−7	298.3	373.1	25.1	−2.33	296.7	228.5	−23.0	−3.28*	302.8	786.3	159.7	1.25
R Middle Frontal Cortex (BA 6/8)	25	22	54	111.7	98.1	−12.2	−4.09**	109.7	60.5	−44.8	−4.93**	117.4	205.4	74.9	−0.33
L Middle Frontal Cortex (BA 6/8)	−20	22	54	93.5	112.0	19.8	−2.64	99.7	72.3	−27.5	−4.14*	75.7	225.6	198.2	0.40
R Orbitofrontal Cortex (BA 11/47)	45	15	−1	190.6	134.3	−29.5	−4.71**	171.8	73.4	−57.3	−5.02**	244.3	308.4	26.2	−1.04
L Orbitofrontal Cortex (BA 11/47)	−45	14	−5	172.6	231.0	33.9	−2.20	166.6	143.8	−13.7	−2.76	189.5	480.2	153.3	0.57
R Temporal Pole (BA 38)	30	13	−22	152.0	127.8	−16.0	−4.38**	140.7	69.4	−50.7	−4.88**	184.4	294.6	59.8	−0.57
L Temporal Pole (BA 38)	−30	13	−22	139.5	195.9	40.4	−2.17	136.8	118.4	−13.5	−2.97	147.2	417.4	183.7	1.04
R Amygdala/Parahippocampal Complex (BA 36/37)	25	−30	−15	52.8	40.3	−23.6	−5.34**	47.2	27.5	−41.8	−5.08**	68.8	77.1	12.0	−2.19
L Amygdala/Parahippocampal Complex (BA 36/37)	−25	−30	−15	59.5	63.6	7.0	−2.76	49.2	41.1	−16.6	−2.44	88.8	128.1	44.3	−1.67
R Insula (BA 13)	35	6	18	83.5	59.0	−29.4	−5.18**	77.5	35.6	−54.0	−5.96**	100.7	125.7	24.8	−0.99
L Insula (BA 13)	−35	6	18	74.7	88.3	18.2	−2.50	75.7	56.3	−25.6	−3.15	71.8	179.6	150.1	0.33
C Subgenual Cingulate Cortex (BA 25)	15	9	−17	93.6	91.7	−2.0	−3.67*	90.8	51.2	−43.6	−4.62**	101.7	207.6	104.2	0.71

Abbreviations: MDD, major depressive disorder; VOI, volume of interest; sLORETA, standardized low-resolution brain electromagnetic tomography; BA, Brodmann area; R, right; L, left; C, central; TAL, Talairach; %, % Change = (Post − Pre) / (Pre) * 100. **One-tailed, $P<0.01$; *One-tailed, $P<0.05$.

by ruminations and worries, while experiencing more self-control in converting negative thoughts into positive ones. They also reported having more goal-directed thoughts leading toward action. Further, Responders showed a significant score reduction on the behavioral inhibition scale, while no significant change was noted regarding the behavioral activation scale. This finding indicates that the decrease in high-beta activity in the cortico-limbic/paralimbic regions may be related to a decrease of inhibited/withdrawal behaviors in depressed participants (Davidson, 1994).

The excessive high-beta activity detected in the right frontal regions is consistent with neurometabolic data showing a right frontal hyperactivity in individuals with MDD (Mayberg, 2003). This right frontal hyperactivity has been interpreted as an exaggerated or maladaptive compensatory process (maybe to psychomotor retardation) resulting in psychomotor agitation and rumination. Such a process would serve to over-ride a persistent negative mood generated by abnormal chronic activity of limbic/paralimbic structures (Mayberg, 2003). With respect to the right frontal hyperactivity seen in MDD, significant positive correlations were found here between the percentage of reduction in self-reported depressive symptoms and the percentage of reduction of high-beta activity in the right cortico-limbic/paralimbic, including orbitofrontal cortex (BA 11/47), medial prefrontal cortex/dorsal anterior cingulate cortex (BA 9/32), amygdala/parahippocampal cortex (BA 36/37), insula (BA 13), temporal pole (BA 38), and subgenual cingulate cortex (BA 25). The orbitofrontal cortex (BA 11, 47) plays a pivotal role in emotional self-regulation whereas the medial prefrontal cortex/dorsal anterior

