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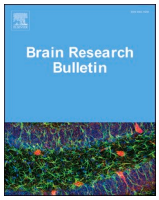

Investigating cortical excitability and inhibition in patients with schizophrenia: A TMS-EEG study

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ABSTRACT

Background: Transcranial magnetic stimulation (TMS) combined with electromyography (EMG) has widely been used as a non-invasive brain stimulation tool to assess excitation/inhibition (E/I) balance. E/I imbalance is a putative mechanism underlying symptoms in patients with schizophrenia. Combined TMS-electroencephalography (TMS-EEG) provides a detailed examination of cortical excitability to assess the pathophysiology of schizophrenia. This study aimed to investigate differences in TMS-evoked potentials (TEPs), TMS-related spectral perturbations (TRSP) and intertrial coherence (ITC) between patients with schizophrenia and healthy controls.

Materials and methods: TMS was applied over the motor cortex during EEG recording. Differences in TEPs, TRSP and ITC between the patient and healthy subjects were analysed for all electrodes at each time point, by applying multiple independent sample t-tests with a cluster-based permutation analysis to correct for multiple comparisons.

Results: Patients demonstrated significantly reduced amplitudes of early and late TEP components compared to healthy controls. Patients also showed a significant reduction of early delta (50–160 ms) and theta TRSP (30-250ms),followed by a reduction in alpha and beta suppression (220–560 ms; 190–420 ms). Patients showed a reduction of both early (50–110 ms) gamma increase and later (180–230 ms) gamma suppression. Finally, the ITC was significantly lower in patients in the alpha band, from 30 to 260 ms.

Conclusion: Our findings support the putative role of impaired GABA-receptor mediated inhibition in schizophrenia impacting excitatory neurotransmission. Further studies can usefully elucidate mechanisms underlying specific symptoms clusters using TMS-EEG biometrics.

1. Introduction

Schizophrenia is a neuropsychiatric disorder characterised by hallucinations, delusions, amotivation and cognitive deficits that emerge during late adolescence and early adulthood (Lieberman et al., 1997). For the last 40 years the dopamine hypothesis has been the prevailing theory underlying the pathophysiology of schizophrenia (Coyle et al., 2003), postulating that psychotic symptoms occur as a result of an overactivity of dopamine cell bodies located in the ventral tegmental area (VTA) of the midbrain, with consequent increase in

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neurotransmission to their terminal fields in the nucleus accumbens and limbic cortex (Lieberman et al., 1997). Although supported by the efficacy of dopamine receptor antagonists in treating positive symptoms, this hypothesis has several limitations (Lieberman et al., 1997), such as no direct evidence of pathologic dopamine neuronal activity, as well as no differences in the percentage of D2 receptor occupancy between responders and non-responders to antipsychotic medication (Coppens et al., 1991; Pilowsky et al., 1993; Wolkin et al., 1989). Additionally, drugs impacting the glutamatergic, serotoninergic, and excitatory amino acid neurotransmission have been shown to induce psychotic states (Snyder et al., 1974). Interestingly, ketamine-induced disruption of NMDA transmission leads to an increase in amphetamine-induced dopamine release in healthy participants similar to that observed in patients with schizophrenia. These findings suggest that alteration of dopamine release in schizophrenia may be a consequence of disruption of glutamatergic neuronal systems regulating dopaminergic cell activity (Coyle et al., 2003; Kegeles et al., 2000). This is supported by post-mortem studies showing a reduction of glutamic acid decarboxylase (GAD67) in parvalbumin (PV) GABAergic interneurons (Hashimoto et al., 2003) and by data suggesting that NMDA receptor hypofunction may lead to reduced GABAergic function in schizophrenia (Grunze et al., 1996; Li et al., 2002). A shift in cortical excitation/inhibition (E/I) balance is thus thought to play a crucial role in the pathogenesis of schizophrenia (Fritschy, 2008; Uhlhaas and Singer, 2012). Therefore, it is important to develop biomarkers that enable to probe the inhibition/excitation balance in individuals with schizophrenia and help to unravel the neurophysiological underpinnings of this disorder.

In the last decades, transcranial magnetic stimulation (TMS) coupled with electromyography (EMG) has emerged as a neurophysiological tool to assess cortical physiology in health and disease (Rawji et al., 2020; Rossini et al., 2015). Information on cortical E/I balance can be obtained with TMS via paired-pulse protocols or intake of drugs with known pharmacodynamic properties (Spampinato et al., 2023; Ziemann et al., 2015). So far, several studies have investigated GABAA-ergic neurotrasmission dysfunction in schizophrenia by testing short intracortical inhibition SICI (Du et al., 2019), a putative marker of GABAAR activity (Peurala et al., 2008; Ziemann et al., 1996a, b). Findings show reduction in SICI, suggesting a deficit in GABA-A receptor–mediated inhibition pathway in this clinical population, which may appear early in the disease course (Hou et al., 2021).

The combination of TMS and electroencephalography (TMS-EEG) allows direct measurement of cortical excitability via EEG responses in the time and time-frequency domains (Cruciani et al., 2023; Hernandez-Pavon et al., 2023). In the time domain, single-pulse TMS (spTMS) applied over the primary motor cortex (M1) elicits a series of positive and negative deflections called TMS-evoked potentials (TEPs), while in the time-frequency domain responses consist in early increases in power in the theta, alpha and beta bands, followed by a later decrease and a final rebound (Biondi et al., 2022; Premoli et al., 2017). Importantly, at least some TEP components (e.g., N45, N100) and oscillatory responses in the alpha and beta frequency range are partly regulated by GABAergic (Darmani et al., 2016; Premoli et al., 2017, 2014a, 2014b) and glutamatergic neurotransmission (Belardinelli et al., 2021). Specifically, pharmaco TMS-EEG studies showed that GABAB-receptors agonists increase the negative deflection occurring at 100 msec (Premoli et al., 2014a), known as N100, whereas the N45 is modulated by a balance of GABAAergic inhibition and NMDA receptor-mediated glutamatergic excitation (Belardinelli et al., 2021). Furthermore, pharmacological interventions indicated that inhibition mediated by GABAA-receptors plays a role in the early increase of α-band, while GABAB-receptors mediated inhibition contributes to the late alpha decrease (Biondi et al., 2022; Premoli et al., 2017).Several studies have shown a deficit in oscillations elicited by TMS over the dorsolateral prefrontal (DLPFC), premotor and motor (M1) cortices of patients with schizophrenia (Farzan et al., 2010; Ferrarelli et al., 2008). The reported impairments in frontal oscillatory activity, especially in the γ band, have been thought to contribute to deficits in cognition, such as working memory and cognitive control (Cho, Konecky and Carter, 2006; Takahashi et al., 2013). Few studies (Noda et al., 2017, 2021) have focused on time domain measures, showing reduced amplitude and longer latency of TEPs evoked by spTMS over the left M1 and DLPFC of schizophrenia patients (Noda et al., 2021). According to the authors, these findings support an alteration of inhibitory and excitatory mechanisms in schizophrenia.

However, most of the mentioned studies have significant limitations, including the lack of masking noise to limit contamination by auditory evoked potentials (AEPs) triggered by the TMS click (Cristofari et al., 2023; Nikouline, Ruohonen and Ilmoniemi, 1999; Rocchi et al., 2021; ter Braack, de Vos and van Putten, 2015), and a stimulation intensity which does not allow to avoid possible responses due to peripheral muscle twitch (Hou et al., 2021). Furthermore, the effect of antipsychotic medication on TEPs and oscillatory responses to spTMS is not known and the relationship between TMS-EEG responses and clinical variables, such as symptom severity and disease duration, has not been clarified in schizophrenia (Hou et al., 2021).

