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# Abnormal brain oscillations persist after recovery from bipolar depression

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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],

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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 $\mu V^2$) [24]. Thereafter, single trials and channels contaminated by residual artifacts were visually inspected and excluded from further analysis. Selected trials were band-pass

filtered between 2–80 Hz, down-sampled to 725 Hz, and re-referenced to the common average reference. Each TMS-evoked response was obtained by averaging 150–250 artifact free trials.

In order to quantify the responses in the time-frequency domain [28], from each TMS/EEG session, we measured the event-related spectral perturbation (ERSP) changes in the power spectrum using wavelet decomposition (3.5 oscillation cycles) across single-trials at the channel closest to the stimulation site (selected channel for single subject: Fz $n = 1$; FC1 $n = 8$; FCz $n = 8$; FC2 $n = 4$; C1 $n = 1$; Cz $n = 4$; C2 $n = 1$). The ERSP was normalized by subtracting the mean baseline power spectrum. Significant ERSP were evaluated by applying a bootstrap statistical method based on a surrogate distribution randomly derived from the pre-stimulus onset (−700 −50 ms). Statistical significance level was set at $P < 0.01$ and only significant values were considered in the analysis. Averaged ERSP values across all trials of a session were calculated between 8 and 50 Hz (1 Hz bin resolution) over a 20–300 millisecond time window, corresponding to the main EEG activity evoked by TMS. The natural frequency was computed as the frequency bin with the largest cumulated ERSP over time [17].

Data were analyzed with Student's *t*-test and Pearson's correlation. Moreover, we performed a repeated measures ANOVA on TMS evoked natural frequencies before/after treatment, with time and response to treatment as independent factors. Analyses were performed in the context of the general linear model (GLM) [29,30]. The significance of the effect of the single independent factor on each dependent variable was estimated (least squares method) by parametric estimates of predictor variables and following standard computational procedures [31].

## 3. Results

Severity of depression markedly decreased after treatment (HDRS day 0: 23.2 ± 5.8; day 7: 8.5 ± 7.5; $t = 8.85$, $P < 0.00001$), with 12 patients (66.6%) achieving response (HDRS 50% reduction) and 9 patients (50%) achieving remission (HDRS < 8).

Data obtained with the TMS/EEG procedure are showed in Fig. 1. Top panel shows the average EEG responses to TMS (grey traces) for the channel closest to the stimulation site (black trace) over the premotor area. To detect the natural frequency, we measured the event-related spectral perturbation (ERSP) for each

