European Psychiatry 41 (2017) 10–15

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

Abnormal brain oscillations persist after recovery from bipolar depression

P. Canali [a,*], S. Casarotto [b], M. Rosanova [b,e], G. Sferrazza-Papa [a], A.G. Casali [f], O. Gosseries [c,d], M. Massimini [b], E. Smeraldi [a], C. Colombo [a], F. Benedetti [a]

[a] Department of clinical neurosciences, scientific institute Ospedale San Raffaele, university Vita-Salute San Raffaele, San Raffaele Turro, 20, via Stamira d'Ancona, 20127 Milano, Italy
[b] Department of biomedical and clinical sciences "L. Sacco", università degli Studi di Milano, Milano, Italy
[c] Coma science group, GIGA research & neurology department, university hospital of Liège, Liège, Belgium
[d] Center for sleep and consciousness, Postle laboratory, department of psychology and psychiatry, university of Wisconsin, Madison, WI, USA
[e] Fondazione Europea di Ricerca Biomedica, FERB Onlus, Milan, Italy
[f] Institute of science and technology, Federal university of São Paulo, 330, Rua Talim, São José dos Campos, Brazil

ARTICLE INFO

Article history:
Received 19 July 2016
Received in revised form 15 October 2016
Accepted 16 October 2016
Available online 3 February 2017

Keywords:
TMS/EEG
Gamma oscillations
Biomarkers
Bipolar disorder
GABAergic circuits

ABSTRACT

When directly perturbed in healthy subjects, premotor cortical areas generate electrical oscillations in the beta range (20–40 Hz). In schizophrenia, major depressive disorder and bipolar disorder (BD), these oscillations are markedly reduced, in terms of amplitude and frequency. However, it still remains unclear whether these abnormalities can be modulated over time, or if they can be still observed after treatment. Here, we employed transcranial magnetic stimulation (TMS) combined with EEG to assess the frontal oscillatory activity in eighteen BD patients before/after antidepressant treatments (sleep deprivation and light therapy), relative to nine healthy controls. In order to detect dominant frequencies, event related spectral perturbations (ERSP) were computed for each TMS/EEG session in all participants, using wavelet decomposition. The natural frequency at which the cortical circuit oscillates was calculated as the frequency value with the largest power across 300 ms post-stimulus time interval. Severity of depression markedly decreased after treatment with 12 patients achieving response and nine patients achieving remission. TMS/EEG resulted in a significant activation of the beta/gamma band response (21–50 Hz) in healthy controls. In patients, the main frequencies of premotor EEG responses to TMS did not significantly change before/after treatment and were always significantly lower than those of controls (11–27 Hz) and comparable in patients achieving remission and in those not responding to treatment. These results suggest that the reduction of natural frequencies is a trait marker of BD, independent from the clinical status of the patients. The present findings shed light on the neurobiological underpinning of severe psychiatric disorders and demonstrate that TMS/EEG represents a unique tool to develop biomarkers in psychiatry.

1. Introduction

Currently, bipolar disorder (BD) is the sixth leading cause of disability [1,2] and affects nearly 1–2% of the population worldwide [3]. During illness episodes of BD patients experience pervasive changes in mood and cognition, and deficits in executive functions, attention, psychomotor speed, verbal and visual memory often persist in euthymia [4], suggesting persistent changes in brain structure and function [5]. Identifying trait markers of persistently abnormal brain function is then a priority to identify new targets for treatment of these dysfunctions [6].

High frequency brain oscillations are rhythmic electrical phenomena, which are generated spontaneously and in response to stimuli, and which parallels the natural mechanism for carrying neural information among brain areas [7] and integrating cortical modules [8]. They are modified in many neuropsychiatric conditions, and in cognitive impairment [9]. Accordingly, they are also markedly reduced in BD. Cross-sectional studies suggest that alterations in the GABA/glutamatergic systems, and in neural circuits that regulate cognitive processing, may be reflected through in altered brain oscillations in BD [10]: even in euthymic conditions, patients showed reduced gamma oscillations [11,12],

* Corresponding author. Tel.: +39 02 26433156; fax: +39 02 26433265.
E-mail address: canali.paola@gmail.com (P. Canali).

http://dx.doi.org/10.1016/j.eurpsy.2016.10.005
0924-9338/

reduced long distance gamma coherence between frontal and temporoparietal regions [11], and decreased beta synchronization in the frontal region [13].

The combination of transcranial magnetic stimulation with electroencephalogram (TMS/EEG) represents a non-invasive, perturbational approach to precisely identify the integrity of thalamocortical circuits by directly challenging the brain's capacity to produce and sustain oscillatory activity [14–16]. With TMS/EEG, we previously reported that each cortical region tends to oscillate at a specific natural frequency [17], and that the main frequencies of frontal EEG responses to TMS were significantly reduced in patients with BD, major depressive disorder, and schizophrenia relative to healthy subjects (11–27 Hz vs 21–50 Hz, respectively) [18].

It remains unclear if these abnormalities change over time, and no longitudinal study has yet assessed high-frequency oscillations before and after response to antidepressants. Sleep deprivation and light therapy (SD + LT) provide a model of antidepressant treatment which allows to study the biological correlates of psychopathology at close time points and without the confounding effects of drugs [19]. Using this model antidepressant, we previously showed that response associates both, with TMS/EEG evoked measures of cortical excitability [20], with cortical volumes and function, and concentrations of neurotrophins [21]. Here, we aimed at investigating the oscillatory properties of the frontal cortex by TMS/EEG before and after treatment with combined chronotherapeutic techniques (SD + LT).