Our aim in the present study was to investigate TEPs and TMS-elicited oscillations in schizophrenia as markers of cortical E/I balance. To avoid contamination by AEPs, from possible reafference potentials and to minimize cranial muscle twitch (Mancuso et al., 2023), we employed subthreshold TMS intensity and used state of the art procedures to suppress the TMS click (Rocchi et al., 2021). We also examined the relationship between clinical and electrophysiological variables and recruited patients treated with a single antipsychotic to reduce possible heterogeneity of TMS-EEG responses. As reduced GABAergic and glutamatergic functions have been postulated to be linked to the pathophysiology of schizophrenia (Jahangir et al., 2021) and to several features of TMS-EEG responses, including the N45 and N100 TEP components and early and late alpha and beta TMS-elicited oscillations (Premoli et al., 2017, 2014a), we hypothesised that patients with schizophrenia would demonstrate a reduction in these measures compared to healthy controls.

2. Materials and methods

2.1. Participants

Patients were recruited from outpatient services within the Psychosis Clinical Academic Group at South London and Maudsley NHS Foundation Trust (SLaM). Nineteen right-handed male patients (age range 18–60) with a diagnosis of schizophrenia or psychotic disorder (ICD-10; World Health Organisation, 2004) took part in the study. Participants were on a single antipsychotic medication: aripiprazole (n = 9), olanzapine (n = 6), paliperidone (n = 3), or risperidone (n = 1). All patients were stable on their current treatment, i.e., no dose changes occurred for at least 3 months preceding the test. A stable dose suggests that the symptom severity was stable and could be reliably assessed. Patients were excluded if they: (1) had a history of a neurological or psychiatric comorbidity; (2) suffered from a serious physical illness (e.g. uncontrolled diabetes, hypertension, heart problems) which may have posed a risk to their safety; (3) used any central nervous system active medications other than a single antipsychotic within 1 month before the study; (4) received electroconvulsive therapy within 6 months prior to the study; (5) had any contraindication to TMS as determined by the TMS Safety Checklist (Rossi et al., 2021); (6) scored 27+ (hazardous or harmful use and probable substance dependence) on any of the psychoactive substances on the Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST V3.0) (Humeniuk et al., 2010). Additionally, patients were instructed not to smoke and avoid caffeinated beverages and alcohol within the 24 hours prior to the visit. Seventeen age matched male and female healthy controls were also recruited through local advertisement from an existing healthy group

study. They were included if they had no history of neurological or psychiatric diseases and were not taking drugs active at the central nervous system level. Written informed consent was obtained from all participants. Ethical approval was granted by the London Camberwell St Giles Research Ethics Committee (patients) and the Human Research Ethics Committee of University College London (healthy controls).

2.2. Experimental procedure

The experimental session comprised the collection of clinical variables by standard scales and a neurophysiological assessment. The latter was performed with subjects seated comfortably in a chair, with hands resting on a pillow on their lap, and included measurement of resting motor threshold (RMT) and a single block of TMS-EEG co-registration by stimulating M1, from which TEPs, TMS-related spectral perturbation (TRSP) and inter-trial coherence (ITC) were calculated (see details below).

2.2.1. Clinical assessment

Clinical symptoms were measured with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987); social and occupational functioning was evaluated using the Social and Occupational Functioning Assessment Scale (SOFAS) (DSM-IV, American Psychiatric Association, 2000) and the side effects of antipsychotic medication were identified using the Glasgow Antipsychotic Side-effect Scale (GASS) (Waddell and Taylor, 2008). The amount of recreational substance use, including cannabis, alcohol, nicotine and other drugs, was assessed in the patients with the Cannabis Experience Questionnaire (Barkus et al., 2006). The PANSS interview and the other questionnaires were administered to the patients by a trained research assistant.

2.2.2. Electroencephalography

EEG was recorded from 64 passive TMS-compatible, c-ring slit electrodes (EASYCAP, Germany) using a TMS-compatible EEG amplifier (BrainAmp MR Plus, BrainProducts GmbH, Germany). Data from all channels were online referenced to the FCz electrode with the AFz electrode serving as the ground. EEG signals were digitised at 5 kHz (filtering: DC-1000 Hz) and impedance was kept below 10 kΩ throughout the experiment.

2.2.3. Transcranial magnetic stimulation

Monophasic TMS pulses with posterior-anterior current induced in the brain were applied through a figure-of-eight coil (90 mm external diameter) connected to a Magstim 200^2 unit (The Magstim Company Limited, Whitland, UK). Electromyography was recorded using Ag-AgCl electrodes placed in a belly tendon montage over the target muscle (filter: 20–2000 Hz; sampling rate: 5 kHz). The experimental procedure started with TMS-EMG acquisition. First, the motor hotspot for the right first dorsal interosseus (FDI) muscle was determined over the left M1 as the site where slightly suprathreshold TMS pulses consistently elicited motor-evoked potentials (MEPs). Then, RMT was determined as the minimum stimulus intensity to evoke at least 5 of 10 MEPs with > 50 μV peak-to-peak amplitude (Rossini et al., 2015).

TMS was then co-registered with EEG. During this part, 150 TMS pulses at 90% RMT were delivered every 5 seconds (20% random variation) over the M1 hotspot. M1 was chosen as a target area due to evidence of reduced SICI in patients with schizophrenia (Hou et al., 2021) and because TMS-EEG responses from M1 are better characterized than other cortical areas (Cruciani et al., 2023; Hernandez-Pavon et al., 2023).

During TMS-EEG acquisition, participants were asked to look at a fixation cross during stimulation to prevent eye movements. The position of the FDI hotspot was marked with a felt tip pen on the EEG cap to ensure constant coil placement throughout the experimental session. A masking noise was played to avoid contamination by auditory potentials evoked by the click of the discharging TMS coil (Massimini et al., 2005; Rocchi et al., 2021). In addition, the perceived loudness of the TMS click was assessed at the end of the TMS-EEG recording by a visual analogue scale (VAS), ranging from 0 (no perception) to 10 (maximal perception).

2.3. Data analysis

2.3.1. TMS-EEG preprocessing

The analysis of TMS-EEG data was performed offline, using Brain Vision Analyzer, Fieldtrip (version 2016, http://www.fieldtriptoolbox.org) and custom scripts in Matlab 2012b (MathWorks Inc., Natick, USA). EEG data were first segmented into epochs from 1 second before to 1 second after the TMS pulse. A short segment of ±10 ms was cut to remove the TMS pulse artifact and then replaced by means of a cubic interpolation. Trials with prominent eye movements, blinks, and muscle artifacts were rejected through visual inspection (number of artifact-free trials: mean 109.21, SD 33.45, in patients; mean 140.82, SD 4.50, in controls). EEG channels (on average 4.26, range 2–8, for patients; 1.3, range 0–3, for controls) excessively contaminated by artifacts were removed from the EEG, and the signal was reconstructed using data from surrounding electrodes. Data were notch filtered (48–52 Hz) and residual artifacts related (e.g., TMS recharge artifact, cranial muscle activation, voltage decay) or unrelated to TMS (e.g, spontaneous eyeblinks, continuous muscle activity, etc.) were removed by Independent Component Analysis (ICA). On average, 21.84 (range 11–33) and 16.4 (range 12–21) ICA components were deleted for the patients and healthy controls, respectively, following the procedure described in a previous report (Premoli et al., 2014a). Lastly, remaining data were baseline corrected (-800 to −200 msec), band-pass filtered (1–100 Hz) and re-referenced to the common average reference.

