NicStim

Enhancing the efficacy of tDCS by nicotinergic stimulation in schizophrenia

Randomisierte, doppelblinde, 4-armige, monozentrische Interventionsstudie zum Nachweis der Überlegenheit der kombinierten Stimulation mittels Varenicline und tDCS gegenüber den Einzelinterventionen oder Plazebo
(NicStim Studie)

Phase II Clinical Trial

Test products:
Champix®

Study Code: KUM_PSY_2017_1

EudraCT Number: 2017-001357-14

First Patient First Visit: 20.08.2018 **– Last Patient Last Visit:** 21.10.2021

Termination of Clinical Trial: 29.11.2021

Sponsor
Klinikum der Universität München – AöR
vertreten durch den Vorstand des Bereichs Humanmedizin
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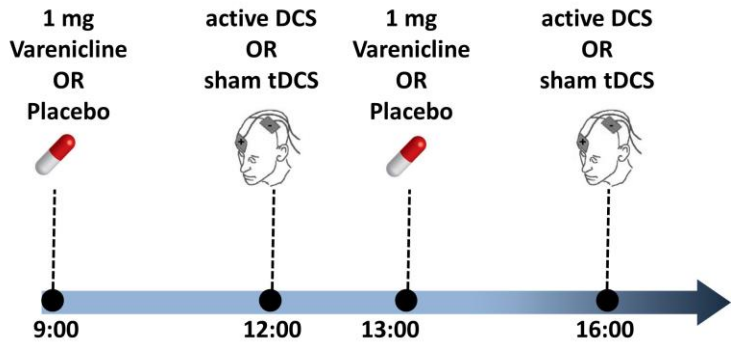
Synopsis

1.	**Sponsor:** Klinikum der Universität München – AöR vertreten durch den Vorstand des Bereichs Humanmedizin, Professor Dr. med. Markus M. Lerch, Marchioninistraße 15, 81377 München **Sponsor Delegated Person (SDP):** Prof. Dr. med. Peter Falkai
2.	**Name of Finished Product:** Champix®
3.	**Name of Active Ingredient:** Varenicline
4.	**Individual Study Table:** (only required for submissions) n.a.
5.	**Study Title:** Enhancing the efficacy of tDCS by nicotinergic stimulation in schizophrenia
	Study Design: Prospective, monocenter, randomized placebo-controlled, double blind, four-arm clinical trial with two arms investigating an active compound (Varenicline) with or without active transcranial direct current stimulation (tDCS) and two placebo arms with or without active tDCS
	Study (Protocol) Code Number: KUM_PSY_2017_1
	Eudra-CT Number: 2017-001357-14
6.	**Investigator:** Prof. Dr. med. Peter Falkai, Direktor der Klinik für Psychiatrie und Psychotherapie, Klinikum der Universität München
7.	**Participating Study Centre:** #1 Klinik für Psychiatrie und Psychotherapie Klinikum der Universität München Nußbaumstraße 7 80336 München, Germany
8.	**Publication:** not published yet
9.	**Study period:** First patient first visit (FPFV): 20.08.2018; LPI: 05.08.2021; Last patient out: 21.10.2021. The clinical trial was prematurely discontinued on 29.11.2021 due to unavailability of IMP and uncertainty, when and if IMP would be available again (Champix® Pfizer Pharma GmbH, containing N-Nitroso-Varenicline in certain batches (none of which used in this clinical trial) above the prespecified daily amount)
	Approvals and Amendments: **Approval**: Bundesinstitut für Arzneimittel und Medizinprodukte（BfArM): 28.09.2017; Ethics Committee (EC): 16.08.2017 **Amendment 1**: The following major changes were included in AM 1: The clinical study protocol (CSP) was adapted for clarification of the timing of the primary endpoint and addition of secondary endpoint assessment of long-term improvement in performance of working memory after intervention period. Approval AM1: BfArM: 15.05.2018; EC: 27.04.2018, CSP Version 3.1, 16.04.2018

	Amendment 2: The following major changes were included in AM 2: Deletion of exclusion criterion “smokers”, addition of CO measurement in smokers, addition of co-variables smoking status, cigarette count. Approval AM2: BfArM: 29.09.2018; EC: 26.09.2018, CSP Version 4.0, 24.08.2018 **Amendment 3:** The following major changes were included in AM 3: Change in SDP (and Coordinating Investigator, LKP) Approval AM3: BfArM: 04.02.2021; EC: 15.02.2021, CSP Version 5.0, 28.01.2021
10.	**Phase of development:** Phase II
11.	**Objectives:** **Primary Objective:** To evaluate whether the combination of tDCS and Varenicline is superior to Varenicline or tDCS alone in improving cognitive functioning (n-back performance) in patients with schizophrenia. **Secondary Objectives:** To evaluate the improvement of other measures of cognition, psychopathology, depressive symptoms, functioning and disease severity.
12.	**Methodology:** To investigate the effects of Varenicline and/or tDCS for the treatment of cognitive symptoms in schizophrenia, 60 patients with schizophrenia were planned to be enrolled (after having obtained written informed consent and fulfilling all inclusion and none of the exclusion criteria) and randomized into either one of four interventional groups receiving either twice daily active tDCS plus Varenicline (group 1), active tDCS plus placebo pill (group 2), placebo tDCS plus Varenicline (group 3) or placebo tDCS plus placebo pill. To evaluate whether the five-day intervention period improves cognitive functioning in schizophrenia, we investigated changes from baseline in each group at V2 (D8/9 after start of intervention), V3 (D28 after V2) and V4 (D56 after V2). The primary outcome (change in working memory, n-back) was evaluated at V2. Sixty patients with complete data were intended to be evaluable for the primary endpoint. Secondary endpoints included other measures of cognition, psychopathology, safety, and biological measures. The trial was registered at: International Clinical Trials Registry Platform: Clinical Trials Register (https://trialsearch.who.int/Trial2.aspx?TrialID=DRKS00013260) and DRKS - Deutsches Register Klinischer Studien (identifier: DRKS00013260). Figures 1 and 2 display main aspects of the trial design including the detailed study steps and the milestones per patient in the trial.  **Figure 1:** Interaction between IMP and tDCS within one day for one patient. Patients received in the morning either Varenicline or placebo followed by tDCS (active or sham) at lunchtime. One hour after, again Varenicline or placebo was administered and then followed by tDCS (active or sham) at lunchtime in the afternoon. This scheme was offered for five consecutive days.

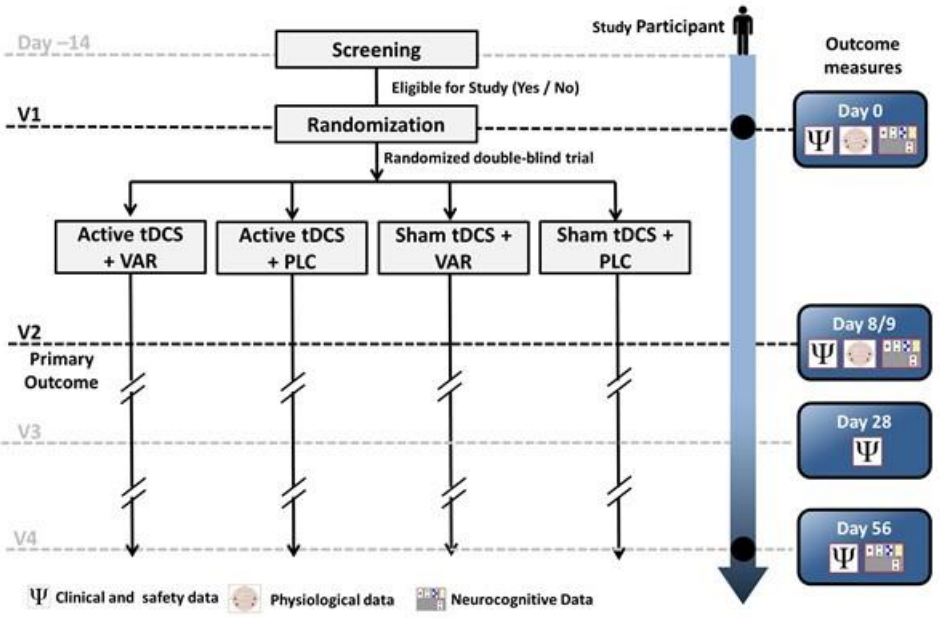


Figure 2: Study flow chart. After screening eligible patients were randomized to one of the four treatment arms (see paragraph 15 below) and treated for five consecutive days (see figure 1). At V2 the primary outcome was assessed followed by a naturalistic follow-up period.

13. **Sample size (planned/analysed):**

Planned: 60 patients

Included: 34 patients

Analysed: Intent-to-Treat (ITT) population: 34 randomized patients who received the intervention at least once

Safety population (SP): 34 patients of the ITT population

Per-protocol (PP) population: 29 patients (4/34 patients did not reach V2)

14. **Patient Population (Diagnosis):**

ICD10: F20
Gender: Both, male and female
Minimum Age: 18 years
Maximum Age: 65 years
These definitions were applied for all analyses population, ITT, SP and PP.

Main criteria for inclusion:

- Male and female patients aged between 18 and 65 with a diagnosis of schizophrenia according to the "Statistical Classification of Diseases and Related Health Problems (ICD-10)" confirmed by the Mini-International Neuropsychiatric Interview (MINI
- Continuous antipsychotic monotherapy or, if clinically indicated, a combination of a maximum of two antipsychotics (with a maximum dosage of 1000 mg chlorpromazine (CPZ) equivalents)
- Patients at time of inclusion in medium severity phase of psychopathology (PANSS Total ≤ 75, no relevant depressive symptoms (CDSS < 8)
- Male patients and female patients of childbearing potential: use of a proper method of contraception (according to the CTFG guideline) and negative pregnancy test (female patients) before study inclusion

	Main criteria for exclusion: • Pregnancy (female participants) • Current suicidality or risk of harming others • Severe neurological or somatic comorbidities • Incapacity to give informed consent or involuntary treatment • Treatment resistance schizophrenia and treatment with Clozapine • Established or suspected non-compliance regarding medication intake • Planned initiation of treatment with antidepressants, benzodiazepines or moo • Alcohol- or substance abuse during the last 6 months before inclusion into study (based on MINI international neuropsychiatric interview) except for coffeine and nicotine; No drugs may be taken during the 1-week intervention except from caffeine and nicotine. • Presentation of active substance use (positive drug urine test or CDT) • History of epileptic seizures • Epileptic potentials in EEG • Abnormal creatinine value • Known intolerance to the study medication (Varenicline) or to tDCS • Clinically relevant interaction between clinically necessary medication and investigational medicinal product (to be tested by mediq software) • Lacking capacity to give informed consent or involuntary treatment • Insufficient understanding of German language • Treatment-resistant or never treated schizophrenia
15.	**Test product, dose and mode of administration:** **Study treatment:** Twice oral daily intake of 1 mg Varenicline (Champix®) for 5 days **Control**: Twice oral daily intake of placebo pill for 5 days **Batch-No. (Ch.-B):** 20180508C (00006657), 20190503H (00015114); 20200512H (00021970); 20210418H (00024872) Group 1: 5 days active tDCS (twice daily) + Varenicline (Champix®) (twice daily 1 mg) Group 2: 5 days active tDCS (twice daily) + placebo pill (twice daily) Group 3: 5 days sham tDCS (twice daily) + Varenicline (Champix®) (twice daily 1 mg) Group 4: 5 days sham tDCS (twice daily) + placebo pill (twice daily)
16.	**Duration of administration:** Maximum five days
17.	**Background therapy:** **Comparator:** Placebo
	Blinding: Yes, investigator, patient, assessor, data analyst
18.	**Criteria for evaluation:** **Primary endpoint:** The primary endpoint was defined as improvement in working memory performance following the intervention. Performance of working memory was analysed using the n-back test before and after intervention. Performance was evaluated using the parameter dPrime (Haatveit et al, 2010). For every n-back level (1-, 2-, 3- back) dprime was calculated and then a mean of all levels was calculated. Primary endpoint is calculated for this variable between all four study groups for the period V1 to V2. **Secondary endpoints:** Changes in other cognitive measures 1 (V2), 4 (V3), and 8 (V4) weeks after start of the intervention (separate analyses of dprime levels, other nBack

	variables such as hit rates, criterion c, false-alarm rate, reaction times, verbal memory (VLMR), trail-making test A and B (TMT A/B), d2-attention test, composite score). Changes in function (GAF), psychopathology (PANSS), disease severity (CGI) and depressive symptoms (CDSS). BMI, alterations in ECG (yes/no) and cotinine measures were assessed).
	Efficacy: Efficacy assessments follow endpoint analysis.
	Safety assessments Safety was assessed from the start of the intervention until V4 (59/60 days after the last intervention). Safety was assessed according to CTCAE v4.03. MedDRA Version 20.1.
19.	**Statistical methods:** All statistical analyses were determined and prespecified prior to unblinding in a statistical analysis plan (SAP). An interim analysis was not planned. The statistician remained blinded until data-base hard-lock. Population for analysis *Intention-to-Treat (ITT) Population:* All randomized patients who received at least one intervention *Per-protocol Population (PP):* All subjects evaluable for the primary endpoint without major protocol deviations *Safety population (SP):* The safety analysis set consists of all patients who entered the trial and was used for conducting all safety analyses (corresponds to the ITT population) Study groups Group 1: 5 days active tDCS (twice daily) + Varenicline (Champix®) (twice daily 1 mg) Group 2: 5 days active tDCS (twice daily) + placebo pill (twice daily) Group 3: 5 days sham tDCS (twice daily) + Varenicline (Champix®) (twice daily 1 mg) Group 4: 5 days sham tDCS (twice daily) + placebo pill (twice daily) Primary endpoint analysis: The primary endpoint was defined as improvement in working memory performance following the intervention. Performance of working memory was analysed using the n-back test before and after intervention. Performance was evaluated using the parameter dPrime (Haatveit et al, 2010). For every n-back level (1-, 2-, 3- back) dprime was calculated and then a mean of all levels was calculated. Primary endpoint is calculated for this variable between all four study groups for the period V1 to V2. Analyses were adjusted for age, sex and years of education. Normality assumption was checked with a Kolmogorow-Smirnow-Test and if this assumption was violated, a Rankit-transformation (Bliss, 1967, Bishara und Hittner 2012) was performed where appropriate. For the intention-to-treat population, the primary outcome was analyzed with a linear mixed model analysis, nonrestrictely assuming an unstructured covariance matrix. Group (Group 1, Group 2, Group 3, Group 4) was defined as fixed-factor and time (V1, V2) as within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group, indicating whether the change of the primary outcome variable over time differed between groups. Secondary endpoint analysis: Secondary endpoints were analysed in the same manner where appropriate. Normality assumption was checked with a Kolmogorow-Smirnow-Test and if this assumption was violated, a Rankit-transformation (Bliss, 1967, Bishara und Hittner 2012) was performed. For the intention-to-treat population, continuous outcomes were analyzed with a linear mixed model analysis, nonrestrictely assuming an unstructured covariance matrix. Group (Group 1, Group 2, Group 3, Group 4) was defined as fixed-factor and time (V1, V2 or V 1 to V4) as within-subject factor. The statistic analyzed for significance

was the interaction between time of measurement and group, indicating whether the change of the primary outcome variable over time differed between groups. In cases where despite the Rankit transformation the normality assumption was not fulfilled, non-parametric tests were used. Categorical variables were analyzed using Chi²-Tests or adapted tests where needed. Where indicated, a correction for multiple comparisons was performed with the Sidak procedure. AEs were summarized by MedDRA Preferred Term and System Organ Class using absolute and relative frequencies. Serious AEs and AEs which are causally related to study medication were tabulated separately.

