Supplementary Online Content

Valiengo LCL, Goerigk S, Gordon PC, et al. Efficacy and safety of transcranial direct current stimulation for treating negative symptoms in schizophrenia: a randomized clinical trial. *JAMA Psychiatry*. Published online October 16, 2019. doi:10.1001/jamapsychiatry.2019.3199

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Sociodemographic variables analyzed as predictors of response

They were age, gender, years of study, employment and marital status, ethnicity, disease duration, number of hospitalizations, previous use of electroconvulsive therapy (ECT), use of clozapine, haloperidol dose-equivalents, as in (Andreasen, Pressler, Nopoulos, Miller, & Ho, 2010) and presence of treatment resistant (lack of satisfactory clinical response to treatment with at least two antipsychotic drugs from different groups, used with therapeutic doses and for at least six weeks of treatment) and ultra-treatment resistant (those meeting criteria for treatment-resistant schizophrenia and with no response to at least six months of clozapine use in doses of at least 300 mg/day) schizophrenia, per recent guidelines (Correll, Kishimoto, Nielsen, & Kane, 2011; Howes et al., 2017).

eAppendix 2. Detailed statistical analysis

In the LMM models, measurements were considered to be nested within patients and patients were considered to be nested within study centers, assuming an unstructured covariance matrix between time points. Time, group and their cross-level interaction were fixed factors. On the patient level, we included a random effect for the intercept taking individual symptomatic variation at baseline into account. In order to account for varying change rates between patients, random slopes were added to the model, if they significantly improved model fit. Nested models were compared using χ^2-likelihood ratio tests. Since group allocation was performed on the patient level (center crossed effect), center specific effects were controlled by including time, treatment and their interaction as random effects on the center level. Parameters were computed using maximum likelihood estimation with Satterthwaite approximation to degrees of freedom. We used similar methodology than in a previous study from our group (Sampaio-Junior et al., 2018).

Effects sizes were calculated as Cohen's d and Odds Ratio for continuous and binary outcomes, respectively. Cohen's d was computed for the regression estimates using the formula d= (Beta x Time) / SDraw provided by (Raudenbush & Xiao-Feng, 2001) and as suggested by (Feingold, 2009), in order to provide effect sizes for linear growth models in the same metric as for classical analyses. We provided the number needed to treat (NNT), which assesses the effectiveness of a clinical intervention, for all outcomes (Kraemer & Kupfer, 2006). For continuous outcomes, they were obtained by transformation of Cohen's d using the cumulative distribution function of the standard normal distribution (Preti, 2015).

Results showed that optimal model fit was found for a random-intercept fixed-slope solution, as including symptomatic change as a random factor resulted in no significant improvement ($\chi^2 = 0.11$; P = 0.946). There were no differences according to study site.

eTable 1. Statistical analysis of primary and secondary outcomes

	Time			Time x Group			Slope of Change (Beta)		Effect size for time x group interaction	
Continuous Outcomes	**F**	**df [Num, Den]**	**P**	**F**	**df [Num, Den]**	**P**	**Active Group**	**Sham Group**	**d (95% CI)**	**NNT (95% CI)**
Trajectory up to week 6										
PANSS negative symptoms (Primary Outcome)	65.90	1,394.11	<.001	12.47	1,394.11	<0.001	-0.87	-0.34	0.36 (0.16 to 0.55)	5.04 (3.29 to 11.22)
PANSS positive symptoms	19.27	1,98.79	<.001	0.48	1,98.79	0.49	-0.35	-0.48	-0.14 (-0.53 to 0.25)	-12.71 (7 to -3.4)
PANSS general symptoms	18.44	1,391.43	<.001	1.07	1,391.43	0.30	-0.47	-0.77	-0.1 (-0.3 to 0.09)	-17.74 (-5.95 to 19.71)
PANSS total	16.82	1,1.09	0.136	1.03	1,1.08	0.49	-1.40	-0.87	0.20 (-0.09 to 0.60)	8.75 (3.07 to -9.41)
PANSS-FSNS	55.49	1,387.23	<.001	5.99	1,387.32	0.015	-0.88	-0.44	0.25 (0.05 to 0.45)	7.13 (4.01 to 35.46)
SANS	40.87	1,98.18	<.001	0.001	1,98.18	0.97	-8.20	-8.11	0.01 (-0.39 to 0.4)	177.25 (-4.60 to 4.49)
CDSS	4.63	1,1.65	0.190	1.10	1,2.11	0.40	-0.73	-0.26	0.19 (-0.17 to 0.55)	9.45 (3.31 to -10.27)
AHRS	0.25	1,387.29	0.620	0.62	1,387.29	0.43	0.23	-0.05	-0.08 (-0.28 to 0.12)	-22.22 (14.87 to -6.39)

