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Cognitive changes in post-stroke depression patients undergoing treatment with transcranial direct current stimulation (tDCS): an exploratory, ancillary analysis of a randomized, sham-controlled clinical trial.

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ABSTRACT

Introduction: Post-stroke depression (PSD) affects approximately 40% of stroke survivors, with cognitive deficits being frequently observed. Transcranial Direct Current Stimulation (tDCS) has shown promise in improving cognitive performance in stroke patients. We explored the effects of tDCS on cognitive performance in PSD.

Methods: An exploratory analysis was conducted in 48 patients from a double-blinded, sham-controlled, randomized clinical trial that investigated the effects of tDCS for treating PSD. A neuropsychological battery was applied at baseline and endpoint. We assessed three key domains: **(1) Stroop effect**, measured by the Stroop test components (color naming, word-reading and word-color interference); **(2) processing speed**, assessed using the Trail Making Test and the Digit Symbol

coding test; **(3) executive function**, evaluated with the Digit Span test and the Frontal Assessment Battery (FAB). A Linear mixed regression models were used to evaluate changes according to groups.

Results: We found that the active tDCS group worsened slightly, while the sham group improved in Executive Function for the adjusted models. Significant interactions were also found for FAB.

Conclusions: We found no consistent evidence that tDCS significantly improved the cognitive domains. The bidirectional association with cognition analysis suggest that tDCS effects may vary based on depression severity and task complexity.

Key-words: cognition; post-stroke depression; non-invasive brain stimulation; tdcs, stroke

Trial registration number: NCT01525524

Introduction

Stroke has been the second leading cause of death worldwide in recent years[1]. Among survivors, common post-stroke complications include mood disorders, with depression being the most prevalent[2]. Post-stroke depression (PSD) hinders the rehabilitation and recovery process, compromises quality of life, and increases mortality[3],[4]. Additionally, the association between PSD with cognitive impairments is well documented[5]. Cognitive impairment and depression are connected and reciprocally influential in the context of stroke. Depressive symptoms are associated with cognitive impairment after stroke [2]. The opposite is also true, as post-stroke cognitive impairment worsens, depression gradually increases [6] and is a risk factor for PSD[7] . The cognitive impairment occurrence in PSD pose a risk for dementia, lead to early and enduring activity limitations, and result in poorer outcomes for both stroke survivors and their caregivers[8,9].

Several meta-analyses have shown that PSD can be treated with non-invasive brain stimulation[10,11], such as the transcranial direct current stimulation (tDCS). TDCS uses a constant, low-intensity current applied over the scalp through

electrodes, modulating neuronal excitability[13,[12,13]]. It has an appealing safety profile in clinical samples, cost-effectiveness, and potential for application in various clinical settings, including home treatment[14]. Our previous randomized clinical trial showed that tDCS was an effective, safe treatment for PSD[15]. Regarding cognition, tDCS is a promising neuromodulation technique. It leverages the brain's capacity for neuroplasticity, potentially promoting neural reorganization and functional recovery after a stroke.

Although cognitive impairment is highly prevalent following a stroke, most research on stroke recovery centers on non-cognitive impairments and less than 5% of peer-reviewed studies involving stroke survivors included assessments of cognitive function[16]. A recent review[17] on tDCS for cognitive recovery concludes that published studies are limited by small sample sizes and inconsistent study designs, highlighting the need for randomized controlled trials to assess its efficacy. Findings also diverge. A meta-analysis showed that tDCS targeting the dorsolateral prefrontal cortex did not significantly improve the general executive function[18], while another meta-analysis concluded that treatment with anodal tDCS improved cognitive performance in general[19].

Therefore, it remains unknown whether the tDCS treatment can improve the cognitive deficits in PSD. The aim of our study was to perform an exploratory analysis of cognition of PSD patients in our previous randomized, sham-controlled, clinical trial [15].

Materials and methods

Study design

This is an ancillary study of a double-blinded, sham-controlled randomized clinical trial that investigated the effects of tDCS versus sham-tDCS for treating patients with PSD [15]. The study was unicentric and conducted at the University Hospital, University of São Paulo, São Paulo, Brazil. We included 48 patients (figure 1, table 1), 24 in the tDCS and 24 in the sham-tDCS group. The primary outcome was the change in the Hamilton Depression Rating Scale (17-items) at 6 weeks. Written, informed consent was collected from all patients before study enrollment according to

the Declaration of Helsinki. The study was approved by the Hospitals' Ethical Committees (CAAE 0062.0.198.000-12 and CAAE: 76259023.3.0000.0068) and registered on ClinicalTrials.gov NCT01525524. Here, we investigated the effects of tDCS on cognitive performance trajectories among PSD patients as secondary outcomes of our trial.

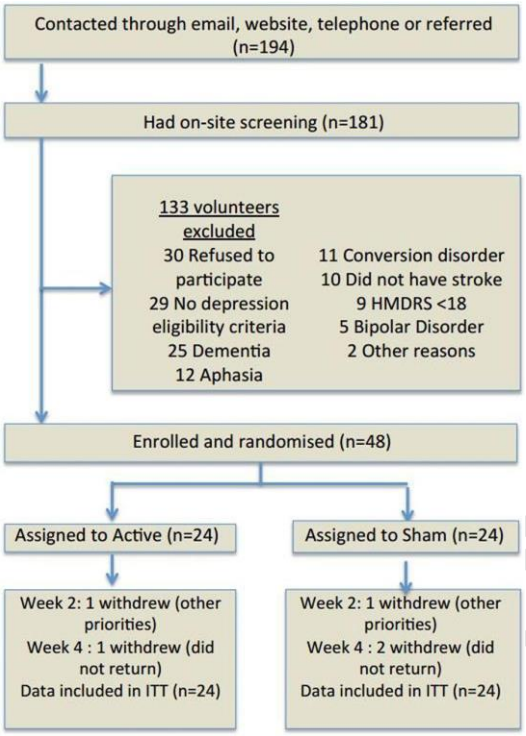


Figure 1. CONSORT flowchart

Table 1 Clinical and demographic characteristics

	tDCS, n=24	sham, n=24	t-test/χ^2	p-value
Gender (n, %)	12 (50%)	12 (50%)	$\chi^2(1) = 0$	1
Age (mean, SD)	62.2(12.3)	61.3(10.8)	t(44.68)=-0.27	0.79
Schooling (mean, SD)	7.75(5.7)	7.57(4.43)	t(43.18)=-0.12	0.90
baseline HDRS-17	22.8(3.14)	21.2(3.57	t(45.25)=-1.63	0.11
endpoint HDRS-17	13.2(6.7)	16.7(4.44)	t(39.92)=2.13	0.04
Number of episodes	1.17(0.48)	1.29(0.62)	t(43.219)=0.78	0.44
Duration of the current MDD episode, in weeks (mean, SD)	8.83(8.11)	19.6(18.2)	t(28.73)=2.54	0.02