Safety: Safety analyses were done on the ITT set using the actual treatment group. AEs were coded using MedDRA Version English 20.1 and summarized by system organ class and preferred term. SAE and non-SAE-AEs were displayed separately.

20.

Summary - Conclusions:

Patient demographics and patient disposition

In total 34 patients were included in the study (FPFV: 20.08.2018; LPLV: 21.10.2021). Sixteen of 34 patients discontinued the study prematurely. Reasons for discontinuation were lost to follow-up (n=6), missing of > two interventions (n=2), and other reasons (n=8).

9 patients were included in group 1 (active tDCS+Varenicline), 9 patients in Group 2 (active tDCS+placebo), 8 patients in Group 3 (sham tDCS+Varenicline), 8 patients in Group 4 (sham tDCS+placebo).

The study visit V2 was completed by 8/9 (89%) patients in Group 1, 8/9 (89%) patients in Group 2, 6/8 (75%) patients in Group 3 and 8/8 (100%) patients in Group 4.

The study visit V3 was completed by 5/9 (56%) patients in Group 1, 7/9 (78%) patients in Group 2, 5/8 (63%) patients in Group 3 and 6/8 (75%) patients in Group 4.

The study visit V4 was completed by 4/9 (44%) patients in Group 1, 5/9 (56%) patients in Group 2, 5/8 (63%) patients in Group 3 and 4/8 (50%) patients in Group 4.

Only adults between 18 and 65 years were included. The median age was 41 (24 to 59) years in group 1 (7 male, 2 female), 34 (20 to 55) years in group 2 (6 male, 3 female), 33 (22 to 56) in group 3 (3 male, 5 female) and 36 (21 to 57) in group 4 (7 male, 1 female).

A

	Group 1 (active tDCS + Varenicline)						Group 2 (actoive tDCS + Placebo)						Group 3 (sham tDCS + Varenicline)						Group 4 (sham tDCS + Placebo)						Group comparison		
	number						number						number						number						F-H	df	p
Gender (male / female)	7/2						6/3						3/5						7/1						4.723		0.192
	n	m	sd	M	min	max	n	m	sd	M	min	max	n	m	sd	M	min	max	n	m	sd	M	min	max	F	df	p
Age (years)	9	41.22	10.24	41	24	59	9	34.11	10.98	34	20	55	8	36.63	13.49	33	22	56	8	35.50	12.11	36	21	57	0.620	3, 30	0.608
Education (years)	9	12.44	1.13	13	10	14	9	12.33	1.22	13	10	14	8	11.63	2.56	11	9	16	8	11.50	1.93	11.5	9	14	0.627	3, 30	0.603
Weight (kg)	8	84.90	24.78	82.5	53.5	120	8	73.38	13.50	72.5	50	93	8	80.26	16.33	82.3	51	98	7	95.26	10.92	92	83	115	2.076	3, 27	0.127
Height (cm)	8	178.4	11.61	175.5	165	198	8	175.5	10.03	179.5	158	186	8	167.9	7.99	170	150	176	7	181.6	7.14	180	171	193	2.957	3, 27	0.0502
Body mass index	8	26.3	5.63	24.1	19.7	36.4	8	23.82	4.00	22.7	18.6	30.1	8	28.33	4.78	27.7	22.7	35.1	7	29.09	4.59	26.9	24.7	36.3	1.856	3, 27	0.161

B

	Group 1 (active tDCS + Varenicline)						Group 2 (actoive tDCS + Placebo)						Group 3 (sham tDCS + Varenicline)						Group 4 (sham tDCS + Placebo)						Group comparison		
	number						number						number						number						F-H	df	p
Gender (male / female)	6/2						5/3						2/3						7/1						3.391		0.352
	n	m	sd	M	min	max	n	m	sd	M	min	max	n	m	sd	M	min	max	n	m	sd	M	min	max	F	df	p
Age (years)	8	43.38	8.50	42	33	59	8	35.25	11.16	35	20	55	5	32.20	13.22	27	22	54	8	35.50	12.11	36	21	57	1.297	3, 25	0.297
Education (years)	8	12.25	1.04	12.5	10	13	8	12.25	1.28	12.5	10	14	5	11.80	2.95	12	9	16	8	11.50	1.93	11.5	9	14	0.331	3, 25	0.803
Weight (kg)	7	84.17	26.67	75	53.5	120	7	72.71	14.44	70	50	93	5	77.10	17.30	82	51	98	7	95.26	10.92	92	83	115	1.947	3, 22	0.151
Height (cm)	7	176.3	10.80	174	165	198	7	174.0	9.82	179	158	185	5	168.2	10.40	172	150	176	7	181.6	7.14	180	171	193	1.981	3, 22	0.146
Body mass index	7	26.6	6.01	23.9	19.7	36.4	7	24.00	4.29	22.7	18.6	30.1	5	27.04	4.49	27.6	22.7	33.9	7	29.09	4.59	26.9	24.7	36.3	1.255	3, 22	0.914

Table 1: Relevant demographic variables in all four study groups. A: ITT Population, B: PP Population

Distributions of relevant demographics at baseline are given in Table 1. Figure 3 shows the CONSORT chart of the trial.

Concomitant therapy during the study

All patients received the routine care treatment in the respective participating study centre including pharmacotherapy, psychotherapy, and psychosocial treatments in accordance with the defined inclusion and exclusion criteria.

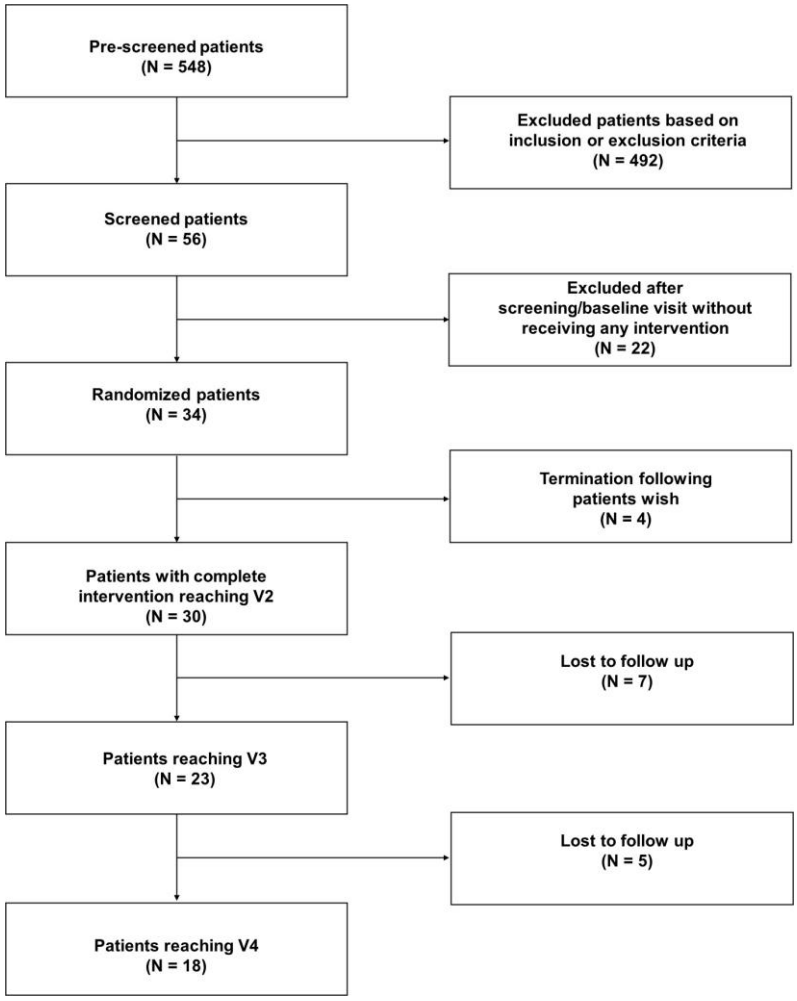


Figure 3: CONSORT chart. Please see text above for further information.

Compliance:

Protocol Deviations (PD):
Fifty-two PD were reported in 28/34 patients. Two PD were rated major (1 inclusion criterion, 1 no tDCS, no V2) and led to the exclusion of the patients from the PP analysis. Fifty PD were rated minor (14 concerning mostly singular lab values; 5 visits omitted; 3 visits and 4 examinations not conducted as scheduled; 16 no singular interventions, 8 singular interventions not conducted as scheduled.

Study medication:
All patients of the ITT population received at least one dose of IMP or at least one intervention. Four patients received IMP but did not reach visit 2. From these 4 patients, 1 was randomized to group 1, 1 was randomized to group 2, 2 were randomized to group 3 and 0 were randomized to group 4. From the 34 randomized patients that received the IMP 9 were randomized to group 1, 9 were randomized to group 2, 8 were randomized to group 3 and 8 were randomized to group 4. From these 34 patients 4 patients received IMP but did not reach visit 2.

Adherence to intervention:
Overall compliance for intervention was good (see PD).

Safety Assessments (all patients included)
Annual Safety Reports have been provided to BfArM and EC for the following periods:
DSUR 1: 20.08.2018-28.09.2018
DSUR 2: 29.09.2018-28.09.2019

DSUR 3: 29.09.2019-28.09.2020
DSUR 4: 28.09.2020-27.09.2021
DSUR 5: 28.09.2021-27.09.2022

Adverse Events and Serious Adverse Events were classified according to CTCAE V. 4.03 and coded according to MedDRA V. 20.1 English.

Safety Results

Safety results are reported in the treatment groups of the actual study treatment, regardless of randomization. Adverse Events and Serious Adverse Events were classified according to CTCAE V. 4.0 and coded according to MedDRA V. 20.1 English.

Adverse Events (AE)

A total of 57 AE were reported in 23 (67.6 %) of 34 patients as detailed in Table 2. 7/9 (77.8%) patients experienced 20 AE in group 1, 6/9 (66.7%) patients experienced 16 AE in group 2, 5/8 (62.5%) patients experienced 9 AE in group 3 and 5/8 patients experienced 12 AE in group 4 with no differences in distribution across groups (Freeman-Halton-Test = 0.831, p = 0.923) as detailed in Table 2.

			adverse event		
			no	yes	Total
group	active tDCS + Varenicilin	Count	2	7	9
		% within group	22.2%	77.8%	100.0%
	active tDCS + Placebo	Count	3	6	9
		% within group	33.3%	66.7%	100.0%
	sham tDCS + Varenicilin	Count	3	5	8
		% within group	37.5%	62.5%	100.0%
	sham tDCS + Placebo	Count	3	5	8
		% within group	37.5%	62.5%	100.0%
Total		Count	11	23	34
		% within group	32.4%	67.6%	100.0%

Table 2: Crosstables for AEs (yes/no) across groups

46/57 (80.7%) AE were rated grade 1 (mild), 10/57 (17.5%) grade 2 (moderate), 1/57 (1.8%) grade 3 (severe), 0 (0%) grade 4 (life-threatening) and 0 (0%) grade 5 (death). No significant differences were observed regarding the AE intensity across groups (Freeman-Halton-Test = 9.686, p = 0.060), whereas groups with active tDCS had a trend for more AE as detailed in Table 3.

			AE intensity			
			mild	medium	severe	Total
group	active tDCS + Varenicilin	Count	15	5	0	20
		% within group	75.0%	25.0%	0.0%	100.0%
	active tDCS + Placebo	Count	16	0	0	16
		% within group	100.0%	0.0%	0.0%	100.0%
	sham tDCS + Varenicilin	Count	6	3	0	9
		% within group	66.7%	33.3%	0.0%	100.0%
	sham tDCS + Placebo	Count	9	2	1	12
		% within group	75.0%	16.7%	8.3%	100.0%
Total		Count	46	10	1	57
		% within group	80.7%	17.5%	1.8%	100.0%

Table 3: Crosstables for AE intensity across groups

23 AE were deemed to be related to varenicline/placebo as detailed in Table 4. Freeman-Halton tests showed a significant different distribution across groups (27.884, p = 0.001).

			AE causal relation Varenicilin					
			no relation	unlikely	possible	likely	sure	Total
group	active tDCS + Varenicilin	Count	1	11	1	3	4	20
		% within group	5.0%	55.0%	5.0%	15.0%	20.0%	100.0%
	active tDCS + Placebo	Count	1	10	5	0	0	16
		% within group	6.3%	62.5%	31.3%	0.0%	0.0%	100.0%
	sham tDCS + Varenicilin	Count	1	3	2	3	0	9
		% within group	11.1%	33.3%	22.2%	33.3%	0.0%	100.0%
	sham tDCS + Placebo	Count	6	1	2	3	0	12
		% within group	50.0%	8.3%	16.7%	25.0%	0.0%	100.0%
Total		Count	9	25	10	9	4	57
		% within group	15.8%	43.9%	17.5%	15.8%	7.0%	100.0%

Table 4: Crosstables for AE relation to varenicline/placebo

21 AE were deemed to be related to active/sham tDCS as detailed in Table 5. Freeman-Halton tests showed a significant different distribution across groups (25.133, p = 0.002).

