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# Disruption of caudate working memory activation in chronic blast-related traumatic brain injury

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ABSTRACT

Mild to moderate traumatic brain injury (TBI) due to blast exposure is frequently diagnosed in veterans returning from the wars in Iraq and Afghanistan. However, it is unclear whether neural damage resulting from blast TBI differs from that found in TBI due to blunt-force trauma (e.g., falls and motor vehicle crashes). Little is also known about the effects of blast TBI on neural networks, particularly over the long term. Because impairment in working memory has been linked to blunt-force TBI, the present functional magnetic resonance imaging (fMRI) study sought to investigate whether brain activation in response to a working memory task would discriminate blunt-force from blast TBI. Twenty-five veterans (mean age = 29.8 years, standard deviation = 6.01 years, 1 female) who incurred TBI due to blast an average of 4.2 years prior to enrollment and 25 civilians (mean age = 27.4 years, standard deviation = 6.68 years, 4 females) with TBI due to blunt-force trauma performed the Sternberg Item Recognition Task while undergoing fMRI. The task involved encoding 1, 3, or 5 items in working memory. A group of 25 veterans (mean age = 29.9 years, standard deviation = 5.53 years, 0 females) and a group of 25 civilians (mean age = 27.3 years, standard deviation = 5.81 years, 0 females) without history of TBI underwent identical imaging procedures and served as controls. Results indicated that the civilian TBI group and both control groups demonstrated a monotonic relationship between working memory set size and activation in the right caudate during encoding, whereas the blast TBI group did not ($p < 0.05$, corrected for multiple comparisons using False Discovery Rate). Blast TBI was also associated with worse performance on the Sternberg Item Recognition Task relative to the other groups, although no other group differences were found on neuropsychological measures of episodic memory, inhibition, and general processing speed. These results could not be attributed to caudate atrophy or the presence of PTSD symptoms. Our results point to a specific vulnerability of the caudate to blast injury. Changes in activation during the Sternberg Item Recognition Task, and potentially other tasks that recruit the caudate, may serve as biomarkers for blast TBI.



## 1. Introduction

Mild traumatic brain injury (TBI) is typically defined as a loss of consciousness (LOC) up to 30 min, posttraumatic amnesia (PTA) not exceeding 24 h, or any period of confusion or disorientation associated with a non-penetrating head injury (Kristman et al., 2014) in which a patient presents for health care with a Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974) score of 13–15. A moderate TBI is defined by PTA up to 7 days and loss of consciousness up to 24 h. Both mild and moderate TBI (TBI) can have long term consequences on cognition (Vanderploeg et al., 2005; Salmond et al., 2006; Ruttan et al., 2008; Silver et al., 2009). The most commonly studied type of TBI results from blunt-force trauma encountered in falls, vehicle accidents, contact sports, and assaults (Andriessen et al., 2011). Diffuse axonal injury, which occurs when the brain accelerates and decelerates within the

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skull (Adams et al., 1989), is considered to be the primary mechanism of blunt-force TBI.

In contrast, the most common type of TBI in military personnel is the result of exposure to improvised explosive devices and grenades. TBI, largely due to blast exposure, has been estimated to occur in 15–30% of service personnel (Hoge et al., 2008; Tanelian and Jaycox, 2008). Blast explosions can result in several types of injury: primary blast resulting from changes in pressure within the brain that lead to injury; secondary blast caused by contact with external objects that are animated by the blast; and tertiary blast occurring when the õindividual is thrown against an external surface, such as the ground or a wall. Any other injury resulting from the explosion, e.g., burns, is referred to as a quaternary blast. While the mechanisms behind secondary and tertiary blast TBI are similar to those found in non-blast settings, less is known about the effects of primary blast on the brain.

Blast explosions are associated with transient increases in air pressure (overpressure) that produce a dose dependent increase in intracranial pressure (Saljo et al., 2009), and have been linked to neuronal injury, hemorrhage, and edema (Cernak et al., 2001; Saljo et al., 2011). Blast has also been associated with acceleration of the brain (Courtney and Courtney, 2011; Goldstein et al., 2012; Sosa et al., 2013). Animal studies of primary blast TBI have revealed a variety of types of damage to structures. Molecular changes have been reported in the thalamus, hypothalamus, and hippocampus in mice (Woods et al., 2013), as well as cell death in the nucleus accumbens in rats (Sajja et al., 2013). In the brainstem, activated microglia, indicators of neuroinflammation, have been found in the substantia nigra of rats exposed to blast (Readnower et al., 2010), consistent with loss of dopaminergic neurons in the substantia nigra of rats with non-blast TBI (Hutson et al., 2011). However, less is known about pathological changes subsequent to blast-related TBI in humans. For example, the brainstem may be equally or even more vulnerable to the effects of blast (Taylor and Ford, 2009; Yeh et al., 2014) than the frontal and temporal regions associated with blunt-force TBI. These regional differences between blast and blunt-force injuries may influence the pattern of neural and cognitive sequelae of TBI.