Participants

Patients were recruited through referrals from neurological and rehabilitation centers and from a naturalistic stroke surveillance cohort study. The inclusion criteria for the study required participants to be aged between 30 and 90 years, with a score of 17 or higher on the Hamilton Depression Rating Scale, 17-item version (HDRS-17), indicating moderate to severe depression. Only individuals experiencing their first depressive episode were eligible, which had to begin 1 to 12 months after the stroke. Additionally, participants needed to have experienced their first stroke within the past five years. A low suicide risk was determined through a clinical interview, with the suicide item in the HDRS-17 (third item) scoring 2 or lower. Finally, participants were required to have a DSM-IV diagnosis of “mood disorder due to a general medical condition (stroke) with a major depressive-like episode.” The exclusion criteria included the presence of any other current Axis I disorders, except for anxiety disorders. Participants with specific contraindications for transcranial direct current stimulation (tDCS), such as metallic plates in the head, were also excluded. Other disqualifying conditions included neurological disorders like dementia and epilepsy, as well as life-threatening clinical conditions. Individuals taking benzodiazepines in doses exceeding 10 mg/day (or the equivalent) were excluded, as were those using any antidepressants, antipsychotics, sedatives, or hypnotics, although anticonvulsant medications were permitted if prescribed for previous stroke-related seizures (for

details please refer to [15]). Stroke diagnosis was confirmed by a physician through history-taking, physical examination, and neuroimaging. Depression diagnosis was conducted by a trained psychiatrist using the Mini-International Neuropsychiatric Interview (MINI) for DSM-IV psychiatric disorders.

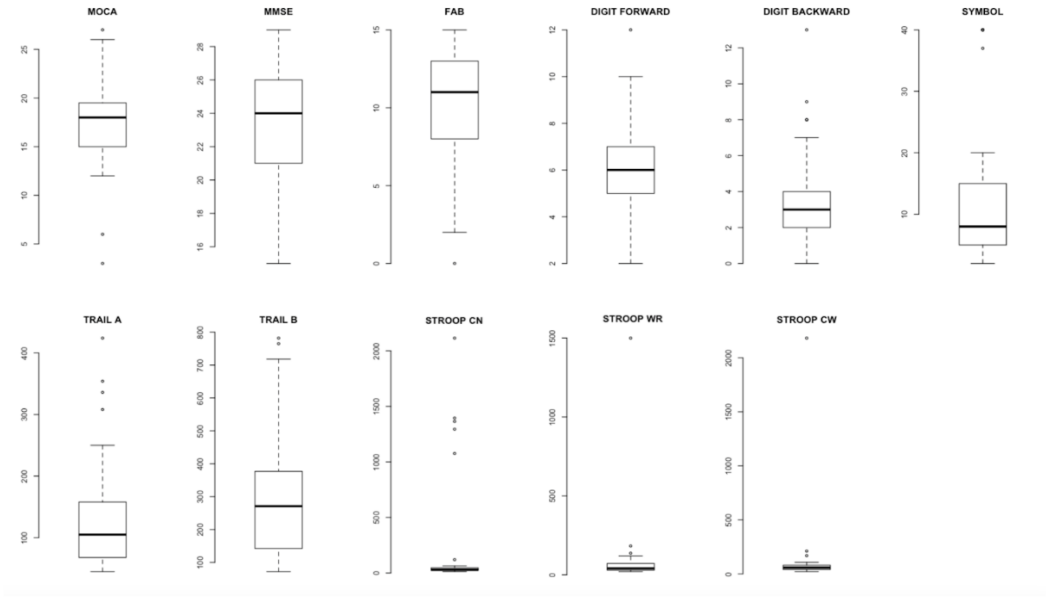
Interventions

Patients were randomly allocated to receive either active or sham-tDCS, following a randomized, sham-controlled, double-blind trial design, with a 1:1 permuted block randomization. Raters, operators, and patients were all blinded to the treatment assignments. To further ensure blinding, contact between participants was minimized. Stimulation was administered using a standard tDCS device (DC-Stimulator, Neuroconn, Ilmenau, Germany) with a bifrontal electrode montage. The anode and cathode were placed over the left and right dorsolateral prefrontal cortex (DLPFC), respectively at the F3 and F4 sites according to the international 10–20 EEG system. Rubber electrodes were placed in 25 cm^2 saline-soaked sponges and fastened with a headband. The current intensity was set at 2 mA. Participants remained seated at rest in a quiet, isolated room without external stimuli, and no specific tasks were assigned during the sessions [15]. Twelve stimulation sessions (anodal left/cathodal right dorsolateral prefrontal tDCS, 30 min each, once daily during weekdays for 2 weeks, then 1 session every other week) were administered over 6 weeks. The endpoint was chosen based on our previous study[20]. To mimic the common skin sensations experienced immediately after stimulation, the sham-tDCS consisted of only 60 seconds of stimulation, followed by no stimulation for the remainder of the session. Randomization was carried out using an automated device that assigned either sham or active stimulation based on a code. The codes were randomized by a research assistant who had no involvement in other aspects of the trial. These codes were then entered by the study nurse, who was blinded to the participants' group assignments.

Neuropsychological assessment

The neuropsychological battery was administered twice: on day 1, before the first stimulation session, and at week 6 (figure 2, and supplementary material "Neuropsychological assessment"). The battery included: 1) Montreal Cognitive Assessment (MOCA) and 2) Mini-Mental State Examination (MMSE), both for cognitive screening [21],[22]; 3) Frontal Assessment Battery (FAB) is a brief battery designed to assess cognitive and behavioral domains of executive function[23]; 4) The Trail Making Test evaluates processing speed, visual scanning, psychomotor activity, and overall executive function. Scores, measured in seconds, indicate worse performance with higher values. Divided into two parts, the first involves connecting numbers in ascending order with a line, and the second requires alternating between numbers (in ascending order) and letters (in alphabetical order) with a line[24]; 5) The Digit Span subtest of the Wechsler Adult Intelligence Scale (WAIS-III) assesses verbal short-term memory and working memory, cognitive control, and executive function. It is divided into two parts: the first part involves verbal repetition in forward order, and the second part involves verbal repetition in backward order[25]; 6) The WAIS-III Digit Symbol Coding subtest requires the reproduction of abstract symbols corresponding to associated numbers. Higher execution times indicate poorer performance[26]; 7) The Stroop Color and Word Test assesses the inhibitory ability to suppress automatic activities. The test consists of 3 parts, with longer execution times indicating poorer performance. Time and errors are recorded [27] .

