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Distinct cortical inhibitory profiles in schizophrenia and bipolar disorder: A TMS-EEG study of GABAb function

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ABSTRACT

Background: EEG recordings associated with transcranial magnetic stimulation (TMS) with paired pulse paradigms allow the in vivo assessment of cortical inhibitory function. The long-interval cortical inhibition (LICI) paradigm can be used to estimate this function related to GABAb receptors.
Methods: We compared LICI values between 25 patients with schizophrenia, 16 patients with bipolar disorder (BD), and 23 healthy controls (HC). We also assessed the relationship between LICI values and cognitive performance, as well as the treatment with antipsychotics, benzodiazepines, and anticonvulsants.
Results: LICI was significantly lower in patients with schizophrenia than in controls, but not in BD patients. In the former group, LICI was negatively associated with cognitive performance and positive symptoms. However, benzodiazepines increased LICI values, which does not explain its decrease in schizophrenia patients.
Conclusions: Our data support the existence of a functional inhibitory deficit mediated by GABAb receptors in schizophrenia, that is associated with cognitive performance and symptoms. In the context of existing literature, this deficit may characterize a subgroup of patients with this diagnosis.

1. Introduction

Cortical inhibition (CI) is a crucial neurophysiological mechanism that generates and regulates coordinated activity within cortical networks (Buzsaki, 2006). Previous results have supported a cortical inhibitory deficit both in schizophrenia and bipolar disorder (BD) (Benes and Berretta, 2001). This has been replicated in post-mortem examinations of the dorsolateral prefrontal cortex (DLPFC) in individuals with schizophrenia (Akbarian et al., 1995; Volk et al., 2012) and, to a lesser degree, in BD (Woo et al., 2004). In vivo, magnetic resonance spectroscopy studies have provided further evidences of an excitatory/inhibitory (E/I) imbalance by analyzing GABA and glutamate levels in the cortex in schizophrenia (Wang et al., 2019), but not in BD (Atagün et al., 2017; Galińska-Skok et al., 2016; Kaufman et al., 2009; Soeiro-de-Souza et al., 2015).

Therefore, it is interesting to compare inhibitory function in vivo in schizophrenia and BD, considering that an E/I imbalance is possible even with normal levels of GABA and/or glutamate neurotransmitters. Such assessment is feasible combining transcranial magnetic stimulation (TMS) with electroencephalography (EEG), using short- (Valls-Solé et al., 1992) and long- (Paulus et al., 2008) interval cortical inhibition paradigms (i.e., SICI and LICI protocols, respectively). These paradigms assess this inhibition mediated by GABAa and GABAb receptors respectively. Specifically, the LICI TMS paradigm is a paired-pulse approach in which a suprathreshold conditioning stimulus (CS) is succeeded by a suprathreshold test stimulus (TS) with interstimulus intervals ranging between 50 and 200 ms (Tremblay et al., 2019). When the response to the test (i.e., paired) pulse is compared with the response

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to an unconditioned equitable pulse, an attenuation of neuronal activity is observed in the former. This attenuation is a measurement of the local inhibitory status (Fitzgerald et al., 2009a).

To date, it is noteworthy that there is a relatively large support for an inhibitory deficit mediated by GABAa receptors in schizophrenia (Lindberg et al., 2016; Noda et al., 2017; Takahashi et al., 2013; Wobrock et al., 2010). However, GABAb receptor function has received less attention. These receptor types have different characteristics: GABAa is ionotropic, resulting in faster responses, while GABAb is metabotropic, resulting in slower responses (Emson, 2007). Furthermore, GABAb modulates GABAa function (Sanger et al., 2001). A recent meta-analysis (Lányi et al., 2024) includes four LICI studies in schizophrenia, and concluded that the combined sample size was insufficient to draw conclusions about GABAb function. Three of those studies stimulated the motor cortex and assessed electromyography effects (Fitzgerald et al., 2003; Mehta et al., 2014, 2021) while the other one stimulated the DLPFC and assessed the effects on EEG activity in patients with schizophrenia and BD (Farzan et al., 2010a). Another study from the latter group reported significant LICI inhibition deficits in the DLPFC of patients with schizophrenia compared with HC and patients with obsessive-compulsive disorder. However, the inhibition deficit of obsessive-compulsive disorder patients was not significantly different compared to healthy subjects (Radhu et al., 2015). Although previous evidence of LICI deficits originates primarily from studies stimulating the motor cortex and using EMG measurements, previous literature shows that EMG measures of LICI in the motor cortex are correlated to EEG measures of LICI in the DLPFC in healthy controls (Daskalakis et al., 2008a, 2008b), which suggests similar underlying mechanisms. While the direct examination of cortical activity changes induced by TMS is challenged by the large artifacts associated to magnetic stimulation, it is possible to eliminate them, and thus TMS-EEG may offer valuable direct information of the E/I status in the DLPFC, a cortical region more closely related to the pathophysiology of schizophrenia and bipolar disorder. Thus, also considering the relatively scarce data on GABAb function in psychoses, we decided to use TMS-EEG approach to assess this function in schizophrenia and bipolar disorder patients.

