Brief report

Shared reduction of oscillatory natural frequencies in bipolar disorder, major depressive disorder and schizophrenia

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ABSTRACT

Introduction: Recent studies have demonstrated that cortical brain areas tend to oscillate at a specific natural frequency when directly perturbed by transcranial magnetic stimulation (TMS). Fast electro-encephalographic (EEG) oscillations, which typically originate from frontal regions, have been reported to be markedly reduced in schizophrenia.
Methods: Here we employed TMS/EEG to assess the natural frequency of the premotor area in a sample of 48 age-matched participants (12 each in major depression disorder (MDD)), bipolar disorder (BPD), schizophrenia (SCZ) and healthy controls. Event related spectral perturbations (ERSP) were obtained for each study participant using wavelet decomposition.
Results: TMS resulted in a significant activation of the beta/gamma band response (21–50 Hz) to frontal cortical perturbation in healthy control subjects. By contrast, the main frequencies of frontal EEG responses to TMS were significantly reduced in patients with BPD, MDD and SCZ (11–27 Hz) relative to healthy subjects.
Conclusions: Patients with bipolar disorder, major depression and schizophrenia showed a significantly lower natural frequency of frontal cortico-thalamocortical circuits compared to healthy controls. These results suggest a common neurobiological mechanism of corticothalamic impairment. The most likely candidates include dysfunction of GABAergic circuits.
Limitations: Further studies are needed to consider other biological markers, gene variants, and their interaction with clinical variables.

1. Introduction

High-frequency gamma oscillations are critical for communication among brain areas, thus allowing integration among cortical modules (Nikolic et al., 2013; Rodriguez et al., 1999; Whittington et al., 2000b). In the last decade clinical research on oscillatory brain dynamics reported altered neuronal oscillations in neuropsychiatric disorders (Basar, 2013; Basar and Guntekin, 2008; Herrmann and Demiralp, 2005; Uhlhaas and Singer, 2010),

suggesting that reduced gamma oscillations could be common to bipolar disorder (BPD), major depressive disorder (MDD) and schizophrenia (SCZ) (Maharajh et al., 2007; O'Donnell et al., 2004b).

Frontal cortical gamma activity (30–50 HZ), as indexed through electroencephalography (EEG), is reduced in patients with SCZ (Uhlhaas et al., 2008), in response to odd-ball paradigm (Gallinat et al., 2004; Haig et al., 2000; Symond et al., 2005) or cognitive control task (Cho et al., 2006). EEG power and phase synchronization in beta/gamma frequencies bands after to 40 Hz auditory stimulation are also reduced (Kwon et al., 1999; Light et al., 2006). Findings in mood disorders are similar. BPD patients in the manic or mixed state show hampered auditory EEG synchronization in beta/gamma band (20–50 Hz) during a click trains paradigm

(O'Donnell et al., 2004a), and reported significantly reduced long distance gamma coherence in a visual odd-ball paradigm (Ozerdem et al., 2010). A recent study reported a decrease of frontal gamma oscillations in patients with MDD and BPD in response to implicit emotional tasks (Lee et al., 2010; Liu et al., 2012). A reduced phase locking and evoked power at 40-Hz auditory steady-state stimulation in first episode psychosis of patients with either schizophrenia or affective disorders has also been reported (Spencer et al., 2008).

The combination of transcranial magnetic stimulation with high-density electroencephalographic recording (TMS/EEG) represents a provocative approach useful to identify the integrity of thalamocortical circuits by directly challenging the brain's capacity to produce and sustain oscillatory activity (Buzsaki and Watson, 2012; Canali, 2014; Rosanova et al., 2012). By combining TMS/EEG we previously demonstrated that each cortical region perturbed by TMS tend to oscillate at specific natural frequency (Rosanova et al., 2009), and we found a deficit in the oscillatory properties in schizophrenia resulting in a reduction of frontal natural frequencies (Ferrarelli et al., 2008; Ferrarelli et al., 2012). Here we hypothesized impairments of the thalamocortical system to produce fast oscillations in bipolar disorder and major depression. We then aimed at investigating the oscillatory properties of the premotor cortex by employing TMS/EEG in two groups of patients with bipolar disorder and major depression, and using a group of healthy subjects as negative controls and a group of patients with schizophrenia as positive controls.

