White matter microstructure of the uncinate fasciculus is associated with subthreshold posttraumatic stress disorder symptoms and fear potentiated startle during early extinction in recently deployed Service Members.

Michelle E. Costanzo^{a,b,c}, Tanja Jovanovic^d, Dzung Pham^e, Suzanne Leaman^a, Krista B. Highland^{a,b,c}, Seth Davin Norrholm^{d,f}, Michael J. Roy^{a,c}

^aUniformed Services University of the Health Sciences, Department of Medicine, Bethesda, MD, USA

^bThe Henry M. Jackson Foundation, Bethesda, MD, USA

^cCenter for Neuroscience and Regenerative Medicine, Bethesda, MD, USA

^dEmory University School of Medicine, Department of Psychiatry & Behavioral Sciences, Atlanta, GA, USA

^eImage Processing Core, Center for Neuroscience and Regenerative Medicine, The Henry M. Jackson Foundation, 10 Center Drive, Bethesda, MD, USA

^fMental Health Service Line, Atlanta Veterans' Affairs Medical Center, Decatur, GA, USA

Address correspondence to Michael J. Roy, MD, MPH, Uniformed Services University of the Health Sciences, Department of Medicine, 4301 Jones Bridge Road, Bethesda MD 20814-4799

Email: michael.roy@usuhs.edu, phone (301) 295-9601

Abstract

Early intervention following combat deployment has the potential to prevent posttraumatic stress disorder (PTSD), but there is a need for greater understanding of the factors that contribute to PTSD symptom progression. This study investigated: (1) fear-potentiated startle during a fear extinction, (2) white matter microstructure, and (3) PTSD symptom severity, in 48 recently deployed service members (SMs) who did not have sufficient PTSD symptoms to meet criteria for a clinical diagnosis. Electromyography startle during a conditional discrimination paradigm, diffusion tensor imaging, and the Clinician Administered PTSD Scale were assessed in a cohort of SMs within 2 months after their return from Iraq or Afghanistan. Significant correlations were found between left uncinate fasciculus (UF) white matter tract integrity and total PTSD symptoms, $r = -0.343$, $p = 0.018$; the left UF and hyperarousal symptoms, $r = -0.29$, $p = 0.047$; right UF integrity and total PTSD symptoms $r = -0.3371$, $p = 0.01$; right UF integrity and hyperarousal symptoms $r = -0.332$, $p = 0.023$; left UF and startle during early extinction, $r = 0.31$, $p = 0.033$. Our results indicate that compromise of UF tract frontal-limbic connections are associated with greater PTSD symptom severity and lower startle response during extinction. In a subthreshold population, such a relationship between brain structure, physiological reactivity, and behavioral expression may reveal vulnerabilities that could have significant implications for PTSD symptom development.

Keywords: subthreshold PTSD, fear-potentiated startle, diffusion tensor imaging, combat veterans

Introduction

Posttraumatic stress disorder (PTSD) is a signature mental health consequence of combat, including the Global War on Terror. However, resilience to combat stress is actually the norm for service members (SMs), as more than three-quarters of Iraq and Afghanistan veterans have not meet criteria for PTSD upon return from deployment [1]. In order to better understand susceptibility to the development of PTSD, this study examined a cohort of SMs within two months of their return from deployment, who exhibited a range of subthreshold PTSD symptoms, in order to explore the impact of recent combat stress exposure. Subthreshold PTSD (also called partial, subclinical, subsyndromal, subdiagnostic or preclinical PTSD) encompasses those with an insufficient number or distribution of symptoms to meet full Diagnostic and Statistical Manual of Mental Disorders based diagnostic criteria, which can nevertheless result in significant functional impairment [2]. Focus on this early clinical timeframe, particularly immediately following deployment, may be critical to better understanding the factors that contribute to PTSD vulnerability and subsequent symptom progression. Efforts to prevent PTSD through early intervention have revealed a critical window for fear activation and extinction of conditioned responses related to traumatic memories [3]. Thus, further investigation of the candidate neural substrates crucial to clinical outcomes may afford valuable insight to inform future study of posttraumatic sequelae.