A



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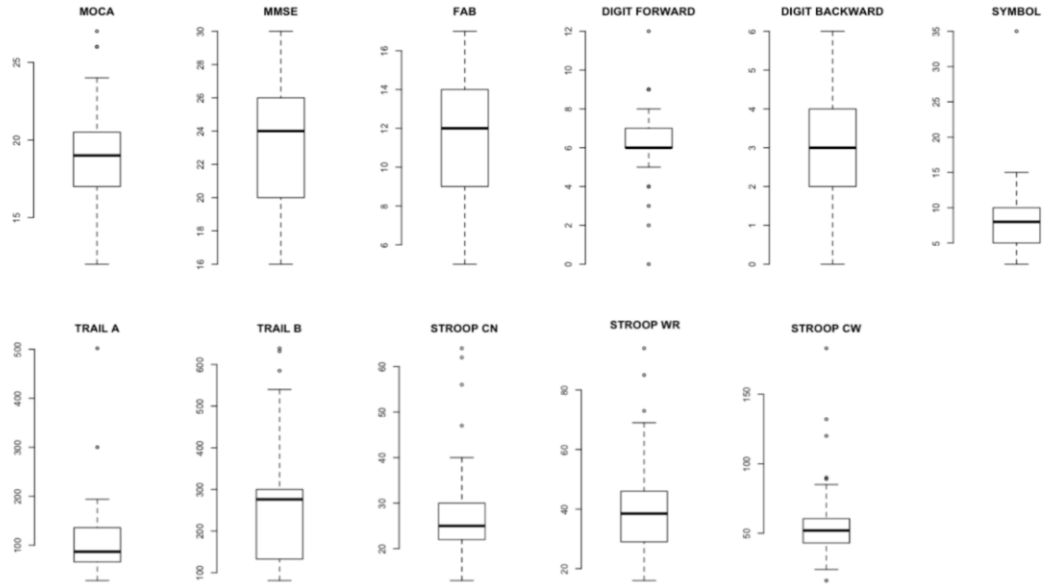

Figure 2. Preprocessing of cognitive outcomes at baseline (A) and week 6 (B).

Note: Raw scores outside of the 5-95% quantile of each cognitive raw score were winsorized. MOCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; Symbol, Digit Symbol Coding; Stroop WR, Stroop Word-Reading; Stroop CN, Stroop Color-Naming; Stroop CW, Stroop Color-Word Interference.

Cognitive domains

The neuropsychological tests were grouped into cognitive domains. A parallel analysis of standardized tests determined the optimal number of 3 factors. Subsequently, an exploratory factor analysis (EFA) with oblique rotation was conducted combining baseline and endpoint data, and confirmatory factor analysis (CFA) was applied using the lavaan package (supplementary material, figures 1, 2, and 3). The domains are: 1) "Stroop effect," which includes cognitive control, attention, and inhibition of cognitive interference (Stroop color naming (CN), word reading (WR), and color-word (CW), 2) "processing speed" (Trail A, Trail B, and symbol), and 3) "executive function" (Digit Forward, Digit Backward, FAB). Raw scores were standardized (z-scores) to create composite measures of cognitive domains. Considering the importance of language and memory, we grouped the respective subtests of MOCA and MEEM. However, due to a high number of missing values and low variability of the subtests, the models did not converge and were not included.

Statistical Analysis

The analysis was conducted using R version 4.3.1 (2023-06-16). Results were considered significant if $p < 0.05$. The number of comparisons was reduced by grouping cognitive domains. Extreme values in raw test scores were winsorized to values outside the 5th to 95th percentiles. The Trail Making Tests A and B were multiplied by (-1). For the Stroop Test, rates (R) were calculated for CN, WR, and CW, taking into account correct responses (C) and time (T) in seconds (RCN = CCN/TCN, RWR = CWR/TWR, RCW = CCW/TCW), based on Scarpina and Tagini, 2017. The rates were then multiplied by (-1).

The change in each cognitive test and domain was modeled using linear mixed models (LMM). Time, group, and their interaction were defined as fixed factors, while measurements were nested within the patients. A random effect for the intercept was included at the patient level. We refrained from imputing missing values, as our analysis assumed their randomness, and LMM is capable of accommodating this variability. The significance of the model factors was computed

using the Satterthwaite approximation for degrees of freedom. Effect sizes were reported as Cohen's [28,29].

As in Moreno et al., 2020 [30] we included three different models for each cognitive test and domains, considering that age, sex, and education are known confounding factors that can impact depression and cognition: 1) unadjusted for covariates, 2) controlled for age, sex, and education, 3) adjusted for age, sex, education, and change in depression (HDRS post- pre-treatment).

We performed two general linear models (GLMs) to examine the relationships between baseline cognitive function and changes in depression symptoms, as well as between baseline depression severity and changes in cognitive function, while considering the potential impact of the treatment group. Specifically, the first GLM assessed whether the initial cognitive state is associated with subsequent changes in depression symptoms, accounting for the treatment group and their interaction. Conversely, the second GLM assessed whether the initial depression state is associated with subsequent changes in cognitive function, also considering the treatment group and their interaction.

Results

Overview

Out of almost 200 volunteers, we included 48 patients who met inclusion criteria (flowchart figure 1[15] and table 1). The groups did not show significant differences in clinical and demographic characteristics, except for the duration of the current episode, which was longer in the sham-tDCS group.

Results for individual cognitive tests

Significant time x group interaction were found for FAB (model2 $F_{1,39.46}=5.238$, $p=0.027$, and model 3 $F_{1,39.46}=5.19$, $p=0.028$, both $d= -0.69$, CI95%= -1.28 to -0.10), and MMSE (model 2 $F_{1, 39.98} = 4.121$, $p=0.049$, $d =0.69$, CI95%= 0.09 to 1.27 and model 3 $F_{1,39.91}=4.147$, $p=0.048$, $d=0.69$, CI95%= 0.09 to 1.28). Digit span forward showed trend results (Supplemental material, table 3). The group mean difference suggests these results were carried out for an improvement in

the performance of the sham-tDCS group in FAB and in the active group in MMSE. In Digit span forward, both groups showed improvement, although the difference was only significant for the sham-tDCS group (table 3). Within-group significant differences were also reported for sham-tDCS group in FAB, Digit Span forward, and trail making A, and in the tDCS group for MOCA, Stroop WR, Stroop CW and Stroop Effect z-score (table 2).

