

Effect of transcranial magnetic pulses on cortical network connectivity in schizophrenia

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ABSTRACT

Introduction: Transcranial magnetic stimulation (TMS) pulses applied to the cortex induce dynamic changes in brain network activity. These changes are useful for the in vivo study of functional connectivity, which may be characterized with the application of network parameters to the pre-stimulus (*i. e.*, baseline) and the post-stimulus (*i. e.*, response) of TMS-mediated electroencephalographic (EEG) recordings. These measures may be altered in schizophrenia, so we hypothesized a basal hyperactive network associated to hypomodulation with TMS in patients.

Material and methods: Twenty-six schizophrenia patients and 26 healthy controls were subjected to TMS pulses during an EEG recording in order to assess the effect on connectivity strength (CS), a parameter summarizing the global EEG synchrony of the cortical network at baseline and its TMS-evoked modulation.

Results: Patients showed a higher baseline CS in all bands except gamma. In controls, TMS increased CS in all bands, more notably on beta and gamma. In comparison to controls, patients showed a lower baseline-to-response multiband activity increase of CS, and significantly lower CS modulation values in the gamma band with TMS pulses. No relationships were found between these measures and antipsychotic dose or other clinical and cognitive variables.

Conclusions: In the context of evidence supporting an inhibitory deficit in schizophrenia, these results may reflect the functional consequences of an inhibitory/GABAergic deficit in the cortex in this syndrome.

1. Introduction

Transcranial magnetic stimulation (TMS) pulses applied to the cortex result in time-locked depolarization of underlying neurons, which can be recorded by means of electroencephalography (EEG) (Tremblay et al., 2019). Local and global EEG changes induced by TMS pulses reflect functional connectivity modulation (Ferrarelli and Phillips, 2021; Hill et al., 2016), with the advantages, in comparison with tasks involving peripheral stimulation, of avoiding prior synaptic chains and being free of motivation or performance bias. The global connective network structure and its modulation can be described combining

parameters derived from graph theory and EEG recordings preceding and following TMS pulses. Among these parameters, connectivity strength (CS) estimates the mean global network functional connectivity: a higher CS reflects larger global synchronization across sensors. Thus, a positive modulation of this parameter with TMS indicates a transitory increase in global functional connectivity induced by the corresponding pulses. Nevertheless, the modulatory effects of TMS on functional neural networks have not been studied using these parameters yet, in spite of the relevance of these global networks in cognition (Sporns et al., 2004). A recent report compared perturbation complexity index (PCI) between schizophrenia patients and controls, showing

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significantly smaller values in patients (Molina et al., 2025). Since PCI is the result of extension and differentiation of the perturbation of activity across the brain following TMS pulses, this result is coherent with a decreased global functional connectivity and supports the interest of assessing it by bands.

Assessing dynamics of that kind of connectivity holds special interest for disorders likely involving functional network alterations, such as schizophrenia. In this syndrome, EEG networks show baseline hyperactivity and hypomodulation when performing a P300 paradigm using CS measures (Cea-Cañas et al., 2020). A significant relation using the same paradigm was found between basal network hyperactivity (*i. e.*, higher CS) and its hypomodulation (Gomez-Pilar et al., 2018), which was replicated in a larger sample (Díez et al., 2024). Thus, network baseline and task-related modulation of CS worth special attention in this disorder. However, the modulatory effects of TMS on cerebral activity in schizophrenia are unclear, since widespread (Radhu et al., 2017) as well as spatially decreased (Ferrarelli et al., 2008) propagation of cortical activity following TMS have been reported in this syndrome. Assessments of global connectivity modulation using TMS may complement similar studies under cognitive paradigms with the advantage of being independent of subjects collaboration and performance.

We have previously reported that TMS pulses induce higher local mean field power in schizophrenia, likely reflecting increased cortical excitability (Fernández-Linsenbarth et al., 2024). In this context, the analysis of network response to TMS in the different bands may help to assess the underpinnings of this syndrome’s hyper-excitability. Of particular interest are gamma oscillations, which are thought to be generated and modulated by GABA neurotransmission (McNally and McCarley, 2016). Thus, the joint finding of the basal hyperactive state supported by previous results (Cea-Cañas et al., 2020; Díez et al., 2024) and lower network fast-band modulation to TMS would support an inhibitory deficit in schizophrenia, which would be coherent with molecular findings (Gonzalez-Burgos and Lewis, 2012).

Therefore, we hypothesized a basal hyperactive network associated to hypomodulation with TMS in patients with schizophrenia. To this end, we analyzed baseline and its response to TMS of the cortical network in theta, alpha, beta and gamma bands using CS as the parameter of interest. The comparison of the pre-stimulus CS and its modulation with TMS in the different bands could allow testing this hypothesis beyond what could be found using any of these measurements alone.

2. Materials and methods

2.1. Study participants

We included 26 schizophrenia patients (SZ, 15 males) of them 14 first episodes (6 males), and 26 healthy controls (HC, 14 males). There were no significant differences in age or sex distribution between groups (Table 1). All patients were receiving antipsychotic treatment at the time of inclusion and evaluation.

These patients overlap with those included in our recent reports analyzing the local mean field power (Fernández-Linsenbarth et al., 2024) and individualization of time windows (Mijancos-Martínez et al., 2024) of the response to TMS in HC and SZ. All the 20 cases in those studies were also included in the present one.

