

## SUPPLEMENTAL MATERIAL

### **Non-invasive brain stimulation as add-on therapy for subacute post-stroke aphasia: a randomized trial (NORTHSTAR)**

*Cover title: The NORTHSTAR trial*

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## Supplemental Methods

### Stimulation devices

TMS: Stimulation devices used were the eXimia NBS4, Nexstim Ltd. (Jewish General Hospital, Burke Rehabilitation Hospital), Magstim R<sup>2</sup>, Magstim Company Ltd. (RehaNova) and MagPro X100, MagVenture A/S (Sunnybrook Hospital and Hôpital Notre-Dame).

tDCS: Stimulation devices used were the 1x1 tDCS-Limited Total Energy, Soterix Medical Inc. (Burke Rehabilitation Hospital) and DC-Stimulator Plus from neuroConn GmbH (all other study sites).

### The Unified Aphasia Score (UnAS)

We derived a standardized T-score, the *Unified Aphasia Score (UnAS)* based on the normative data available for approved language specific batteries: The Aachen Aphasia Test in German (AAT)<sup>1</sup>, the Protocole Montréal-Toulouse-86 in French (MT86)<sup>2</sup>, and the Western Aphasia Battery in English (WAB)<sup>3</sup>. For the WAB, the UnAS was the so-called Language Quotient, which is a T score based on oral and written language subtests. We used the mean T score from an equivalent set of subtests in the AAT (subtests Token test, Repetition, Written language, Naming, and Comprehension) and the MT86 (Interview, Oral picture description, Naming, Verbal fluency, Written questionnaire, Written picture description, Auditory comprehension, Verbal commands, Written comprehension, Repetition, Copying, Writing to dictation, Reading, Repetition of numbers, Bucco-facial commands).

## Supplemental Results

### Safety – Individual results

AEs were rare. In the rTMS group, one patient reported headache (1/10 sessions) and another felt dysesthesia (1/10 sessions). In the ctDCS group, two participants reported dysesthesia for one session each. A third patient reported several adverse events (mild-moderate neck pain for 10 sessions, mild dysesthesia for 7 sessions, and headache for 1 session). In the sham group, one patient reported headache for two sessions.

We reported one SAE for one ctDCS patient. This patient discontinued the study after two treatment sessions because of chest pain starting several hours after the last stimulation session. Fifteen days later, he underwent cardiac surgery complicated by a simple focal seizure three hours post-surgery. The SAE was not thought to have been related to the study intervention.

## Supplemental Tables

**Supplemental Table 1 – Demographic & baseline data in the subgroup of patients with affected or non-affected Broca’s area**

	rTMS	ctDCS	Sham	Between-group ANOVAs p-value
<b>Patients with affected Broca’s area</b>				
N	8	11	9	
Male; Female	3;5	8;3	5;4	
English; French; German language	3;1;4	5;2;4	3;4;2	
Age, mean (SD)	65.5 (9.6)	57.9 (11.3)	64.8 (11.0)	.242
Days post-stroke at recruitment, mean (SD)	23.4 (13.5)	19.2 (12.8)	15.2 (11.0)	.415
Naming Z-score, mean (SD)	-6.11 (4.16)	-9.18 (6.37)	-9.82 (2.82)	.264
Semantic fluency Z-score, mean (SD)	-2.87 (1.04)	-3.49 (1.02)	-3.10 (0.43)	.314
Oral comprehension Z-score, mean (SD)	-8.64 (5.13)	-11.39 (5.32)	-12.72 (4.01)	.236
Unified Aphasia Score, mean (SD)	52.65 (23.73)	38.52 (23.82)	21.60 (22.22)	.036 (rTMS > sham)
<b>Patients with non-affected Broca’s area</b>				
N	12	13	10	
Male; Female	7;5	6;7	7;3	
English; French; German language	3;5;4	7;1;5	4;1;5	
Age, mean (SD)	67.5 (10.2)	71.6 (11.5)	69.7 (12.3)	.666
Days post-stroke at recruitment, mean (SD)	19.8 (13.5)	21.5 (16.6)	16.5 (11.9)	.713
Naming Z-score, mean (SD)	-5.93 (2.95)	-5.17 (3.03)	-5.14 (5.56)	.855
Semantic fluency Z-score, mean (SD)	-2.64 (1.07)	-2.55 (0.80)	-2.26 (1.43)	.703
Oral comprehension Z-score, mean (SD)	-6.08 (5.20)	-8.00 (3.76)	-6.56 (4.56)	.549
Unified Aphasia Score, mean (SD)	43.09 (21.67)	50.75(20.8)	53.74 (21.15)	.476