Neurobiological investigations of PTSD have identified a fundamental role for the medial prefrontal cortex (mPFC), amygdala, and hippocampus in symptom presentation, particularly with regard to impaired fear inhibition and extinction learning [4]. Furthermore, the degree of integrity of the white matter tracts within this limbic-prefrontal circuitry appears to correlate with fear extinction learning [5]. Specifically, the white matter microstructure of the uncinate

UNCINATE FASCICULUS, PTSD SYMPTOMS, STARTLE

fasciculus (UF), a fiber tract connecting the amygdala with the mPFC, and the cingulum, a white matter bundle that connects the hippocampus and frontal cortical regions, have been reported to be negatively associated with anxiety symptoms [6, 7] and fear-potentiated startle (FPS) [5], respectively. Thus, compromised connectivity between these regions may impair extinction learning processes following exposure to combat stress, which in turn, could lead to elevated fear-related PTSD symptoms (e.g., re-experiencing, intrusive memories). The current study employed Diffusion Tensor Imaging (DTI) to examine the white matter microstructure of the UF and cingulum, a well-established conditional discrimination paradigm to examine FPS during extinction learning [8] and the gold-standard Clinician Administered PTSD Scale (CAPS) [9] to assess PTSD symptom severity. We hypothesized a negative relationship between the (1) white matter microstructure integrity in the UF and PTSD symptoms; (2) white matter microstructure integrity in the cingulum and PTSD symptoms; (3) white matter microstructure integrity in the UF and FPS during early extinction; and (4) white matter microstructure integrity in the cingulum and FPS during early extinction. We also predicted a positive relationship between FPS during early extinction and PTSD symptoms.

Methods

Participants

Forty-eight (42 male, 6 female) SMs, who had been deployed for at least 3 months to either Iraq or Afghanistan (Operations Iraqi Freedom/Operation New Dawn, OIF/OND, and Operation Enduring Freedom, OEF, respectively), were assessed within 2 months after their return and were included in the analyses. The mean age of participants was 29.5 years (SD 8.0; range 19-51) and participants were drawn from military units across the continental United States. Four identified

UNCINATE FASCICULUS, PTSD SYMPTOMS, STARTLE

themselves as African-American, 31 as Caucasian, 2 as Asian, and 4 as Hispanic, while 7 declined to provide a racial identity. SMs reported a mean 8.2 (SD 4.8) years of service and 1.6 (SD 1.1) deployments. Exclusion criteria included the presence of an unstable medical condition; active suicidal or homicidal ideation; psychotic features; a reported history of combat head injury (based on the Defense Veteran's Brain Injury Center (DVBIC) screen, International Classification of Diseases, 10th Clinical Modification (ICD-10) criteria for postconcussive syndrome, a physician-administered history and physical assessed for combat TBI and consequent PCS and the mini-version of the Military Acute Concussion Evaluation (MACE)); a PTSD Checklist, Military version (PCL-M) [10] score of 50 or more; or a Patient Health Questionnaire-9 (PHQ-9) [11] score of 10 or more. In addition, the CAPS was utilized to confirm that participants did not meet criteria for PTSD.

Procedure

The study design was approved by institutional review boards at Walter Reed National Military Medical Center (WRNMMC), Uniformed Services University of the Health Sciences (USUHS), and the National Institutes of Health (NIH), and written informed consent was obtained from each participant. Psychophysiological and clinical assessments were completed at the National Intrepid Center of Excellence at WRNMMC. FPS was assessed during a conditional discrimination paradigm that has been previously utilized with PTSD populations [8]. Electromyography (EMG) recordings of the startle reflex to a 106dB white noise acoustic probe (termed noise alone trials, or NA) were acquired with a Biopac MP150 for Windows (Biopac Systems, Inc., Aero Camino, CA) sampled at 1000 Hz, digitized at 16 bit A/D resolution, and amplified using Biopac Acknowledge software. The conditioned stimuli were two colored geometric shapes presented on a computer monitor. During conditioning, one shape (termed the reinforced conditioned stimulus or CS+; see [8, 12]) was always

UNCINATE FASCICULUS, PTSD SYMPTOMS, STARTLE

paired with an aversive airblast (termed the unconditioned stimulus, US) while the other shape was never paired with the airblast (termed the non-reinforced conditioned stimulus or CS-). During the six blocks of extinction, neither shape was paired with the airblast. Each block consisted of four trial types of each type (NA, CS+, CS-). Startle probes were delivered on each trial. CAPS assessments were completed on the same day by a licensed psychologist. DTI was completed at the National Institutes of Health Clinical Center. Diffusion weighted images were acquired on a Siemens Biograph mMR 3T scanner with parameters TR=17000ms, TE=98ms, Flip angle=90 degrees, Voxel size=2x2x2mm, Matrix size=128x128, and Slices=75. The acquisition phase included 10 images at $b=0$ s/mm², 10 images with non-collinear directional gradients at $b=300$ s/mm², and 60 images with non-collinear directional gradients at $b=1100$ s/mm².