Table 2 Scores and change in scores for each test and cognitive domains

Measure	tDCS		Sham-tDCS		Change	
	Baseline	Week 6	Baseline	Week 6	tDCS	Sham
FAB	11.6(2.90)	11.4(3.37)	9.33(3.02)	11(2.96)	-0.25(2.73)	**1.19(3.12)***
MOCA	18.1(3.27)	19.5(3.71)	17.2(3.61)	18.4(2.44)	**1.30(2.52)***	0.75(2.62)
MMSE	23.3(3.24)	24.4(3.79)	23.6(3.02)	23(3.38)	1.05(3.23)	-1.1(3.49)
Digit span - forward	6.32(1.85)	6.48(1.82)	5.25(1.77)	6.19(1.28)	0.13(1.66)	**1.02(1.69)***
Digit span - backward	3.52(2.06)	3.19(1.47)	3.55(2.36)	3.04(1.49)	-0.43(1.77)	-0.80(2.56)
Digit symbol coding	2.45(4.53)	0.927(1.81)	0.94(1.95)	1.24(1.98)	-1.76(3.89)	0.242(3.12)
Trail making A	-123(84.2)	-103(50.5)	-141(83.7)	-111(56.4)	2.29(39.3)	**23.8(59.2)***
Trail Making B	-312(239)	-213(150)	-313(169)	-324(160)	26.9(69.9)	13(173)
Stroop CN	-8.48(18.2)	-1.19(0.43)	-7.66(18)	-1.08(0.32)	8.67(20)	6.90(18.6)
Stroop WR	-2.68(2.05)	-1.62(0.78)	-2.41(1.53)	-1.79(0.46)	**0.84(1.69)***	0.22(1.18)
Stroop CW	-4.25(3.23)	-2.85(1.58)	-3.13(2.17)	-2.74(1.34)	**1.2(2.53)***	-0.09(1.11)
Stroop effect z-score	0.01(2.63)	1.32(0.88)	0.63(1.53)	1.18(0.68)	**1.21(2.50)***	0.17(0.99)
Processing speed z-score	0.517(2.72)	0.716(1.66)	-0.23(1.55)	0.4(1.45)	-0.47(1.08)	0.87(1.19)
Executive function z-score	0.640(2.24)	0.519(2.09)	-0.601(1.60)	0.177(1.81)	-0.31(1.93)	0.55(1.77)

Note: Mean and standard deviation for each group at baseline and week 6.Change in scores was calculated as the score at baseline minus the score at 6 weeks, with greater increases indicating better cognitive functioning. Trail Making A, B, and Stroop CN, WR, and CW were multiplied by (-1), therefore higher values indicate better performance. Asterisks in change column indicate significant within-group change.

Table 3 Unadjusted and adjusted changes in cognitive domains

Measure	Model	sham-tDCS vs tDCS		
		Difference	p-value	Effect size
Stroop effect	1	0.16(0.15)	0.305	0.38 (-0.31 – 1.08)
	2	0.11(0.16)	0.485	0.28(-0.42 – 0.97)
	3	0.11(0.16)	0.515	0.26(-0.44 – 0.95)
Processing speed	1	-0.22(0.12)	0.100	-0.51 (-1.42 – 0.42)
	2	-0.24(0.14)	0.111	-0.54 (-1.45 – 0.39)
	3	-0.24(0.14)	0.109	-0.54(-1.45 – 0.38)
Executive function	1	-0.18(0.11)	0.135	-0.45(-1.05 – 0.15)
	2	-0.24(0.11)	**0.035**	–0.62 (-1.23 – -0.01)
	3	-0.24(0.11)	**0.035**	-0.62 (-1.23 – -0.01)

Note: Model 1 was an unadjusted linear mixed model with time, group and their interaction as fixed factors; Model 2 additionally included age, sex, and education; Model 3 additionally included time varying HDRS-17 depression scores as a covariate; d Cohens d; Effect sizes are displayed with 95% confidence intervals in parenthesis; Numbers rounded to two decimal points.

Results for cognitive domains

Significant time x group interactions were found for *executive function* in both adjusted models 2 and 3 (F1,38.36=4.76, p=0.035, d=-0.62, CI95%=-1.23 to -0.01). The group mean differences indicated that these effects were carried by a slight worsening in the active-tDCS and a slight improvement in the sham-tDCS group. Groups did not significantly differ at the endpoint. No significant effects were found for the Stroop effect and processing speed (table 3).

Associations with improvement in cognitive function

A significant interaction effect was found between group and depressive symptoms for Stroop CN (β = -5.657, SE = 1.745, t(30) = -3.241, p = 0.003, pFDR =

0.006) and Stroop CW (β = -0.448, SE = 0.180, t(26) = -2.490, p = 0.020, pFDR = 0.039) (table 4 and supplementary fig. 4). Improvement in Stroop CN was associated with worse depressive scores at baseline for the sham-tDCS group, whereas the tDCS group exhibited the opposite pattern, with improvement linked to lower HDRS scores. For Stroop CW, the sham-tDCS group did not show changes in Stroop scores related to HDRS baseline, while the tDCS group demonstrated better performance associated with lower scores of HDRS. A trend towards a significant interaction effect was observed between group and depressive symptoms for Trail Making B (β = -37.233, SE = 17.332, t(16) = -2.148, p = 0.047, pFDR = 0.054). This interaction suggested that improvement in Trail B was more affected by baseline depression scores in the sham-tDCS group.