Patients were diagnosed by two expert psychiatrists (VM and CR) according to the Diagnostic and Statistical Manual of Mental Disorders (5th edition) (American Psychiatric Association, 2013). Exclusion criteria were (i) neurological disease, (ii) history of head trauma with loss of consciousness, (iii) current substance abuse (except nicotine or caffeine), (iv) Intelligence Quotient (IQ) less than 70, and (v) any psychiatric treatment for controls, or (vi) current diagnosis other than schizophrenia for patients. All participants gave written informed consent after receiving complete printed information. The ethical committees of the University Hospital of Valladolid endorsed the study

Table 1
Sociodemographic, clinical and cognitive values in patients with schizophrenia (SZ) and healthy controls (HC).

	SZ (N = 26)	HC (N = 26)
Age	35.81 (12.09)	29.85 (10.57)
Sex distribution (M:F)	15:11	14:12
Illness duration (months)	77.08 (121.12)	N/A
Education (years)	13.23 (3.60) *	15.31 (2.84)
Father education (years)	10.79 (5.07)	13.43 (4.26)
Antipsychotic dose (mg/d, CPZ equivalents)	397.58 (226.05)	N/A
PANSS – Positive scale	13.60 (5.24)	N/A
BNSS – Total score	22.74 (19.07)	N/A
HAM-D – Total score	4.83 (6.50)	N/A
WAIS – Total IQ	97.92 (19.98) *	111.20 (10.27)
BACS – Verbal memory	45.28 (10.51) **	54.24 (8.50)
BACS – Working memory	19.15 (4.67) *	21.90 (3.62)
BACS – Motor speed	62.23 (14.22) **	74.52 (13.67)
BACS – Verbal fluency	22.10 (7.02) **	27.33 (5.02)
BACS – Processing speed	52.73 (14.13) **	66.81 (10.10)
BACS – Problem solving	17.65 (2.91)	18.14 (2.52)
WCST – % Perseverative errors	11.36 (7.21)	8.65 (4.08)

*p < 0.05, **p < 0.01 (t-test or chi-squared test as appropriate).

(protocol PI-21-2623).

2.2. Clinical and cognitive assessment

Patients’ positive and negative symptoms were respectively assessed using the positive subscale of the ‘Positive and Negative Syndrome Scale for Schizophrenia’ (PANSS) (Kay et al., 1987), and the ‘Brief Negative Symptom Scale’ (BNSS) (Kirkpatrick et al., 2011). Depressive symptoms were scores using the ‘Hamilton Depression Rating Scale’ (HAM—D) (Hamilton, 1960) Cognitive performance was assessed using the Spanish version of the ‘Brief Assessment in Cognition in Schizophrenia Scale’ (BACS) (Segarra et al., 2011), and the ‘Wisconsin Card Sorting Test’ (WCST: percentage of perseverative errors) (Grant and Berg, 1948). IQ was estimated using the ‘Wechsler Adult Intelligence Scale-III’ (WAIS-III) (Wechsler, 1999). The cognitive assessment was done for descriptive purposes to ensure that patients have equivalent impairment to that of our previous studies.

The sociodemographic, clinical and cognitive characteristics of patients and controls can be found in Table 1.

2.3. Transcranial magnetic stimulation (TMS)

TMS stimulation was performed using a figure-of-8-coil (MCF-B70) and a MagPro X100 stimulator (MagVenture, Denmark). Participants sat comfortably and were instructed to look ahead with their eyes open. The resting motor threshold (RMT) was determined over the left motor cortical region following the relative frequency method (Groppa et al., 2012). For this purpose, electromyographic (EMG) electrodes were placed over the right abductor pollicis brevis (APB).

Thereafter, seventy-five monophasic TMS single pulses were administered over the left dorsolateral prefrontal cortex (DLPFC). Following previous studies (Fernández-Linsenbarth et al., 2024; Mijancos-Martínez et al., 2023; Mijancos-Martínez et al., 2024), the intensity of the pulses was set to 120 % RMT and their administration was semi-randomized, with an inter-stimulus interval varying between 5 and 7 s to prevent anticipation of the next pulse. The specific stimulation site was the midpoint of a line between the F3 and F5 electrodes with a 45° rotation relative to the midline. In the absence of neuronavigational equipment, this position provides the most accurate estimation of the left DLPFC (Fitzgerald et al., 2009; Rusjan et al., 2010).

2.4. Electroencephalographic (EEG) recording

EEG activity was recorded during TMS using a 64-channel system amplifier [Brain Vision (Brain Products GmbH)] following the

international 10–10 system. The impedance for all electrodes was lowered to $\leq 5 \text{ k}\Omega$ and the sampling rate was set at 25 kHz. The channels were referenced over Cz during acquisition.

2.5. TMS-EEG data processing

TMS-EEG processing was performed using Fieldtrip (Oostenveld et al., 2011) and MATLAB (R2021b; The Mathworks Inc., Natick, MA), following the procedure performed in Mijancos-Martínez et al. (Mijancos-Martínez et al., 2023; Mijancos-Martínez et al., 2024). The data was epoched from -1000 ms to 1000 ms relative to TMS-pulse onset. Given their irretrievable nature, data samples from -1 ms to 10 ms related to the TMS-pulse onset were removed and cubic interpolated (Rogasch et al., 2014). Afterward, the data was re-referenced to common average, and an independent component analysis (ICA) was applied to remove artefacts. Independent components were manually selected by three different experts based on their trial-averaged amplitude, time-frequency maps, and spatial distribution and activation maps (Rogasch et al., 2014). Then, bad channel interpolation and bad trial rejection were automatically performed. It is noteworthy that there were no differences in the number of rejected trials between HC and SZ groups ($p\text{-value} = 0.9716$). Finally, a baseline correction was applied using an interval of 800 ms before the TMS-pulse onset, and the data was resampled to 500 Hz and band-pass filtered between 0.5 Hz and 70 Hz .