2.3.2. Analysis of TEPs

We computed the global mean field potential (GMFP) averaged across both groups (Lehmann and Skrandies, 1980), and according to the average GMFP waveform, we selected 4 time windows of interest (TOIs) which were used for statistical analysis: TOI1 (15 – 36 msec), TOI2 (37 – 66 msec), TOI3 (67 – 130 msec) and TOI4 (131 – 360 msec) (see Fig. 1).

2.3.3. Analysis of TMS-related spectral perturbation and intertrial coherence

TMS-related spectral perturbation (TRSP) and inter-trial coherence (ITC) were computed with the Fieldtrip toolbox. TRSP was defined as the event-related change in spectral power over time in a broad frequency range. This approach takes into account both the phase-locked and non-phase locked EEG activity triggered by TMS (Makeig, 1993; Rosanova et al., 2009). Differently, ITC reflects the degree to which a stimulus induces phase synchrony of ongoing oscillations at specific frequencies across all trials (Tallon-Baudry et al., 1996).

Time-frequency representation of TMS-related oscillatory power changes was calculated by means of Morlet Wavelet convolution (3.5 cycles, frequency steps of 1 Hz from 2 to 45 Hz) (Delorme and Makeig, 2004). We then applied a single trial normalization by z-transforming the power spectrum of each trial for each frequency band, based on the mean and standard deviation of the full-length trial. Successively, we applied an absolute baseline correction for each trial, by subtracting the average of the −1000 to −50 msec period for each frequency to ensure z-values represented a change from pre-TMS baseline (Fecchio et al., 2017; Premoli et al., 2017). The mean values of TRSP and ITC were calculated over a time period of 30–800 msec and classified in five frequencies of interests (FOIs): delta (2–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (13–30 Hz) and gamma (30–45 Hz) frequency bands.

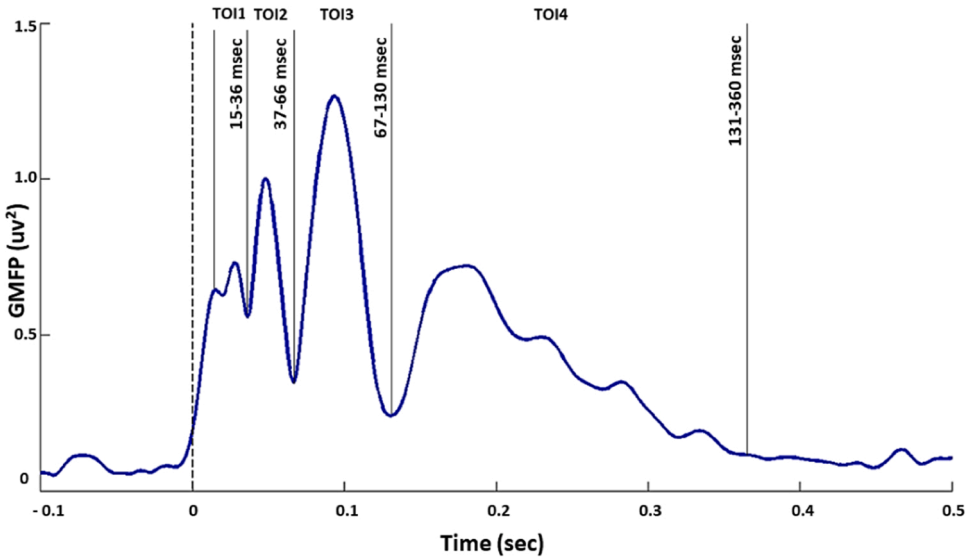

Fig. 1. Average GMFP waveform of patients and healthy controls, and the four time windows of interest (TOIs, indicated by solid vertical lines). The dotted vertical line at 0 s represents the TMS pulse.

3. Statistics

3.1. TMS-EEG

Multiple independent sample t-test were separately applied for each TOI in all the electrodes to calculate significant differences between schizophrenic patients and healthy controls in TEP amplitudes, TRSP and ITC. To correct for multiple comparisons (i.e., electrodes, time points), we conducted a non-parametric cluster-based permutation analysis as implemented in fieldtrip (Oostenveld et al., 2011). Specifically, statistical tests for TEPs were computed separately for each TOI in all the electrodes, while TMS-related oscillations were compared in a single time window of interest from 30 to 800 msec. This approach was preferred instead of a predetermined set of time windows, given the absence of a consensus for time windows of interest to be used in the TMS oscillation analysis (Biondi et al., 2022; Gordon et al., 2018) The statistical comparisons were done with respect to the maximum values of summed t-values. By means of a permutation test (i.e., randomizing data across conditions and rerunning the statistical test 1500 times), we obtained a reference distribution of the maximum of summed cluster t-values to evaluate the statistics of the actual data. A significant cluster was defined as adjacent time-channel pairs for which the t-statistic exceeds a threshold of 0.05. Cluster-level statistics were calculated by taking the sum of the t-values within every cluster. A critical value of 0.05 was used as cluster-statistical significance threshold for all comparisons.

3.2. Correlation analysis

To determine if a possible difference in RMT between the patients and healthy controls might have contributed to between-group differences in TMS-EEG measures, we assessed the correlation between RMT and TEPs, TRSP and ITC. We extracted the maximum and minimum amplitudes – from the significant electrodes of the positive and negative clusters, respectively – from the time intervals which showed a significant difference in TEP amplitudes between groups. For TRSP and ITC, we extracted the average TRSP and ITC for each time interval and frequency band which showed a significant difference between groups. Since participants' rating on the loudness of residual TMS clicks perceived during TMS-EEG registration were significantly different across groups (Mann-Whitney $U = 93$, $p = 0.043$), we assessed the correlation of the rating with the extracted TEPs, TRSP and ITC values as well. Additionally, to determine if the patients' symptom severity and medications might have influenced their TMS-EEG data, we ran correlation tests between the PANSS scores, daily medication dose (as measured by Chlorpromazine, or CPZ, equivalent mg/day) (Leucht et al., 2014; Woods, 2003), level of antipsychotic-induced side effects (as measured by GASS) and the extracted TEPs, TRSP and ITC values of the patients.

First, we checked for and removed outliers using 1.5 times the interquartile range from the above-mentioned variables including the TEPs, TRSP and ITC values. Then, data distributions were tested for normality using the Kolmogorov-Smirnov test. Since some of the variables were not normally distributed, we performed the Spearman's rho correlation test to assess the linear relationship among the variables and applied the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) to control the false discovery rate (FDR) with an accepted FDR of 0.05. Also, we used two methods to deal with the missing values from the GASS variable and both were entered into the correlation analysis: (1) we excluded 3 patients with missing values and (2) we excluded a patient who did not complete the GASS questionnaire and for the other two patients the missing value was replaced with the mean of the rest of their own scores.

3.3. TEPs and TRSP in male vs female healthy controls

Patients and healthy controls had a different sex composition: 100% of the patients were males, whereas only 47% of the healthy controls were males (Table 2). To gauge whether sex of the controls might have confounded the results, we compared the TEP amplitude, TMS-related spectral perturbation and intertrial coherence between the male and female controls using the extracted TEPs, TRSP and ITC values.

