Network-targeted TMS stimulation via individualized target selection: a new route toward enhanced reliability

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Introduction and Aims

Transcranial Magnetic Stimulation (TMS) is a widely used technique for the noninvasive manipulation of brain states, of the neurobiological mechanisms sustaining them, as well as of their behavioral manifestations (Hallett, 2000). Although extensively used for research and clinical purposes, recent studies have questioned the reliability of TMS findings because of the high inter-individual variability that has been observed. In the present study, we argue that most of such variability is imputable to the selection of the stimulation target. We hypothesize that stimulation sites that rely on group-level analyses fail to consider the specificity of the individual connectivity profile, hence resulting in suboptimal stimulation scenarios compared to personalized approaches. Our first aim was to test if TMS single pulse protocols targeting cortical functional networks can be considered reliable interventions across extended follow-up periods (1 month apart). Secondly, we aimed to assess if reliability across visits is related to the selection of the stimulation site, in this case targeting the Dorsal Attention Network (DAN) and the Default Mode Network (DMN).

Methods

PARTICIPANTS AND DESIGN.

A total of 24 healthy subjects (age = 33.4 ± 8.6 years, range 19-49 years old) participated in the study. After obtaining consent, all subjects underwent the acquisition of structural and functional magnetic resonance imaging (rs-fMRI) for the identification of the individual resting state networks to stimulate. Afterwards, each participant took part to a neuronavigated, single pulse TMS protocol (MagPro X-100 stimulator by MagVenture A/S for 120 pulses at 120% of the individual resting motor threshold) during concomitant electroencephalography (EEG, 64 channels) recording. Stimulation sites for both the DAN and the DMN network were based on 2 different approaches for the identification of the superior parietal gyrus (SPG) and angular gyrus (ANG) respectively (Fig. 1A,B). For our group-based or "c" approach, the stimulation site was identified by projecting the point of maximum confidence from a sample of 1000 healthy individuals (Yeo et al., 2011) after having morphed the cortical maps into the individual anatomy, so that the point of maximum confidence could be individualized at the single voxel level. For our individualized "i" approach, the site of stimulation was chosen by means of a seed-based approach, which was iteratively performed starting from each node of the Yeo et al. (2011) network of interest, until the SPG and ANG could be identified respectively. Furthermore, a small subsample of our participants (n=10) underwent a third stimulation condition, where the stimulation target was even more individualized. In this case, independent component analyses (ica) was performed over 3 runs of rs-fMRI and the local maxima of the SPG and ANG were identified by one of the experimenters. All stimulation visits were again repeated after one month and their reliability compared on a hierarchy of derived measures, in particular: TMS evoked potentials (TEPs), induced time-frequency changes and source-derived inter-network changes in connctivity (Fig. 1C).

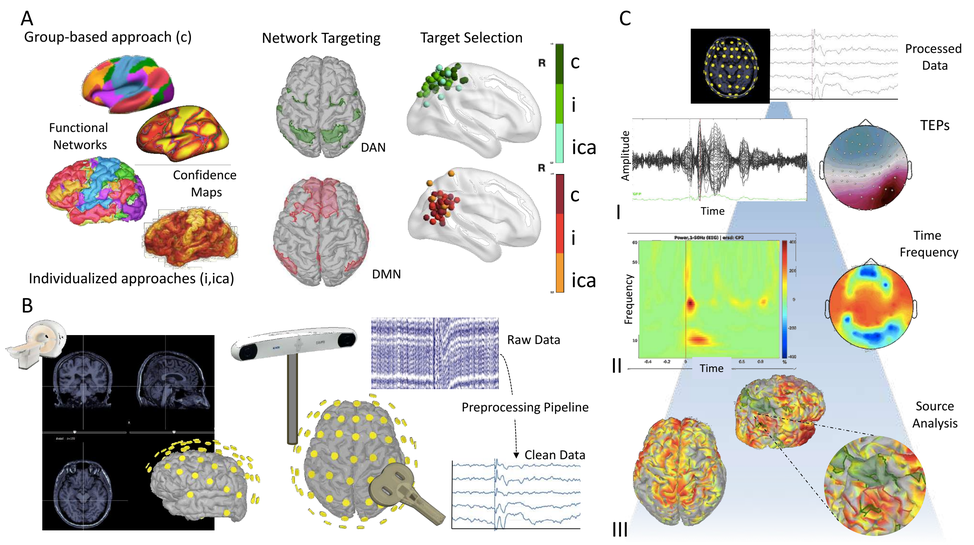

Figure 1. Methodological Workflow and Measures of Interest. A) Group-based and Individualized stimulation targets were compared in their reliability of the induced effects following network-targeting of the DAN and DMN. Interindividual differences based on target selection are shown. B) Individual neuroanatomy was used for both target selection and neuronavigation purposes during concomitant TMS-EEG. All visits were repeated 1 month apart. C) From the processed EEG data, a hierarchy of measures (ranging from the electrode space to the source level) were assessed in terms of their reliability across visits as a function of the stimulation site.

