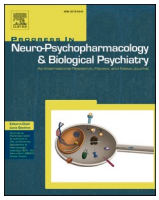
Progress in Neuropsychopharmacology & Biological Psychiatry 137 (2025) 111254

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

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



Lower perturbational complexity index after transcranial magnetic stimulation in schizophrenia patients

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ARTICLE INFO

Keywords:
Perturbational
Complexity
Schizophrenia
Transcranial
Stimulation

ABSTRACT

Background: Informational integration and differentiation of the cortex can be tested by methods such as the perturbational complexity index (PCI) combined with TMS-induced activity perturbation. The PCI is obtained by stimulating the cortex with TMS and measuring the resulting spatiotemporal cortical responses with high-density EEG.
Methods: We have compared PCI between 26 patients with schizophrenia (15 males), 15 of them First Episode (FE) (7 males), and 22 healthy controls (12 males).
Results: Values of PCI were significantly lower in patients with schizophrenia, as well as in FE considered alone. There was no significant relation between anomalous self-experiences or symptoms and PCI values in the patients: PCI values were unrelated to treatment doses or illness duration.
Conclusions: Our data suggest that spatiotemporal cortical responses to TMS pulses are reduced in patients regarding variability or spatial extension, which could imply a lower capacity for sustaining informational complexity.

1. Introduction

Transcranial magnetic stimulation (TMS) pulses induce time-locked depolarization of underlying neurons which induces a transient synchronization of neural firing that can be observed using electroencephalography (EEG) recordings (Tremblay et al., 2019). Local and global EEG changes induced by TMS pulses allow assessment of functional connectivity modulation (Ferrarelli and Phillips, 2021; Hill et al., 2016), independently of prior synaptic chains and motivation or performance bias; an advantage in comparison with tasks involving peripheral stimulation.

Higher mental functions require a brain both informationally integrated and differentiated (Mashour et al., 2020). Since brain's information processing is probably altered in schizophrenia, it could be expected that one or both of these functions (integration and/or differentiation) may be also hampered in this syndrome. These properties can be tested by methods such as the perturbational complexity index (PCI (Casali et al., 2013)) combined with TMS-induced activity perturbation, which therefore may be helpful in evaluating the cerebral underpinnings of schizophrenia. The PCI is obtained by stimulating the

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https://doi.org/10.1016/j.pnpbp.2025.111254
Received 27 September 2024; Received in revised form 10 January 2025; Accepted 13 January 2025
Available online 17 January 2025

cortex with TMS and measuring the resulting spatiotemporal cortical responses with high-density EEG. In this context, PCI has been applied to assess the brain's capacity for sustaining consciousness, by roughly indexing its potential for information differentiation and integration (i.e., the PCI would be large if responses following stimuli are widespread and vary across areas, and low if the responses are local and/or similar across areas (Casali et al., 2013)). Particularly, the PCI has been used in the assessment of consciousness level after brain damage (Sarasso et al., 2020), disorders of consciousness (Bai et al., 2016), and effects of sub-anesthetic ketamine (Farnes et al., 2020).

To our knowledge, the combination of TMS and PCI has not been previously considered to assess cortical activity modulation properties in psychotic disorders. The potential value of this combination is supported by a report showing that, in a small sample of patients with schizophrenia, the propagation of cortical activity following TMS was more spatially limited (i.e., localized to the stimulated area) than in Healthy Controls (HC) (Ferrarelli et al., 2008). This suggests that patients may have lower PCI due to a limited spread of the cortical response. Moreover, the substrates of the mental functions, altered in psychotic disorders, involve the coordinated activity of most of the cerebral cortex, changing throughout milliseconds and propagating broadly across the cortex. Consequently, an objective assessment of signal propagation as provided by the combination of TMS and PCI can be useful to investigate the brain substrates of schizophrenia. Qualitative alterations of consciousness in the form of abnormal self-experiences (ASEs) have been consistently reported in this disorder (Raballo et al., 2021; Saas and Parnas, 2007), even in the premorbid stages of illness (Parnas et al., 2016). These abnormal self-experiences are different from altered states of consciousness: the subject with those experiences remains alert, but both states have in common that the subject cannot form the subjective, pre-reflective experience of existing as a conscious being (in a milder form in schizophrenia).

Therefore, in the present report we hypothesize that patients with schizophrenia will exhibit (i) a reduced PCI reflecting a decreased capacity for information differentiation and integration in the brain and (ii) a relation between PCI and the severity of ASEs.