			AE causal relation tDCS					
			no relation	unlikely	possible	likely	sure	Total
group	active tDCS + Varenicilin	Count	1	14	4	1	0	20
		% within group	5.0%	70.0%	20.0%	5.0%	0.0%	100.0%
	active tDCS + Placebo	Count	1	6	3	6	0	16
		% within group	6.3%	37.5%	18.8%	37.5%	0.0%	100.0%
	sham tDCS + Varenicilin	Count	2	3	0	4	0	9
		% within group	22.2%	33.3%	0.0%	44.4%	0.0%	100.0%
	sham tDCS + Placebo	Count	5	4	1	0	2	12
		% within group	41.7%	33.3%	8.3%	0.0%	16.7%	100.0%
Total		Count	9	27	8	11	2	57
		% within group	15.8%	47.4%	14.0%	19.3%	3.5%	100.0%

Table 5: Crosstables for AE relation to varenicline/placebo

Serious AE (SAE)
Two SAE were reported in two patients in Group 4 as detailed in Table 6. Freeman-Halton-Test did not show a difference in distribution across groups (4.607, p = 0.064).

			AE SAE		
			no SAE	yes	Total
group	active tDCS + Varenicilin	Count	20	0	20
		% within group	100.0%	0.0%	100.0%
	active tDCS + Placebo	Count	16	0	16
		% within group	100.0%	0.0%	100.0%
	sham tDCS + Varenicilin	Count	9	0	9
		% within group	100.0%	0.0%	100.0%
	sham tDCS + Placebo	Count	10	2	12
		% within group	83.3%	16.7%	100.0%
Total		Count	55	2	57
		% within group	96.5%	3.5%	100.0%

Table 6: Crosstables for SAE distribution across groups

Suspected Serious Adverse Reactions (SAR)
One of the 2 SAE was reported as possibly related (SAR).

Suspected Unexpected Serious Adverse Reactions (SUSAR)
No SUSAR was reported in the study.

Non-serious Adverse Events (AE)
A total of 55 non-serious AE in 23/34 (67.6%) patients were reported during the study. 7 patients in group 1 (77.8%), 6 patients in group 2 (66.7%), 5 patients in group 3 (62.5%) and 5 patients in group 4 (62.5%) reported AE with no differences in distribution across groups (Freeman-Halton-Test = 0.831, p = 0.923) as detailed above.

ECG
ECG investigations did not show any alterations (abnormal yes/no) in any group at any time point of the study.

Efficacy Results

Primary Endpoint

One-sample Kolmogorov-Smirnov test confirmed a normal distribution of the data ($p > 0.200$) and variance homogeneity was confirmed with Levene's test ($p = 0.171$). The primary endpoint analyses in the ITT-population could not establish a significant time x group interaction for the comparison of the four study groups between V1 and V2. A significant of TIME could be observed ($F_{(1, 26.101)} = 4.715$, $p = 0.039$) which can be explained by the expected learning effects. No significant effect of GROUP ($F_{(3, 27.378)} = 1.769$, $p = 0.177$) and no TIME x GROUP interaction ($F_{(3, 26.092)} = 0.977$, $p = 0.419$) could be observed. Table 7 shows the full model, Table 8 mean values of the primary endpoint analyses and Figure 4 the bar plots of the primary endpoint analysis.

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	27.103	5.443	0.027
time	1	26.101	4.715	0.039
group	3	27.378	1.769	0.177
Sex	1	26.978	0.013	0.908
Age	1	27.058	2.045	0.164
School_Education	1	26.989	1.244	0.274
time * group	3	26.092	0.977	0.419

Table 7: LMM outcome for the primary endpoint analyses (ITT population)

time	group	Mean	N	Std. Deviation
V1	active tDCS + Varenicilin	2.070338	9	0.6530025
	active tDCS + Placebo	2.397077	9	0.5165675
	sham tDCS + Varenicilin	1.923681	8	0.2737650
	sham tDCS + Placebo	2.484212	8	0.7899777
	Total	2.219703	34	0.6076236
V2	active tDCS + Varenicilin	2.510037	8	0.7814174
	active tDCS + Placebo	2.612948	8	0.9350099
	sham tDCS + Varenicilin	1.931360	6	0.4122957
	sham tDCS + Placebo	2.699556	8	0.4141978
	Total	2.472283	30	0.7139826
Total	active tDCS + Varenicilin	2.277256	17	0.7290585
	active tDCS + Placebo	2.498663	17	0.7267997
	sham tDCS + Varenicilin	1.926972	14	0.3251948
	sham tDCS + Placebo	2.591884	16	0.6194010
	Total	2.338100	64	0.6664754

Table 8: Mean values of primary endpoint analyses

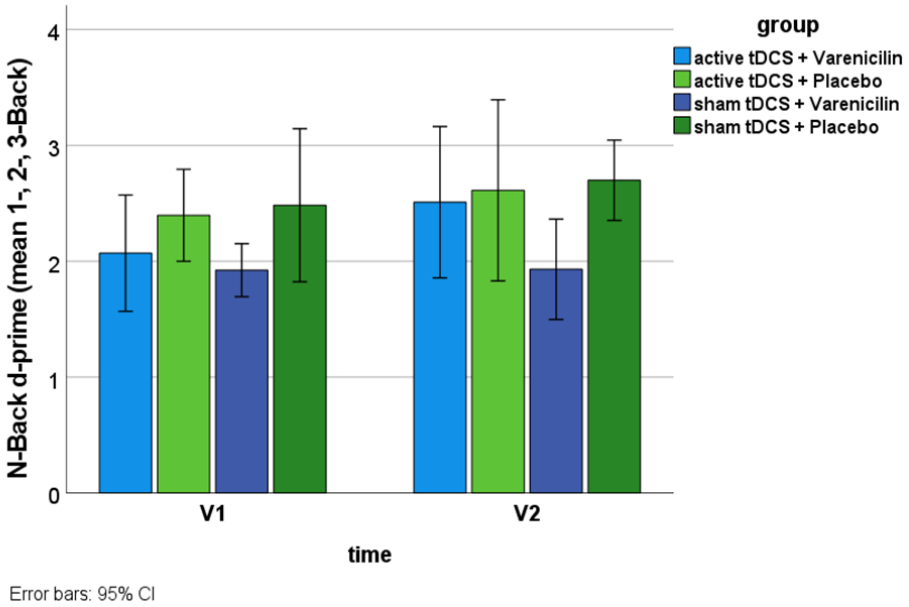


Figure 4: Visualisation of mean dPrime values. Error bars refer to 95%CI

The same analyses were repeated using the PP population. Here, analyses showed no significant effects (all $p \geq 0.218$) as detailed in the complete model description in Table 9. In contrast to the analyses using the ITT population no effect of TIME could be observed here. Figure 5 shows the visualization of mean dPrime values in the PP population.

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	4.050	1	4.050	4.598	0.045
V1_age	1.431	1	1.431	1.625	0.218
V1_school_education	0.034	1	0.034	0.039	0.846
group	3.846	3	1.282	1.455	0.258
V1_sex	0.061	1	0.061	0.069	0.796
group * V1_sex	0.196	3	0.065	0.074	0.973
Error	16.735	19	0.881		

Table 9: LMM outcome for the primary endpoint analyses (PP population)

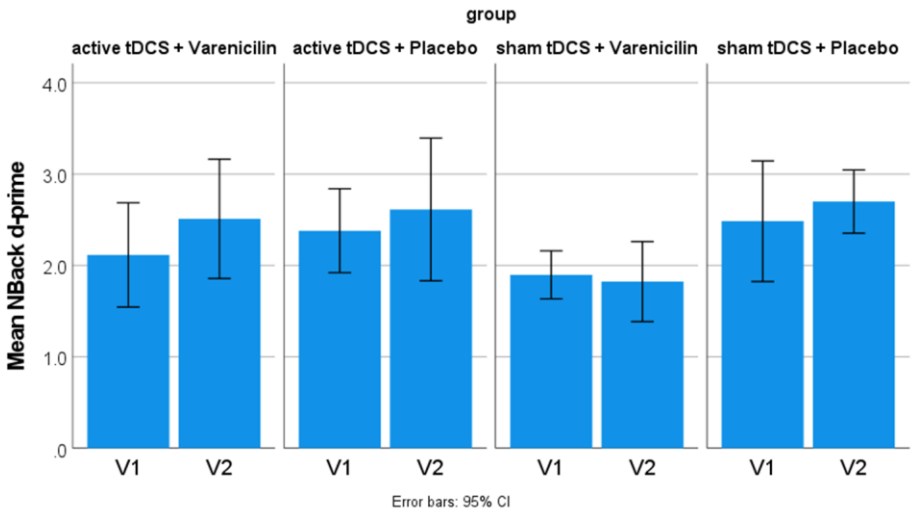


Figure 5: Visualisation of mean dPrime values in the PP population. Error bars refer to 95%CI

Secondary Endpoints

Secondary Endpoints calculated for V1 vs V2 and V1 to V4

The following paragraphs describe the analyses for the secondary endpoints for the V1 vs V2 contrasts. Figures show all available data for all performed visits (V1, V2, V3, V4). For neuropsychology, all n-back associated variables were assessed at four time points, were as all other tests were assessed at visits 1, 2 and 4.

Neuropsychology:

Dprime 1-back: Analyses did not show any significant main effects or interaction regarding the factors group or time (V1/V2 or V1-V4) as detailed in Appendix Tables.

Relative hits 1-back: Nonparametric analyses did not show any significant group or time (V1/V2 or V1-V4) effects (see Appendix).

False alarm 1-back: Nonparametric analyses did show a significant group effect at V2 only (Kruskal-Wallis test: $p = 0.021$, post hoc analyses: group 3 > group 4 ($p = 0.018$, Sidak corrected) and a significant time effect for group 4 only ($p = 0.038$) with no significant post hoc effects (see Appendix).

Criterion c 1-back: Analyses (both analyses Rankit transformed) did not show any significant main effects or interaction regarding the factors group or time (V1/V2 or V1-V4) as detailed in Appendix Tables.

Reaction times 1-back: Analyses (both analyses Rankit transformed) did not show any significant main effects or interaction regarding the factors group or time (V1/V2 or V1-V4) as detailed in Appendix Tables.

Dprime 2-back: Analyses (both analyses Rankit transformed) did not show any significant main effects or interaction regarding the factors group or time (V1/V2 or V1-V4) as detailed in Appendix Tables.

Relative hits 2-back: Analyses did not show any significant main effects or interaction regarding the factors group or time (V1/V2 or V1-V4) as detailed in Appendix Tables.

False alarm 2-back: Analyses (Rankit transformed) did not show any significant main effects or interaction regarding the factors group or time (V1/V2 or V1-V4) as detailed in Appendix Tables.

Criterion c 2-back: Analyses did not show any significant main effects or interaction regarding the factors group or time (V1/V2 or V1-V4) as detailed in Appendix Tables.

Reaction times 2-back: Analyses did not show any significant main effects or interaction regarding the factors group or time (V1/V2 or V1-V4) as detailed in Appendix Tables.

Dprime 3-back: Analyses did not show any significant main effects or interaction regarding the factors group or time (V1/V2 or V1-V4) as detailed in Appendix Tables.

Relative hits 3-back: Analyses did not show any significant main effects or interaction regarding the factors group or time (V1/V2 or V1-V4) as detailed in Appendix Tables.

False alarm 3-back: Analyses (Rankit transformed) did not show any significant main effects or interaction regarding the factors group or time (V1/V2 or V1-V4) as detailed in Appendix Tables.

Criterion C 3-back: Analyses did not show any significant main effects or interaction regarding the factors group or time for V1/V2 but a significant time * group interaction for V1 to V4 ($F_{(9, 17.852)}=0.328$, $p = 0.015$) as detailed in Appendix Tables. Post-hoc Sidak corrected subanalysis

for this interaction showed no significant interaction time (V1 vs V2) * group (p=0.8) or (V1 vs V3) * group (p=0.52), but a significant interaction time (V1 vs V4) * group (0.0355).

Reaction times 3-back: Analyses did not show any significant main effects or interaction regarding the factors group or time for V1/V2 but a significant effect of time ($F_{(3, 19.285)}$ = 3.421, p = 0.038) as detailed in Appendix Tables.

Mean dprime N-back (V1 to V4): Analyses did not show any significant main effects or interaction regarding the factors group or time (V1-V4) as detailed in Appendix Table.

Mean relative hits N-back: Analyses did not show any significant main effects or interaction regarding the factors group or time (V1/V2 or V1-V4) as detailed in Appendix Tables.

Mean relative false alarm rates N-back: Analyses (Rankit transformed) did not show any significant main effects or interaction regarding the factors group or time (V1/V2 or V1-V4) as detailed in Appendix Tables.

Mean criterion C N-back: Analyses did not show any significant main effects or interaction regarding the factors group or time (V1/V2 or V1-V4) as detailed in Appendix Tables.

Mean reaction times N-back: Analyses did not show any significant main effects or interaction regarding the factors group or time (V1/V2 or V1-V4) as detailed in Appendix Tables.

Neuropsychological composite score: Analyses showed for the V1 vs V2 comparison a significant effect of time ($F_{(1, 26.002)}$=16.501, p < 0.001) and a significant time x group interaction ($F_{(3, 25.999)}$=3.164, p = 0.041). However, all following contrasts did not reach significance level. V1 to V4 analyses showed a significant main effect of time ($F_{(2, 17.274)}$=8.466, p = 0.003), but no group effects or interactions. The main effect is explained by an improvement in performance between V2 and V1 (post-hoc test p=0.007, Sidak corrected).

(Verbaler Lern-und Merkfähigkeitstest, VLMT): For VLMT supra span, VLMT 5th trial (Rankit transformed), VLMT 1 to 5, VLMT 7th trial, analyses did not show any significant any significant main effects or interaction regarding the factors group or time (V1/V2 or V1-V4) as detailed in Appendix Tables. VLMT 5 – 7 was tested due to a violation of the assumption of normal distribution with Kruskal-Wallis-Test showing for V1 a significant effect (H=12.4 p = 0.006) with differences between group 3 and 1 (p=0.024), group 3 and 2 (p=0.012) and group 4 and 3 (p=0.059,) Regarding the extension to V4, VLMT 5-7 showed a significant group difference at V4 (H = 0.830, p = 0.040, Sidak corrected post hoc comparisons were non-significant). All other analyses between groups (V2: H=5.299, p = 0.151) and within groups (Wilcoxon) remained non-significant. All analyses for VLMT recognition score (W-F) between groups (V1: H = 5.614, p = 0.132; V2: H = 2.683, p = 0.443, V4: H = 7.699, p = 0.053) and between timepoints (group 1: chi^2 = 1.08, p = 0.584, group 2: chi^2 = 5.33, p = 0.069, group 3: chi^2 = 5.06, p = 0.080, group 4: chi^2 = 5.60, p = 0.061) remained non-significant.

