Neuro-Cardiac-Guided TMS (NCG TMS)*: probing DLPFC-sgACC connectivity using heart rate

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INTRODUCTION

The efficacy of rTMS in the treatment of major depressive disorder (MDD) has been well established in recent years. Most studies to date have employed the '5-cm' rule for targeting the Dorsolateral Prefrontal Cortex (DLPFC). New variations and improvements of this targeting technique include a '6-cm' rule, the Beam-F3 method, and neuronavigated rTMS.

It has been proposed that the efficacy of rTMS in MDD is more related to stimulating the area that is functionally connected to the subgenual anterior cingulate cortex (sgACC) rather then to specific cortical areas (Fox et al., 2012). Therefore, we set-out to develop and test a new method that employs knowledge about the functional role of the sgACC to establish in real time if the right cortical area is targeted: Neuro-Cardiac-Guided TMS (NCG-TMS).

METHODS

Several studies have shown that areas in the ventromedial prefrontal cortex are involved in parasympathetic regulation such as heart rate and respiration, and that neurostimulation of these areas led to heart rate decreases

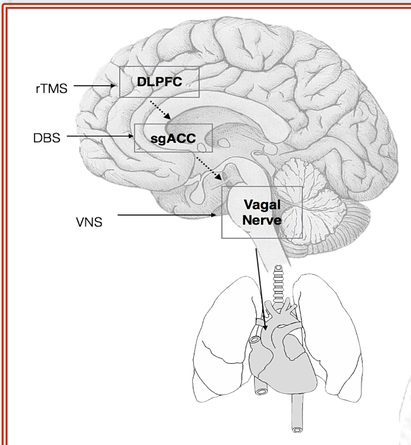


Fig 1: Schematic overview of the proposed functional connectivity pathways and their ways to be modulated by neuro-modulation methods. When targeting the correct area, a heart rate decrease should be observed. Neuro-modulation methods have shown decreases in HR after stimulation, but not yet during stimulation.

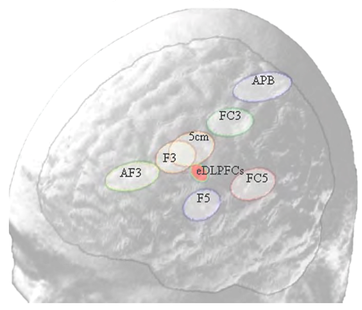


Fig 2: "DLPFC" locations as localized with various methods. We hypothesize that, when targeting the 'correct' DLPFC, a decrease in HR will be observed. (*image adapted from Rusjan et al., 2010)

(Makovac et al., 2016), most likely through connectivity with the vagus nerve. Therefore, based on the notion that rTMS aims to transsynaptically stimulate the sgACC, we stimulated various frontal locations while recording electrocardiogram (ECG), to establish the location that most consistently resulted in a heart rate deceleration. To this aim, 10 subjects where tested for 7 sites (3 left-sided, 3 right-sided, and 1 control location (Pz)). Each locations was stimulated 3x in a random order (within one hemisphere) with 5 sec. trains of 10 Hz.

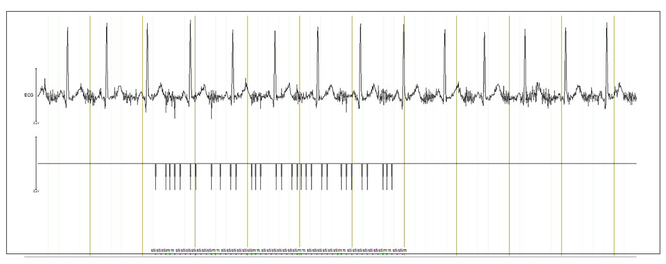


Fig 3: Example heart rate data and rTMS pulse recording (subject 8).

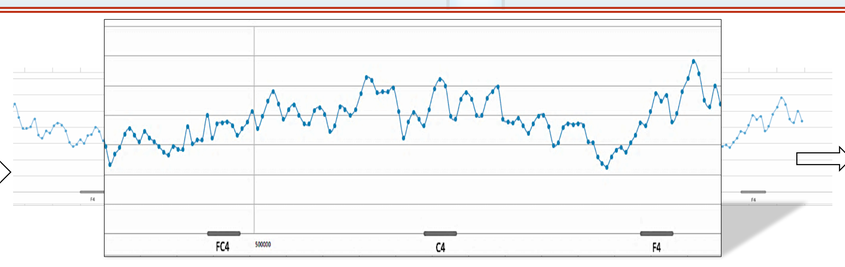


Fig 4: Heart rate data converted into RR interval data (subject 8).

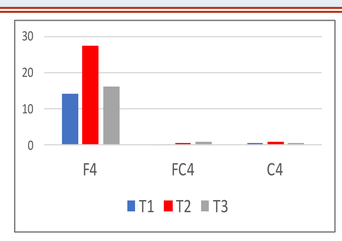


Fig 5: Results from figure 4. Z-scores of 3 time-points during stimulation were calculated, for each site (subject 8).

