Schizophrenia Research 206 (2019) 436–439

Contents lists available at ScienceDirect

Schizophrenia Research

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

Abnormalities in the evoked frontal oscillatory activity of first-episode psychosis: A TMS/EEG study

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ARTICLE INFO

Article history:
Received 8 October 2018
Received in revised form 30 October 2018
Accepted 7 November 2018
Available online 23 November 2018

Keywords:
TMS
EEG
Cortical oscillations
First-episode psychosis

ABSTRACT

TMS with simultaneous EEG allows assessing the intrinsic oscillatory activity of cortical neurons. We recently showed reduced frontal cortical oscillations in chronic schizophrenia (SCZ). Here we investigated the oscillatory activity of first-episode psychosis (FEP) patients after TMS of a frontal area, the motor cortex. Compared to healthy controls, FEP patients had significantly reduced beta/low gamma oscillations, which were associated to worse clinical symptoms. Altogether, this study demonstrates that TMS/EEG recordings: 1) are feasible in acute, early-course psychotic patients; and 2) reveal intrinsic oscillatory deficits at illness onset, which may help design more effective, early interventions in SCZ.

1. Introduction

Converging post-mortem (Volk and Lewis, 2014), neuroimaging (Barch and Ceaser, 2012; Heilbronner et al., 2016), and neurophysiological (Uhlhaas and Singer, 2015) data point to dysfunctions in the cerebral cortex, especially the frontal lobe, in schizophrenia (SCZ). Transcranial Magnetic Stimulation (TMS) can noninvasively probe the human cortical surface (Hallett, 2007). Furthermore, TMS with EEG allows characterizing the neurophysiological properties of frontal cortical areas (Farzan et al., 2016) directly and without any conscious effort or motivation, thus minimizing some of the confounds reported in patients with SCZ (Miniussi and Thut, 2010).

In previous work, we found reduced TMS-evoked EEG responses in frontal areas, including the motor cortex, but not parietal regions, in SCZ patients relative to healthy controls (HC). These reductions were observed mainly in the frequency domain, in the high-beta/low gamma range, and were particularly prominent in the prefrontal cortex (Ferrarelli et al., 2008; Ferrarelli et al., 2012). Although promising, these findings, which were recently replicated by another research group (Canali et al., 2015), were established in chronic SCZ patients with long-term exposure to antipsychotic medications.

Here we measured, for the first time, the EEG responses of first-episode psychosis (FEP) patients, who were medication naïve or minimally treated (<1 month), after TMS of a frontal area, the motor cortex. We chose motor cortex for two reasons. First, we wanted to show the feasibility of TMS/EEG recordings in FEP patients, who are very difficult to engage, by targeting a cortical area that is easy to access. Second, we wanted to examine whether early-course patients had reduced EEG frontal oscillations after TMS of the motor cortex, as previously found in chronic SCZ. Thus, we performed TMS/EEG recordings in FEP patients and HC, and investigated group differences in TMS-evoked EEG activity, both in the time and frequency domains.

2. Methods

Sixteen FEP patients and eleven HC were recruited (Table 1). This study was approved by the University of Pittsburgh Institutional Review Board, and all participants provided written informed consent prior to completing any study procedures. TMS was applied to the left primary motor cortex (M1), which was identified both anatomically and functionally. The precentral gyrus of the frontal lobe, corresponding to M1, was identified on T1 individual MRI. M1 location was also established by calculating the individual resting motor threshold (RMT). Specifically, RMT was established as the TMS intensity necessary to observe a response in the first dorsal interosseous muscle in 5 out of 10 trials. TMS was delivered at 110% of RMT; however, to avoid re-afferent somatosensory activity (Fecchio et al., 2017; Petrichella et al., 2017), we targeted a motor region adjacent to the hand area and ensured that no hand movement was observed in, or reported by, any participant. A TMS neuronavigation system (Localite, LTD) was utilized to reliably stimulate M1 throughout the TMS/EEG sessions. It was also used to calculate the distance between the TMS scalp location and the cortical surface. RMT and scalp-to-cortex distance findings are presented in supplementary material. TMS-evoked EEG responses were recorded

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https://doi.org/10.1016/j.schres.2018.11.008
0920-9964/

Table 1
Clinical variables of study groups.

