Enhanced resting-state functional connectivity in spatial navigation networks after targeted transcranial direct current stimulation

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Introduction: Spatial navigation is an important function of daily life. Navigation ability (especially allocentric processing) declines with age [1], and in Alzheimer's disease (AD) [2], and enhancing this skill may result in functional improvement in these populations. Previous studies [1,2] have shown that spatial navigation evokes activation in associative areas(posterior and medial parietal regions), spatial memory areas in medial temporal lobe, visual processing (especially scene) areas in occipital (OC) and occipito-temporal cortices, as well as fronto-striatal (FS) networks involved in stimulus response conditioning and semantic processing, and fronto-parietal attention networks. Transcranial direct current stimulation (tDCS) is a non-invasive stimulation technique devised to modulate the cortical excitability and cognition by means of a constant direct current (1-2mA) [3]. TDCS has been seen to enhance visual target detection, which is important for navigation [4]. This paper reports on a pilot study [5] that was devised to explore appropriate brain regions for tDCS-based excitation and inhibition/suppression in order to enhance activation in navigation networks, and monitor the changes through resting state functional connectivity (rsFC) measured with rs-fMRI.

Methods: Six right-handed normal subjects (4 male; mean age ~25 yrs) were first administered tDCS (at 2mA for 20 minutes). The anode was placed at Pz (in the10-20 EEG electrode placement system) over posterior and medial parietal regions since medial superior parietal lobule (SPL) and precuneus (PCUN) exhibited strong BOLD activation during spatial navigation (reported in [5]). The cathode was place at AF4 over right lateral frontal cortex since this region exhibited suppression during spatial navigation [5]. The participants were scanned in a Siemens 3T Tim Trio using a 32-channel array receive-only head coil, 10 minutes after the tDCS session. Informed consent was obtained from all the participants and the protocol was approved by the Emory University Institutional Review Board. Participants underwent a 7-minute rs-fMRI scan during which they lay quietly in the scanner with their eyes open while scans were acquired with an axial whole-brain gradient echo EPI (TR/TE = 3000/24 ms, FA = 90°, in-plane resolution = 3 mm x 3 mm; 48 slices with thickness 3 mm). The fMRI time-series were motion-corrected, spatially normalized to the MNI template, followed by spatial smoothing with a FWHM = 5 mm isotropic gaussian kernel and low-pass filtered (cutoff frequency = 0.1 Hz). ROI-averaged reference vectors were obtained from 5mm spherical seed ROIs placed at predefined areas in SPL, left and right **d**orsol**l**ateral **pref**rontal **c**ortex (LDLPFC and RDLPFC). Cross-correlation analysis on the reference seed vectors were performed on each subject-dataset, as well as on 20 age-matched normal subject-datasets (non-tDCS) from a different study [6]. Student t-test was employed to assess the differences in rsFC between the tDCS-group and the non-tDCS group. The resultant statistical parametric maps were clustered and significance of activation was assessed using Monte Carlo modeling to correct for multiple comparisons (*3dClustSim tool in AFNI*). The results reported in this abstract are controlled for multiple comparisons at $p < 0.05$ at the cluster level. Data analysis was conducted with AFNI and FSL, software suites.

Results: The tDCS group exhibited ***increased*** rsFC compared to non-tDCS group (Fig.1), of SPL with a number of areas involved in navigation including: SPL, precuneus, angular gyrus, anterior hippocampus (Hb), left parahippocampal cortex (PHC), thalamus (THAL) and basal ganglia (BG), lateral LDLPFC, and cerebellum, as did its rsFC to fronto-parietal attention network (frontal eye fields (FEF) and inferior parietal lobule (IPL)). However the SPL-rsFC to right hemisphere posterior fusiform gyrus (FFG) and posterior PHC were ***reduced***. The tDCS group showed ***increased*** rsFC of LDLPFC (Fig.2) with a number of navigation areas: DLPFC, dorsal anterior cingulate, dorsal striatum (DSTr), Hb, posterior PHC and posterior FFG, retrosplenial cortex, occipital cortex, cerebellum and lateral parietal cortex, as well as semantic processing network areas: left inferior frontal gyrus and left superior temporal gyrus (STG). SPL also showed a marked decrease in rsFC with ventrolateral PFC, and increased rsFC with sensorimotor areas. As expected, due to inhibition/suppression of RDLPFC, its rsFC (Fig.3) to spatial navigation areas: SPL, precuneus, and posterior right occipitotemporal cortex were ***reduced***. However, RDLPFC's rsFC to FS networks involved in spatial navigation ***increased***.

