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ÁÁÁÁF cxkf ''N0Dtqf {.'O F ''Rj F ÁÁ
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ŞÞÓŞNÞÓŒÁÔŠÞİÁÁÛÈUÈÁNã↑]ÁRæä↔´á→ÁÞæbæáã´åÁá^äÁRá\æã↔æ→ÁO~↑↑á^äÁ
ÁÁÁÁÁÁÁÁÁÁÁÁÁÁÔ~ã\ÁŒæ\ã↔´←ÊÁRáã]→á^äÁÁGFÍ€GËI€FGÁ
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ÁÁÁÁÁ□[ÁÁN**ã~{æäÁà~ãÁ*|â→↔´Áãæ→æábæÌÁä↔b\ã↔â|\↔~^Á|^→↔↑↔\æäÁ
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ÚåæÁ{↔æ}bÊÁ~*↔^↔~^bÁÁ^äÐ~ãÁà↔^ä↔^&bÁ´~^\á↔^æäÁ↔^Á\å↔bÁãæ*~ã\ÁáãæÁ\å~bæÁ~àÁ\åæÁ
á|\å~ãÇbDÁá^äÁbå~|→äÁ^~\ÁáâæÁ´~^b\ã|æäÁÁbÁ^Á~àà´↔↔á→á´↔æ*áã\↑æ^\Á~àÁ\åæÁNã↑]Á
~b↔\↔~^ÊÁ~→↔´]Á~ãÁ´↔´~^ÊÁ|^→æbb↔b~Áä↔ã^áâbÁ↔^→áãâæä↔↔&^á\æäÁâ]Á~\åæãÁä~´|æ^\á\↔~^ÈÁ

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F9DCFH8C7IA9BH5H=CB D5;9

Ú˘à|åÆ^]'|¦cå'*Æà˘¦å^}Á{¦Æc@ÑÆ/Æ{||^&cå}Æ¦-Æ¶-¦{¦{ æcå}Æ¶âÆ^•cå¯æc^åÆ{Æ¦Æ^&[æq^¦æð^ÆÆÁ@¯'¦Á^¦Á^^•][}•^Æ¶¶&¦¯åå¯}•Æc@^Æcå¦¯^Æ¦¦Á^çà¯¸å¯*Æ¶•d¯&cå}•Æ¦Æ^æ¶&@å¯*Æ¶çã¯cå}*Æ¶æ桿A[¯¦&^•Æ¦â¯æc@¦|å*Æ¶¦å¯æ¦å]cæå̶å̯*Æ¶Ác@Á
åæ桶å^^å˘å̶æ}å̶å̯{¦]^cå¯æc@¦|å^çã̶¸å¯*Á@ˆÑÆ¶å||^&cå}Á¶-Æ¶-¦{¦{ æcå}Æ¶âÆ¶{{¦^}¯¦Á^^¯æåå̶*Æ¶c@ÑÆ̶|å^}Æ{{^}¯¦Á^¦¦Á^&å̶̶¦*Á^¦¯&çã¶cå̶̶*Á^¦Á^å˘å̶̶8å^Á
c@ÑÆ̶|å^}Á{|å̶}Æ¦ÆÕ^]æå̶c^}Á^qÁ~ÑÕ^~}•Æ¶ÆÝ̶æ¶@å̶*{¦}Æ¶Áˆ¶ååˆ˘¶æåc^|•Á^¦}çå̶•Æ¶ÆÕÑ̶&¦{|æ桶å{¦|Á¦Á^}^•cå̶c@^̶|å^}Æ¦ÆÁ^•&@åÑÆ¶•|å^}Æ{¦{¦å̶æ¶}ÁÂU]^}æ¶}•Æ¶åÑÆ¶ÂU]^¶¦[|cˆ¶ÆÕc EÑFÛ̶¦DÑFÇF¦ÃR^~^˘|}ÁÂÕÑ@æcå̶̶ÆAˆ¶Pâ¯@¯æÑ¶ÛU¯̶æˆÆ¶FÇÑÁ̶ˆÆÑÕÆ||å̶*¯c}ÁãÑÈKÆÕÁ̶GÑÑ̶GÑˆÆÑ
IH¶€ÑÕÂÕÑÀÕ^•][}å^}¯¦Á^Á¯¶#^@¯*|åÑÆ/^Æ桶æå^å˘æå̶̶[¦çÃ̶æ¶̶@ˆç桶} åå̶*Æ桶̶̶å^¶c@å̶|¦Á^¦Á^c@Ñ̶Á{¦-̶Æ¶Á^¦Á^•|¶Á@åÑÆ^¦Á^•̶åˆ&[̶^¦Á^Á¸å}qˆ¶Á^{åc¶Á^¦Á^åæÑ̶æq¦æ̶AÅ{¦¦¦Á̶Æ桶ÑÅ{{¶}Á^¦Á̶æ¶̶@ˆå̶@åÑ&{||^&cå̶}Æ¦-Æ¶-¦{¦{ æcå̶}Á¦Á¦æ¶}̶Á̶/¶Á^•[¦¶åã¶|̶æå̶Æ̶{|̶^}Á
çæ桶å̶AÚ˘TÁÕÑ&}d'|ÁÑ˘{¯à^¦ÆÁD̶@å5G9˘8C¯BCH¯F9HIFB̶MCIF̶CFA̶HC¯H<9¯56CJ9¯588F9GGÁ

4. H=H@9 5B8 GI 6H=H@9		**5a. 7CBHF57H BIA69F**
Nä{á^´æäÁRÞØÁ↔^ÁN´\æÁR↔×↔\áã]ÁÚÑØÁ		**5b. ;F5BH BIA69F**
		ÁÂÙÎFVÙÒË€ÎÊGÈ€€IJFÁÁ
		5c. DFC;F5A 9@9A9BH BIA69F
6. 5IH<CFfGŁ		**5d. DFC>97H BIA69F**
Fcxkf N0Dtqf{		**5e. H5G? BIA69F**
go cknˑdtqf{f B pgwtq0y wuvŁfw		**5f. KCF? IB=H BIA69FÁ**

7. D9F:CFA=B; CF; 5B=N5H=CB B5A9fGŁ5B8 588F9GGf9GŁ		**8. D9F:CFA=B; CF; 5B=N5H=CB F9DCFH BIA69F**
Ùábå↔^&\~^ÁÛ^↔{æãb↔\]Á		
IJIJ€ÁUÁÓ|´→↔äÁN{æÁÑ~[ÁÎFFF		
U\ÁQ~|↔bÊÁRŠÁIJ GFF€Á		

9. GDCBGCF=B; #ACB=HCF=B; 5;9B7M B5A9fGŁ5B8 588F9GGf9GŁ		**10. GDCBGCF#ACB=HCF G 57FCBMAfGŁ**
WÈÙ̶ÆÕE{^ÁT^åãRæ¶ÁÙ^•^æå̶&@Áå̶ÁÁTæ桶¦ãæ̶|ÁÕ̶[{{æ}å		
Á/́/́/̶Q[¦c̶ÆÕ^¶c̶Æ̶Ñ̶æˆ̶|æ̶å̶ÁÁG̶FÏ̶€GÈ€FGÁ		**11. GDCBGCF#ACB=HCF G F9DCFH BIA69FfGŁ**

12. 8=GHF=6IH=CB #5J5=@56=@=HMGH5H9A9BH
OÇ]|¦[ç^åÁ{¦Á̶˘à|åÆ^|^æ桶^Lå̶åâ̶cã桶¯cå̶}Á̶}|ã̶̶ã̶æ̶åÁ

13. GIDD@9A9BH5FM BCH9G

14. 56GHF57H
Vj g qdlgevkxg qh vj g tqplgev ku q vu v y q cf xcpegf OT Ko gvj qf u. F VKcpf tgukpi /ucvg hOTK eqttgncvkqp cpcp{uku kp o krkct{ VDK cvgpvu cewuge chygt kplwt{ cpf eqttgncvg hkpf kpi u y kj VDK tgncvgf enkpkecn qwveqo gu 8/34 o qpyj u ncvgt 0Cp cf fkvkqpcn qdlgevkxg ku q vu v y g kpvgtcevkqp qh ecf kf cvg i gpgvke xwnpgtcdknkv{ hcevqtu y kj r cvgpu qh kplwt{0 Vj gug eqo dkpgf o gvj qf u o c{ cff enkpkecn{ wughwn rgf kevkxg kphqo cvkqp hqo wy kpi tcwo cvke dtckp kplwt{ y j cv eqwnf dg hcuukuncpeg kp uncf ctf k|kpi fkci pquvke etkvgtkc hqt VDK o cnkpi tgvwtp/vq/fwv{ vtkci g f gekukqpu i wkf kpi r qpv kplwt{ y j gj cdknkcvkqp cpf f gxgnqr kpi pqxgn vj gtcr gwvkeu 0Vj g qxgtctej kpi j {r qvj guku ku vcv tcwo cvke czqpcn kplwt{ |. kpvgtcevkpi y kj i gpgvke xwnpgtcdknkv{ hcevqtu ku c r tkpekr cn ecwug qh o rgf kgt dtckp hwpevkqp hqo kpi dncpu tgncvgf cpf pqp/dncpu tgncvgf VDK0
Vj g uvf { ku c r tqur gevkxg nqpi kwf kpcn uvf { y kj uwdlgev gptqmo gpv cpf kpkkcn gxcnwcvkqp cv Ncpf uvwj n Tgi kqpcn O gfkecn Egpvgt kp Ncpf uvwj n I gto cp{ cpf cv 4 ukgu kp Chi j cpkvcp0Hqnqy /w gxcnwcvkqpu ctg r gthqo gf cv Y cuj kpi vqp Wpkxgtukv{ kp U˘Nqwku0
Gptqmo gpv y cu enquge Lwpg 3. 42350 Hqnqy /w y cu eqo r ngvg qp P qxgo dgt 39. 42350 477 uvdlgev y gtg gptqmgf cv NTO E cpf 452 uvdlgvu y gtg gptqmgf kp Chi j cpkvcp0 3 4 uvdlgev gptqmgf cv NTO E cpf 95 uvdlgvu gptqmgf kp Chi j cpkvcp j cxg eqo r ngvge hqnqy /w gxcnwcvkpu0Vj gvg j cxg dggp pq cf xgtug gxgpu0Y g ctg ewttgpvn{ cpcn{|kpi fcvc cpf r tgr ctkpi o cpuuetkr vu hqt r wdnkecvkqp0

15. GI 6>97H H9FAG
Úãá|↑á\↔´ÁÑãá↔^ÁØ^↓|ã]ÈÁÑ→áb\ÈÁRÞÈÁŒ↔àà|b↔~^ÁÚæ^b~ãÁØ↑á&↔^&ÈÁ§~b\Ë\ãá|↑á\↔´ÁU\ãæbbÁŒ↔b~ãäæãÁ

16. G97IF=HM7@5GG=:=75H=CB C:			**17. @=A=H5H=CB C: 56GHF57H**	**18. BIA69F C: 5;9G**	**19a. B5A9 C: F9GDCBG=6@9 D9FGCB** WÙŒÆÜTÔÆ
a. F9DCFH Á	**b. 56GHF57HÁ** Á U	**c. H<=G D5;9** ÁÛ	ÛÛ	FÍÎ Á	**19b. H9@9D<CB9 BIA69F** *(include area code)* Á

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=ntroduction

Vj g''qdlgevkxg''qh''vj g''r tqlgev''ku''vq''\guv''y q''cf xcpegf''O T Ko gyj qf u.''F VKcpf ''tguvkpi /uvcvg''hO T Keqttgncvkqp cpcn{uku.''kp''o krkct{''VDKr cvkgpvu''cewugn''chgt''kplwt{''cpf ''eqttgncvg''hkf kpi u'y kj ''VDKtgncvgf ''enkpkecn'qweqo gu'' 8/34''o qpyj u'ncvgt0Vj g''kpvgtcevkqp''qh''ecp'kf cvg''i gpgvke''xwrpgtcdknkv{''hcevqtu'y kj ''r cwtpu'qh''kplwt{''y knn'dg'' gxcnwcvgf 0Vj gug''eqo dkpgf ''o gyj qf u''c{''cf f ''enkpkecn''wughwn'r tgf kevkxg'kphqto cvkqp''hqnnqy kpi ''vtcwo cvke''dtckp'' kplwt{''yj cv'eqwnf ''dg''qh''cuukuvcpeg''kp''uvcpf ctf|kpi ''f kci pquvke''etkvgtkc''hqt''VDK''o cmkpi ''tgwwtp/vq/f wv{''vtkci g'' f gekukqpu.''i wkf kpi ''r quv/kplwt{''tgj cdknkvcvkqp.''cpf ''f gxgmqr kpi ''pqxgn'yj gtcr gwwkeu0

Vj g''qxgtctej kpi ''j {r qyj guku''ku''yj cv'vtcwo cvke''czqpcn'kplwt{.''kpvgtcevkpi ''y kj ''i gpgvke''xwrpgtcdknkv{''hcevqtu.''ku''c'' r tkpekr cn'ecwug''qh''ko r cktgf ''dtckp''hwpevkqp''hqnnqy kpi ''dmcuv/tgncvgf ''cpf ''pqp/dmcuv/tgncvgf ''VDK0
"

Vj g''ur gekhke''cko u'qh''vj g''r tqr qucn'ctg''cu''hqnnqy u<

Cko ''3+Áq''f gvgto kpg''y j gyj gt''F VKcpf ''heO T Ky knn'pqpkpxcukxgn{''tgxgcn'cdpqto cnk6kgu''yj cv'ctg''pqv'r tgugpv''qp'EV'' qt''eqpxgpvkqpcn'O T Kcewgn''hqnnqy kpi ''dmcuv/tgncvgf ''cpf ''pqp/dmcuv/tgncvgf ''VDK0Hqt''yj ku''cko .''yj g''i qcn'' y cu''vq''gptqm'c''vqvcn'qh'422''r ctvkekr cpvu''y kj ''VDK'322''y kj ''dmcuv/tgncvgf ''kplwtkgu'cpf ''322''y kj ''pqp/dmcuv/ tgncvgf ''kplwtkgu.''cv'NTO E0

Cko ''4+Áq''cuuguu''yj g''htgs wgpe{''qh''enkpkecn{''qeewm'tcwo cvke''czqpcn'kplwt{''tguwnkpi ''htqo ''dmcuv'cpf ''pqp/dmcuv' o gej cpkuo u'yj cv'ku''f gvgevkdmg''wukpi ''F VK'heO T K'cpf ''eqpxgpvkqpcn'O T K0Hqt''yj ku''cko .''yj g''i qcn'y cu''vq'' gptqm'c''vqvcn'qh'422''r ctvkekr cpvu''y kj qw'VDK'dww'y kj ''qyj gt''kplwtkgu''cv'NTO E'f wtkpi ''yj g''uco g''4''{gct'' r gtkqf <322''y kj ''dmcuv/tgncvgf ''kplwtkgu'cpf ''322''y kj ''pqp/dmcuv/tgncvgf ''kplwtkgu0

Cko ''5+Áq''wug''F VKcpf ''eO T Kq''enctkh{''yj g''r tkpekr cn'uko knctkukgu''cpf ''f khhgtgpegu'dgwy ggp''dmcuv/tgncvgf ''VDKcpf '' VDKf wg''vq''qyj gt''o gej cpkuo u'*g0I 0o qvqt''xgj keng''cekf gpvu.''hcmu.''cpf ''f ktgev''dmqy u'vq''yj g''j gcf +0Vj ku''y km' dg''cpcn|{ gf ''wukpi ''yj g''uco g''6''i tqwr u'qh'r ctvkekr cpvu'f guetkdgf ''cdqxg''kp''cko u''3'cpf ''40

Cko ''6+Áq''vguv'yj g''j {r qyj guku''yj cv'ur gekhke''r cwgtp'qh'kplwtkgu'f gvgevgf ''y kj ''yj gug''o gyj qf u''knn'r tgf kev'ur gekhke'' mpi gt/vgto ''pgwtqmi kecn'cpf ''pgwtqr u{ej qmi kecn'f ghkekvu0Y g''y km'eqmgev'f gvckngf ''enkpkecn'kphqto cvkqp'' qp''VDKtgncvgf ''qweqo gu'8/34''o qpyj u'chgt''kplwt{''cv'Y cuj kpi vqp''Wpkxgtuky{0Vj ku''y km'kpemwf g'' uvcpf ctf|{ gf ''pgwtqdgj cxkqtcn'cuuguuo gpvu.''pgwtqr u{ej qmi kecn'vguvkpi .''cpf ''uvtwewwtgf ''kpvgtxkgy u'hqt'' f gr tguukqp''cpf ''r quv/vtcwo cvke''uvtguu'f kuqtf gt0Ugxgtcn'rtg''ur gekhkef ''j {r qyj gugu'dcugf ''qp''mpqy p''dtckp'' cpcvqo kecn'enkpkecn'eqttgncvkqpu'y km'dg''vguvgf 0Cnuq.''gzr mqtcvqt{''cr rqcej gu'y km'dg''wugf ''cu''yj g'' uvtwewwtcn'dcugu''hqt''o cp{''r quv/vtcwo cvke''f ghkekvu''cpf ''f kuqtf gtu''ctg''pqv'y gm'wpf gtuvqqf 0

Cko ''7+Áq''vguv'yj g''j {r qyj guku''yj cv'ur gekhke''i gpgvke''hcevqtu'kpvgtcev'y kj ''r cwtpu'qh''kplwtkgu''vq''hwtyj gt''kpetgcug''yj g'' tkum'qh''ur gekhke''pgwtqmi kecn'pgwtqr u{ej qmi kecn'cpf ''r u{ej kcvtke''f ghkekvu''cpf ''f kuqtf gtu0Cv'hqmqy /wr .'' dmqqf ''y km'dg''f tcy p''hqt''i gpgvke''vguvkpi 0I gpgvke''vguvkpi ''y km'dg''r gthqto gf ''hqt''*GABRA2* cpf ''*FKBP5* r qn{o qtr j kuo u''cuuqekcvgf ''y kj ''*RVUF* .''*5-HTTLPR*'r qn{o qtr j kuo u''cuuqekcvgf ''y kj ''kpetgcugf ''tkum'qh'' f gr tguukqp''cpf ''*RVUF* ''hqnnqy kpi ''uvtguuqtu.''cpf ''*APOE*''cpf ''*IL1β*''i gpqv{r gu''cuuqekcvgf ''y kj ''r qqt''tgeqxgt{'' htqo ''VDK0
"

Cf f kvkqpcn'hwpf kpi ''htqo ''FCTRC''uwr r qtvgf ''yj g''cpcn{uku'qh'F VKcpf ''enkpkecn'f cvc''ceswktgf ''kp'Chi j cpkuvcp''wukpi '' O T Kuecppgtu'kpuvcnngf ''kp''yj cv'eqwpvt{''cv'5'WU''o krkct{''dcugu0Vj g''j {r qyj gug''i wkf kpi ''yj g''uvwf kgu''kp'Chi j cpkuvcp'' ku''yj cv'cewg''F VKcdpqto crkvkgu''chgt''dmcuv/tgncvgf ''VDKy km'tgxgcn'czqp''kplwt{''pqv'crrctgpv'cv'ncvgt''vko gu.''cpf '' j gmr ''i wkf g''gctn{''tgwwtp/vq/f wv{''f gekukqpu0
"
"

"

Body

F wtkpi "vj g"hqwtj "{gct"qh"vj g"r tqlgev."y g"j cxg"eqo r ngvgf "gptqmo gpv"cpf "hqmqy /wr ."r wdnkuj gf "4"r cr gtu." uwdo kwgf "4"cf f kkqpcn'o cpwuetkr vu."j cxg"c"5 tf "o cpwuetkr v"kp"r tgr ctcvkqp"cpf "ctg"eqpvkpwkpi "vq"cpcn| g"f cvc0"
Vj g"hqmqy kpi "cdng"uwo o ctk| gu"vj g"f go qi tcr j ke"ej ctcevgtkukeu"qh"vj g"uwdlgevu"vj cv"eqo r ngvgf "hqmqy /wr "8/34" o qpvj u"chvgt"gptqmo gpv0"

Follow Up Participant Characteristics						
	Enrolled at LRMC				**Enrolled in AFG**	
Characteristic	Non-blast CTL (n=69)	Blast CTL (n=27)	Non-blast TBI (n=29)	Blast TBI (n=53)	Non-blast CTL (n=34)	Blast TBI (n=38)
Age in years:			"			
median (range)	31 (21-49)	34 (22-46)	28.5 (20-50)	26 (19-47)	28 (19-44)	26 (20-41)
Education in years:			"			
median (range)	14 (9-28)	13 (10-19)	14 (9-18)	12 (12-18)	15 (12-24)	13 (12-18)
Gender no (%)			"			
Male	63 (91%)	25 (92%)	26 (87%)	51 (96%)	27 (79%)	36 (95%)
Female	6 (9%)	2 (8%)	3 (13%)	2 (4%)	7 (21%)	2 (5%)
Race/ethnicity no (%)			"			
White	50 (73%)	20 (77%)	19 (60%)	40 (76%)	22 (65%)	29 (77%)
African American	16 (23%)	4 (12%)	7 (27%)	4 (6%)	5 (15%)	2 (5%)
Hispanic/Latino	3 (4%)	2 (8%)	3 (10%)	7 (14%)	7 (20%)	7 (18%)
Asian	0	1 (3%)	1 (3%)	2 (4%)	0	0
Branch of Service no (%)			"			
US Army	55 (80%)	24 (89%)	26 (90%)	46 (90%)	13 (38%)	32 (84%)
US Air Force	11 (16%)	0	2 (7%)	1 (2%)	2 (6%)	0
US Marine Corps	3 (4%)	3 (11%)	1 (3%)	5 (6%)	3 (9%)	6 (16%)
US Navy	0	0	0	1 (2%)	16 (47%)	0
Military Rank no (%)			"			
Enlisted	63 (91%)	24 (89%)	27 (93%)	52 (98%)	24 (71%)	35 (92%)
Officer	6 (9%)	3 (11%)	2 (7%)	1 (2%)	10 (29%)	3 (8%)
Theatre of Operation no (%)			"			
Afghanistan	55 (80%)	21 (77%)	18 (60%)	50 (94%)	34 (100%)	38(100%)
Iraq	14 (20%)	6 (23%)	11 (40%)	3 (6%)	0	0