4. Results

4.1. Participants

The demographic and clinical characteristics of the participants are displayed in Table 1. The age and RMT of the patients and the healthy controls were all normally distributed. An independent t-test showed that on average, the patients had significantly higher RMT than the healthy controls, with a medium-sized effect ($r = 0.42$). The TEP amplitude, TRSP and ITC of the male and female controls are shown in Table 2. Specifically, compared to the healthy controls, the patients

Table 2
Extracted TEP amplitudes, TMS-related spectral perturbation and intertrial coherence values in male vs female healthy controls; mean (SD).

		Males	Females
TEP (μV)	TOI1	1.77 (1.14)	1.53 (1.64)
	TOI2	2.34 (1.49)	2.30 (1.18)
	TOI4	1.23 (1.13)	0.90 (0.31)
TRSP (z-scores)	Delta 50–160 msec	0.44 (0.29)	0.36 (0.14)
	Theta 30–250 msec	0.59 (0.41)	0.52 (0.19)
	Gamma 50–110 msec	0.19 (0.12)	0.19 (0.04)
	Alpha 220–560 msec	-0.12 (0.16)	-0.04 (0.06)
	Beta 190–420 msec	-0.10 (0.11)	-0.05 (0.05)
	Gamma 180–230 msec	0.06 (0.08)	-0.04 (0.03)
ITC	Alpha 30–260 msec	0.37 (0.17)	0.37 (0.13)

Note: For TOI1, the maximum amplitude extracted from the positive cluster (Fig. 3) was used to represent the amplitude of the P30 which may be present in this TOI. For TOI2 and TOI4, the absolute values of the maximum and minimum amplitudes extracted from the positive and negative clusters (Fig. 3), respectively, were averaged to show an overall level of TMS-evoked activity within each TOI. The TRSP and ITC values were extracted as described in the Method section.

exhibited reduced amplitude of the TEPs within the first (in the positive cluster), second and fourth TOIs, and a smaller increase of initial delta, theta and gamma TRSP and subsequent suppression of alpha, beta and gamma TRSP (see Sections 4.2 and 4.3). The patients also had lower ITC in the alpha band from 30 to 260 msec (Section 4.3). However, the male controls did not show the same pattern of change in TEPs and TRSP compared with the female controls (except for gamma suppression between 180 and 230 msec), and had slightly lower ITC than the female controls, suggesting that the significant differences seen between the patients and controls was unlikely to be influenced by sex.

4.2. TMS-Evoked EEG potentials

The spatiotemporal profile of the TEPs is reported in Fig. 2. The grand-average TMS-evoked EEG response after single pulse TMS of M1 in healthy volunteers showed the typical TEPs components across the pre-specified TOIs and over scalp topographies (Fig. 2B). Cluster based permutation analysis showed significant differences between patients and healthy controls with amplitudes of early (TOI1; TO2) and late (TOI4) TEPs being significantly smaller in patients (Fig. 3D). The comparison of TEPs performed within each TOI (1−4) showed left central-parietal significant positive clusters at 15–36 msec (TOI1; $p < 0.001$), 37–66 msec (TOI2; $p < 0.001$) and at 183–360 msec (TOI4; $p < 0.001$) (Fig. 3). An inverse pattern indicating a negative cluster was observed over the right central-frontal hemisphere at 15–36 msec (TOI1; $p < 0.001$), 37–66 msec (TOI2; $p < 0.001$) and at 201–360 msec ($p = 0.01$) (Fig. 3). No significant differences were found from 67 to 130 msec (TOI3).

4.3. TMS-related oscillations and intertrial coherence

There were significant differences between patients and healthy controls in delta (2–4 Hz), theta (4–7 Hz), alpha (8–12 Hz) beta (13–30 Hz) and gamma TRSP (30–45 Hz) (Fig. 4). Specifically, the profile of the TRSP in healthy controls was consistent with previous reports, showing an early increase in TRSP in the theta, alpha and beta bands up to 200 msec followed by alpha, beta and gamma suppression and a final beta rebound, as described previously (Gordon et al., 2018). Patients, compared to healthy controls, showed a significant reduction of delta (50–160 msec; 2 positive clusters: $p = 0.045$; $p = 0.036$) and theta TRSP (30–250 msec; $p = 0.04$) over the stimulated area and the contralateral temporal electrodes, followed by a reduction in alpha and beta suppression (220–560 msec, $p < 0.01$; 190–420 msec, $p < 0.01$) in both hemispheres. Finally, patients showed a reduction of early (50–110 msec) gamma increase and late (180–230 msec) gamma suppression, respectively ($p = 0.04$; $p = 0.01$). The effect on early gamma was located in the channels close to the stimulated site, as well as over the anterior and temporal electrodes in the contralateral hemisphere. The difference in late gamma TRSP involved a large area including bilateral anterior and temporal electrodes, as well as parietal and occipital channels over the left hemisphere. Similarly, the difference in alpha and beta suppression was widely spread over the bilateral anterior, central, and posterior electrodes.

The ITC was significantly higher in healthy controls than in patients in alpha band, from 30 to 260 msec (2 positive clusters: $p = 0.04$; $p = 0.045$). The difference occurred in a cluster of electrodes over the stimulated site, as well in frontal and temporal electrodes over the contralateral site (Fig. 5). We did not find any difference in ITC in delta, theta, beta and gamma bands ($p > 0.05$).

4.4. Correlation analysis

RMT was not significantly correlated with TEPs, TRSP or ITC in

Table 1
Demographic and clinical characteristics of the participants.

	Schizophrenia	Healthy control	Statistic	p value
	(n = 19)	(n = 17)		
Gender (number of males)	19	9		
Age: mean (SD)	39.89 (12.84)	39.88 (4.62)	[c]$t(23.05) = 0.004$	p = 1.00
RMT: mean (SD)	53 (9.38)	45.06 (8.20)	$t(34) = 2.69$	p < 0.05
CPZ equivalent (mg/day): mean (SD)	305.39 (168.99)			
Duration of illness (years): mean (SD)	11.95 (10.61)			
PANSS: mean (SD)				
Positive	17.95 (4.68)			
Negative	20.21 (5.11)			
General psychopathology	35.58 (6.23)			
Total	74.53 (11.81)			
[a]SOFAS: mean (SD)	67.58 (11.81)			
[b]GASS: mean (SD)	10.04 (9.21)			
Alcohol (units per week)	0.39 (1.30)			
Smoking (number of cigarettes or roll-ups per day)	6.47 (7.54)			
[d]Status of cannabis use				
No. of current users	2 (11%)			
Type of cannabis used	skunk (n=1); hash or skunk (n=1)			
No. of joints per week	32 (n=1); 3 (n=1)			
No. of self-identified current users				
Cocaine	1			
Ecstasy	[e]1			
Crystal meth	1			

[a] . Assessed current functioning, as in past week.
[b] . Each patient's sub-scores were summed to obtain an individual GASS score. Two of the patients did not answer the questions related to prolactinaemic side effects. Thus, for these two patients we replaced the missing value with the mean of the rest of their own scores. Also, the score for a patient is missing due to the participant not completing the questionnaire. As a result, the mean GASS score in the table is the average of 18 patients.
[c] . Equal variances not assumed
[d] . Based on self-report
[e] . Same person as the current cocaine user