Several issues should be evaluated to further elucidate the potential relevance of the E/I misbalance in psychotic patients. Firstly, none of the aforementioned TMS-EEG studies reported above controlled for the possible contamination of the late evoked response of the conditioning pulse in the early evoked response of the test stimulus (Daskalakis et al., 2008a, 2008b). Secondly, the effect of treatment should be considered: while the effect of dopamine (DA) antagonists on LICI seems negligible (Sanger et al., 2001; Ziemann et al., 2015), to our notice the effect of the GABA-agonistic benzodiazepines and anticonvulsants has not been evaluated in psychoses. Thirdly, the cognitive consequences of the E/I imbalance have not been assessed, although is suggested by the significant association between LICI and working-memory performance in healthy controls (HC) (Daskalakis et al., 2008a).

This study has two main objectives. The first one is to assess LICI in patients with schizophrenia, bipolar disorder, and HC in the DLPFC using TMS-EEG, controlling for the possible contamination in the paired pulse condition and the effect of treatment. Secondly, it aimed to explore the association between LICI and cognitive and clinical variables. It was hypothesized that patients with schizophrenia would show LICI deficits in the DLPFC compared to HC and patients with bipolar disorder, and that these deficits would not be explained by treatment. Finally, we hypothesized that altered cortical inhibitory transmission, as assessed by LICI, would be associated with worse cognitive performance.

2. Materials and methods

2.1. Participants

This study included 25 schizophrenia patients (13 of which were first episode), 16 BD patients, and 23 healthy controls (HC). Patients were recruited from mental health facilities and a psychiatric day center belonging to the public regional health system. The ethical committee of the University Hospital of Valladolid endorsed the study (protocol PI-21-2623).

The exclusion criteria were: (i) a total Intelligence Quotient (IQ) below 70; (ii) a history of neurological disorders; (iii) past or present substance abuse, except for nicotine or caffeine; (iv) the presence of any other psychiatric process for patients; (v) any history of psychiatric diagnosis or treatment for controls; and (vi) not being safe to receive TMS.

2.2. Clinical and cognitive assessment

Patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (American Psychiatric Association). Positive and negative symptoms were scored using the Spanish version of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Brief Assessment of Negative Symptoms (BNSS) (Kirkpatrick et al., 2011). All schizophrenia patients and 13 BD patients were receiving stable doses of atypical antipsychotics. Six bipolar and 2 schizophrenia patients were receiving anticonvulsants.

Sociodemographic data were screened through personal interviews. Global Intelligence Quotient (IQ) and cognitive performance were respectively assessed using the Spanish versions of the Wechsler Adult Intelligence Scale – 3rd Edition (WAIS-III) (Fuentes Durá et al., 2010) and the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004) and the Wisconsin Card Sorting Test (WCST).

2.3. Transcranial magnetic stimulation

TMS pulses were administered to the left DLPFC of each participant using a figure of-8-coil (MCF_B70) and MagProX100 stimulator (MagVenture, Denmark). The stimulation site was the midpoint of the line connecting the F3 and F5 electrodes, rotated 45° relative to the midline. This positioning was chosen for its accurate estimation of the left DLPFC and to prevent inter-subject variability in the absence of neuronavigational equipment (Fitzgerald et al., 2009b; Rusjan et al., 2010). LICI paradigm consisted of 75 single-pulses (intensity 120 % of the resting motor threshold, RMT) and 75 paired-pulses (CS and TS 120 % RMT, with an interstimulus interval of 100 ms). These TMS-pulses were administered randomly while participants sat comfortably with their eyes open, looking straight ahead. Besides, TMS-pulses were administered semi-randomly with a 5 to 7 s interval to prevent anticipation. To determine the intensity of the TMS-pulses, the RMT of each participant was obtained following the methodology described in Groppa et al. (Groppa et al., 2012), where RMT is defined as the minimum intensity required to elicit a motor-evoked potential (MEP) with a peak-to-peak amplitude higher than 50 μV in at least five out of ten subsequent trials. The RMT was determined by administering TMS-pulses over the left motor cortex, with MEPs were recorded through electrodes placed on the right abductor pollicis brevis muscle.

2.4. EEG data acquisition

EEG was recorded concurrently with LICI protocol using a 64-channel system [Brain Vision (Brain Products GmbH)], following the international 10–10 system. Data was sampled at 25 kHz, with all channels referenced to the Cz electrode. Electrode impedance was maintained below 5 kΩ throughout all recordings.

2.5. TMS-EEG pre-processing and processing

Data pre-processing and processing were performed using MATLAB (R2021b; The MathWorks Inc., Natick, MA, USA) and Fieldtrip (Robert et al., 2011).

The procedure was similar to the one performed in Mijancos-

Martínez et al. (2024). First, data were segmented into two-seconds epochs centred around the TS (the only TMS-pulse of single-pulse (SP) signals or the second TMS-pulse of the paired-pulse (PP) signals). Then, samples around the pulses were removed (from -1 ms to 10 ms for the SP signals and the TS in PP signals; and from -110 ms and -90 ms for the CS in PP signals), after which cubic interpolated were performed on removed samples. Independent component analysis was performed after re-referencing the data to the common average to reduce artifacts. Independent components (IC) were manually selected by four different experts, based on time-frequency maps, trial-averaged amplitude, and activation and spatial distribution maps. The selection was based on the guidelines in Rogasch et al. (2014). Next, a downsampling to 5 kHz and a band-pass filter between 0.5 Hz and 70 Hz were applied, followed by an automatic interpolation of bad channels and rejection of trials still containing artifacts. The artifact-free data were baseline corrected using the 800 ms interval before the first TMS-pulse onset. Finally, the trials were averaged to obtain the TMS-evoked response signal.