"

Kp"vj g"hktuv"r wdnkecvkqp"*O ce"F qpcnf "gv"cn04236c+."y g"f ghkpgf "vj g"hwpevkqpcn'qwveqo gu"hqmqy kpi "dncuv/tgncvgf " VDKlkp"o kkkct{"r gtuqppgn'gptqmgf "kp"cctnkgt"eqj qtu."uwr r qtvgf "d{"vj g"enqug"RV2974; ; "ay ctf 0Vq"uwo o ctk| g." o qf gtcvg"qvgtcn'f kucdknkt{"kp"63 l69"*: 9" +"dncuv"r nu"VDKluwdlgevu"cpf "c"uwduvcpvkcn'dw"o cngt"pwo dgt"*33 l8: ." 83' .'r "? "2023; +"qh'f go qi tcr j klecm{"uko knct"WU'o knkct{"eqpvtqnu"y kj qw'VDKlgxcewcvgf "hqt"qvj gt"o gf kecn' tgcuqpu0Eqi pkkkxg"wpfvkqp"cuuguugf "y kj "c"pgwtqr u{ej qmqi kecm'vgu'dcwgt{"y cu"pqv"f khhgtgpv'dgwy ggp"dncuv'r nu" VDKluwdlgevu"cpf "eqpvtqn="r gthqto cpeg"qh'dqvj "i tqwr u"y cu"i gpgtcm{"kp"vj g"pqto cl'tcpi g0P q"uwdlgev"y cu"hqwpf " vq"j cxg"hqecm'pgwtqmqi kecn'f ghkekvu0J qy gxgt."4; l69"*79" +"qh'dncuv'r nu'uwdlgevu"y kj "VDKlo gv'cnl'etkgtkc"hqt" r quv/ctwo cvke"uvtguu'f kuqtf gt"*RVUF +'xgtuwu'7l3: "*4: ' +"qh'eqpvtqnu"*r "? "2023t+0RVUF "y cu'j ki j n{ "cuuqekcvgf " y kj "qxgtcn'f kucdknkt{="53l56"r cvkgpvu"y kj "RVUF "xgtuwu'3; l53"r cvkgpvu"y j q"f kf "pqv'o ggv'hwn'RVUF "etkvgtkc"j cf "

"

o qfgtcvg"vq"ugxgtg"fkucdknkv{"*'r"?"202225+0'U{o r vqo u"qh"fgrtguukqp"y gtg"cnuq"o qtg"ugxgtg"kp"\j g"VDKi tqwr"*'r "

? "2027+."cpf "j ki j n{"eqttgncvgf "y kvj "RVUF "ugxgtkv{"*'t"?"20 8."r ">"202223+0'

"

Kp"\j g"ugeqpf "r wdnkecvkqp"*'O ce'Fqpcnf "gv'cn04236d+."y g"fktgevn{"eqo r ctgf "erkpkecn'qwveqo gu"kp"o knkvct{"

r gtuqppgn'y kj "dncuv/tgncvgf "VDKxu"pqpdncuv/tgncvgf "VDK0'Vj ku"y qtm'y cu"uwr r qtvgf "d{ "\j g"RV2; 2666"cy ctf 0'Vq "

uwo o ctk{ g."i nqdcn'qwveqo gu."j gcfcej g"ugxgtkv{."pgwtqru{ej qnqi kecn'r ghqto cpeg."cpf "uwtr tkukpi n{"gxgp'RVUF "

ugxgtkv{"cpf "fgrtguukqp"y gtg"kpfkuvkpi wkuj cdng"dgwy ggp"\j g"y q "VDKi tqwr u."kpfgrgpfgpv'qh"o gej cpkuo "qh"

kplwt{0'Dqyj "VDKi tqwr u"j cf "j ki j gt'tcvgu'qh'o qfgtcvg"vq"ugxgtg"qxgtcrn'fkucdknkv{"\j cp"\j g'tgur gevkxg"eqpvtqn'

i tqwr u<63175"*99 +'qh'dncuv'r nwu'ko r cev'VDKcpf "4514; "*9; ' +'qh'pqpdncuv'VDKxu035149"*7; ' +'qh'dncuv/

gzr qugf "eqpvtqn'cpf "4: 18; "*63' +'qh'pqp/dncuv/gzr qugf "eqpvtqn0'Kp"cffkvkqp."dncuv/gzr qugf "eqpvtqn'j cf "y qtug"

j gcfcej gu"cpf "o qtg"ugxgtg'RVUF "\j cp"pqp/dncuv/gzr qugf "eqpvtqn0'Ugrh/tgr qtvgf "eqo dcv'gzr quwtg"kpvgpukv{"y cu"

j ki j gt'kp"\j g"dncuv'r nwu'ko r cev'VDKi tqwr "\j cp"kp"pqpdncuv'VDKi tqwr "cpf "y cu'j ki j gt'kp"dncuv/gzr qugf "eqpvtqn'

y cp"kp"pqp/dncuv/gzr qugf "eqpvtqn0'J qy gxgt."eqo dcv'gzr quwtg"kpvgpukv{"fkf "pqv'eqttgncvg"y kvj "RVUF "ugxgtkv{"kp"

\j g"VDKi tqwr u."dww'c"o qfguv'r qukkxg"eqttgncvkqp"y cu'qdugtxgf "kp"\j g"eqpvtqn0'Qxgrcrn'qwveqo gu"y gtg"o quv'

uvtqpi n{"eqttgncvgf "y kvj "fgrtguukqp."j gcfcej g"ugxgtkv{."cpf "pwo dgt'qh'cdpqto crkvkgu'qp'pgwtqru{ej qnqi kecn'

vguvkpi 0'J qy gxgt'c"uwduvcpvkcn'htcevkqp"qh'\j g'xctkcpeg"kp'qxgrcrn'qwveqo g"y cu"pqv'gzr nckpgf "d{ "cp{"qh"\j g"

cuuguugf "o gcuwtgu0"

"

"

Y g'j cxg'"4"o cpwuetkr u'ewttgpvn{"wpfgt'tgxkgy "fguetkdkpi "vj g'tcf kqmqi kecn'cpf "enkpkecn'qweqo gu'htqo "vj g"
eqj qtvu'gptqmgf 'kp'Chi j cpkuvcp0'Vj g'hktuv'o cpwuetkr v."Cf co ."O ce"F qpcnf ."gv'cn'ku'ewttgpvn{"wpfgt'tgxkgy "cv"
<u>P gwtqmqi {0"</u>
Vj g'qdlgevkxg'qh'vj g'uwfd{"y cu'vq"gxcnwcvg'y gvj gt'fkhhwukqp'vgpuqt'ko ci kpi "*F VK+'y knl'pqpkpxcukxgn{"tgxgcn'
y j kg'o cwgt'ej cpi gu'pqv'r tgugpv'qp'eqpxgpvkqpcn'O TK.kp"cewg'dncuv'tgncvgf "o VDK'cpf "vq"fgvgto kpg"eqttgncvkqpu"
y kj "enkpkecn'o gcuwtgu'cpf "tgeqxgt{0'Y g'r gthqto gf 'c'r tqur gevkxg'qdugtxcvkqpcn'uwf {"qh'; 7"o VDK'cpf "323"
j gcnj {"eqpvtqn'WU'o krkct{'ugtxkeg'o go dgtu'gptqmgf 'y kj kp'9'fc{u'htqo "kplwt{'kp'Chi j cpkuvcp0'Cuuguuo gpvu"
kpenwfgf 'Tkxgto gcf 'Rquv'Eqpewuukxg'U{o r vqo "S wguvkqppcktg'*TREUS +.'Rquv'Vtcwo cvke"Utguu'F kuqtfgt"
Ej gemkuv'*O krkct{'*RENO +.'Dgem'F gr tguukqp'Kpxgpvqt{'*DF K+.'Dcncpeg'Gttqt'Ueqtkpi "U{uvgo "*DGUU+."
Cwqo cvgf "P gwtqeqi pkvkxg'Cuuguuo gpv'O gvtke'*CP CO +.'eqpxgpvkqpcn'O TK'cpf 'F VK0'Y g'hqwpf "uki pkhkecpv{"
i tgcvgt'ko r ckto gpv'y cu'qdugtxgf 'kp'o VDK'r ctvkekr cpu'xgtuwu'eqpvtqn<'TREUS "*3; 09Õ34.0 "xu050Õ903. "
r >20223+.'RENO "*54Õ3504. "xu0420 Õ903. "r >20223+.'DF K'*906Õ80 "xu0407Õ60 ."r >20223+.'cpf "DGUU'*3 04Õ 06"xu0'
370Õ05. "r ?2023+0'Vj g'ncti guv'ghhgev'uk g'kp'CP CO "r gthqto cpeg'f gerkpg'y cu'kp'uko r ng'tgcevkqp'vko g'*o VDK'
9607Õ36: 06"xu0'eqpvtqn'/33Õ680 8"o u. "r >20223+0'Htcevkqpcn'cpkuqvtqr {'y cu'uki pkhkecpvn{'tgf wegf 'kp'o VDK'
eqo r ctgf 'vq'eqpvtqn'kp'vj g'tki j v'uwr gtkqt'nqpi kwf kpcn'hcuekewnu'*205; 5Õ20244"xu020627Õ20245. "r >20223+0'P q'
cdpqto cnkkgu'y gtg'f gvgevgf 'y kj "eqpxgpvkqpcn'O TK0'Vko g'vq'tgwtp/vq'fw{"eqttgncvgf 'y kj "TREUS "*t?2075."
r >20223+.'CP CO "uko r ng'tgcevkqp'vko g'f gerkpg"*t?206; ."r >20223+.'RENO "*t?2069.'r >20223+.'cpf "DF K'*t?2058"
r ?202227+0'Vj wu. "kp'eqpenwukqp. "uqo cvke. "dgj cxkqtcn'cpf "eqi pkkkxg'u{o r vqo u'cpf 'r gthqto cpeg'f ghkekku'ctg'
uwduvcpvkcm{"gngxcvgf 'kp'cewg'dncuv'tgncvgf 'o VDK0'Rquv/eqpewuukxg'u{o r vqo u'cpf 'r gthqto cpeg'qp'o gcuwtgu'qh'
r quv/tcwo cvke'utguu'f kuqtfgt. 'f gr tguukqp'cpf 'pgwtqeqi pkkxg'r gthqto cpeg'cv'kpkkcl'r tgugpvcvkqp'eqttgncvg'y kj "
tgwtp/vq'fw{ 'vko g00'Cnj qwi j "ej cpi gu'kp'Htcevkqpcl'Cpkuqvtqr {'ctg'wpeqo o qp'cpf "uwdvng. 'F VK'ku'o qtg'
ugpukkxg'y cp'eqpxgpvkqpcn'O TK'kp'ko ci kpi "y j kg'o cwgt'kpvgi tk{'kp'dncuv'tgncvgf "o VDK'cewg{0'
"

Vj g'ugeqpf "o cpwuetkr v. "O ce'F qpcnf . "Cf co "gv'cl'ku'ewttgpvn{"wpfgt'tgxkgy "cv'<u>Dtckp0"</u>
Vq'uwo o ctk{ g. 'j ki j "tcvgu'qh'cf xgtug'qweqo gu'j cxg'dggp'tgr qtvgf 'hqmqy kpi "dncuv'tgncvgf "eqpewuukxg'tcwo cvke"
dtckp'kplwt{'*"VDK+'kp'WU'O krkct{'r gtuqppgl'dw'vj g'gzvgpv'vq'y j kej "uwej 'cf xgtug'qweqo gu'ecp'dg'r tgf kevgf "
cewgn{"chvgt'kplwt{ 'ku'wpmpqy p0""Y g'r gthqto gf 'c'r tqur gevkxg. 'qdugtxcvkqpcn'uwf {"qh'WU'O krkct{'r gtuqppgl'
y kj "dncuv'tgncvgf "eqpewuukxg'VDK'*p?05: +'cpf "eqpvtqn'*p?56+'gptqmgf 'dgwy ggp'O ctej "cpf "Ugr vgo dgt'42340'
Ko r qtcpv{"cm'uwdlgev'tgwtpgf 'vq'fw{'cpf 'f kf 'pqv'tgs wktg'gxcewcvkqp0'Uwdlgev'y gtg'gxcnvcvgf 'cewgn{"2/9"
f c{u'chvgt'kplwt{'cv'y q'uhkgu'kp'Chi j cpkuvcp'cpf 'ci ckp'8/34'o qpyj u'ncvgt'kp'yj g'Wpkvgf 'Utcvgu0'Cewg'cuuguuo gpv"
tgxgcngf 'j ki j 'ngvgpgf 'r quv/eqpewuukxg. 'r quv/tcwo cvke'utguu. 'cpf 'f gr tguukxg'u{o r vqo u'cnqpi "y kj 'y qtug"
eqi pkkxg'r gthqto cpeg'kp'VDK.uwdlgewu0'Cv'8/34'o qpyj 'hqmqy "wr. '85 "qh'VDK.uwdlgewu'cpf '42 "qh'eqpvtql.j cf '
o qf gtcvg'vq'xgtcm'f kucdknk{0'VDK.uwdlgewu'uj qy gf 'o qtg'ugxgtg'pgwtqdgj cxkqtcl'r quv/tcwo cvke'utguu. 'cpf "
f gr tguukqp'u{o r vqo u'cnqpi "y kj 'o qtg'htgs wgpv'eqi pkkxg'r gthqto cpeg'f ghkeku'cpf 'o qtg'uwduvcpvkcl'j cf cej g"
ko r ckto gpv'y cp'eqpvtqnu0'Nqi kuvke'tgi tguukqp'o qf gmpi "wkk kpi "qpn{'cewg'o gcuwtgu'kf gpkhkgf 'yj cv'c'fkci pquku"
qh'VDK'qnfgt'ci g. 'cpf 'o qtg'ugxgtg'r quv/tcwo cvke'utguu'u{o r vqo u'r tqxkf gf 'c'i qqf 'r tgf kevkqp'qh'ncvgt'cf xgtug"
i nqdcl'qweqo gu'*ctgc'wpfgt'yj g'tgegkxgt/qr gtcvkpi "ej ctcevgtkuvke'ewtxg'?"20 6+0'Vj wu. 'WU'o krkct{'r gtuqppgl'
y kj "eqpewuukxg'dncuv'tgncvgf 'VDK.kp'Chi j cpkuvcp'y j q'tgwtpgf 'vq'fw{ 'urkml'hctgf 'swkg'r qqtn{ 'qp'o cp{'enkpkecl'
qweqo g'o gcuwtgu'8/34'o qpyj u'hqmqy kpi "kplwt{0'Rqqt'i nqdcl'qweqo g'cr r gctu'vq'dg'ncti gn{'f tkxgp'd{"
r u{ej qmqi kecl'j gcnj 'o gcuwtgu'ci g. 'cpf 'VDK.ucwwu0'Vj g'ghhgev'qh'gctn{'kpvgtxgpvkqpu'cpf 'nqpi gt'vgto "
ko r nkecvkqpu'qh'yj gug'hkpf kpi u'ctg'wpmpqy p0'
"

"

Kp''vj g''vj ktf ''o cpwuetkr v.''y g''cpcn{|gf ''vj g''eqo dkpgf ''vj g''f cvc''ugw''htqo ''uwdlgewu''gptqmgf ''dgw ggp''422: ''cpf ''4235..
uwr r qtvgf ''d{''dqyj ''vj g''RV29''cpf ''RV2; ''i tcpvu0''Y g''wugf ''vj ku''qr r qtwpkv{ ''vq''kpetgcug''qwt''uvcvkuvkecn'r qy gt''cpf ''
cuuguu''vj g''tguwnu''qh''vj g''÷pcwtcn'gzr gtko gpv÷kpkvkcvgf ''y kj ''vj g''kuuwcpeg''qh''vj g''F ktgevkvg''V{r g''O go qtcpf wo ''
*F VO ''2; /255÷'kp''42320'Vj g''F VO ''j cf ''vj g''qdlgevkxg''vq''÷kf gpvkh{.''tcem'cpf ''gpuwtg''vj g''cr r qr tkcvg'r tqvgevkqp''qh''
Ugtxkeg''o go dgtu''gzr qugf ''vq''r qvgpvkcn'eqpewuukxg''gxgpvu.''kpenwf kpi ''dncuv'gxgpvu.''vq''vj g''o czko wo ''gzvgpv'
r quukdng0'÷''Y g''hqwpf ''vj cv'i mqdcn'f kucdkmv{.''pgwtqdgj cxkqtcn'ko r ckto gpv.''f gr tguukqp''ugxgtkv{.''cpf ''r quv'vtcwo cvke''
uvtguu''f kuqtf gt''*RVUF +'ugxgtkv{ ''y gtg''y qtug''kp''cm'eqpewuukxg''VDKi tqwr u''kp''eqo r ctkqp''vq''eqpvtqn''r >2022223+0'
Vj gtg''y cu''c''o qf guv'dwv'uvcvkuvkecm{''uki pkhkecpv'vtgpf ''vqy ctu''ko r tqxgf ''RVUF ''kp''ncvgt''eqj qtu''tgncvkxg''vq''gctmgt''
eqj qtu0'Dncuv÷gzr qugf ''eqpvtqn''y kj qw''cr r ctgpv'VDKcmuq''gzj kdkvgf ''uki pkhkecpv{''y qtug''i mqdcn'f kucdkmv{ ''
*r ? 2022226+.'pgwtqdgj cxkqtcn'ko r ckto gpv''r ? 2022223+.'f gr tguukqp''*r ? 2022228+'cpf ''RVUF ''ugxgtkv{ ''*r >2022223+''vj cp''
pqp/dncuv'gzr qugf ''eqpvtqn0'O qtv'uwdlgewu''j cf ''qpto cn'pgwtqr u{ej qmi kecn'r gthqto cpeg.''dw'uwdugw''qh''uwdlgewu''
y kj ''VDKcpf ''dncuv'gzr qugf ''eqpvtqn''j cf ''ko r ckt¿f ''pgwtqr u{ej qmi kecn'r gthqto cpeg0'Qxgtcm'f kucdkmv{ ''y cu''
ncti gm{ ''f tkxgp''d{''VDKf kci pqugu.''gxecwvkqp''uvcwu.''f gr tguukqp.''cpf ''RVUF ''ugxgtkv{ .''dw'pqv'd{ ''
pgwtqr u{ej qmi kecn'r gthqto cpeg.''ci g.''gf wecvkqp.''ugmh/tgr qtvgf ''umgr ''f gr tkxcvkqp.''qt''kplwt{ o gej cpkuo 0'Vj wu.''
f gur kvg''ej cpi gu''kp''ectg''hqt''WU''o kmvct{ ''r gtuqppgn'y kj ''dncuv'tgncvgf ''eqpewuukxg''VDK'8/34''o qpyj ''qweqo gu''j cxg''
ko r tqxgf ''qpm{ ''o qf guv{ ''cpf ''ctg''qhvgp''r qqt0'Hwwtg''hqewu''qp''o gpvcn'j cmj ''tgcvo gpv'cvj etg''eqpewuukxg''VDKcpf ''
chvgt''dncuv'gzr quwtg''y kj qw''cr r ctgpv'VDKcr r gctu''y cttcpvgf 0'J qy gxgt.''cf xgtug''qweqo gu''ctg''kpeqo r ngvgn{ ''
gzr nckpgf .''cpf ''cf f kkqpcn'f qo ckpu''qh''cuugui o gpv'y km'dg''tgs wktgf ''vq''hwm{ ''cf f tguu''vj g''ecwugu''qh''f kucdkmv{ ''chvgt''
y ctko g''kplwt{0'
"
F t0'Mkj y cp''J cp''*pqy ''cv'WV'F cmcu÷'ku''eqpvkpwkpi ''vq''cpcn{ g''tguwmvkpi ''uvcwg''hwpevkqpcn'eqppgevkxkv{ ''f cvc''*J cp''gv'
cn0'4235+'htqo ''vj g''eqj qtv'gptqmgf ''cv'NTO C0'Vj ku''j cu''dggp''ej cmgpi kpi ''f wg''vq''vj g''uco g''ko ci kpi ''s wcmkv{ ''kuuwgu''
ctkukpi ''y kj ''vj g''F VKf cvc0'
"
F t0'Ej tkuvkpg''O ce''F qpcnf ''*pqy ''cv'W'Y cuj kpi vqp+'ku''eqpvkpwkpi ''vq''cpcn{ g''emkpkecn'f cvc0'Uj g''uweeguuhwm{ ''
uwo kwgf ''4'i tcpvu''*EGP C''uwdcy ctf ''cpf ''P KI ''T23+'vq''r gthqto ''7/9''{gct''hqmqy /wr ''gxcnwcvkqpu''qp''vj g''uwdlgewu''
gptqmgf ''cv'NTO C0'Vq''qwt''mpqy ngf i g.''vj ku''y km'dg''vj g''hktuv'mqpi gt/vgto ''mqpi kwf kpcn'qweqo g''uwf {''qh''WU''
o kmvct{ ''r gtuqppgn'y kj ''dncuv'tgncvgf ''VDKhtqo ''vj g''y ctu''kp''Kcs ''cpf ''Chi j cpkuvcp0'