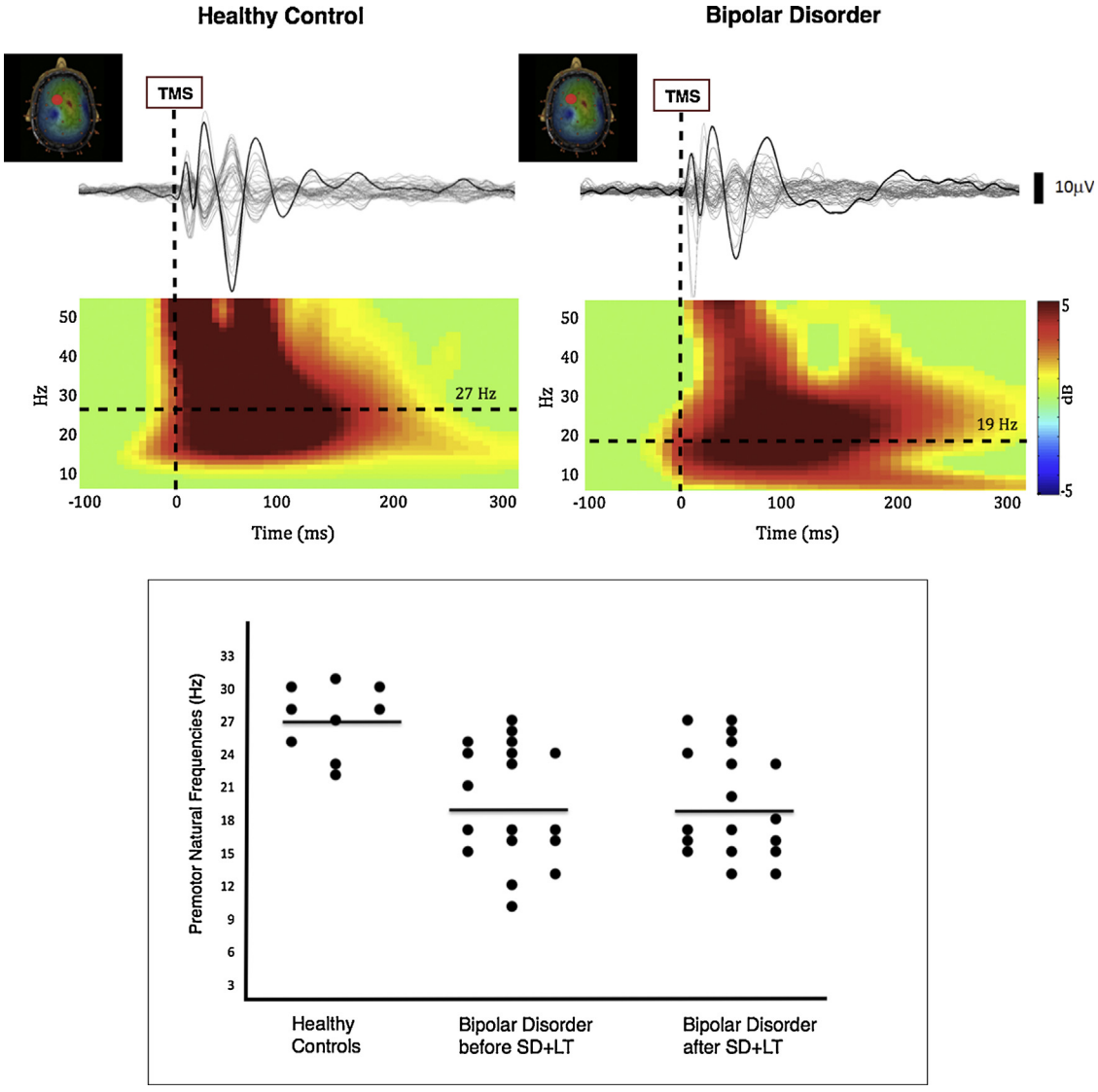


**Fig. 1.** Top panel: average EEG responses to TMS (grey traces represent the 60 recording channels) for the channel closest to the stimulation site (black trace) over the premotor area; color-coded: event-related spectral perturbation (ERSP) plots reflect the significant TMS related changes in amplitude and their duration. Dotted lines show the frequency with the highest activity (natural frequency). Data are shown from a representative healthy subject and for a BD patient. Bottom panel: individual natural frequency values for healthy control subjects and patients with bipolar disorder before/after the antidepressant treatments (SD + LT).

single subject. Specifically, we cumulated the ERSP between 8–50 Hz and 20–300 ms evoked by TMS. The main frequency at which a system oscillates was selected by the frequency showing the largest activity across time. Data shown in Fig. 1 are from a representative subject.

TMS resulted in a significant activation of the beta/gamma band response in healthy controls ($27.0 \pm 3.0$ Hz, range 23–33). In patients, the main frequencies of frontal EEG responses to TMS did not significantly change before/after treatment (day 0: $19.44 \pm 5.41$ Hz, range 10–27; day 7: $19.30 \pm 4.99$ Hz, range 13–27; $t = 0.391$, $P = 0.700$), and at both time points were significantly lower than those of controls (day 0: $t = 3.87$, $P = 0.0006$; day 7: $t = 4.22$, $P = 0.0002$). Values were closely similar in patients eventually achieving remission, or not (remitters: day 0, $20.37 \pm 5.50$ and day 7, $20.21 \pm 4.93$; non remitters: day 0, $18.51 \pm 5.46$ and day 7, $18.40 \pm 5.18$). Values before/after treatment were highly correlated ($r = 0.9616$, $P < 0.0001$).

A repeated measures ANOVA gave no effects of time and of response to treatment on EEG measures before/after treatment (time: $F_{1,16} = 0.14$, $P = 0.709$; response: $F_{1,16} = 0.56$, $P = 0.467$; interaction: $F_{1,16} = 0.006$, $P = 0.941$). Moreover, natural frequencies did correlate neither with HDRS scores before/after treatment, nor with their delta change, nor with clinical and demographic characteristics of the patients.

## 4. Discussion

In this study, we assessed natural frequencies of cortical circuits before and after antidepressant treatment in BD. Notably, neither changes over time nor any correlation with the severity of depression were observed. Evoked brain oscillations remained lower than those of healthy controls, and comparable in patients achieving remission and in those not responding to treatment. This suggests that the reduction of natural frequencies is a trait marker of BD, independent from the current clinical status of the patients.