Data Analysis

Electromyograph (EMG) data were band pass filtered at 28-500Hz and rectified, consistent with previous studies[5]. Difference scores used to measure startle were computed by extracting the peak amplitude recorded between 20 and 200 ms after the startle probe offset and subtracting the startle magnitude in response to the NA (noise alone) probe from the startle magnitude in the presence of a conditioned-stimulus in each conditioning block. DTI images were processed using the CATNAP software for tensor estimation [13]. Briefly, images were preprocessed for motion correction and eddy current correction, with adjustments to the gradient table performed based on anatomical position relative to diffusion sensitization, and diffusion tensors. Distortions due to echo planar imaging (EPI) susceptibility artifacts were corrected by performing a deformable registration to an anatomic T2-weighted acquisition (TR=3200ms, TE=409ms, Flip angle=120 degrees, Voxel size=1x1x1mm, Matrix size=256x256, Slices=176). Specifically, mutual-information registration was used by taking the undistorted anatomical T2 images to correct the geometry of the distorted EPI diffusion-weighted

UNCINATE FASCICULUS, PTSD SYMPTOMS, STARTLE

acquisitions, which corrects geometric distortion and co-registers the diffusion-weighted images to structural images. Linear tensor estimation was performed, followed by computation of fractional anisotropy (FA), and segmentation of white matter tracts with the Diffusion-Oriented Tract Segmentation (DOTS) software [14]. IBM SPSS Statistics was used for repeated measures ANOVA, t-test, and Pearson correlations.

Results

PTSD Symptoms

The mean CAPS sub scale scores were 3.73 (SD 3.65, range 0-12) for re-experiencing symptoms, 5.08 (SD 4.51, range 0-21) for avoidance symptoms, and 10.1 (SD 5.97, range 0-24) for hyperarousal symptoms. The mean total CAPS score was 18.92 (SD 9.92, range 2-46), see Figure 1.

Fear-Potentiated Startle

Repeated measures ANOVA [CS Type (CS+, CS-)*Block (1,2,3)] of FPS during fear acquisition revealed a significant CS Type* Block interaction $F(2,43)=10.19$ $p < 0.001$, with FPS increasing over the blocks for CS+ relative to CS-. Examination of FPS to the CS+ during the extinction phase using repeated measures ANOVA [Block (1,2,3,4,5,6)] revealed a main effect for Block $F(5,43)=6.06$, $p < 0.001$, with FPS to the CS+ significantly decreasing across blocks.

White Matter Microstructure and PTSD Symptoms

Figure 2 provides graphic displays of the significant relationships between uncinate fasciculus integrity and PTSD symptoms. Bivariate correlation between the left UF integrity and total PTSD symptoms revealed a significant inverse correlation ($r = -0.343$, $p = 0.018$), while

UNCINATE FASCICULUS, PTSD SYMPTOMS, STARTLE

controlling for age. Further analysis of symptom clusters revealed a significant inverse correlation between left UF integrity and hyperarousal ($r=-0.29$, $p = 0.047$). Significant inverse correlations were similarly observed between right UF integrity and total PTSD symptoms ($r=-0.3371$, $p =0.01$), as well as between right UF microstructural integrity and hyperarousal $r =-0.332$, $p=0.023$ (Figure 2). No significant correlations were observed for re-experiencing or avoidance symptoms and UF integrity, nor between PTSD symptoms and cingulum microstructural integrity.