Fig. 1 illustrates the grand-averaged raw evoked response potentials (ERPs) across trials and subjects at the DLPFC electrodes for both HC and SZ groups.

2.6. Connectivity strength calculation

From a mathematical point of view, the human brain can be seen as a complex network formed by a set of nodes interconnected by network edges. Particularly, for EEG-based brain networks, the nodes are represented by the EEG electrodes and the network edges can be calculated using different coupling metrics between each pair of electrodes (Stam and van Straaten, 2012).

In this study, network edges were computed using the phase locking value (PLV) across successive trials (Lachaux et al., 1999), as it is sensitive to small amplitude oscillations (Spencer et al., 2003) and nonlinearities (van Diessen et al., 2015). Among the different approaches to

compute the PLV, we used the continuous wavelet transform (CWT) because it is able to filter and extract the instantaneous phases of two elicited signals (in this case, TMS-evoked potentials) in only one operation (Bob et al., 2008). Finally, PLV is computed as the variability of the phase difference across successive trials (Lachaux et al., 1999).

$$PLV_{xy}(k, s) = \frac{1}{Nt} \left| \sum_{n=1}^N e^{\Delta\phi_{xy}(k, s, n)} \right|$$

where Nt is the number of trials, $\Delta\phi_{xy}$ is the instantaneous phase difference between the signals x and y , k is the time interval, and s is the scaling factor of the mother wavelet.

The main limitation of the CWT is the variation of wavelet energy caused by a discontinuity at the edge of the ERP signals, that are finite and short-time recordings (Torrence and Compo, 1998). Hence, a cone of influence (COI) can be defined to select the Heisenberg boxes in which edge effects can be ignored (Torrence and Compo, 1998). In this study, two different COIs were evaluated as trials were decomposed into two time windows: (i) the pre-stimulus window, which corresponded to a baseline period before the TMS pulse from -1000 ms to the TMS pulse; and (ii) the post-stimulus window from 15 to 315 ms after the TMS pulse, which is related to the TMS response and include the TMS-evoked potentials.

This procedure used to obtain the adjacency matrices was applied in the conventional EEG frequency bands: theta (θ , $4\text{--}8 \text{ Hz}$), alpha (α , $8\text{--}13 \text{ Hz}$), beta-1 (β_1 , $13\text{--}19 \text{ Hz}$), beta-2 (β_2 , $19\text{--}30 \text{ Hz}$) and gamma (γ , $30\text{--}70 \text{ Hz}$); as well as in the global band (broadband, $4\text{--}70 \text{ Hz}$). Delta band (δ , $1\text{--}4 \text{ Hz}$) was not analyzed because there was less than one signal cycle at its lower frequency included in the response window and no Heisenberg boxes were completely included in the response COI.

From these matrices, the connectivity strength (CS) was computed to summarize the averaged edge values of all of the nodes in the network:

$$CS = \frac{\sum_{i=1}^N \sum_{j>i}^N w_{ij}}{N(N-1)/2}$$

where w_{ij} refers to PLV value between nodes i and j , and N is the total number of nodes of the network (Gomez-Pilar et al., 2018). CS was computed in the pre-stimulus (baseline; -300 to 0 ms) and in the post-stimulus (response, 15 to 315 ms) windows. CS modulation was defined

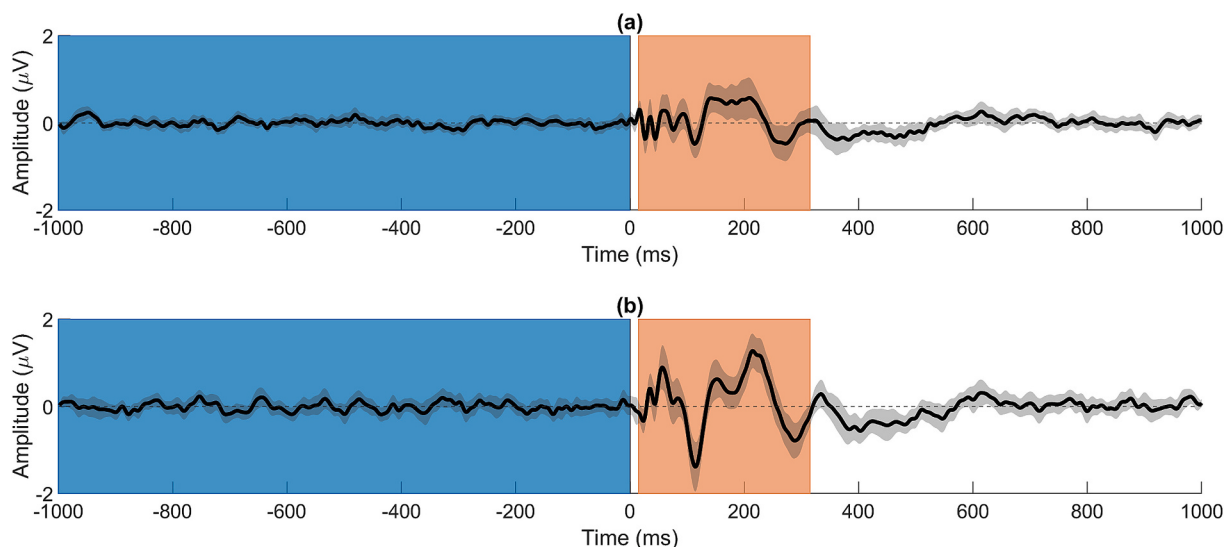


Fig. 1. Grand-averaged raw ERPs and wavelet scalogram across trials and subjects at the DLPFC electrodes for (a) healthy controls, and (b) schizophrenia patients. In the ERPs representations, the solid black lines indicate the average values while the shaded areas represent the standard deviation across all subjects. Pre-stimulus and post-stimulus windows are indicated in blue and orange, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