TMT-A and TMT-B: For TMT-A-scores, analyses (Rankit transformed data) did not show any significant main effects or interaction regarding the factors group or time (V1/V2), but a significant effect of time (V1-V4: $F_{(1, 20.736)}$ = 5.425, p = 0.013) as detailed in Appendix Tables. For TMT-B-Scores, analyses (Rankit transformed data) showed a significant effect of time ($F_{(1, 26.487)}$ = 5.521, p = 0.027) for the V1/V2 contrast and the V1-V4 contrast ($F_{(2, 23.350)}$ = 4.441, p = 0.023), but no significant effect of group or interactions between time and group. Analyses of TMT difference B-A (analyses with Rankit transformed data) followed this pattern with significant effects for time (p=0.027) for V1/V2. Please see Appendix tables.

d2 Attention test: The following parameters were analyzed: d2-total number, score D2F (omission errors), score D2F2 (confusion errors), and D2KL (concentration performance). For d2-total number, analyses showed for the V1/V2 contrast a significant effect of time ($F_{(1, 26.354)}$ = 7.866, p = 0.009) without any further main effects of interactions. The same pattern was observed for V1-V4 with a significant main effect of time ($F_{(2, 18.497)}$ = 9.036, p = 0.002). For D2F and D2F2 (both Rankit transformed), no significant group or time effects could be observed.

For D2KL, a significant effect of time ($F_{(1, 25.860)}$ = 15.436, p = 0.001) and a significant time x group interaction ($F_{(3, 25.761)}$ = 3.012, p = 0.048) was revealed for the V1/V2 contrast. However, all subsequent post-hoc comparisons did not reach significance level for this analysis. A related pattern was observed for the V1 to V4 analyses with a significant effect of time ($F_{(2, 18.131)}$ = 10.759, p = 0.001) and a significant time x group interaction ($F_{(6, 18.078)}$ = 2.765, p = 0.044, post hoc: V1 vs V2: p = 0.005, V1 vs V4: p =0.060, Sidak corrected).

Figure 6 shows the visualization of different n-back parameters for every load separately. Error bars indicate 95% confidence intervals.

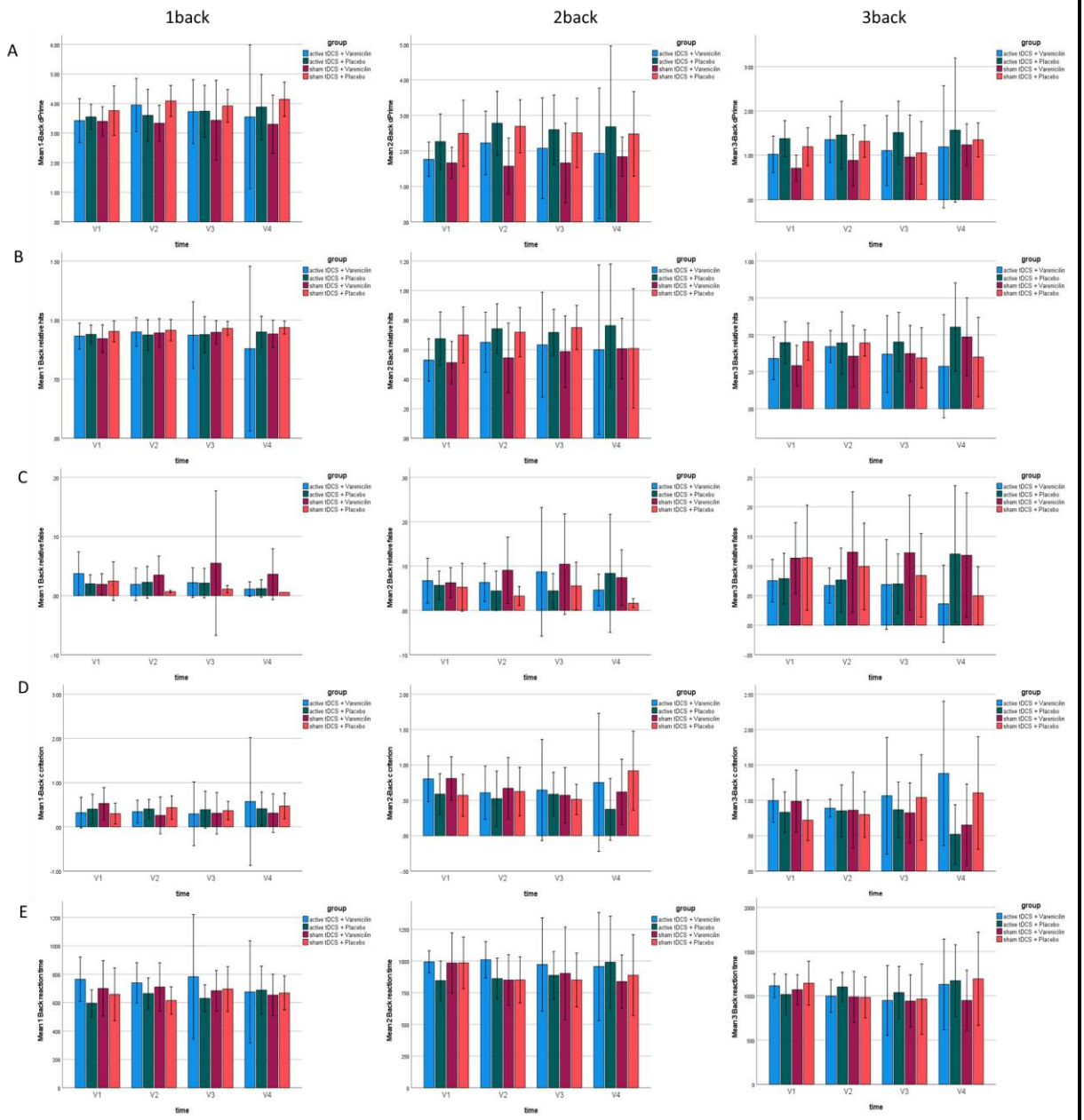


Figure 6: Visualization of different n-back parameters. A: dPrime, B: relative hits, C: false alarm rate, D: criterion C, E: reaction times. Error bars show 95%CI.

Figure 7 shows the visualization for different nBack parameters derived from the meannBack values. Figure 8 presents the data of other neurocognitive measures. Error bars indicate 95% confidence intervals.

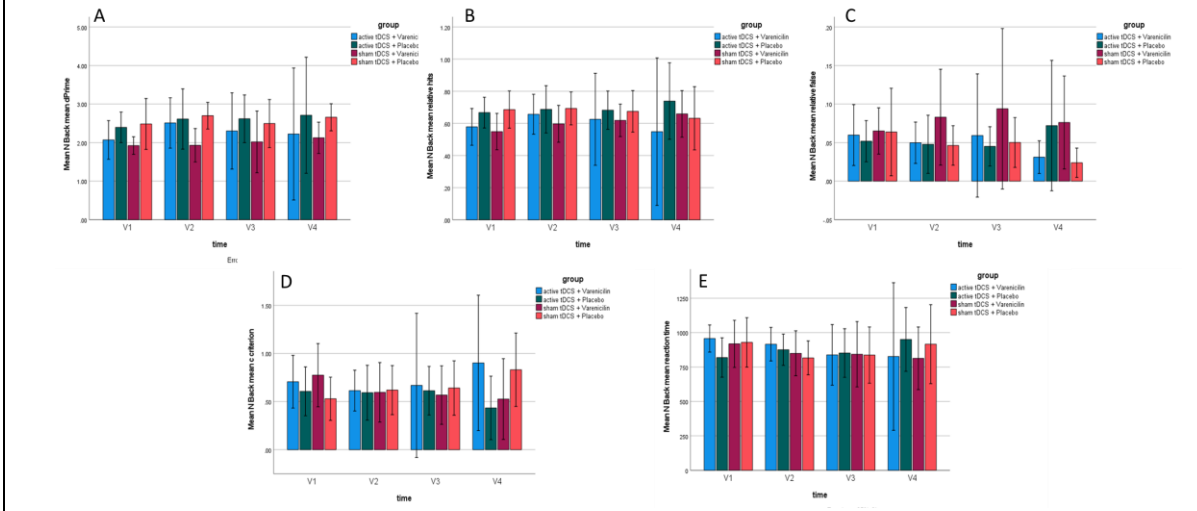


Figure 7: Visualization of mean n-back parameters. A: dPrime, B: relative hits, C: false alarm rate, D: criterion C, E: reaction times. Error bars show 95% CI

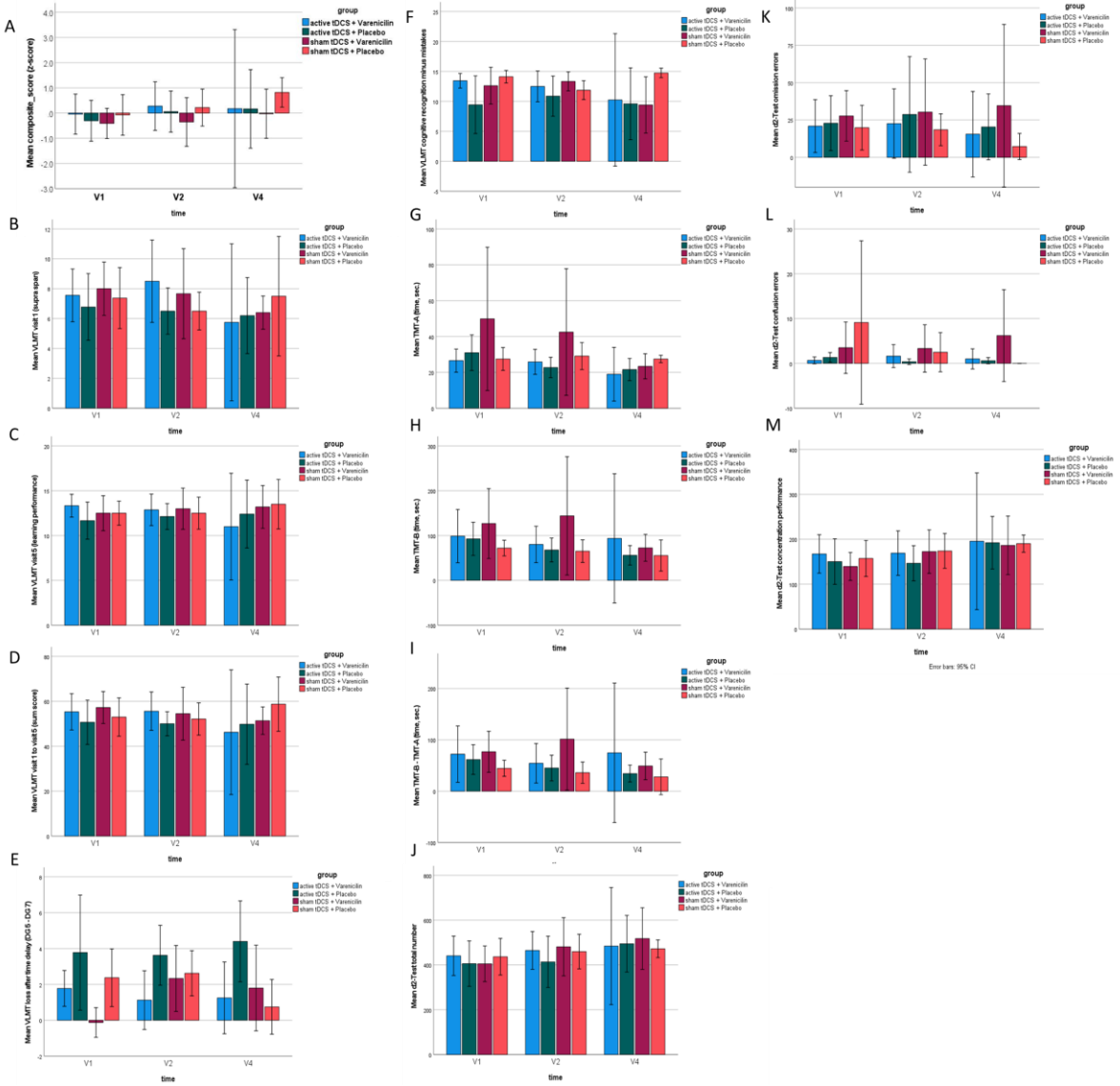


Figure 8: Visualization of various secondary cognitive outcomes as described in the main text: A: composite score; B: VLMT supra span; C: VLMT 5th trial, D: VLMT 1-5; E: VLMT: 5-7; F: VLTM W-F (recognition score); G: TMT A time; H: TMT B time; I: TMT B-A time; J: total D2 number; K: D2F score; L: D2F2 and M: D2KL. Error bars show 95% CI

Psychopathology, Depression, Severeness of the Disease and Functioning:

GAF: Analyses showed no significant main effects or interaction regarding the factors group or time (V1/V2), but a significant time effect for the V1-V4 analysis ($F_{(3, 16.269)} = 6.268$, $p = 0.005$, post hoc analyses: V1 vs V4: $p = 0.011$ (Sidak corrected)) as detailed in Appendix Tables. Please see figure 9 for the visualization.

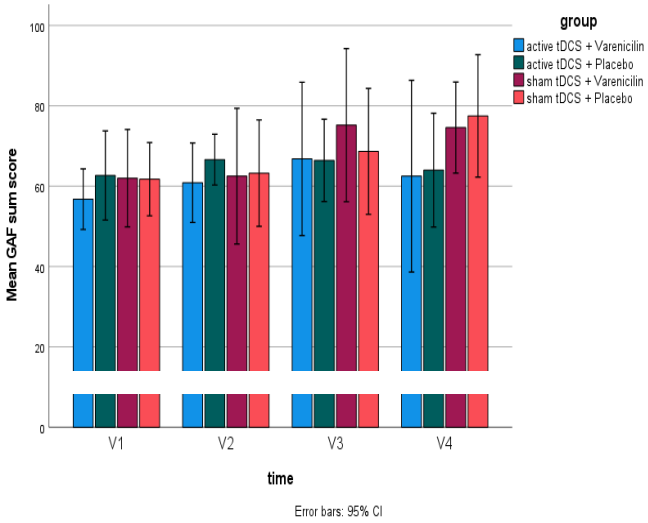


Figure 7: Mean GAF values over all visits. Error bars show 95%CI.