White Matter Microstructure and FPS

Bivariate correlations between FPS during CS+ of acquisition and white matter microstructure were not significant (controlling for age). Bivariate correlation revealed a significant positive correlation between left UF integrity and FPS during early extinction (block 1), $r=.31$, $p =0.033$ (Figure 3) and a trending positive correlation between right UF integrity and FPS during early extinction, $r=.28$, $p =0.06$, controlling for age. To further explore this relationship, UF integrity and FPS were examined, controlling for total PTSD and hyperarousal symptoms. There was a significant positive correlation between the left UF integrity and FPS during early extinction (block 1) when controlling for total PTSD symptoms $r=.3$, $p =0.048$ and hyperarousal symptoms $r=.35$, $p= 0.018$. Examination of the right UF integrity and FPS during early extinction revealed a trending positive correlation when controlling for total PTSD symptoms $r=.26$, $p=0.08$, and a significant positive correlation when controlling for hyperarousal symptoms $r = .32$, $p =0.028$. . No correlations were observed between cingulum microstructural integrity and FPS measures.

PTSD symptoms and FPS

UNCINATE FASCICULUS, PTSD SYMPTOMS, STARTLE

Bivariate correlations revealed that there were not any significant relationships between FPS during early extinction and PTSD symptoms in this population (Cluster B and FPS, $r=-.275$, $p=0.059$; Cluster C and FPS, $r=-.102$, $p=.49$; Cluster D and FPS $r= -.162$, $p =.276$; Total Symptoms and FPS $r=-.255$, $p=0.083$), see electronic supplementary material.

Discussion

Investigation of SMs recently exposed to combat stress, who do not have sufficient PTSD symptoms for a clinical diagnosis, represent an important population with which to better understand vulnerability to the development of PTSD. Consistent with our hypothesis, reductions in UF white matter microstructural integrity were associated with elevated hyperarousal symptoms and overall PTSD symptoms. Although we predicted that degraded white matter microstructure would be related to elevated FPS response, this was not evident in our population, as those with less white matter integrity demonstrated lower startle. Moreover, our data did not reveal a significant relationship between startle and PTSD symptoms. In summary, compromised frontal-limbic connections mediated by the UF tract are associated with higher PTSD symptom severity and lower startle response during extinction.

There are several possible explanations for our results. Psychological models of PTSD indicate that hyperarousal symptoms may lead to maladaptive coping such as avoidance and emotional numbing [15, 16] and thus tend to predict avoidance and re-experiencing symptom clusters of PTSD [17-19]. Therefore our data may represent an early clinical period, during which differences in the white matter microstructure, which connects the amygdala to the mPFC, could impact fear processing, thereby enhancing susceptibility to hyperarousal symptoms following combat stress. Consistent with this notion, examination of specific PTSD symptoms has suggested that hyperarousal may be more closely linked to compromised prefrontal inhibition, whereas re-experiencing may relate to FPS and hyperactivity of the amygdala[8]. Thus our results suggest that those with reduced UF tract connections may be exhibiting

UNCINATE FASCICULUS, PTSD SYMPTOMS, STARTLE

compromised inhibitory control, accounting for elevated hyperarousal and overall symptoms, without translating into elevated FPS during extinction. Furthermore, given that our population was assessed in close temporal proximity to combat stress, it is possible that those with white matter dysfunction would present the “fear load” phenotype of elevated FPS during extinction if symptoms persisted or increased over time [12]. Thus, the more typical presentation of a positive relationship between FPS during extinction and PTSD symptoms may be specific to those with more severe symptoms. Alternatively, given the putative role of the UF in memory and emotion [20], it is possible that the attenuated startle in those with degraded UF white matter may reveal a deficit in fear extinction learning, perhaps through a failure in fear activation. A blunted startle response such as this could then, in turn, potentially increase susceptibility to chronic problems due to communication deficits between affect-generating and affect-modulating brain regions, interfering with activation of extinction processes to reduce conditioned fear responses. Furthermore, it may be a reflection of blunted responding in those with higher symptoms of higher trauma exposure (for example if individuals had early childhood trauma or repeated traumatic events), which has been observed in some populations with exposure to multiple traumatic events [21], but this would need to be further examined in follow up studies. In addition, we cannot rule out the possibility that given the recent proximity to combat stress, we may be detecting an allostatic effect which could represent an adaptive change or stress response that is essential for survival when deployed [22]. Indeed, a key element of resilience is neural plasticity, thus we cannot say with certainty that these changes are negative [22]. Future studies would benefit from more detailed longitudinal follow up assessments to help determine if these effects definitively relate to resilience or vulnerability. Nonetheless, given the significance of the hyperarousal symptoms and evidence that allostatic overload can

UNCINATE FASCICULUS, PTSD SYMPTOMS, STARTLE

lead to pathophysiology[22], our results may still reveal important insight into vulnerabilities to PTSD development; however, additional studies are needed to understand these relationships.