1.1. Methods and materials

We included 26 patients with schizophrenia (15 males), 15 of them First Episode (FE) (7 males), and 22 HC (12 males) (Table 1). Mann-Whitney and Chi-Square tests, respectively, revealed non-significant differences between groups in age and sex. Twenty-five patients were receiving antipsychotics, and 1 of them discontinued the treatment for more than one month at the time of inclusion in the study.

These patients overlap in part with those included in our recent reports analyzing the local mean field power (Fernandez-Linsenbarth et al., 2024) and time windows individualization (Mijancos-Martinez et al., 2024) of TMS response in HC and schizophrenia. All 20 cases from those studies were also included in the present study.

Patients were diagnosed by two expert psychiatrists (VM and CR) according to the Diagnostic and Statistical Manual of Mental Disorders (5th edition). Exclusion criteria were: (i) presence of any 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 diagnosis for HC, or (vi) diagnosis of other disorder than schizophrenia for patients. Socio-demographic, behavioral, cognitive, and clinical data are shown in Table 1. All participants gave written informed consent after receiving complete information. The ethical committee of the University Hospital of Valladolid endorsed the study (protocol PI-21-2623).

ASEs were assessed using the IPASE (Inventory of Psychotic-Like Anomalous Self-Experiences) (Cicero et al., 2017), a 57-item self-report scale with a 5-factor structure. Participants, in the presence of the researcher, rated their agreement with statements on a scale ranging from 1 (Strongly Disagree) to 5 (Strongly Agree). Factors included: Cognition, focusing on thought process difficulties like thought interference; Self-Awareness and Presence, covering aspects related to loss of self or basic identity and disconnection from the world; Consciousness, encompassing alterations in time perception, intentionality, and difficulty discerning between imagination and reality; Somatization, addressing disturbances in bodily experiences such as changes in body shape or lack of control, and feelings of physical or psychological absence from one's own body; and Demarcation/Transitivism, concerning the dissolution of boundaries between self and world or a sense of nonexistence. We used the total scores to assess the relationship between ASEs and PCI.

Table 1
Socio-demographic, clinical and PCI data of the patients and HC included in the study. Statistically significant between-group differences are marked with asterisks *$p < 0.05$ (Mann–Whitney U test). CPZ: Chlorpromazine. IPASE: Inventory of Psychotic-Like Anomalous Self-Experiences PCI: Perturbational Complexity Index. FE: First Episode. HC: Healthy Controls. M: Male. F: Female.

	Patients (n = 26)	Chronic (n = 11)	FE (n = 15)	HC (n = 22)
Age (years)	36.27 (12.56)	42.18 (11.03)	31.93 (12.17)	31.64 (10.54)
Sex (M:F)	15:11	8:3	7:8	12:10
Antipsychotic dose (CPZ eqs)	387.96 (226.83)	460.18 (309.97)	335.00 (128.79)	
Benzodiacepines	8	4	6	
Anticonvulsants	3	2	0	
Illness duration (months)	72.5 (121.6)	154.0 (160.0)	18.13 (31.2)	
IPASE total	116.05 (40.97)	124.75 (48.79)	110.25 (35.46)	N/A
PCI	8.191 (2.250)**	8.624 (1.826)	7.874 (2.531)*	10.237 (2.684)

*p < 0.05, all comparisons were made with HC.
* $p < 0.05$.
** $p < 0.01$ in comparison to HC.

1.2. Transcranial magnetic stimulation

TMS stimulation was performed using a figure-of-8-coil (MCF-B70) and a MagPro X100 stimulator (MagVenture, Denmark). Participants were seated comfortably and were instructed to look straight with their eyes open. The resting motor threshold (RMT) was determined over the left motor cortical region following the relative frequency method (Groppa, Oliviero et al. 2012). For this purpose, electrodes were placed over the right abductor pollicis brevis (APB). Seventy-five monophasic TMS single pulses were administered over the left dorsolateral prefrontal cortex (DLPFC). The intensity of the pulses was set at 120 % RMT and their administration was semi-randomized, with an inter-stimulus interval varying between 5 and 7 s to avoid anticipation of the next pulse. The specific stimulation site was the midpoint of a line between electrodes F3 and F5 with a rotation of 45° with respect to the midline. In the absence of neuronavigation equipment, this position provides the most accurate estimation of the left DLPFC (Fitzgerald et al., 2009; Rusjan et al., 2010).

