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Evaluating the Efficacy of Transcranial Magnetic Stimulation in Symptom Relief and Cognitive Function in Obsessive–Compulsive Disorder, Substance Use Disorder, and Depression: An Insight from a Naturalistic Observational Study

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Abstract: The utilization of non-invasive neurostimulation techniques, such as transcranial magnetic stimulation (TMS), is increasingly prevalent in psychiatry due to their efficacy and safety. Although the precise therapeutic mechanisms remain partially unclear, repetitive TMS, particularly high-frequency stimulation, may enhance cognitive functions, contributing to therapeutic benefits. This within-subjects study examined the impact of TMS on cognitive and symptomatic outcomes in patients with obsessive–compulsive disorder (OCD), substance use disorder (SUD), and major depressive disorder (MDD). A total of 44 patients underwent cognitive tests and symptom assessments before and after an intensive four-week TMS treatment phase, followed by a four-week maintenance phase. Cognitive assessments included Raven's matrices, verbal fluency, and digit span tests, while symptom severity was measured using the Italian version of the SCL-90-R. Decision-making performance was also evaluated by administering a delay discounting (DD) test. Principal component analysis was used to generate a dimensional characterization of subjects along cognitive and symptom-related axes before and after treatment. The results indicated that TMS significantly improved symptom scores, but no significant cognitive enhancement was observed. Statistical analysis based on linear mixed-effects models confirmed these findings, showing a significant fixed effect of TMS treatment on symptoms but not on cognitive performance. DD metrics remained unchanged. These findings suggest that while TMS effectively alleviates clinical symptoms, it does not produce consistent or appreciable enhancement of cognitive functions in these protocols. This study highlights the need for more personalized and combined therapeutic approaches to maximize the benefits of TMS, potentially incorporating cognitive enhancement strategies. Future studies will be useful to explore whether the results we obtained are valid for other pathologies, cognitive tests, and stimulation protocols.

Keywords: TMS; addiction; MDD; OCD; cognitive performance

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1. Introduction

Nowadays, the use of non-invasive neurostimulation techniques is increasingly widespread in psychiatric clinical centers due to their safety and therapeutic efficacy [1]. However, the precise therapeutic mechanism remains not fully understood. While more invasive techniques, such as electroconvulsive therapy, can cause cognitive deficits [2], transcranial magnetic stimulation (TMS) might instead have a cognitive enhancement effect, particularly when high-frequency stimulation is used [3]. This cognitive enhancement could contribute to therapeutic benefits and improvements in patients' everyday lives. For instance, schizophrenic patients benefit from TMS, likely due to the rehabilitative effects of the stimulation on cognitive deficits, which are considered core symptoms of the disorder [4]. Similarly, a TMS protocol applied to depressed adolescents not only improved symptoms but also memory and delayed verbal recall [5], reinforcing the idea that symptom improvements follow cognitive improvements. In substance use disorder (SUD), deficits in memory, attention, executive functions, and decision making are reported, and cognitive enhancement therapies can play a crucial role in rehabilitation [6]. Similar deficits have been found in patients with obsessive–compulsive disorder (OCD) [7]. Understanding the causal relationship between cognitive deficits and psychopathologies is complex. However, TMS stimulation offers an excellent opportunity to explore this relationship. From a neurophysiological perspective, TMS interacts with synaptic plasticity processes, altering not only neuronal activity but also gene expression [8]. These mechanisms could lead to cognitive enhancement by both linear and non-linear actions on neuronal networks [9–11]. Indeed, interventions that improve synaptic plasticity seem to benefit cognitive performance [12]. Although the cognitive enhancement effect might be specific to the pathology, stimulation site, protocol, and cognitive domain, to validate this hypothesis as broadly as possible, we analyzed clinical data from the TMS center (CIP-TMS Milan), where patients with different pathologies—OCD, SUD, and major depression (MDD)—were treated using disorder-specific protocols (see the Section 2), considering both cognitive and symptomatic aspects. Patients at the center underwent cognitive tests (i.e., digit span, verbal fluency, Raven's matrices); specifically, the cognitive dimension in this context can be understood as 'Cold' cognition, which refers to the processing of information devoid of any emotional influence [13], Symptom Checklist-90-R to assess symptom severity and progression, and delay discounting (DD), a psychological domain impaired in most psychopathologies [14], and these can be assimilated into 'Hot' functions, i.e., affective/reward-related processes [15]. The data were subsequently analyzed using first a data-driven approach and then a hypothesis-driven approach.

2. Method

2.1. Study Design

A within-subjects (pretest-posttest) design was employed. The clinical protocol involved administering five TMS sessions per week (Monday to Friday), referred to as the "intensive phase", for the initial four weeks. Subsequently, a "maintenance phase" followed, consisting of one session per week, lasting an additional 4 weeks. Each participant underwent testing at two time points: one before treatment and one after the end of the intensive phase.