Vj gtg'j cxg"dggp"y q"uwduvcpvkcn'ej cpigi gu<"

3+ÁVj g'u wcrkv{'qh'vj g"O TK'ecpu"htqo "vj g"5V"uecppgt'kp"NTOE"y cu"pqv"cu"i qqf "cu"qtki kpcn{'j qr gf 0'Y g"ctg"
y qtkkpi "kp"eqmcdqtcvkqp"y kj "F t0'Ectq'Rkgtr cqrk'cv'P KI "cpf "tgugctej gu"cv'Y cuj W'vq"cwgo r v'vq"eqttgev"
uqo g"qh'vj g"uki pcn'f kuvqtvkqpu"r tgugpv'kp"vj g"uecpu0'Y g"j qr g"vj cv'vj ku"y km'cmqy "ceewtcvg"cpcvqo kecn'
cpcn{uku"qh'vj g"F VK'f cvc0"Io r qtvcpv{.'vj g"gpvktg"hkgnf "qh'cf xcpegf "O TK'tgugctej "j cu"dgeqo g"o wej "o qtg"
cwupgf "vq"f cvc"s wcrkv{"kuuwgu"*Lqpgu"gv'cn0'4235+0'Hqt"uwdugs wgpv'uwfkgu."y g"ctg"r wukpi "vqi gj gt"c"ugv'qh'
wr /htqpv'swcrkv{"eqpvtqn'o gtkeu"vj cv'y km'gpuwtg"vj cv'i qqf "s wcrkv{'f cvc"ku'qdvckpgf "htqo "vj g"dgi kppkpi "qh'
vj g"r tqlgev'uq"vj cv'vj gug"kuuwgu'ecp"dg"o kpko k| gf 0'Ur gekhkecn{.'y g'y km'gpuwtg"vj cv"'

        c0Á uki pcn'vq"pqkug"ku"@47'hqt"cm'tgi kqpu"qh'kpvgtguv'kpenwf kpi "vj g"qtdkqhtqpvcn'tgi kqpu"vj cv'ctg"
            xwpgtcdrg"vq"uwuegr vkdkrkv{"ctvkhcev."

        d0Ávguv/tgvguv'tgrkcdkrkv{"qp"vj g"uco g"pqto cn'uwdlgev'ku"@; 7' "kp'cm'tgi kqpu'qh'kpvgtguv."

        e0Á I kddu'tkpi kpi "ku"pqv'r tgugpv."

        f 0Áhkgnf "qh'xkgy "kpenwf gu"vj g"y j qrg"dtckp"kpenwf kpi "dtckpuvgo ."

        g0Á uwdlgev'o qvkqp"ku"o kpko k| gf "wukpi "j gcf "eqkn'r cf f kpi "cpf "c"pqug"dtkf i g0"

        h0Á Gff {'ewttgpv'f kuvqtvkqpu'ctg'eqttgevgf "d{"qdvckpkpi "4"ugvu'qh'ko ci gu'y kj "qr r qukvg"r j cug"
            gpeqf kpi "f ktgevkqpu0"

        i 0Á O wnkr ng"d/| gtq"ko ci gu'ctg' ces wktgf "vq"tgf weg"pqkug"kp"o gcp'f khhwukxkv{'o gcuwtgo gpu0"

"

"

4+"Vj g"pwo dgt"qh'uwdlgevu"y kj "eqo r ngvg"hqmqy /wr 'j cu'r tqxgp'vq"dg'vqq"uo cm'vq"r gthqto "i gpgvke'cpcn{ugu"y kj "
uwhhkekgpv'uvcvkuvkecn'r qy gt"kp"vj gug"o kzgf "cpegut{'r qr wncvkqp0'Qwt'kpkkcl'hkpf kpi "vj cv'r qn{o qtr j kuo u'kp"vj g"
HMDR7'cmgng'cr r gctgf "vq"kphnwgpeg"RVUF "ugxgtkv{'*ECRU+'hqmqy kpi "VDK'y gtg"pqv'eqphkto gf "y kj "cpcn{uku'qh'
cf f kvkqpcl'uwdlgevu0'Vj gtg"y gtg"vqq"hgy "uwdlgevu"y kj "vj g"tctg"CC"cmgng"y j ej "y g"j cf "j {r qvj uk| gf "eqwf "dg"
r tqvgevkxg"htqo "RVUF "hqmqy kpi "VDK"*pqv'vj g"ncti g"gttqt"dctu+0Qwt'r ncp'ku'vq"eqo dkpg"qwt'f cvc"y kj "vj qug"htqo "
qvj gt"eqj qtu'ctqwpf "vj g"eqwpvt{'vq"ko r tqxg"uvcvkuvkecn'r qy gt0'Y g"j cxg"f kuewuugf "vj ku'y kj "F t0'Mgtt{'Tguungt'cv"
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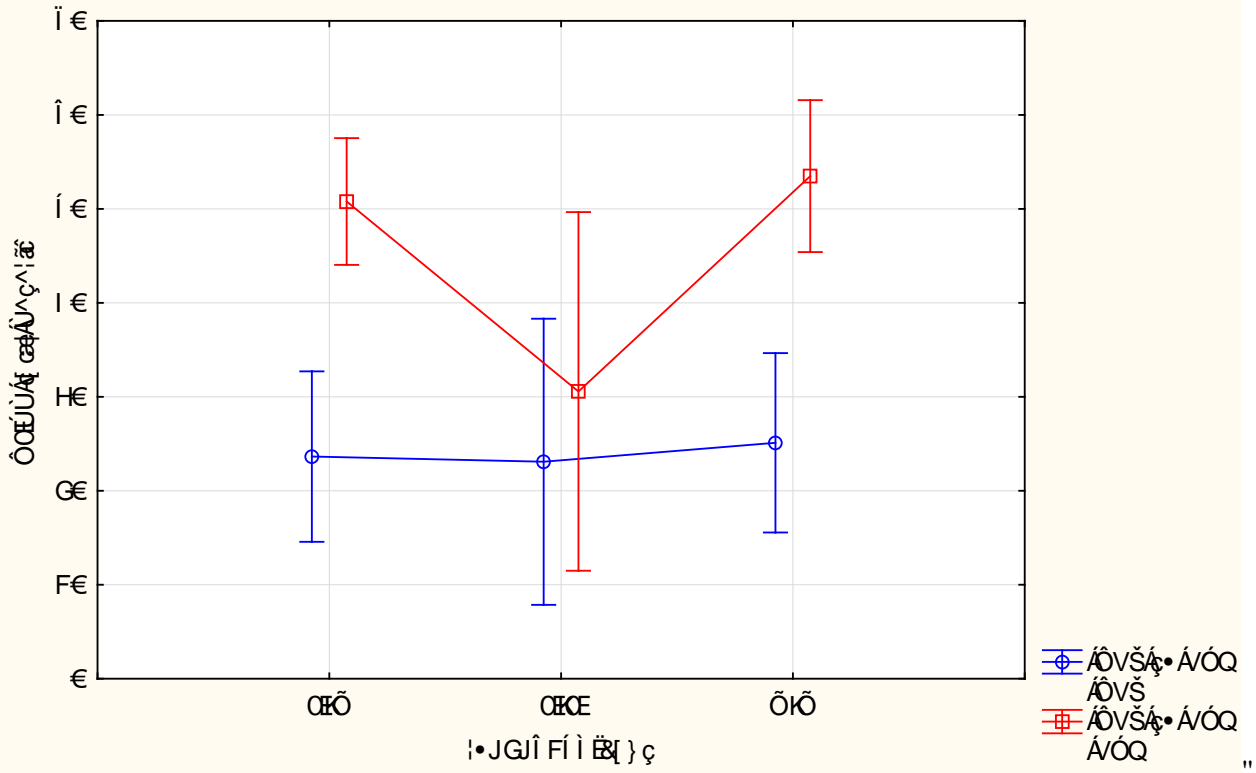
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Appendices:

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Original Investigation

Prospectively Assessed Clinical Outcomes in Concussive Blast vs Nonblast Traumatic Brain Injury Among Evacuated US Military Personnel

Christine L. Mac Donald, PhD; Ann M. Johnson; Linda Wierzechowski, RN; Elizabeth Kassner, RN; Theresa Stewart, RN; Elliot C. Nelson, MD; Nicole J. Werner, PhD; David Zonies, MD, MPH; John Oh, MD; Raymond Fang, MD; David L. Brody, MD, PhD

IMPORTANCE Blast injury has been identified as the signature injury in the conflicts in Iraq and Afghanistan. However it remains to be determined whether fundamental differences may exist between blast-related traumatic brain injury (TBI) and TBI due to other mechanisms.

OBJECTIVES To determine similarities and differences between clinical outcomes in US military personnel with blast-related vs. non-blast-related concussive TBI and to identify the specific domains of impairment that best correlate with overall disability.

DESIGN, SETTING, AND PARTICIPANTS Prospective cohort study involving active duty US Military personnel evacuated from Iraq or Afghanistan to Landstuhl Regional Medical Center, in Landstuhl, Germany. Four groups of participants were enrolled from 2010 to 2013: (1) blast plus impact complex TBI (n=53), (2) non-blast related TBI with injury due to other mechanisms (n=29), (3) blast-exposed controls evacuated for other medical reasons (n=27) (4) non-blast-exposed controls evacuated for other medical reasons (n=69). All patients with TBI met Department of Defense criteria for concussive (mild) TBI. The study participants were evaluated 6-12 months after injury at Washington University in St Louis. In total, 255 subjects were enrolled in the study, and 183 participated in follow-up evaluations, 5 of whom were disqualified.

MAIN OUTCOMES AND MEASURES In-person clinical examinations included evaluation for overall disability, a standardized neurological exam, headache questionnaires, neuropsychological test battery, combat exposure and alcohol use surveys, and structured interview evaluations for post-traumatic stress disorder (PTSD) and depression.

RESULTS Global outcomes, headache severity, neuropsychological performance, and surprisingly even PTSD severity and depression were indistinguishable between the two TBI groups, independent of mechanism of injury. Both TBI groups had higher rates of moderate to severe overall disability than the respective control groups: 41/53 (77%) of blast plus impact TBI and 23/29 (79%) of nonblast TBI vs. 16/27 (59%) of blast-exposed controls and 28/69 (41%) of non-blast-exposed controls. In addition, blast-exposed controls had worse headaches and more severe PTSD than non-blast-exposed controls. Self-reported combat exposure intensity was higher in the blast plus impact TBI group than in nonblast TBI group and was higher in blast-exposed controls than in non-blast-exposed controls. However, combat exposure intensity did not correlate with PTSD severity in the TBI groups, but a modest positive correlation was observed in the controls. Overall outcomes were most strongly correlated with depression, headache severity, and number of abnormalities on neuropsychological testing. However a substantial fraction of the variance in overall outcome was not explained by any of the assessed measures.

CONCLUSIONS AND RELEVANCE One potential interpretation of these results is that TBI itself, independent of injury mechanism and combat exposure intensity, is a primary driver of adverse outcomes. Many other important factors may be as yet unmeasured, and adverse outcomes following war-time injuries are difficult to fully explain.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01313130.

Author Affiliations: Author affiliations are listed at the end of this article.

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Traumatic brain injury (TBI) affects approximately 3.5 million individuals annually in the United States,[1] and approximately 75% are due to "mild" or concussive events.[2] In the US military, it is estimated that approximately 20% of the deployed force experienced a head injury in the wars in Iraq and Afghanistan,[3] of whom 83.3% endured a mild, uncomplicated TBI or concussion.[4] Blast injury has been identified as the signature injury in these conflicts. However, it remains to be determined whether fundamental differences may exist between blast-related TBI and TBI due to other mechanisms.

Previous studies have attempted to compare blast and nonblast TBI outcomes, with evaluations based largely on self-reporting,[5-12] retrospective medical record review,[13-16] and later stages after injury.[17,18] Findings from previous investigations comparing patients with blast vs nonblast TBI vary. Specifically, similarities have been observed in neurocognitive performance,[14,19,20] symptom complaints,[6,20] and mental health,[5,20] while other investigations have found individuals with blast TBI to be worse compared with individuals with nonblast TBI in all 3 of these domains[13] or solely in mental health.[21] Other studies[22,23] have shown that self-reporting is poorly associated with actual performance on measures such as neuropsychological testing not only in civilian populations but also specifically in the military, motivating further research using thorough clinical examinations in a prospective fashion.

Two main objectives of the present study were (1) to determine similarities and differences between clinical outcomes in US military personnel with blast-related vs non-blast-related concussive TBI and (2) to identify the specific domains of impairment that best correlate with overall disability. We prospectively enrolled and followed up patients with blast and nonblast TBI injured in the wars in Iraq and Afghanistan and then assessed clinical measures at 6 to 12 months. In addition, a blast-exposed control group (hereafter blast control) was compared with a non-blast-exposed control group (hereafter nonblast control) to explore whether blast exposures not resulting in a diagnosis of TBI could also contribute to outcomes. These cohorts were enrolled from October 2010 to May 2013 as part of an ongoing collaborative research effort at Landstuhl Regional Medical Center, Landstuhl, Germany. Results from previous cohorts, enrolled from 2008 to 2010, have been reported elsewhere.[24-27]

Methods

The research protocol was approved by the Human Research Protection Office at Washington University, the Institutional Review Board for Landstuhl Regional Medical Center at Brooke Army Medical Center, and the Clinical Investigation Regulatory and Human Research Protection Offices of the US Army Medical Research and Materiel Command. Written informed consent was obtained from all patients in person at Landstuhl Regional Medical Center; no surrogate consent was allowed by the funding agency. See the supplemental methods on the author's website for additional information (http://neuro.wustl.edu/index.php/download_file/view/2071/1054/). We en-

rolled 255 patients at Landstuhl Regional Medical Center after medical evacuation from combat theaters. The following 4 groups of active duty US military personnel evacuated from Iraq or Afghanistan were assessed: (1) nonblast control, (2) blast control subjects, (3) nonblast TBI (ie, TBI from mechanisms other than blast), and (4) blast plus impact TBI. See the supplemental methods on the author's website for specific inclusion and exclusion criteria. The mean (SD) times from injury to enrollment were 11.5 (9.6) days (blast plus impact TBI group) and 13.8 (10.1) days (nonblast TBI group), with a total range of 0 to 30 days. Of these patients, 183 were followed up at Washington University in St Louis at 6 to 12 months after injury. Of those who were followed up, 5 patients were disqualified (supplemental methods on the author's website), and data from 178 patients were used for analyses (eTable 1 on the author's website). Most patients were young, white, male enlisted service members in the US Army (Table 1), consistent with a previous Landstuhl Regional Medical Center cohort.[26]

For the blast plus impact TBI group, all available clinical histories indicated blast exposure plus another mechanism of head injury such as a fall, motor vehicle crash, or strike by a blunt object. None experienced an isolated blast injury. The mechanisms of injury for the nonblast TBI group were falls (9 of 29), motor vehicle crashes (6 of 29), or strike by a blunt object that did not involve blast exposure (14 of 29). Diagnosis of TBI was typically made based on self-report of alteration of neurological function due to an injury.[28] Medical evacuations of both control groups were mostly for gastrointestinal, dermatological, women's health, and orthopedic reasons. Clinical histories from the control subjects indicated no current or previous diagnoses of TBI, with the blast control group endorsing a history of blast exposure. All clinical histories were verified by study personnel (L.W., E.K., and T.S.) taking additional clinical history and reviewing medical records. None who screened positive for TBI were determined not to have had a TBI on further inspection.

Clinical Assessments

All examiners (C.L.M., E.C.N., N.J.W., and D.L.B.) were blinded to other clinical information and imaging results. However, in the course of the interviews, it often became clear whether the patients were in the TBI or control groups based on their endorsements of prior events.

Overall clinical outcomes were assessed using the Glasgow Outcome Scale-Extended[29,30] by telephone or e-mail monthly for 6 to 12 months. See the supplemental methods on the author's website for additional information.

In-person clinical evaluations included a standardized neurological examination, a neuropsychological test battery, and a psychiatric evaluation. The neuropsychological test battery consisted of 9 standard quantitative tests with well-documented performance norms. See the supplemental methods on the author's website for details. The neurological assessment included a structured interview designed for patients with TBI (Neurobehavioural Rating Scale-Revised[31]), 2 headache interviews capturing recent frequency and intensity (Migraine Disability Assessment [MIDAS] and Headache Impact Test 6,[32,33] and the Neurological Outcome Scale for

Table 1. Characteristics of Study Participants

Variable	Nonblast Control Follow-up (n = 69)	Nonblast Control No Follow-up (n = 28)	Blast Control Follow-up (n = 27)	Blast Control No Follow-up (n = 8)	Nonblast TBI Follow-up (n = 29)	Nonblast TBI No Follow-up (n = 15)	Blast Plus Impact TBI Follow-up (n = 53)	Blast Plus Impact TBI No Follow-up (n = 26)
Age, median (range), y	31 (21-49)	30 (22-49)	34 (22-46)	29 (20-39)	28 (20-50)	24 (22-48)	26 (19-47)[a]	24 (20 43)
Education, median (range), y	14 (9-28)	12 (12-15)	13 (10-19)	12 (12-14)	14 (9-18)	12 (12-14)	12 (12-18)	12 (12-16)
Sex, No. (%)								
Male	63 (91.3)	24 (85.7)	25 (92.6)	6 (75.0)	26 (89.7)	14 (93.3)	51 (96.2)	24 (92.3)
Female	6 (8.7)	4 (14.3)	2 (7.4)	2 (25.0)	3 (10.3)	1 (6.7)	2 (3.8)	2 (7.7)
Race/ethnicity, No. (%)[b]								
White	50 (72.5)	18 (64.3)	20 (74.1)	5 (62.5)	19 (65.5)	12 (80.0)	40 (75.5)	23 (88.5)
African American	16 (23.2)	6 (21.4)	4 (14.8)	1 (12.5)	7 (24.1)	2 (13.3)	4 (7.5)	1 (3.8)
Hispanic or Latino	3 (4.3)	3 (10.7)	2 (7.4)	1 (12.5)	3 (10.3)	0	7 (13.2)	1 (3.8)
Asian	0	1 (3.6)	1 (3.7)	1 (12.5)	1 (3.4)	1 (6.7)	2 (3.8)	2 (7.7)
Branch of service, No. (%)								
US Army	55 (79.7)	25 (89.3)	24 (88.9)	6 (75.0)	26 (89.7)	10 (66.7)	46 (86.8)	20 (76.9)
US Air Force	11 (15.9)	3 (10.7)	0	1 (12.5)	2 (6.9)	1 (6.6)	1 (1.9)	2 (7.7)
US Marine Corps	3 (4.3)	0	3 (11.1)	1 (12.5)	1 (3.4)	3 (20)	5 (9.4)	4 (15.4)
US Navy	0	0	0	0	0	1 (6.7)	1 (1.9)	0
Duty status, No. (%)								
Active	43 (62.3)	16 (57.1)	19 (70.4)	7 (87.5)	20 (69.0)	12 (80.0)	39 (73.6)	21 (80.8)
National Guard	23 (33.3)	7 (25.0)	7 (25.9)	0	4 (17.2)	0	10 (18.9)	4 (15.4)
Reserve	3 (4.3)	5 (17.9)	1 (3.7)	1 (12.5)	5 (17.2)	3 (13.3)	4 (7.5)	1 (3.8)
Military rank, No. (%)								
Enlisted	63 (91.3)	26 (92.9)	24 (88.9)	8 (100.0)	27 (93.1)	15 (100.0)	52 (98.1)	25 (96.2)
Officer	6 (8.7)	2 (7.1)	3 (11.1)	0	2 (6.9)	0	1 (1.9)	1 (3.8)
Theater of operation, No. (%)								
Afghanistan	55 (79.7)	23 (81.1)	21 (77.8)	5 (62.5)	18 (62.1)	13 (86.7)	50 (94.3)	24 (92.3)
Iraq	14 (20.3)	5 (17.9)	6 (22.2)	3 (37.5)	11 (37.9)	2 (13.3)	3 (5.7)	2 (7.7)
Concussion severity MACE score, median (range)	NA	NA	NA	NA	26 (21-30)	26 (10-30)	26 (12-30)	25 (16-30)

Abbreviations: MACE, Military Acute Concussion Evaluation[28]; NA, not applicable; TBI, traumatic brain injury.

[a] $P = .000026$ for blast controls vs blast plus impact TBI by Mann-Whitney test.