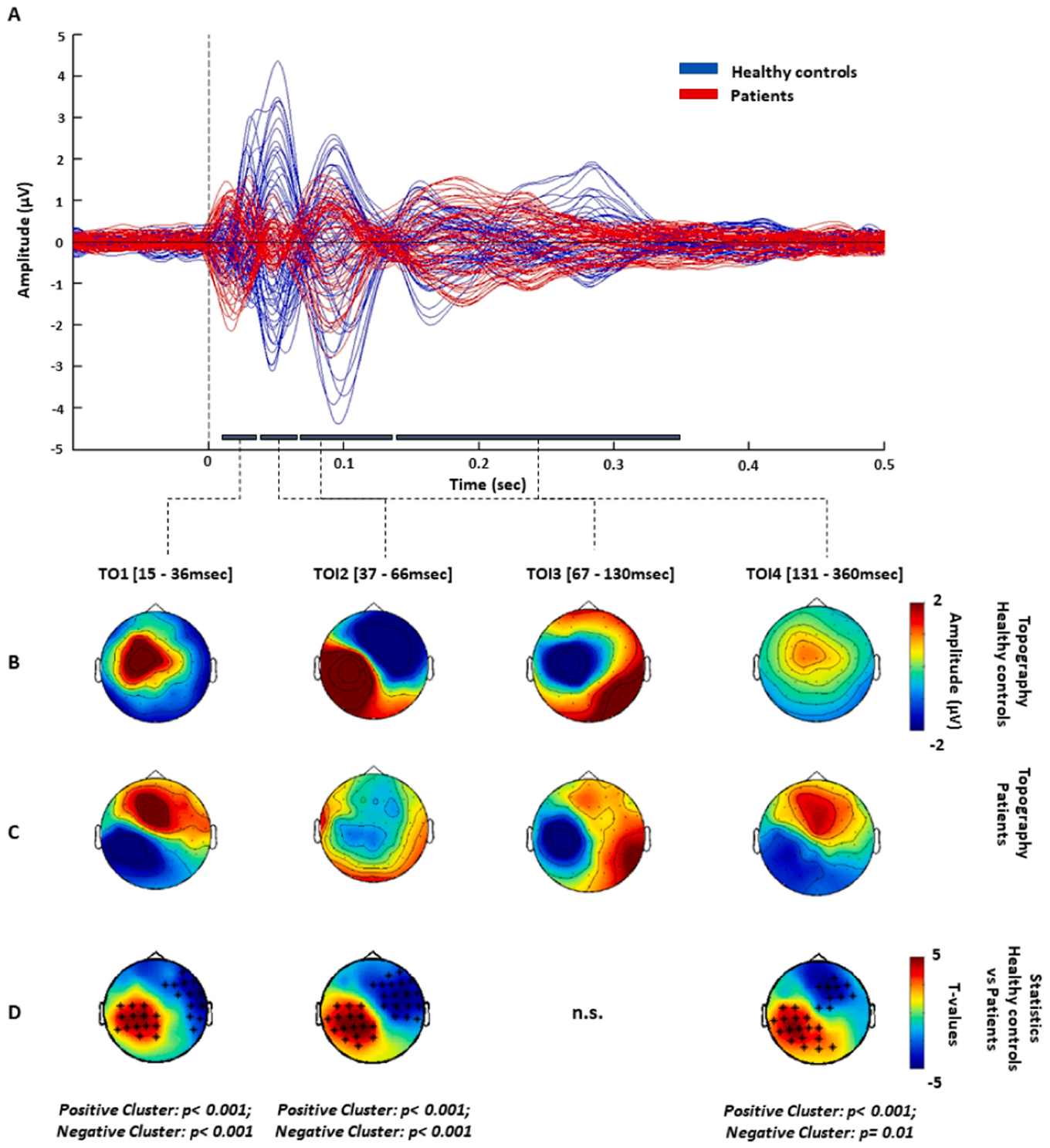

Fig. 2. Spatiotemporal profile of TEPs for patients and healthy controls. Panel A shows grand average butterfly plots for healthy controls (blue) and patients with schizophrenia (red): each line represents TEPs recorded at a single EEG channel; grey bars represent each TOIs used for the analysis. Panel B and C show the topographical distribution of TEP amplitudes (μV) calculated as average over each TOI for healthy controls and patients, respectively. Panel D represents t-statistic maps of the TEP amplitude showing healthy controls versus patients difference. Asterisks show individual channels composing significant positive (red) and negative (blue) clusters.

either the patients or healthy controls, suggesting that the observed between-group differences in TEPs, TRSP and ITC are not related to the between-group differences in RMT. In patients, perceived loudness of the residual TMS click was significantly correlated with ITC when the outliers in ITC were included ($r(16) = .65$, $p = .004$), but not when the outliers were excluded. In healthy controls, there was no significant correlation between perceived loudness of the residual TMS click and the extracted TEPs, TRSP and ITC values.

In the patient group, the PANSS scores, daily medication dose and antipsychotic-induced side effects were not significantly correlated with the amplitudes of the TEPs, TRSP or ITC, indicating that TMS-EEG responses might have reflected stable abnormalities associated with