2.2. Setting

Treatment and testing were performed from April 2021 to June 2023 by the TMS operators working at CIP-TMS (Milan).

The TMS stimulation was administered in a quiet dedicated treatment room using a MagPro R30 device equipped with the Cool-B80 figure-of-eight coil (MagVenture, Falun, Denmark). Before launching the protocol, the resting motor threshold (rMT) was estimated through a manual procedure based on observation of contralateral (right) hand twitches evoked by left primary motor cortex (M1) stimulation with a single TMS pulse. The M1 hotspot was identified by moving in the coronal plane ~5 cm to the left from the vertex.

The coil was positioned over the presumed M1 region, with the main coil axis forming a 45° angle with the head's midline, and adjusted until a consistent abductor *pollicis brevis* response at the lowest stimulator intensity was identified. For subjects with SUD, the treatment entailed two trains per day of intermittent theta-burst stimulation (iTBS) over the left dlPFC, each lasting for 3 min, delivered at an intensity equal to 100% of rMT. The theta-burst stimulation pattern was composed of bursts of 3 biphasic pulses with an inter-pulse interval of 20 ms, repeated at 5 Hz. We employed a standard iTBS protocol consisting of 20 stimulation trains, each lasting for 2.0 s (10 bursts, 30 pulses), with an inter-train interval of 8.0 s [16]. A total of 1200 pulses per visit were administered across the two sessions. Turning to MDD patients, the treatment included a daily session of iTBS over the left dlPFC, lasting for 17 min, delivered at an intensity equal to 120% of rMT. This iTBS stimulation pattern was composed of bursts of 2 biphasic pulses with an inter-pulse interval of 10 ms, repeated at 10 Hz. We employed a custom iTBS protocol consisting of 75 stimulation trains, each lasting for 2.0 s (40 bursts, 80 pulses), with an inter-train interval of 11.0 s. A total of 6000 pulses per visit were administered. For subjects suffering from OCD, the treatment comprised six sessions of cTBS over the pre-supplementary motor area (pre-SMA), each lasting for 10 min, delivered at an intensity equal to 110% of rMT. The theta-burst stimulation pattern was composed of bursts of 2 biphasic pulses with an inter-pulse interval of 20 ms, repeated at 1 Hz. We employed a standard cTBS protocol consisting of 6 uninterrupted stimulation trains, each lasting for 40.0 s (100 bursts, 200 pulses) [16]. A total of 7200 pulses per visit were administered across the six stimulation trains.

The dlPFC stimulation site was identified on the scalp by moving 5 cm rostrally from the M1 hotspot towards the pupil, whereas pre-SMA was localized 2 cm anterior to the vertex [17]. Figure 1a illustrates the specific placement of the stimulation, confined to the left dlPFC, as well as a smooth approximation of the electromagnetic filed induced by TMS. Similarly, Figure 1b depicts the precise location of the stimulation, limited to the pre-SMA, along with a smooth representation of the electromagnetic field generated by TMS.