Results

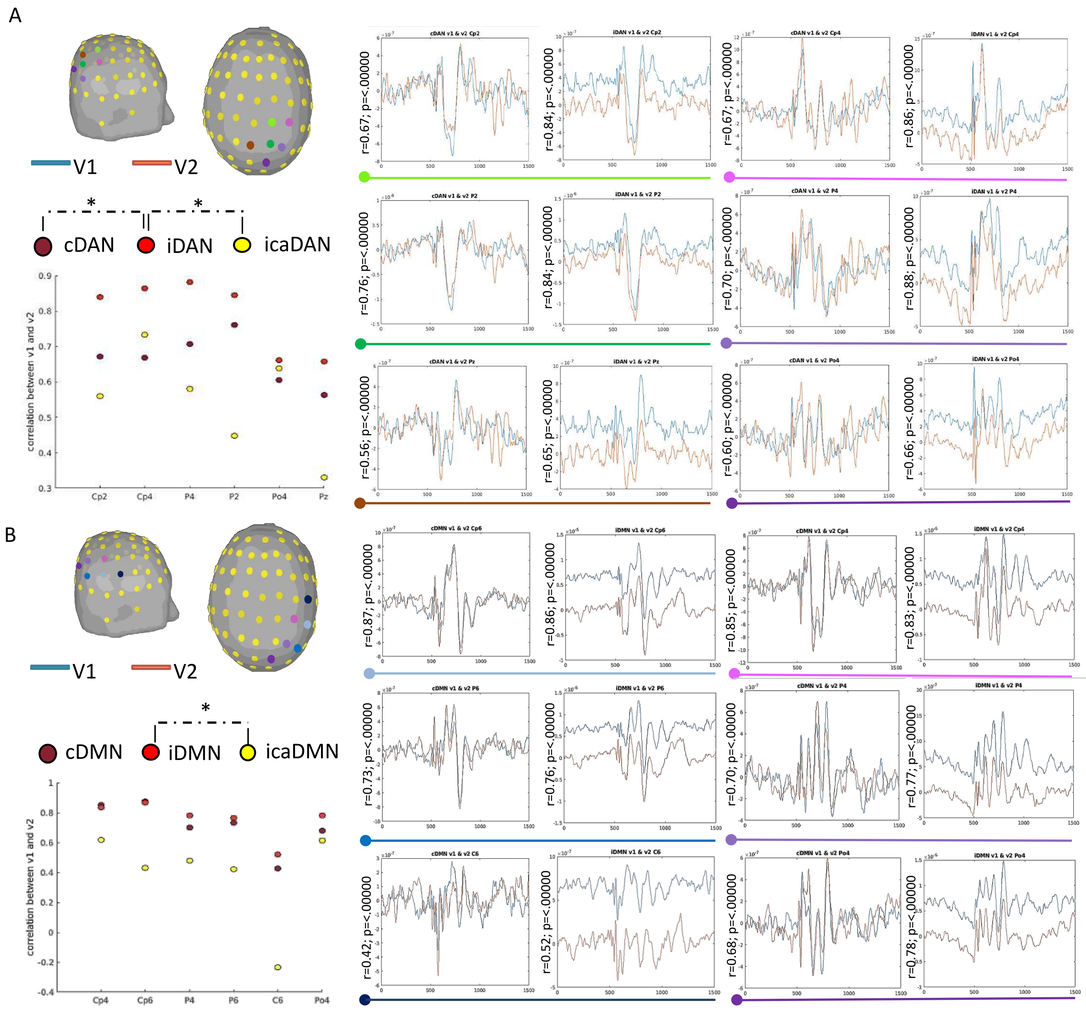

Figure 2. Electrode Level Analyses. TEPs analysis was conducted on the 6 electrodes closer to the stimulation site. A) For the DAN stimulation, higher test-retest reliability was observed for the individualized "i" approach compared to the group-based "c" condition ($t_{(5)}$=-5.51, p=0.003). Subsequent comparison with a small subsample of subjects revealed higher reliability of the "i" approach compared to the "ica" approach ($t_{(5)}$=4.29, p=0.008). B). For the DMN stimulation, no significant difference could be observed between the individualized "i" and group-based "c" approach. However, the "i" approach was observed to outperform the "ica" stimulation condition ($t_{(5)}$=4.28, p=0.008).