GAF	3.99	1,87.87	0.049	0.15	1,87.87	0.70	2.60	1.76	0.08 (-0.5 to 0.34)	21.67 (5.32 to -3.62)
Trajectory up to week 12										
PANSS negative symptoms	66.08	1,491.43	<.001	16.87	1,491.43	<0.001	-0.70	-0.23	0.37 (0.19 to 0.55)	4.84 (3.32 to 9.18)
PANSS positive symptoms	28.87	1,486.35	<.001	0.24	1,486.36	0.63	-0.28	-0.33	-0.04 (-0.22 to 0.13)	-40.19 (13.28 to -8.02)
PANSS general symptoms	13.92	1,485.18	<.001	0.30	1,485.18	0.58	-0.35	-0.47	-0.05 (-0.23 to 0.13)	-35.46 (-7.74 to 13.65)
PANSS total	13.86	1,1.46	0.103	1.21	1,1.51	0.42	-1.60	-0.84	0.30 (0.23 to 0.82)	6.05 (2.28 to -7.70)
PANSS-FSNS	55.55	1,480.39	<.001	10.27	1,480.40	0.001	-0.72	-0.29	0.29 (0.11 to 0.47)	6.16 (3.84 to 16.13)
SANS	53.70	1,193.08	<.001	0.12	1,193.08	0.73	-4.64	-5.10	-0.05 (-0.33 to 0.23)	-35.46 (-5.42 to 7.74)
CDSS	3.62	1,1.79	0.212	1.11	1,1.54	0.43	-0.60	-0.29	0.19 (-0.17 to 0.56)	9.17 (3.28 to -10.63)
AHRS	1.18	1,481.7	0.279	0.37	1,481.7	0.54	0.23	0.06	-0.06 (-0.23 to 0.12)	-31.96 (14.41 to -7.61)

GAF	4.88	1,172.31	0.029	0.08	1,172.31	0.77	1.30	1.00	0.04 (-0.34 to 0.25)	40.04 (7.01 to -5.22)
Binary Outcomes				**z-value**		**P**	**Active Group (OR)**	**Sham Group (OR)**		**NNT (95% CI)**
Week 6										
Response (20% improvement)				3.69		<0.001	17.78	0.04		2.78 (1.98 to 4.68)
Week 12										
Response (20% improvement)				3.57		<0.001	16.29	0.04		2.88 (2.02 to 4.98)

Note: Numbers rounded to two decimal points; [a] model included random slopes because improved model fit was indicated by χ^2-likelihood-ratio-test; PANSS Positive and Negative Syndrome Scale; CDSS Calgary Depression Scale for Schizophrenia; AHRS Average scores of Auditory Hallucinations Scale; GAF Global Assessment of Functioning; SANS, Scale for the Assessment of Negative Symptoms, df degrees of freedom; Num numerator, Den denominator; NNT Number needed to treat; OR Odds Ratio. d Cohens d; Effect sizes are representative of the regression model slopes.

eTable 2. Change of PANSS negative symptoms subscale in percentages

Group	Week 1	Week 2	Week 4	Week 6	Week 12
Active tDCS, mean (SD)	-11.78 (10.85)	-12.54 (12.43)	-10.58 (13.58)	-17.65 (12.72)	-15.80 (15.63)
Sham tDCS, mean (SD)	-9.20 (11.53)	-6.07 (11.03)	-7.91 (14.25)	-7.45 (7.40)	-6.97 (7.68)

Note: Numbers rounded to two decimal points.