Clinical measures	Healthy controls	First-episode psychosis (FEP) patients	p Value
Age (years)	22.6 ± 6.3	22.5 ± 5.2	NS
Gender (# Female)	3	4	NS
SAPS scores	N/A	18.3 ± 12.5	N/A
SANS scores	N/A	31.0 ± 11.5	N/A

using a 64-electrode cap and a TMS-compatible amplifier (BrainAmp, BrainVision). Each session consisted of 250–300 stimuli delivered at 0.4 to 0.6 Hz according to international safety guidelines (Rossi et al., 2009). Data analysis was performed with Matlab R2015a (The Mathworks, Natick, MA). EEG signals were segmented in a time window of ±800 ms around the stimulus and epochs were visually inspected to reject trials and channels contaminated by environmental noise and/or muscle activity as in previous studies (Casali et al., 2013; Ferrarelli et al., 2012; Rosanova et al., 2009). Bad channels were interpolated using the spherical function of the public license toolbox EEGLAB, and TMS-evoked potentials were then calculated by averaging the resulting baseline-corrected and average-referenced epochs. In the time domain, TMS-evoked global activity was computed at each time-point as the root mean-squared value of the voltages across all channels (GMFP). In the frequency domain, TMS-evoked activations between 8 and 45 Hz were assessed by calculating the event-related spectral perturbation (ERSP) and inter-trial coherence (ITC) using Morlet wavelets, as implemented in the EEGLAB toolbox. ERSP and ITC matrices were averaged between 20 and 300 ms for each channel, and power spectra were also expressed as the percentage of power in a given frequency (relative spectral power, RSP). Natural frequency was calculated as the frequency with the largest average spectral power (averaged from 20 to 300 ms). A non-parametric, Monte Carlo FDR-adjusted permutation test was employed to assess GMFP significance and clustering analysis was performed on spatial-temporal matrices as well as spatial-frequency matrices of ERSP, ITC, and RSP to identify channels and frequency bands with significant between-group differences. After outlier analysis, data was tested for normality with the Shapiro-Wilk test and Pearson correlation analyses were performed between TMS-evoked measures and the Scale for the Assessment of the Positive and Negative Symptoms (SAPS and SANS) scores in FEP patients. For additional information, see supplemental material.

3. Results

We found that both FEP patients and HC had several evoked EEG oscillations occurring in the first 300 ms after TMS of M1 (Fig. 1A). In the time domain, the TMS-evoked global response, assessed with GMFP, did not differ between groups (Fig. 1B). Similarly, clustering analyses of spatio-temporal matrices of EEG voltage established no difference between FEP and HC In the frequency domain, FEP patients showed lower activity in the beta/low gamma bands relative to HC. Specifically, FEP showed a significantly decreased RSP in the 27–33 Hz range in a cluster of fronto-central electrodes overlying the motor cortex (clustering analysis, $p = 0.01$, Fig. 2A and Table 2). ITC and ERSP values were also decreased at trend level significance (Table 2). RSP values were then averaged across the electrodes showing significant effects and cumulated in this frequency range. Cumulated RSP (cRSP) values were then compared between groups and found to be significantly decreased in FEP patients relative to HC (Wilcoxon-ranksum test, $p = 0.0004$, Fig. 2B). In the same cluster, the NF was reduced at trend level significance (HC = 27.45 ± 5.9, FEP = 22.16 ± 6.2, $p = 0.05$). Furthermore, after removal of an outlier lower cRSP were associated with both worse positive symptoms (SAP, Pearson, $R = -0.52$, $p = 0.047$, Fig. 3A) and negative symptoms (SAN, Pearson, $R = -0.54$, $p = 0.037$, Fig. 3B). Significant correlations between cRSP and SAPS/SANS were also found with Spearman rank coefficients from all FEP patients (Supp. Fig. 1). In contrast, no significant correlation was found between ERSP, ITC, NF and clinical scores (Supp. Table 1).

4. Discussion

This study investigated, for the first time, EEG responses in FEP patients after TMS of a frontal area, M1. We found that, compared to HC, FEP patients had reduced beta/low gamma oscillations in a fronto-central cluster overlying M1, and this reduction correlated with the severity of their clinical symptoms.

Reduced beta/gamma frontal EEG oscillations were reported by previous electrophysiological studies in SCZ (Uhlhaas and Singer, 2015). SCZ patients had decreased synchronization in beta and gamma bands in contralateral motor cortex during self-paced button presses, consistent with dysfunction of motor-sensory communication (impaired efference motor copy/corollary discharge) (Ford et al., 2008). Reduced EEG frontal gamma oscillations were also observed during all phases (encoding, maintenance, retrieval) of a working memory task (Haenschel et al., 2009), as well as during cognitive control tasks (Cho et al., 2006; Minzenberg et al., 2010) in SCZ patients compared to HC. Furthermore, in two recent studies we found that SCZ patients had decreased frontal beta/gamma EEG activity after TMS of frontal areas, including M1, relative to HC (Ferrarelli et al., 2008; Ferrarelli et al., 2012). In contrast, other electrophysiological studies failed to report reduced EEG fast oscillations after TMS of M1 in patients with SCZ relative

