Abnormal Striatal Functional Connectivity in Gulf War Illness: Effects of Modulating fcMRI Continuous States

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Introduction: Gulf War Illness (GWI) is a multi-symptom disorder characterized by cognition (e.g. attention, memory), emotion and somatosensory deficits [1] as well as structural abnormalities in a number of areas including basal ganglia, thalamus and hippocampus [1]. In the basal ganglia the dorsal striatum (DS) is strongly connected with attention and somatosensory networks [2], and ventral striatum (VS) is associated with emotion and default mode networks (DMN) [2,3]. DS and VS are also strongly connected with each other [2]. This study used resting state or functional connectivity MRI (fcMRI) to examine functional connectivity of the DS and VS in GWI veterans with Syndrome1 (Syn1), 2 (Syn2), 3 (Syn3) [4], as well as a healthy control veteran group.

Methods: Ninety-two right–handed Gulf-War Veterans (19 Syn1 (mild cognitive impairment: ages 38-69 yrs; mean 49.2 yrs), 23 Syn2 (severe confusion-ataxia: ages 38-65 yrs; mean 49.4 yrs), 20 Syn3 (central pain: ages 40-67 yrs; mean 49.9 yrs), and 30 controls (ages 39-66 yrs; mean 49.8 yrs)), statistically sampled from a national survey of over 8,000 veterans of the 1991 Gulf War, 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 three 11-minute runs: 1) eyes open resting ("REST"), 2) visual fixation on a red cross presented on a gray background ("FIX") and 3) readily perceptible bilateral transcutaneous electrical stimulation ("TENS") applied to index fingers applied continuously at 3Hz. 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 [5], registered, and wavelet filtered (Daubechies 'db4' wavelet order 1), followed by spatial smoothing with a FWHM = 5 mm isotropic gaussian kernel. ROI-averaged time-series were obtained for DS and VS for both hemispheres, segmented using established practices [6]. Separate voxelwise cross-correlation analyses were performed to assess the connectivity of left and right DS and VS with other brain regions. The linear fit coefficient from cross-correlation analysis from each subject was warped to Talairach template and 3-way (Group X Condition X Laterality) ANOVA was performed to assess inter-group differences in functional connectivity to each of the two striata (DS and VS). The resultant statistical parametric maps were clustered and significance of cluster-level activation was assessed with Monte-Carlo modeling [7].

Results & Discussion: All three syndrome groups exhibited abnormal functional connectivity patterns compared to controls, with strong dependence of between-group functional connectivity differences on the continuous state employed, particularly in Syn2, the most impaired group [1]. Details of Syn1 and Syn3 results will be reported elsewhere. During the REST condition, Syn2 exhibited significantly ($p < 0.05$) weaker functional connectivity than controls between bilateral DS (Figure 1; Table 1) and DMN areas including posterior cingulate, prefrontal cortex, and medial dorsal thalamus. This difference in striatal connectivity to DMN vanished during the FIX condition, and was much reduced in the TENS condition. On the other hand, during FIX Syn2 exhibited significantly ($p < 0.05$) stronger functional connectivity compared to controls between DS and attention, sensory and motor network areas (e.g. DLPFC, IPL, DACC, SMA, S1, S2, insula, M1; see Table 1). This increased DS functional connectivity with sensory and attention areas in Syn2 persisted, though to a lesser extent, during REST. During TENS, Syn2 exhibited stronger DS functional connectivity than controls with somatosensory network areas (e.g. SMA, DACC, S1, S2 and insula). Syn2 also exhibited (not shown) weaker VS (bilateral) functional connectivity than controls during REST with DMN areas (similar to DS), additionally exhibiting less VS connectivity with limbic areas (e.g VLPFC, amygdala and hippocampus). Just as for DS, VS-DMN functional connectivity differences between controls and Syn2 vanished during FIX and TENS. Syn2 also exhibited stronger VS functional connectivity than controls with sensory and attention areas during FIX and TENS, though not as strongly as seen in the DS functional connectivity maps.

Thus functional connectivity differences between controls and Syn2 seems to depend on the continuous state condition employed. During REST, Syn2 exhibited weaker striatal functional connectivity than controls to DMN, which is consistent with an aging model [8] that can be applied to GWI. However, this deficit was not apparent during the more active continuous states, especially during FIX. On the other hand, during FIX and TENS, DS functional connectivity to sensory and attention areas were significantly stronger in Syn2 than controls, indicating hyperarousal/hyperattentiveness during continuous low level sensory stimulation in GWI. The results also lend support to the value of investigating abnormal functional connectivity in diseased populations with multiple continuous states.

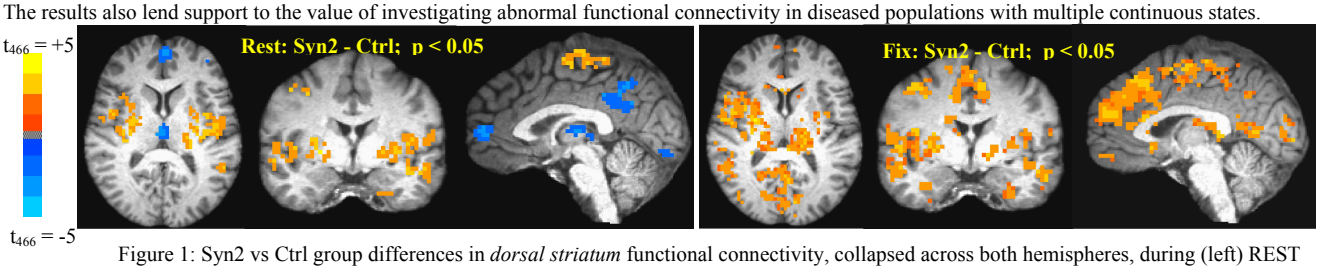

Figure 1: Syn2 vs Ctrl group differences in *dorsal striatum* functional connectivity, collapsed across both hemispheres, during (left) REST and (right) FIX conditions

Table 1: Syn2 vs Ctrl *dorsal striatum* (collapsed across both hemispheres) functional connectivity differences ($p < 0.05$)

REST	
Syn2 > Ctrl ($p < 0.05$)	Bilateral: insula, primary (S1) and secondary (S2) somatosensory cortex, paracentral lobule (PCL), primary motor cortex (M1), ventrolateral (VL) thalamus, supplementary motor area (SMA), inferior parietal lobule (IPL), lateral Brodmann Area 7 (BA7), cuneus, ventral putamen
Syn2 < Ctrl ($p < 0.05$)	Bilateral: ventromedial prefrontal cortex (VMPFC), medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), medial precuneus, medial dorsal (MD) thalamus
FIX	
Syn2 > Ctrl ($p < 0.05$)	Bilateral: insula, S1,S2, PCL, M1, VL thalamus, dorsal anterior cingulate (DACC), dorsolateral prefrontal cortex (DLPFC), SMA, pre-SMA, IPL, lateral BA7, cuneus, ventral putamen
TENS	
Syn2 > Ctrl ($p < 0.05$)	Bilateral: pre-SMA, DACC, insula, S1,S2, superior temporal gyrus (STG), ventral putamen
Syn2 < Ctrl ($p < 0.05$)	Bilateral: VMPFC, MPFC, DACC

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