**Supplemental Table 2 - Real (rTMS or ctDCS) versus Sham Stimulation. Change in primary outcomes relative to baseline at post-treatment (Day 1) and at one-month follow-up (Day 30).** Medians (and interquartile ranges) are displayed for each intervention condition as well as *p*-values of median tests. Significance level = .05. BNT: Boston Naming Test, SF: Semantic Fluency, TT: Token Test.

Z-score change		Real	Sham	p-value
<b>Naming (BNT)</b>	Day 1	1.00(1.11)	0.73(0.94)	.118
	Day 30	1.37(1.74)	1.02(1.71)	.934
<b>Verbal fluency (SF)</b>	Day 1	0.00(0.33)	0.00(0.20)	.843
	Day 30	0.41(0.75)	0.73(1.14)	.334
<b>Sentence comprehension (TT)</b>	Day 1	0.94(1.87)	1.12(1.87)	.976
	Day 30	2.10(2.40)	2.07(2.57)	.493

**Supplemental Table 3 – Correlations of outcome variables with baseline scores and days post-stroke at recruitment.**

Change relative to baseline		Spearman's correlation	Spearman's correlation coefficient
		coefficient with baseline score and <i>p-value</i>	with post-stroke days at recruitment and <i>p-value</i>
<b>Naming (BNT)</b>	Day 1	0.212 .095	0.078 .541
	Day 30	0.064 .619	-0.019 .880
<b>Verbal fluency (SF)</b>	Day 1	-0.118 .358	-0.140 .274
	Day 30	0.254* .045	-0.134 .296
<b>Comprehension (TT)</b>	Day 1	-0.048 .709	-0.214 .092
	Day 30	-0.186 .145	-.315* .012
<b>Unified Aphasia Score (UnAS) percent change</b>	Day 1	-0.450** <.001	-0.524** <.001
	Day 30	-0.552** <.001	-0.511** <.001