1.3. EEG recordings

EEG activity was recorded during TMS using a 64-channel system amplifier (Brain Vision, Brain Products GmbH) following the international 10–10 system. Two of the channels were placed on the outer side of each eye to monitor eye movement artifacts. All electrodes were referenced to the Cz electrode during acquisition. EEG signals were recorded at a sampling rate of 25 kHz.

1.4. TMS-EEG signal preprocessing

TMS-EEG signals were segmented related to the TMS pulse. Each epoch included 1000 ms pre-stimulus baseline and 1000 ms post-stimulus activity. Due to the magnetic pulse artifact, data samples from – 1 ms to 10 ms related to the TMS pulse were removed and cubic interpolated (Rogasch et al., 2014). Then, the data was referenced to a common average. Next, an independent component analysis (ICA) was applied and independent components representing artifacts were manually and blindly selected by three experts. The artifact selection was based on time-frequency maps, trial-averaged amplitude, and spatial distribution and activation maps (Rogasch et al., 2015; Rogasch et al., 2014). Afterward, bad channel interpolation and contaminated trial rejection were automatically performed. Next, a baseline correction was applied using an interval of 800 ms before the TMS pulse onset. Finally, signals were down-sampled to 5 kHz, and a band-pass filter between 0.5 Hz and 70 Hz was applied. TMS-EEG signal preprocessing was done using MATLAB (R2021b; The Mathworks Inc., Natick, MA) and Fieldtrip (Oostenveld et al., 2011).

1.5. Perturbational complexity index

In this study, we used the PCI State Transitions (PCI ST) (Comolatti et al., 2019) a novel evolution of the PCI that overcomes the limitations of the original index, namely its reliance on offline processing, most importantly the necessity for source estimation and lengthy permutation-based statistics at the single trial level (PCI Lempel-Ziv Complexity, PCI LZC) (Casali et al., 2013). While conceptually similar to PCI LZC, PCI ST is a less complex measure, making it computationally more efficient, more sensitive in scenarios with different amplitude scales, and applicable to any type of evoked brain signal) (Comolatti et al., 2019). PCI ST is based on the idea the brain response to TMS represents transitions between different states: a "response state" and a "non-response" or "baseline state". Consequently, systems that exhibit multiple patterns of transitions between these states following an initial perturbation should display high values of PCI (Comolatti et al., 2019).

The computation of the PCI ST can be summarized as follows:

1. Evoked potentials are decomposed in Principal Components that account for 99 % of the response square mean field power. In this way, the dimensionality of the data is reduced and components with low SNR (signal-to-noise ratio) are discarded.
2. For each component, the amplitude difference between every sample in the baseline period is calculated. This process is repeated for the response period, resulting in two matrices summarizing the amplitude distance between samples.
3. These matrices are thresholded using different scales, which can be considered as a hyper-parameter of the algorithm.
4. For each scale, binary matrices representing state changes (based on the aforementioned scales) are constructed; and the number of state transitions (NST) are calculated for the baseline (NST_{Base}) and the response ($NST_{Response}$) separately.
5. The complexity in the response of each component is the maximum difference (across scales) between NST_{Base} and $NST_{Response}$.
6. Finally, the PCI ST is calculated by summing this difference across the different components. In this regard, it can be said that PCI ST measures the spatiotemporal complexity (measured by means of the difference in NST) and the spatial differentiation (measured by means of the number of components) of a brain response.

PCI ST is designed to be high when a brain response exhibits multiple linearly independent components (spatial differentiation), with each component contributing significantly to the number of state transitions (temporal complexity). Conversely, PCI ST is expected to be low if the perturbation elicits a strongly correlated response across components, or if the components show few temporal transitions compared to the baseline. Deeper insights on this methodology, as well as a graphical summary, can be found in (Comolatti et al., 2019).

1.6. Statistics

We compared the PCI between patients with schizophrenia and HC using two-sample Mann-Whitney (MW) *U* tests. This was followed by a confirmatory comparison between FE and HC, also using MW tests. The relationship between patients' ASEs and PCI values was explored using Spearman's ρ correlation coefficients. In addition, we tested the relations between PCI and treatment doses and illness duration using Spearman's ρ correlation coefficients.