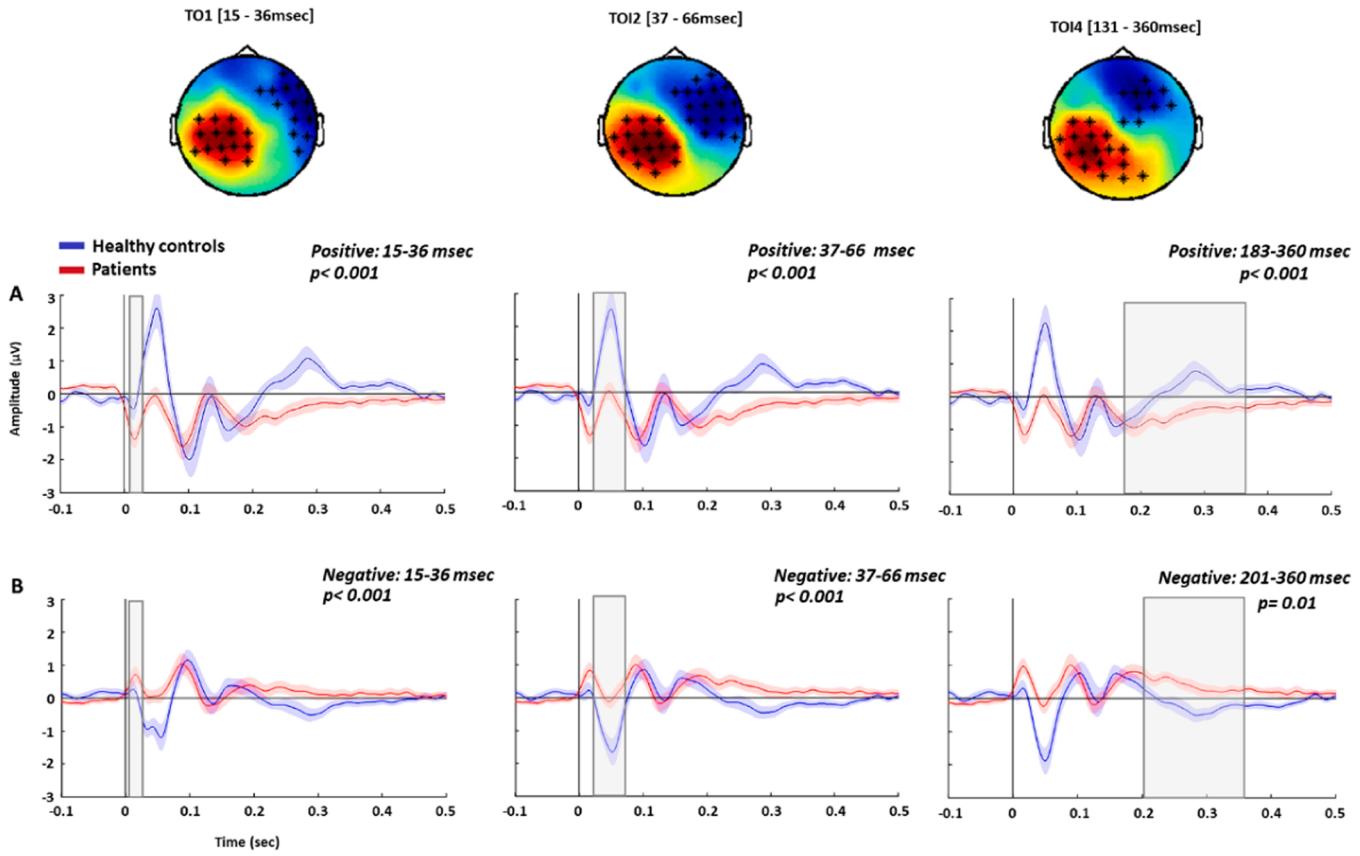

Fig. 3. TOIs 1–4 analysis: grand-average TEPs recorded for patients (red) and healthy volunteers (blue). The signal has been averaged over channels composing positive (Panel A) and negative clusters (Panel B) at each TOI. The transparent bars on the bottom panels represent the time windows that showed the significant differences for within each TOI comparison.

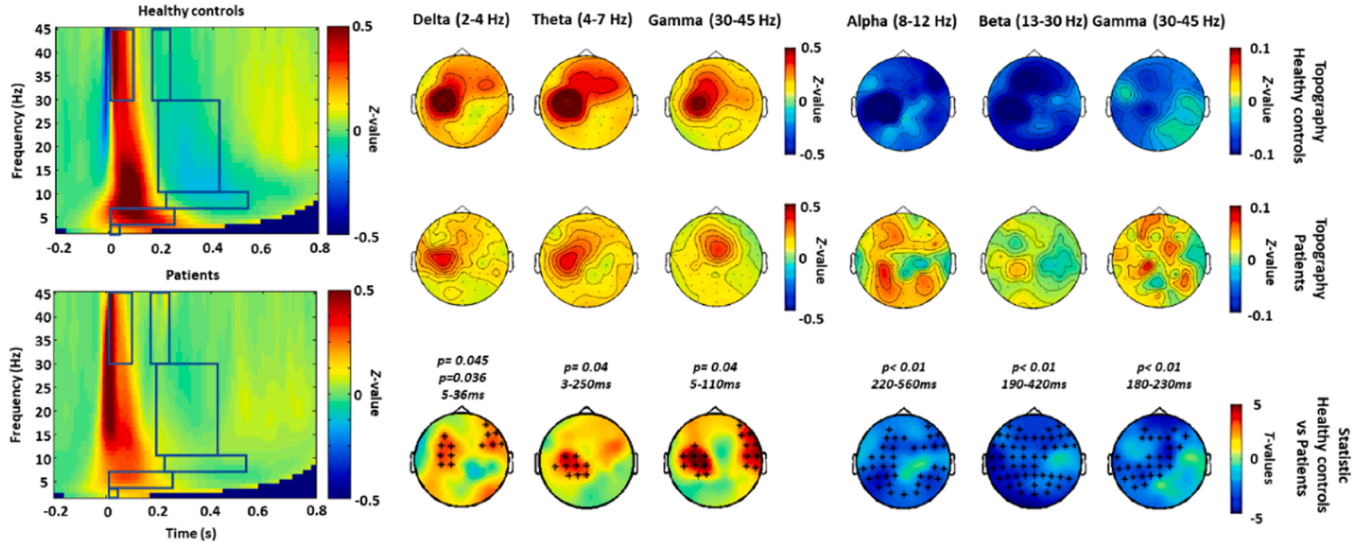

Fig. 4. Significant differences in TMS-related spectral perturbation (TRSP) between the patients and healthy controls. Grand averages of the time-frequency representation of TRSP (averaged over all EEG channels for both patients and healthy controls) are shown on the left panel. The blue boxes correspond to the time and frequency windows where comparisons between the patients and controls were significant. Topographical distributions of the significant differences in delta ($p < 0.05$, 50–160 msec), theta ($p < 0.05$, 30–250 msec), alpha ($p < 0.01$, 220–560 msec), beta ($p < 0.01$, 190–420 msec) and gamma ($p < 0.05$, 50–110 msec; $p < 0.01$, 180–230 msec) TRSP are shown on the right panel. Significant electrodes are represented with asterisks in the t-statistic maps.

schizophrenia, and not be influenced by current symptom severity, medication dose or antipsychotic side effects.

There was no significant relationship between RMT and perceived loudness of the residual TMS click in both study groups

5. Discussion

We investigated the differences in cortical excitability between schizophrenia patients and healthy controls using various TMS-EEG

