

LONG-TERM IMPAIRMENTS IN COGNITION AND QUALITY OF LIFE FOLLOWING MODERATE-SEVERE MILITARY TRAUMATIC BRAIN INJURY: THE ADVANCE-TBI STUDY



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Poster Number: Sunday-0656

BACKGROUND

- Traumatic Brain Injury (TBI) is a significant dose-related risk factor for progressive neurodegenerative conditions.¹
- Military personnel are at an increased occupational risk of TBI.²
- ADVANCE (Armed SerVices TrAuma and RehabilitationN OutComeE) is a prospective study of long-term combat trauma outcomes. The ADVANCE-TBI sub-study examines the impact of TBI.²⁻³

AIMS

- To establish battlefield TBI prevalence in the ADVANCE cohort.
- Examine the association between TBI and cognitive performance.
- Examine the association between TBI and mental health outcomes.
- Investigate associations between TBI and functional and health-related quality of life.
- Assess TBI related differences in brain structure and white matter microstructural integrity.

STUDY DESIGN

- ADVANCE cohort (n=1145)
 - 579 exposed to combat trauma
 - 566 unexposed to trauma
- Current mean age ~ 40 years

ADVANCE-TBI Variables:

- n=1010 cognitive assessments
- n=865 T1w MRI scans
- n=781 DTI MRI scans

Neuropsychology Battery:

- Test of pre-morbid functioning (TOPF)
- Trails A & B
- Delis-Kaplan Executive Function System (DKEFS) Colour Word Inhibition Test
- Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
- CogAssess iPad Reaction Speed Assessment

METHODS

TBI Classification

- Joint Trauma Theatre Registry (JTTR)
- Past Medical History (PMH)
- Ohio State University TBI Identification Method (OSU TBI-ID)
- Clinical MRI Reports from ADVANCE Study visit

Mayo Classification used.

Battlefield TBI = Classification of TBI sustained from combat trauma in Afghanistan in the exposed cohort.

Mayo Classification	Symptomatic (possible)	Mild (probable)	Moderate-severe (definite)
Loss of Consciousness	-	Momentary-30 minutes	≥30 minutes
Post Traumatic Amnesia	-	Momentary-24 hours	Present ≥24 hours
Glasgow Coma Scale	-	-	<13
Neuroimaging	-	Depressed, basilar or linear skull fracture	Intracerebral haematoma Subdural haematoma Extradural haematoma Confusion (haemorrhagic) Penetrating injury (of dura) Subarachnoid haemorrhage Brainstem injury
Symptoms	Visual blurring Mental state change/ confusion Dazed Dizziness Focal neurological symptoms Headache Nausea	-	-

Statistics:

Linear and Poisson regression models fitted with uninjured as reference, bootstrapped 95% CIs, FDR-corrected for multiple comparisons.

Neuroimaging

Brain volume:

T1w MRI → Spm12 segmentation & DARTEL registration → Voxel Based Morphometry (VBM) for GM & WM volumes, threshold free cluster enhancement (TFCE), family wise error (FWE) p<0.05

White matter microstructure:

DTI MRI → TBSS FSL pre-processing and tensor estimation, DTITK registration → Voxel-wise analysis, TFCE with FWE correction (p<0.05).

RESULTS

i. TBI in 60% of combat-injured personnel

60% sustained a combat trauma TBI. 16% with msTBI. 91.8 % of all TBIs were due to blast injury.

Sample Characteristics	Injured no TBI	Symptomatic (possible) symTBI	Mild (probable) mpTBI	Moderate-severe (definite) msTBI
n	208	81	144	81
Ethnicity, n (%)				
White	185 (88.9%)	74 (91.4%)	132 (91.7%)	73 (90.1%)
Junior	142 (68.3%)	63 (77.8%)	95 (66.0%)	62 (76.5%)
Military Rank, n (%)				
Senior	44 (21.2%)	9 (11.1%)	34 (23.6%)	11 (13.6%)
Officer	22 (10.6%)	9 (11.1%)	15 (10.4%)	8 (9.9%)
Lower limb amputation n (%)	40 (19.2%)	28 (34.6%)	43 (29.9%)	29 (35.8%)
Time Since Injury, mean (SD)	13.68 (2.07)	13.41 (1.75)	13.77 (1.79)	13.93 (1.80)

Table 2. Sample characteristics by battlefield TBI classification.

ii. TBI associated with multi-domain cognitive impairment

msTBI: poorer memory, attention, executive functions and reaction speeds.

msTBI: ~2x higher risk of below-expectation performance across multiple domains.

A.

B.

iii. Anxiety, depression and PTSD elevated in highest severity TBI groups

Anxiety (GAD-7), depression (PHQ-9) & PTSD (PCL-5) symptoms all significantly elevated in msTBI and mpTBI groups.

Depression & PTSD also elevated in Injured no TBI.

Symptom burden increases with TBI severity.

A.

iv. TBI is associated with poorer quality of life and higher unemployment

Unemployment risk increases with TBI severity (msTBI ~11-fold). Health related quality of life significant lower in all injury groups.

A.

B.

v. TBI associated with chronic white matter and volumetric changes

A. Voxel-wise analyses of skeletonised Fractional Anisotropy maps

i. Uninjured > msTBI

ii. Injured no TBI > msTBI

iii. mpTBI > msTBI

B. Voxel Based Morphometry of White Matter Volume

i. Injured no TBI > msTBI

ii. Injured no TBI > symTBI

iii. Injured no TBI > Uninjured

C. Voxel Based Morphometry of Grey Matter Volume

i. mpTBI > symTBI

ii. mpTBI > msTBI

REFERENCES: [1] Maas AIR et al. (2022) Lancet Neurol 21(11) 1004-60; [2] Graham NSN et al. (2023) BMJ Open 13(3) e069243; [3] Bennett AN et al. (2020) BMJ Open 10(10) e037850

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FUNDING: ADVANCE-TBI is funded by the ADVANCE Charity (ADV-HC-TBI). The main contributors include the Headley Court Charity (principal funder), HM Treasury (LIBOR Grant), Help for Heroes, Nuffield Trust for the Forces of the Crown, Forces in Mind Trust, National Lottery Community Fund, Blesma-The Limbless Veterans and the UK Ministry of Defence. DS is funded by the UK DRI.

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