[b] Individuals were allowed to choose more than 1 response.

Traumatic Brain Injury (NOS-TBI).[34-36] The Neurobehavioural Rating Scale–Revised was analyzed using a published 5-subdomain model.[37] The psychiatric evaluation included the Clinician-Administered PTSD Scale for *DSM-IV* (CAPS),[38] Montgomery-Åsberg Depression Rating Scale,[39] Combat Exposures Scale (CES),[40] and Michigan Alcoholism Screening Test.[41] The CAPS was scored using standard scoring rules by Blake et al.[42]

Statistical Analysis

See the supplemental methods on the author's website for complete details on the statistical analyses. Briefly, statistical software (Statistica 10.0; StatSoft Inc) was used for the analyses. Continuous variables are summarized as means (SDs). *t* Test and Mann-Whitney test were used based on the distribution of the data. Uncorrected *P* values are reported but were considered significant only at $P < .05$ after Bonferroni correction for multiple comparisons within each class of variables. The 4 main comparisons of interest were (1) nonblast control group vs nonblast TBI group, (2) nonblast control group vs blast control group, (3) blast control group vs blast plus impact TBI group, and (4) blast plus impact TBI group vs nonblast TBI group, so $P < .0125$ (0.05 divided by 4) was considered significant for most comparisons between groups. Correlations are reported from Spearman rank correlation because of the nature of the data analyzed. Logistic regression analysis was used to explore the relationship between global outcomes and multiple quantitative measures of specific symptoms and impairments.

Results

Global Outcomes

Global outcomes assessed by the Glasgow Outcome Scale–Extended were worse in both TBI groups than in either control group (**Figure 1**). Patients with nonblast TBI were significantly more disabled than nonblast controls ($P = .00003$). Likewise, patients with blast plus impact TBI were significantly worse than blast control subjects ($P = .01$), replicating previous results.[27] No differences in global outcomes were observed between the blast plus impact TBI vs nonblast TBI

Figure 1. Worse Global Outcomes After Traumatic Brain Injury (TBI) Than in Control Subjects Among Evacuated US Military Personnel
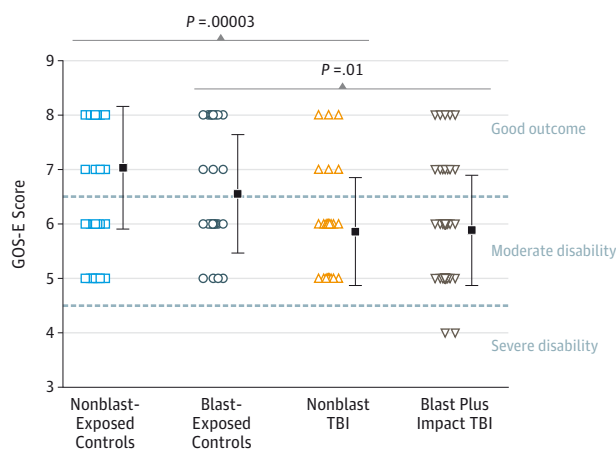
Results were assessed at 6 to 12 months after enrollment. *P* values were calculated using 1-tailed Mann-Whitney test and were reported if significant after correction for multiple comparisons at *P* < .0125. GOS-E indicates Glasgow Outcome Scale–Extended.

groups (*P* = .82); similarly, no differences were found between the blast control vs nonblast control groups (*P* = .10). At an individual subject level, 41/53 blast plus impact TBI subjects (77%) and 23/29 nonblast TBI subjects (79%) had moderate to severe disability defined as GOS-E score of 6 or less; 16/27 blast controls (59%) and 28/69 nonblast controls (41%) also met this criteria. The disabled proportion was significantly greater in non-blast TBI subjects in comparison to non-blast controls (p=0.0005, chi-square). Blast-exposed controls and non-blast-exposed controls did not significantly differ (p=0.10, chi-square), nor did blast controls and blast-plus TBI subjects (p=0.09, chi-square) or blast-plus TBI and non-blast TBI subjects (p=0.84, chi-square) in proportion of disabled subjects.

Neuropsychological Testing

In general, all 4 patient groups performed well on neuropsychological testing, and no significant differences were observed across groups (eTable2 on the author's website). However, analysis of individual patients' neuropsychological performance revealed abnormalities that were not apparent at the group level (**Figure** 2A). Abnormal performance for an individual patient was defined as a score that fell 2 SDs outside the mean for the nonblast control group in the direction of worse performance for each assessment. For each individual patient, the number of tests for which performance was abnormal was counted. By chance, of 18 test variables, 66% of patients would be expected to have abnormal performance on 0 tests, 28% would be expected to have abnormal performance on 1 test, and 5% would be expected to have abnormal performance on 2 or more tests. Both the nonblast-exposed TBI (hereafter nonblast TBI) and blast plus impact TBI groups had more patients with abnormalities on neuropsychological testing in 2 or more assessments than would be expected by chance (nonblast TBI, *P* = .0002 and

blast plus impact TBI, *P* = .0001; χ^2 test). The proportion of patients with blast plus impact TBI did not differ from the proportion of patients with nonblast TBI. No apparent trend was found in the profiles of test abnormalities within this subset of patients. Blast and nonblast controls did not differ, and neither control group had more patients with abnormal performance on 2 or more neuropsychological tests than would be expected by chance. This result indicates that subsets of patients in both the blast plus impact TBI and nonblast TBI groups were impaired in neuropsychological performance, although the group means were generally not different from those of the controls.

Neurobehavioral Assessment

Clinician ratings in multiple neurobehavioral domains using the Neurobehavioural Rating Scale–Revised revealed more substantial impairments in the patients with TBI compared with the controls. However, no significant differences were observed between the blast plus impact TBI and nonblast TBI groups. More severe neurobehavioral impairments were found in blast controls compared with nonblast controls (eFigure 1 and supplemental results on the author's website).

Focal Neurological Examination Findings

As assessed using the NOS-TBI, few focal neurological deficits were observed among the patients across groups overall. The NOS-TBI identified significant impairment only in patients with nonblast TBI compared with nonblast controls (*P* = .008, Mann-Whitney test) (eFigure 2 on the author's website). The most common focal deficits were in the domain of olfaction, found in 11 of 69 nonblast controls (15.9%), 6 of 27 blast controls (22.2%), 15 of 29 patients with nonblast TBI (51.7%), and 9 of 53 patients with blast plus impact TBI (17.0%). This was followed by hearing deficits, observed in 2 of 69 nonblast controls (2.9%), 3 of 27 blast controls (11.1%), 4 of 29 patients with nonblast TBI (13.8%), and 10 of 53 patients with blast plus impact TBI (18.9%). The difference in frequency of olfactory deficits between the nonblast TBI group and the nonblast control group was statistically significant (*P* = .0003, χ^2 test), as was the difference between the nonblast TBI group and blast plus impact TBI group (*P* = .0009, χ^2 test). None of the group comparisons for hearing loss were significant. No difference across groups was observed on the NOS-TBI supplement assessing gait and limb ataxia.

Headache

Headache impairment was substantially higher in patients with TBI compared with controls as assessed using the 2 validated self-report measures of MIDAS (Figure 2B and eFigure 3 on the author's website) and Headache Impact Test 6 (eFigure 4 on the author's website). However, no differences were observed between the blast plus impact TBI and nonblast TBI groups (MIDAS, *P* = .48; MIDAS grade, *P* = .31; MIDAS-A for frequency, *P* = .07; and MIDAS-B for pain severity, *P* = .77; Mann-Whitney test). Patients with nonblast TBI scored significantly higher than nonblast controls on the MIDAS total (*P* = .000001) and each of its subscores (MIDAS grade, *P* = .000001; MIDAS-A, *P* = .000001; and MIDAS-B, *P* = .0005).

Figure 2. Clinical Measures Collected at 6 to 12 Months After Injury
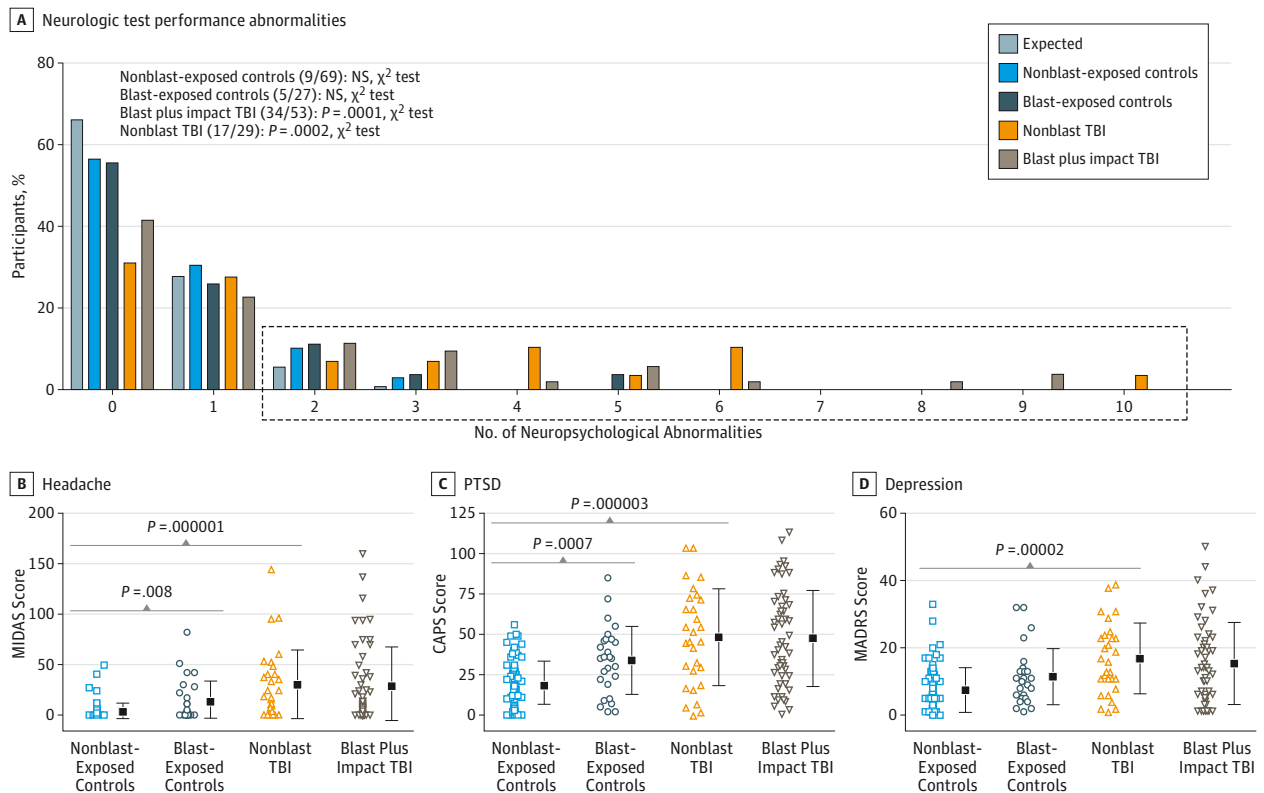
A, Neuropsychological test performance abnormalities were detected in subsets of patients with traumatic brain injury (TBI). The number of patients with neuropsychological test abnormalities (defined as >2 SDs outside the mean for the nonblast control group) is displayed by group compared with what would be expected by chance (blue bars). The percentage of patients is shown to account for the differences in the numbers of patients across groups. The dotted box indicates the group of patients who had poor performance on 2 or more of 18 neuropsychological assessments. P values were calculated using χ^2 test between each group vs expected numbers by chance. B, Headache impairment was assessed by the Migraine Disability Assessment (MIDAS)

(maximum score, 180). C, Posttraumatic stress disorder (PTSD) severity was assessed by the Clinician-Administered PTSD Scale for *DSM-IV* (CAPS) (maximum score, 136). The CAPS total severity comparison of blast control subjects vs patients with blast plus impact TBI was not significant (P = .06). D, Depression severity was assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS) (maximum score, 60). Higher scores indicate worse impairment. P values were calculated using 1-tailed Mann-Whitney test and were reported if significant after correction for multiple comparisons at P < .0125. NS indicates not significant.

Blast controls also had more impairment than nonblast controls on the MIDAS-A (P = .0003). No differences were found between the patients with blast plus impact TBI and the blast controls (MIDAS total, P = .56; MIDAS grade, P = .07; MIDAS-A, P = .07; and MIDAS-B, P = .39).

Posttraumatic Stress Disorder and Depression

Psychiatric evaluations revealed worse severity of depression and posttraumatic stress disorder (PTSD) symptoms in both TBI groups than in controls (Figure 2C and D), but surprisingly no differences were observed between the blast plus impact TBI and nonblast TBI groups. Specifically, 41.5% (22 of 53) of patients with blast plus impact TBI and 48.3% (14 of 29) of patients with nonblast TBI met all *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria for PTSD, while 22.2% (6 of 27) of blast controls and only 5.8% (4 of 69) of nonblast controls met these criteria. This outcome represented significantly more patients in the nonblast TBI group compared with the nonblast controls (P = .0000001, χ^2 test).

Comparing blast controls vs nonblast controls (P = .018), blast controls vs patients with blast plus impact TBI (P = .09), or patients with blast plus impact TBI vs patients with nonblast TBI (P = .56), the differences in the numbers of patients were not significant by χ^2 test after correction for multiple comparisons (P < .0125).

Furthermore, no difference was found in any of the PTSD severity scores between the nonblast TBI and blast plus impact TBI groups (Figure 2C and eFigure 5 on the author's website) (CAPS total, P = .90; CAPS-B severity–reexperiencing traumatic events, P = .46; CAPS-C severity–avoidance and numbing, P = .55; and CAPS-D severity–increased arousal and hypervigilance, P = .76; Mann-Whitney test). The CAPS total scores for PTSD severity were significantly increased in the nonblast TBI group compared with nonblast controls (P = .000003). Of the 3 CAPS subseverity scores, CAPS-D (P = .00002) was most affected, followed by CAPS-B (P = .0001) and CAPS-C (P = .0004). Blast controls were more severely affected than nonblast controls on all measures (CAPS total, P = .0007; CAPS-B, P = .0003;

Figure 3. Correlations Between Combat Exposure Intensity and Posttraumatic Stress Disorder
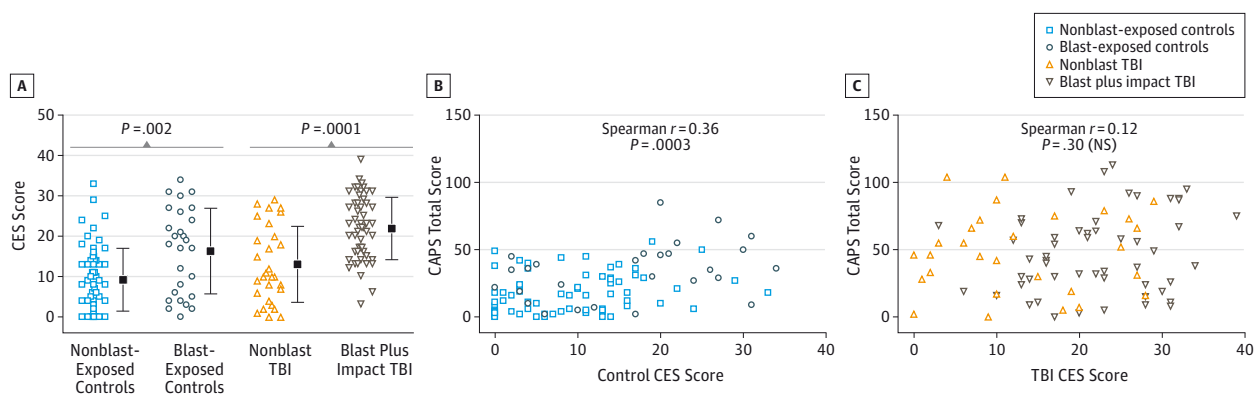
A, Combat exposure intensity was assessed by the Combat Exposures Scale (CES). Higher scores indicate greater self-reported combat exposure (maximum score, 41). P values were calculated using 1-tailed Mann-Whitney test and were reported if significant after correction for multiple comparisons at $P < .0125$. B, A positive correlation was found between the Clinician-Administered PTSD

Scale for *DSM-IV* (CAPS) total score and the combat exposure intensity measured by the CES in control subjects. C, In contrast, no correlation was observed between the CAPS total score and the CES score in the traumatic brain injury (TBI) groups. NS indicates not significant.

CAPS-C, $P = .004$; and CAPS-D, $P = .003$). The difference in PTSD severity between patients with blast plus impact TBI and blast controls was marginal (CAPS total, $P = .06$; CAPS-B, $P = .05$; CAPS-C, $P = .13$; and CAPS-D, $P = .16$).

Likewise, comparing depression severity scores of the blast plus impact TBI group vs the nonblast TBI group ($P = .38$, Mann-Whitney test), no difference was observed (Figure 2D). Depression symptoms were significantly worse in the nonblast TBI group compared with the nonblast controls ($P = .00002$). A trend was observed in blast controls toward worse depression compared with nonblast controls, but it did not reach significance after correction for multiple comparisons ($P = .014$). No difference was observed comparing patients having blast plus impact TBI with blast controls ($P = .24$).

Combat Exposure Intensity

In contrast to psychiatric symptom severity, the intensity of self-reported combat exposure was highest in the blast plus impact TBI group and the blast controls (**Figure 3**A). Blast controls reported significantly higher levels of combat exposure than nonblast controls ($P = .002$), as did the blast plus impact TBI group compared with the nonblast TBI group ($P = .0001$). No difference was found after correction for multiple comparisons between patients with blast plus impact TBI and blast controls ($P = .03$); similarly, no difference was observed between patients with nonblast TBI and nonblast controls ($P = .08$). Therefore, the relationship between group and combat exposure intensity differed substantially from the relationship between group and adverse clinical outcomes.

Alcohol Misuse

No significant differences were found in the scores for any of the groups on the Michigan Alcoholism Screening Test (range, $P = .04$ to $P = .85$ across groups; Mann-Whitney test). See eFigure 6 on the author's website for more details.

Poor Sleep

An index of poor sleep was obtained from subsection D-1 of the CAPS comparing the mean number of hours of sleep reported with the mean number of hours of sleep desired (eFigure 7 on the author's website). We refer to this difference as the Poor Sleep Index. It was found to strongly correlate with total severity scores on the CAPS ($r = 0.55$, $P < .0001$), Montgomery-Åsberg Depression Rating Scale ($r = 0.55$, $P < .0001$), Neurobehavioural Rating Scale–Revised ($r = 0.42$, $P < .0001$), MIDAS ($r = 0.47$, $P < .0001$), and Headache Impact Test 6 ($r = 0.46$, $P < .0001$). It did not correlate with the metrics of combat exposure, alcohol misuse, or neuropsychological testing performance.

Relationship Between Combat Exposure and PTSD Severity

The intensity of self-reported combat exposure was differentially related to PTSD severity in controls and patients with TBI (Figure 3B and C). In controls, a modest but statistically significant correlation was found between the total PTSD severity measured by the CAPS and the combat exposure intensity measured by the CES ($r = 0.36$, $P = .0003$) (Figure 3B). This relationship held for each of the subdomains (eFigure 8 on the author's website), including CAPS-B ($r = 0.36$, $P = .0003$), CAPS-C ($r = 0.24$, $P = .02$), and CAPS-D ($r = 0.34$, $P = .0007$). Surprisingly, this was not the case for the patients with TBI: no correlation was observed between the combat exposure intensity and the CAPS total score ($r = 0.12$, $P = .30$ [not significant]) (Figure 3C) or any of the subdomains, including CAPS-B ($r = 0.19$, $P = .08$ [not significant]), CAPS-C ($r = 0.09$, $P = .44$ [not significant]), and CAPS-D ($r = 0.07$, $P = .56$ [not significant]). In a generalized linear model that included CES and group identity, an almost significant interaction between CES and group identity ($P = .06$) was seen. Therefore, any difference in the relationships between patients with TBI and controls should be considered hypothesis generating rather than definitive.

Table 2. Models With the Best Fit in Logistic Regression Analyses for Global Outcomes

Variable	Estimate (95% CI)	P Value
Model 1[a,b]		
Intercept	−0.9477 (−1.5376 to −0.3576)	.0016
MADRS	0.0689 (0.0199 to 0.1179)	.0059
No. of neuropsychological abnormalities	0.4381 (0.1173 to 0.7589)	.0074
MIDAS	0.02349 (0.00002 to 0.04696)	.0498
Model 2[c]		
Intercept	−0.7573 (−1.3837 to −0.1309)	.0178
MADRS	0.0663 (0.0162 to 0.1163)	.0094
No. of neuropsychological abnormalities	0.4077 (0.0755 to 0.7399)	.0161
MIDAS	0.0182 (−0.0055 to 0.0418)	.1323
TBI vs control groups	−0.3546 (−0.7273 to 0.0182)	.0623

Abbreviations: GOS-E, Glasgow Outcome Scale–Extended; MADRS, Montgomery-Åsberg Depression Rating Scale; MIDAS, Migraine Disability Assessment; TBI, traumatic brain injury.

[a] The overall Akaike information criterion was 202.5, and the likelihood ratio by χ^2 test was 44.04.

[b] Model 1 includes the GOS-E, MADRS, number of neuropsychological abnormalities, and MIDAS.