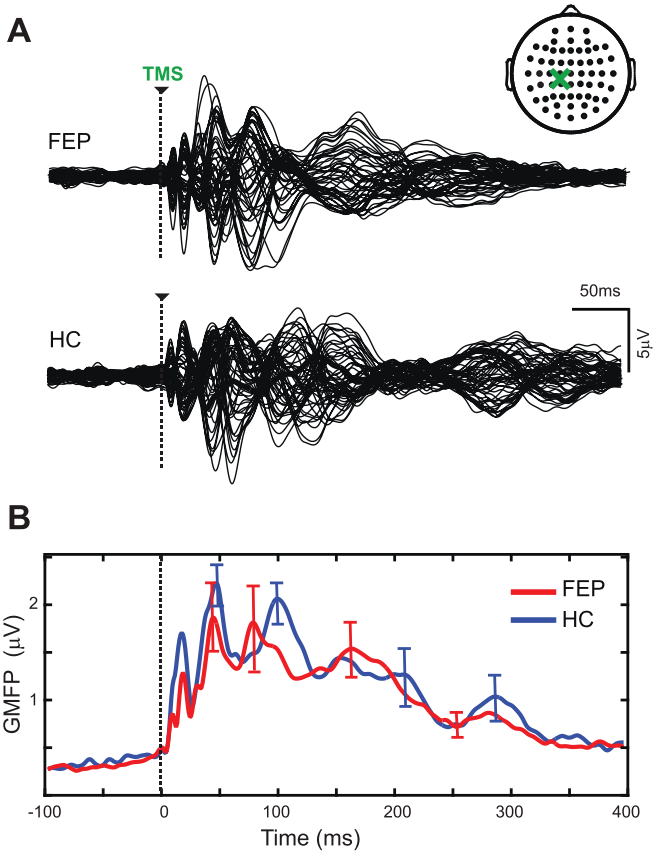

Fig. 1. In the time domain, evoked EEG responses after TMS of the motor cortex did not differ between FEP and HC. A: In both FEP and HC participants, TMS of the motor cortex (green cross) evoked several EEG components, as shown in the butterfly plot from a representative subject per each group. B: TMS-evoked global response, measured with the global mean field power (GMFP), did not significantly differ between FEP (red) and HC (blue, non-parametric Monte Carlo FDR-adjusted permutation test).

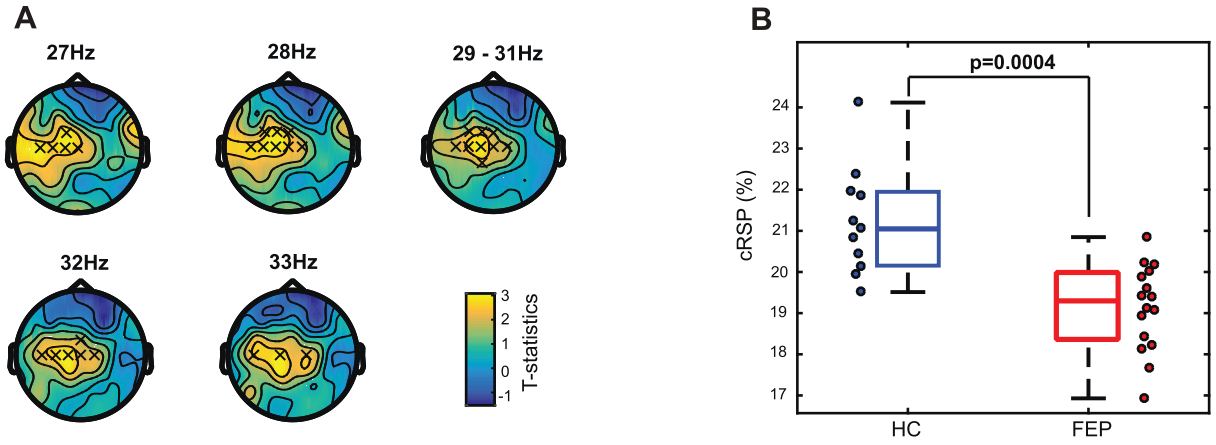

Fig. 2. FEP patients had a reduction in TMS-evoked frontal beta/low gamma activity relative to HC. A: Topographic plots show the T-statistics of the difference in relative spectral power (RSP) between HC and FEP groups for the frequency band (27-33 Hz) in which a significant difference was observed (clustering analysis, 5000 permutations, alpha<0.05). Channels showing significant effects are marked with an X. B: Cumulated relative spectral power (cRSP) was significantly decreased in FEP patients (red boxplot) relative to HC (blue boxplot, $p = 0.0004$, Wilcoxon ranksum test). cRSP values for individual subjects are shown as blue (HC) and red (FEP) circles.