eTable 3. Summary of all scales used in the trial at each measurement

Characteristic	Baseline	Week 1	Week 2	Week 4	Week 6	Week 12
Active Group						
PANSS negative symptoms, mean (SD)	25.00 (3.93)	22.04 (4.4)	21.81 (4.6)	22.27 (4.42)	20.51 (4.27)	20.94 (4.64)
PANSS positive symptoms, mean (SD)	14.26 (4.27)	14.20 (4.91)	13.29 (4.58)	13.68 (4.54)	13.15 (3.86)	13.38 (3.84)
PANSS general symptoms, mean (SD)	34.36 (10.21)	32.08 (8.91)	31.77 (9.34)	31.53 (9.38)	32.67 (8.63)	32.02 (7.69)
PANSS total symptoms, mean (SD)	73.62 (15.76)	68.32 (15.52)	66.88 (15.98)	67.45 (15.07)	66.28 (13.98)	66.00 (12.64)
PANSS-FSNS, mean (SD)	24.22 (5.13)	21.08 (4.57)	20.83 (4.96)	21.22 (5.24)	19.78 (4.85)	19.66 (5.03)
SANS, mean (SD)	60.12 (13.80)	---	---	---	52.07 (15.01)	50.40 (17.04)
CDSS, mean (SD)	2.32 (3.77)	2.02 (3.25)	1.38 (2.18)	1.70 (2.38)	1.02 (1.68)	1.24 (1.86)
AHRS, mean (SD)	9.44 (11.91)	7.66 (11.79)	7.88 (11.35)	9.47 (12.59)	9.91 (12.09)	9.91 (11.75)
GAF, mean (SD)	46.47 (12.4)	---	---	---	48.74 (11.77)	49.30 (10.61)
Sham Group						
PANSS negative symptoms, mean (SD)	25.10 (3.44)	22.88 (4.77)	23.6 (4.29)	23.12 (4.77)	23.26 (3.91)	23.36 (3.75)
PANSS positive symptoms, mean (SD)	14.24 (4.09)	14.22 (4.74)	12.82 (4.23)	12.84 (3.96)	12.54 (4.43)	12.98 (4.04)
PANSS general symptoms, mean (SD)	34.58 (8.66)	33.80 (9.19)	31.40 (9.75)	31.42 (9.99)	31.92 (8.34)	32.65 (8.03)

PANSS total symptoms, mean (SD)	73.92 (13.36)	70.90 (15.55)	67.82 (15.33)	67.38 (15.83)	67.49 (13.76)	69.04 (12.86)
PANSS-FSNS, mean (SD)	24.22 (3.56)	21.62 (5.45)	22.20 (4.50)	21.65 (4.98)	21.98 (3.70)	22.10 (3.76)
SANS, mean (SD)	62.32 (11.11)	---	---	---	53.96 (14.05)	51.96 (14.28)
CDSS, mean (SD)	2.26 (3.15)	2.68 (3.04)	1.56 (2.47)	1.51 (2.28)	1.59 (2.45)	1.57 (2.48)
AHRS, mean (SD)	7.66 (12.74)	6.72 (11.7)	6.52 (11.16)	7.69 (12.16)	6.88 (11.48)	7.80 (12.11)
GAF, mean (SD)	46.40 (11.04)	---	---	---	48.21 (11.84)	48.57 (11.09)

Note: Numbers rounded to two decimal points.

eTable 4. Results of moderation analyses

	Moderator		Moderator x Group	
Characteristic	**F-Value**	**P-Value**	**F-Value**	**P-Value**
Age in years	1.17	0.282	0.11	0.737
Women	1.95	0.165	2.57	0.112
Years of study	0.06	0.813	0.06	0.813
Unemployed	0.53	0.861	0.09	0.912
Not married	0.73	0.485	2.34	0.130
Self-declared white ethnicity	0.04	0.988	0.12	0.892
Duration of disease in years	0.07	0.792	0.11	0.739
Number of hospitalizations	5.68	**0.019**	0.64	0.426
Previous clozapine use	4.62	**0.035**	4.82	**0.031**
Treatment resistant schizophrenia	4.49	**0.037**	4.25	**0.042**
Ultra-treatment resistant schizophrenia	4.51	**0.036**	5.21	**0.025**
Equivalent Haloperidol dose, mg/day	5.46	**0.022**	4.96	**0.029**

Electroconvulsive therapy (ECT)	0.02	0.89	0.54	0.464
Patients with no auditory hallucinations per AHRS	1.09	0.298	0.20	0.653
Smoker	0.18	0.67	0.04	0.85
Patients with no depressive symptoms per CDSS	1.18	0.280	0.08	0.778

Note: Numbers rounded to two decimal points; PANSS Positive and Negative Syndrome Scale; CDSS Calgary Depression Scale for Schizophrenia; AHRS Average scores of Auditory Hallucinations Scale

eTable 5. Change in PANSS negative symptoms subscale score for subgroups showing significant moderation effects