The PP signal was corrected to remove the late response generated by the CS from the TS following Daskalakis et al. (Daskalakis et al., 2008a, 2008b). To do so, the SP signal averaged across trials for each subject and channel was time-shifted by 100 ms to align with the CS onset of the PP signal averaged across trials for each subject and channel. Then, the shifted SP signal was subtracted from the PP signal (Daskalakis et al., 2008a, 2008b; Opie et al., 2017; Premoli et al., 2014; Rogasch et al., 2015). From now on, the corrected PP signal will be referred to as the PP signal. Finally, averaging across the channels that covers the left DLPFC ROI (i.e., Fp1, Af7, Af3, F7, F5, F3, F1, Fc5, Fc3, and Fc1) (Cash et al., 2017) was computed for both SP and PP signals.

2.6. Long-interval cortical inhibition assessment

Two approaches were used to evaluate the cortical inhibition in different populations: one evaluating the LICI in a global manner, and another assessing the TMS-evoked potentials (TEPs) more specifically, in both of them using the signal obtained from the left DLPFC ROI.

First, to obtain a global metric, the signal was divided into early (15-100 ms) and late (100-250 ms) responses (Daskalakis et al., 2008a, 2008b; Farzan and Bortoletto, 2022), obtaining an early and late time windows. Then, the mean amplitudes of these time windows were extracted both for the SP and PP signals. Moreover, the topographic distribution of both time windows was computed.

Secondly, TEPs were evaluated individually for each participant. In particular, the N45, P60 and N100 TEPs were assessed as they occur within the time window of GABAb receptor inhibitory post-synaptic potentials elicited by the CS (Farzan et al., 2010a). Previous work from our group demonstrated that individualised identification of TEPs provides their more accurate characterisation (Mijancos-Martínez et al., 2024). Therefore, the time windows associated with TEPs were identified individually, subject by subject. Specifically, the N45 was defined as the most negative minimum within 30-60 ms after TMS onset. The subsequent largest positive peak occurring between the N45 latency and 100 ms was identified as P60. The N100 peak was identified as the most negative peak within 80–150 ms post-TMS. Following this procedure, individual latencies were determined for each peak in every subject. Finally, personalized time windows were defined for each TEP, centred on the corresponding latencies obtained previously and with widths of 10 ms for the N45 and P60, and 30 ms for the N100. Once the time window was selected, it was applied to the signals to obtain the mean amplitude of each TEP. In addition to TEP amplitude, peak-to-peak measures for N45-P60 and P60-N100 were calculated by subtracting the amplitude of the negative TEP to the positive TEP amplitude.

Finally, LICI inhibition was assessed by subtracting the PP values from the SP values (SP-PP) of the aforementioned metrics. If the result of the subtraction is positive, it indicates that there has been inhibition after the paired-pulse stimulation; otherwise, facilitation has occurred.

2.7. Statistical analysis

Demographic characteristics of the HC and both patient populations were compared using a Wilcoxon rank-sum test.

Cognitive factors were normalized using z-scores to prevent a bias arising from the disparity between the values. Principal component analysis of the scores in the BACS (verbal memory, working memory, motor speed, verbal fluency, performance speed and problem solving) and WCST (percentage of perseverative errors) was employed to summarize the cognitive variables. A table showing the factor loadings is now included in supplementary material (table S1), showing a single factor that explains 55,24 % of total variance. The number of factors retained was determined by examining the scree plot. Data analyses were performed using SPSS statistical software, version 29 (IBM).

Wilcoxon rank sum test was used to compare the results of the different populations (HC vs schizophrenia patients, HC vs BD, schizophrenia patients vs BD) for the global time windows amplitude (early and late), TEP amplitudes and peak-to-peak amplitudes. Finally, the FDR correction for multiple comparisons was conducted. Effect sizes were assessed using Cohen's d, along with confidence intervals (CI) to quantify the differences between pairs of groups. Analogously, a statistical topography analysis using the Wilcoxon rank-sum test was carried out.

LICI in the early response (i.e., the subtracted mean amplitude (SP-PP) of the early time window) was chosen as the EEG parameter with which to compare with medication, symptomatology, and cognition because it is a global measure of the LICI. The normality of the data was checked using Shapiro-Wilk test and a Pearson's or Spearman's correlation was used accordingly. Addtional correlation analyses were carried out to explore the relationship between LICI and the symptomatology and cognition of the patients. Furthermore, a third correlation analysis was performed to compute the relationship between LICI at the early response and the medication dose.

Finally, the Wilcoxon rank-sum test was used to compare patients taking or not taking anticonvulsants or benzodiazepines (BZD), and to investigate the association between these medications and the EEG feature of LICI in the early response to TMS-stimulation.

3. Results

3.1. Participants characteristics

The demographic and clinical data of the subjects is presented in Table 1. No significant differences were obtained between populations in terms of age, sex, educational level nor RMT.