as the percentage change between those pre-stimulus and the post-stimulus windows:

$$CS_{mod} = \frac{CS_{post-stim} - CS_{pre-stim}}{CS_{pre-stim}} \cdot 100$$

2.7. Local connectivity analysis

To complement our global connectivity analysis and address the local effects of TMS in the targeted area, we also performed a regional connectivity analysis using the PLV values. For this purpose, the whole brain was divided into five distinct regions of interest (ROIs) based on established anatomical and functional divisions (Cash et al., 2016; Noda et al., 2016): Left Frontal (FP1, AF7, AF3, F7, F5, F3, F1, FT7, FC5, FC3, FC1), Right Frontal (FP2, AF4, AF8, F2, F4, F6, F8, FC2, FC4, FC6, FT8), Frontal-Central (F1, FZ, F2, FC1, FCZ, FC2, C1, CZ, C2), Left Central-Parietal (FC5, FC3, FC1, C5, C3, C1, CP5, CP3, CP1), and Right Central-Parietal (FC2, FC4, FC6, C2, C4, C6, CP2, CP4, CP6).

For each frequency band, inter-regional connectivity was computed as the average PLV value between all pair-wise electrodes of the two different ROIs. Intra-regional connectivity was calculated as the average PLV between all electrode pairs within each ROI. These connectivity results were calculated for the pre-stimulus and post-stimulus windows, similarly to CS. Regional PLV modulation was defined as the percentage change between these two windows, consistent with the CS modulation calculation.

2.8. Statistical analysis

Prior to contrast studies, normality of CS baseline, response and modulation values in each band was confirmed using Kolmogorov-Smirnoff tests. In a first step, the effects of the group (SZ versus HC) and condition (CS baseline versus response windows) factors, as well as their interaction, were studied using a general linear model (GLM) for repeated measures. The variable condition was entered as within-subjects factor, while group was the between-subjects factor. Bonferroni corrections for multiple comparisons were applied within the model. The study was performed independently for the different frequency bands (theta, alpha, beta-1, beta-2 and gamma), as well as the broadband. Those frequency bands that showed significant differences in this first step were selected for a second analysis, where CS modulation was compared between SZ patients and HC using *t*-tests for independent samples.

Differences in inter- and intra-regional PLV values in the different time windows (baseline, response, and modulation) between SZ patients and HC for each frequency band were assessed using Mann-Whitney *U* test, as the PLV results were not normally distributed.

The possible effects of medication (Chlorpromazine equivalent doses, CPZ) and/or cognitive and clinical data (*i. e.*, positive symptoms) on TMS-induced CS modulation were then calculated using correlation coefficients (Pearson's *r*). These were performed only for those baseline and modulation network values that showed significant differences between groups in the previous steps of the statistical analysis.

Statistical analyses were performed using IBM SPSS Amos 29 for Windows.

3. Results

CS baseline, response and modulation values in each band followed a normal distribution according to Kolmogorov-Smirnoff tests.

Table 1 shows the significance levels of the contrasts between groups for sociodemographic, clinical and cognitive variables. There were no significant differences in age ($t(50) = 1.892, p = 0.064$) or sex ($\chi^2(1) = 0.088, p = 0.780$) distribution between SZ patients and HC, but educational level ($t(50) = 2.308, p = 0.025$) was lower in the SZ group. IQ ($t(50) = 2.698, p = 0.010$) and cognitive performance in SZ patients was

lower on all cognitive dimensions except for BACS problem solving ($t(50) = 0.608, p = 0.546$) and the WCST percentage of perseverative errors ($t(50) = 1.536, p = 0.131$).

3.1. Connectivity strength and TMS-induced modulation

In the general linear model (GLM) for repeated measures, the overall Multivariate analysis resulted in a significant effect of condition (Wilks' Lambda = 0.520, $F(6) = 6.920, p < 0.001$), but not for the condition-by-group interaction (Wilks' Lambda = 0.879, $F(6) = 1.031, p = 0.418$). The test for inter-subject effects showed a group effect for all frequency bands except gamma (Type III sum of squares = 3.560, $F(1) = 2.787, p = 0.101$). Multivariate test for group effect (Wilks' Lambda = 0.809, $F(6) = 1.772, p = 0.127$) resulted in higher power values in SZ patients for all frequency bands, except gamma (mean difference = 0.370, $p = 0.101$).