Characteristic		**Active tDCS**	**Sham tDCS**	**Difference**
Clozapine use, mean (SD)	Never	-5.94 (4.28)	-2.32 (1.53)	3.63
	Previous	-3.57 (1.81)	-1.11 (1.62)	2.46
	Current	-3.11 (2.72)	-2.43 (1.99)	0.68
Treatment resistant schizophrenia, mean (SD)	Yes	-3.86 (3.00)	-1.83 (1.76)	2.04
	No	-6.56 (4.56)	-1.87 (2.03)	4.69
Ultra-treatment resistant schizophrenia, mean (SD)	Yes	-3.29 (2.51)	-1.95 (2.01)	1.34
	No	-5.57 (4.17)	-1.86 (1.66)	3.89
Equivalent Haloperidol dose, mg/day - slope		0.25	0.006	0.24

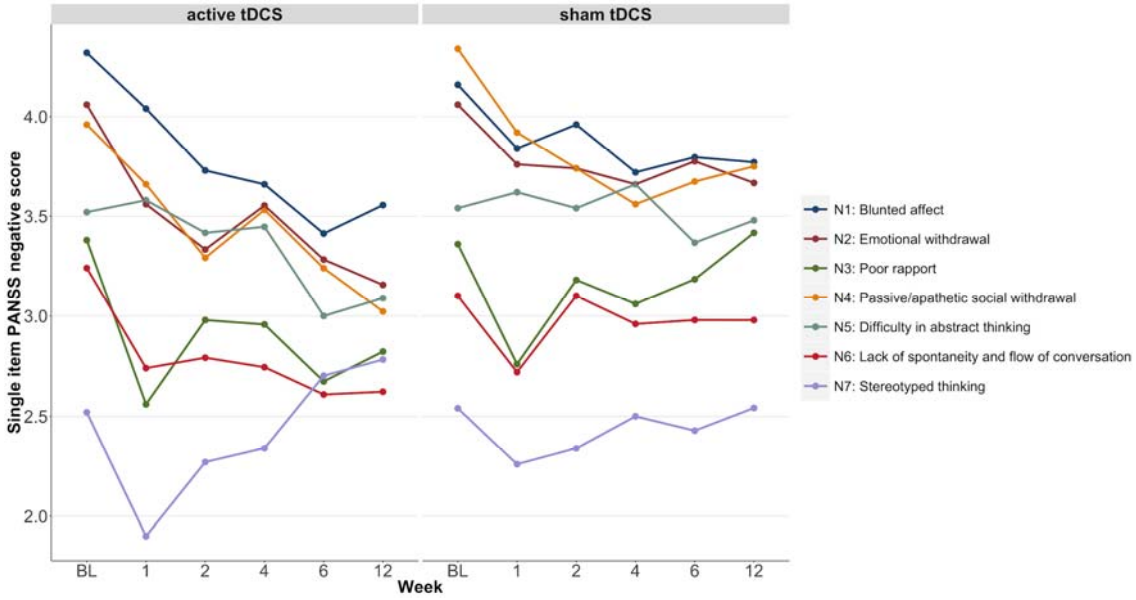
Note: Numbers rounded to two decimal points; Change in the score was calculated as the score at baseline minus the score at 6 weeks

eTable 6. Group differences in PANSS negative symptoms subscale single item scores