3.2. Global metrics

Topographies of the early and late time windows, statistical topography between populations, as well as the averaged SP-PP mean amplitudes in the DLPFC ROI for both time windows for HC and schizophrenia patients are depicted in Fig. 1. As it can be observed both on the statistical topography and the bar graph, significantly higher values of subtracted amplitudes (SP-PP) were obtained for the HC group compared to schizophrenia patients in the DLPFC ROI for the early time window (p-$value = 0.023$, Cohen's $d = 0.742$, CI 95 % = [0.16, 1.31]). The HC population had positive values whereas the schizophrenia patients showed negative ones. No significant differences were obtained for the late time window, with positive values for both populations after subtraction.

Fig. 2 shows SP-PP topographies for the early and late time windows, their corresponding statistical topographies and the subtracted mean amplitudes for HC and bipolar patients. For both time windows and both populations, the values after the subtraction were positive and no statistical significance was found.

Nevertheless, no significant differences were found comparing

Table 1
Demographic and clinical data of the participants.

	Healthy controls	Schizophrenia	Bipolar disorder
Sample size (n)	23	25	16
Age (years)	29.57 (11.32)	36.60 (11.98)	37.38 (11.30)
Sex (M/F)	14/9	14/11	7/9
Education level (years)	15.26 (2.301)	13.48 (3.31)	14.06 (3.39)
Cognition	0.59 (0.45)	−0.39 (1.03) **	−0.56 (0.73) **
RMT	60.17 (9.06)	60.20 (8.49)	61.38 (8.05)
Illness duration (months)	NA	93.52 (124.25) #	167.50 (143.95) #
Lifetime hospitalizations	NA	1.61 (1.34) #	4.44 (5.01) #
CPZ equivalents	NA	377.06 (255.87) #	248.750 (194.07) #
Benzodiazepines (n yes)	NA	13	5
Anticonvulsants (n yes)	NA	2 #	8 #
PANSS positive	NA	13.78 (5.54) ##	8.13 (2.48) ##
PANSS negative	NA	15.65 (6.97) #	9.53 (4.73) #
PANSS total	NA	53.65 (19.61) ##	36.87 (8.50) ##
BNSS	NA	22.22 (17.34) #	9.87 (13.34) #

Data is expressed as mean (standard deviation).
Cognition is expressed as fist principal component value.
Significance is defined as $p < 0.05$.
RMT: resting motor threshold; CPZ: chlorpromazine; PANSS: Positive and Negative Symptoms Scale; BNSS: Brief Negative Symptoms Scale.
** $p < 0.001$ compared to HC.
# $p < 0.05$ between patients' groups.
$p < 0.001$ between patients' groups.

schizophrenia patients and BD as it can be observed in Fig. 3.

3.3. TEP parameters

The Wilcoxon rank sum test showed no statistically significant differences (*p-values* > 0.05) for N45, N100, and peak-to-peak N45-P60 between HC vs schizophrenia patients nor between HC vs BD or between schizophrenia patients vs BD. Nevertheless, when the schizophrenia patients were compared with the HC, reduced LICI is observed for P60 and peak-to-peak P60-N100 (lower values of SP-PP, even negative for P60) with *p-value* = 0.035, Cohen's d = 0.674, CI (95 %) = [0.097, 1.245] for P60 and, *p-value* = 0.027, Cohen's d = 0.522, CI (95 %) = [−0.047, 1.086] for P60-N100. For these parameters, no significant differences were obtained when comparing HC vs BD patients or schizophrenia patients vs BD. Fig. 4 depicts the mean SP-PP amplitudes for P60, N100 and the peak-to-peak P60-N100 are depicted for HC, schizophrenia patients, and BD patients.

Mean values and standard deviation values for all populations in each parameter are presented in Table S2.

3.4. Association between LICI and symptomatology and cognition

The first principal component for cognition summarized most of the information, accounting for 49.49 % of the variance (eigenvalue 3.46). All cognitive variables except percentage of perseverative errors of the WCST contributed positively to this factor. Therefore, all BACS scores (verbal memory, working memory, motor speed, verbal fluency, performance speed and problem solving) contributed directly to this factor, while WCST perseverative errors contributed inversely to it (suppl table 1).

LICI in the early time window was almost significantly correlated to PANSS positive punctuation ($r = 0.395$, *p-value* = 0.06) and significantly correlated to cognition ($r = 0.430$, *p*-value = 0.03) for the schizophrenia patients. No statistically significant correlations were found for BD patients. In Fig. 5 the association between LICI in the early time window and cognition is depicted.

3.5. Association between LICI and medication

3.5.1. Association between LICI and anticonvulsants

No significant differences in LICI values at the early response were found between patients taking anticonvulsants and those not taking them.

3.5.2. Association between LICI and benzodiazepines

There were statistically significant differences in the LICI values at the early response stage between patients taking and not taking benzodiazepines, with higher LICI values observed in patients taking