In the study of group-by-condition interaction, multivariate analysis performed separately within each group showed a significant condition effect for both groups (HC: Wilks' Lambda = 0.649, $F(6) = 4.065, p = 0.002$; and SZ: Wilks' Lambda = 0.659, $F(6) = 3.886, p = 0.003$). In the HC group, single pulses of TMS induced a significant CS increase (*i. e.*, baseline to response) in the broadband (mean difference = 0.186, $p < 0.001$) as well as in the other individual frequency bands analyzed except alpha (mean difference = 0.256, $p = 0.129$). In SZ patients, single TMS pulses induced a significant increase in all frequency bands except alpha (mean difference = 0.186, $p = 0.267$) and gamma (mean difference = 0.084, $p = 0.058$).

Baseline and response CS values and their significant differences between groups and conditions can be found in Table 2 and Fig. 2.

General Lineal Model, post hoc pairwise comparison of the estimated marginal means (Bonferroni confidence interval adjustment).

Patients vs. Controls: * $p < 0.05$, ** $p < 0.01$.

Baseline vs. Response: # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$.

In the second step of our analysis, the between-group comparison of CS modulation resulted in significantly lower values in the patient group in the gamma band only ($t(50) = -2.063, p = 0.022$). Table 3 and Fig. 3 show the CS modulation values and their contrast between groups.

3.2. Local connectivity differences

Fig. 4 shows that our PLV results revealed that EEG activity in SZ patients is characterized by an overall connectivity increase for all frequency bands except gamma in the pre-stimulus and post-stimulus windows. However, these differences were not significant in the modulation condition.

Table 2

CS values in baseline (pre-stimulus) and response (post-stimulus; following the TMS pulse) in schizophrenia patients (SZ) and healthy controls (HC). General Lineal Model, post hoc pairwise comparison of the estimated marginal means (Bonferroni confidence interval adjustment). Patients vs. Controls: * $p < 0.05$, ** $p < 0.01$. Baseline vs. Response: # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$.

	SZ Patients (N = 26)		HC (N = 26)	
	Baseline	Response	Baseline	Response
Theta	0.409 (0.030) **##	0.441 (0.059)	0.390 (0.022) ##	0.414 (0.050)
Alpha	0.434 (0.032) **	0.440 (0.041) *	0.407 (0.038)	0.416 (0.037)
Beta-1	0.407 (0.031) ###	0.424 (0.047) *	0.384 (0.029) ##	0.396 (0.029)
Beta-2	0.382 (0.033) ###	0.390 (0.041) *	0.358 (0.026) ##	0.367 (0.026)
Gamma	0.333 (0.028)	0.336 (0.028)	0.319 (0.027) ###	0.325 (0.025)
Broadband	0.367 (0.028) ###	0.373 (0.030) *	0.348 (0.022) ##	0.354 (0.021)