Table 4 Bi-directional associations with cognition

	Cognitive function predicting depression change (HDRS)				Depression predicting cognitive function change			
	Cognition		Cognition x Group		Depression symptom		Depression symptom x Group	
Measures	F-value	P-value	F-value	P-value	F-value	P-value	F-value	P-value
MOCA	0.57	0.45	<0.01	0.99	0.09	0.76	0.11	0.74
MMSE	0.11	0.74	0.81	0.37	2.09	0.16	0.23	0.59
FAB	0.69	0.41	0.20	0.66	0.53	0.47	0.05	0.83
Digit span - forward	2.00	0.16	0.47	0.50	0.45	0.50	0.10	0.76
Digit span - backward	0.28	0.60	0.013	0.91	0.23	0.63	1.49	0.23
Digit symbol coding	1.70	0.20	0.03	0.86	0.38	0.54	0.81	0.38
Trail Making A	0.88	0.35	0.11	0.74	0.55	0.46	0.15	0.70
Trail Making B	<0.01	0.96	0.07	0.79	1.65	0.29	4.73	**0.05***
Stroop CN	0.85	0.36	0.27	0.60	1.10	0.30	10.53	**<0.01***
Stroop WR	0.55	0.46	0.14	0.71	0.87	0.36	3.07	0.09
Stroop CW	2.14	0.15	0.05	0.82	4.42	0.04	6.21	**0.02***

Stroop effect z-score	1.49	0.23	0.31	0.58	3.47	0.07	4.07	0.05
Processing speed z-score	0.93	0.35	0.24	0.63	0.07	0.80	3.13	0.11
Executive function z-score	1.30	0.26	0.11	0.74	0.01	0.91	0.03	0.86

Note: Numbers rounded to 2 decimals, significance of model factors computed using anova.

Discussion

In this ancillary study of Valiengo et al., 2017 [15], in which the efficacy of tDCS for PSD was investigated, we explored the effects of tDCS in the cognitive domains of Stroop effect, processing speed and executive function. Furthermore, we analyzed several individual tasks. Among the strengths of this study were the effective blinding and the antidepressant-free sample, as antidepressant drugs can interfere with cognition. Our findings revealed no consistent evidence that tDCS significantly improved cognitive domain performance, but for individual tasks, active tDCS showed improvement in MMSE compared to sham-tDCS, while the sham-tDCS showed improvement in FAB.

Specifically, in the domain of Executive Function, we observed a slight worsening in the active-tDCS group compared to a slight improvement in the sham-tDCS group. The association of PSD with cognitive impairment is particularly well-established for executive dysfunction[31]. Corroborating our finding, a meta-analysis of 27 studies targeting the dorsolateral prefrontal cortex revealed that tDCS did not significantly improve the general executive function[18]. For individual tasks, interestingly active tDCS showed improvement in MMSE compared to sham-tDCS. The MMSE is a widely used screening test for identifying cognitive impairment and dementia in both clinical and research settings. The test consists of a short battery that includes subitems that evaluate orientation, short memory, attention, and language. Although it is usually useful for investigating dementia and mild cognitive impairments, previous studies have demonstrated that PSD had significantly lower MMSE scores than non-depressed post-stroke patients with comparable lesion location and volume[32]. This finding suggest tDCS may auxiliate in general cognitive

function. On the other hand, the improvement of the sham-tDCS in FAB may be due to practical effects, since the FAB is a brief cognitive test, participants may become more familiar with the tasks through repeated exposure, leading to better performance even in the absence of an actual treatment effect.

A bi-directional associations with cognition that investigated 1) the cognitive function predicting depression change, and 2) depression predicting cognitive function change, showed significant results for the second for Stroop CN and Stroop CW, and a trending result for Trail B. For Stroop CN, a congruent subtest in which the participant had to tell the color names of inked squares, patients in the active-tDCS group with less severe depression (measured by the HDRS) showed greater performance, while sham-tDCS group improvement was associated with more severe depression. In contrary, for the more complex CW Stroop subitem, which requires inhibiting the automatic response of reading the word and instead naming the ink color, improvement following tDCS was associated with higher HDRS scores. This suggests a distinct pattern of interaction between the DLPFC and tDCS, with depression severity influencing cognitive processing differently. It potentially indicates that varying cognitive mechanisms or neural pathways may be influenced by the complexity of the task and the level of depression, leading to differential tDCS effects on performance.

Cognitive improvements after tDCS exhibit significant intra- and inter-subject variability when used for stroke treatment, likely due to the specific brain regions affected by the stroke and the extent of impairment [33],[34]. Another crucial factor is the timing of the tDCS application for optimal results. The post-stroke acute and subacute stages are ideal for receiving the stimulation, with the greatest improvement in cognition typically occurring within the first six months[35]. However, in PSD, depression can occur even 12 months after the stroke, potentially missing the optimal window. Additionally, our sample showed a relatively long duration of the depressive episode, and only 16.6% of our sample was treating depression with antidepressants prior to the drug washout. The duration, severity, and untreated state of depression can significantly exacerbate cognitive dysfunction[36].

Limitations should be underscored. Cognition was an ancillary outcome of the

main trial. Hence, the tDCS treatment parameters and sample size might not have been adequate for inducing effects on cognition. Besides, the multiple analysis of cognitive outcomes could have lead to false positive results, so we have to interpret the data based on that. Another limitation is not having controlled the cognitive profile of the patients by localization of the stroke. Different topographical lesions can lead to different deficits in cognitive function. Another possible limitation is not taking into account the effects of circadian rhythms and sleep pressure. Both could impact cognition and neuroplasticity induced by tDCS [37–39]. Although all the participants collected the cognition measurements at the same time of the day we did not control sleep pressure.

Conclusion

In conclusion, this ancillary study found no consistent evidence that tDCS significantly improved cognitive performance in broad domains like Stroop Effect, processing speed, or executive function for patients with PSD. While the active-tDCS group showed improvement in the MMSE, the sham-tDCS group improved in the FAB, likely due to practice effects. A key finding was a slight worsening in Executive Function in the active-tDCS group compared to a slight improvement in the sham group, aligning with previous research showing no significant tDCS effects on general executive function. The bidirectional analysis of depression and cognition revealed that depression severity influenced cognitive task performance differently in the active-tDCS and sham groups. In the Stroop CN task, patients with less severe depression showed greater improvement in the active-tDCS group, while in the more complex Stroop CW task, higher depression severity was linked to improvement after active-tDCS. These findings may highlight the complexity and variability of cognitive improvements after tDCS, which may be influenced by depression severity, and task complexity. Additionally, the timing of tDCS in relation to stroke recovery is critical, as applying tDCS during the acute and subacute phases may yield better cognitive outcomes.

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Credit authorship contribution statement

LV, AR, AG, JO designed and conducted the study, including patient recruitment and data collection. RM, TZ, RV, BP, IB, AB, and LV performed the data analysis and interpretation of data. All authors approved the final manuscript.

