Title: Translational plasma lipidomic profiling in military populations with TBI, PTSD and TBI+PTSD and correlation to mouse models of these conditions.

Author names and affiliations:

Authors: Tanja Emmerich[1, 2, 3], Laila Abdullah[1, 2, 3],Gogce Crynen[1, 2], Michael Dretsch[4, 5], James Evans[1], Ghania Ait-Ghezala[1, 2, 3], Jon Reed[1, 3], Hannah Montague[1], Helena Chaytow[1], Justin Martin[1], Robert Pelot[1, 2, 3], Scott Ferguson[1,2, 3], Benoit Mouzon[1,2,3], Joseph Ojo[1,2,3], Alex Bishop[1], John Phillips[1], Venkatarajan Mathura[1, 2, 3], Michael Mullan[1, 2], and Fiona Crawford [1, 2, 3].

Affiliations:

1. The Roskamp Institute, 2040 Whitfield Avenue, Sarasota, FL, 34243, U.S.A.

2. The Open University, Walton Hall, Milton Keynes, Buckinghamshire MK7 6AA, U.K.

3. James A. Haley Veteran's Hospital, 13000 Bruce B. Downs Blvd., Tampa, FL, 33612,

4. National Intrepid Center of Excellence, Walter Reed National Military Medical Center, 4860 South Palmer Road, Bethesda, MD 20889-5849, USA

5. U.S. Army Aeromedical Research Laboratory, 6901 Farrel Road, Fort Rucker, AL 22206, USA

Corresponding author:

Tanja Emmerich; The Roskamp Institute, 2040 Whitfield Avenue, Sarasota, FL, 34243, U.S.A.; temmerich@roskampinstitute.net

Abstract

Background: Traumatic brain injury (TBI) is often associated with long-term sequelae including neurological dysfunction. In military service members and veterans there is a high prevalence of comorbid TBI and posttraumatic stress disorder (PTSD) due to the inherent risk of psychological trauma associated with combat. An objective panel of biomarkers for TBI, PTSD and TBI+PTSD comorbidity would enable acute triage and appropriate medical management, and may indicate ongoing pathogenic processes, provide guidance in therapeutic development, and could be used to monitor outcome and response to treatment.

Methods: In this study we generated plasma phospholipid (PL) profiles in a cohort of 120 active-duty soldiers diagnosed with these conditions, via liquid chromatography/mass spectrometry, and correlated these profiles with similarly generated profiles in our mouse models of TBI, PTSD and TBI+PTSD. As evidence suggests that TBI patients with one or more copies of the APOE ε4 allele have poor cognitive and functional outcomes compared to those without the ε4 allele, soldiers were additionally genotyped for APOE ε4 and genetic influence on the phospholipid profiles evaluated.

Results: We observed comparable lipid plasma profiles in human subjects and mouse models. Furthermore, APOE4 (+) subjects exhibited higher PL levels than their APOE4 (-) counterparts in the same diagnostic group in human subjects.

Conclusion: This first step into identifying lipid profiles for discriminating between militarily relevant diagnostic categories and controls forms the basis of ongoing validation efforts and creates a link between these conditions in humans and our

established mice models. We will then correlate the mouse blood profiles with the mouse brain profiles. Given the similarities in blood biomarker profiles in humans and animals we may then be able to extrapolate further from human blood profiles to infer correlative brain profiles. This would give us an understanding on how to correlate plasma with brain profiles in humans to identify underlying mechanisms behind TBI and PTSD.