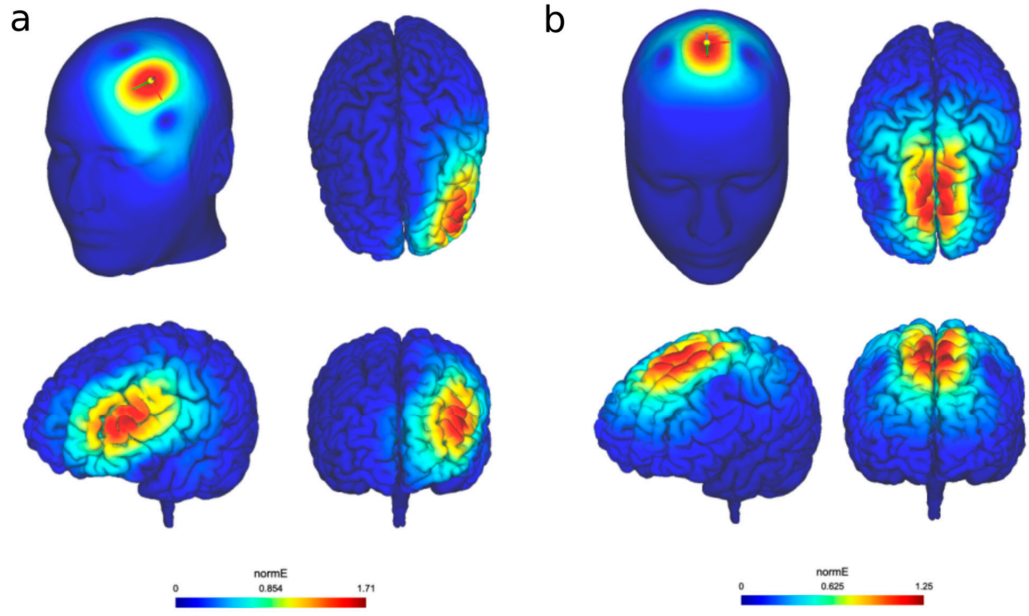

Figure 1. Simulation of the electrical field distribution generated by TMS stimulation. SimNIBS 4.1.0 (https://simnibs.github.io/simnibs/build/html/index.html, accessed on 12 June 2021) was used in order to estimate the normalized electric field (normE) induced by TMS [18]. Among the validated coil models currently available [19], a MagVenture MC-B80 figure-of-eight coil was chosen for running the simulation. The 10–20 system was used as a reference for positioning. The coil was placed over the F3 site to simulate electrical field distribution generated by TMS stimulation over dlPFC, for SUD and MDD (**a**). Conversely, the coil was positioned over FCz to simulate electrical field distribution generated by TMS stimulation over pre-SMA, for OCD (**b**).

2.3. Participants

Forty-four subjects, encompassing 29 males and 15 females with a mean age of 43.02 ± 11.34 years, were involved in the study. The participants were already clinically diagnosed by other professionals or clinical centers, representing a population resistant to conventional treatments. Patient recruitment included a cognitive/neuropsychologic and psychiatric evaluation to assess their suitability for participation. Most of the participants (n = 21) had a high school diploma, while the remaining ones possessed either a middle school diploma (n = 9) or a bachelor's degree (n = 14). These individuals voluntarily sought outpatient treatment for SUD (n = 26), OCD (n = 8), or MDD (n = 10). Subjects were eligible for inclusion if they met the following criteria: (1) age greater than 18 and less than 70 years and (2) taking a stable psychoactive medication (i.e., with no change in the preceding 4 weeks) or no treatment. Exclusion criteria were as follows: (1) presence of any metallic object or implant in the brain, skull, scalp, or neck (e.g., screws or clips from surgery), (2) presence of implantable devices (e.g., cardiac pacemaker or defibrillators), (3) unstable medical conditions, including serious heart disease or serious brain injury due to stroke or trauma, (4) history of epileptic seizures or other neurological disorders; and (5) currently pregnant or lactating [20].

2.4. Ethical Consideration

The study adhered to the ethical principles outlined in the Declaration of Helsinki and received approval from the Ethics Board of the Faculty of Psychotherapy Science and the Faculty of Psychology at Sigmund Freud University (protocol number: JBWXE8CIAVWD788416). All subjects involved signed an informed consent form.

2.5. Variables

Treatment effect was examined with regard to both cognitive functions: decision-making domain and severity of psychological symptoms.

2.5.1. Cognition

The following cognitive domains were explored: non-verbal intelligence, i.e., thinking and problem-solving skills that do not require verbal language production and comprehension [21]; language, specifically lexical access ability, i.e., the capacity to retrieve words from the mental lexicon, both in recognition and in production ability [22]; short-term verbal memory, i.e., the capacity for temporarily maintaining verbal information when the external stimulus is no longer available to the sensory systems [23]; and working memory, considered as a multi-component system that holds and manipulates information in short-term verbal memory [24].

2.5.2. Delay Discounting

The following decision-making domains were explored: delay discounting (DD), i.e., the decline in the present value of a reward with delay to its receipt [25].

2.5.3. Psychological Symptoms

Turing to psychological distress, the following clusters of symptoms were evaluated: somatization (SOM), which reflects disorders arising from the perception of bodily dysfunctions; obsessive–compulsive (OBS), i.e., thoughts, impulses, or actions experienced as incoercible and unwanted by the individual; interpersonal sensitivity (INT), i.e., feelings of inadequacy and inferiority towards other people; depression (DEP), i.e., the spectrum of symptoms concomitant with a depressive syndrome; anxiety (ANX), considered as the set of symptoms and behaviors related to high levels of overt anxiety (e.g., tremor, sweating, palpitations); hostility (HOS), comprising thoughts, feelings, and actions characteristic of a state of anger, irritability, or resentment; phobic anxiety (PHOB), i.e., a persistent irrational and disproportionate fear response towards specific stimuli, leading to avoidance behaviors; paranoid ideation (PAR), meant as thought disorders characterized by suspicion,

fear of loss of autonomy mixed with hostility, and ideas of reference; psychoticism (PSY), i.e., a continuous dimension of human experience characterized by withdrawal, isolation, and schizoid tendencies; and sleep disorders (SLEEP), consisting of insomnia and disturbed sleep, as well as early awakening episodes [26].