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Supplementary Material

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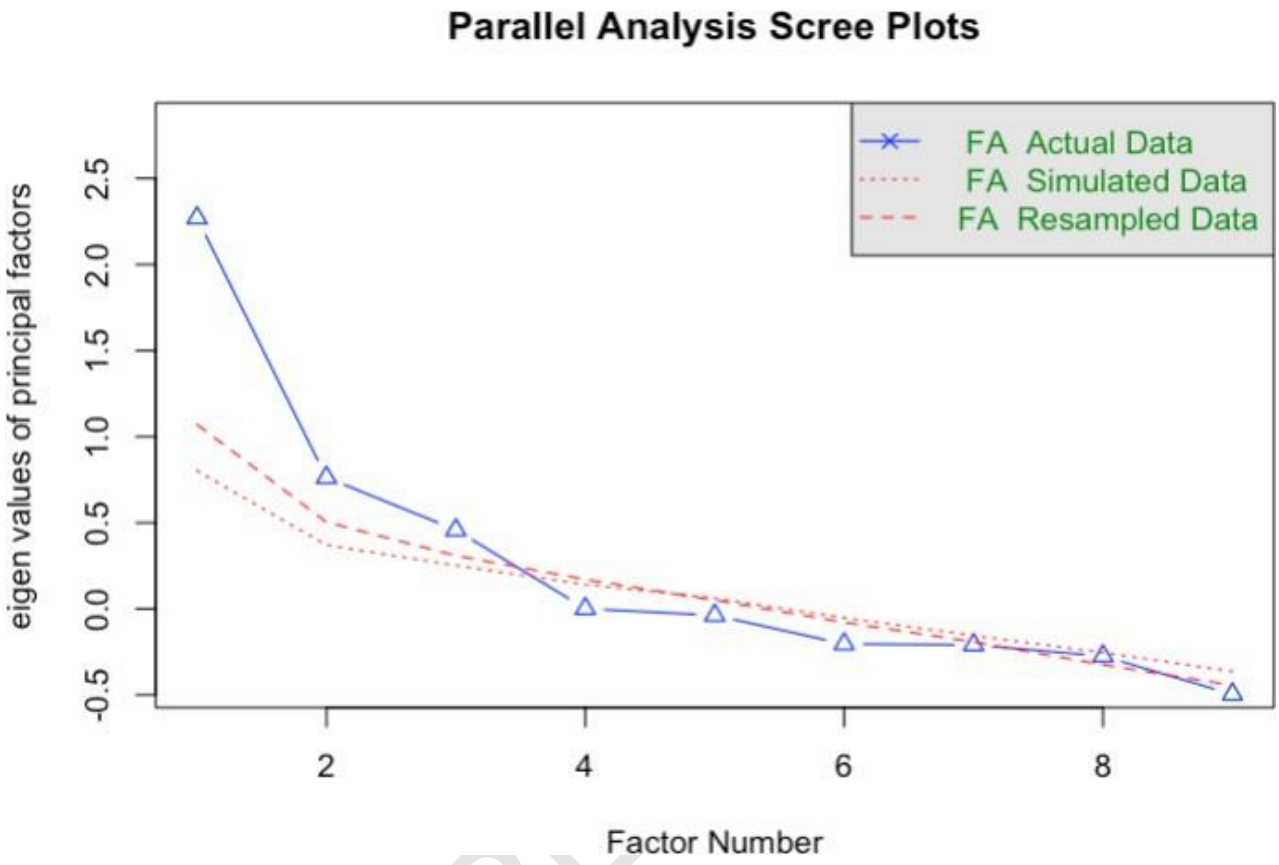
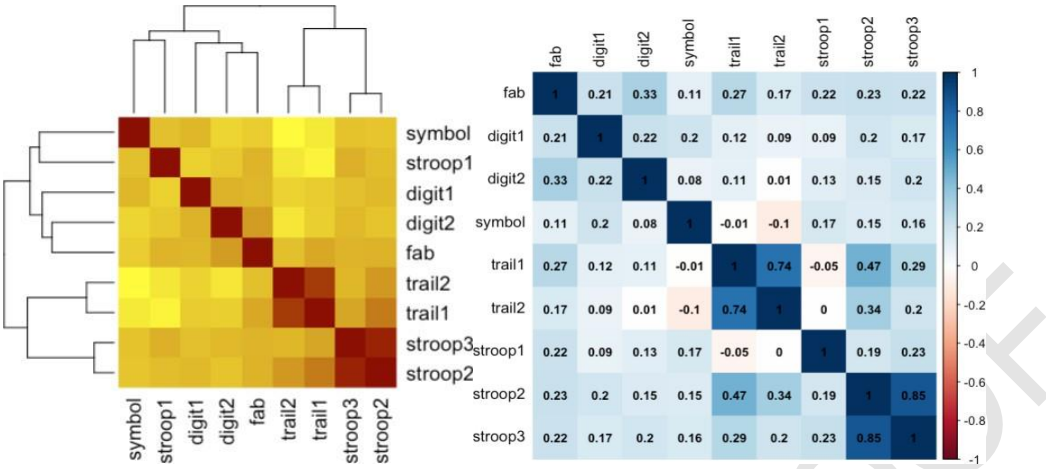
Supplementary figure 1 - Parallel analysis scree plot



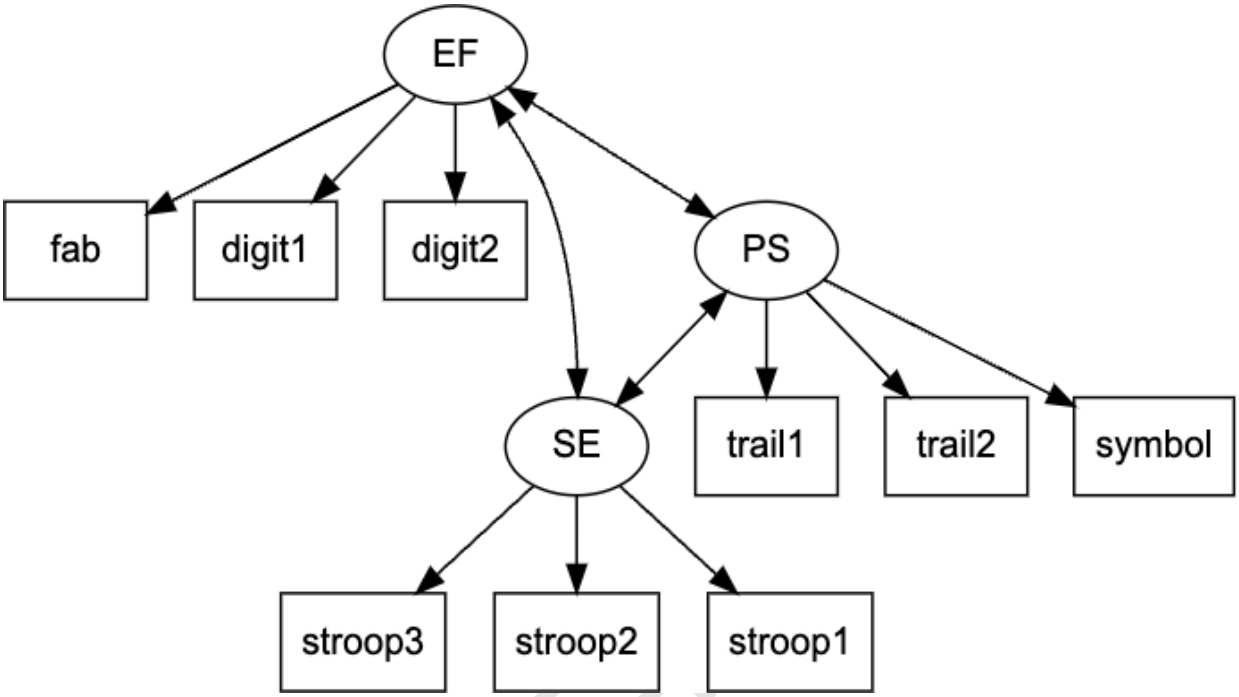
Note: FA Factor analysis; Parallel analysis compares the scree of factors by extracting factors until the eigenvalues of the real data are less than the corresponding eigenvalues of a random data set of the same size. Parallel analysis suggests 3 factors.