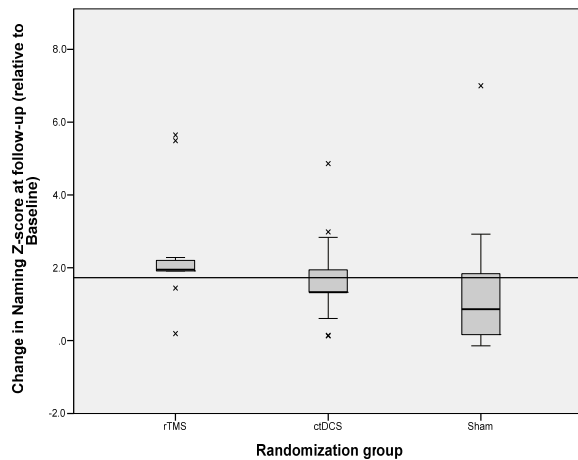
## Supplemental Figures

### Supplemental Figure 1 - Change in Naming at 30-days follow-up relative to baseline (Boston Naming Test Z-score).

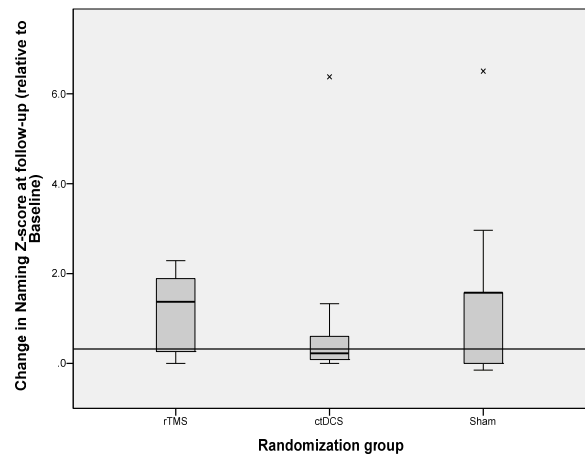
Patients with intact Broca's area: rTMS, N=12, Mdn=+1.95, IQR=0.33; ctDCS, N=13, Mdn=+1.33, IQR=1.42; Sham, N=10, Mdn=+0.86, IQR=1.95;  $p=.01$ . Pairwise post-hoc median tests were not significant.

Patients with lesions in Broca's area: rTMS, N=8, Mdn=+1.37, IQR=1.66; ctDCS, N=11, Mdn=+0.23, IQR=0.88; Sham, N=9, Mdn=+1.57, IQR=2.27;  $p=.489$ .

Patients with intact Broca's area



Patients with lesions in Broca's area

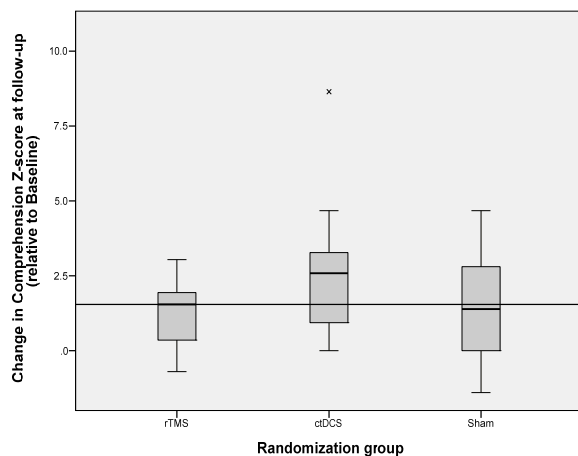


### Supplemental Figure 2 - Change in Comprehension at 30-days follow-up relative to baseline (Token Test Z-score).

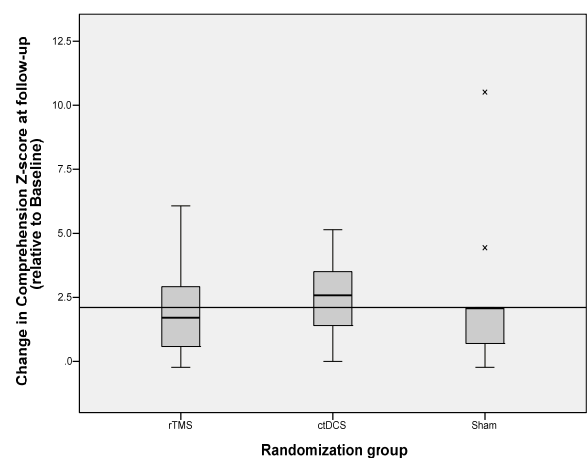
Patients with intact Broca's area: rTMS, N=12, Mdn=+1.54, IQR=1.85; ctDCS, N=13, Mdn=+2.58, IQR=2.92; Sham, N=10, Mdn=+1.39, IQR=2.98;  $p=.177$ .

Patients with lesions in Broca's area rTMS, N=8, Mdn=+1.71, IQR=2.69; ctDCS, N=11, Mdn=+2.58, IQR=3.51; Sham, N=9, Mdn=+2.07, IQR=2.80;  $p=.152$ .

Patients with intact Broca's area



Patients with lesions in Broca's area



## Supplemental References

1. Huber W, Poeck K, Weniger D, Willmes K. *Der aachner aphasia test (aat)*. Göttingen, Germany: Hogrefe; 1983.
2. Nespoulous J, Lecours A, Lafond D, Lemay A, Puel M, Joannette Y. Protocole montréal-toulouse d'examen linguistique de l'aphasie [montreal-toulouse protocol of aphasia linguistic examination](mt86). *Isbergues, France: L'Ortho-Edition*. 1992
3. Kertesz A. Western aphasia battery–revised (wab-r) pro-ed. *Austin, TX*. 2006