

# Genomic links between blast exposure, brain injury, and Alzheimer disease

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*Neurol Genet*  
2017;3:e196; doi: 10.1212/  
NXG.000000000000196

Military personnel are at high risk of exposure to blasts during military service, both during combat and training. Evidence continues to build that supports exposure to blasts, particularly when repetitive, are associated with brain dysfunction which is usually transient but can be prolonged or permanent. Chronic traumatic encephalopathy (CTE), a consequence to repetitive brain injury noted in professional athletes, has received a lot of attention lately, and the suspicion that blast exposures in military personnel lead to CTE or a CTE-like syndrome<sup>1</sup> has appropriately received much attention in the scientific and lay press. Approximately 49% of injured military personnel are injured by explosions,<sup>2</sup> and up to 15% of service members returning from a combat theater report having experienced traumatic brain injury (TBI) during a year-long deployment.<sup>3</sup> Being able to identify the biological networks that are disrupted by these injuries holds great promise for the development of therapeutics to improve neurologic recovery.

In this issue of *Neurology*<sup>®</sup> *Genetics*, Gill et al.<sup>4</sup> report on the biological impact of moderate blast injury in military personnel. A unique feature of this study, which allowed a high level of scientific rigor, is that the authors were able to measure the intensity of the blast, collect biological data before blast injury, and compare those data with data after blast injury within an individual. This was possible because participants were active-duty military service members enrolled in a blast training program, which involved repeated exposures to controlled explosions. A total of 69 male participants (mean age of 30 years and mean duration of service of 10 years) were enrolled, and during training, 29 were exposed to a moderate blast (mean peak pressure of 7.9 psi), while the remaining 40 had no or low blast exposure. Blast exposures were measured using bilateral sensors attached to the participant's helmet. Symptoms (i.e., headache, dizziness, nausea/vomiting, sensitivity to sound, sleep disturbances, fatigue, irritability, depression/sadness, frustration, anxiety, memory, concentration, attention, visual disturbances, and balance issues) and blood

samples were collected on each day of training. Gene expression data representing all genes were collected using RNA-Seq, and data before and after blast were compared. This approach has the advantage that no a priori biological hypotheses are tested; instead, all genes are interrogated allowing for the discovery of novel biological processes affected by blast exposure. The biological network that was most altered following blast injury was amyloid precursor protein (APP). The gene expression findings were followed up by the evaluation of APP protein levels, and the pattern of APP concentrations differed over time in the moderate blast exposure group but not in the no or low blast exposure group. Of interest, APP levels significantly decreased on days 8 and 9 after moderate blast exposure returning to normal by day 10 and changes in APP correlated with blast force exposure. While headache and concentration problems occurred more often in the group exposed to moderate blast, changes in APP levels were not correlated with any symptom.

APP is a transmembrane glycoprotein that has been extensively studied and is probably best known for its role in the pathophysiology of Alzheimer disease (AD). The normal function of APP is still unclear, but evidence so far supports its role in neuronal network formation including neuronal migration during brain development; cell cycle progression in neural stem cells; maintenance of synapsis including calcium homeostasis; and restoration of axonal and neuronal functions after injury.<sup>5</sup> Evidence presented by Gill et al. indicates that APP levels decrease after moderate blast exposure. This is seemingly in contradiction to evidence in the TBI literature, which indicates that APP production in brain tissue increases after injury and may play a neuroprotective role,<sup>6</sup> indicating that more research is needed to fully understand the peripheral patterns of APP after brain injury and blast exposure. Additional directions for future research also include investigating other genes in the

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Funding information and disclosures are provided at the end of the article. Go to [Neurology.org/ng](http://Neurology.org/ng) for full disclosure forms. The Article Processing Charge was funded by the authors.

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APP biological network, particularly epistatic roles for genes involved in APP processing.

The most important clinical implications for the findings presented in the article by Gill et al. are that biological changes occur as a result of exposure to moderate blasts, that these changes involve biomarkers implicated in neurologic disorders, and that a discovery-based approach led to putative biological links between TBI and AD. The social concern regarding the effects of blast exposure during military service on long-term neurologic function has led to large investments in research focused on better understanding of the relationship between TBI and AD and discovering therapeutics to prevent or mitigate TBI-related neurodegeneration. With increased evidence for biomarkers in common between TBI and AD, the fruits of AD research may affect treatment for patients who have sustained a TBI and vice versa.

#### STUDY FUNDING

No targeted funding reported.

#### DISCLOSURE

Dr. Conley and Dr. Diaz-Arrastia report no disclosures. Go to [Neurology.org/ng](http://Neurology.org/ng) for full disclosure forms.

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