	Sham tDCS (N=50)	Active tDCS (N=50)	Sham tDCS vs. Active tDCS		
PANSS Negative Item			**Difference in Scores**	**P Value**	**FDR corrected**
Trajectory to Week 6					
Blunted affect	-0.37 ± 0.73	-0.83 ± 0.9	0.46 (0.12 to 0.79)	**0.004**	**0.031**
Emotional withdrawal	-0.29 ± 0.68	-0.78 ± 0.84	0.5 (0.18 to 0.81)	**0.021**	**0.035**
Poor rapport	-0.14 ± 0.74	-0.74 ± 0.93	0.6 (0.25 to 0.94)	**0.021**	**0.035**
Passive/apathetic social withdrawal	-0.67 ± 1.11	-0.74 ± 1.02	0.07 (-0.37 to 0.5)	0.827	0.827
Difficulty in abstract thinking	-0.2 ± 0.96	-0.57 ± 0.83	0.36 (0 to 0.73)	**0.025**	**0.035**
Lack of spontaneity and flow of conversation	-0.08 ± 0.98	-0.63 ± 1.1	0.55 (0.12 to 0.97)	**0.012**	**0.035**
Stereotyped thinking	-0.12 ± 0.56	0.17 ± 3.3	-0.29 (-1.27 to 0.69)	0.460	0.536
Trajectory to Week 12					
Blunted affect	-0.4 ± 0.74	-0.64 ± 1.07	0.25 (-0.13 to 0.63)	**0.019**	**0.028**
Emotional withdrawal	-0.42 ± 0.65	-0.89 ± 0.98	0.47 (0.13 to 0.82)	**0.011**	**0.028**
Poor rapport	0.08 ± 0.68	-0.58 ± 0.99	0.66 (0.31 to 1.01)	**<0.001**	**0.006**
Passive/apathetic social withdrawal	-0.65 ± 1.14	-0.93 ± 1.25	0.29 (-0.21 to 0.78)	0.262	0.262
Difficulty in abstract thinking	-0.08 ± 0.77	-0.42 ± 1.01	0.34 (0.03 to 0.71)	**0.016**	**0.028**

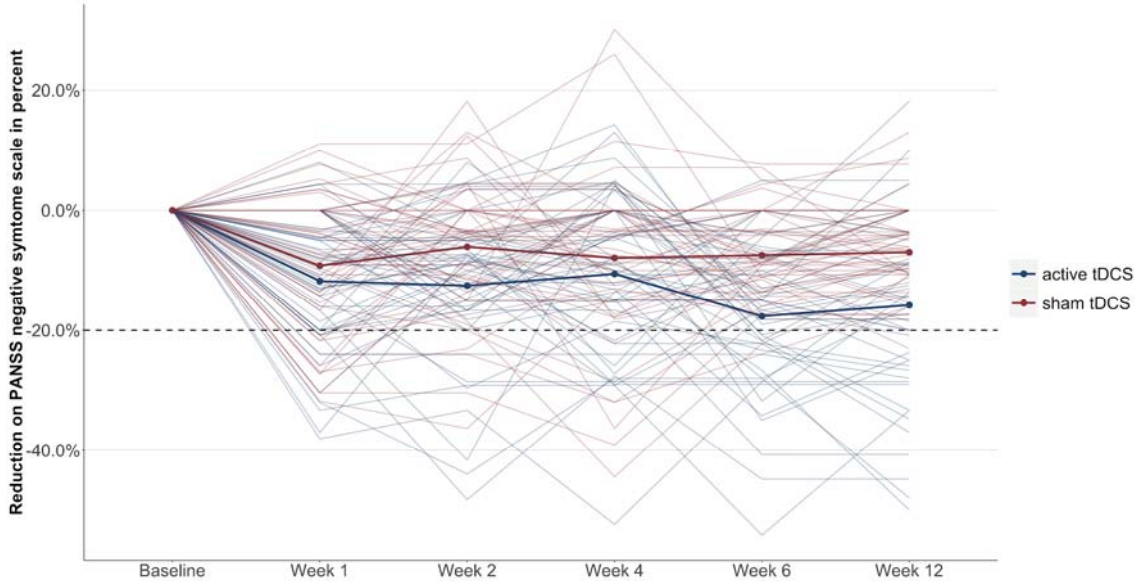
Lack of spontaneity and flow of conversation	-0.08 ± 1.01	-0.58 ± 1.2	0.49 (0.04 to 0.95)	**0.020**	**0.028**
Stereotyped thinking	-0.04 ± 0.71	0.24 ± 3.22	0.28 (-1.26 to 0.7)	0.232	0.262

eFigure 1. Changes in individual items of the PANSS negative symptoms subscale



Note: Displayed are the mean reduction (bold) of the single items of the PANSS negative scale (intention-to-treat-analysis) in both treatment groups from baseline to week 12; Higher scores indicate more severe negative symptoms; BL Baseline.

eFigure 2. Plot showing individual trajectories for patients' PANNS negative symptoms subscale scores



Note: Displayed are the mean reduction (bold) of the PANSS negative symptom scores (intention-to-treat-analysis) in both treatment groups from baseline to week 12 as well as patients' individual trajectories (faded). Dashed line at 20% reduction indicates threshold for showing response. Higher scores indicate more severe negative symptoms.

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