2. Materials and methods

2.1. Participants, treatment and data collection

We studied 18 consecutively admitted inpatients (14 females; mean ± SD age: 42.6 ± 9.6; age at onset of illness: 27.9 ± 7.4; years at school: 13.5 ± 4.3; previous depressive episodes: 6.1 ± 5.3; previous manic episodes: 3.1 ± 2.2) suffering from a major depressive episode, without psychotic features, affected by BD (DSM-IV criteria, SCID interview). Inclusion criteria were a baseline Hamilton depression rating scale (HDRS) score of 18 or higher; absence of other diagnosis on axis I and of mental retardation on axis II; absence of pregnancy, history of epilepsy, or major medical and neurologic disorders; absence of a history of drug or alcohol dependence within the last 6 months; no treatment with long-acting neuroleptic drugs in the last 3 months before admission. Nine healthy participants (6 females, age 38.9 ± 10.5) served as controls. After a complete description of the study, a written informed consent was obtained. All the research activities were approved by the local ethical committee.

All patients were treated for one week with SD + LT [22]. They were totally sleep deprived on days 1, 3 and 5, from 7:00 am to 7:00 pm of the subsequent day; and were allowed to recover sleep on days 2, 4, and 6. All patients were administered a 10,000-lux white light for 30 minutes, given at 3:00 am during the SD night and in the morning after recovery sleep, half an hour after awakening. Five patients were on ongoing lithium treatment (mean ± SD daily dose: 750 ± 251 mg), and continued it; thirteen started it together with the chronotherapeutic procedure (600 mg/day) to enhance its effect and prevent relapse [22]. No other psychotropic drug was administered during the study.

Severity of depression was rated at baseline (day 0) and after treatment (day 7) on the 21-item HDRS.

2.2. TMS/EEG procedure

TMS/EEG was performed before and after treatment (day 0 and 5, at 08:30 am). Stimulation parameters (location, intensity, angle, coil orientation) were maintained constant and reproducible through a neuronavigation system (Nexstim, Helsinki, Finland). Spontaneous EEG was continuously recorded for about 3 min before each TMS/EEG recording session.

Prior to the TMS/EEG recording sessions, anatomical whole head images of each patient were obtained with a 3.0-T scanner (Gyroscan Intera, Philips, Netherlands; T1-weighted MPRAGE sequence; TR 2500 ms, TE 4.6 ms, yielding 220 transversal slices with a thickness of 0.8 mm). The acquired volume was then segmented to obtain a 3D model of the surface of the scalp and of the cortex, to be uploaded in the brain navigation software.

The experimental setup included TMS with a Focal Bipulse 8-Coil (Eximia TMS stimulator; Nexstim Ltd., Helsinki, Finland) equipped with a navigated brain stimulation system (NBS; Nexstim Ltd.) and a 3D-infrared tracking position sensor unit (Polaris, Northem Digital Inc., Waterloo, Canada). EEG was recorded with a 60-channel TMS-compatible EEG amplifier (Nexstim Ltd, Helsinki, Finland) equipped with sample-and-hold circuits that prevent the recording from the powerful TMS-related artifacts [23]. EEG cap was repositioned before each session, controlling for reproducibility of location using the NBS system. Impedances were kept below 5 kΩ. EEG signals were band-pass filtered between 0.1–500 Hz, and sampled at 1.450 Hz with 16-bit resolution. Electro-oculogram was recorded with two additional electrodes on the forehead to measure ocular movements and blinks.

This equipment provides in real time the TMS coil position and subject's head, within the reference space of individual magnetic resonance imaging (MRI) by the co-registration between the fiducials points (nasion, left tragus and right tragus) selected on the individual MRI with the corresponding digitized scalp landmarks. The exact location of the stimulation site was adjusted on the individual MRI in order to prevent accidental muscle twitches that often affect EEG recordings, and to estimate the electrical field induced by TMS pulses, which depends on the stimulation intensity (V/m). The TMS intensity was adjusted according to the maximum electric field intensity (expressed in V/m) estimated on the cortical surface, rather than relying on individual motor threshold or on the percentage of maximum stimulator output.

To ensure significant EEG responses [24] TMS intensity was always > 90 V/m as estimated by the NBS system, for each patient. TMS was delivered on the convexity of the middle caudal portion of the superior frontal gyrus close to the midline (Brodmann's areas 6), with the current perpendicular to its main axis. These brain areas showed the highest changes of metabolic rate and EEG correlates between wake and sleep [25] and have been associated with the antidepressant effects of SD [19].

To obtain significant TMS evoked potentials (TEP) with a good signal-to-noise ratio, about 200–300 stimuli were delivered for each session at frequency randomly distributed between 1.5–1.8 s (equivalent to about 0.5–0.6 Hz). This stimulation rate does not induce significant reorganization/plasticity processes that might possibly interfere with longitudinal measurements [26]. During TMS stimulation patients were laying on an ergonomic chair, with eyes open looking at a fixation point on a screen, and wore inserted earplugs continuously playing a masking noise that abolished the auditory potentials elicited by TMS-associated click [27].

2.3. Data analysis

Data analysis was carried out using Matlab (2007b, The Mathworks Inc., Natick, MA). TMS evoked potentials containing activity from sources other than neural, such as spontaneous muscles activity or ocular movements, were automatically identified and rejected using a semi-automatic algorithm (EOG > 70 μV or absolute power of EEG channel F8 above 25 Hz, > 0.9 μV^2) [24]. Thereafter, single trials and channels contaminated by residual artifacts were visually inspected and excluded from further analysis. Selected trials were band-pass