We did not observe a relationship between the integrity of the cingulum and either FPS or PTSD symptom severity. We previously identified a relationship between cingulum integrity and the severity of re-experiencing symptoms of PTSD in SMs with a history of combat TBI [23], while others have seen the same in civilians [5]. Chronic stress may lead to amygdala sensitization and cingulum remodeling, leading to structural changes that could further impact symptom severity [24], but further investigation is required.

There are several limitations to this work. First, all data were obtained post-deployment. As such, we cannot be certain whether the observed structural differences relate to stress exposure or pre-existing individual differences. Pre-deployment data would further improve our understanding of vulnerability factors associated with PTSD. In addition, we only examined the index trauma of each participant related to combat, so we do not know how childhood traumas or total trauma history may contribute to our findings. There is evidence that early and repeated trauma exposure can result in changes in white matter, FPS and mental health outcomes [21, 25, 26], so to some extent our data represent a culmination of life experiences and endogenous factors; however greater detail on trauma history could inform if a dose response relationship is present. We did, however, control for PTSD symptoms when examining the relationship between FPS and UF integrity, suggesting that vulnerability be a greater contributing factor to our results rather than trauma load. In addition, the cross-sectional design does not allow causal inference between neural structure, physiological response, and PTSD symptoms and the study would be strengthened by comparing SMs with PTSD during a similar period of recent combat deployment

UNCINATE FASCICULUS, PTSD SYMPTOMS, STARTLE

in order to further explore the relationship between white matter microstructure and PTSD symptoms. Further studies are needed to examine these associations.

Conclusion

In summary, careful assessment of those recently returned from combat with subthreshold symptoms may reveal greater understanding of those at risk for PTSD development, which could lead to beneficial early intervention. Our results suggest a dynamic relationship between brain structure, physiological reactivity and behavioral expression. These hypothesis-generating results suggest avenues for further elucidating the neural mechanisms through which trauma leads to PTSD for some, while affording protection to others.

Acknowledgements

This research was supported by a grant from the Center for Neuroscience and Regenerative Medicine (CNRM) and Henry M. Jackson Foundation for the Advancement of Military Medicine. Any opinions or assertions expressed are solely those of the authors and do not necessarily represent those of Uniformed Services University, the U.S. Army, U.S. Navy, Department of Defense, or the U.S. Government. There are no financial contributions, dual commitments or other potential conflicts of interest.

References

1. Fulton, J.J., et al., *The prevalence of posttraumatic stress disorder in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans: A meta-analysis*. J Anxiety Disord, 2015. **31**: p. 98-107.
2. Mylle, J. and M. Maes, *Partial posttraumatic stress disorder revisited*. J Affect Disord, 2004. **78**(1): p. 37-48.
3. Rothbaum, B.O., et al., *Early intervention may prevent the development of posttraumatic stress disorder: a randomized pilot civilian study with modified prolonged exposure*. Biol Psychiatry, 2012. **72**(11): p. 957-63.
4. Jovanovic, T. and S.D. Norrholm, *Neural mechanisms of impaired fear inhibition in posttraumatic stress disorder*. Front Behav Neurosci, 2011. **5**: p. 44.
5. Fani, N., et al., *Fear-potentiated startle during extinction is associated with white matter microstructure and functional connectivity*. Cortex, 2015. **64**: p. 249-59.
6. Phan, K.L., et al., *Preliminary evidence of white matter abnormality in the uncinate fasciculus in generalized social anxiety disorder*. Biol Psychiatry, 2009. **66**(7): p. 691-4.
7. Tromp, D.P., et al., *Reduced structural connectivity of a major frontolimbic pathway in generalized anxiety disorder*. Arch Gen Psychiatry, 2012. **69**(9): p. 925-34.
8. Norrholm, S.D., et al., *Fear extinction in traumatized civilians with posttraumatic stress disorder: relation to symptom severity*. Biol Psychiatry, 2011. **69**(6): p. 556-63.
9. Weathers, F.W., T.M. Keane, and J.R. Davidson, *Clinician-administered PTSD scale: a review of the first ten years of research*. Depress Anxiety, 2001. **13**(3): p. 132-56.
10. Forbes, D., M. Creamer, and D. Biddle, *The validity of the PTSD checklist as a measure of symptomatic change in combat-related PTSD*. Behav Res Ther, 2001. **39**(8): p. 977-86.