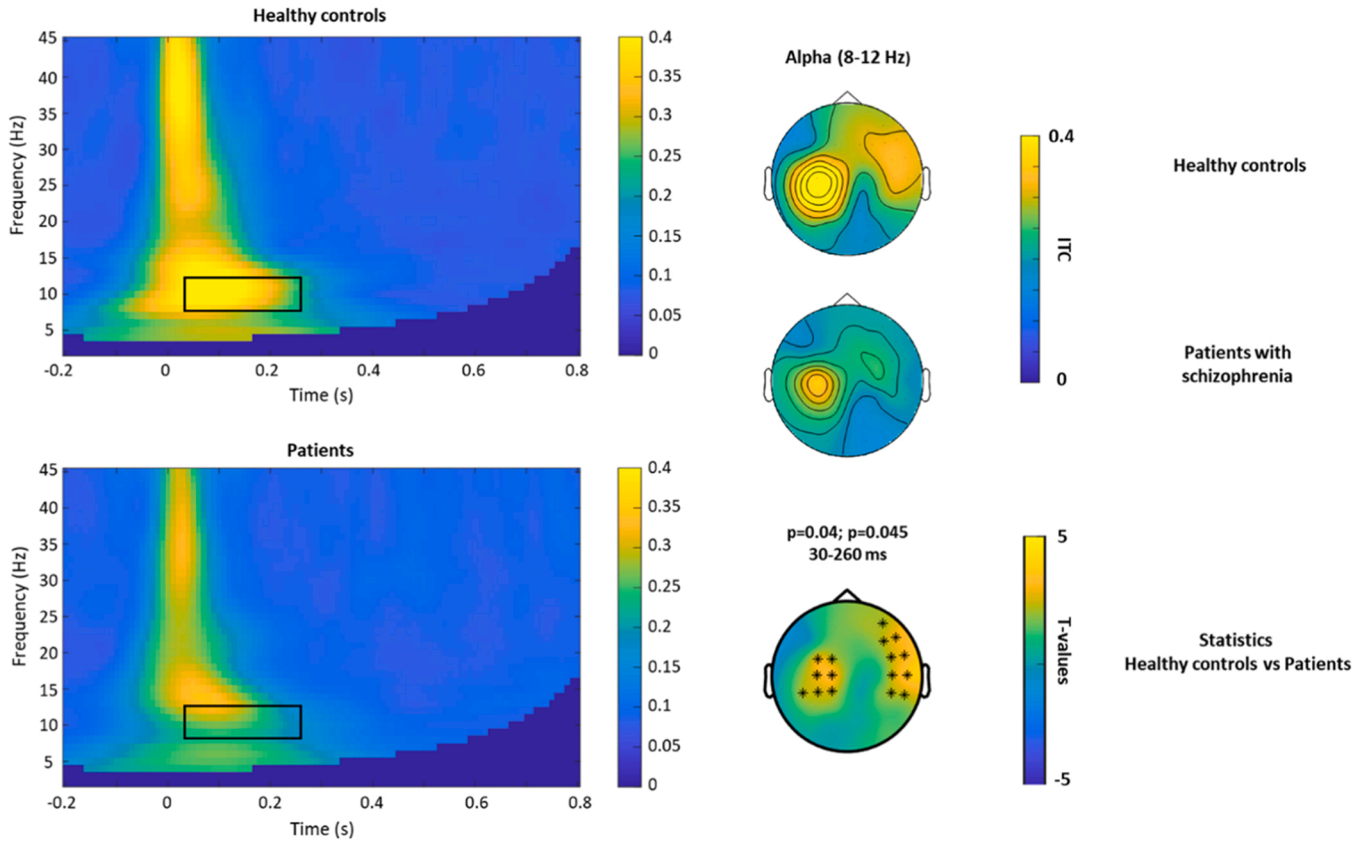

Fig. 5. Significant differences in intertrial phase coherence (ITC) between the patients and healthy controls. Grand averages of the time-frequency representation of ITC (signal averaged over the EEG channels that showed a significant group difference in ITC) in both groups are shown on the left panel. The black boxes correspond to the time and frequency window where the difference was significant (8–12 Hz, 30–260 msec, $p < 0.05$). Topographical maps of the location of the significant difference in the ITC of alpha oscillations are shown on the right panel. Significant electrodes are represented with asterisks in the t-statistic map.

measures. Patients with schizophrenia showed reduced amplitudes of TEPs between 15 and 66 msec, as well as between 201 and 360 msec. Furthermore, patients showed reduction of the early delta, theta, and gamma TRSP, as well as of late alpha, beta, and gamma suppression, compared to healthy controls, and decreased ITC in the alpha band (30–260 msec). We did not find any significant correlations between these TMS-EEG indices and clinical characteristics such as symptom severity, antipsychotic-induced side effects or daily dose of medication. Finally, while there was a significantly higher RMT in patients relative to healthy controls, this was not significantly correlated with any of the TMS-EEG indices or clinical variables.

Previous investigations employing TMS-EEG in schizophrenia have presented inconsistent outcomes, largely attributed to methodological disparities. Some studies incorporated paired-pulse TMS (Farzan et al., 2010; Noda et al., 2017) introducing potential confounds related to the interplay between test and conditioning stimuli (Hou et al., 2021; Premoli et al., 2018; Rawji et al., 2021), and targeted regions beyond M1 where (Farzan et al., 2010; Ferrarelli et al., 2019; Noda et al., 2017; Radhu et al., 2017) evidence linking TMS-EEG measures with neurotransmission remains scant (Rogasch et al., 2020). Furthermore, the application of masking noise to suppress AEPs has been inconsistently applied across studies (Hou et al., 2021). In contrast, our investigation employed a well-established subthreshold single-pulse TMS-EEG paradigm within M1 to interrogate the E-I hypothesis of SCZ, facilitating more robust deductions regarding neurotransmission mechanisms (Rogasch et al., 2020), while meticulously controlling for indirect brain activation induced by auditory and somatosensory inputs (Mancuso et al., 2023). Notably, our study also delved into the correlation between electrophysiological parameters and additional patient characteristics, including disease manifestations and antipsychotic medication. Lastly, our investigation thoroughly scrutinized the primary analytical variables commonly derived from TMS-EEG signals (TEPs, TRSP, ITC), unveiling a noteworthy and novel positive finding concerning alpha band ITC.

5.1. *TMS-Evoked potentials*

The analysis of TEPs revealed distinct differences in cortical excitability between patients with schizophrenia and healthy controls. The amplitudes of TEPs in specific time windows were found to be significantly reduced in patients compared to controls, indicating altered neural responses to TMS stimulation.

During the early response phase (TOI1), corresponding to the initial neural response following TMS stimulation, patients exhibited significantly lower TEP amplitudes compared to controls. This reduction in amplitude suggests a diminished level of cortical excitability in response to TMS in individuals with schizophrenia. It is important to note that TOI1 reflects the immediate neural response to TMS and is not prone to contamination by auditory evoked potentials induced by the TMS click (Rocchi et al., 2021).

The first TEP component observed in our TOI1 (15–36 msec) was the P30 (Fig. 2). A similar decrease of the amplitude of P30 component has been associated with a reduction of motor cortical excitability in pharmaco-TMS-EEG studies in healthy volunteers following administration of XEN1101 (a Kv7 potassium channel opener) and Carbamazepine (a sodium channel blocker) (Darmani et al., 2016; Premoli et al., 2019). Thus, the decrease in the amplitude of P30 in patients likely reflects reduced neuronal excitability with regards to early motor cortical responses to TMS. Glutamate concentration as assessed by magnetic resonance spectroscopy (MRS), but not MRS-GABA, in the M1 was

positively correlated with MEP amplitude (Stagg et al., 2011), which in turn was positively correlated with P30 amplitude (Mäki and Ilmoniemi, 2010). The N45 and P60 were the next components observed in our second time window of interest (TOI2). The generation of the N45 potential has previously been linked to rapid inhibitory post-synaptic potentials mediated by GABAA receptors containing the α1 subunit (Premoli et al., 2014a) as well as tonic inhibition mediated by GABAA receptors containing the α5 subunit located outside of synapses (Darmani et al., 2016). Thus, the reduced amplitude of the N45 component observed in patients may reflect compromised synaptic and tonic GABAergic neurotransmission within this population. These findings align with existing literature that supports a specific reduction in short intracortical inhibition (SICI) assessed by TMS-EMG in patients with schizophrenia at various stages of the illness (Hou et al., 2021); similar to the TEP N45, SICI is believed to reflect post-synaptic inhibition of corticospinal neurons mediated by α2 and/or α3 subunits of GABAA receptors. Furthermore, Belardinelli at al., 2021 found that dextromethorphan, an NMDA receptor antagonist, increased the amplitude of the N45. Taken together, our results show that the reduced N45 amplitude in patients with schizophrenia may reflect altered excitation–inhibition balance regulated by NMDA and GABAA receptors (Belardinelli et al., 2021).

The P60 is a positive deflection occurring around 60–70 msec after the TMS pulse, over the stimulated hemisphere. A previous study found that P60 amplitude was decreased by Perampanel, a glutamate receptor antagonist (AMPA receptor antagonist); it is thus possible that glutamatergic excitation through AMPA receptors contributes to P60 expression (Belardinelli et al., 2021). In summary, these findings suggest that reduced N45 and P60 amplitudes in patients TEPs index alteration of GABAergic and glutamatergic pathways that are reflected through inhibition and excitation imbalance in this population.