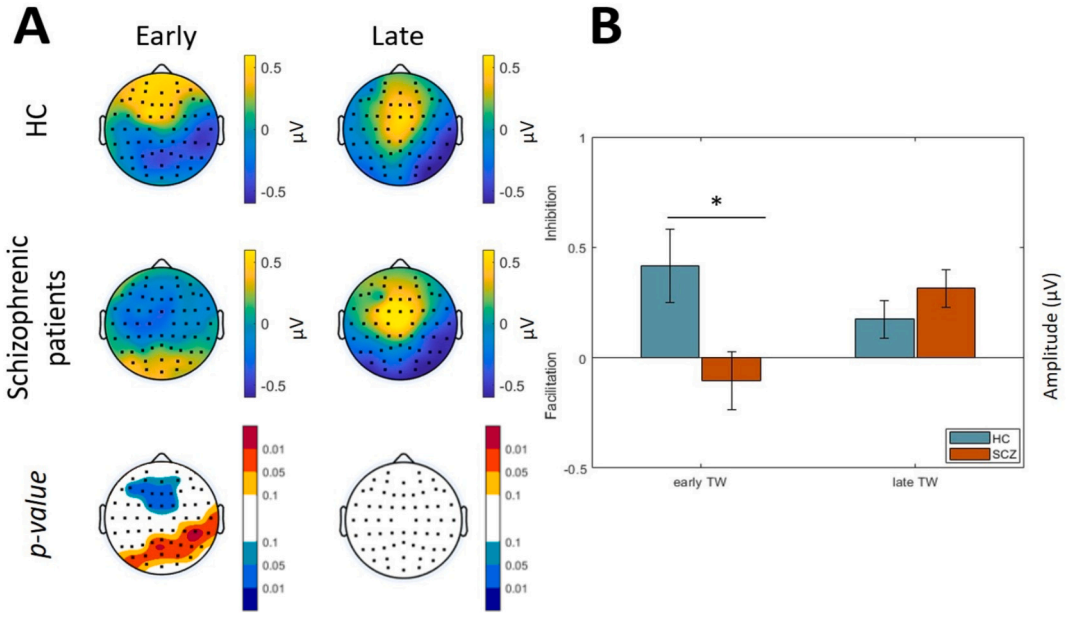

Fig. 1. A) averaged topographies of HC, schiziophrenia patients, and statistical topography for early and late time window (left and right, respectively). B) Averaged subtraction of the mean amplitudes (SP-PP) of the averaged channels of the ROI for early and late time windows for HC (green) and schizophrenia patients (orange). Asterisk (*) indicates p-value <0.05. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

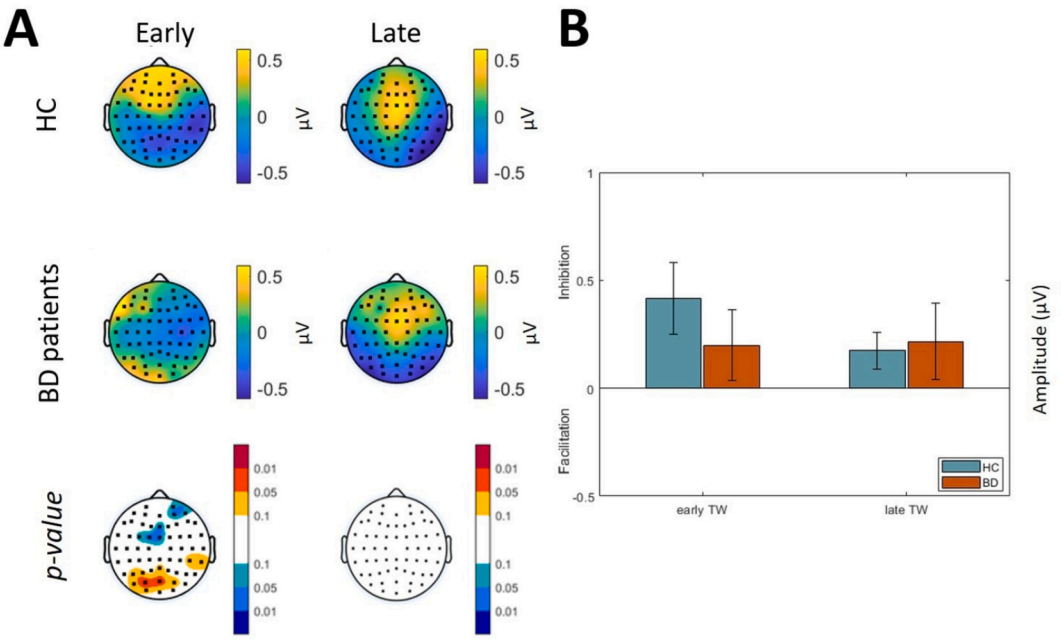

Fig. 2. A) averaged topographies of HC and bipolar patients, and statistical topography for early and late time window (left and right, respectively). B) Averaged subtraction of the mean amplitudes (SP-PP) of the averaged channels of the ROI for early and late time windows for HC (green) and BD population (orange). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