[c] Model 2 includes the GOS-E, MADRS, number of neuropsychological abnormalities, MIDAS, and TBI vs control groups.

Multivariate Correlates of Global Outcomes

We assessed many possible correlates and found that the number of neuropsychological abnormalities, severity of depression, and extent of headache-related disability were most strongly related to overall disability (**Table 2**). Specifically, we performed logistic regression analysis using the dichotomized Glasgow Outcome Scale–Extended as the dependent variable. Scores of 7 or 8 were defined as good outcomes, and scores of 6 or below were defined as disabled (Figure 1). We entered the following possible correlates into the model: PTSD severity (CAPS), self-reported Poor Sleep Index, combat exposure intensity (CES), headache-related disability (MIDAS), overall headache impairment (Headache Impact Test 6), severity of neurological deficits (NOS-TBI), the number of neuropsychological abnormalities, and depression severity (Montgomery-Åsberg Depression Rating Scale). All possible subsets of models were assessed, and models were ranked based on the Akaike information criterion. The best model by the Akaike information criterion included the number of neuropsychological abnormalities, depression severity, and headache-related disability (model 1 in Table 2).

However, this model accounted for only a moderate proportion of global disability (area under the receiver operating characteristic curve, 0.78) (eFigure 9A on the author's website). To determine whether unmeasured factors associated with TBI provided explanatory power, we added the dichotomous variable TBI vs control groups to the model. In this model, the effect of headache-related disability was no longer significant, and the effect of TBI vs control groups was marginal (P = .06) (model 2 in Table 2). The addition of TBI vs control groups negligibly improved the receiver operating characteristic curve area to 0.79 (eFigure 9B on the author's website).

This result indicated very little contribution of unmeasured factors associated with TBI. However, it leaves a substantial fraction of the variance in outcomes still unaccounted for in these patients.

Discussion

In summary, the blast plus impact TBI and nonblast TBI groups were essentially indistinguishable with regard to clinical outcomes at 6 to 12 months after injury. Overall global outcomes, neurobehavioral impairments, neuropsychological performance, headache-related disability, depression, and PTSD were all similar in the blast plus impact TBI and nonblast TBI groups. Although few group-level impairments were found in the neuropsychological testing, subsets of individuals in both TBI groups had worse performance than would be expected by chance. Only a slightly higher rate of olfactory impairment in the patients with nonblast TBI distinguished the groups. However, it must be emphasized that all patients with blast-related TBI in the study had complex mechanisms of injury, including blast plus another type of injury such as a fall, motor vehicle crash, or strike by a blunt object. None had an isolated primary blast injury, suggesting as in previous work[24,26] that such injuries may be rare among evacuated US military personnel.

The exacerbation of depression and PTSD symptoms after concussive brain injury is consistent with investigations examining patients with blast TBI after loss of consciousness,[17] self-report surveys in Operation Enduring Freedom and Operation Iraqi Freedom veterans,[23] and subjective complaint measures comparing predeployment and postdeployment.[43] A recent retrospective study[44] reported similar findings specifically in Marines at 3 months after deployment; however, questions remained about the generalizability to other branches of the military and the longer-term effect on outcomes. A novel finding from our study is that combat exposure intensity did not correlate with PTSD severity in patients with TBI but correlated with PTSD severity in controls. Although this requires replication, the present investigation is the first to date to examine this relationship in a prospectively collected cohort of patients with blast plus impact TBI and nonblast TBI at 6 to 12 months. Among potential explanations for this relationship, the hypothesis that injury to specific brain regions sustained in both TBI groups impaired the extinction of traumatic combat memories and contributed to the chronic effects of posttraumatic stress[45] is perhaps most intriguing. However, definitive evidence for this hypothesis will require detailed correlations between imaging and clinical outcomes, which were beyond the scope of this study.

Logistic regression modeling identified a modest relationship between global outcomes and other clinical measures, most notably depression severity, the number of neuropsychological performance abnormalities, and headache impairment. Negligible improvement in the strength of the model was observed when TBI diagnoses were included. However, the area under the receiver operating characteristic curve was 0.78, which suggests that much of the underlying cause

of poor global outcomes is unaccounted for by our present evaluation measures. Clearly, new assessment techniques in additional domains, such as specific duty-related cognitive assessments, social and emotional intelligence testing, and methods to capture disabilities unrelated to head injury, should be explored.

An additional major finding was that blast controls were significantly worse on neurobehavioral outcomes, psychiatric measures, and headache impairment but not neuropsychological test performance compared with nonblast controls. Several possible explanations include that (1) associated increases in combat exposure could negatively influence outcomes, (2) direct structural adverse effects could result from subconcussive blast exposure, (3) some of the blast controls could have been misclassified with respect to TBI, or (4) other events associated with blast exposure may be involved.

Strengths of this study include the prospective design, direct comparison of patients with blast and nonblast TBI, the addition of a blast control group, blinded clinical evaluations completed by trained personnel, and rigorous quantitative analysis techniques. Limitations include the modest sample size, potential selection bias given that these were all patients who were medically evacuated from combat theaters, and a lack of preinjury or early postinjury clinical data for comparison with later outcomes. In addition, we were unable to obtain objective measures of sleep disorders, and we could not control for medication use and current interventions at the time of follow-up evaluations. With regard to headache, we only globally collected headache information and did not explore the underlying causes or chronic pain unrelated to headache. This limitation is discussed in more detail in the supplemental discussion on the author's website.

Conclusions

Based on this prospective study of evacuated US military personnel, we conclude that the clinical outcomes after blast-related concussive TBI are generally similar to those after non-blast-related concussion sustained during deployment. The rate of disability seen after both blast-related and non–blast-related concussive TBI is much higher than that in otherwise comparable civilian studies,[46-54] which may be owing to common elements involved in TBI in a deployed setting rather than the mechanisms of injury per se. However, the finding that the specific domains assessed still do not fully capture overall adverse outcomes indicates substantial room for further investigation into the causes of disability after wartime concussive TBI.

REFERENCES

1. Coronado VG, McGuire LC, Sarmiento K, et al. Trends in traumatic brain injury in the U.S. and the public health response: 1995-2009. *J Safety Res*. 2012;43(4):299-307.

2. National Center for Injury Prevention and Control, Centers for Disease Control and Prevention (CDC). *Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem.* Atlanta, GA: Centers for Disease Control and Prevention; 2003.

3. Taniellian T, Jaycox L. *Invisible Wounds of War: Psychological and Cognitive Injuries, Their Consequences, and Services to Assist Recovery.* Santa Monica, CA: RAND Corporation; 2008.

4. Defense and Veterans Brain Injury Center. DoD numbers for traumatic brain injury worldwide: totals 2000-2013 (Q1-Q3). 2013. http://dvbic.dcoe .mil/dod-worldwide-numbers-tbi. Accessed June 10, 2014.

5. Kennedy JE, Leal FO, Lewis JD, Cullen MA, Amador RR. Posttraumatic stress symptoms in OIF/OEF service members with blast-related and non–blast-related mild TBI. *NeuroRehabilitation*. 2010;26(3):223-231.

6. Belanger HG, Proctor-Weber Z, Kretzmer T, Kim M, French LM, Vanderploeg RD. Symptom complaints following reports of blast versus non-blast mild TBI. *Clin Neuropsychol*. 2011;25(5): 702-715.

7. Schneiderman AI, Braver ER, Kang HK. Understanding sequelae of injury mechanisms and mild traumatic brain injury incurred during the conflicts in Iraq and Afghanistan. *Am J Epidemiol*. 2008;167(12):1446-1452.

8. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. soldiers returning from Iraq. *N Engl J Med*. 2008; 358(5):453-463.

9. Polusny MA, Kehle SM, Nelson NW, Erbes CR, Arbisi PA, Thuras P. Longitudinal effects of mild traumatic brain injury and posttraumatic stress disorder comorbidity on postdeployment outcomes in National Guard soldiers deployed to Iraq. *Arch Gen Psychiatry*. 2011;68(1):79-89.

10. Thomas JL, Wilk JE, Riviere LA, McGurk D, Castro CA, Hoge CW. Prevalence of mental health problems and functional impairment among active component and National Guard soldiers 3 and 12 months following combat in Iraq. *Arch Gen Psychiatry*. 2010;67(6):614-623.

11. Wilk JE, Herrell RK, Wynn GH, Riviere LA, Hoge CW. Mild traumatic brain injury (concussion), posttraumatic stress disorder, and depression in U.S. soldiers involved in combat deployments. *Psychosom Med*. 2012;74(3):249-257.

12. Wilk JE, Thomas JL, McGurk DM, Riviere LA, Castro CA, Hoge CW. Mild traumatic brain injury (concussion) during combat: lack of association of blast mechanism with persistent postconcussive symptoms. *J Head Trauma Rehabil*. 2010;25(1):9-14.

13. Kontos AP, Kotwal RS, Elbin RJ, et al. Residual effects of combat-related mild traumatic brain injury. *J Neurotrauma*. 2013;30(8):680-686.

14. Cooper DB, Chau PM, Armistead-Jehle P, Vanderploeg RD, Bowles AO. Relationship between mechanism of injury and neurocognitive functioning in OEF/OIF service members with mild traumatic brain injuries. *Mil Med*. 2012;177(10):1157-1160.

15. Eskridge SL, Macera CA, Galarneau MR, et al. Influence of combat blast-related mild traumatic brain injury acute symptoms on mental health and service discharge outcomes. *J Neurotrauma*. 2013;30(16):1391-1397.

16. Galarneau MR, Woodruff SI, Dye JL, Mohrle CR, Wade AL. Traumatic brain injury during Operation Iraqi Freedom. *J Neurosurg*. 2008;108(5):950-957.

17. Verfaellie M, Lafleche G, Spiro A III, Tun C, Bousquet K. Chronic postconcussion symptoms and functional outcomes in OEF/OIF veterans with self-report of blast exposure. *J Int Neuropsychol Soc*. 2013;19(1):1-10.

18. Fischer BL, Parsons M, Durgerian S, et al. Neural activation during response inhibition differentiates blast from mechanical causes of mild to moderate traumatic brain injury. *J Neurotrauma*. 2014;31(2):169-179.

19. Belanger HG, Kretzmer T, Yoash-Gantz R, Pickett T, Tupler LA. Cognitive sequelae of blast-related versus other mechanisms of brain trauma. *J Int Neuropsychol Soc*. 2009;15(1):1-8.

20. Luethcke CA, Bryan CJ, Morrow CE, Isler WC. Comparison of concussive symptoms, cognitive performance, and psychological symptoms between acute blast- versus nonblast-induced mild traumatic brain injury. *J Int Neuropsychol Soc*. 2011;17(1):36-45.

21. Maguen S, Madden E, Lau KM, Seal K. The impact of head injury mechanism on mental health symptoms in veterans: do number and type of exposures matter? *J Trauma Stress*. 2012;25(1):3-9.

22. Spencer RJ, Drag LL, Walker SJ, Bieliauskas LA. Self-reported cognitive symptoms following mild traumatic brain injury are poorly associated with neuropsychological performance in OIF/OEF veterans. *J Rehabil Res Dev*. 2010;47(6):521-530.

23. Drag LL, Spencer RJ, Walker SJ, Pangilinan PH, Bieliauskas LA. The contributions of self-reported injury characteristics and psychiatric symptoms to cognitive functioning in OEF/OIF veterans with mild traumatic brain injury. *J Int Neuropsychol Soc*. 2012;18(3):576-584.

24. Mac Donald C, Johnson A, Cooper D, et al. Cerebellar white matter abnormalities following primary blast injury in US military personnel. *PLoS One*. 2013;8(2):e55823. doi:10.1371/journal.pone.0055823.

25. Han K, Mac Donald CL, Johnson AM, et al. Disrupted modular organization of resting-state cortical functional connectivity in U.S. military personnel following concussive "mild" blast-related traumatic brain injury. *Neuroimage*. 2014;84:76-96.

26. Mac Donald CL, Johnson AM, Cooper D, et al. Detection of blast-related traumatic brain injury in U.S. military personnel. *N Engl J Med*. 2011;364(22):2091-2100.

27. Mac Donald CL, Johnson AM, Nelson EC, et al. Functional status after blast-plus-impact complex concussive traumatic brain injury in evacuated United States military. *J Neurotrauma*.2014;31(10):889-898.

28. Dempsey KE, Dorlac WC, Martin K, et al. Landstuhl Regional Medical Center: traumatic brain injury screening program. *J Trauma Nursing*. 2009;16(1):6-12.

29. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale. *J Neurotrauma*. 1998;15(8):573-585.

30. Pettigrew LE, Wilson JT, Teasdale GM. Reliability of ratings on the Glasgow Outcome Scales from in-person and telephone structured interviews. *J Head Trauma Rehabil*. 2003;18(3):252-258.

31. Levin HS, High WM, Goethe KE, et al. The Neurobehavioural Rating Scale: assessment of the behavioural sequelae of head injury by the clinician. *J Neurol Neurosurg Psychiatry*. 1987;50(2):183-193.

32. Stewart WF, Lipton RB, Whyte J, et al. An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. *Neurology*. 1999;53(5):988-994.

33. Kosinski M, Bayliss MS, Bjorner JB, et al. A six-item short-form survey for measuring headache impact: the HIT-6. *Qual Life Res*. 2003;12(8):963-974.

34. McCauley SR, Wilde EA, Kelly TM, et al. The Neurological Outcome Scale for Traumatic Brain Injury (NOS-TBI), II. *J Neurotrauma*. 2010;27(6):991-997.

35. Wilde EA, McCauley SR, Kelly TM, et al. The Neurological Outcome Scale for Traumatic Brain Injury (NOS-TBI), I. *J Neurotrauma*. 2010;27(6):983-989.

36. Wilde EA, McCauley SR, Kelly TM, et al. Feasibility of the Neurological Outcome Scale for Traumatic Brain Injury (NOS-TBI) in adults. *J Neurotrauma*. 2010;27(6):975-981.

37. McCauley SR, Levin HS, Vanier M, et al. The Neurobehavioural Rating Scale–Revised: sensitivity and validity in closed head injury assessment. *J Neurol Neurosurg Psychiatry*. 2001;71(5):643-651.

38. Weathers FW, Keane TM, Davidson JR. Clinician-Administered PTSD Scale: a review of the first ten years of research. *Depress Anxiety*. 2001;13(3):132-156.

39. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382-389.

40. Keane TM, Fairbank JA, Caddell JM, Zimering RT, Taylor KL, Mora CA. Clinical evaluation of a measure to assess combat exposure. *Psychol Assess*. 1989;1(1):53-55. doi:10.1037/1040-3590.1.1.53.

41. Selzer ML. The Michigan Alcoholism Screening Test. *Am J Psychiatry*. 1971;127(12):1653-1658.

42. Blake DD, Weathers FW, Nagy LM, et al. The development of a Clinician-Administered PTSD Scale. *J Trauma Stress*. 1995;8(1):75-90.

43. Vasterling JJ, Brailey K, Proctor SP, Kane R, Heeren T, Franz M. Neuropsychological outcomes of mild traumatic brain injury, post-traumatic stress disorder and depression in Iraq-deployed US Army soldiers. *Br J Psychiatry*. 2012;201(3):186-192.

44. Yurgil KA, Barkauskas DA, Vasterling JJ, et al. Association between traumatic brain injury and risk of posttraumatic stress disorder in active-duty Marines. *JAMA Psychiatry*. 2014;71(2):149-157.

45. Myers KM, Davis M. Mechanisms of fear extinction. *Mol Psychiatry*. 2007;12(2):120-150.

46. Sigurdardottir S, Andelic N, Roe C, Schanke AK. Cognitive recovery and predictors of functional outcome 1 year after traumatic brain injury. *J Int Neuropsychol Soc*. 2009;15(5):740-750.

47. Benedictus MR, Spikman JM, van der Naalt J. Cognitive and behavioral impairment in traumatic brain injury related to outcome and return to work. *Arch Phys Med Rehabil*. 2010;91(9):1436-1441.

48. Alexander MP. Mild traumatic brain injury: pathophysiology, natural history, and clinical management. *Neurology*. 1995;45(7):1253-1260.

49. Thornhill S, Teasdale GM, Murray GD, McEwen J, Roy CW, Penny KI. Disability in young people and adults one year after head injury: prospective cohort study. *BMJ*. 2000;320(7250):1631-1635.

50. Mosenthal AC, Livingston DH, Lavery RF, et al. The effect of age on functional outcome in mild traumatic brain injury: 6-month report of a prospective multicenter trial. *J Trauma*. 2004;56(5):1042-1048.

51. McMahon P, Hricik A, Yue JK, et al; TRACK-TBI Investigators. Symptomatology and functional outcome in mild traumatic brain injury: results from the prospective TRACK-TBI study. *J Neurotrauma*. 2014;31(1):26-33.

52. Lannsjö M, Raininko R, Bustamante M, von Seth C, Borg J. Brain pathology after mild traumatic brain injury: an exploratory study by repeated magnetic resonance examination. *J Rehabil Med*. 2013;45(8):721-728.

53. Jacobs B, Beems T, Stulemeijer M, et al. Outcome prediction in mild traumatic brain injury: age and clinical variables are stronger predictors than CT abnormalities. *J Neurotrauma*. 2010;27(4):655-668.

54. Stulemeijer M, van der Werf SP, Jacobs B, et al. Impact of additional extracranial injuries on outcome after mild traumatic brain injury. *J Neurotrauma*. 2006;23(10):1561-1569.

SUPPLEMENTAL MATERIAL:

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"**Prospectively Assessed Clinical Outcomes in Concussive Blast vs. Non-blast Traumatic Brain Injury in Evacuated US Military Personnel.**"

1.SUPPLEMENTAL METHODS

1.1 Approval

The research protocol was approved by the Human Research Protection Office at Washington University, the Institutional Review Board for LRMC at Brooke Army Medical Center, and the Clinical Investigation Regulatory and Human Research Protection Offices of the U.S. Army Medical Research and Materiel Command.

1.2 Inclusion Criteria

Inclusion criteria for the TBI groups were as follows: 1) a positive screen for TBI at LRMC based on standard US military clinical criteria[1] including self-report of blast exposure or non-blast mechanism such as blunt trauma resulting in loss of consciousness, amnesia for the event, or change in neurological status, 2) injury from blast or non-blast mechanisms of injury within 30 days of enrollment, 3) US military, 4) ability to provide informed consent in person, 5) no contraindications to MRI such as retained metallic fragments, 6) no prior history of moderate to severe TBI based on Department of Defense criteria, 7) no prior history of major psychiatric disorder, 8) agreement to communicate by telephone or email monthly for 6-12 months and then travel to Washington University for in-person follow-up. Inclusion criteria for the control groups were the same except for a negative screen for TBI at LRMC with or without a history of blast exposure.

1.3 Informed Consent

Competence to provide informed consent was assessed in a standardized fashion based on responses to questions regarding the purpose of the study, expected requirements for participation, and potential risks. Additional written consent was obtained from the subjects at the time of follow-up at Washington University. Active duty military subjects were not paid for participation, though travel expenses to St Louis were covered. Subjects not on active military duty status at the time of follow-up in St Louis were paid $240 plus travel expenses for participation.

1.4 Clinical Histories

Medical documentation regarding duration of loss of consciousness and post-traumatic amnesia was often not available or not reliable. All available clinical histories indicated change in level of consciousness or loss of consciousness for a few minutes and post-traumatic amnesia for less than 24 hours. The requirement for in-person informed consent made more severe TBI patients typically not eligible and none were enrolled. No intracranial abnormalities were detected on non-contrast head CT. Thus, all TBI subjects met the DoD criteria for uncomplicated 'mild' TBI. While previous literature has used the term 'mild' to describe TBI on the lower end of the spectrum of severity, we now prefer the term 'concussive' to describe these injuries.

In addition, initial records of clinical status in TBI subjects assessed at LRMC using the military acute concussion evaluation (MACE) [1] were reviewed. This brief cognitive test assesses orientation, immediate verbal memory, concentration, and short term delayed verbal memory.

1.5 Reasons for Lack of Follow Up

Reasons for inability of subjects to follow-up at Washington University included redeployment to Afghanistan, reassignment to military position overseas, inability or unwillingness to travel to St. Louis, withdrawal of consent, and inability to maintain telephone or email contact. 5 subjects were disqualified at the time of follow up due to readily apparent malingering (n=3) and/or unwillingness to complete the necessary assessments (n=2).

1.6 Glasgow Outcome Scale Extended

The last assessment prior to in-person follow-up was considered the final outcome. Information was gathered separately from both the subject and a collateral source (typically a spouse, parent, or sibling) whenever possible. When

information collected from the subject and the collateral source differed, the worse outcome was used. The GOS-E is scored from 1-8: 1=dead, 2=vegetative, 3-4=severe disability, 5-6=moderate disability, 7-8=good recovery. Moderate disability (GOS-E = 5-6) is defined as one or more of the following: 1) inability to work to previous capacity 2) inability to resume the majority of regular social and leisure activities outside the home 3) psychological problems which have frequently resulted in ongoing family disruption or disruption of friendships. Severe disability is defined as reduced ability to perform activities of daily living such that supervision is required. Standardized, structured interviews were performed according to published guidelines [2].

1.7 Data Safety and Monitoring

Subjects were assigned a random 4 digit code number to protect confidentiality and all research data was identified by code number only. A board certified psychiatrist (Dr. Nelson) was immediately available in case the CAPS examination exacerbated PTSD symptoms. No exacerbations requiring medical intervention occurred, though additional support from study staff was required on several occasions.