2. Results

Both the overall patients and the FE showed a significantly lower PCI compared to HC (Table 1; Fig. 1) with a large effect size (d = 0.83). The analysis of the statistical power showed that a 0.99 likelihood to detect a large effect size with this sample size. PCI values and total IPASE scores were not significantly correlated in the patient sample ($p = -0.15$, $p = 0.44$) (Table 1). Similarly, illness duration ($p = -0.04$, $p = 0.85$) and treatment dose ($p = 0.24$, $p = 0.22$) were not significantly correlated with PCI values in the patients.

In order to mitigate the impact of Type II errors on this results, we performed Bayesian Spearman's correlations, which showed moderate evidence against significant relationships between PCI and illness duration (Bayesian Factor = 0.462) and between PCI and IPASE scores (Bayesian Factor = 0.481). These analyses showed anecdotical evidence of positive significant association between PCI and treatment doses (Bayesian Factor = 1.271, being the *p* coefficient positive).

3. Discussion

In our sample, PCI values were significantly reduced in the patients with schizophrenia, revealing a smaller change in cortical activity after stimulation with TMS pulses compared to HC. This modulation deficit is consistent with that observed during cognitive tasks using entropy (Bachiller et al., 2014; Molina et al., 2018) and network parameters (Gomez-Pilar et al., 2017; Molina et al., 2020). The absence of any cognitive requirement with TMS pulses supports that modulation deficit is a primary deficit in schizophrenia, regardless of the method used to elicit it.

There are two possible explanations for the lower PCI in patients: (i) a local restriction of TMS-induced changes and (ii) a larger similarity of

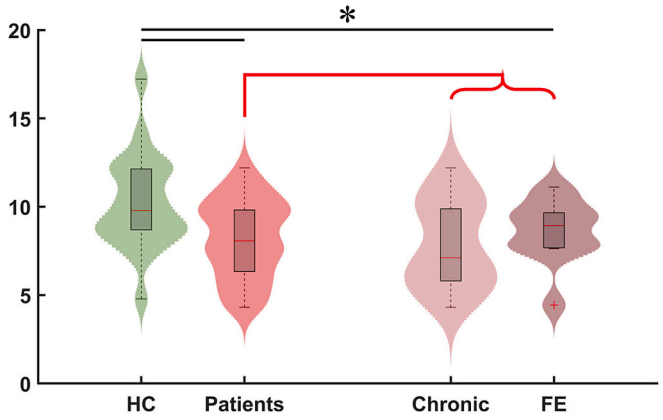

Fig. 1. PCI distribution. On the left side, Healthy Controls (HC) in green and patients with schizophrenia in red. On the right, the same patients divided into Chronic (light red) and First Episode (FE, dark red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

these changes across regions. These possibilities have not been addressed in our study, but prior results support the first possibility (Ferrarelli et al., 2008).

While PCI is very valuable for assessing the features underlying large changes in consciousness level, psychotic patients do not show quantitatively altered states of consciousness, except if catatonic or drowsy due to the effects of treatment or illegal drugs. There were no catatonic patients in our group; acute use of illegal drugs was an exclusion criterion, and treatment effects are unlikely (see below). Thus, the reduced PCI value in our patients supports a deficit in the ability for integration and/or differentiation of information in schizophrenia, which can hinder real-life adaptation.

The GABA hypofunction described in the cortex in schizophrenia (Gonzalez-Burgos and Lewis, 2012; Lewis et al., 2012) could be related to such a modulation deficit. Such GABA hypofunction may reasonably result in a hyperactive resting state that hinders stimulus-related modulation. Indeed, we have described a significant relationship between basal hyperactivity and task-related modulation deficits (Iglesias-Tejedor et al., 2022). In this regard, a relationship between PCI deficit and GABA dysfunction deserves further attention.

Contrary to our hypothesis, we could not confirm that ASEs were associated with PCI values. It is possible that these abnormal experiences are better explained by other deficits in functions related to self-experience, such as corollary discharge (CD). This function under normal conditions is key to preconsciously differentiating self-generated stimuli from those originating in the environment (Roach et al., 2019), and requires a signal from the efferent area that primes the receptive cortex to attenuate the sensory consequences of self-generated sounds. Indeed, recent reports support a significant relation between decreased CD to the perception of self-generated sounds and the severity of ASEs (Beno-Ruiz-de-la-Sierra et al., 2024). However, since CD requires a complex modulation of cortical activity in terms of both spatial and variability, it cannot be discarded that PCI alterations may underpin CD deficits; hence, it can be a useful tool for examining the cortical correlates of ASEs and, in general, functional properties of cortex in schizophrenia.