to HC (Farzan et al., 2010; Frantseva et al., 2014; Radhu et al., 2015). Of note, all these studies were conducted in chronically medicated SCZ patients. Here we showed that a reduction in EEG beta/low gamma range oscillations after TMS of the motor cortex is observed in first-episode, antipsychotic naive or minimally treated psychotic patients. This indicates that deficits in TMS-evoked EEG responses are present at illness onset. It also suggests that medications, which can significantly affect brain oscillations (Premoli et al., 2017), are unlikely to account for these findings. Furthermore, in FEP patients reduced frontal beta/low gamma activity was associated to higher SAP/SAN scores. Thus, this association point to an involvement of reduced TMS-evoked frontal fast oscillations in the clinical manifestation of psychosis, which could in part regulate the severity of FEP patients' symptoms.

Building on these initial findings, future work is needed to address the limitations of the present study. First, we recorded a relatively small sample of FEP patients, which were eventually diagnosed with SCZ ($N = 10$) or other psychotic disorders ($N = 6$). Thus, additional studies in larger samples will help establishing whether reduced fast oscillations are present in all FEP patients, regardless of their final diagnoses or medication status. However, here we found no difference in any of the main TMS-evoked parameters between patients eventually diagnosed between FEP-SCZ and FEP-non SCZ as well as between medication naïve vs antipsychotic medication FEP patients (Supp. Table 2). Furthermore, there was no significant correlation between medication dose, calculated as chlorpromazine equivalents, and these TMS-evoked EEG parameters (Supp. Table 3). Second, here we focused on the relationship between TMS-related EEG measures and clinical symptoms. However, future studies should also investigate the association between TMS-evoked EEG parameters and cognitive measures in FEP patients. Finally, it will be important to investigate TMS-evoked EEG responses of other cortical areas, including dorsolateral prefrontal cortex, in first-episode psychosis. Nonetheless, here we demonstrated that TMS/EEG recordings can be performed in early course, acutely psychotic patients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.11.008.

Conflict of interest

All authors declare that there are no potential conflicts of interest.

Funding sources

This work was supported by The Pittsburgh Foundation Emmerling Rising Star Award in Psychiatric Research (Reference No. FPG00031) and São Paulo Research Foundation (FAPESP) grants #2016/08263-9 and #2016/20422-5.

CRediT authorship contribution statement

Fabio Ferrarelli: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Rachel E. Kaskie:** Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **Bianca Graziano:** Investigation, Writing - review & editing. **Catarina Cardoso Reis:** Formal analysis, Writing - review & editing. **Adenauer G. Casali:** Formal analysis, Writing - review & editing.

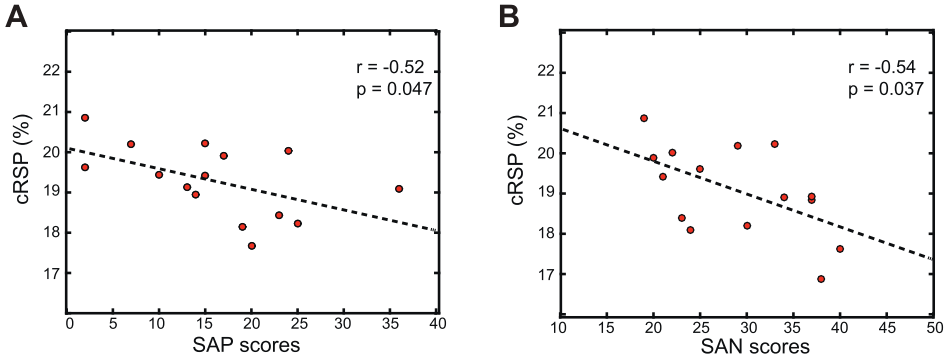

Fig. 3. In FEP patients, reduced beta/low gamma activity (cRSP) was associated with worse positive and negative clinical symptoms. Panels show Pearson's correlation coefficients between cRSP and SAP (panel A, $r = -0.52$, $p = 0.047$) and SAN scores (panel B, $r = -0.54$, $p = 0.037$) after removing one sample identified as outlier.

Table 2
Clustering analyses of differences in TMS-evoked EEG activity between FEP and HC.

	p-Value	Cluster-level statistic	Band (Hz)	Channels
ITC	0.0524	97.509	28–42	Fcz, C1
ERSP	0.0502	90.278	26–40	Fcz, C1
RSP	0.0146	156.65	27–33	Left central

Acknowledgements

The authors would like to thank Kevin Eklund, Debra Montrose, Elizabeth Radomsky, Alicia Thomas and others at Western Psychiatric Institute and Clinic for recruitment and assessment of participants. We also thank Julia Badyna, Joanne Chiu, Soukaina Eljamri, Adelle Hamilton, and Alicia Thomas for their assistance in conducting TMS studies.

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