2. Methods

We studied 12 healthy subjects as controls (HC), and 36 consecutively admitted inpatients suffering from three different psychiatric disorders (DSM-IV criteria, SCID interview): either major depressive episode, without psychotic features, in course of BPD ($n=12$) or in course of MDD ($n=12$), or chronic undifferentiated schizophrenia ($n=12$). Inclusion criteria were the absence of other diagnoses 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 dependency or abuse within the last 6 months. Six BPD were taking lithium salts. All MDD patients were on antidepressant treatment, also with benzodiazepines ($n=8$) or mood stabilizers ($n=3$). SCZ patients were taking antipsychotics (typical neuroleptics: $n=5$; a typical antipsychotics: $n=7$). A written informed consent was obtained for all study participants. The local ethics committee approved the experimental protocol.

The experimental setup included a TMS compatible 60-channel EEG amplifier (Nexstim) equipped with sample-and-hold circuits that prevents the recording from the powerful TMS-related artifact (Virtanen et al., 1999). Accuracy and reproducibility of TMS/EEG responses were controlled with a Navigated Brain Stimulation (NBS) system (Nexstim) and a 3D-infrared Tracking Position Sensor Unit (Northem Digital Inc). (For details of methods, see Rosanova et al. (2009) and Supplementary materials.)

TMS was delivered on the convexity of the middle caudal portion of the superior frontal gyrus close to the midline (Broadmann's areas 6), with the current perpendicular to its main axis. To ensure significant EEG responses (Casali et al., 2010; Komssi et al., 2007; Rosanova et al., 2009) intensity of TMS induced electric field was always > 90 V/m as estimated by the NBS system, for each study participant. We delivered about 200–300 stimuli for each session at a frequency randomly jittered between 1.5 and 1.8 s (equivalent to about 0.5–0.6 Hz). (See Supplementary for detailed description.)

Data analysis was carried out using Matlab (The Mathworks Inc.) with the EEGLAB toolbox (Delorme and Makeig, 2004). Each TMS-evoked response was obtained by averaging 150–250 artifact free trials. (For detailed TMS-evoked potential acquisition and analyses, see Casali et al. (2010) and Supplementary materials.)

In order to quantify the responses in the time-frequency domain (Delorme and Makeig, 2004), 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. 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 (ranging from -700 to -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 milliseconds 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 (Rosanova et al., 2009). Differences between the frontal natural frequencies of the four study groups were analyzed with one-way ANOVA followed by post-hoc Newman–Keuls's tests. Pearson correlation analysis between medications doses, clinical variables and natural frequency were performed. Analyses were carried out using a commercial available software (StatSoft Statistica) and following standard computational procedures (Hill and Lewicki, 2006).

3. Results

Clinical and demographic characteristics of the sample divided according to diagnosis, and the evoked natural frequencies, are resumed in Table 1.

All four groups were closely age-matched. Patients with bipolar or unipolar depression had a similar age at onset and duration of illness and did not differ on the Hamilton Depression Rating Scale (HDRS) score. Patients with schizophrenia reported positive and negative symptoms as measured by PANSS.

Data obtained with the TMS/EEG procedure are resumed in Fig. 1.

Table 1
Demographic and Clinical Characteristics of the study groups[a].

	Healthy subjects	Bipolar disorder	Major depression	Schizophrenia	F	P
Gender (m/f)	5/7	2/10	4/8	9/3		
Age (yrs)	39 (15)	36 (7)	46 (8)	38 (9)	2.1	0.1
Age at onset (yrs)		25 (6)	29 (9)	25 (6)	1.1	0.3
Duration of illness (yrs)		11 (9)	18 (10)	13 (6)	0.1	0.1
PANSS (positive)				18 (4)		
PANSS (negative)				18 (4)		
PANSS (general)				37 (5)		
HDRS (baseline)		26 (6)	24 (7)		1.1	0.8
Frontal natural frequency (Hz)	27.25 (3.22)	20.30 (3.72)	19.24 (5.03)	20.30 (4.22)		

[a] Values are expressed as mean and standard deviations.