Patients also demonstrated a significantly decreased amplitude of the TEP within the fourth TOI bilaterally (left: 183–360 msec; right: 201–360 msec) (Fig. 3). TOI4 (131–360 msec) contains a positive peak occurring around 200 msec after spTMS, known as P180 or P200. This peak has often been associated with auditory evoked activity generated by the coil click during stimulation. However, it has been shown that auditory stimulation alone induces potentials between 100 and 200 msec, both distributed around the vertex, which can be suppressed with noise masking (Nikouline, Ruohonen and Ilmoniemi, 1999; Rocchi et al., 2021). The masking noise was applied in our protocol for both healthy participants and patients and the topographical distribution of TMS-EEG responses the no contamination by AEPs occurred (Fig. 2). While the interpretation of the difference between patients and healthy controls in early TOI4 is not clear from the literature, late TEP components, such as the P180, may be controlled by axonal excitability. In fact, the administration of the voltage-gated sodium channel blockers Lamotrigine and Carbamazepine resulted in a depression of the P180 amplitude showing this late response is reactive to excitability-lowering drugs (Darmani et al., 2019).

5.2. TMS-related spectral perturbations and inter-trial coherence

Patients with schizophrenia exhibited significantly reduced TRSP in delta (50–160 msec), theta (30–250 msec), and gamma (50–110 msec) frequency bands over the stimulated cortex (Fig. 4). The decrease in early delta and theta TRSP in patients may be associated with decreased neural excitation, as the use of antiepileptic drugs that reduce neuronal excitation have been shown to decrease delta and theta TRSP in healthy individuals (Biondi et al., 2022). Impaired synaptic GABAAergic inhibition may contribute to the reduction of early theta TRSP, as positive modulation of GABAA receptors with GABA-modulating drugs has been found to increase theta oscillatory power in the rat motor cortex in vitro (Berretta et al., 2004; Coyle, 2006; Gisabella et al., 2005).

Patients also exhibited reduced early gamma TRSP (50–110 msec), consistent with previous findings showing a decrease in gamma amplitude and synchronization after spTMS over the frontal cortex in schizophrenia patients compared to controls (Ferrarelli et al., 2008). Selective gamma impairment has been reported in patients with schizophrenia, and post-mortem studies have shown reductions in glutamic acid decarboxylase (GAD67) in a subclass of GABAergic interneurons associated with gamma frequency activity (Hou et al., 2021; Rogasch et al., 2014). This may be relevant in the neural dysconnectivity thought to underpin the symptoms in schizophrenia. Reductions in synaptic connectivity can produce deficits in gamma oscillations, and this observed deficit in patients could be a marker of reduced synaptic connectivity underlying cortical networks. Indeed, gamma oscillations have been proposed as a more sensitive indicator of circuit integrity than other structural measures (Spencer, 2009).

The subsequent suppression of alpha and beta TRSP observed in healthy controls from around 200 msec after TMS (Fig. 5) has been reported previously (Fecchio et al., 2017; Gordon et al., 2018; Premoli et al., 2017). Coincidentally, gamma power was also reduced, albeit to a lesser extent, in healthy controls (Fig. 5) (Fecchio et al., 2017; Gordon et al., 2018). Positive modulators of subunit-unspecific GABAA receptors, such as Alprazolam and Diazepam, as well as the GABAB receptor agonist baclofen, have been shown to enhance the reduction of beta power observed around 200 msec after TMS, suggesting the possible influence of both GABAAergic and GABABergic activity (Premoli et al., 2017). Patients with schizophrenia exhibited less suppression of alpha (220–560 msec), beta (190–420 msec), and gamma (180–230 msec) TRSP compared to healthy controls (Fig. 5), suggesting a potential reduction in GABAAR- and GABABR-mediated inhibition and glutamatergic neurotransmission. Specifically, the enhanced reduction of beta TRSP in healthy controls by positive modulators of GABAARs containing α1-, α2-, α3-, and α5-subunits (Alprazolam and Diazepam), but not by Zolpidem (which mainly binds to α1-containing GABAARs), suggests impaired activity at α2-, α3-, and/or α5-subunits of GABAARs in patients. This finding is consistent with the reduced N45 amplitude and short intracortical inhibition (SICI) observed in schizophrenia patients, as the N45 component involves tonic inhibition mediated by extrasynaptically-located α5 subunit-containing GABAARs, and SICI is related to α2- and/or α3-GABAAR-mediated synaptic inhibition of corticospinal neurons (Darmani et al., 2016; Di Lazzaro et al., 2007; Teo et al., 2009). Animal models support this interpretation, as mice heterozygous for GAD67 deficiency primarily in gabaergic Parvalbumin interneurons V neurons have been observed to exhibit abnormalities such as deficits in pre-pulse inhibition, social memory, and reduced inhibitory synaptic transmission as observed in schizophrenia (Fujihara et al., 2015).

The analysis of the ITC, which is considered a measure of the synchronization of the phase of TMS-evoked EEG responses across trials, showed lower synchronization of early oscillatory responses (30–260 msec) between 8 and 13 Hz in patients compared to controls. Our results may indicate that the lower TMS-evoked responses in the time domain (i.e. TEPs) may be, at least in part, related to reduced synchronisation of early oscillatory response in the alpha band. Decreased alpha ITC has also been observed in schizophrenia patients compared to healthy controls during selective attention to the target tones in an auditory oddball task (Koh et al., 2011), and during deviance detection in an auditory mismatch negativity task (Sauer et al., 2023). Overall, these findings suggest that the brain of schizophrenia patients may be less capable of aligning the phase of ongoing alpha oscillations in response to TMS and during certain cognitive processes.

6. Limitations and conclusion

The study has some limitations. First, the sex composition of the schizophrenia patients and healthy controls were different – all the patients were males, whereas half of the healthy controls were females. This could potentially introduce a confound since menstrual cycle was shown to affect the cortical excitability of women (Smith et al., 1999).

Although the male controls did not show the same pattern of change as the patients when compared with the female controls, future work should include both male and female patients with schizophrenia to further evaluate the effect of sex on cortical excitability.

Additionally, the medication status of the patients could be a potential confound due to the effects of antipsychotics on cortical excitability. Antipsychotics primarily act on the central nervous system dopaminergic system via attenuating post synaptic dopamine action; however, they could induce secondary effects on the glutamate and GABA neurotransmitter systems, and hence could potentially influence cortical excitability. Further research could involve medication-naïve or minimally treated patients to address this issue. Moreover, the interpretation of the observed patterns of TMS-induced changes in brain oscillations is based on limited evidence, and further studies are needed to enhance our understanding of the neurophysiology underlying these changes in both healthy individuals and schizophrenia patients. Lastly, albeit the difference was not statistically significant (Mann-Whitney's U $= -1.844$, $p = 0.066$), the number of independent components in the patient group was higher than that in healthy controls; therefore, our results might, at least in part, have been driven by overcorrection of data by ICA.

In summary, the findings from the analysis of TEPs, TRSP, and ITC collectively provide compelling evidence for altered cortical excitability and disrupted neural oscillatory activity in patients with schizophrenia compared to healthy controls. The observed reductions in TEP amplitudes, TRSP in delta, theta, and gamma frequency ranges, as well as lower ITC in alpha band, suggest aberrant neural dynamics and impaired neural communication in individuals with schizophrenia. These findings support both the premise of reduced glutamatergic activity and lower excitability contributing to the pathophysiology of schizophrenia and the altered function of GABAergic function directly impacting oscillatory activity and enhancing neural dysconnectivity. This provides an excellent test bed for the development of novel therapeutic interventions targeting cortical excitability and neural oscillations to improve cognitive and perceptual deficits in this disorder.

Author agreement statement

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process. He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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