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Neuro-Cardiac-Guided TMS (NCG-TMS): Probing DLPFC-sgACC-vagus nerve connectivity using heart rate – First results

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A B S T R A C T

Background: Given that many studies suggest a role of DLPFC-sgACC connectivity in depression and prior research demonstrating that neuromodulation of either of these nodes modulates parasympathetic activity and results in a heart rate deceleration, a new method is proposed to individualize localization of the DLPFC. This can, among others, be useful for rTMS treatment of depression.

Methods: Ten healthy subjects received three trains of 10Hz rTMS randomly over 7 target regions (10–20 system).

Results: Overall, F3 and F4 expressed the largest heart rate deceleration, in line with studies suggesting these are the best 10–20 sites to target the DLPFC. On the individual level, 20–40% subjects expressed the largest heart rate deceleration at FC3 or FC4, indicating individual differences as to the 'optimal site for stimulation'.

Conclusions: These results show that the NCG-TMS method is valid to localize the entry into the DLPFC-sgACC network.

Dear Editor:

Autonomic regulation is disturbed in patients with major depressive disorder (MDD), indicated by a higher heart rate (HR) and lower heart rate variability (HRV). Moreover, the heart is functionally connected via the vagus nerve (VN) to other brain structures that are dysregulated in depression, such as the subgenual anterior cingulate cortex (sgACC) [1], and the dorsolateral prefrontal cortex (DLPFC), suggesting dysregulated network function in MDD [2–4]. In line with this network dysregulation hypothesis of MDD, optimal transcranial magnetic stimulation (TMS) sites are currently thought to be those that show functional connectivity to the sgACC such as the DLPFC [2].

Current DLPFC localization methods for TMS are the 5cm rule, or BEAM-F3 method [5]. These are valid on the group-level, but do only limitedly take individual variation into account [6]. Functional and structural neuro-navigation methods do, but are expensive, time-consuming and navigate based on blood-oxygen-level-dependent (BOLD) signal or structural targets e.g. Brodmann areas and do not take knowledge about functional connectivity into account. Here, we propose a new functional neuronavigation method for localizing the frontal area representation of DLPFC-sgACC connectivity using HR, called: Neuro-Cardiac-Guided TMS (NCG-TMS).

Multiple studies now indicate that stimulation of the (sg)ACC, as well as transcranial direct current stimulation (tDCS) and TMS at the DLPFC, lead to HR decreases [7,8], indicative of parasympathetic activation. Similarly, stimulating the VN, directly activates the parasympathetic system.

Thus, we hypothesized that this influence on parasympathetic activity could be used as a functional outcome measure reflecting adequate targeting of the DLPFC-sgACC network, similar to the motor evoked potential (MEP) as functional key measure for primary motor cortex stimulation. In a pilot-study, we set out to validate this notion by stimulating various 10–20 sites using repetitive (r)TMS and co-registering the stimulation pulses with the electrocardiogram (ECG). Here we report that on the group-level, in line with earlier work [9], F3 and F4 demonstrate the largest HR-suppression, the control sites (C3/C4/Pz) show no HR-suppression and FC4 and FC3 show an intermediate suppression. Furthermore, we report individual differences in the site that results in maximum HR-suppression.

Material and methods

We recruited ten healthy volunteers. All subjects underwent 5 sec. trains of 10Hz rTMS (100% MT) to 7 different locations: left (F3/FC3/C3), right (F4/FC4/C4), and midline (Pz), with 30-s intervals. Each stimulation site was stimulated three times in a randomized order (same order for all subjects). An ECG electrode was attached on both wrists and one ground electrode was placed on one upper wrist. Recordings were obtained using an 'r-wave trigger' device (neuroConn, Ilmenau, Germany). During the stimulation protocol the subject was asked to sit relaxed and breath steadily. The data were imported in Brain Vision Analyzer where automatic R-peak detection was used to mark the R-peaks in the

Abbreviations: HR, Heart rate; VN, Vagus nerve; DLPFC, Dorsolateral prefrontal cortex; sgACC, subgenial anterior cingulate cortex; TMS, transcranial magnetic stimulation; NCG, Neuro-cardiac-guided.

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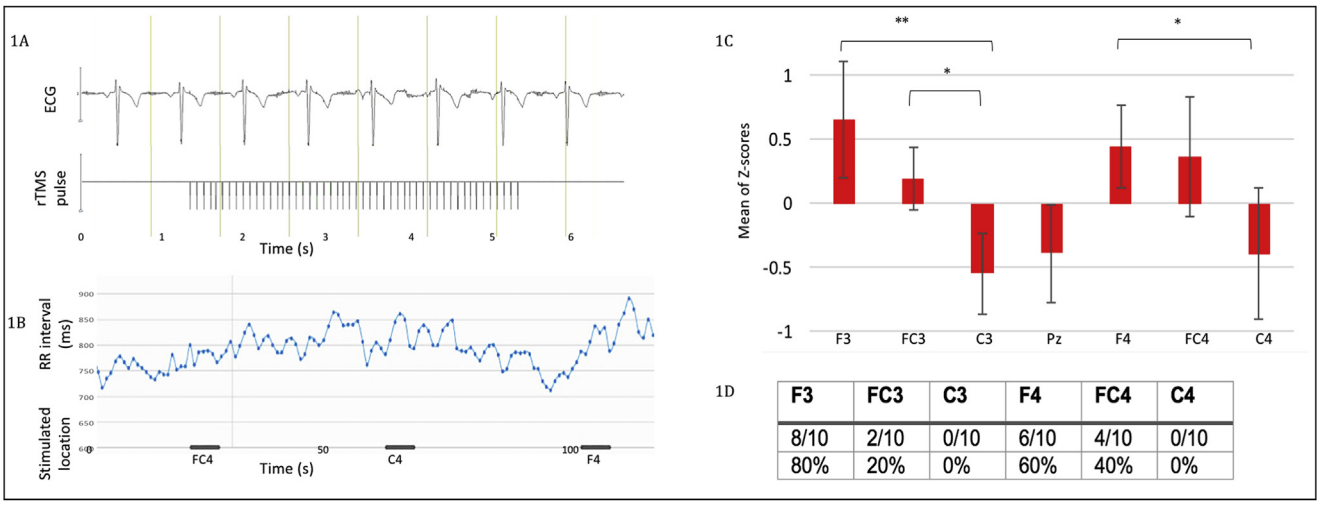