2.6. Measurement

A repeated battery of neuropsychological tests was used to assess the different cognitive domains, whereas a unique screening tool was administered to measure psychological distress.

2.6.1. Cognition

Non-verbal intelligence was measured using Raven's Standard Progressive Matrices (SPM; [27]). All 5 sets, i.e., A, B, C, D, and E, were administered, and subjects' performance was scored as the sum of the absolute number of correct responses in each set.

Lexical access ability was assessed through the verbal fluency test [28]. Here, participants were given 1 minute to produce as many unique words as possible within a designated semantic category (i.e., semantic fluency) or starting with a given letter (i.e., phonemic fluency). Subjects' raw scores in each task were computed as the absolute number of unique correct words.

The digit span test evaluated participants' memory capacity [29]. In particular, short-term verbal memory was appraised through the digits forward component, whereas working memory was estimated through the digits backward component of the task [30]. In each case, digit sequences were presented beginning with a length of two digits, and two trials were presented at each increasing list length. Testing ceased when the subject failed to accurately report either both trials at one sequence length or when the maximal list length was reached. The total number of lists reported correctly by the participants was used to produce two separate raw scores, i.e., one for the forward component and the other for the backward component of the task.

2.6.2. Delay Discounting

DD was assessed through a computerized custom-made monetary intertemporal choice task (MICT) developed in jsPsych (www.jspsych.org, accessed on 15 January 2024). This task determined the subjective value/indifference point for two reward values (i.e., EUR 500 and EUR 10,000) across six temporal delays (i.e., 1, 6, 12, 24, 60, and 120 months). Participants were given choices between an immediate but adjusted reward and a maximal but delayed reward at each task step.

2.6.3. Psychological Symptoms

Psychological symptoms and psychological distress severity were gauged with the Italian version of Symptom Checklist-90-R (SCL-90; [31]), a self-report symptom inventory consisting of 90 items on a 5-point Likert scale, ranging from 0 ('not at all') to 4 ('extremely'). Elevated scores are indicative of heightened psychological distress, whereas diminished scores reflect lower levels of psychological distress. The nine primary symptom dimensions of the SCL-90 were computed for each subject, namely SOM, OBS, INT, DEP, ANX, HOS, PHOB, PAR, PSY, and SLEEP. Moreover, the global severity index (GSI), i.e., the average score of all items, was considered as a global quantification of participants' psychological distress.

2.7. Statistical Methods

Indifference points (IPs) obtained from each subject/session using the MICT were utilized to conduct the DD analysis. A hyperbolic function $IP = A/(1 + k \cdot Delay)$ [32] was fitted to the IPs using a nonlinear least-mean squares method, with A representing either EUR 10,000 or EUR 500 depending on the subtask, and Delay standing for the temporal delays of 1, 6, 12, 24, 60, and 120 months. Estimates of the devaluation coefficient k (measured in 1/days) were obtained by curve fitting. Once all variables were computed,

the original dataset was subdivided into two data frames, i.e., one containing the pre-treatment data and the other enclosing the post-treatment data. Principal component analysis (PCA) was conducted on pre-treatment data, and the loadings of the first two principal components were extracted. Such loadings were then applied to pre- and post-treatment data and merged in a unique data frame. Finally, we fitted a linear mixed-effects model (LME) to these data, including the two principal components as dependent variables and different fixed and random effect factors as detailed in the Section 3, followed by ANOVA. The normality of the two principal component distributions and the LME residuals were evaluated graphically using qqplots and histograms. All analyses were conducted using custom algorithms developed in R (Version 4.4.0; https://www.r-project.org/, accessed on 15 January 2024).

3. Results

The primary objective of this study was to understand whether the improvement in cognitive performance was a fundamental step in the therapeutic process of TMS. Therefore, we measured cognitive and clinical symptom variables before starting the treatment and at the end of the "intensive" period across three different pathologies and three different stimulation protocols (Figure 1). Obtaining a synthetic index of such a diverse set of cognitive assessment data can be problematic, so we decided to use a custom data-driven approach based on PCA. The scree plot of the PCA results applied to the data obtained during the first visit indicates that two components sufficiently describe the dataset. In fact, these two axes explain more than 50% of the variance. The biplot of these two principal components shows that variables related to clinical symptoms (all SCL-90 subscales) align along the first axis (PC1), whereas those related to demographic (education) and cognitive measures (SPM, verbal fluency, forward and backward digit span) align along the second axis (PC2) (Figure 2). To observe the effect of the TMS protocols on these two axes, we applied the same loadings of the two principal components to the same variables measured after the "intensive" period. Thus, we obtained a full set of pre- and post-treatment data in terms of PC1 and PC2 components. To determine whether the treatment, diagnosis, or an interaction between these two variables caused alterations in the two axes, two different LMEs (one for each principal component) were fitted to these data using the following formula (Wilkinson notation):