CDSS: Analyses (Rankit transformed data) did not show any significant main effects or interaction regarding the factors group or time (V1/V2 or V1-V4) as detailed in Appendix Tables. Please see figure 10 for the visualization.

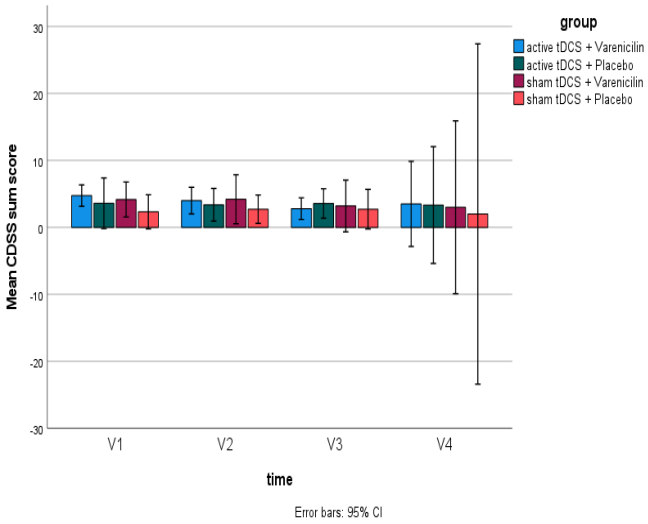


Figure 8: Mean CDSS values over all visits.. Error bars show 95%CI.

CGI: This variable was tested with non-parametric tests showing no differences between group for all evaluated time points (Kruskal-Wallis tests: V1: $H = 0.097$, $p = 0.992$; V3: $H = 1.864$, $p = 0.601$ and V4: $H = 4.660$, $p = 0.198$). Within-subject tests (factor time) with Friedman tests remained non-significant as well. Please see figure 11 for the visualization.

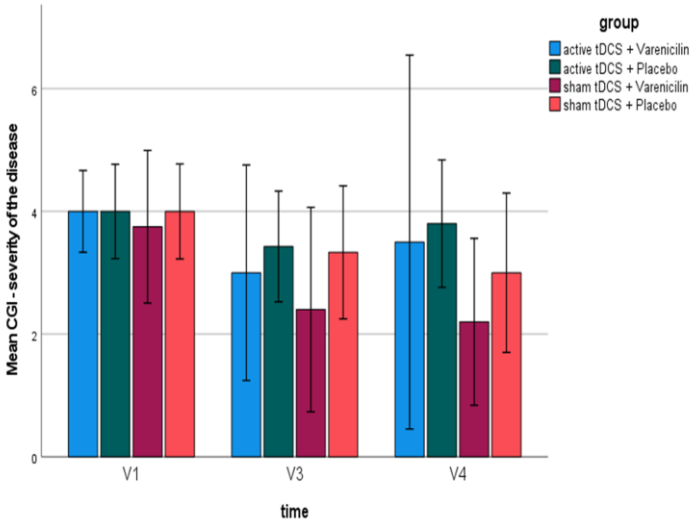


Figure 9: Mean CGI values over all visits. Error bars show 95%CI.

PANSS: PANSS positive, PANSS negative, PANSS general and PANSS total were analyzed. As several unspecific time effects without any time x group interaction or main effect of group were observed, we refer to the Appendix tables regarding the detailed test statistics. In short, for the V1/V2 analyses significant effects were shown for PANSS positive (p = 0.008), PANSS negative (p = 0.017) and PANSS total (p = 0.006). For V1 to V4 analyses significant effects were shown for PANSS positive (p = 0.008), PANSS general (p = 0.005) and PANSS total (p = 0.004). Please see figure 12 for the visualization.

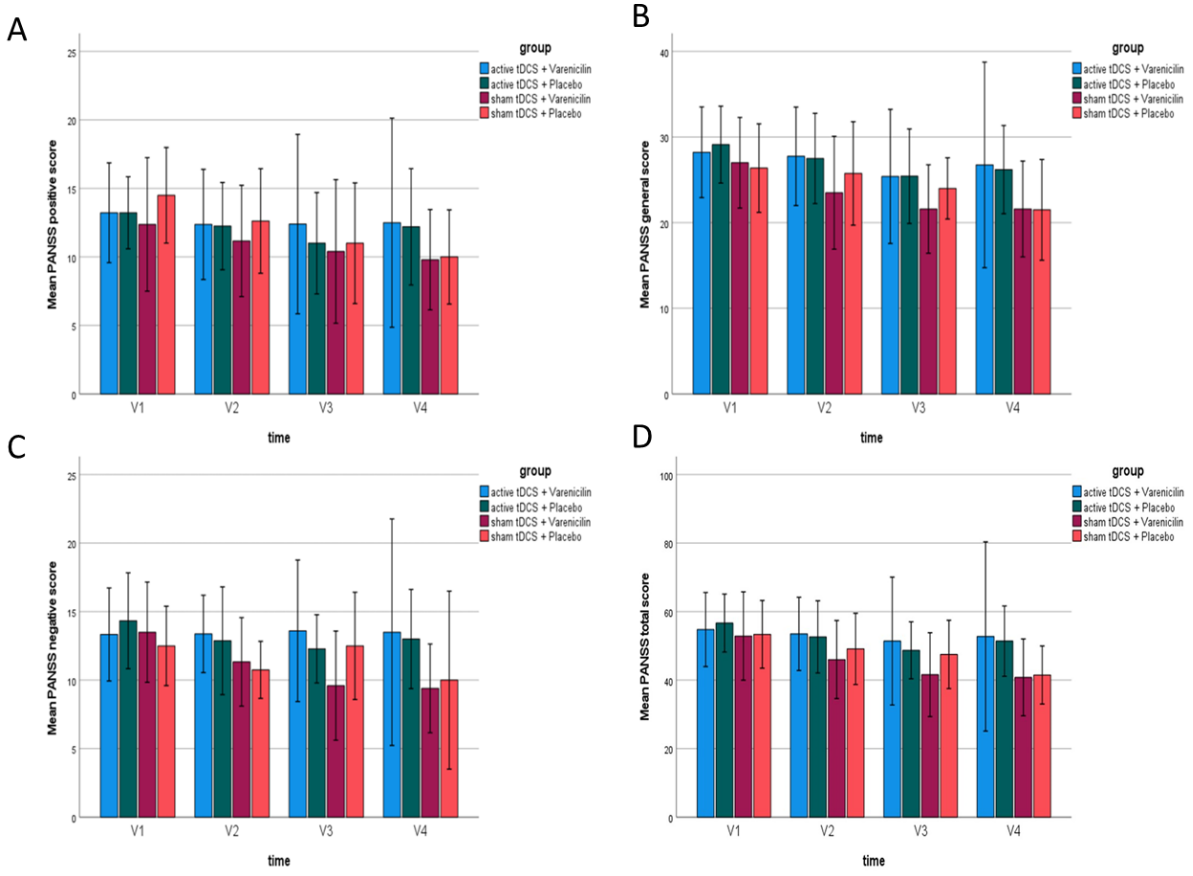


Figure 10: Mean PANSS values over all visits. A: PANSS positive, B: PANSS general, C: PANSS negative, D: PANSS total. Error bars show 95%CI

Further analyses

Next, an analysis with pooled tDCS data (yes/no) and pooled varenicline data (yes/no) was performed for the primary outcome variable. V1/V2: For the analysis comparing patients with and without tDCS, a significant effect of time ($F_{(1, 28.020)}$ = 5.319, p = 0.029), but no group effect ($F_{(1, 28.491)}$ = 0.647, p = 0.647) or time x group interaction ($F_{(1, 28.017)}$ = 1.426, p = 0.242) were observed (see Figure 13).

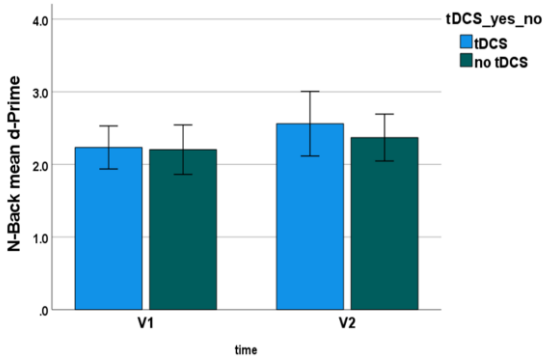


Figure 11: Pooled analysis of primary outcome variable with tDCS yes/no as grouping variable. Error baris show 95% CI

The analysis comparing patients with and without varenicline showed a significant effect of time ($F_{(1, 28.044)}$ = 5.393, p = 0.028), but no significant group effect ($F_{(1, 29.051)}$ = 3.440, p = 0.0754) or time x group interaction ($F_{(1, 28.043)}$ = 0.011, p = 0.911) (see Figure 14).

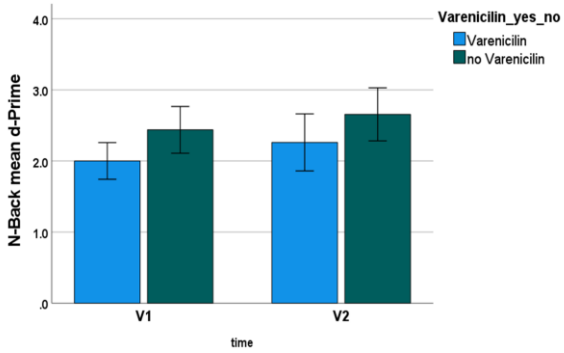


Figure 12: Pooled analysis of primary outcome variable with varenicline yes/no as grouping variable. Error baris show 95% CI

Cotinine: Analyses did not show a significant effect of time or group and no significant time x group interaction. Please see Appendix Tables and Figure 15.

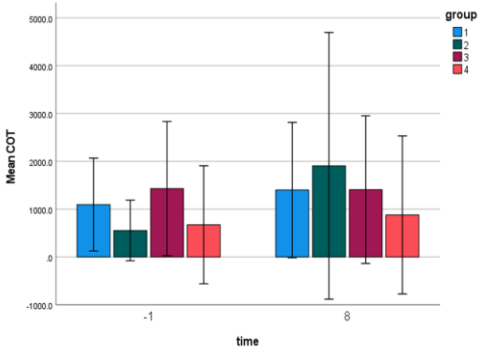


Figure 13: Cotinine levels during across groups. Error bars show 95% CI

Fagerström-Assessement and number of cigarettes:

For the V1/V2 and V1 to V 4 analyses (both: Linear Mixed Model (LMM), smoking (V1 vs. V2) (no covariates, diagonal covariance matrix the sample size was too small, LMM with unstructured covariance matrix and with covariates was therefore not possible), significant group effects were observed for the Fagerström assessment (Rankit) and cigarettes as detailed in the Appendix Tables. As presented in Figure 16, these group differences were already present at baseline. Due tot the limited data, these analyses should be interpreted with caution. Please see Figure 16 for visualization.

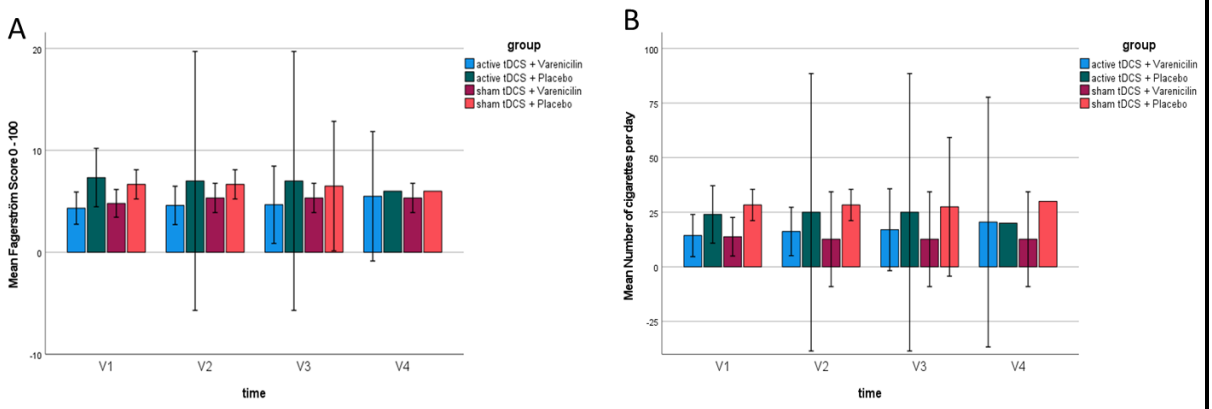


Figure 14: A: Fagerström values and B: number of cigarettes/day. Error bars show 95% CI

Overall Conclusion:

The clinical trial was prematurely discontinued after recruiting 34 patients due to unavailability of IMP and uncertainty, when and if IMP would be available again. Recruitment was delayed since April 2020 to the limitations of the SarsCov2-pandemic. In the end, only 34 out of 60 planned patients (57%) could be recruited. No relevant between-group differences could be shown with respect to the primary and the secondary endpoints. Thus, the trial must be considered as negative. Subtle differences over time in cognitive outcomes can be explained by learning effects independent from the respective study groups and are yet unspecific. Also, subtle differences in some psychopathological outcomes over time with no group differences can be led back to unspecific factors of participating in a clinical trial.

Reported AE/SAE were in accordance with the known safety profile of the intervention in this patient population and did not show any relationship to our study groups. Both SAE occurred in the placebo/sham tDCS group and can be explained by the main condition of schizophrenia.

In conclusion, this study provides no evidence that combining varenicline with tDCS over 5 days (two interventions per day) is superior to varenicline alone, tDCS alone or a complete placebo condition.