Supplementary figure 2 - Heatmap and plot for the correlation matrix between the tests included in the exploratory factor analysis.



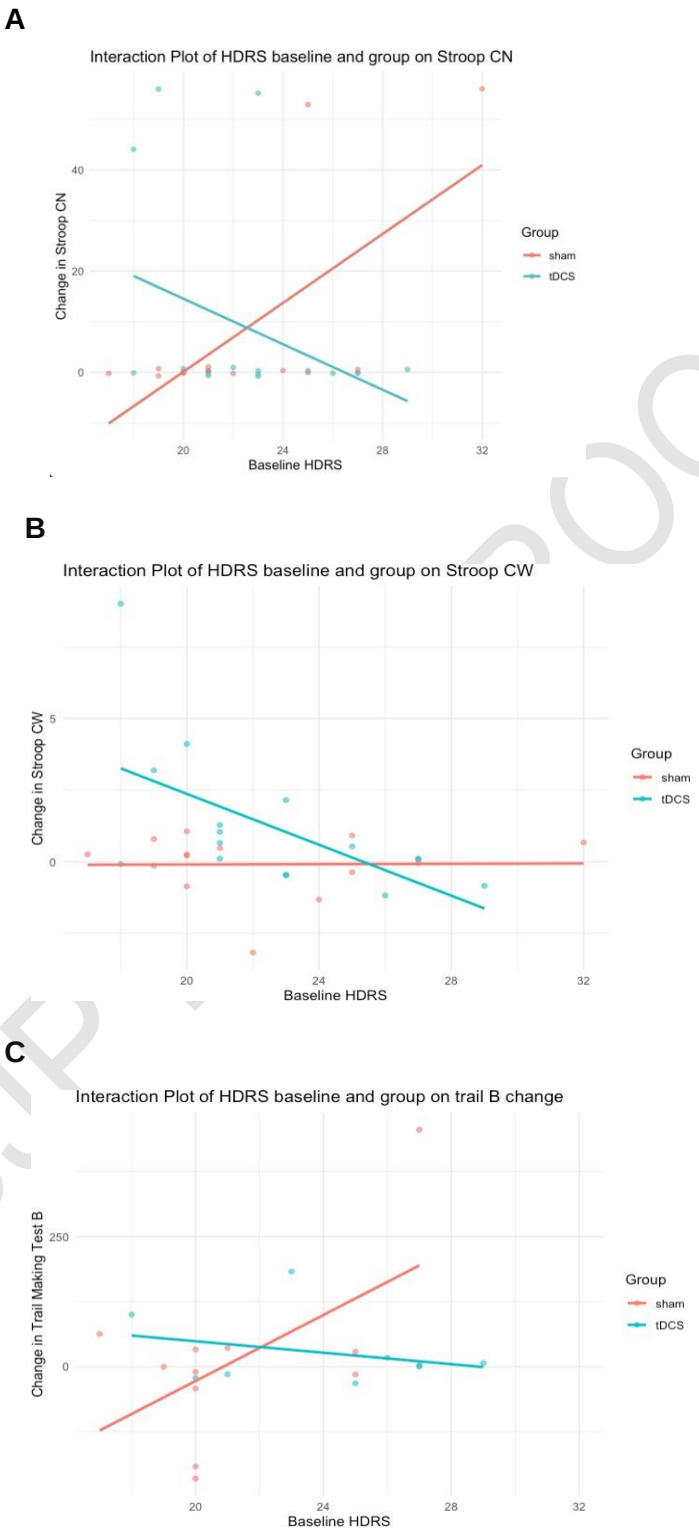
Note: FAB, Frontal Assessment Battery; Symbol, Digit Symbol Coding; Stroop 1, Stroop Color-Naming; Stroop 2, Stroop Word-Reading; Stroop 3, Stroop Color-Word Interference.

Supplementary figure 3 - Confirmatory factor analysis of neuropsychological tests in cognitive domains.



Note: EF, executive function; PS, processing speed and SE, Stroop Effect. FAB, Frontal Assessment Battery; Symbol, Digit Symbol Coding; Stroop 1, Stroop Color-Naming; Stroop 2, Stroop Word-Reading; Stroop 3, Stroop Color-Word Interference.

Supplementary figure 4 - Interaction Plots of bi-directional associations with cognition



Note: Baseline HDRS; baseline score Hamilton Depression Rating Scale, 17 items. A -

Stroop CN, Stroop Color-Naming; B- Stroop CW, Stroop Color-Word interference.