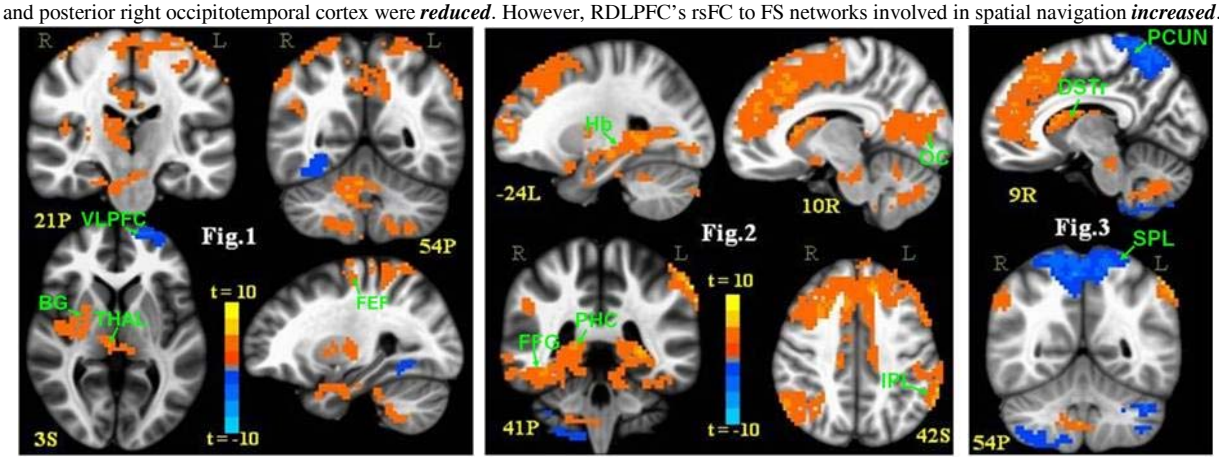

Figure captions
tDCS – non-tDCS rsFC difference t-stat maps (multiple comparison corrected cluster-level $p < 0.05$), for rsFC to
Fig.1: SPL
Fig2: LDLPFC
Fig.3: RDLPFC
Slice locations in MNI co-ordinates

Discussion: The ***goal*** of the project was to enhance connectivity (and hence rsFC) in spatial navigation networks through tDCS. This was ***achieved***, as the tDCS had the ***desired*** effect of ***increasing*** rsFC in most areas of the spatial navigation networks. SPL's rsFC to posterior, medial parietal and medial temporal areas involved in spatial and associative processing [1,2] ***increased*** as did its connectivity to parietal attention networks, which are involved in spatial navigation. LDLPFC also exhibited ***increased*** rsFC with a number of areas associated with spatial navigation. In addition to parietal and medial temporal regions, LDLPFC also exhibited ***increased*** rsFC with FS networks that are involved in strategic control aspects of spatial navigation and left hemisphere language network areas (involved in semantic aspects of navigation). The suppression/inhibition of RDLPFC resulted in the ***desired decrease*** of its rsFC with parietal areas involved in spatial navigation. However rsFC of RDLPFC to FS networks increased. This increase could be due to the modulatory affects of the LDLPFC which can be excited with RDLPFC inhibition [7]. Finally, before this study *there was limited evidence* that tDCS affects areas not relevant to sensorimotor processing. These results ***demonstrate clearly*** that tDCS can be used to *effect changes in other important local and extended brain regions and networks* (e.g. spatial navigation) with exquisite control.

Conclusion: A framework for increasing the connectivity and hence excitability of spatial navigation networks through tDCS, and monitoring the increase in connectivity in navigation through rsFC measured with rs-fMRI, was introduced in this pilot study. The results validate this framework, and future research will aim to refine this approach and apply it to elderly and AD populations.

References: [1] Moffat SD., et al., Neurobiol. Aging, 27:965, 2006; [2] Lithfous S., et al., Ageing Res. Rev., 12:201, 2013; [3] Sehm B., et al., J. Neurophysiol., 108:3253, 2012 ; [4] Medina J., et al., Brain Stimul., 6:433, 2008; [5] Hampstead B., et al., (submitted to Brain Stimul.); [6] Gopinath et al., Proc. ISMRM., 21:2254, 2013; [7] Turriziani P., et al., Front. Hum. Neurosci., 6:62, 2012.