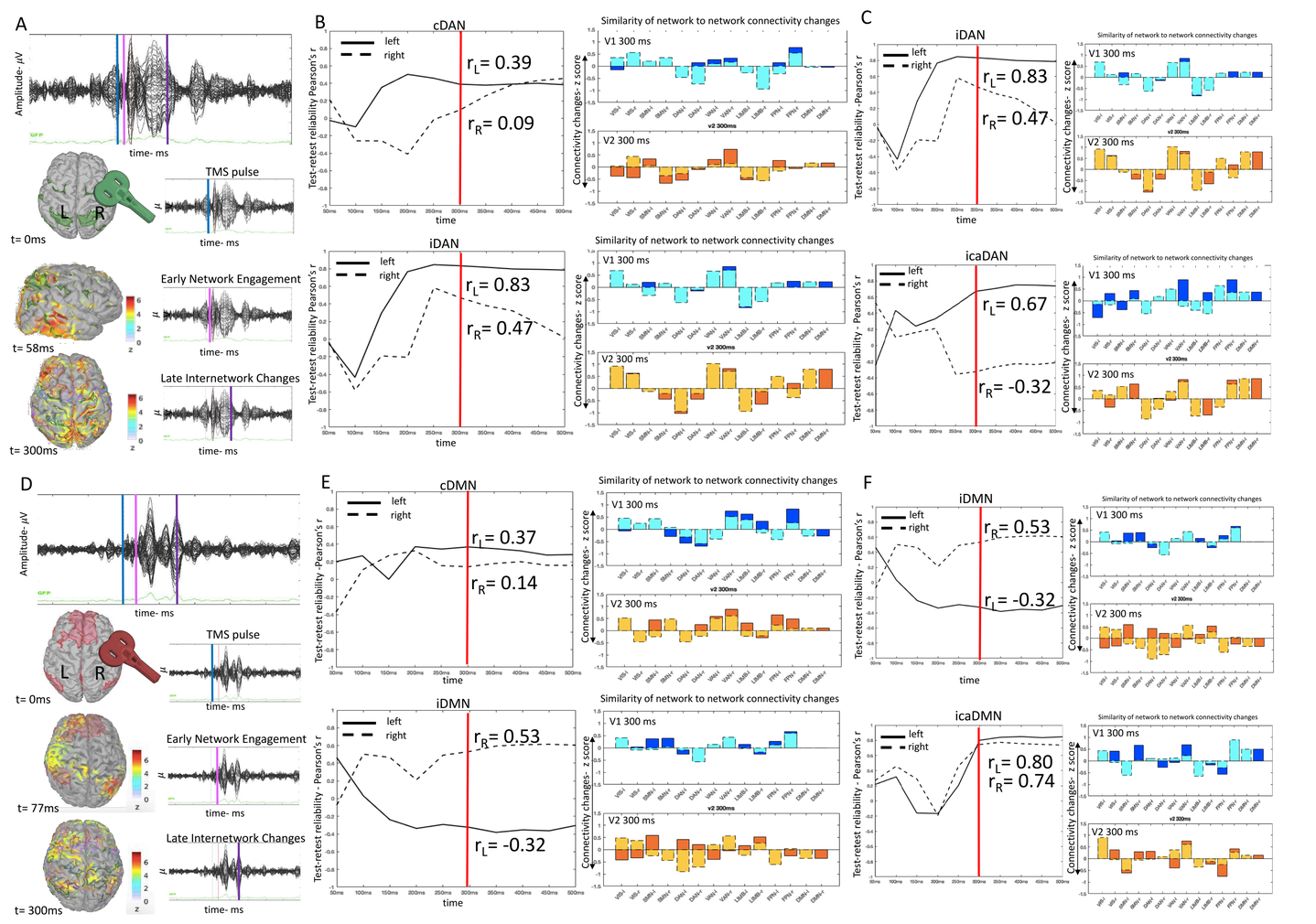

Figure 3. Source Level Analyses. A) The cortical response following the stimulation of the DAN network was computed with a sliding-window approach across the 500ms following the pulse. B) Network-to-network connectivity changes of the left DAN were observed to be more reliable following individualized "i" stimulation compared to the group-based "c" approach ($t_{(9)}$=-2.67,p= 0.02). C) No significant difference was instead observed between the two individualized approaches (i vs ica). D) Analysis of the source response following stimulation of the DMN. E) Network-to-network connectivity changes of both the left and right DMN were observed to be more reliable following individualized "i" stimulation compared to the group-based "c" approach (left: $t_{(9)}$=4.82,p= <0.0001; right: $t_{(9)}$=-5.92,p= <0.0001). F) Left DMN connectivity changes were observed to be even more more reliable in a small subsample of subjects ($t_{(9)}$=-3.71,p= 0.005) following ica-based stimulation.

Conclusions

In the present study we have addressed the test-retest reliability of TMS protocols, which represents a highly debated topic in the literature. In particular, we argue that traditional approaches relies on target selection based on generalized and group-based analyses, which although are time and cost efficient, they also fail to consider interindividual differences in the underlying individual connectome. Indeed, our preliminary results prove that the reliability of various measures, ranging from the electrode to the surface space, can greatly benefit from the individualization of the stimulation target compared to the traditional scenarios. For a small subsample of our subjects, we further added a second and even more individualized approach. However, we mostly didn't observe any desirable higher reliability for this approach, possible due to the insufficient power in the analyses. Future studies in the field should address the magnitude of such increase in the reliability of individualized vs group-based approaches and in particular determine at which point a plateau is reached, thus help finding the best tradeoff between costs and benefits of advanced target selection.

RELEVANT BIBLIOGRAPHY

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