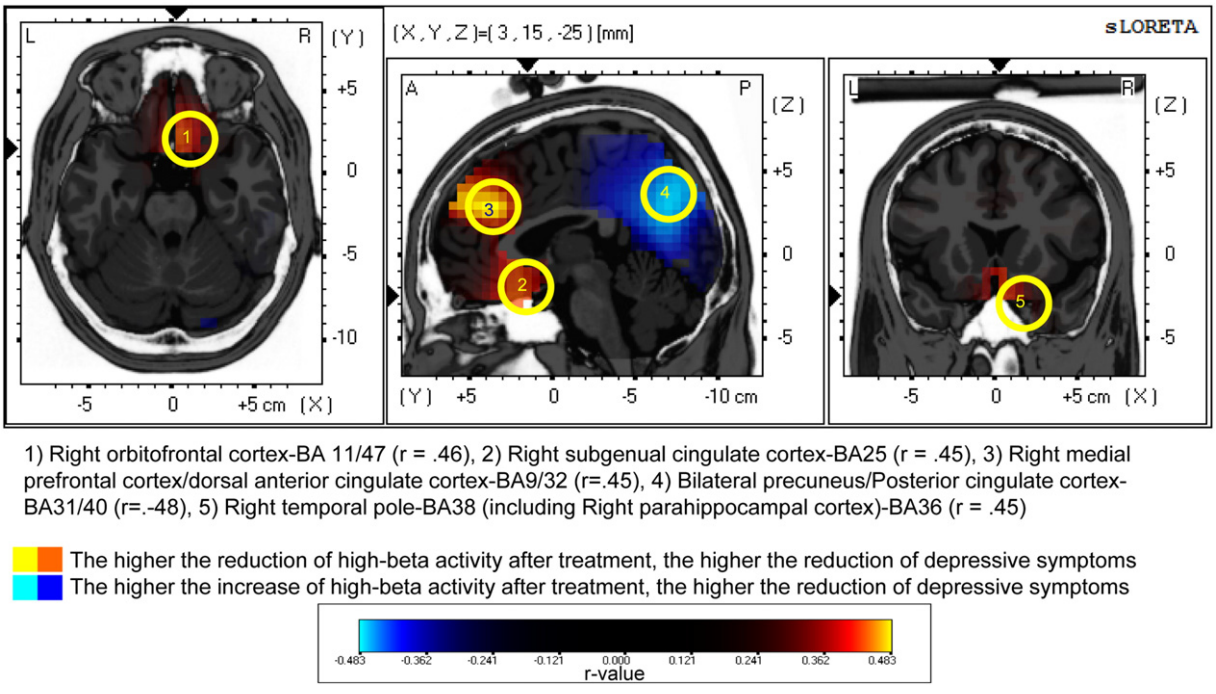

Fig. 2. Correlation between percentage change in Beck Depression Inventory score after PNT and change in absolute power of high-beta (18–30 Hz) activity measured with sLORETA. L, left; R, right; A, anterior; P, posterior; PNT, psychoneurotherapy.

cingulate cortex (BA 9/32) appear to be crucially involved in the metacognitive representation of one's own emotional states (Beauregard, 2004). The amygdala/parahippocampal complex, the insula, and the temporal pole are implicated in the mediation of the cognitive, physiological, and experiential aspects of emotional responses, respectively (Beauregard, 2004; Beauregard et al., 2006). As for the subgenual cingulate cortex, this region is implicated in primary autonomic and homeostasic processes (Freedman et al., 2000) and chronic deep stimulation of BA 25 has been shown to reduce depressive symptoms in treatment-resistant MDD (Mayberg et al., 2005). Interestingly, a recent [^{18}F]-2-fluorodeoxyglucose (^{18}FDG) PET study designed to measure brain changes associated with cognitive-behavioral therapy (CBT) in unipolar MDD patients has demonstrated that clinical improvement was associated with decreased metabolic activity in these regions (Goldapple et al., 2004). Importantly, reduced serotonin, glutamate/glutamine and GABA functions have also been found in several of these regions (Hasler et al. 2007) before treatment. It thus seems conceivable that the frontal metabolic hyperactivity and the neurochemical imbalances seen in MDD may be linked with excessive high-beta activity.