Studies that have directly compared blast and blunt-force TBI on symptom, neurocognitive, and psychiatric measures have typically reported no differences between the groups (Kennedy et al., 2010; Belanger et al., 2011; Luethcke et al., 2011; Cooper et al., 2012; Mendez et al., 2013; Dretsch et al., 2014; Mac Donald et al., 2014). In one study (Lippa et al., 2010), veterans with blast TBI endorsed elevated cognitive symptoms on the Neurobehavioral Symptom Inventory (NSI) (Cicerone and Kalmar, 1995), a measure of postconcussion symptoms, approximately 3 years after injury, and the severity of symptoms was similar to those reported by veterans with non-blast TBI; however, the NSI queries general cognitive functioning and may not identify subtle differences. Belanger et al. (2009) administered four standardized tests measuring visual and verbal memories, interference resolution, and IQ to veterans and reported no differences in performance between the two types of TBI.

Another approach to identifying potential differences between blast and blunt-force injuries involves structural brain imaging. Our group found no differences when directly comparing blast and blunt-force TBI groups on the presence of brain lesions and brain region volumes (Fischer et al., 2014). Another study (Jorge et al., 2012) used diffusion tensor imaging (DTI) to investigate changes in white matter in veterans with blast TBI and civilians with blunt-force TBI by measuring fractional anisotropy (FA) of whole white matter tracts and examining heterogeneity in FA, or "potholes". The authors reported no significant group differences when measurements were taken for an entire tract, but civilians with acute blunt-force TBI had more potholes than veterans with blast TBI. In a recent DTI study (Yeh et al., 2014), no white matter differences were found between blast and blunt-force TBI groups in a whole brain diffusion measure; however, when hemispheric asymmetries of FA were examined using tract-based spatial statistics (Smith et al., 2006), the blast TBI group demonstrated more asymmetries than a blunt-force TBI group in tracts extending inferiorly to superiorly. In an autopsy study, identical neuropathology was found in the brains of veterans and mice exposed to blast and athletes with blunt-force TBI (Goldstein et al., 2012).

The strongest evidence for identifying differences between blast and blunt-force TBI comes from functional imaging studies. Patients with blast TBI showed greater hypometabolism on positron emission tomography (PET) than patients with blunt-force TBI in the right superior parietal lobe (Mendez et al., 2013). Within the blast group, higher postconcussive symptom severity scores were related to decreased metabolism in the posterior cingulate cortex, while poorer performance on the Paced Auditory Serial Addition Test (Gronwall, 1977), a task involving sustained attention, cognitive processing speed, and working memory, was associated with hypometabolism in the medial frontal gyrus. In a functional magnetic resonance imaging (fMRI) study using the stop signal activation task, a measure of response inhibition, our group differentiated blast from blunt-force TBI by identifying alterations in an orbitofrontal–striatal inhibitory control circuit more than 4 years after blast exposure (Fischer et al., 2014). When correctly performing the inhibition task, veterans with blast TBI had alterations in activation similar to those in a civilian control group with TBI. However, when failing to inhibit, the blast TBI group demonstrated increased activation in the caudate nucleus, consistent with other studies that link the striatum, particularly the caudate, to successful response inhibition (Li et al., 2008; Ghahremani et al., 2012; Ness and Beste, 2013). Moreover, increased activation was also found in cortical regions that enervate the striatum, the lateral orbitofrontal, anterior cingulate, and inferior temporal gyri (Alexander et al., 1986), suggesting that striatal pathways may be particularly vulnerable to blast injury.

An additional frontostriatal circuit involving the dorsolateral prefrontal cortex (DLPFC) has been closely linked to working memory (Levy et al., 1997), an executive function involved in maintaining and manipulating information in short term memory (Baddeley, 1986). The DLPFC–striatal working memory circuit extends from the DLPFC to the caudate, which in turn projects to other subcortical structures (globus pallidus, brainstem, and thalamus) and then back to the DLPFC. Given the vulnerability of the orbitofrontal–striatal inhibitory control circuit to blast as evidenced by the stop signal task in our previous study (Fischer et al., 2014), we hypothesized that blast injury may also have a selective effect on the DLPFC–striatal working memory circuit. To address this hypothesis, we compared veterans with blast TBI (military TBI; milTBI) and civilians with blunt-force (acceleration–deceleration) TBI (civTBI) performing a working memory task, the Sternberg Item Recognition Task (SIRT) (Sternberg, 1966), during fMRI. Veterans and non-veteran civilians without histories of blast exposure or TBI served as control groups. We also studied the presence of long term neuropsychological sequelae in the TBI groups (Vanderploeg et al., 2005; Lippa et al., 2010). We predicted that the two TBI groups would demonstrate differing activation patterns in working memory circuits.

## 2. Methods

### 2.1. Participants

All procedures and recruitment strategies were reviewed and approved by the institutional review boards of the Cleveland Clinic, Baylor College of Medicine (BCM), Louis Stokes Veterans Affairs Medical Center (VAMC) (Cleveland), Michael E. DeBakey VAMC (Houston), and the U.S Department of Defense. Four groups of participants were enrolled: (1) veterans who had been deployed in the Afghanistan and Iraq wars (Operation Enduring Freedom and Operation Iraqi Freedom, OEF–OIF) who had experienced blast-related TBI (milTBI), (2) OEF–OIF veterans who had never experienced blast and/or head injury and who served as controls to the milTBI group (milCON), (3) civilians with TBI (civTBI)