$$Y \sim 1 + TMS + Diagnosis + TMS \cdot Diagnosis + (1 \mid subject)$$

where Y is PC1 or PC2. Among the fixed effects, TMS is a dichotomous pre/post treatment variable, Diagnosis is the categorical variable of the three treated pathologies (i.e., SUD, MDD, and OCD), and TMS · Diagnosis is the interaction of the two. Finally, a random effect of the subject was included. In the first LME (i.e., where Y = PC1), the TMS variable was the only significant factor ($\chi^2 = 13.5034$, $p < 0.001$, Figure 3a), while in the second LME (i.e., where Y = PC2), only the Diagnosis variable was significant ($\chi^2 = 7.3725$, $p = 0.025$, Figure 3b). These analyses, therefore, support the effectiveness of TMS treatment on clinical symptoms but refute the original hypothesis that this improvement was preceded by cognitive enhancement. Indeed, PC2 does not change after the treatment.

Since DD represents a transdiagnostic factor belonging to the hot psychological domains [15], to determine whether there were effects related to diagnosis or treatment, two additional linear mixed-effects models were performed as follows (specifically considering the devaluation coefficient k, as performed in other studies [33]): one for low rewards, i.e., DD Low, and the other for high rewards, i.e., DD High. This was carried out using the following formula (Wilkinson notation):

$$Y \sim 1 + TMS + Diagnosis + TMS \cdot Diagnosis + (1 \mid subject)$$

where Y is DD Low and DD High. Among the fixed effects, TMS is a dichotomous pre/post treatment variable, Diagnosis is the categorical variable of the three treated pathologies

(SUD, MDD, and OCD), and TMS · Diagnosis is the interaction of the two. Finally, a random effect of the subject was included. However, no variable was significant, indicating that DD is not modified by any of the TMS protocols (Figure 4).