A correlation was found between the reduction in depressive symptoms and an increase of high-beta activity in the bilateral precuneus/posterior cingulate cortex (BA 40/31). Abnormally low high-beta activity has been found in these cortical areas in individuals with MDD (Pizzagalli et al., 2002). Furthermore, increased activity in precuneus/posterior cingulate cortex has been shown to correlate with symptom remission following pharmacological treatment (Mayberg, 2003) or interpersonal therapy (Martin et al., 2001). Since the highest level of cortical glucose metabolism during resting state occurs in these brain regions in healthy participants (Raichle et al., 2001), it is plausible that pharmacological treatment, interpersonal therapy and the PNT tested here may all contribute to restore the default mode of the brain. In keeping with such a view, increased high-beta activity in the precuneus/posterior cingulate region may be a predictor of treatment response in MDD. In other respects, there is some evidence that the precuneus/posterior cingulate regions are part of a neural system supporting self-reflective thought and self-representation (Johnson et al., 2002). It is credible to think that the increased high-beta activity noted after the PNT was linked to the reduction of the frequency of ruminations.

4.1. Limitations

By virtue of the following limitations, the present findings should be considered suggestive but not conclusive. First, different features of the PNT may contribute to the clinical outcome, namely the psychotherapeutic component, the fact that the therapist was not blind, and the credibility that patients attribute to its neurotechnological component (see “the placebo effect of the machine”, Schwitzegebel and Traugott, 1968). Given this, it is paramount to evaluate the clinical impact of each of these components. It is also important to compare the clinical and neurobiological effects of the PNT with those of traditional treatments of MDD, such as cognitive-behavioral therapy, interpersonal therapy and pharmacotherapy. Second, because no “waiting-list” or non-depressed reference group were included in this study, it was not possible to evaluate the possible contribution of passage of time to clinical and brain changes. However, the test–retest stability of computerized PSA within the same individual is remarkably high, even over several years (Kondacs and Szabó, 1999; Vuga et al., 2006). This suggests that the distinction between the patterns of clinical and brain changes in Responders and Non-Responders was not causally related with the passage of time. Third, the interpretation of the difference in brain activity changes between Responders and Non-Responders (e.g. see Fig. 1) should be done cautiously because these two post-hoc categories were also different on their pre-treatment level of BAS-rr and on their male/female ratio. It would thus be theoretically possible that the differences in brain activity changes were mainly due to gender or to the difference in baseline BAS-rr levels. However, the test–retest stability of computerized PSA is also an argument against that alternate hypothesis. It is also possible that gender and or the baseline BAS-rr score moderate the response to PNT. However, additional studies are necessary to assess these post-hoc hypotheses. Fourth, there are some confounding factors pertaining to the heterogeneity of our outpatient sample such as age, gender, number of depressive episodes, medication intakes and comorbid anxiety. Nevertheless, it could be argued that our sample of MDD participants was more representative of depressed individuals in the general population. Fifth, we used only 19 electrodes to perform brain source localization pre- vs. post-treatment. Still, the University of Maryland LORETA normative database was created with the same number of electrodes (Thatcher et al., 2003). Moreover, there is some evidence that when sLORETA is tested with a decreasing number of electrodes, resolution decreases gradually, but localization hardly deteriorates (Congedo, 2006). In other regard, the LORETA VOI selection was apparently to large parts driven by the electrode sites where the effects were found. This eliminates some of the possible confounders of the scalp based data (volume conduction and reference), but also means that the result space of the inverse solution inherits the limitations of the result space of the scalp data. While the validity of the presented results seems thus well established, it remains much more open whether all of the essential differences have been captured. Therefore, a more exhaustive analysis is necessary to fully understand the effects in the 3D source space. Finally, given the exploratory nature of this study, it was not justified to use a double-blind, randomized, placebo-controlled approach. Hence, we do not know the extent to which the clinical and brain changes measured following the PNT may be ascribable to a placebo effect. Placebo-controlled studies are thus needed to determine the clinical efficacy of PNT in MDD.

5. Conclusion

In conclusion, the results of this study suggest that the normalization of high-beta (18–30 Hz) activity in cortico-limbic/paralimbic regions can be associated with a significant reduction of MDD symptoms such as rumination, negative thoughts, anxiety and behavioral inhibition. The present results also suggest that the PNT used in the present investigation has the potential to contribute to the normalization of EEG activity in depressed individuals. Further, this study provides evidence that PSA combined with EEG normative databases and brain source localization methods constitutes a useful and relatively inexpensive neuroimaging procedure for detecting brain abnormalities in MDD and identify biomarkers of treatment response.

Acknowledgements

We acknowledge the financial support to VP and MB from the Fonds de Recherche en Santé du Québec (FRSQ). We also thank Marc-André Bouchard, Ph.D., Robert Thatcher, Ph.D. and Marco Congedo, Ph.D. for their useful recommendations.

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