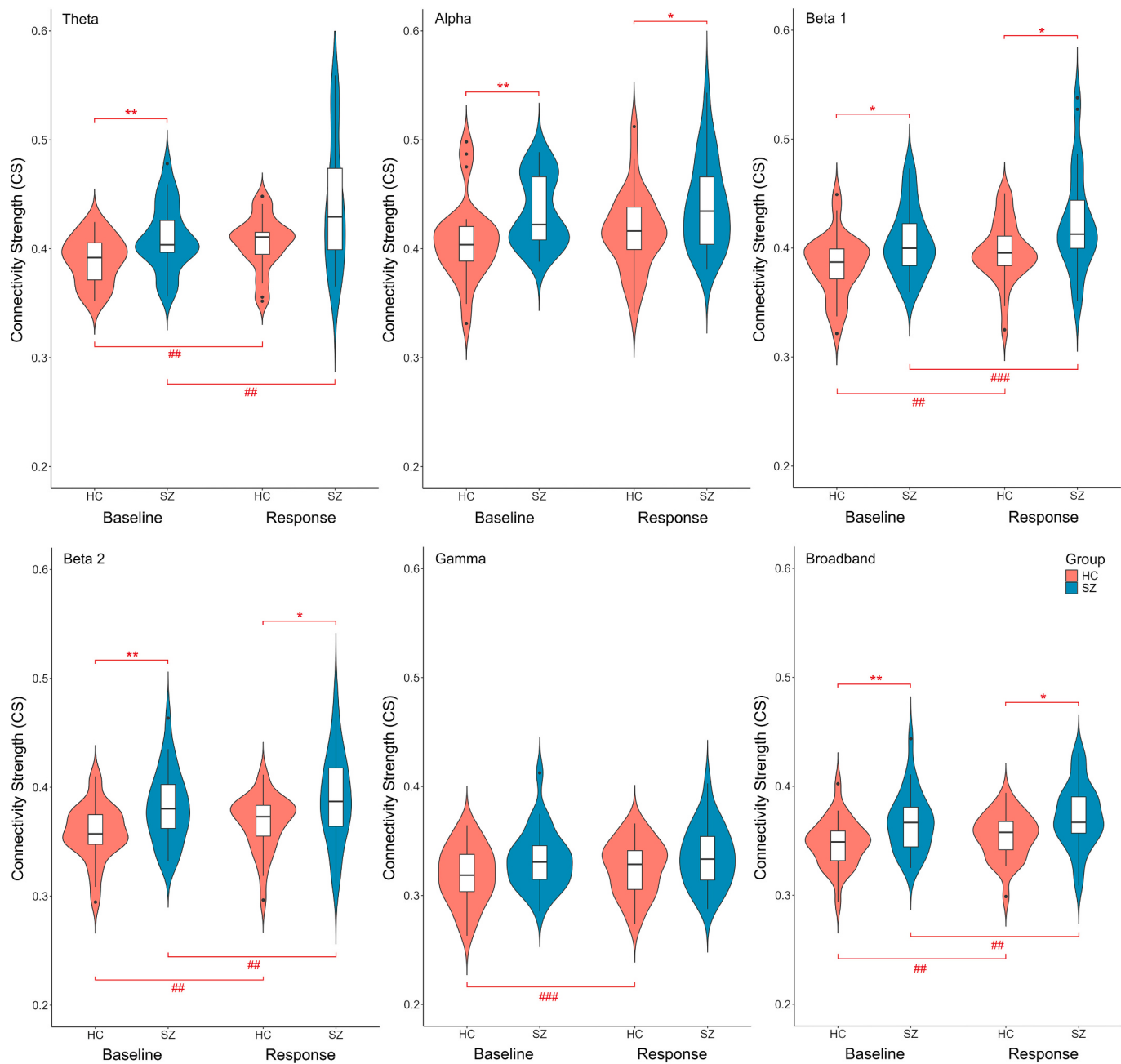


Fig. 2. Boxplots depicting CS value distributions from healthy controls (HC; blue) and schizophrenia patients (SZ; red) in the pre-stimulus (baseline) and the post-stimulus (response, following TMS pulse) windows for the different frequency bands. Significant differences between groups are included (SZ vs. HC: * $p < 0.05$, ** $p < 0.01$; Baseline vs. Response: # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Comparison of modulation differences in CS between schizophrenia patients (SZ) and healthy controls (HC) measured as a percentage change and displayed as mean (SD).

	SZ (n = 26)	HC (n = 26)
Theta modulation	7.459 (10.526)	6.246 (11.706)
Alpha modulation	1.419 (5.631)	2.375 (7.691)
Beta 1 modulation	4.286 (6.973)	3.322 (4.334)
Beta 2 modulation	2.189 (3.920)	2.551 (3.533)
Gamma modulation	0.838 (1.770) *	2.165 (2.761)
Broadband modulation	1.618 (2.697)	1.818 (2.166)

* $p < 0.05$ (t-test for independent samples).

3.3. Effects of medication, and clinical and cognitive scores

In the SZ group, neither antipsychotic dose nor any cognitive or symptomatology measure was related to the degree of CS modulation with TMS in any of the frequency bands.

4. Discussion

In our sample, TMS pulses increased CS in the cortical network in HC, more specifically in the faster bands (beta and gamma). This agrees with previous data showing that TMS induces global increase of activity in healthy subjects during the 100–200 ms following pulses (Frantseva et al., 2014), (although in this report, oscillatory increases with TMS

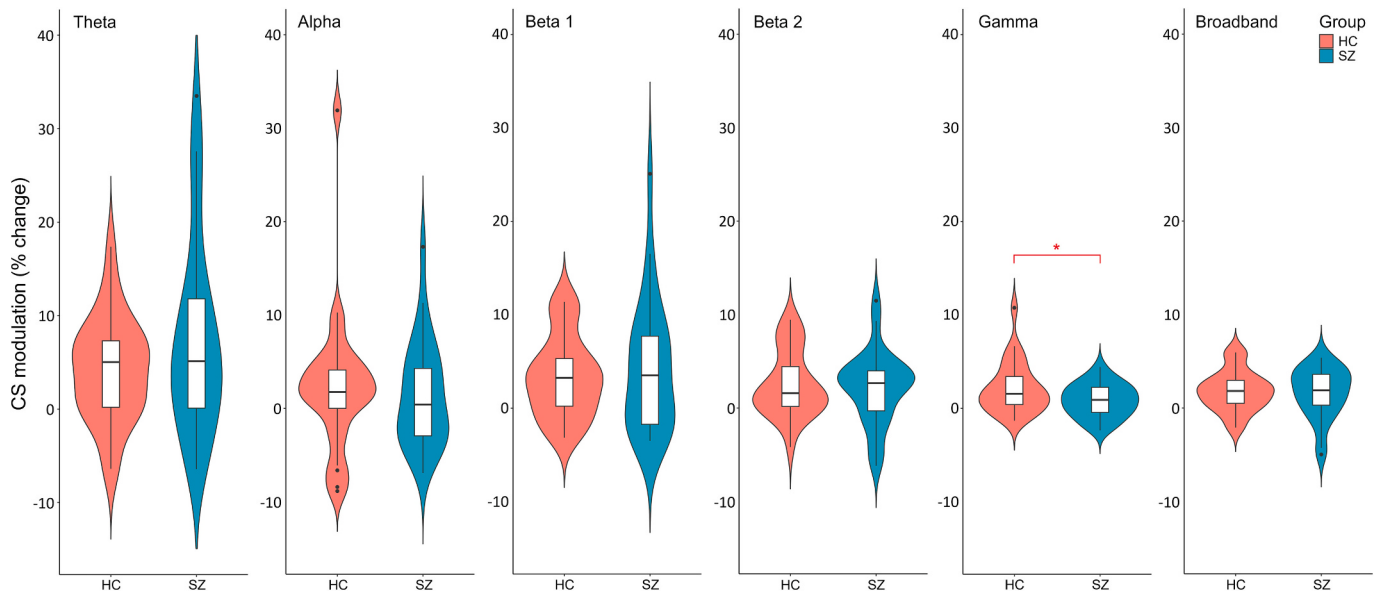


Fig. 3. Boxplots depicting percentual CS variation distributions (*i. e.*, modulations) from healthy controls (HC; blue) and schizophrenia patients (SZ; red) for the different frequency bands. Positive values indicate an increase from the pre-stimulus to the post-stimulus windows, while negative values indicate a decrease. Significant differences between groups are included ($*p < 0.05$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