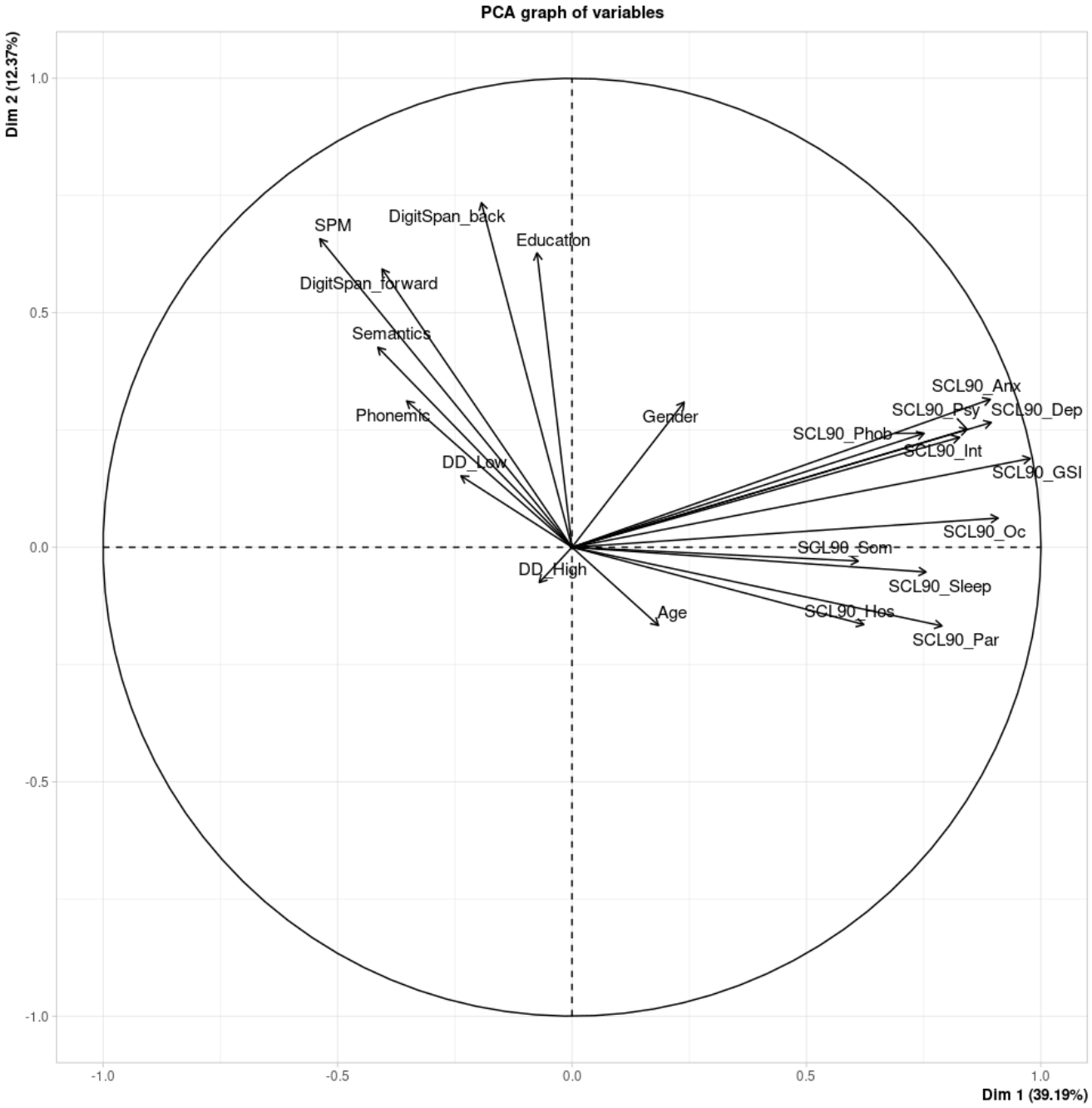

Figure 2. Biplot of the first two principal components. The arrows represent how much each experimental variable influences the two axes (SPM: Raven's matrices; DD_Low: the fitting k of the DD curve for low rewards; DD_High: the fitting k of the DD curve for high rewards).