21. **Date of report:**

Date: 25.11.2022 **Signature:** _____

SDP: Prof. P. Falkai

Date: 25.11.2022 **Signature:** _____

SDP until 30.01.2021: Prof. A. Hasan

APPENDIX

Table 1 Demographics and Baseline Characteristics (A: ITT-Population, B: PP-Population)

A

	Group 1 (active tDCS + Varenicline)						Group 2 (actoive tDCS + Placebo)						Group 3 (sham tDCS + Varenicline)						Group 4 (sham tDCS + Placebo)						Group comparison		
	number						number						number						number						F-H	df	p
Gender (male / female)	7/2						6/3						3/5						7/1						4.723		0.192
	n	m	sd	M	min	max	n	m	sd	M	min	max	n	m	sd	M	min	max	n	m	sd	M	min	max	F	df	p
Age (years)	9	41.22	10.24	41	24	59	9	34.11	10.98	34	20	55	8	36.63	13.49	33	22	56	8	35.50	12.11	36	21	57	0.620	3, 30	0.608
Education (years)	9	12.44	1.13	13	10	14	9	12.33	1.22	13	10	14	8	11.63	2.56	11	9	16	8	11.50	1.93	11.5	9	14	0.627	3, 30	0.603
Weight (kg)	8	84.90	24.78	82.5	53.5	120	8	73.38	13.50	72.5	50	93	8	80.26	16.33	82.3	51	98	7	95.26	10.92	92	83	115	2.076	3, 27	0.127
Height (cm)	8	178.4	11.61	175.5	165	198	8	175.5	10.03	179.5	158	186	8	167.9	7.99	170	150	176	7	181.6	7.14	180	171	193	2.957	3, 27	0.0502
Body mass index	8	26.3	5.63	24.1	19.7	36.4	8	23.82	4.00	22.7	18.6	30.1	8	28.33	4.78	27.7	22.7	35.1	7	29.09	4.59	26.9	24.7	36.3	1.856	3, 27	0.161

B

	Group 1 (active tDCS + Varenicline)						Group 2 (actoive tDCS + Placebo)						Group 3 (sham tDCS + Varenicline)						Group 4 (sham tDCS + Placebo)						Group comparison		
	number						number						number						number						F-H	df	p
Gender (male / female)	6/2						5/3						2/3						7/1						3.391		0.352
	n	m	sd	M	min	max	n	m	sd	M	min	max	n	m	sd	M	min	max	n	m	sd	M	min	max	F	df	p
Age (years)	8	43.38	8.50	42	33	59	8	35.25	11.16	35	20	55	5	32.20	13.22	27	22	54	8	35.50	12.11	36	21	57	1.297	3, 25	0.297
Education (years)	8	12.25	1.04	12.5	10	13	8	12.25	1.28	12.5	10	14	5	11.80	2.95	12	9	16	8	11.50	1.93	11.5	9	14	0.331	3, 25	0.803
Weight (kg)	7	84.17	26.67	75	53.5	120	7	72.71	14.44	70	50	93	5	77.10	17.30	82	51	98	7	95.26	10.92	92	83	115	1.947	3, 22	0.151
Height (cm)	7	176.3	10.80	174	165	198	7	174.0	9.82	179	158	185	5	168.2	10.40	172	150	176	7	181.6	7.14	180	171	193	1.981	3, 22	0.146
Body mass index	7	26.6	6.01	23.9	19.7	36.4	7	24.00	4.29	22.7	18.6	30.1	5	27.04	4.49	27.6	22.7	33.9	7	29.09	4.59	26.9	24.7	36.3	1.255	3, 22	0.914

Table 2: Detailed secondary outcome analyses

Analyses for 1-back dPrime V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.355	7.480	0.011
time	1	26.736	1.509	0.230
group	3	26.308	1.007	0.405
Sex	1	26.178	0.530	0.473
Age	1	27.096	0.438	0.514
School_Education	1	26.305	0.904	0.350
time * group	3	26.639	0.761	0.526

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	25.899	6.448	0.017
time	3	11.770	0.634	0.607
group	3	17.612	0.720	0.553
Sex	1	23.726	0.243	0.626
Age	1	26.283	0.057	0.813
School_Education	1	24.944	1.020	0.322
time * group	9	12.021	0.527	0.829

Analyses for 1-back relative hits

time	group	Mean	N
V1	active tDCS + Varenicilin	0.8648	9
	active tDCS + Placebo	0.8796	9
	sham tDCS + Varenicilin	0.8438	8
	sham tDCS + Placebo	0.9042	8
	Total	0.8730	34
V2	active tDCS + Varenicilin	0.9000	8
	active tDCS + Placebo	0.8750	8
	sham tDCS + Varenicilin	0.8917	6
	sham tDCS + Placebo	0.9146	8
	Total	0.8956	30
V3	active tDCS + Varenicilin	0.8733	5
	active tDCS + Placebo	0.8786	7
	sham tDCS + Varenicilin	0.8967	5
	sham tDCS + Placebo	0.9306	6
	Total	0.8949	23
V4	active tDCS + Varenicilin	0.7583	4
	active tDCS + Placebo	0.9000	5
	sham tDCS + Varenicilin	0.8833	5
	sham tDCS + Placebo	0.9375	4
	Total	0.8722	18

Nonparametric analyses did not show any significant group or time (V1/V2 or V1-V4) effects. Factor group: Kruskal-Wallis tests (V1, V2, V3, V4): all $H < 1.6$, $p > 0.67$. Factor time: Friedman tests (groups 1 to 4): all $Chi^2 < 5.4$, all $p > 0.15$.

Analyses for 1-back false alarms

V1	active tDCS + Varenicilin	0.0372	9
	active tDCS + Placebo	0.0201	9
	sham tDCS + Varenicilin	0.0192	8
	sham tDCS + Placebo	0.0247	8
	Total	0.0255	34
V2	active tDCS + Varenicilin	0.0192	8
	active tDCS + Placebo	0.0227	8
	sham tDCS + Varenicilin	0.0348	6
	sham tDCS + Placebo	0.0069	8
	Total	0.0200	30
V3	active tDCS + Varenicilin	0.0220	5
	active tDCS + Placebo	0.0212	7
	sham tDCS + Varenicilin	0.0549	5
	sham tDCS + Placebo	0.0110	6
	Total	0.0260	23
V4	active tDCS + Varenicilin	0.0110	4
	active tDCS + Placebo	0.0121	5
	sham tDCS + Varenicilin	0.0363	5
	sham tDCS + Placebo	0.0055	4
	Total	0.0171	18

False alarm 1-back: Nonparametric analyses did show a significant group effect at V2 (Kruskal-Wallis test: $p = 0.021$, group 3 > group 4 ($p = 0.018$, Sidak corrected). For all other visits (V1, V3, V4) there were no significant group effects (Kruskal-Wallis test: all $H < 6.1$, $p > 0.11$). Further, there was a significant time effect for group 4 only ($p = 0.038$) with no significant post hoc effects. For all other groups (1, 2, 3) there were no significant time effects (Friedman tests: all $Chi^2 < 4.0$, $p > 0.26$).

Analyses for 1-back criterion C (Rankit transformed) V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	24.310	0.095	0.761
time	1	28.213	0.028	0.869
group	3	26.420	0.404	0.751
Sex	1	24.010	7.523	0.011
Age	1	25.928	0.231	0.635
School_Education	1	24.271	0.206	0.654
time * group	3	28.107	2.321	0.097

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	25.022	0.000	0.983
time	3	21.944	0.200	0.895
group	3	21.750	0.195	0.899
Sex	1	23.018	10.825	0.003
Age	1	25.911	0.156	0.696
School_Education	1	24.493	0.000	0.991
time * group	9	21.932	1.034	0.445

Analyses for 1-back reaction times (Rankit transformed) V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	24.095	1.481	0.235
time	1	27.438	0.678	0.417
group	3	25.311	1.611	0.212
Sex	1	23.908	7.028	0.014
Age	1	25.845	0.636	0.433
School_Education	1	24.168	2.773	0.109
time * group	3	27.289	0.922	0.443

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	24.518	1.137	0.297
time	3	18.625	1.380	0.280
group	3	20.786	0.610	0.616
Sex	1	23.269	10.808	0.003
Age	1	25.853	1.032	0.319
School_Education	1	24.300	2.306	0.142
time * group	9	18.859	1.404	0.255

Analyses for 2-back dPrime (Rankit transformed) V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	27.184	0.012	0.915
time	1	26.098	2.710	0.112
group	3	26.595	1.816	0.168
Sex	1	27.007	0.000	0.990
Age	1	27.069	4.011	0.055
School_Education	1	27.016	1.042	0.316
time * group	3	26.092	1.208	0.326

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	28.193	0.174	0.680
time	3	18.361	1.039	0.399
group	3	21.771	1.697	0.197
Sex	1	25.991	0.009	0.927
Age	1	27.648	3.133	0.088
School_Education	1	27.321	1.632	0.212
time * group	9	18.375	0.642	0.748

Analyses for 2-back relative hits V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.268	0.150	0.701
time	1	27.500	1.790	0.192
group	3	26.713	2.170	0.115
Sex	1	26.104	0.025	0.875
Age	1	27.415	0.013	0.908
School_Education	1	26.285	4.702	0.039
time * group	3	27.372	0.575	0.636

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.308	0.120	0.732
time	3	20.021	0.607	0.618
group	3	17.598	1.953	0.158
Sex	1	21.322	0.001	0.975
Age	1	25.834	0.130	0.721
School_Education	1	24.989	5.391	0.029
time * group	9	20.006	0.418	0.910

Analyses for 2-back false alarm (Rankit transformed) V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.548	3.658	0.067
time	1	27.402	1.068	0.310
group	3	26.736	0.545	0.656
Sex	1	26.386	0.920	0.346
Age	1	27.557	3.156	0.087
School_Education	1	26.551	2.081	0.161
time * group	3	27.286	1.173	0.338

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	27.331	2.767	0.108
time	3	15.612	0.816	0.504
group	3	22.394	0.720	0.551
Sex	1	24.970	0.322	0.575
Age	1	27.571	3.152	0.087
School_Education	1	26.614	1.322	0.260
time * group	9	16.216	0.862	0.575

Analyses for 2-back criterion C V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	25.067	14.829	0.001
time	1	26.913	0.694	0.412
group	3	25.438	0.983	0.416
Sex	1	24.882	0.179	0.676
Age	1	26.456	0.838	0.368
School_Education	1	25.096	6.567	0.017
time * group	3	26.760	0.429	0.734

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.110	16.924	0.000
time	3	18.006	0.395	0.758
group	3	19.419	1.270	0.312
Sex	1	19.502	0.005	0.946
Age	1	24.796	2.101	0.160
School_Education	1	24.194	5.730	0.025
time * group	9	18.132	1.118	0.399

Analyses for 2-back reaction times V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	25.666	21.306	0.000
time	1	27.201	1.657	0.209
group	3	25.860	2.083	0.127
Sex	1	25.480	6.916	0.014
Age	1	26.941	1.106	0.302
School_Education	1	25.679	0.222	0.642
time * group	3	27.055	0.989	0.413

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	27.402	25.304	0.000
time	3	19.198	0.596	0.625
group	3	21.416	1.016	0.405
Sex	1	24.800	7.114	0.013
Age	1	27.879	0.729	0.400
School_Education	1	26.557	0.797	0.380
time * group	9	19.137	0.574	0.802

Analyses for 3-back dPrime V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.617	1.820	0.189
time	1	26.201	2.328	0.139
group	3	26.429	1.843	0.164
Sex	1	26.419	0.089	0.768
Age	1	26.896	0.487	0.491
School_Education	1	26.484	0.309	0.583
time * group	3	26.146	0.139	0.936

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	21.161	0.205	0.655
time	3	22.992	1.307	0.296
group	3	26.748	1.408	0.262
Sex	1	13.389	1.077	0.318
Age	1	18.240	1.684	0.211
School_Education	1	18.175	1.890	0.186
time * group	9	24.052	0.879	0.556

Analyses for 3-back relative hits V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	25.987	0.034	0.856
time	1	26.094	0.513	0.480
group	3	25.831	1.433	0.256
Sex	1	25.877	0.602	0.445
Age	1	26.603	0.521	0.477
School_Education	1	25.976	2.854	0.103
time * group	3	26.011	0.335	0.800

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.537	0.063	0.803
time	3	19.636	1.293	0.305
group	3	25.356	2.076	0.129
Sex	1	25.326	0.520	0.477
Age	1	26.873	0.231	0.635
School_Education	1	26.259	3.533	0.071
time * group	9	20.218	2.210	0.067

Analyses for 3-back false alarm (Rankit transformed) V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.163	3.031	0.093
time	1	26.162	1.348	0.256
group	3	25.955	0.999	0.409
Sex	1	26.040	0.302	0.587
Age	1	26.712	3.459	0.074
School_Education	1	26.132	1.385	0.250
time * group	3	26.085	0.068	0.976

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.743	3.197	0.085
time	3	16.419	0.700	0.565
group	3	23.400	0.974	0.422
Sex	1	24.221	0.308	0.584
Age	1	26.940	3.954	0.057
School_Education	1	25.625	1.275	0.269
time * group	9	16.436	1.885	0.127

Analyses for 3-back criterion C V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	24.845	14.555	0.001
time	1	25.488	0.238	0.630
group	3	25.088	1.121	0.359
Sex	1	24.727	0.964	0.336
Age	1	25.748	2.916	0.100
School_Education	1	24.865	3.188	0.086
time * group	3	25.370	0.334	0.801

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	25.123	15.395	0.001
time	3	17.677	0.883	0.469
group	3	22.270	2.502	0.085
Sex	1	24.163	0.813	0.376
Age	1	25.759	2.452	0.130
School_Education	1	24.825	3.584	0.070
time * group	9	17.852	3.284	0.015

Analyses for 3-back reaction times V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.926	22.286	0.000
time	1	27.655	2.264	0.144
group	3	27.293	0.513	0.677
Sex	1	26.748	4.503	0.043
Age	1	27.832	2.243	0.145
School_Education	1	26.898	0.491	0.490
time * group	3	27.545	1.284	0.299

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	27.594	22.982	0.000
time	3	19.285	3.421	0.038
group	3	27.526	0.341	0.796
Sex	1	27.010	4.935	0.035
Age	1	28.206	2.119	0.156
School_Education	1	27.268	0.730	0.400
time * group	9	21.336	1.257	0.315

Analysis for mean N-back dPrime V1 to V4

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	27.308	5.087	0.032
time	3	15.465	1.994	0.157
group	3	24.236	1.544	0.229
Sex	1	26.776	0.011	0.916
Age	1	27.085	1.720	0.201
School_Education	1	26.948	1.358	0.254
time * group	9	15.373	0.656	0.735

Analyses for mean N-back relative hits V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.349	1.951	0.174
time	1	26.063	1.623	0.214
group	3	25.983	1.894	0.155
Sex	1	26.251	0.010	0.922
Age	1	26.748	0.053	0.819
School_Education	1	26.320	4.140	0.052
time * group	3	26.006	0.549	0.653

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.606	1.738	0.199
time	3	19.687	0.827	0.495
group	3	22.112	1.704	0.195
Sex	1	25.820	0.053	0.819
Age	1	26.687	0.080	0.779
School_Education	1	26.273	4.324	0.047
time * group	9	19.745	0.708	0.695