For clinical evaluations, the principal investigator audited 1 in 10 randomly selected subjects' data sets to ensure that data was scored and entered correctly. These audits revealed only minor discrepancies in scoring criteria which were then corrected across the entire cohort of subjects.

1.8 Subject Examination Details

Subjects took all medications as prescribed by their clinical providers. All tests were performed between 9 am and 5 pm in private, quiet, well-lighted rooms. All examiners were clinicians who underwent standardized training in administering the assessments. The standardized neurological exam and interview required approximately 1 hour per subject. The psychiatric assessments and neuropsychological test battery both required approximately 2 hours per subject.

The neuropsychological test battery consisted of the following: Conner's Continuous Performance Test II [3], a computer-based assessment of attention, impulsivity, reaction time, and vigilance; the California Verbal Learning Test II [4], an assessment of verbal declarative memory; the 25 hole grooved pegboard test [5], an assessment of upper extremity motor speed and coordination; a timed 25 foot walk; the Trail Making test [6], an assessment of visual scanning, coordination and mental flexibility; the Controlled Oral Word Association test [7], an assessment of verbal fluency; the Wechsler Test of Adult Reading [8] as an estimate of pre-injury verbal intelligence; the Iowa Gambling Test[9], a computer-based assessment of impulsivity and decision making; the D-KEFS Color-Word Interference Test [10], an multi-domain assessment of executive function similar to the Stroop test; and the Ruff-Light Trail Learning Test[11], an assessment of visual-spatial memory. A relatively easy forced choice test embedded in the California Verbal Learning Test was used to assess adequacy of effort.

1.9 Statistical Analysis

All data was analyzed using Statistica10.0 (Statsoft Inc). Continuous variables have been summarized as mean ± standard deviation unless otherwise specified. The normal distribution of each continuous variable was assessed using the Shapiro-Wilk test. For normally distributed variables, Analysis of Variance and student's t tests were used to compare groups. For non-normally distributed variables, the nonparametric Kruskal-Wallis Tests and Mann-Whitney U (MWU) tests were used. We pre-specified the hypothesis that TBI subjects would have worse outcomes than controls, but did not pre-specify any hypotheses regarding blast + impact TBI vs non-blast TBI subjects. One-sided tests were used when hypotheses were pre-specified, and two-sided tests were used otherwise.

In addition to between group comparisons, individual subject data from neuropsychological testing was analyzed. Specifically, an individual subject's performance was considered abnormal if it was worse than two standard deviations below the mean of the performance of the non-blast control group. The number of tests for which performance was abnormal for each subject was then tabulated. To determine the number of abnormal tests that would expected by chance, the binomial distribution was used with $p=0.02275$ and $n=18$ for the 18 neuropsychological variables examined (eTable 2). Prior to this analysis, all neuropsychological variables were confirmed to be statistically independent as is required by the assumptions of this approach.

For correlation analyses, nonparametric rank-based Spearman correlations were utilized. Pearson correlations were attempted, but the residuals were not normally distributed as determined by the Shapiro Wilk test.

Logistic regression analysis was utilized to explore the relationship between global outcome and multiple quantitative measures of specific symptoms and impairments. The Statistica 10.0 'generalized linear/nonlinear model building' algorithm was used with the selection of the 'logit' link function. This algorithm generated a distinct model for each possible subset of quantitative measures of specific symptoms and impairments. Models were then ranked by Akaike information criterion. Detailed data and receiver-operator curves (ROC) were then generated for the top ranked models. Step-wise forward entry and step-wise removal of variables was also performed, which yielded identical results.

2. SUPPLEMENTAL RESULTS

2.1 Glasgow Outcome Scale Extended

At an individual subject level, 41/53 blast + impact TBI subjects (77%) and 23/29 non-blast TBI subjects (79%) had moderate to severe disability defined as GOS-E score of 6 or less. 16/27 blast controls (59%) and 28/69 non-blast controls (41%) also met this criteria. The disabled proportion was significantly greater in non-blast TBI subjects in comparison to non-blast controls (p=0.0005, chi-square). Blast controls and non-blast controls did not significantly differ (p=0.10, chi-square), nor did blast controls and blast + impact TBI subjects (p=0.09, chi-square) or blast + impact TBI and non-blast TBI subjects (p=0.84, chi-square) in proportion of disabled subjects.

The above results were derived only from subjects who were available for in-person follow-up. However, the outcomes in the subjects not available for in person follow-up 6-12 months after enrollment did not differ from those that were available for follow-up based on GOS-E obtained by telephone and email (p-value range across groups 0.46-0.85, MWU tests).

2.2 Military Acute Concussion Evaluation

Scores on the military acute concussion evaluation (MACE) completed after medical evacuation to Landstuhl, Germany did not significantly differ between non-blast and blast + impact TBI subjects (25.32 ± 3.36 non-blast TBI, 24.8 ± 3.22 blast + impact TBI, p=0.42, 2-sided Student's t) suggesting similar levels of initial concussion impairment. MACE was not performed in the control subjects.

2.3 Neuropsychological Test Abnormalities

There were few statistically significant differences between groups. Significantly worse performance was noted in the non-blast TBI group in comparison to the non-blast controls on 25-foot walk (p=0.0024), and Grooved Peg Board (p=0.0027). There were no differences in performance in the blast control vs. non-blast control groups, blast + impact TBI vs. blast control groups, or blast + impact TBI vs. non-blast TBI groups.

2.4 Neurobehavioral Assessment

Clinician ratings in multiple neurobehavioral domains using the neurobehavioral rating scale-revised revealed more substantial impairments in the TBI subjects compared with controls (eFigure1). However, there were no significant differences between blast + impact TBI and non-blast TBI patients (NRS total:p=0.93, mood/affect:p=0.18, executive/cognitive:p=0.92, oral/motor:p=0.29, positive symptoms:p=0.39, negative symptoms:p=0.62, MWU). Comparisons between non-blast TBI and non-blast controls indicated more substantial impairments overall and in several specific domains. (Total NRS:p=0.000001, mood/affect:p=0.000007, executive/cognitive:p=0.00002, oral/motor:p=0.0001, positive symptoms:p=0.08, negative symptoms:p=0.002, MWU).

Somewhat surprisingly, the blast + impact TBI group did not differ significantly from the blast control group, though there were trends towards greater impairments in the blast + impact TBI group. (Total NRS:p=0.08, mood/affect:p=0.18, executive/cognitive:p=0.17, oral/motor p=0.57, positive symptoms p=0.31, negative symptoms:p=0.14, MWU).

There were also more severe neurobehavioral impairments in blast controls compared with non-blast controls. There were significant differences on total NRS (p=0.0004), and mood/affect (p=0.0008), executive/cognitive (p=0.007), negative symptoms (p=0.01) subdomains (MWU). Oral/motor (p=0.06) and positive symptom (p=0.16) subdomains were not significantly different.

2.5 Headache Impairment

Similar to the results for MIDAS, there were also no significant differences on the HIT-6 between non-blast TBI and blast + impact TBI patients (eFigure 4) (HIT-6:p=0.22, Severe headache pain:p=0.56, Headache limited abilities:p=0.96, Subject wishes to lie down:p=0.04, Tired due to headache:p=0.05, Irritated due to headache:p=0.08; Headache limited concentration:p=0.88, MWU). Non-blast TBI subjects showed significantly higher levels of headache impairment in comparison to non-blast controls on the HIT-6 (p=0.0000001) and on all of the specific questions (Severe headache pain:p=0.002, Headache limited abilities:p=0.0004, Subject wishes to lie down:p=0.000001, Tired due to headache:p=0.0000001, Irritated due to headache:p=0.0000001, Headache limited concentration:p=0.0000001; MWU). Blast controls had more impairment than non-blast controls on the HIT-6 total (p=0.0009), severe headache pain, (p=0.008) and headache limited abilities (p=0.009). There was no significant differences on the HIT-6 between blast + impact TBI and blast controls (HIT-6:p=0.09; Severe headache pain:p=0.67, Headache limited abilities:p=0.26, Subject wishes to lie down:p=0.21, Tired due to headache:p=0.06, Irritated due to headache:p=0.06, Headache limited concentration:p=0.011, MWU). While 23% of non-blast controls were found to have impairment due to headache significant enough warrant suggested follow up with a physician by the HIT-6 criteria[12], 46% of blast control, 64% of blast + impact TBI, and 83% of non-blast TBI subjects also met this criterion.

2.6 Logistic Regression Modeling for Dichotomized Glasgow Outcome Scale Extended

The second best model included number of neuropsychological abnormalities, depression severity, overall headache-related impairment, and severity of neurological deficits. The third best model was similar to the first model but substituted overall headache-related impairment for headache-related disability. Identical results were obtained using step-wise forward entry and step-wise removal of variables (not shown).

3. SUPPLEMENTAL DISCUSSION

The general lack of neuropsychological findings by group is in line with previous work[13,14]. However our single subject level analysis uncovered significantly impaired performance in subsets of subjects from both TBI groups. Thus, an implication of this study is that single subject level analyses should be considered for this type of research.

The overall findings regarding headache impact were also consistent with prior reports although on the higher side of the very broad range of previously published prevalence following concussive brain injury[15]. While 23% of non-blast controls were found to have impairment due to headache significant enough warrant suggested follow up with a physician by the HIT-6[12] criteria, 46% of blast control, 64% of blast + impact TBI, and 83% of non-blast TBI also met this criterion. This is higher than the 20% previously reported in the military following concussion[16], but within the broad range of 18-90% noted in prior studies of individuals with post-traumatic headache following 'mild' brain injury [15,17-22].

A surprising finding from this study was that combat exposure intensity did not correlate with PTSD severity in the TBI subjects, but did correlate with PTSD severity in the controls. Many explanations for this relationship are possible. First, the relationship could have occurred by chance, as the p-value for the interaction between group and combat exposure intensity was marginal. Second, the self-reported measure of combat exposure intensity, the CES, may not accurately capture the war-time experiences that drive PTSD severity. Third, and most intriguingly, is the hypothesis that there may be phenocopies of PTSD-like symptoms that cannot be distinguished using the CAPS; TBI-related emotional dysregulation due to structural injury to brain circuits could be indistinguishable using clinical evaluations alone from the psychological effects of combat and other stressful life experiences.

This study and prior work have identified very high levels of co-occurring post-traumatic headache and PTSD following 'mild' TBI in veterans[23-25]. Future work will be required to understand the underlying mechanism of how concussive brain injury contributes to poor psychiatric outcome and significant headache impairment in this population. For example, it has been suggested by others that signaling involving the pituitary adeylate cyclase-activating peptide (PACAP) may be involved in the pathogenesis of both PTSD and migraine headache[26,27]. PACAP is known to regulate

cellular stress response and was recently found to have a strong association with PTSD diagnosis in both clinical studies of traumatized individuals and preclinical models fear physiology[26]. It has also been implicated in a recent study as a potent vasodilator in dural vasculature; specifically the middle meningeal artery, suggesting it may play an important role in the development of migraine[27]. It is possible that a better understanding of this relationship will lead to new treatments for both phenomena positively impacting outcome in these patients. Likewise, other potential contributions to headache such as cervical segmental joint dysfunction, neck flexor endurance, or neck musculature tightness, among others that are commonly known to contribute to chronic post-traumatic headache[28].

The finding of significant olfactory deficits in the non-blast TBI group warrants further investigation and possibly lends support to the hypothesis that structural brain injury contributed to outcomes; The location of the olfactory bulbs are adjacent to brain anatomy thought to be involved in emotion regulation. Injury to the region in general may be contributing to both deficits in olfaction as well as the inability to extinguish fear memories and thus the exacerbation of PTSD symptomatology. In future studies, more thorough examination of the olfactory bulbs would be required including focused high resolution imaging of the structure itself and comprehensive, repeated quantitative assessment of olfactory acuity.

4. SUPPLEMENTAL TABLES AND FIGURES

Group	Total Enrolled	Completed Follow UP	Disqualified at Follow up	Final Group Size
Non-blast CTL	97	71	2	69
Blast CTL	35	27	0	27
Non-blast TBI	44	32	3	29
Blast + impact TBI	79	53	0	53
TOTAL	255	183	5	178

eTable 1. Group enrollment and 6-12 month follow up attrition.

eTable 2. Neuropsychological Test Performance

Test	Non Blast CTL (n=69)	Blast CTL (n=27)	Non Blast TBI (n=29)	Blast + impact TBI (n=53)
25-Foot Walk (seconds)				
(Motor Strength, Balance, Coordination)	3.92 ± 0.82	4.22 ± 0.66	4.76 ± 1.16 [A]	4.59 ± 1.17
Conners' Continuous Performance Test II				
Omission Errors (T-score):				
(Attention Lapses)	48.29 ± 12.17	47.45 ± 7.51	53.30 ± 15.11	56.06 ± 19.8
Commission Errors (T-score):				
(Impulsivity)	50.40 ± 10.60	50.02 ± 8.19	52.46 ± 9.81	54.05 ± 10.6
Hit Rate (T-score):				
(Reaction Time)	48.94 ± 11.72	48.98 ± 8.67	52.10 ± 12.22	47.83 ± 8.63
Hit Rate Block Change (T-score):				
(Sustained Vigilance)	52.05 ± 10.62	48.01 ± 8.82	51.64 ± 13.75	48.73 ± 12.0
Iowa Gambling Test (T-score)				
(Impulsivity)	49.52 ± 10.40	48.3 ± 9.65	47.62 ± 9.91	48.96 ± 11.1
Ruff-Light Trail Learning Test (T-score)				
Trials Correct *(Visual Memory)*	49.53 ± 11.10	52.52 ± 6.54	50.41 ± 10.10	49.24 ± 10.85
Wechsler Test of Adult Reading (Standard Score)				
(Estimate of Pre-injury Verbal Intelligence)	102.88 ± 14.55	100.56 ± 10.99	98.52 ± 11.10	99.49 ± 11.66
California Verbal Learning Test II				
Long-Delay Free Recall (Standard Score)				
(Verbal Memory)	-0.17 ± 1.10	-0.15 ± 0.95	-0.32 ± 1.27	-0.58 ± 1.21
Total Intrusions (Standard Score)				
(Falsely Recalled Items)	0.22 ± 1.00	0.22 ± 0.95	0.52 ± 1.42	0.45 ± 1.38
List B vs. Trial 1 List A (Standard Score)				
(Proactive Memory Interference)	0.08 ± 0.87	-0.15 ± 0.89	0.58 ± 1.03	-0.16 ± 1.12
Grooved Pegboard				
(Motor Speed & Coordination)				
Average Dom & Non-Dom Time (seconds)	69.03 ± 17.7	69.04 ± 10.56	75.84 ± 15.85 [B]	75.54 ± 15.52
Trail Making Test				
Trails A time (seconds)				
(Visual Scanning, Coordination)	22.10 ± 8.61	24.26 ± 7.41	26.57 ± 14.10	28.5 ± 16.69
Trails B time (seconds)				
(Trails A + Mental Flexibility)	57.12 ± 24.77	57.00 ± 14.97	67.52 ± 31.28	61.19 ± 21.40
Controlled Oral Word Association				
Total Score: *(Verbal Fluency)*	42.1 ± 10.18	40.37 ± 9.05	37.62 ± 9.98	37.75 ± 9.30
D-KEFS Color-Word Interference Test				
(Executive Function)				
Color & Word Naming (summed scaled score)	21.07 ± 4.98	18.67 ± 5.85	18.59 ± 7.25	18.64 ± 6.95
Inhibition (scaled score)	10.55 ± 3.02	10.19 ± 2.92	9.28 ± 4.57	9.83 ± 3.39
Inhibition/Switching (scaled score)	10.41 ± 2.88	9.30 ± 3.17	9.25 ± 4.16	9.29 ± 3.20