UNCINATE FASCICULUS, PTSD SYMPTOMS, STARTLE

11. Spitzer, R.L., K. Kroenke, and J.B. Williams, *Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire*. JAMA, 1999. **282**(18): p. 1737-44.
12. Norrholm, S.D., et al., *Fear load: The psychophysiological over-expression of fear as an intermediate phenotype associated with trauma reactions*. Int J Psychophysiol, 2014.
13. Landman, B.A., et al., *System for integrated neuroimaging analysis and processing of structure*. Neuroinformatics, 2013. **11**(1): p. 91-103.
14. Bazin, P.L., et al., *Direct segmentation of the major white matter tracts in diffusion tensor images*. Neuroimage, 2011. **58**(2): p. 458-68.
15. Foa, E.B., D.S. Riggs, and B.S. Gershuny, *Arousal, numbing, and intrusion: symptom structure of PTSD following assault*. Am J Psychiatry, 1995. **152**(1): p. 116-20.
16. Litz, B.T., et al., *Predictors of emotional numbing in posttraumatic stress disorder*. J Trauma Stress, 1997. **10**(4): p. 607-18.
17. Stam, R., *PTSD and stress sensitisation: a tale of brain and body Part 1: human studies*. Neurosci Biobehav Rev, 2007. **31**(4): p. 530-57.
18. Weems, C.F., et al., *A prospective test of the association between hyperarousal and emotional numbing in youth with a history of traumatic stress*. J Clin Child Adolesc Psychol, 2003. **32**(1): p. 166-71.
19. Schell, T.L., G.N. Marshall, and L.H. Jaycox, *All symptoms are not created equal: the prominent role of hyperarousal in the natural course of posttraumatic psychological distress*. J Abnorm Psychol, 2004. **113**(2): p. 189-97.
20. Von Der Heide, R.J., et al., *Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis*. Brain, 2013. **136**(Pt 6): p. 1692-707.

UNCINATE FASCICULUS, PTSD SYMPTOMS, STARTLE

21. McTeague, L.M., et al., *Aversive imagery in posttraumatic stress disorder: trauma recurrence, comorbidity, and physiological reactivity*. Biol Psychiatry, 2010. **67**(4): p. 346-56.
22. Karatsoreos, I.N. and B.S. McEwen, *Psychobiological allostasis: resistance, resilience and vulnerability*. Trends Cogn Sci, 2011. **15**(12): p. 576-84.
23. Costanzo, M.E., et al., *Connecting combat-related mild traumatic brain injury with posttraumatic stress disorder symptoms through brain imaging*. Neurosci Lett, 2014. **577C**: p. 11-15.
24. Fani, N., et al., *White matter integrity in highly traumatized adults with and without post-traumatic stress disorder*. Neuropsychopharmacology, 2012. **37**(12): p. 2740-6.
25. Daniels, J.K., et al., *White matter integrity and its relationship to PTSD and childhood trauma--a systematic review and meta-analysis*. Depress Anxiety, 2013. **30**(3): p. 207-16.
26. Wu, G., et al., *Understanding resilience*. Front Behav Neurosci, 2013. **7**: p. 10.

Figures

Figure 1: Range of symptom severity. Histograms illustrate frequency of symptoms based on symptom clusters and total PTSD symptoms.

Figure 2: Associations between the white matter microstructure integrity of the uncinate fasciculus and PTSD symptoms. Scatterplots illustrate significant inverse correlations bilaterally between fractional anisotropy (FA), and overall PTSD symptoms as well as hyperarousal, respectively.

Figure 3: Relationship between the white matter microstructure of the uncinate fasciculus and fear potentiated startle (FPS) during early extinction (left panel). Scatterplot illustrate significant positive correlations between fractional anisotropy (FA) and startle. Rendering of Uncinate Fasciculus based on the Diffusion-Oriented Tract Segmentation mask overlaid on a sagittal slice (right panel).

Figure 1

Figure2

Figure3