Fig. 1. A) Example of concurrent recording of ECG and TMS pulses; B) Example of ECG converted into R-R intervals. Note that in (A) only a single TMS period is shown, but in (B) three. The peaks and troughs of the respiratory waves were scored; C) Whole group mean z-scores of T1, T2 and T3. F3 and F4 express the largest HR deceleration. Error bars in standard error of the mean (SEM); D) percentage of subjects showing the largest HR deceleration per specific site, demonstrating inter-individual variability.

ECG (Fig. 1A). The ECG was then converted into R-R intervals (Fig. 1B). The peaks and troughs within this R-R signal reflect respiration-induced heart-rate modulation. By limiting the subsequent analysis to R-R values at the troughs, the effect of respiration was effectively removed, and the room to detect HR deceleration was maximized. Pre-stimulation troughs were labelled as T0. The first 3 troughs during and/or after stimulation were labelled as T1, T2, T3. The 3 trials per location were averaged and transformed into Z-scores (computed as (T1-T0)/sd(T0), where sd(t0) is the standard deviation of T0 across the 3 repeated stimulations for that location; same for T2 and T3). The normalization using sd(T0) was performed to reduce variance in effects of TMS due to individual differences and to the different timing for different locations. The Z-scores of T1-T3 were subsequently averaged. On group level, paired t-tests were performed for these average z-scores. On individual level, the best location was determined by the largest Z-score.

Results

Ten subjects were included (23–61 years of age; 40% male). One subject was excluded from group analysis due to one extreme Z-score (>3 times the SD across subjects for that location (F4)). Between locations SD(T0)s did not differ. As can be seen in Fig. 1C, at the group-level, paired t-tests indicated a significant HR change between F3-C3 ($p = 0.009$), FC3-C3 ($p = 0.032$), and F4-C4 ($p = 0.036$). The largest HR-deceleration was observed for both F3 and F4, followed by FC3 and FC4. Opposite effects were seen for C3, C4 and Pz. Furthermore, inter-individual variability was observed, where for some subjects the largest HR-decrease was found for FC3 (20%) or FC4 (40%) instead of F3 or F4, also see Fig. 1D.

Discussion

This pilot-study shows first preliminary evidence that HR can be used as functional outcome measure to identify specific frontal regions that likely reflect DLPFC-sgACC-VN network activation. On the group-level, we found a site-specific HR-deceleration for F3 and F4, as hypothesized. As can be seen in Fig. 1C, the effects showed site-specificity with largest effects for F3/F4, followed by FC3/4 and none or reversed effects for control sites overlaying the motor (C3/4) and parietal cortex (Pz), in line with previous results [8,10]. Furthermore, the results show a perfect mirror image for left vs. right hemisphere. At individual level, for 20% of subjects HR decelerated stronger after stimulation at FC3 and for 40% at FC4 confirming our expectation of inter-individual variability.

These findings indicate that – in line with the notion put forward by Fox and colleagues [2] – this method of Neuro-Cardiac-Guided TMS could potentially be used as a functional outcome measure to localize an individualized stimulation location for rTMS treatment in MDD. Furthermore, such a method could eventually be used in similar ways as the motor threshold for the primary motor cortex and could assist in establishing individual stimulation thresholds for DLPFC-sgACC stimulation, investigate angular sensitivity and investigate in more detail neuroplasticity effects, that are now all modelled on the motor system. Further studies need to validate these results in larger groups and patients, and establish the association with treatment response (i.e. do MDD responders exhibit associated HR decreases during stimulation, suggestive of 'accurate targeting'?). With this individualized approach relying on a functional outcome measure, TMS targeting could become more consistent and possibly, could enhance response to DLPFC-TMS treatment.

Disclosures

MA reports options from Brain Resource (Sydney, Australia), is director and owner of Research Institute Brainclinics, a minority shareholder in neuroCare Group (Munich, Germany); TAI and MA are co-inventor on a patent application covering NCG-TMS, but do not own the patent nor receive any proceeds related to this patent; Research Institute Brainclinics received research funding from Brain Resource (Sydney, Australia) and neuroCare Group (Munich, Germany); equipment support from Deymed, neuroConn and Magventure, however data analyses and writing of this manuscript were unconstrained.

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