Analyses for mean N-back false alarm rate (Rankit transformed) V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	25.939	3.788	0.063
time	1	26.129	2.766	0.108
group	3	25.873	0.584	0.631
Sex	1	25.828	0.000	0.996
Age	1	26.600	4.414	0.045
School_Education	1	25.934	1.675	0.207
time * group	3	26.041	0.508	0.680

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	27.156	3.466	0.073
time	3	19.440	1.280	0.309
group	3	23.648	0.589	0.628
Sex	1	23.921	0.000	0.999
Age	1	27.114	6.009	0.021
School_Education	1	26.191	1.011	0.324
time * group	9	19.751	0.990	0.479

Analyses for mean N-back criterion C V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	24.505	13.179	0.001
time	1	25.887	0.097	0.758
group	3	25.627	0.776	0.518
Sex	1	24.355	0.098	0.757
Age	1	25.730	1.955	0.174
School_Education	1	24.540	3.817	0.062
time * group	3	25.739	0.948	0.432

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	25.026	14.463	0.001
time	3	20.288	0.684	0.572
group	3	23.542	1.102	0.368
Sex	1	22.472	0.382	0.543
Age	1	25.476	2.816	0.106
School_Education	1	24.555	3.784	0.063
time * group	9	23.713	1.816	0.118

Analyses for mean N-back reaction times V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	25.772	33.547	0.000
time	1	27.962	1.861	0.183
group	3	26.677	1.368	0.274
Sex	1	25.594	7.234	0.012
Age	1	27.292	0.545	0.467
School_Education	1	25.826	1.278	0.269
time * group	3	27.807	1.556	0.222

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.946	30.866	0.000
time	3	19.718	1.320	0.296
group	3	27.574	0.159	0.923
Sex	1	25.809	9.029	0.006
Age	1	28.114	0.199	0.659
School_Education	1	26.631	0.943	0.340
time * group	9	19.657	1.538	0.203

Analyses for the neuropsychological composite score V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.993	3.279	0.081
time	1	26.002	16.501	0.000
group	3	26.901	0.329	0.805
sex	1	26.963	0.076	0.785
age	1	26.988	0.755	0.392
school_education	1	26.967	6.015	0.021
time * group	3	25.999	3.164	0.041

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	25.326	3.535	0.072
time	2	17.274	8.466	0.003
group	3	24.992	0.221	0.881
sex	1	18.344	0.884	0.359
age	1	23.714	1.630	0.214
school_education	1	23.737	7.459	0.012
time * group	6	17.018	2.210	0.093

Analyses for the VLMT supraspan score V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	24.518	0.069	0.794
time	1	28.208	0.084	0.774
group	3	25.570	1.276	0.304
Sex	1	24.334	6.865	0.015
Age	1	26.288	0.003	0.959
School_Education	1	24.598	15.177	0.001
time * group	3	28.076	0.715	0.551

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	25.179	0.068	0.796
time	2	19.236	2.885	0.080
group	3	20.139	0.643	0.596
Sex	1	22.018	8.910	0.007
Age	1	25.718	0.361	0.553
School_Education	1	24.670	13.101	0.001
time * group	6	19.122	0.828	0.563

Analyses for the VLMT 5th trial V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	25.376	4.276	0.049
time	1	26.590	0.011	0.918
group	3	25.888	0.510	0.679
Sex	1	25.227	0.084	0.775
Age	1	26.526	0.047	0.829
School_Education	1	25.404	6.312	0.019
time * group	3	26.452	0.536	0.662

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	25.624	4.723	0.039
time	2	18.480	0.303	0.743
group	3	18.219	0.351	0.789
Sex	1	23.197	0.529	0.474
Age	1	25.978	0.075	0.787
School_Education	1	25.126	6.968	0.014
time * group	6	18.341	0.654	0.687

Analyses for the VLMT 1 to 5 V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	24.529	2.982	0.097
time	1	27.762	0.483	0.493
group	3	26.490	1.008	0.405
Sex	1	24.323	2.879	0.103
Age	1	26.234	0.096	0.759
School_Education	1	24.580	15.342	0.001
time * group	3	27.616	0.486	0.695

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	24.763	2.404	0.134
time	2	18.427	2.179	0.141
group	3	17.665	0.639	0.600
Sex	1	23.050	2.344	0.139
Age	1	25.819	0.284	0.599
School_Education	1	24.401	16.857	0.000
time * group	6	18.309	0.849	0.549

Analyses for the VLMT 7th trial V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	23.552	0.951	0.339
time	1	26.867	0.378	0.544
group	3	25.333	3.768	0.023
Sex	1	23.356	0.768	0.390
Age	1	25.285	0.226	0.639
School_Education	1	23.615	6.600	0.017
time * group	3	26.717	1.551	0.224

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	23.449	0.435	0.516
time	2	19.569	0.308	0.739
group	3	12.811	3.144	0.062
Sex	1	20.244	1.910	0.182
Age	1	24.027	0.006	0.938
School_Education	1	22.935	7.684	0.011
time * group	6	19.444	1.249	0.325

Analyses for the VLMT recognition score (W-F)

time		Mean	N
V1	active tDCS + Varenicilin	13.44	9
	active tDCS + Placebo	9.44	9
	sham tDCS + Varenicilin	12.63	8
	sham tDCS + Placebo	14.13	8
	Total	12.35	34
V2	active tDCS + Varenicilin	12.50	8
	active tDCS + Placebo	10.88	8
	sham tDCS + Varenicilin	13.33	6
	sham tDCS + Placebo	11.88	8
	Total	12.07	30
V4	active tDCS + Varenicilin	10.25	4
	active tDCS + Placebo	9.60	5
	sham tDCS + Varenicilin	9.40	5
	sham tDCS + Placebo	14.75	4
	Total	10.83	18
Total	active tDCS + Varenicilin	12.48	21
	active tDCS + Placebo	10.00	22
	sham tDCS + Varenicilin	12.00	19
	sham tDCS + Placebo	13.35	20
	Total	11.91	82

Nonparametric analysis for VLMT recognition score (W-F) showed no significant differences between groups (V1: H = 5.614, p = 0.132; V2: H = 2.683, p = 0.443, V4: H = 7.699, p = 0.053) nor between timepoints (group 1: chi^2 = 1.08, p = 0.584, group 2: chi^2 = 5.33, p = 0.069, group 3: chi^2 = 5.06, p = 0.080, group 4: chi^2 = 5.60, p = 0.061).

Analyses for the TMT-A scores V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.524	1.011	0.324
time	1	27.261	2.941	0.098
group	3	26.791	1.284	0.300
Sex	1	26.363	0.063	0.804
Age	1	27.445	1.433	0.241
School_Education	1	26.513	2.663	0.115
time * group	3	27.148	2.015	0.135

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	28.049	1.577	0.220
time	2	20.736	5.425	0.013
group	3	25.183	1.313	0.292
Sex	1	23.886	0.205	0.655
Age	1	27.900	1.078	0.308
School_Education	1	27.339	3.826	0.061
time * group	6	20.734	2.438	0.061

Analyses for the TMT-B scores V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.982	3.171	0.086
time	1	26.487	5.521	0.027
group	3	27.356	1.107	0.363
Sex	1	26.875	0.012	0.912
Age	1	27.255	0.009	0.924
School_Education	1	26.928	3.769	0.063
time * group	3	26.444	0.790	0.510

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	27.063	2.934	0.098
time	2	23.350	4.441	0.023
group	3	26.603	1.125	0.357
Sex	1	26.871	0.012	0.913
Age	1	27.254	0.009	0.926
School_Education	1	26.927	3.799	0.062
time * group	6	26.378	1.674	0.167

Analyses for the TMT B-A scores V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	27.031	3.976	0.056
time	1	26.280	5.485	0.027
group	3	27.436	1.191	0.332
Sex	1	26.902	0.026	0.874
Age	1	27.140	0.586	0.450
School_Education	1	26.936	3.620	0.068
time * group	3	26.253	0.579	0.634

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	27.151	3.167	0.086
time	2	21.112	3.136	0.064
group	3	24.154	1.904	0.156
Sex	1	25.610	0.003	0.955
Age	1	26.893	0.513	0.480
School_Education	1	26.725	3.111	0.089
time * group	6	21.215	1.097	0.396

Analyses for d2-total number V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.048	5.472	0.027
time	1	26.354	7.866	0.009
group	3	26.331	0.278	0.841
Sex	1	25.945	2.386	0.135
Age	1	26.779	0.491	0.489
School_Education	1	26.060	0.569	0.457
time * group	3	26.261	0.816	0.497

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.113	5.916	0.022
time	2	18.497	9.036	0.002
group	3	25.006	0.185	0.906
Sex	1	25.798	2.424	0.132
Age	1	26.766	0.480	0.494
School_Education	1	26.061	0.546	0.466
time * group	6	18.512	2.379	0.071

Analyses for D2F (omission errors) V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	27.060	2.154	0.154
time	1	26.486	0.000	0.998
group	3	27.528	0.188	0.903
Sex	1	26.957	0.149	0.702
Age	1	27.288	0.107	0.746
School_Education	1	27.003	3.453	0.074
time * group	3	26.449	0.278	0.841

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.961	2.538	0.123
time	2	21.479	0.306	0.740
group	3	25.319	0.367	0.777
Sex	1	23.892	0.170	0.684
Age	1	26.538	0.000	0.996
School_Education	1	26.363	3.568	0.070
time * group	6	22.628	0.698	0.654

Analyses for D2F2 (confusion errors) V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	25.890	1.448	0.240
time	1	27.133	2.118	0.157
group	3	26.309	0.415	0.743
Sex	1	25.731	0.001	0.975
Age	1	27.052	0.376	0.545
School_Education	1	25.912	2.583	0.120
time * group	3	27.000	2.224	0.108

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	25.979	1.572	0.221
time	2	24.089	1.073	0.358
group	3	22.267	0.560	0.647
Sex	1	23.357	0.009	0.927
Age	1	26.399	0.177	0.678
School_Education	1	25.523	2.638	0.117
time * group	6	24.106	2.337	0.064

Analyses for D2KL (concentration performance) V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	25.505	2.271	0.144
time	1	25.860	15.436	0.001
group	3	26.482	0.163	0.920
Sex	1	25.405	1.570	0.222
Age	1	26.263	1.730	0.200
School_Education	1	25.522	1.803	0.191
time * group	3	25.761	3.012	0.048

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	25.537	2.676	0.114
time	2	18.131	10.759	0.001
group	3	25.489	0.032	0.992
Sex	1	24.769	1.634	0.213
Age	1	26.133	2.043	0.165
School_Education	1	25.408	1.819	0.189
time * group	6	18.078	2.765	0.044

Analyses for GAF V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	28.971	58.092	0.000
time	1	27.401	2.082	0.160
group	3	28.548	0.501	0.684
Sex	1	28.111	0.391	0.537
Age	1	28.938	0.706	0.408
time * group	3	27.321	0.223	0.880

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	28.101	75.776	0.000
time	3	16.269	6.268	0.005
group	3	24.995	0.740	0.538
Sex	1	24.381	1.245	0.275
Age	1	27.782	0.467	0.500
time * group	9	16.691	0.575	0.799

Analyses for CDSS V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	27.261	3.697	0.065
time	1	18.786	1.665	0.213
group	3	27.170	1.032	0.394
Sex	1	27.999	0.000	0.996
Age	1	27.123	3.376	0.077
time * group	3	18.174	0.061	0.980

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	27.486	2.934	0.098
time	2	22.976	1.016	0.378
group	3	26.105	0.713	0.553
Sex	1	26.845	0.004	0.949
Age	1	26.937	2.898	0.100
time * group	6	22.883	0.315	0.923

Analyses for CGI

time	group	Mean	N
V1	active tDCS + Varenicilin	4.00	9
	active tDCS + Placebo	4.00	9
	sham tDCS + Varenicilin	3.75	8
	sham tDCS + Placebo	4.00	8
	Total	3.94	34
V3	active tDCS + Varenicilin	3.00	5
	active tDCS + Placebo	3.43	7
	sham tDCS + Varenicilin	2.40	5
	sham tDCS + Placebo	3.33	6
	Total	3.09	23
V4	active tDCS + Varenicilin	3.50	4
	active tDCS + Placebo	3.80	5
	sham tDCS + Varenicilin	2.20	5
	sham tDCS + Placebo	3.00	4
	Total	3.11	18
Total	active tDCS + Varenicilin	3.61	18
	active tDCS + Placebo	3.76	21
	sham tDCS + Varenicilin	2.94	18
	sham tDCS + Placebo	3.56	18
	Total	3.48	75

CGI was tested with non-parametric tests showing no differences between group for all evaluated visits (Kruskal-Wallis tests: V1: H = 0.097, p = 0.992; V3: H = 1.864, p = 0.601 and V4: H = 4.660, p = 0.198). There were no significant results for factor time (Friedman tests: group 1: Chi^2 = 0.5, p = 0.779, group 2: Chi^2 = 2.0, p = 0.368, group 3: Chi^2 = 5.6, p = 0.061, group 4: Chi^2 = 0.67, p = 0.717).

