Suppression of Functional Connectivity in Somatosensory and Attention Networks During Strong Transcutaneous Electrical Nerve Stimulation

K Gopinath[1,2], W Ringe[3], L Ouyang[2], K Carter[3], L Butler[2], B Thapa-Chhetry[2], A Goyal[2], P Gandhi[2], H Dinse[4], R Haley[5], and R Briggs[2,5]
[1]*Department of Radiology & Imaging Sciences, Emory University, Atlanta, GA, United States,* [2]*Department of Radiology, UT Southwestern Medical Center, Dallas, TX, United States,* [3]*Department of Psychiatry, UT Southwestern Medical Center, Dallas, TX, United States,* [4]*Institut für Neuroinformatik, Ruhr-University, Bochum, Germany,* [5]*Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, United States*

Introduction: Resting state fluctuations in BOLD fMRI time-series have been increasingly employed to study functional connectivity networks in the brain [1, 2]. FcMRI studies have employed different conditions, e.g. resting with eyes open (REST) [1], visual fixation [2], and continuous bilateral transcutaneous medial nerve stimulation (TENS) [3] to assess brain functional connectivity. Basal ganglia are an integral part of a number of networks studied with fcMRI [1, 2]. The dorsal and ventral striatum (DS and VS, respectively) are thought to engage functionally distinct networks in the brain [4-6]. DS has been associated with connections from dorsolateral prefrontal cortex such as Brodmann (BA) Areas 6, 9, 32, 45, 46, and is involved in stimulus-response learning, attention and cognitive flexibility. VS is connected with ventromedial prefrontal cortex (i.e., ventral portions of BA 10, 11, 12, as well as 24, 25, 38, 47) and is associated with basic drive states, internal motivation and classically conditioned learning. In a previous study [3, 7], we reported increased functional connectivity of DS with somatosensory and attention areas during minimally perceptible TENS compared to REST. In this study we examined resting state striatal functional connectivity networks under REST and strongly perceptible (but not painful) TENS conditions.

Methods: Twenty-eight healthy subjects (21 male, 7 female; mean age = 49.8 yrs) were scanned in a Siemens 3T Tim Trio scanner using a 12-channel array receive-only head coil. Written informed consent was obtained from all participants in the protocol approved by the local Institutional Review Board. In the fcMRI paradigm, subjects lay quietly in the scanner with their eyes open for two 11-minute runs: 1) eyes open resting, a neutral affective condition ("REST"), and 2) strongly perceptible (but not painful) bilateral transcutaneous electrical stimulation ("TENS-Hi") continuously applied to index fingers at 3Hz The subjects were asked to pay attention to the stimulation. FcMRI scans were acquired with a sagittal whole-brain gradient echo EPI (TR/TE = 2000/24 ms, FA = 90 deg, in-plane resolution = 3 mm x 3 mm; 40 slices with thickness 3.5 mm). The fcMRI time-series were corrected for physiological noise [8], registered, spatially normalized to the Talairach template, and low-pass filtered (0-0.1Hz), followed by spatial smoothing with a FWHM = 5 mm isotropic gaussian kernel. ROI-averaged time-series were obtained for bilateral DS and VS, segmented using established practices [9]. Separate voxelwise cross-correlation analyses (CCA) were performed to assess the connectivity of left and right DS and VS with other brain regions. Mixed-effects ANOVA (Condition X Laterality X Subjects) tests were performed on the linear fit coefficient from CCA. A priori ROIs [3] of dorsal somatosensory and attention areas (dorsolateral prefrontal cortex (DLPFC), dorsal anterior cingulate (DACC), paracentral lobule (PCL) and primary somatosensory cortex (S1)) and of ventral limbic areas (ventral ACC (VACC), ventrolateral PFC (VLPC), amygdala and hippocampus) were formed as described in [3]. Multiple comparison correction was achieved by Monte-Carlo modeling to determine significantly activated clusters of voxels [10]. Data analysis was conducted with AFNI, FSL and Matlab.

Results & Discussion: Both REST and TENS-Hi conditions exhibited significant ($p < 0.0001$) functional connectivity of DS and VS with all the a priori ROIs (see left DS functional connectivity map in Figure 1). No significant differences in VS functional connectivity between REST and TENS-Hi conditions were observed, for any of the a priori ROIs. DS exhibited significantly ($p < 0.03$) *weaker* functional connectivity (Figure 2) bilaterally with the dorsal attention and somatosensory ROIs of DLPFC, DACC, PCL and S1 during TENS-Hi compared to REST.

The *weaker* functional connectivity of DS with somatosensory and attention areas during TENS-Hi compared to REST is diametrically opposite to the result of the *stronger* functional connectivity of DS with somatosensory and attention areas that was seen during minimally perceptible continuous bilateral TENS ("TENS-Lo") compared to REST in a separate group of subjects [3, 7]. One reason for this phenomenon could be the decreased attention load engendered by the TENS-Hi condition compared to the TENS-Lo condition, where subjects presumably had to pay more attention to sense the stimuli. Since attention and somatosensory networks are coupled during TENS [11], DS functional connectivity to these networks may also decrease. The decreased low frequency fluctuations in somatosensory networks may also be related to the suppression of ongoing activity after stimulus onset that has been reported in electrophysiological studies [12-13]. These results, combined with previous reports of modulation of striatal connectivity to somatosensory and attention networks by TENS [3, 7], indicate the need to study functional connectivity during TENS by systematically varying stimulus intensity and frequency.

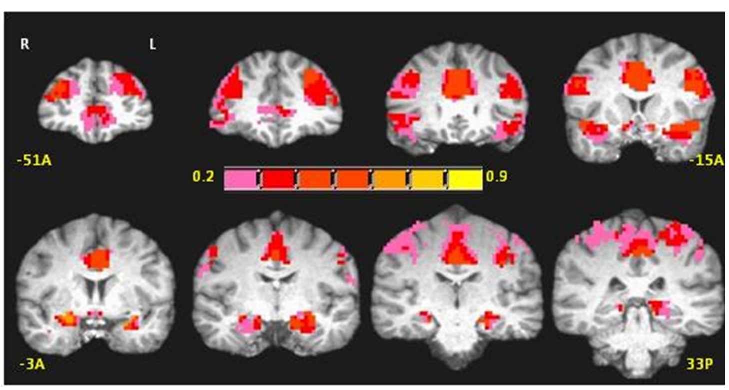

Figure 1: Left DS functional connectivity map ($p < 0.00001$) during REST

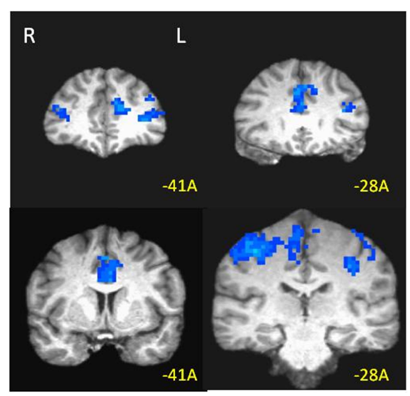

Figure 2: Areas showing significantly ($p < 0.03$) weaker DS functional connectivity in TENS-Hi compared to REST

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