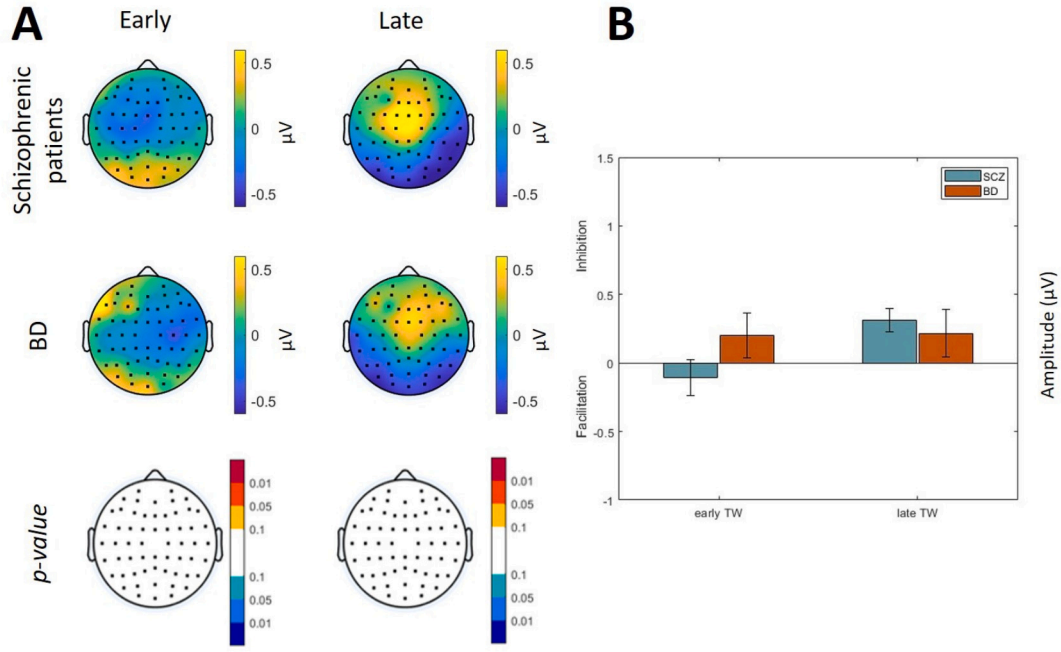

Fig. 3. A) averaged topographies of schizophrenia and bipolar patients, and statistical topography for early and late time window (left and right, respectively). B) Averaged subtraction of the mean amplitudes (SP-PP) of the averaged channels of the ROI for early and late time windows for schizophrenia (green) and bipolar patients (orange). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

benzodiazepines (*p-value* = 0.01).

Furthermore, statistically significant differences were obtained when comparing the HC to the patients whose medication include benzodiazepines ($n = 18$, 13 of which are schizophrenia patients). Fig. 6 shows the topographies for the early response time window for the three populations (HC, patients taking BZD and patients not taking BZD) as well as the statistical topography between HC and each patients' population. Significantly lower values of CI in the DLPFC ROI were observed in the patients not taking BZD compared to the HC group.

3.5.3. Association between LICI and antipsychotics dose

There was no significant correlation between LICI at the early response and antipsychotics dose.

4. Discussion

Our results support an inhibitory deficit mediated by GABAb-receptors in schizophrenia but not in bipolar patients, who showed intermediate LICI values between HC and schizophrenia patients, in both

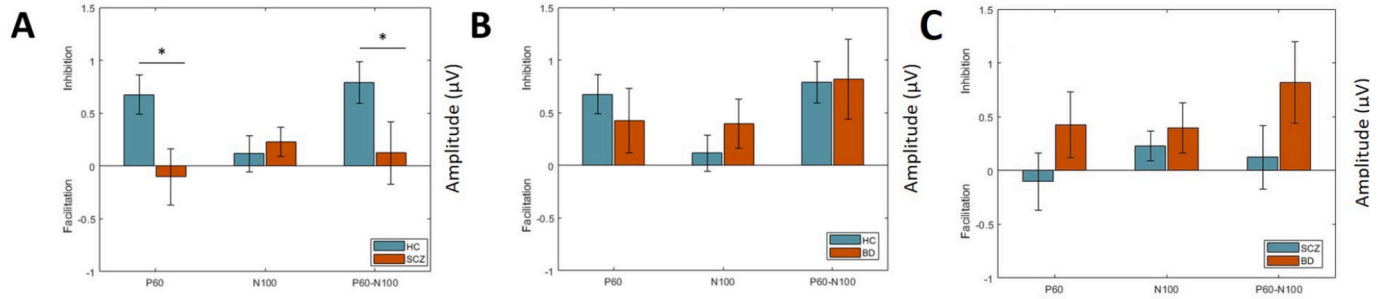

Fig. 4. Average of SP-PP mean amplitudes of the averaged channels of the ROI for P60, N100, and P60-N100 for A) HC and schizophrena patients. B) HC and BD population, and C) schizophrenia and bipolar patients. Asterisk (*) indicates *p*-value <0.05.

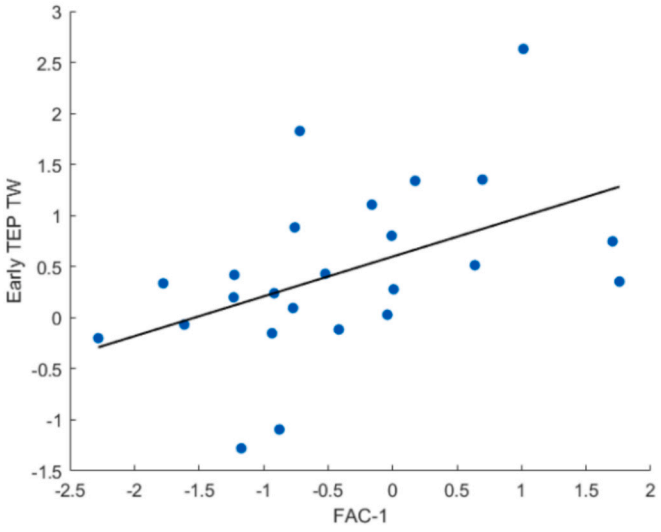

Fig. 5. Association between LICI in the early time window and the first principal component of cognitive assessment.