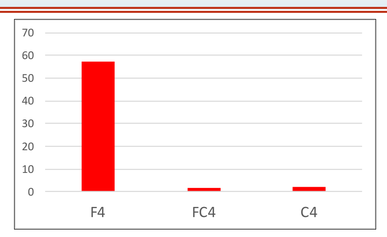
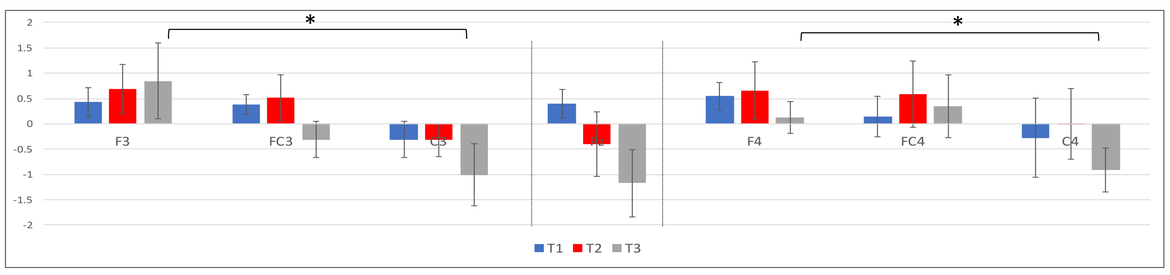


Fig 6: Sum of the 3 z-scores. Calculated for each site. For this subject, the F4 location shows the largest HR deceleration (subject 8).

FIRST RESULTS

GROUP



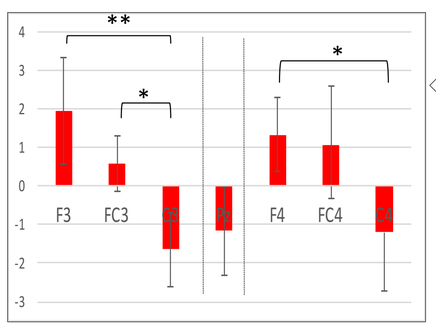


Fig 7: Group Z-scores of the mean of 3 rounds, for seven locations, for N=9. Z-scores were calculated for 3 time-points during/after stimulation. One subject violated the sphericity with very high z-scores and was excluded from group analysis. Error bars represent the standard error of the mean (SEM).

Fig 8: Sum of the Z-scores of 3 time-points. On the group level, F3 and F4 express a higher HR deceleration, as expected. Error bars represent the standard error of the mean (SEM).

INDIVIDUALIZED

Subject	Left	Right
1	F3	F4
2	F3	FC4
3	FC3	F4
4	FC3	F4
5	F3	FC4
6	F3	F4
7	F3	FC4
8	F3	F4
9	F3	F4
10	F3	FC4

Table 1: Preferred stimulation site per individual for HR deceleration. As hypothesized, the preferred stimulation site for HR deceleration is not found on F3 and F4 in every individual.

F3	FC3	C3	F4	FC4	C4
8/10	2/10	0/10	6/10	4/10	0/10
80%	20%	0%	60%	40%	0%

Table 1: Amount of individuals per location with that specific location as the most optimal for achieving HR deceleration

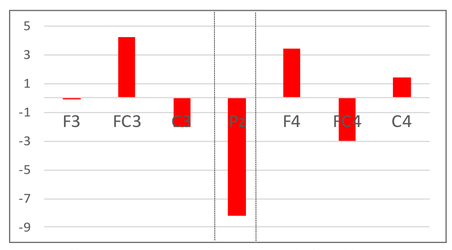


Fig 9: Example, subject 3. Sum of z-scores of the mean of 3 rounds.

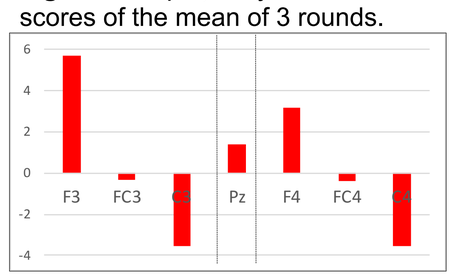


Fig 10: Example, subject 9. Sum of z-scores of the mean of 3 rounds.

Discussion

Our results validate the NCG-TMS method and confirm top down control of heart rate via the DLPFC-sgACC-vagus nerve network. On group level, we found a site-specific HR deceleration for F3 and F4. The individualized data show inter-individual variability. For some subjects FC3 or FC4 shows the highest HR deceleration, confirming our hypothesis. This variation indicates that it might be useful to select the optimal stimulation site for antidepressant treatment according to HR deceleration (NCG-TMS).

To this end, the method needs to be validated in depressed patients undergoing rTMS treatment, and to result in a higher response rate.

1) Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A (2012): Efficacy of Transcranial Magnetic Stimulation Targets for Depression Is Related to Intrinsic Functional Connectivity with the Subgenual Cingulate. *Biol Psychiatry.*
2) Rusjan PM , Barr MS , Farzan F, Arenovich T, Maller JJ, Fitzgerald PB, Daskalakis ZJ (2010): Optimal transcranial magnetic stimulation coil placement for targeting the dorsolateral prefrontal cortex using novel magnetic resonance image-guided neuronavigation. *Human Brain Mapping*
3) Makovac E, Thayer JF, Ottaviania C (2016): A meta-analysis of non-invasive brain stimulation and autonomic functioning: Implications for brain-heart pathways to cardiovascular disease. *Neuroscience and Biobehavioral Reviews*
* Arns, M., Iseger, T. & Brandwijk, A. (Patent pending) A method of identifying and guiding cortical stimulation sites for the application of a focal-neuromodulation technique using trans-synaptical target identification: Neuro-Cardiac-Guided rTMS (NCG-rTMS), Dutch Patent office: P100241NL00

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