Superscripted letters indicate significance after correction for multiple comparisons (p<0.0125).
Uncorrected p-values are reported.
[A] Non-blast control vs. Non-blast TBI – Mann-Whitney U, p=0.0025
[B] Non-blast control vs. Non-blast TBI – Mann-Whitney U, p=0.0027
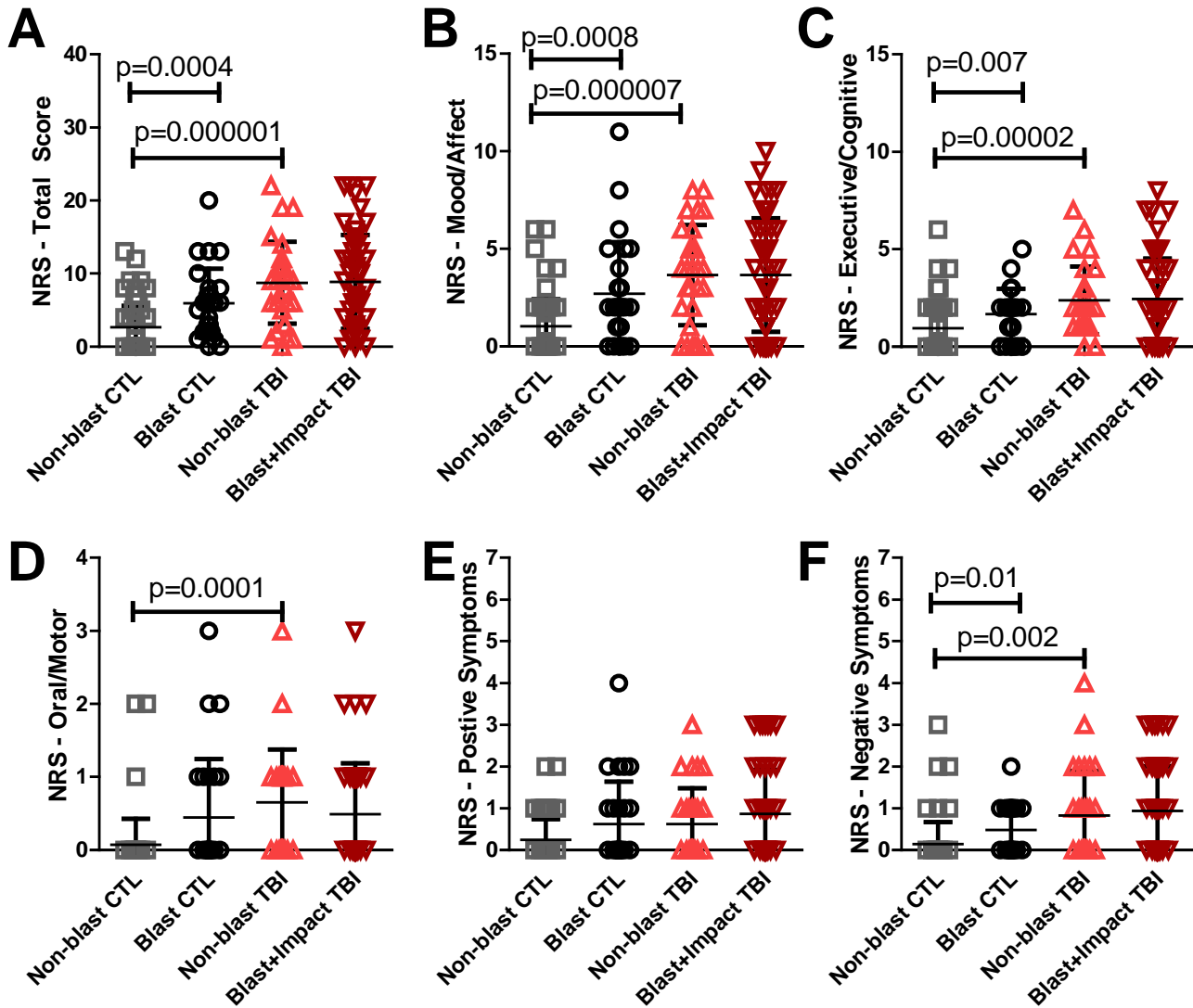
eFigure 1: Neurobehavioral measures of outcome. **A.** Neurobehavioral outcome assessed using the Neurological Rating Scale-Revised (NRS) Total Score: (Max 87). **B.** Mood/affect domain (Max 15). **C.** Executive/Cognitive domain (Max 24). **D.** Oral/motor domain (Max 12). **E.** Positive Symptoms domain (Max 21). **F.** Negative Symptoms domain (Max 12). Higher scores on all of the measures indicate worse impairment. P-values calculated using 1-tailed Mann-Whitney U tests and reported if significant after correction for multiple comparisons (p<0.0125).
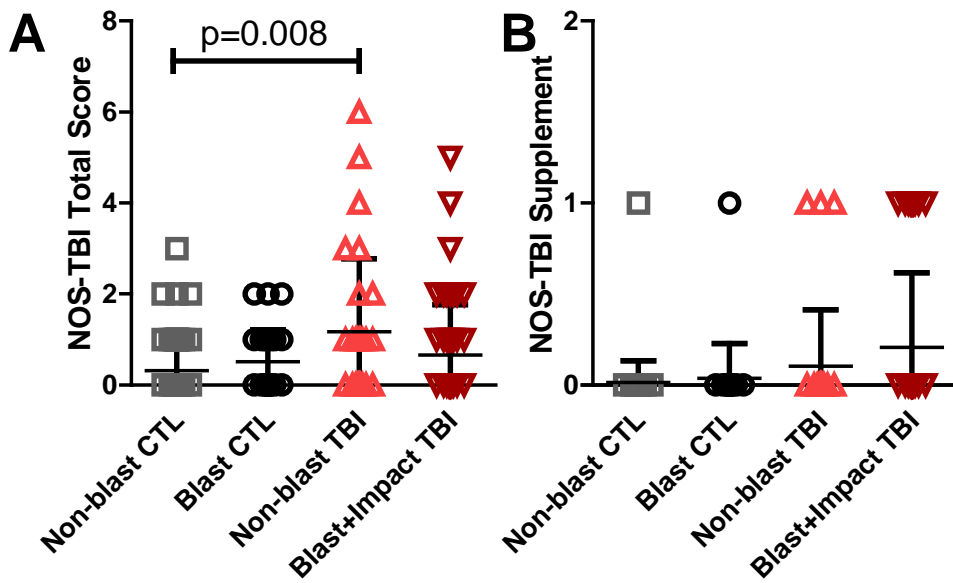
eFigure 2: Focal Neurological Deficits **A.** Focal neurological deficits commonly observed following traumatic brain injury assessed using the Neurological outcome scale for Traumatic Brain Injury (NOS-TBI). **B.** NOS-TBI Supplement for gait and limb ataxia. Higher scores on both measures indicate worse impairment. P-values calculated using 1-tailed Mann-Whitney U tests and reported if significant after correction for multiple comparisons (p<0.0125).
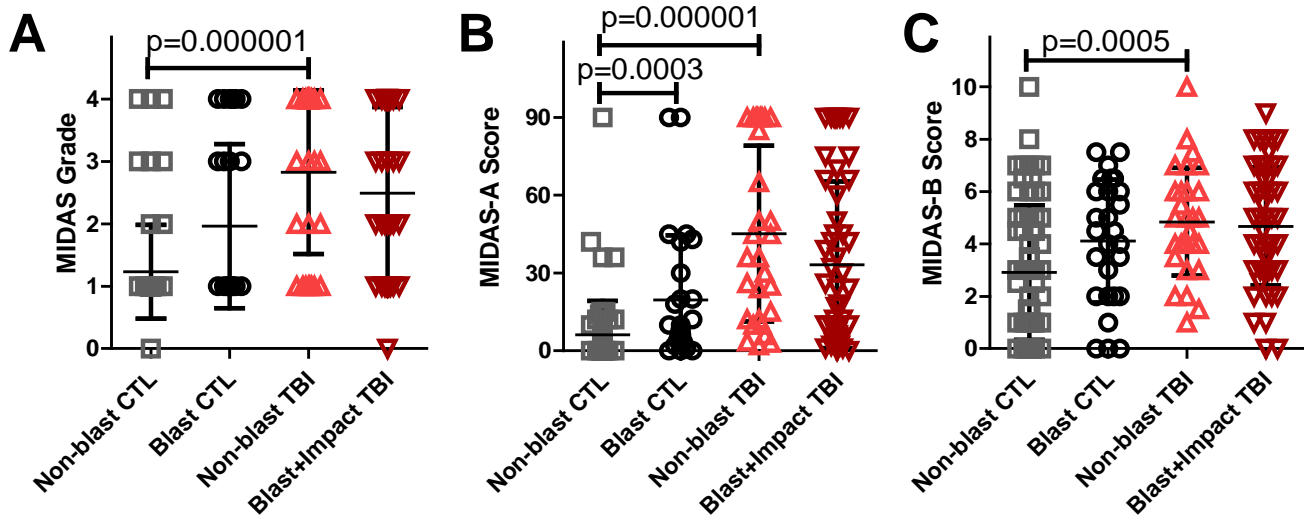
eFigure 3: Migraine Disability Assessment Subdomains. **A.** Total headache grade score for headache impact severity (Max 4). **B.** MIDAS-A assessment for headache frequency (Max 90). **C.** MIDAS-B assessment for headache pain (Max 10). Higher scores on all of the measures indicate worse impairment. P-values calculated using 1-tailed Mann-Whitney U tests and reported if significant after correction for multiple comparisons ($p < 0.0125$).
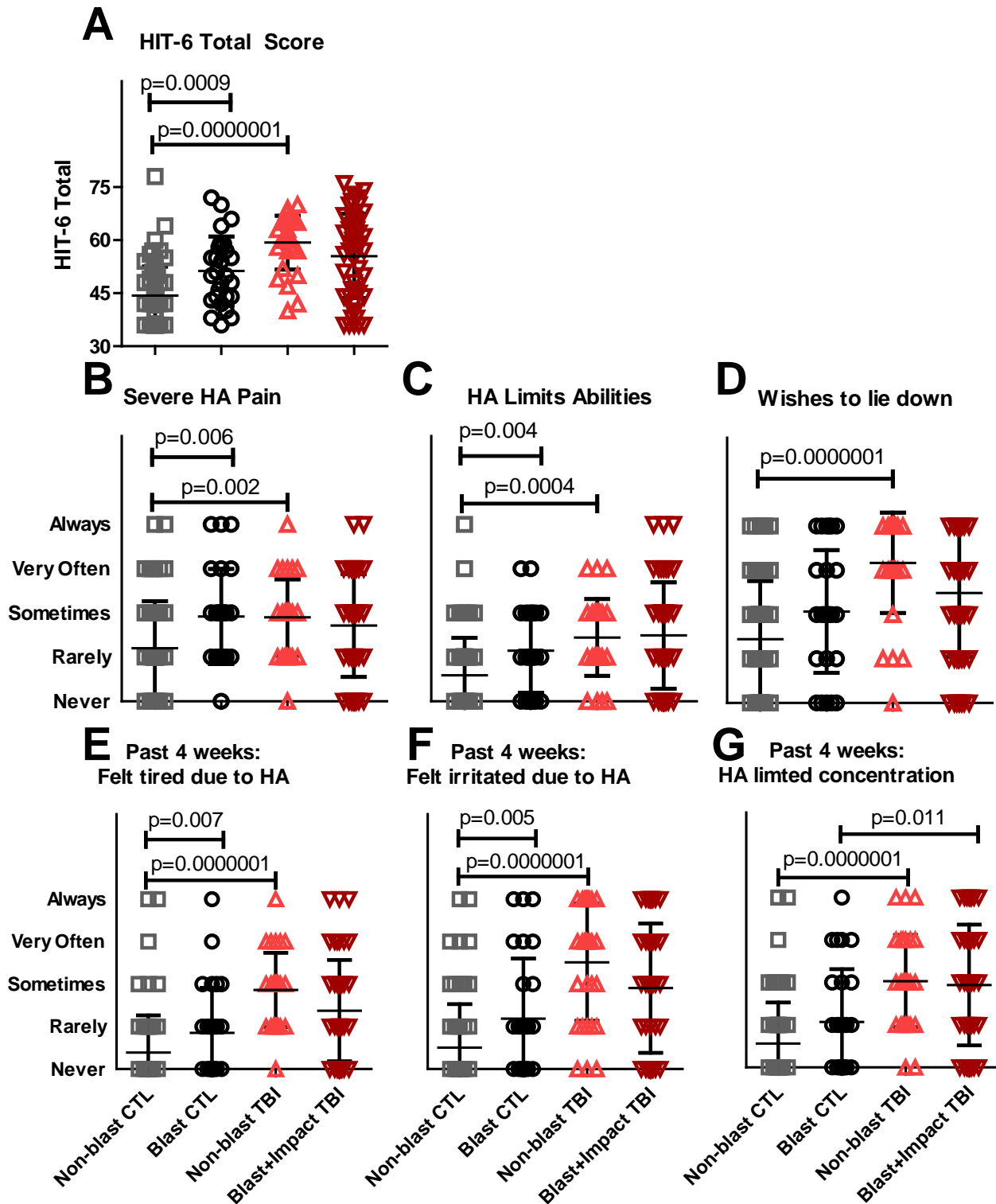
eFigure 4: Headache Impairment. **A.** Headache impairment assessed by the headache impact test (HIT-6) (Max 78). **B.** Frequency of severe headache pain. **C.** Frequency of headaches limiting ability to complete daily activities. **D.** Impact of headache determined by how often a subject wishes to lie down. **E.** Impact of headache in the past 4 weeks on how often a subject felt tired **F.** Impact of headache in the past 4 weeks on how often a subject felt fed up or irritated. **G**. Impact of headache in the past 4 weeks on how often a subject was limited in their concentration at work. P-values calculated using 1-tailed Mann-Whitney U and reported if significant after correction for multiple comparisons (p<0.0125).

A. CAPS B Severity

p=0.0001
p=0.0003

B. CAPS C Severity

p=0.0004
p=0.004

C. CAPS D Severity

p=0.00002
p=0.003
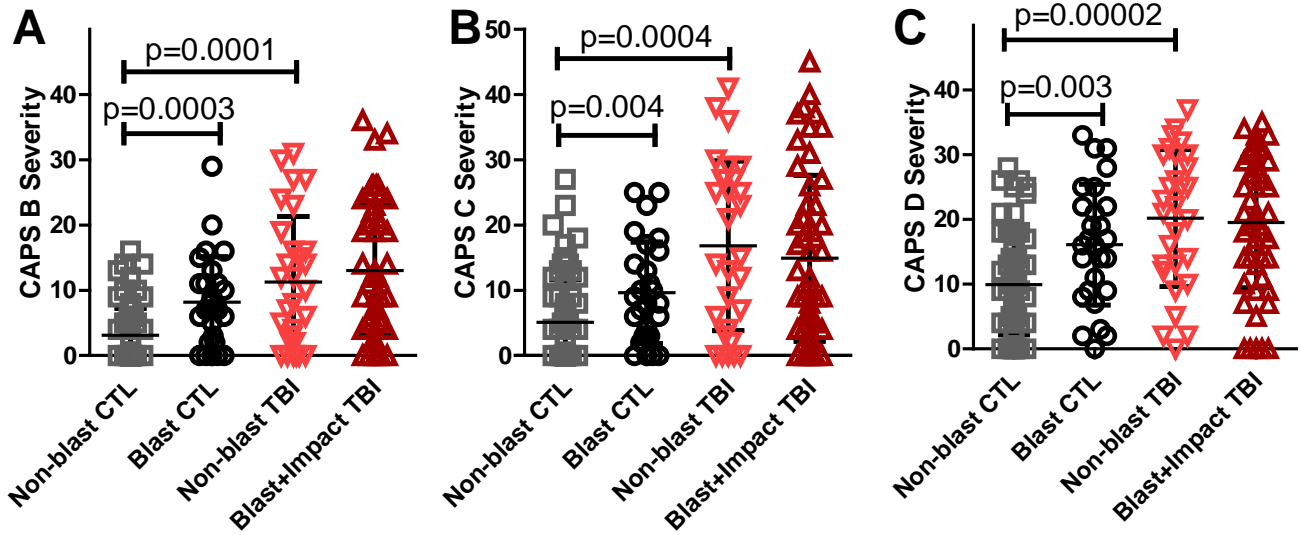
eFigure 5: Post-Traumatic Stress Disorder Severity Subdomains of the Clinician Administered PTSD scale for DSM IV (CAPS). **A.** CAPS B Severity – Re-experiencing (Max 40). **B.** CAPS C Severity – Avoidance and Numbing (Max 56). **C.** CAPS D Severity – Increased Arousal and hypervigilance (Max 40). Higher scores on all of the measures indicate worse impairment. P-values calculated using 1-tailed Mann-Whitney U tests and reported if significant after correction for multiple comparisons (p<0.0125).
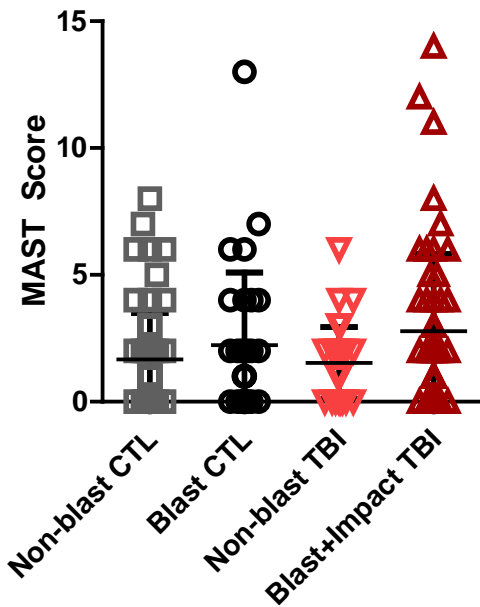
eFigure 6: Alcohol Misuse. Alcohol misuse was assessed using the Michigan Alcohol Screening Test (MAST: Max 22). No significant differences were observed across groups.
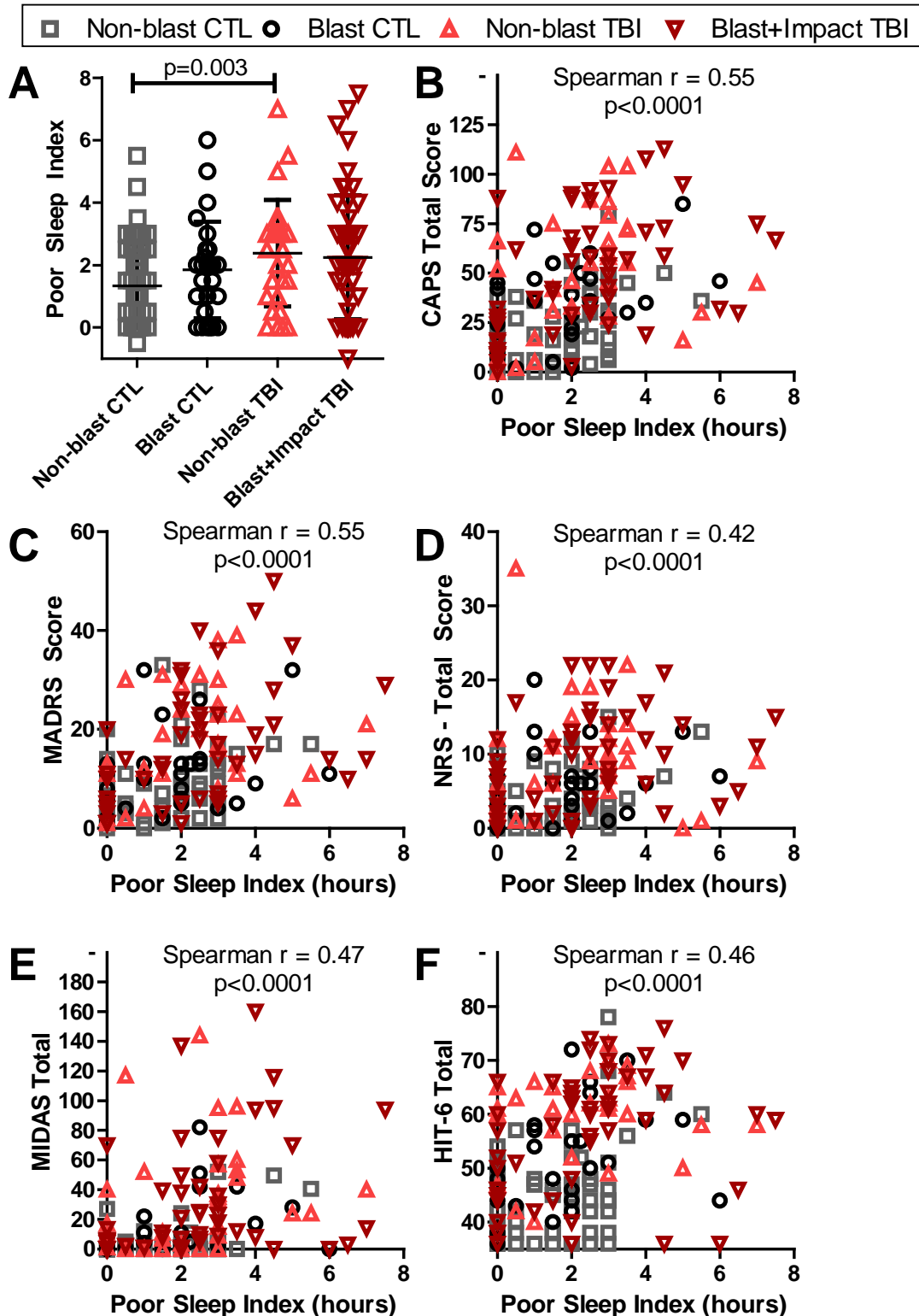
eFigure 7: Correlations between self-reported poor sleep index and measures of clinical evaluation. A. Poor sleep index, defined as the self-reported number of desired hours of sleep minus the number of acquired. **B.** Positive correlation with CAPS total severity for PTSD. **C.** Positive correlation with MADRS total severity for depression. **D.** Positive correlation with Neurobehavioral Rating Scale (NRS) for overall neurobehavioral outcome. **E.** Positive correlation with MIDAS for migraine disability. **F.** Positive correlation with HIT-6 for headache impact. Higher scores indicate worse impairment on all of the measures.
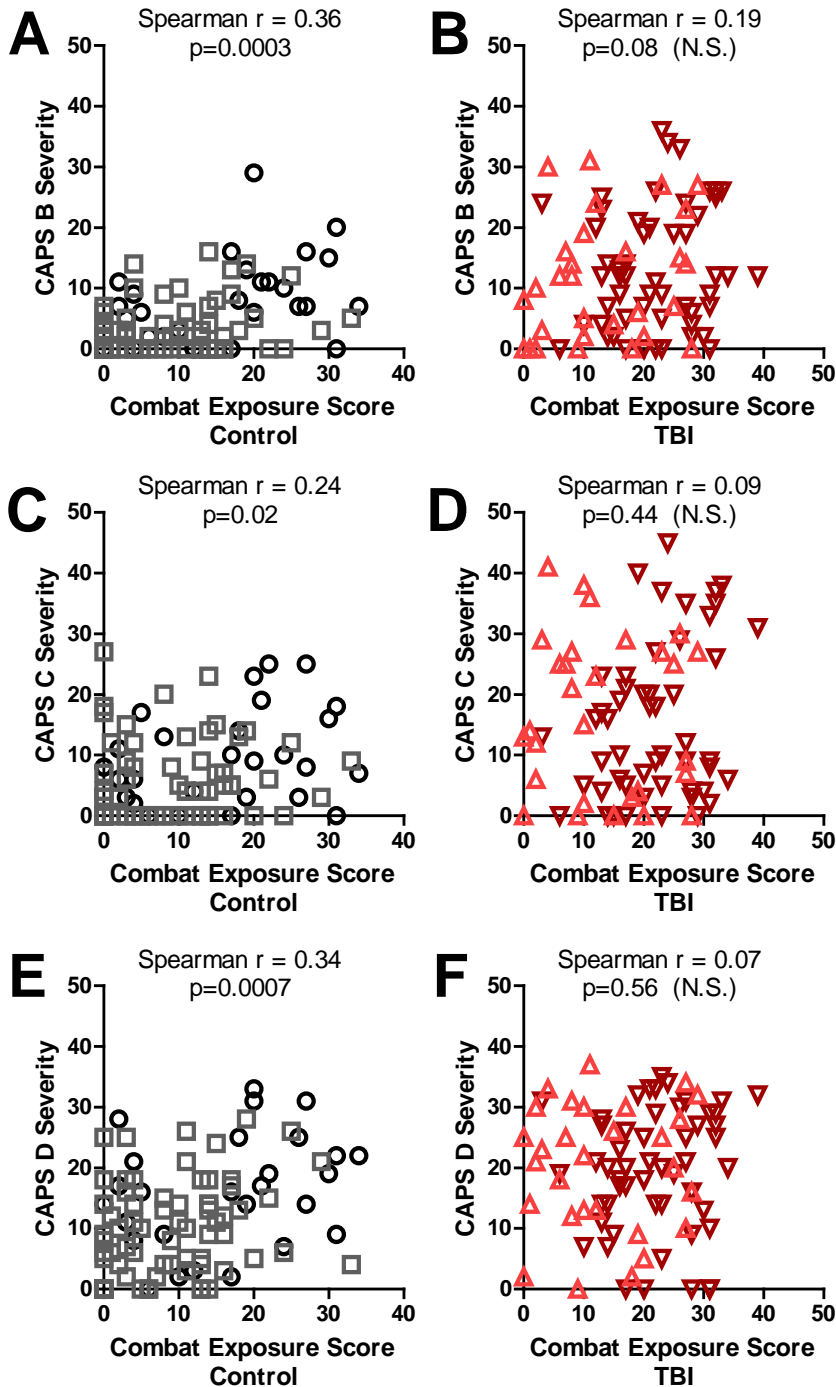
eFigure 8: Correlations between Clinician Administered PTSD Scale (CAPS) Subdomains and Intensity of Combat Exposure Scale (CES). **A**. Positive correlation between CAPS B severity (re-experiencing the traumatic event) and CES in control subjects. **B**. No correlation was observed between CAPS B severity and CES in the TBI groups. **C**. Positive correlation between CAPS C severity (avoidance and numbing) and CES in control subjects. **D**. No correlation was observed between CAPS C severity and CES in the TBI groups. **E**. Positive correlation between CAPS D severity (increased arousal and hypervigilance) and CES in control subjects. **F**. No correlation was observed between CAPS D severity and CES in the TBI groups.