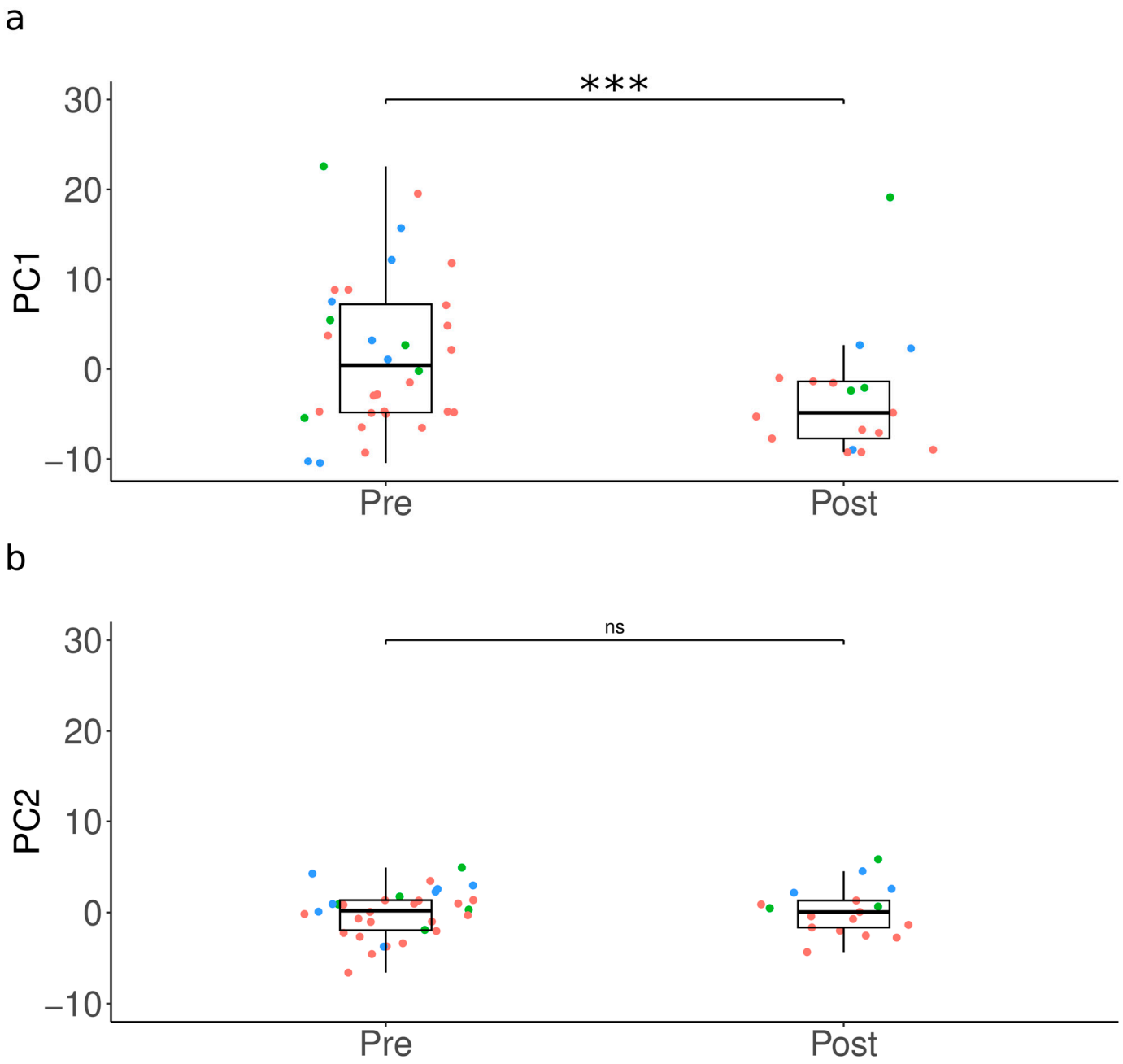

Figure 3. Effect of TMS on the two principal components. (**a**) The boxplot shows the values of the subjects' first component (PC1) before (PRE) and after (POST) TMS treatment (Chi-sq$_1$: 13.5034, $p < 0.001$). (**b**) The boxplot shows the values of the subjects' second component (PC2) before and after TMS treatment (Chi-sq$_1$: 0.2371, $p = 0.626$). (Red dots are SUD subjects, blue dots are MDD subjects, green dots are OCD subjects; *** $p < 0.001$; ns $p > 0.05$).