Supplementary table 1 - Fit indices for CFA of cognitive domains

Fit-Index	Value
chi-squared	28.525
degrees of freedom	24.000
p-value	0.239
CFI	0.962
AIC	504.268
BIC	536.931
RMSEA	0.073
SRMR	0.122

Note: CFI, Comparative-Fit-Index; AIC, Akaike-Information-Criterion; BIC Bayes-Information-Criterion; RMSEA, Root-Mean-Square-Error of Approximation; SRMR, Standardized-Root-Mean-Residual

Supplementary table 2 - Unadjusted and adjusted changes in cognitive outcome for each test, winsorized

Measure		sham-tDCS vs active-tDCS		
	Model	**Difference**	**p-value**	**Effect size**
MOCA	1	0.09(0.16)	0.555	0.13(-0.44 – 0.71)
	2	0.08(0.16)	0.639	0.11(0.71 – 0.68)
	3	0.08(0.16)	0.644	0.11(-0.46 – 0.68)
MMSE	1	0.38(0.20)	0.068	0.61(0.02 – 1.19)
	2	0.43(0.21)	**0.049**	0.69 (0.09 – 1.27)
	3	0.43(0.21)	**0.048**	0.69(0.09 – 1.28)
FAB	1	-0.33(0.18)	0.076	-0.56(-1.14 – 0.028)
	2	-0.41(0.18)	**0.027**	-0.69(-1.28 – -0.10)
	3	-0.41 (0.18)	**0.028**	-0.69(-1.28 – -0.10)
Digit spam - forward	1	-0.17(0.10)	0.110	-0.46(-1.05 – 0.13)
	2	-0.17(0.10)	0.102	-0.46(-1.06 – 0.13)
	3	-0.17(0.10)	0.099	-0.47(-1.06 – 0.12)
Digit spam - backward	1	0.05(0.13)	0.735	0.13(-0.46 – 0.71)
	2	-0.04(0.13)	0.734	-0.12(-0.71 – 0.46)
	3	-0.04(0.13)	0.734	-0.12(-0.71 – 0.46)
Digit symbol coding	1	-0.38(0.25)	0.145	-0.56(-1.23 – 0.12)
	2	-0.38(0.28)	0.181	-0.56 (-1.24 – 0.12)
	3	-0.38(0.28)	0.186	-0.56 (-1.23 – 0.12)
Trail making A	1	-3.72(3.44)	0.289	-0.22(-0.84 – 0.40)
	2	-3.81(3.67)	0.307	-0.23 (-0.85 – 0.40)
	3	-3.79(3.67)	0.310	-0.23(-0.85 – 0.40)
Trail Making B	1	9.04(11.90)	0.456	-0.09(-0.87 – 0.70)
	2	9.98(12.35)	0.428	-0.09(-0.87 – 0.70)
	3	10.05(12.42)	0.428	-0.09(-0.87 – 0.70)
Stroop CN	1	0.14(1.22)	0.908	0.04(-0.59 – 0.67)
	2	-0.15(1.31)	0.910	-0.04(-0.67 – 0.60)
	3	-0.11(1.31)	0.931	-0.03(-0.66 – 0.60)

Stroop WR	1	0.10(0.11)	0.355	0.40(-0.25 – 1.04)
	2	0.09(0.11)	0.422	0.26(-0.38 – 0.90)
	3	0.09(0.11)	0.428	0.26(-0.39 – 0.90)
Stroop CW	1	0.23(0.15)	0.146	0.43(-0.24 – 1.09)
	2	0.19(0.16)	0.238	0.35(-0.31 – 1.01)
	3	0.18(0.15)	0.253	0.34 (-0.33 – 1.00)

Note: WR: word reading; CN: name colors; CW: Color-Word

Neuropsychological assessment

For all tests we used the Brazilian version, which is specifically adapted for Portuguese-speaking populations.

The **Montreal Cognitive Assessment (MoCA)** is a cognitive screening tool designed to assist in detecting mild cognitive impairment and early signs of dementia. It is a brief test commonly used in clinical and research settings to evaluate multiple cognitive domains, including visuospatial/executive, attention, memory, language, visuospatial abilities, executive function, and orientation. The maximum score for the MoCA is 30 points, with a higher score indicating better cognitive performance. This version ensures cultural relevance and accommodates linguistic differences that can impact cognitive testing. For individuals with a level of education equal to or lower than 12 years, an additional point is added to the final score. This adjustment accounts for the potential influence of lower formal education on test performance, helping ensure that the MoCA score more accurately reflects cognitive ability rather than educational attainment.

Mini-Mental State Examination (MMSE): The MMSE is another widely used cognitive screening tool that assesses functions such as orientation, recall, attention, calculation, language, and the ability to follow simple commands. It is useful in identifying cognitive impairments, particularly in assessing the severity of dementia. Like the MoCA, lower scores on the MMSE suggest cognitive decline and the maximum score is 30.

Frontal Assessment Battery (FAB): This brief battery is specifically designed to assess executive functions and behaviors associated with the frontal lobe. It includes tasks that evaluate similarities, verbal fluency, inhibitory control, motor programming, mental flexibility, and sensitivity to interference. The maximum score is 18 points.

Digit Span (WAIS-III): The Digit Span subtest from the Wechsler Adult Intelligence Scale (WAIS-III) evaluates aspects of memory and cognitive control.

- **Forward Span**: Participants repeat a sequence of numbers in the same order, primarily assessing verbal short-term memory (maximum 16 points)
- **Backward Span**: Participants repeat a sequence of numbers in reverse order, evaluating executive function, working memory, and cognitive control. The difficulty increases with the length of the sequence, and higher scores indicate stronger performance (maximum 14 points).
-

Trail Making Test (TMT): The TMT is divided into two parts, each assessing different aspects of cognitive function:

- **Part A**: After an example where they should connect numbered circles from 1 to 8, without lifting the pencil from the paper, participants connect numbered circles in ascending order (1 to 25), assessing processing speed, visual scanning, and psychomotor ability.
- **Part B**: Also without lifting the pencil from the paper, participants alternate between numbers (in ascending order) and letters (in alphabetical order) - 1-A, 2-B, 3-C, etc, assessing more complex executive functions such as cognitive flexibility, attention, and task-switching, and processing speed. Performance is measured in seconds for each part, with longer times reflecting lower efficiency in these cognitive areas.

Digit Symbol Coding (WAIS-III): This subtest from the WAIS-III measures processing speed, visual-motor coordination, and associative learning. Participants are required to quickly pair abstract symbols with corresponding numbers according to a provided key. Performance is measured in terms of speed and accuracy, and patients should complete the maximum of coding in 90 seconds. A higher number of correct answers indicates a better performance (maximum total of 120 symbols to be coded, with 10 as an example).

Stroop Color and Word Test: This test assesses cognitive control, specifically the ability to inhibit automatic responses. Performance is measured in seconds for each part, with longer times indicating lower efficiency. Our Stroop version includes these three tasks:

- **Color Naming (CN)**: Participants name the colors of printed blocks.
- **Word Reading (WR)**: Participants read color names printed in black ink.
- **Color-Word (CW)**: Participants name the ink color of words that spell out different color names, requiring inhibition of the automatic response to read the word.