Analyzing White Matter Integrity Changes Associated with Posttraumatic Stress Disorder in Veterans

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Introduction: War-related posttraumatic stress disorder (PTSD) is a common persistent medical problem in veterans, characterized by recurrent trauma memories, and fear response / physiological reactivity to the trauma reminders [1]. Previous neuroimaging studies have revealed cortical and subcortical abnormalities in PTSD, indicated by the reduced volumes of prefrontal cortex (PFC), anterior cingulate cortex (ACC) and hippocampus [2-3]. Moreover, high-resolution MRI at higher field has facilitated the volumetry to the detailed internal structures of hippocampal subfields, such as the CA3 and dentate gyrus (CA3&DG) [4]. Nevertheless, little is known about the patho-physiological changes of the neuronal pathways connecting these cortical regions. We present here a study using diffusion tensor imaging (DTI) to measure the axonal integrity of WM tracts in both PSTD and healthy veterans. We aim to detect the regional changes of fractional anisotropy (FA) in PTSD, and reveal the correlations with PTSD severity and the related hippocampal subfields. We hypothesized that significant correlations should appear on the WM tracts approximating cortical regions, such as PFC and ACC, which are known to be associated with PTSD pathology.

Methods: Veteran volunteers of PTSD positive diagnosis (N=19, all male, age=41±13 yrs) with trauma exposure measured by structured Clinical-Administrated PTSD Scale (CAPS) [5] (mean=61±13) participated the present MRI study. An age-matched group of PTSD negative veterans (N=19, all males, age=41±15 yrs) served as the controls. Subjects were excluded if they had diagnosis of any other neurological disorder, central nervous system infection, seizures, or history of alcohol and/or drug abuse. Each subject had MRI scans at 4T (Siemens) equipped with 8-channel body coil to acquire DTI, fluid-attenuated inversion recovery (FLAIR), T1-weighted imaging (MPRAGE), and a high-resolution T2 weighted imaging for hippocampal subfield volumetry. MRI data showing strong motion artifact or with substantial presence of WM lesion, identified as abnormal hyperintensities in the FLAIR image, were also excluded from the analysis. The tract-based spatial statistics (TBSS) technique [6] was implemented for DTI post-processing and spatial normalization. The bilateral averaged subfields volumes were obtained based on a manual marking procedure on the high-resolution T2 image as described in [4]. A 3-D multivariate linear regression analysis program (3dRegAna) from the Analysis of Functional NeuroImage (AFNI) [7] was applied to account for age effects, and estimate the PTSD-related WM alternations.

Results: Compared with controls, reduced FA ($p<0.01$) in PTSD is shown as blue clusters overlaid on the mean FA map of all subjects in Fig.1, primarily distributed on the WM in prefrontal lobe, internal capsule, and cingulate bundle. In the PTSD patient group, significant negative correlations ($p<0.01$) between FA and CAPS are found in the WM tracts nearby PFC and ACC, as shown in Fig.2, indicating that the regional degradation of WM integrity are parallel with increasing clinical measurements to the PTSD severity. For hippocampal subfield study, CA3&DG volumes exhibit the most significant reduction in PTSD, which will be reported separately. In Fig.3, the significant correlations ($p<0.01$) between FA and CA3&DG volumes in the PTSD group are found again in the WM tracts approximating PFC and ACC. The red clusters here represent a positive correlation, suggesting that the reduced CA3&DG volumes are associated with reduced FA in these regions.

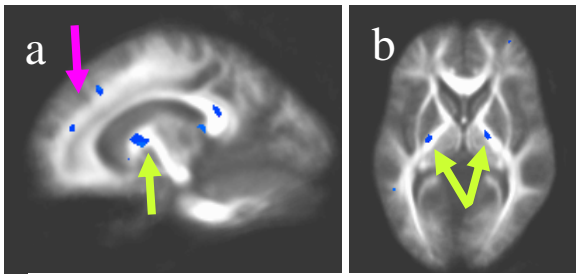

Fig 1: Reduced FA in PTSD (a) Sagittal and (b) Axial.

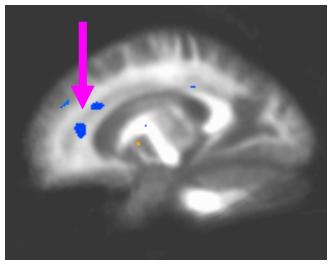
Fig 2: FA~CAPS correlations in PTSD.

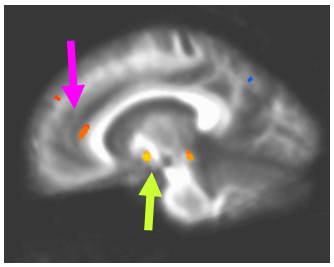
Fig 3: FA~CA3-DG correlations

Discussion: As hypothesized, PTSD-related FA reductions are revealed in WM tracts close to PFC and ACC, supporting the results of previous voxel-based morphometry (VBM) [2-3] and ROI-based DTI [8] studies. Furthermore, consistent regional patterns are demonstrated for correlations of FA with either CAPS scores or CA3&DG volumes in PTSD. Taken together, our data demonstrate the strong associations among the increased PTSD severity, reduced hippocampal CA3&DG volume, and the damaged axonal integrity in the WM tracts connecting the cortical / subcortical areas, which play an important role in PTSD pathology. The neural mechanism of the DTI abnormalities and the involvement of motor function related areas, e.g. internal capsule, will be further investigated by including other modalities, such as cortical thickness analysis.

Reference: [1] Nayback, J Psychosoc Nurs Ment Health Serv. 46(6):41-51, 2008. [2] Bryant et al., J Psychiatry Neurosci, 33:142-146, 2008. [3] Jatzko et al., J Affective Disord, 94:121-126, 2006. [4] Mueller et al. Neurobiol Aging, 28:719–726, 2007. [5] Blake et al., J Trauma Stress, 8:75-90, 1995. [6] Smith S.M, et al., NeuroImage, 31:1487-1505, 2006. [7] http://afni.nimh.nih.gov/afni. [8] Kim et al., NeuroReport, 16:1049-1053, 2005.