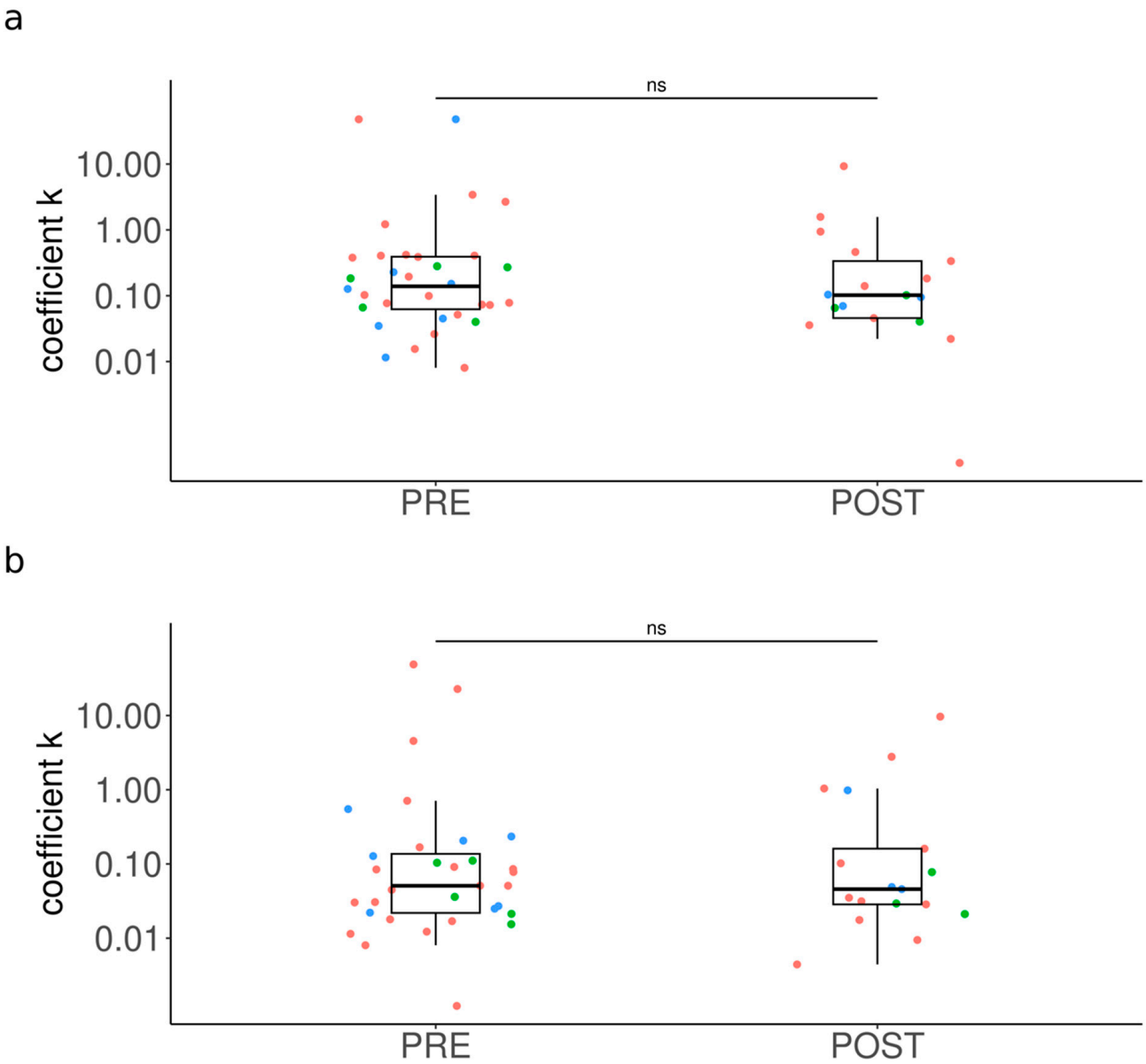

Figure 4. Effect of TMS on DD. (**a**) The boxplot shows the values of the subjects' devaluation coefficient k of DD when the reward is EUR 500 before (PRE) and after (POST) TMS treatment (Chi-sq$_1$: 1.1765, p = 0.278). (**b**) The boxplot shows the values of the subjects' devaluation coefficient k of DD when the reward is EUR 10,000 before and after TMS treatment (Chi-sq$_1$: 0.1639, p = 0.685). (Red dots are SUD subjects, blue dots are MDD subjects, green dots are OCD subjects; ns $p > 0.05$).

4. Discussion

Here, we investigated the effects of clinical rTMS treatments applied to different psychiatric conditions, both on clinical symptomatology and cognitive domains. Our results suggest that these specific brain stimulations produced amelioration of clinical symptomatology but did not induce any appreciable enhancement of cognitive functioning as a simple effect or in interaction with the diagnosis. Notably, the use of a custom data-driven approach for the statistical analysis allowed us to produce a dimensional characterization of the subjects' profile and to parallelly test the effect of TMS protocols on clinical outcomes and cognitive functioning. Thus, our results do not support the "global" hypothesis that TMS protocols lead to symptomatic improvements only through cognitive domain enhancements. This does not necessarily imply that TMS of the areas we stimulated does not produce effects on cognitive domains (as reported by several studies, e.g., [34,35]),

but rather that these effects do not remain stable over time in the clinical subjects we considered. Important limitations of our study relate to the absence of a sham group, the fact that some subjects were concurrently undergoing psychotherapy and pharmacological treatments, and a possible learning effect due to the repeated administration of tests. However, given that no general cognitive enhancement effect was found, we can affirm that these TMS protocols did not impact the cognitive domain in a broad sense. Regarding MDD, most studies investigating the effect of TMS stimulation on cognitive performance in subjects with major depression did not find cognitive improvements [36], supporting our analysis results. As for TMS clinical pathways in subjects with OCD and SUD, we found no literature references to cognitive enhancement. One hypothesis could be that, by facilitating TMS-induced plasticity phenomena, cognitive remediation interventions should be incorporated into the clinical pathway. For Alzheimer's disease, it has been observed that cognitive enhancement is greater when compared to TMS [35]. In the future, combining TMS and cognitive training could "boost" the therapeutic effect of TMS more effectively. It remains uncertain which factors TMS acted on in our protocols to improve clinical symptomatology in a general and nonspecific manner. Considering less "cold" psychological domains [15], such as DD, a transdiagnostic factor was impaired in all three pathologies and can be modulated by non-invasive brain stimulation [37]. Other limitations concern the sample size. However, it is possible to find articles in the literature with a similar or even smaller sample size [38–42]. Furthermore, the statistical analyses are still capable of detecting effects, as in the case of the treatment effect on PC1 and the diagnosis effect on PC2.

We can conclude by hypothesizing that cognitive improvement may not be strictly necessary for symptom improvement. It is important to emphasize that our results do not exclude the possibility that cognitive enhancement could be a valid therapeutic strategy for the conditions we treated, but this was not observed in the clinical pathway we analyzed. To create more personalized and effective therapeutic pathways, it is useful to identify the factors and psychological domains on which different stimulation protocols act. In the future, it would be useful to evaluate such a dichotomy between symptoms and cognitive functioning in relation to other pathologies and stimulation protocols and also to consider other psychological domains, such as the metacognitive domain, which is impaired in many pathologies, particularly for these specific clinical protocols [43]. In this context, other neuromodulation techniques such as transcranial electrical stimulation might act differently [44], since their range of action might include subcortical areas as well, such as the visual thalamus [45], a structure involved in the therapeutic effects of eye movement desensitization and reprocessing.

Author Contributions: A.S.M., D.S., M.F., A.V. and J.L. conceptualized the experiments; A.S.M. and D.S. performed the experiments; A.S.M., D.S. and S.G. analyzed data; A.S.M. was involved in writing—original draft preparation; A.S.M. and J.L. were involved in writing—review and editing; G.M.R., R.G.G., N.P., S.C., M.F., S.S. (Simona Scainiand), S.S. (Sandra Sassaroli), J.L. and A.M. were involved in supervision. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Due to ethical restrictions, the datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest: The authors declare no competing interests.

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