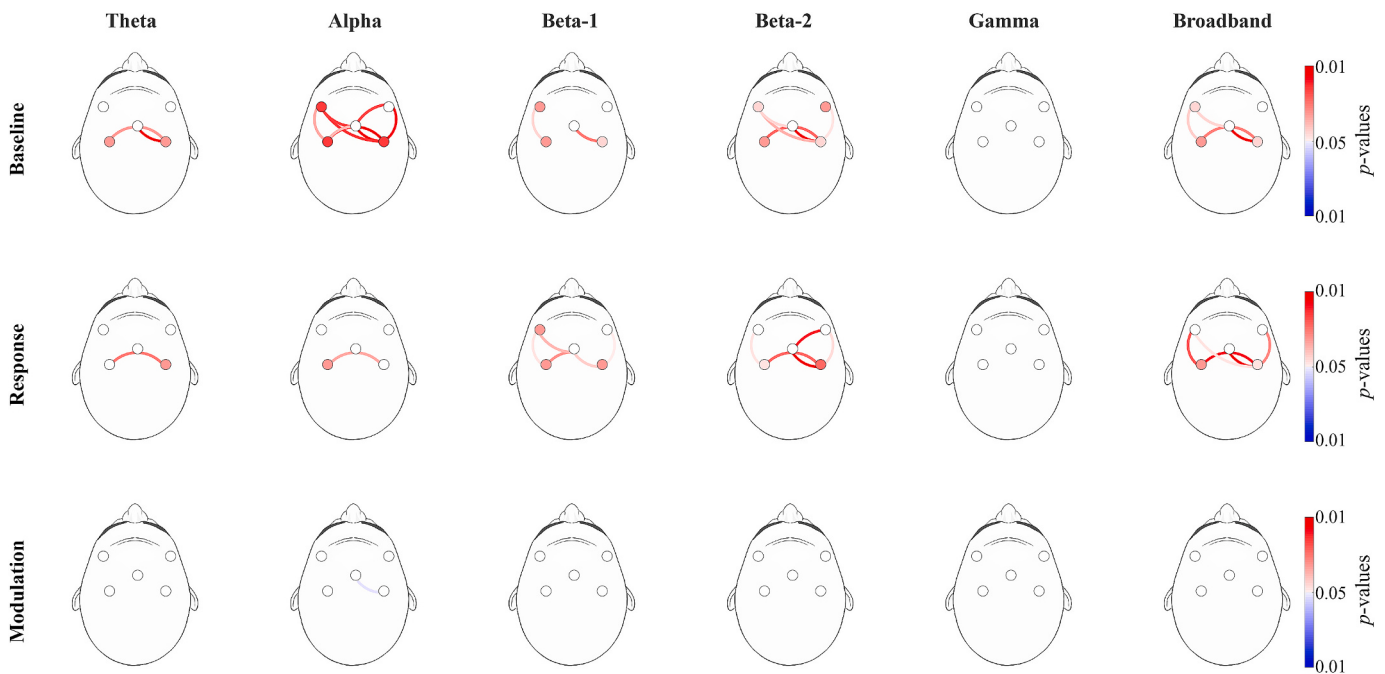


Fig. 4. PLV results for each classical EEG-frequency band and condition. Connections inter- and intra-ROIs were only displayed when statistically significant within group differences were obtained (Mann–Whitney U test, FDR-corrected p -values < 0.05). Red colour tones indicate statistically significant connectivity increases in schizophrenia patients compared to healthy controls, whereas blue colour tones denote significant decreases. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

were higher in the schizophrenia group), and with the increase in functional connectivity after TMS assessed with magnetic resonance (fMRI) (Xue et al., 2017). When analyzing specific oscillations, the enhancing effect of TMS may be more evident in the gamma band in healthy subjects (Barr et al., 2009). Instead, in our SZ patients, modulation was significantly lower in the gamma band, which is coherent with the decrease in evoked gamma oscillations by TMS and its reduced propagation reported in schizophrenia (Ferrarelli et al., 2008). In our patients, this reduced modulation was accompanied in the pre-stimulus

window by higher CS across bands (except for gamma). Since CS modulation represents connectivity changes among sensors, its smaller increase in our patients is coherent with the reduced connectivity of the PFC after TMS in SZ using a measurement of current propagation (Ferrarelli et al., 2015).

The combination in our SZ patients of increased CS at baseline in all bands except gamma with the smaller CS modulation in the gamma band in comparison to HC is coherent with a hypofunction of GABA interneurons in SZ, that is, TMS pulses probably depolarize the underlying

neurons (Tremblay et al., 2019) and, since gamma oscillations are thought to be generated and modulated by GABA neurotransmission (Buzsáki, 2006; McNally and McCarley, 2016), a functional deficit in those neurons may underlie the smaller increase of CS in the gamma band in patients. Besides, a hypofunction of GABA interneurons may also reasonably contribute to the cortical hyperactivity in our patients in the other bands, given its global inhibitory effect. Such a dysfunction in SZ is supported by postmortem (Gonzalez-Burgos et al., 2011; Gonzalez-Burgos and Lewis, 2012) and spectroscopy (Reddy-Thootkur et al., 2022) data, functional findings showing basal hyperactivity (Iglesias-Tejedor et al., 2022; Manoach, 2003), graph analyses showing global hypersynchrony (Cea-Cañas et al., 2020) and pharmacological data supporting a NMDA hypofunction (Snyder and Gao, 2020). Similarly, the reduced 40 Hz auditory steady-state response has been proposed to reflect impaired inhibitory cortical function in SZ reflected in lower gamma band modulation (Grent-t-Jong, T, et al., 2023). Paired TMS paradigms also point in this direction: short (SICI) and long (LICI) interval cortical inhibition paradigms assess the functional status of transmission respectively mediated by GABA-A (Daskalakis et al., 2003) and GABA-B (Fitzgerald et al., 2003) systems, and support an inhibitory deficit in SZ in LICI (Fitzgerald et al., 2003) and SICI (Noda et al., 2017) studies.