The reported PCI deficits in quantitative alterations of consciousness are much larger in magnitude than those found in our patients (Casali et al., 2013), suggesting that abnormal self-experiences and altered states of consciousness may not share a similar basis. However, the PCI differences in our cases are larger as compared to those induced by sub-anesthetic doses of ketamine: in subjects receiving these doses, PCI did not differ from normal wakefulness (Farnes et al., 2020). This suggests an important deficit in the ability to integrate and differentiate information in the brains of our patients.

Interestingly, PCI deficits remained significant when comparing FE alone with HC, which, together with its lack of relation to treatment doses and illness duration, supports their relevance for the schizophrenia syndrome. Although we cannot completely rule out that lower PCI values could relate to the sedative effects of treatment, this is unlikely since in this case a relation would be expected between doses and PCI values. Indeed, the post-hoc Bayesian analyses suggest a positive relation between PCI and treatment dose, i.e., that higher doses could if anything tend to normalize PCI. Furthermore, the lower PCI values in the FE, which received smaller treatment doses, also argue against this possibility.

Our data suggests that the effects of illness progression on PCI may be small, given the similar alterations observed in both FE and chronic cases. Previous data on this topic are scarce and primarily limited to quantitative alterations of consciousness. One case report (Bai et al., 2016) demonstrated an improvement in PCI alongside changes in consciousness level, highlighting the potential value of longitudinal PCI assessments in psychotic disorders.

While FE showed a significant PCI decrease, chronic patients did not differ significantly from HC in this parameter. The smaller sample size in this group may contribute to such lack of significance, but a more marked PCI alteration in early phases of illness and/or a beneficial effect of continued treatment on this parameter cannot be ruled out.

3.1. Limitations

Limitations of our study include the sample size and the possible effects of treatment on TMS reactivity. Larger samples are needed, especially considering the possibility that the effects described may be limited to subgroups of cases. Future studies employing a longitudinal design should investigate how PCI changes in response to treatment and therapeutic outcomes. This study's strengths include the first application of PCI, to our knowledge, to assess TMS-induced integration and differentiation in the brain in schizophrenia. Furthermore, we employed a well-characterized and relatively large sample of both patients and controls. Therefore, our findings could significantly impact future research on the pathophysiology of schizophrenia.

4. Conclusions

In conclusion, pulses of TMS induced a lower perturbational complexity index in schizophrenia patients, supporting a lower ability for differentiation and/or integration of cortical activity in this syndrome.

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.

CRediT authorship contribution statement

Vicente Molina: Writing – original draft, Project administration, Funding acquisition, Formal analysis, Conceptualization. **Inés Fernández-Linsenbarth:** Writing – review & editing, Supervision, Software, Data curation. **Rosa Beño-Ruiz- de- la- Sierra:** Writing – review & editing, Software, Methodology. **Emma Osorio-Iriarte:** Investigation. **Alejandro Roig:** Writing – review & editing, Software, Methodology. **Antonio Arjona:** Investigation. **Víctor Rodríguez:** Methodology, Data curation. **Pablo Núñez:** Methodology, Data curation. **Jesús Poza:** Methodology, Data curation. **Alvaro Díez-Revuelta:** Writing – review & editing, Conceptualization. **Claudia Rodríguez-Valbuena:** Investigation. **Gema Mijancos-Martínez:** Formal analysis, Investigation. **Alejandro Bachiller:** Methodology, Data curation. **Miguel Angel Mañanas:** Methodology, Data curation.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Acknowledgments

This work was supported by the following grants: 'Instituto de Salud Carlos III' (PI-22/00465), and 'Gerencia Regional de Salud de Castilla y León' (GRS-2685/A1/2023) and partially supported by the "Ministerio de Ciencia e Innovación (MICINN)" (grant ID PID2020-117751RB-I00), and "Fundació La Marató de TV3" (grant ID 202219-30-31), "MICIU/AEI/10.13039/501100011033" and by "ERDF A way of making Europe" through the project PID2022-138286NB-I00, and by "CIBER en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN)" through "Instituto de Salud Carlos III" co-funded with ERDF funds and by the ERA-Net FLAG-ERA JTC2021 project ModelDXConsciousness (Human Brain Project Partnering Project). Two research training grants by the 'Consejería de Educación – Junta de Castilla y León' and the 'European

Social Fund' (VA-223-19 and VA-183-18) were respectively awarded to PhD candidates RBRS and IFL. GMM is in receipt of a FI-2022 grant from "Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR)". These funding sources had no other role than that of providers of financial support.

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