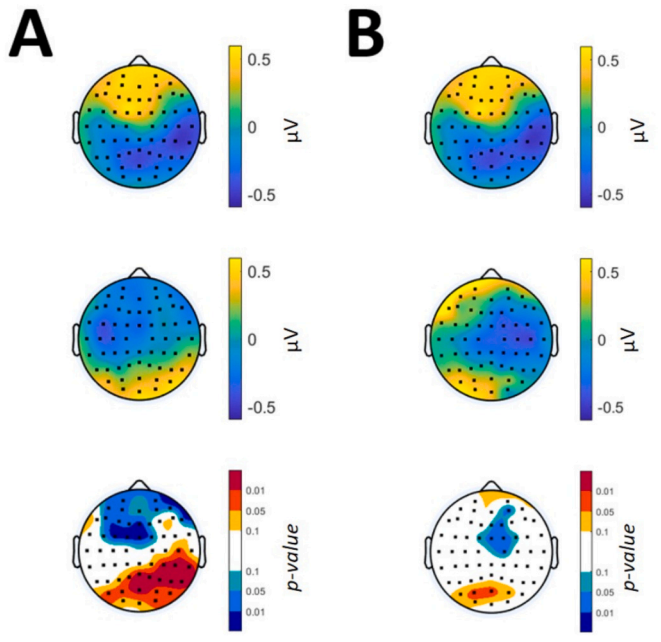

Fig. 6. A (top to bottom): Averaged topographies of HC, patients no taking BZD, and statical topography between populations for the early time window. B (top to bottom): Averaged topographies of HC, patients taking BZD, and statical topography between populations for the early time window.

the global and TEP measures (see Fig. 1,Fig. 2 andFigure 4). The results showed significant differences in reduction LICI; concretely in amplitudes of P60, peak-to-peak P60-N100 and early response time window between HC and schizophrenia patients. Early TW and P60 amplitudes showed moderate to large effect sizes and CI that did not include zero, indicating robust and meaningful group differences. For P60-N100, the effect size was moderate, with the CI crossing zero, suggesting that the difference should be interpreted with caution. Although LICI was not significantly decreased in BD, these patients occupied an intermediate position between schizophrenia and HC subjects. In addition, we found a significant positive association between cognitive performance and LICI values, as shown in Fig. 5.

Previous studies have reported LICI assessments in schizophrenia and BD after stimulation of the motor cortex and the assessment of motor-evoked potentials (Basavaraju et al., 2017; Mehta et al., 2021; Radhu et al., 2015; Ruiz-Veguilla et al., 2016) or after stimulation of DLPFC and examination of TMS-evoked potentials (Farzan et al., 2010a). However, the corresponding results are not equivalent: although LICI results from stimulation of the motor cortex (i.e., comparing MEPs) and DLPFC (i.e., comparing TEPs) showed a broad coincidence, beta and gamma bands were inhibited only after DLPFC stimulation and the respective total cortical inhibition values were uncorrelated (Farzan et al., 2010b).

Indeed, LICI studies that applied TMS pulses to the DLPFC in psychoses (Farzan et al., 2010a; Radhu et al., 2015) found an inhibition deficit in schizophrenia following DLPFC stimulation but not motor cortex stimulation. In the first of these studies, the authors tested LICI values in the different EEG bands and found significantly reduced inhibition in the gamma band in patients with schizophrenia ($n = 14$) but not in BD patients (n = 14). This finding is consistent with our data (Farzan et al., 2010a). In particular, this deficit was observed within the 50–150 ms post-stimulus interval, in agreement with the selective deficit in the early TEPs observed in our study. A subsequent study by the same research group involving a larger sample of patients with schizophrenia ($N = 38$) replicated the inhibition deficit in the DLPFC (Radhu et al., 2015), which was found to correlate with Brief Psychiatric Rating Scale scores. Another report based on assessments of motor-evoked potentials after stimulating the motor cortex described a normal LICI in BD (Ruiz-Veguilla et al., 2016).

In discrepancy with this, two studies from the same research group, which used motor cortex stimulation and electromyography, reported increased LICI values in schizophrenia and BD patients (Basavaraju et al., 2017; Mehta et al., 2021). The effect of treatment could potentially contribute to it, given that previous reports have shown that benzodiazepines can enhance LICI at N100 (Premoli et al., 2018), and of the cortical silent period (Premoli et al., 2018; Ziemann et al., 2015). However, the authors state that acutely manic patients had been free of medication for longer than 2 months and that 43 % of schizophrenia patients had not received any treatment. The discrepancy with our data may also be due to the different methods used, since, as previously mentioned, the inhibition deficit in schizophrenia was found after

stimulation on the DLPFC but not on the motor cortex (Farzan et al., 2010a; Radhu et al., 2015).

A significant inhibitory deficit in schizophrenia but not BD would be coherent with the basal hyperactive cortical network found in schizophrenia but not in the BD (Cea-Cañas et al., 2020). This deficit is associated with an inability to modulate neural activity in response to a cognitive task (Gomez-Pilar et al., 2018). Interestingly, previous data suggest that these categorical diagnoses may include different proportions of patients with and without inhibitory deficits (Volk et al., 2016), indicating that the inhibitory deficit may characterize a singular biotype comprising some schizophrenia patients and a smaller proportion of BD patients. Such heterogeneity could determine that patients with and without inhibitory deficits might be inadvertently included in the current diagnostic categories of schizophrenia and BD. Thus, it could explain discrepancies between LICI studies showing increased inhibition in BD and schizophrenia (Basavaraju et al., 2017; Mehta et al., 2021), lower inhibition in schizophrenia and normal inhibition in BD (Farzan et al., 2010a; Radhu et al., 2015; Ruiz-Veguilla et al., 2016) or decreased inhibition in BD (Levinson et al., 2007), depending on the proportion of cases with or without inhibitory deficits in the sample included in those studies.