Analyses for PANSS positive V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	28.504	18.611	0.000
time	1	27.105	8.195	0.008
group	3	28.024	0.069	0.976
Sex	1	27.593	3.788	0.062
Age	1	28.547	0.104	0.749
time * group	3	27.012	0.317	0.813

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.833	24.228	0.000
time	3	20.942	5.101	0.008
group	3	27.217	0.029	0.993
Sex	1	21.981	5.066	0.035
Age	1	26.373	0.000	0.999
time * group	9	21.277	1.008	0.464

Analyses for PANSS negative V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	29.896	36.139	0.000
time	1	29.228	6.375	0.017
group	3	28.870	0.595	0.623
Sex	1	28.251	0.002	0.963
Age	1	29.869	0.223	0.640
time * group	3	29.098	1.001	0.406

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	26.329	68.140	0.000
time	3	21.132	2.738	0.069
group	3	22.511	1.525	0.235
Sex	1	22.911	0.258	0.616
Age	1	26.310	3.071	0.091
time * group	9	21.116	0.836	0.592

Analyses for PANSS general V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	28.432	47.877	0.000
time	1	26.589	3.666	0.066
group	3	28.208	0.413	0.745
Sex	1	27.932	0.019	0.891
Age	1	28.374	0.046	0.832
time * group	3	26.544	0.446	0.722

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	22.613	79.049	0.000
time	3	20.791	5.626	0.005
group	3	22.337	1.116	0.364
Sex	1	19.038	2.552	0.127
Age	1	22.503	0.937	0.343
time * group	9	22.106	0.857	0.575

Analyses for PANSS total V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	28.894	47.138	0.000
time	1	27.540	8.904	0.006
group	3	28.316	0.302	0.824
Sex	1	27.936	0.530	0.473
Age	1	28.936	0.041	0.840
time * group	3	27.445	0.559	0.647

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	24.829	67.194	0.000
time	3	21.598	6.037	0.004
group	3	23.695	0.810	0.501
Sex	1	21.226	3.090	0.093
Age	1	24.767	1.080	0.309
time * group	9	24.015	0.676	0.723

Analyses for Cotinine

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	18.554	0.336	0.569
time	1	14.199	1.982	0.181
group	3	22.667	0.831	0.491
sex	1	20.614	0.002	0.966
age	1	17.499	0.549	0.468
time * group	3	13.877	1.310	0.311

Analyses for Fagerström values V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	19.713	2.424	0.135
time	1	19.713	0.030	0.863
group	3	19.658	9.832	0.000
time * group	3	19.658	0.138	0.936

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	20.602	2.622	0.121
time	3	8.549	0.158	0.922
group	3	20.616	10.287	0.000
time * group	9	9.383	0.518	0.830

Analyses for number of cigarettes V1 vs. V2 (upper table) and V1 to V4 (lower table)

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	19.239	192.773	0.000
time	1	19.239	0.022	0.884
group	3	19.195	6.246	0.004
time * group	3	19.195	0.062	0.979

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	12.552	261.677	0.000
time	3	6.561	0.015	0.997
group	3	12.771	7.578	0.004
time * group	9	7.624	0.148	0.995

Table 3: All AEs

	Label	AE_AESPID	original term	ready for coding	m_version	llt_name	pt_name	hlt_name	hlgt_name	soc_name
1	101-Randomisiert	1	Kopfschmerzen	Headache	20.1 English	Headache	Headache	Headaches NEC	Headaches	Nervous system disorders
2	101-Randomisiert	2	Schlafstörungen	Sleep disturbance	20.1 English	Sleep disturbance	Sleep disorder	Sleep disorders NEC	Sleep disorders and disturbances	Psychiatric disorders
3	101-Randomisiert	3a	Übelkeit/Erbrechen	Nausea	20.1 English	Nausea	Nausea	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
4	101-Randomisiert	3b	Übelkeit/Erbrechen	Vomiting	20.1 English	Vomiting	Vomiting	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
5	101-Randomisiert	4a	Übelkeit/Erbrechen	Nausea	20.1 English	Nausea	Nausea	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
6	101-Randomisiert	4b	Übelkeit/Erbrechen	Vomiting	20.1 English	Vomiting	Vomiting	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
7	101-Randomisiert	5	Schlafstörungen	Sleep disturbance	20.1 English	Sleep disturbance	Sleep disorder	Sleep disorders NEC	Sleep disorders and disturbances	Psychiatric disorders
8	103-Randomisiert	1	Schwindel	Dizziness	20.1 English	Dizziness	Dizziness	Neurological signs and symptoms NEC	Neurological disorders NEC	Nervous system disorders
9	104-Randomisiert	1	Hyperkaliämie	Hyperkalemia	20.1 English	Hyperkalemia	Hyperkalaemia	Potassium imbalance	Electrolyte and fluid balance conditions	Metabolism and nutrition disorders
10	104-Randomisiert	2	Leukopenie	Leukopenia	20.1 English	Leukopenia	Leukopenia	Leukopenias NEC	White blood cell disorders	Blood and lymphatic system disorders
11	104-Randomisiert	3	Kribbeln nach Stimulation	Tingling	20.1 English	Tingling	Paraesthesia	Paraesthesias and dysaesthesias	Neurological disorders NEC	Nervous system disorders
12	104-Randomisiert	4	Brennen nach Stimulation	Burning sensation	20.1 English	Burning sensation	Burning sensation	Paraesthesias and dysaesthesias	Neurological disorders NEC	Nervous system disorders
13	105-Randomisiert	1	Kopfschmerzen	Headache	20.1 English	Headache	Headache	Headaches NEC	Headaches	Nervous system disorders
14	110-Randomisiert	1	Erbrechen	Vomiting	20.1 English	Vomiting	Vomiting	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
15	108-Randomisiert	1	Verschlechterung psychotischer Symptomatik - vermehrtes Stimmenhören	Psychosis aggravated	20.1 English	Psychosis aggravated	Psychotic disorder	Psychotic disorder NEC	Schizophrenia and other psychotic disorders	Psychiatric disorders
16	111-Randomisiert	1	Überlkeit	Nausea	20.1 English	Nausea	Nausea	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
18	111-Randomisiert	2	Übelkeit	Nausea	20.1 English	Nausea	Nausea	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
18	111-Randomisiert	3	Harnwegsinfekt	Urinary tract infection	20.1 English	Urinary tract infection	Urinary tract infection	Urinary tract infections	Infections - pathogen unspecified	Infections and infestations
19	112-Randomisiert	1	Schwindelgefühl	Dizziness	20.1 English	Dizziness	Dizziness	Neurological signs and symptoms NEC	Neurological disorders NEC	Nervous system disorders
20	113-Randomisiert	1	Schwindel	Dizziness	20.1 English	Dizziness	Dizziness	Neurological signs and symptoms NEC	Neurological disorders NEC	Nervous system disorders
21	113-Randomisiert	2	Kopfschmerzen links	Headache	20.1 English	Headache	Headache	Headaches NEC	Headaches	Nervous system disorders
22	113-Randomisiert	3	Kopfschmerzen links	Headache	20.1 English	Headache	Headache	Headaches NEC	Headaches	Nervous system disorders
23	115-Randomisiert	1	Nervosität	Nervousness	20.1 English	Nervousness	Nervousness	Anxiety symptoms	Anxiety disorders and symptoms	Psychiatric disorders
24	116-Randomisiert	1	Übelkeit	Nausea	20.1 English	Nausea	Nausea	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
25	117-Randomisiert	1	Erbrechen	Vomiting	20.1 English	Vomiting	Vomiting	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders
26	117-Randomisiert	2	Schwindel	Dizziness	20.1 English	Dizziness	Dizziness	Neurological signs and symptoms NEC	Neurological disorders NEC	Nervous system disorders
27	117-Randomisiert	3	Bauchschmerzen	Stomachache	20.1 English	Stomachache	Abdominal pain upper	Gastrointestinal and abdominal pains (excl oral and throat)	Gastrointestinal signs and symptoms	Gastrointestinal disorders
28	117-Randomisiert	4	Kopfschmerzen	Headache	20.1 English	Headache	Headache	Headaches NEC	Headaches	Nervous system disorders
29	117-Randomisiert	5	Beinschmerzen	Leg pain	20.1 English	Leg pain	Pain in extremity	Musculoskeletal and connective tissue pain and discomfort	Musculoskeletal and connective tissue disorders NEC	Musculoskeletal and connective tissue disorders
30	117-Randomisiert	6	Schwindel	Dizziness	20.1 English	Dizziness	Dizziness	Neurological signs and symptoms NEC	Neurological disorders NEC	Nervous system disorders

	Label	AE_AESP ID	original term	ready for coding	m_version	llt_name	pt_name	hlt_name	hlgt_name	soc_name
31	119-Randomisiert	1	Müdigkeit	Tiredness	20.1 English	Tiredness	Fatigue	Asthenic conditions	General system disorders NEC	General disorders and administration site conditions
32	120-Randomisiert	1	Druck im Kopf	Head pressure	20.1 English	Head pressure	Head discomfort	Neurological signs and symptoms NEC	Neurological disorders NEC	Nervous system disorders
33	120-Randomisiert	2	Manie	Mania	20.1 English	Mania	Mania	Mood alterations with manic symptoms	Manic and bipolar mood disorders and disturbances	Psychiatric disorders
34	121-Randomisiert	1	Kribbeln unter Elektroden	Tingling	20.1 English	Tingling	Paraesthesia	Paraesthesias and dysaesthesias	Neurological disorders NEC	Nervous system disorders
35	121-Randomisiert	2	Müdigkeit	Tiredness	20.1 English	Tiredness	Fatigue	Asthenic conditions	General system disorders NEC	General disorders and administration site conditions
36	121-Randomisiert	3	Müdigkeit	Tiredness	20.1 English	Tiredness	Fatigue	Asthenic conditions	General system disorders NEC	General disorders and administration site conditions
37	122-Randomisiert	1	Anspannung	Strain	20.1 English	Strain	Muscle strain	Muscle, tendon and ligament injuries	Injuries NEC	Injury, poisoning and procedural complications
38	122-Randomisiert	2	Angst	Fear	20.1 English	Fear	Fear	Fear symptoms and phobic disorders (incl social phobia)	Anxiety disorders and symptoms	Psychiatric disorders
39	123-Randomisiert	1	EEG Veränderung	EEG abnormal	20.1 English	EEG abnormal	Electroencephalogram abnormal	Neurologic diagnostic procedures	Neurological, special senses and psychiatric investigations	Investigations
40	125-Randomisiert	1	Kopfschmerzen	Headache	20.1 English	Headache	Headache	Headaches NEC	Headaches	Nervous system disorders
41	126-Randomisiert	1	Vermehrte Wahrnehmung optischer Sinnestäuschung	Optical illusion	20.1 English	Optical illusion	Illusion	Perception disturbances	Disturbances in thinking and perception	Psychiatric disorders
42	126-Randomisiert	2	Kurze Lichtblitze linksseitig	Visual flashes	20.1 English	Visual flashes	Photopsia	Visual disorders NEC	Vision disorders	Eye disorders
43	126-Randomisiert	3	Kurze Lichtblitze linksseitig	Visual flashes	20.1 English	Visual flashes	Photopsia	Visual disorders NEC	Vision disorders	Eye disorders
44	126-Randomisiert	4	Gleichgewichtsstörung	Balance disorder	20.1 English	Balance disorder	Balance disorder	Coordination and balance disturbances	Neurological disorders NEC	Nervous system disorders
45	126-Randomisiert	5	Kurze Lichtblitze linksseitg	Visual flashes	20.1 English	Visual flashes	Photopsia	Visual disorders NEC	Vision disorders	Eye disorders
46	126-Randomisiert	6	Verstärktes psychot. Erleben	Psychosis aggravated	20.1 English	Psychosis aggravated	Psychotic disorder	Psychotic disorder NEC	Schizophrenia and other psychotic disorders	Psychiatric disorders
47	126-Randomisiert	7	Gleichgewichtsstörung	Balance disorder	20.1 English	Balance disorder	Balance disorder	Coordination and balance disturbances	Neurological disorders NEC	Nervous system disorders
48	126-Randomisiert	8	Antriebslosigkeit	Listlessness	20.1 English	Listlessness	Listless	Mood disorders NEC	Mood disorders and disturbances NEC	Psychiatric disorders
49	126-Randomisiert	9	Hyponatriämie	Hyponatremia	20.1 English	Hyponatremia	Hyponatraemia	Sodium imbalance	Electrolyte and fluid balance conditions	Metabolism and nutrition disorders
50	127-Randomisiert	1	Diskrete GPT Erhöhung	GPT increased	20.1 English	GPT increased	Alanine aminotransferase increased	Liver function analyses	Hepatobiliary investigations	Investigations
51	127-Randomisiert	2	Verstärkte akustische Halluzinationen	Hallucinations aggravated	20.1 English	Hallucinations aggravated	Hallucination	Perception disturbances	Disturbances in thinking and perception	Psychiatric disorders
52	130-Randomisiert	1	Schwindel	Dizziness	20.1 English	Dizziness	Dizziness	Neurological signs and symptoms NEC	Neurological disorders NEC	Nervous system disorders
53	132-Randomisiert	1	Ohrenpfeifen (nur Vormittags)	Tinnitus	20.1 English	Tinnitus	Tinnitus	Inner ear signs and symptoms	Inner ear and VIIIth cranial nerve disorders	Ear and labyrinth disorders
54	132-Randomisiert	2	Muskelkater am ganzen Körper	Muscle stiffness	20.1 English	Muscle stiffness	Musculoskeletal stiffness	Musculoskeletal and connective tissue signs and symptoms NEC	Musculoskeletal and connective tissue disorders NEC	Musculoskeletal and connective tissue disorders
55	132-Randomisiert	3	Muskelkater am ganzen Körper	Muscle stiffness	20.1 English	Muscle stiffness	Musculoskeletal stiffness	Musculoskeletal and connective tissue signs and symptoms NEC	Musculoskeletal and connective tissue disorders NEC	Musculoskeletal and connective tissue disorders
56	132-Randomisiert	4	Suizidgedanken	Suicidal ideation	20.1 English	Suicidal ideation	Suicidal ideation	Suicidal and self-injurious behaviour	Suicidal and self-injurious behaviours NEC	Psychiatric disorders
57	133-Randomisiert	1	Übelkeit	Nausea	20.1 English	Nausea	Nausea	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Gastrointestinal disorders

Zeilenbeschriftungen	Anzahl von pt_name
Blood and lymphatic system disorders	**1**
Leukopenia	1
Ear and labyrinth disorders	**1**
Tinnitus	1
Eye disorders	**3**
Photopsia	3
Gastrointestinal disorders	**11**
Abdominal pain upper	1
Nausea	6
Vomiting	4
General disorders and administration site conditions	**3**
Fatigue	3
Infections and infestations	**1**
Urinary tract infection	1
Injury, poisoning and procedural complications	**1**
Muscle strain	1
Investigations	**2**
Alanine aminotransferase increased	1
Electroencephalogram abnormal	1
Metabolism and nutrition disorders	**2**
Hyperkalaemia	1
Hyponatraemia	1
Musculoskeletal and connective tissue disorders	**3**
Musculoskeletal stiffness	2
Pain in extremity	1
Nervous system disorders	**18**
Balance disorder	2
Burning sensation	1
Dizziness	6
Head discomfort	1
Headache	6
Paraesthesia	2
Psychiatric disorders	**11**
Fear	1
Hallucination	1
Illusion	1
Listless	1
Mania	1
Nervousness	1
Psychotic disorder	2
Sleep disorder	2
Suicidal ideation	1
Gesamtergebnis	**57**

Table 4: SAEs

CIOMS II Summary Tabulation

Study Short Name: NicStim / EudraCT: 2017-001357-14

Cumulative Summary Tabulation of all serious Adverse Events

System Organ Class Preferred Term	Number of events Total up to 27.09.2022
Psychiatric disorders	**2**
Mania	1
Suicidal ideation	1