In this context, our data seems compatible with a hyperactive basal state that hampers TMS-induced modulation of the global network. In other words, the higher baseline CS in patients could reflect a lower inhibitory tone, while the smaller stimulation of gamma oscillations could reflect a hypo-response of GABA interneurons, perhaps with a similar substrate.

However, other results obtained with TMS in schizophrenia may seem contradictory with the proposed low inhibitory tone. Our previous study (including 20 of the 24 patients in the present one) that assessed local mean field power a measurement of local activation in the prefrontal region following TMS pulses, revealed larger activation over this region (Fernández-Linsénbarth et al., 2024; Mijancos-Martínez et al., 2023). This may seem contrary to the lower gamma CS increase with TMS in patients. However, that study did not assess network changes in the different bands, neither assessed the global cortical network. Since most patients in those studies overlapped with the present sample, it seems indeed plausible that a smaller reorganization in the gamma band of the cortical network with TMS would coexist with a larger global activation reflected in higher amplitudes of the TMS-evoked potentials, both resulting from an inhibitory deficit. In support of this possibility, higher glutamate and lower GABA concentrations measured with spectroscopy resulted in a higher cortical excitability (reflected in N100 amplitude) following TMS (Du et al., 2018).

Characterizing global changes following TMS is especially interesting in the context of a possible definition of biotypes in the psychotic syndrome. We have proposed a biotype characterized by cognitive deficit and hyperactive cortical state (i. e., with high connectivity strength) (Fernández-Linsénbarth et al., 2021), coherent with the findings reported by Clementz et al. (Clementz et al., 2022). Molecular findings support that inhibitory deficits may characterize a subset of cases (Volk et al., 2016). The possibility that different patterns of TMS-evoked responses are found in different groups of patients is supported by opposite findings concerning patterns of signal propagation of TMS (Ferrarelli et al., 2008; Radhu et al., 2017).

We did not find significant relations between clinical or cognitive scores and modulation values, despite the significant differences in cognitive performance between groups. This may indicate an absence of clinical consequences of these modulation alterations, or an insufficient sample size, which may be the case when considering that different biotypes may be defined in schizophrenia according to cognitive performance (Du et al., 2018). Thus, mixing patients from diverse biotypes may obscure cognitive or clinical correlations with network properties; that is, if the inhibitory deficit suggested by our findings applies only to a subset of patients, the joint assessment of correlations between clinical/

cognitive data and CS may yield negative results. Indeed, convergent results suggest a hyperactive baseline in patients with larger cognitive deficits (Clementz et al., 2022; Fernández-Linsénbarth et al., 2021). It is thus possible that relations between gamma CS and cognition and/or symptoms would be clearer in that biotype. However, it is also possible that other network parameters may show clearer clinical or cognitive correlations than CS. Thus, the assessment of connectivity modulation with TMS in different biotypes of psychoses could yield relevant results to understand its underpinnings, but a much larger sample size would be needed to that end.

The limitations of our study include the limited sample size and the possible effects of treatment on TMS reactivity, although we found a lack of relationship with the dose of antipsychotic medication. Therefore, clearly larger samples are needed in future studies, especially considering the possibility that the described effects could be limited to subgroups of cases. Finally, neuronavigator was not used in the stimulation of the DLPFC region, so further studies should improve the accuracy of the region stimulated with this tool.

5. Conclusion

The specific alterations in the modulation of the gamma-band connectivity strength found in patients with schizophrenia after single pulses of TMS are compatible with previous literature providing evidence of an inhibitory deficit in this syndrome, whose possible substrate would be a deficit of GABAergic inhibitory activity.

CRedit authorship contribution statement

Vicente Molina: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Saul J. Ruiz-Gómez:** Visualization, Formal analysis. **Inés Fernández-Linsénbarth:** Investigation, Data curation. **Rosa M. Beño-Ruiz-de-la-Sierra:** Investigation, Data curation. **Emma Osorio:** Investigation. **Alejandro Roig:** Investigation. **Gema Mijancos-Martínez:** Visualization, Investigation. **Claudia Rodríguez-Valbuena:** Investigation. **Alejandro Bachiller:** Writing – review & editing, Methodology, Formal analysis. **Miguel Ángel Mañanas:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Álvaro Díez:** Writing – review & editing, Visualization, Formal analysis.

Ethical statement

The study was approved by the Research Board of the Clinical University Hospital of Valladolid and was conducted in compliance with the Declaration of Helsinki of 1975, as revised in 2008. Each participant signed a written informed consent after being fully informed about the details of the experiment.

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Declaration of competing interest

The authors have no competing interests to declare.

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Data availability

Data will be made available on request.

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