We have reported elsewhere that basal EEG hyperactivation may characterize a biotype across schizophrenia and BD primarily identified by the severity of cognitive deficit (Fernández-Linsenbarth et al., 2021). In this context, the presence of such hyperactivation, alongside the relationship between cognitive deficits and LICI in the present sample would suggest that this biotype could also show significant GABAergic deficits as a key pathophysiological underpinning. This biotype would therefore be coherent with a subgroup characterized by a significant inhibitory deficit supported by neuropathology (Volk et al., 2016). Kimoto et al. (Kimoto et al., 2015) suggested that reduced mRNA for the neuronal activity-regulated pentraxin (NARP) gene could lead to a lower excitatory input to parvalbumin interneurons in schizophrenia. Patients carrying such deficit may express it as a hyperactive cortical networks and/or inhibitory deficits in paired TMS assessments.

Intriguingly, our topographic maps (Fig. 1) revealed increased inhibition in posterior regions in patients as well as an inhibitory deficit in the DLPFC. This raises the possibility of observing distant compensatory effects may be observed after stimulating this region, if an excess of excitatory connections would arise from the DLPFC as a consequence of inhibitory deficits at this level after TMS.

Among the limitations, our sample size is small, although it is larger than those of previous similar reports on BD and schizophrenia. Medication-free patients were not possible to be included because of difficulties in their recruitment, however the effect of antipsychotics seems to be minimal in different measures of cortical inhibition following TMS (Daskalakis et al., 2003). In a previous comparison between neuroleptic-naïve and medicated patients, LICI did not differ, but SICI deficits were larger in the former (Mehta et al., 2014). The evidence concerning benzodiazepines is contradictory, since reports support an enhancement of inhibition mostly at N100 (Daskalakis et al., 2003; Premoli et al., 2018) as well as no significant effect on LICI values (Ziemann et al., 2015). This does not explain the deficits found in our patients. When we compared patients using BZD or not, we found lower LICI values in users, discarding the reduced LICI in schizophrenia because of this treatment. This suggests the potential relevance of GABA agonists to compensate GABA deficits in schizophrenia, since BZD-treated patients did not show significant LICI alterations. In the BD population it would be also necessary to assess the effect of mood-stabilizers (i.e., anticonvulsants) as a possible compensating factor of an even greater inhibitory deficit in the treatment-free state, although our preliminary data do not support a role for these drugs in decreasing LICI response. In a previous study on temporal epilepsy, doses of anti-epileptic drugs (mostly carbamazepine and valproate) did not have any effect on LICI values (Huang et al., 2020). The possible role of BSD and anticonvulsants in decreased LICI values in schizophrenia and BD should be confirmed with more balanced specific designs. Other possible confounders of LICI comparisons include sleepiness (Chia et al., 2021) and chronic caffeine consumption (Vigne et al., 2023), which were not controlled in the present sample. However, sleepiness has not influence on LICI (Chia et al., 2021) and caffeine has been reported to affect repetitive TMS plasticity (Vigne et al., 2023), not applied in the present study. Longitudinal studies are needed to confirm the stability of lower LICI values along illness and treatment response progresses. Regarding the methodology, with manual selection of ICs, there is a possibility of bias that may influence reproducibility, though this approach is commonly used in similar studies. Finally, no neuronavigational system was employed to localize the left DLPFC. However, following previous literature in the field, the coil was located allowing a precise estimation of this brain area (Fitzgerald et al., 2009b; Rusjan et al., 2010).

In summary, we demonstrated a significant deficit of inhibition mediated by GABAb receptors in the DLPFC in patients with schizophrenia compared to HC, while BD patients occupied an intermediate position between these groups.

CRediT authorship contribution statement

Gema Mijancos-Martínez: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Inés Fernández-Linsenbarth:** Writing – original draft, Supervision, Software, Formal analysis. **Alejandro Bachiller:** Writing – review & editing, Methodology, Data curation. **Rosa Beño-Ruiz de la Sierra:** Writing – review & editing, Software, Methodology. **Emma Osorio-Iriarte:** Investigation. **Alejandro Roig:** Investigation. **Claudia Rodríguez-Valbuena:** Investigation. **Juan Carlos Fiorini-Talavera:** Investigation. **Saúl J. Ruiz-Gómez:** Writing – review & editing. **Ricardo D. Mancha:** Data curation. **Vicente Molina:** Writing – review & editing, Writing – original draft, Project administration, Funding acquisition, Formal analysis, Conceptualization. **Miguel Angel Mañanas:** Project administration, Methodology, Funding acquisition.

Ethical statement

The study was approved by the Research Board of the Clinical University Hospital of Valladolid (protocol PI-21-2623).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.

Declaration of competing interest

The authors declare no competing financial interests or personal relationships that could have influenced the work reported in this paper

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2025.111593.

Data availability

Data will be made available on request.

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