The present observation that successful antidepressant treatment is unable to normalize thalamocortical circuits in BD is consistent with previously reported reduced gamma coherence in euthymic patients with BD [11]. Recently, we showed that the reduction of natural frequencies is detectable in schizophrenia, BD, and major depressive disorder [18]. The observation of its persistence in BD after treatment now suggests that this trait marker could be linked to persistent trait characteristics of brain structure and function in BD. Based on existing literature, the most likely candidates are GABAergic and glutamatergic neurotransmission.

Fast activity of parvalbumin GABA interneurons is needed for high-frequency oscillations [32,33], with gamma suppression resulting from their inhibition [34]. GABA inhibitory interneurons produce and sustain complex large-scale network oscillations in fast frequency bands (40–100 Hz) [35], also generating inhibitory potentials in excitatory pyramidal neurons [36]. This GABAergic activity results in gamma oscillations [37–40], and is reduced in BD. *Post-mortem* studies showed a reduced density of GABAergic neurons in the cortex of patients with BD [35], with a reduction in the numerical density of parvalbumin- and somatostatin-positive interneurons [41] and in the prefrontal cortex reduced markers of the parvalbumin subpopulation [42]. *In vivo*, MR spectroscopy confirmed low GABA levels in the prefrontal cortex [43].

In the generation and maintenance of high frequency oscillations, GABAergic mechanisms are likely to interact with glutamatergic mechanisms, involving NMDA and AMPA receptors [44]. Glutamate levels in brain tissue were increased both *in vivo* [45], and *post-mortem* [46] in patients with BD. Genetic ablation of NMDA receptors in parvalbumin interneurons resulted in increased gamma power [47]. The decrease of excitatory input to fast spiking parvalbumin interneurons, induced by the NMDA antagonist ketamine [48,49], lead to increased gamma activity [50–52]. AMPA receptor antagonists inhibit gamma oscillations [32]. Ketamine has rapid and marked antidepressant effects in BD [53], and it is not the only therapeutic agent to act on brain oscillations. Evoked beta responses from lithium-treated BD patients were higher than those in both drug-free euthymic BD patients and healthy controls [54], and interestingly, *post-mortem* GABA levels were increased after lithium treatment [46].

Altogether, these data support the hypothesis that abnormal GABAergic and glutamatergic neurotransmission could be critical to explain the abnormal gamma oscillations observed in our patients [34,55], and that these abnormalities are persistent and detected both during the lifespan, and *post-mortem*. Alternative interpretations cannot be ruled out; for instance, EEG power in high frequency bands has been positively correlated with arterial spin labelling MRI measures of resting cerebral perfusion in healthy subjects [56].

Fast oscillatory dynamics are needed for large-scale integration and synchronous communication between brain regions, are thought to parallel the emergence of coherent behavior and cognition [57], and are implicated in many brain functions including the processing of sensory stimuli [36], language comprehension [58], cognitive skills [59], cognitive processing in recognition memory [60]. It is tempting to hypothesize that their persistent abnormality in BD could mark the persistent deficits in higher cognitive functions and brain network connectivity associated with the disorder [4,5,61]. Further research is needed to clarify this issue.

Strengths of the present study include a focused research question, state-of-the-art TMS/EEG methods, and straightforward effects. However, our experimental setting did not allow to directly assess the role of deeper structures, such as hippocampus, which contribute to gamma oscillations [62]. We obtained an excellent power to study group differences, but could not consider other biological markers, gene variants, and their interaction with clinical variables. Patients were non drug-naïve. Recruitment was in a single ethnic group, thus raising the possibility of population stratifications limiting the generalizability of the findings.

## Authors and contributors

F.B., P.C., M.M. and M.R. designed the study. E.S., F.B. and M.M. obtained the funding. C.C., F.B. and P.C. were involved in participants' recruitment and selection. P.C. and G.S.P. collected the clinical data with the supervision of F.B. P.C., S.C., G.S.P. and O.G. carried out the TMS-EEG experimental procedures. P.C., M.R., M.M., S.C., G.S.P., A.C. and OG designed the data analyses and carried it out with contributions from F.B. P.C. and F.B. wrote the first draft of the manuscript, with other authors contributing to data interpretation and final manuscript preparation. F.B. and P.C. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors take final responsibility for the decision to submit for publication.

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## Disclosure of interest

The authors declare that they have no competing interest.

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