A GOS-E model:
MADRS, # NP Abs, MIDAS

Area = 0.7765

B GOS-E model:
MADRS, # NP Abs, MIDAS, TBI vs. CTL

Area = 0.7896
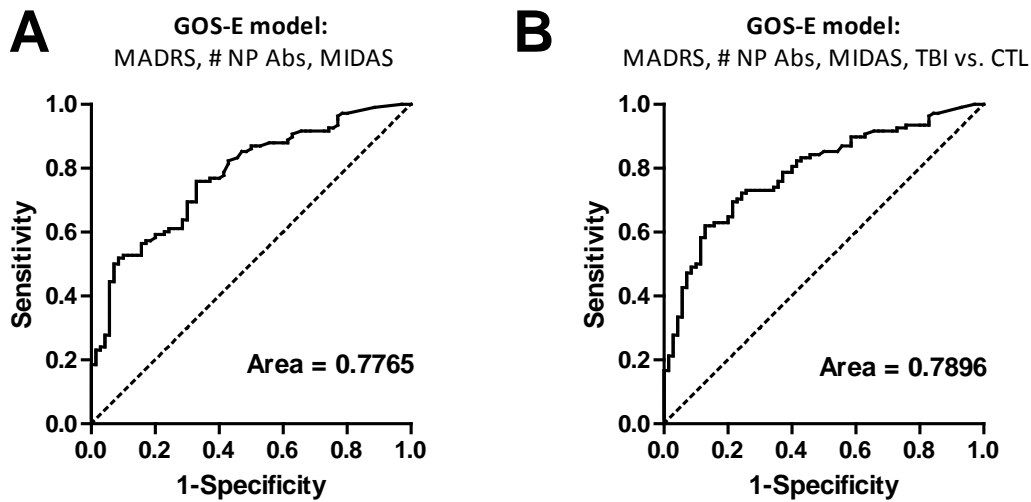
eFigure 9: Receiver- Operator Curves for Logistic Regression Models of Global Outcome. **A**. Receiver-operator curve for best fit model of overall disability defined as the dichotomized GOS-E of 7 or 8 – good outcome, and = 6 or below –disabled. The best model included the total severity of depression based on the Montgomery Asberg Rating Scale (MADRS), the number of neuropsychological test abnormalities (# NP Abs), and the Migraine Disability Scale for headache impairment (MIDAS). **B**. Receiver-operator curve for logistic regression model of overall disability with addition of TBI vs Control as a categorical variable showing negligible improvement over the original best fit model.

SUPPLEMENTAL REFERENCES

1. Dempsey KE, Dorlac WC, Martin K, et al. Landstuhl Regional Medical Center: traumatic brain injury screening program. *J Trauma Nurs.* 2009;16(1):6-7, 10-12.
2. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. *Journal of neurotrauma.* 1998;15(8):573-585.
3. Conners C, Staff. M. *Conners' Continuous Performance Test II: Computer program for Windows technical guide and software manual*. North Tonwanda, NY: Multi-Health Systems; 2000.
4. Delis D, Kramer J, Kaplan E, B O. *California Verbal Learning Test Manual: Second Edition, Adult Version*. San Antonio, Tx: Psychological Corporation; 2000.
5. Matthews C, Kløve H. *Instruction manual for the Adult Neuropsychology Test Battery*. Madison, WI: University of Wisconsin Medical School; 1964.
6. Reitan R. *Trail Making Test manual for administration and scoring*. Tuscon, AZ: Reitan Neuropsychology Laboratory; 1992.
7. Benton A, Hamsher K, A S. *Multilingual Aphasia Examination (3rd ed.)*. Iowa City, Ia: AJA Associates; 1983.
8. Wechsler D. *Wechsler Test of Adult Reading (WTAR) Manual*. New York: Psychological Corporation; 2001.
9. Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition.* 1994;50(1-3):7-15.
10. Delis DC, Kaplan, E. & Kramer, J.H. *Delis-Kaplan Executive Function System (D-KEFS): Examiner's manual*. San Antonio, TX: The Psychological Corporation; 2001.
11. Ruff R, Light R, Parker S. Visuospatial learning: Ruff Light Trail Learning Test. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists.* 1996;11(4):313-327.
12. Kosinski M, Bayliss MS, Bjorner JB, et al. A six-item short-form survey for measuring headache impact: the HIT-6. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2003;12(8):963-974.
13. Spencer RJ, Drag LL, Walker SJ, Bieliauskas LA. Self-reported cognitive symptoms following mild traumatic brain injury are poorly associated with neuropsychological performance in OIF/OEF veterans. *Journal of rehabilitation research and development.* 2010;47(6):521-530.
14. Drag LL, Spencer RJ, Walker SJ, Pangilinan PH, Bieliauskas LA. The contributions of self-reported injury characteristics and psychiatric symptoms to cognitive functioning in OEF/OIF veterans with mild traumatic brain injury. *J Int Neuropsychol Soc.* 2012;18(3):576-584.
15. Theeler B, Lucas S, Riechers RG, 2nd, Ruff RL. Post-traumatic headaches in civilians and military personnel: a comparative, clinical review. *Headache.* 2013;53(6):881-900.
16. Theeler BJ, Flynn FG, Erickson JC. Chronic daily headache in U.S. soldiers after concussion. *Headache.* 2012;52(5):732-738.
17. Lucas S, Hoffman JM, Bell KR, Walker W, Dikmen S. Characterization of headache after traumatic brain injury. *Cephalalgia : an international journal of headache.* 2012;32(8):600-606.
18. Lew HL, Lin PH, Fuh JL, Wang SJ, Clark DJ, Walker WC. Characteristics and treatment of headache after traumatic brain injury: a focused review. *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists.* 2006;85(7):619-627.
19. Nampiaparampil DE. Prevalence of chronic pain after traumatic brain injury: a systematic review. *JAMA : the journal of the American Medical Association.* 2008;300(6):711-719.
20. Hoffman JM, Lucas S, Dikmen S, et al. Natural history of headache after traumatic brain injury. *Journal of neurotrauma.* 2011;28(9):1719-1725.
21. O'Neil M, Carlson K, Storzbach D. *Complications of Mild Traumatic Brain Injury in Veterans and Military Personnel: A Systematic Review. Vol Project #05-225.* Washington, DC: Department of Veterans Affairs Health Services Research & Development Service;2012.
22. Keidel M, Diener HC. [Post-traumatic headache]. *Der Nervenarzt.* 1997;68(10):769-777.
23. Ruff RL, Riechers RG, 2nd, Wang XF, Piero T, Ruff SS. A case-control study examining whether neurological deficits and PTSD in combat veterans are related to episodes of mild TBI. *BMJ open.* 2012;2(2):e000312.

24. Ruff RL, Riechers RG, 2nd, Wang XF, Piero T, Ruff SS. For veterans with mild traumatic brain injury, improved posttraumatic stress disorder severity and sleep correlated with symptomatic improvement. *Journal of rehabilitation research and development.* 2012;49(9):1305-1320.

25. Ruff RL, Riechers RG, Ruff SS. Relationships between mild traumatic brain injury sustained in combat and post-traumatic stress disorder. *F1000 medicine reports.* 2010;2:64.

26. Ressler KJ, Mercer KB, Bradley B, et al. Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor. *Nature.* 2011;470(7335):492-497.

27. Syed AU, Koide M, Braas KM, May V, Wellman GC. Pituitary adenylate cyclase-activating polypeptide (PACAP) potently dilates middle meningeal arteries: implications for migraine. *Journal of molecular neuroscience : MN.* 2012;48(3):574-583.

28. Treleaven J, Jull G, Atkinson L. Cervical musculoskeletal dysfunction in post-concussional headache. *Cephalalgia : an international journal of headache.* 1994;14(4):273-279; discussion 257.

Original Articles

Functional Status after Blast-Plus-Impact Complex Concussive Traumatic Brain Injury in Evacuated United States Military Personnel

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Col. Raymond Fang,[2,3] Col. (ret) Stephen F. Flaherty,[2,4] and David L. Brody[1]

Abstract

Fundamental questions remain unanswered about the longitudinal impact of blast-plus-impact complex traumatic brain injuries (TBI) from wars in Iraq and Afghanistan. This prospective, observational study investigated measures of clinical outcome in US military personnel evacuated to Landstuhl Regional Medical Center (LRMC) in Germany after such "blast-plus" concussive TBIs. Glasgow Outcome Scale-Extended assessments completed 6–12 months after injury indicated a moderate overall disability in 41/47 (87%) blast-plus TBI subjects and a substantial but smaller number (11/18, 61%, $p = 0.018$) of demographically similar US military controls without TBI evacuated for other medical reasons. Cognitive function assessed with a neuropsychological test battery was not different between blast-plus TBI subjects and controls; performance of both groups was generally in the normal range. No subject was found to have focal neurological deficits. However, 29/47 (57%) of blast-plus subjects with TBI met all criteria for post-traumatic stress disorder (PTSD) versus 5/18 (28%) of controls ($p = 0.014$). PTSD was highly associated with overall disability; 31/34 patients with PTSD versus 19/31 patients who did not meet full PTSD criteria had moderate to severe disability ($p = 0.0003$). Symptoms of depression were also more severe in the TBI group ($p = 0.05$), and highly correlated with PTSD severity (r = 0.86, $p < 0.0001$). Thus, in summary, high rates of PTSD and depression but not cognitive impairment or focal neurological deficits were observed 6–12 months after concussive blast-plus-impact complex TBI. Overall disability was substantially greater than typically reported in civilian non-blast concussive ("mild") patients with TBI, even with polytrauma. The relationship between these clinical outcomes and specific blast-related aspects of brain injuries versus other combat-related factors remains unknown.

Key words: blast; clinical outcomes; PTSD; TBI

Introduction

BLAST-RELATED TRAUMATIC BRAIN INJURY (TBI) has been a common occurrence in US military personnel during the wars in Iraq and Afghanistan. Based on the Defense and Veterans Brain Injury Center website, there have been 266,810 physician diagnosed TBIs from 2000–2012, of which approximately 80% have been categorized as concussive or "mild" (http://www.dvbic.org/dod-worldwide-numbers-tbi). The RAND report survey[1] indicated that the numbers could be substantially higher if the self-report measures used are accurate. Based on a survey of US Army soldiers injured in Iraq, approximately 75% of concussive (mild) TBIs are blast-related.[2]

Previous studies have reported that subjects with blast-related concussive (mild) TBI have impaired cognitive performance acutely after injury[3] and substantial long-lasting symptoms,[2,4–11] but generally normal cognitive performance at later times.[7,12–16] U.S. military personnel with concussive (mild) TBI have also been reported to have a high rate of post-traumatic stress disorder (PTSD) and depression.[2,6–9,11,15,17–21] It has been argued that PTSD symptoms may account for the mismatch between cognitive symptoms and performance.[2,15] Many of these previous studies, however, have been based largely on self-report and screening tools,[2,6,9,20] rather than direct clinical assessments in prospectively identified cohorts.

In addition, the previous studies of sub-acute to chronic clinical outcomes have been based on subjects enrolled after they have

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returned to the United States. Few of them needed evacuation from the combat theater for their injuries. There have been no previous reports to our knowledge on the clinical outcomes of US military personnel with injuries that met criteria for concussive (mild) TBI[22] but nonetheless were substantial enough to necessitate evacuation. These more substantially injured US military personnel are typically evacuated from the theater to the Landstuhl Regional Medical Center (LRMC) in Landstuhl, Germany. LRMC has served as the sole level IV strategic evacuation hub for the wars in Iraq and Afghanistan, and has used a comprehensive TBI screening protocol for all evacuated casualties[23] since 2006.

As part of an ongoing prospective study involving advanced magnetic resonance imaging (MRI)-based methods to evaluate acute military TBI,[24] we enrolled US military personnel with blast-related TBI as well as blast-exposed controls with other injuries and illnesses at LRMC. We report clinical outcomes assessed in these subjects 6–12 months after enrollment at the time of their follow-up evaluations at Washington University in St. Louis.

Methods

Subjects

Inclusion criteria for the TBI group were as follows: (1) a positive screen for TBI at LRMC based on standard US military clinical criteria[23] including self-report of blast exposure resulting in loss of consciousness, amnesia for the event, or change in neurological status; (2) injury from blast with or without additional mechanisms of injury within 90 days of enrollment; (3) US military; (4) ability to provide informed consent in person; (5) no contraindications to MRI such as retained metallic fragments; (6) no history of moderate to severe TBI based on Department of Defense (DoD) criteria; (7) no history of major psychiatric disorder; (8) agreement to communicate by telephone or e-mail monthly for 6–12 months and then travel to Washington University for in-person follow-up. Inclusion criteria for the control group were the same except for a negative screen for TBI at LRMC.

The research protocol was approved by the Human Research Protection Office at Washington University, the Institutional Review Board for LRMC at Brooke Army Medical Center, and the Clinical Investigation Regulatory and Human Research Protection Offices of the U.S. Army Medical Research and Materiel Command. Written informed consent was obtained from all subjects in

person at LRMC; no surrogate consent was allowed by the funding agency. Competence to provide informed consent was assessed in a standardized fashion based on responses to questions regarding the purpose of the study, expected requirements for participation, and potential risks. Additional written consent was obtained from the subjects at the time of follow-up at Washington University. Active duty military subjects were not paid for participation, although travel expenses to St. Louis were covered. Subjects not on active military duty status at the time of follow-up in St. Louis were paid $240 plus travel expenses for participation.

We enrolled 63 subjects with TBI and 21 controls at LRMC over 5 non-contiguous months during 2008–2009 (Fig. 1). Median time from injury to enrollment was 14 days (range 1–90 days). The demographics of the TBI subjects and controls were similar (Table 1). Most subjects were young, white, enlisted, soldiers in the US Army. All were male. We did not specifically exclude females but did not have an opportunity to enroll any during the period of this study.

All available clinical histories indicated blast exposure plus another mechanism of head injury such as a fall, motor vehicle crash, or being struck by a blunt object. None had an isolated blast injury. Thus, these subjects can be best described as having sustained blast-plus-impact complex TBIs. We refer to this type of injury as ''blast-plus,'' to distinguish it from isolated blast injury. Diagnosis of TBI was typically made based on self-report of blast exposures with alteration of neurologic function. Specifically, questions included the following[23]:

1. During this deployment, did you experience any of the following events? Blast (improvised explosive device, rocket-propelled grenade, landmine, grenades, etc), fall (striking head), other significant contact with blunt object (above the shoulders), bullet wound (above the shoulders), vehicular crashes (any vehicle including aircraft), fragment wound (above the shoulders).
2. If you answered yes to Question #1, did you experience any of these symptoms IMMEDIATELY afterward? Loss of consciousness (knocked out), being dazed, confused, or ''seeing stars'' (feeling disconnected from yourself or the environment), not remembering the injury.

Medical documentation regarding duration of loss of consciousness and post-traumatic amnesia was often not available or not reliable. All available clinical histories indicated change in
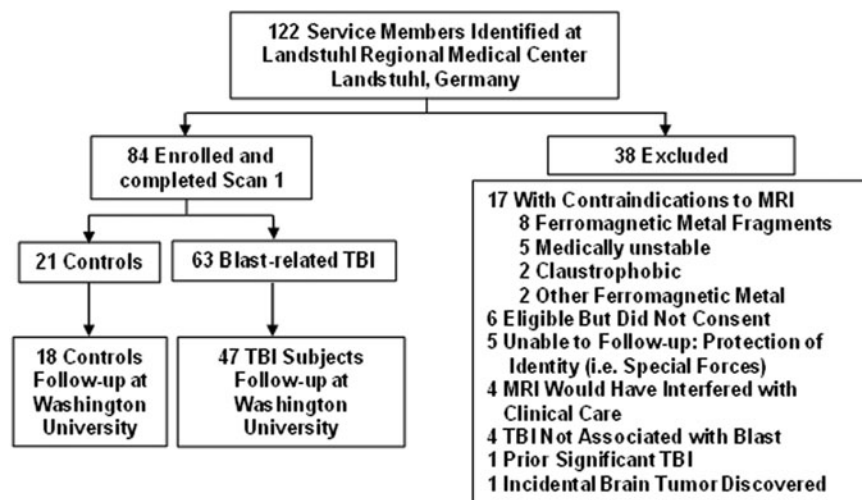
FIG. 1. Screening, enrollment, and exclusion characteristics of the study participants. TBI, tramautic brain injury; MRI, magnetic resonance imaging.

TABLE 1. CHARACTERISTICS OF STUDY PARTICIPANTS

Characteristic	Control (n=21)	Control follow-up (n=18)	TBI (n=63)	TBI follow-up (n=47)
Age in years: median (range)	32 (19–53)	32 (21–53)	25 (19–58)	25 (19–58)
Education in years: median (range)	N/A	12.5 (11–17.5)	N/A	12 (8–17)
Race/ethnicity[a] – no (%)				
White	17 (80.9%)	15 (83.3%)	48 (76.2%)	34 (72.3%)
African American	3 (14.2%)	2 (11.1%)	7 (11.1%)	5 (10.6%)
Hispanic/Latino	1 (4.7%)	1 (5.5%)	9 (14.3%)	6 (12.7%)
Asian	0	0	2 (3.2%)	2 (4.3%)
Branch of Service – no (%)				
US Army	18 (85.7%)	15 (83.3%)	56 (88.9%)	42 (89.3%)
US Air Force	2 (9.5%)	2 (11.1%)	0	0
US Marine Corps	1 (4.8%)	1 (4.5%)	7 (11.1%)	5 (10.7%)
US Navy	0	0	0	0
Military rank – no (%)				
Enlisted	19 (90.5%)	16 (88.9%)	60 (95.2)	44 (93.6)
Officer	2 (9.5%)	2 (11.1%)	3 (4.7)	3 (6.4)
Theater of operation – no (%)				
Iraq	15 (71.4%)	12 (66.7%)	25 (39.7%)	21 (44.7%)
Afghanistan	6 (28.6%)	6 (33.3%)	38 (60.3%)	26 (55.3%)

N/A, not assessed in subjects that did not follow up.
[a]Self-reported. Subjects were not limited to one choice.
TBI, traumatic brain injury.

level of consciousness or loss of consciousness for a few minutes and post-traumatic amnesia for less than 24 h. The requirement for in-person informed consent made patients with more severe TBI typically not eligible, and none were enrolled. No intracranial abnormalities were detected on non-contrast head computed tomography. Thus, all subjects with TBI met the DoD criteria for uncomplicated mild TBI. While previous literature has used the term mild to describe TBI on the lower end of the spectrum of severity, we now prefer the term concussive to describe these injuries, with the understanding that concussive and mild TBI are operationally defined identically.

All clinical histories were verified by study personnel by taking additional clinical history and review of medical records. Based on this review, four subjects were excluded because of TBI not associated with blast, and one was switched from the control group to the TBI group because of evidence of TBI on MRI. None who screened positive for TBI was determined not to have had a TBI.

Of these subjects, 47 with TBI and 18 controls were followed up at Washington University 6–12 months after enrollment. Reasons for inability of 19 subjects (3 controls and 16 with TBI) to follow up at Washington University included inability or unwillingness to travel to St. Louis (10 subjects), withdrawal of consent (4 subjects), inability to maintain telephone or e-mail contact (2 subjects), severe psychiatric illness (1 subject), redeployment overseas (1 subject), and other severe illness (1 subject). The TBI subjects not available for in-person follow-up did not differ from those who were available for follow-up in demographic characteristics (Table 1), Military Acute Concussion Evaluation (MACE) performance ($p=0.54$, Mann-Whitney U test), or most recent telephone-based Glasgow Outcome Scale-Extended (GOS-E) score ($p=0.75$, Mann-Whitney U test).

Clinical assessments

Initial records of clinical status in subjects with TBI assessed at LRMC using the MACE[23] were reviewed. This brief cognitive test assesses orientation, immediate verbal memory, concentration, and short-term delayed verbal memory.

Overall clinical outcome was assessed using the GOS-E[25,26] by telephone or e-mail monthly for 6–12 months. The GOS-E is scored from 1–8: 1=dead, 2=vegetative, 3–4=severe disability, 5–6=moderate disability, 7–8=good recovery. Moderate disability (GOS-E=5–6) is defined as one or more of the following: (1) inability to work to previous capacity; (2) inability to resume the majority of regular social and leisure activities outside the home; (3) psychological problems that have frequently resulted in ongoing family disruption or disruption of friendships. Severe disability is defined as reduced ability to perform activities of daily living such that supervision is needed. Standardized, structured interviews were performed according to published guidelines.[25] The last assessment before in-person follow-up was considered the final outcome. Information was gathered separately from both the subject and a collateral source (typically a spouse, parent, or sibling) whenever possible. When information from the subject and the collateral source differed, the worse outcome was used.

The in-person clinical evaluations included a standardized neurological examination and structured interview designed for patients with TBI (Neurobehavioral Rating Scale-Revised[27,28]), a neuropsychological test battery (Table 2), and psychiatric assessments including the Clinician-Administered PTSD Scale for the *Diagnostic and Statistical Manual of Mental Disorders-IV* (DSM-IV) (CAPS)[29] plus the Montgomery-Asberg Depression Rating Scale.[30] The CAPS was scored using the standard scoring rules from the National Center for Post-traumatic Stress Disorder, July 1998 revision, from Blake and associates. The standardized neurological examination and interview required approximately 1 h per subject. The psychiatric assessments needed approximately 2 h per subject, and the neuropsychological battery needed approximately 2 h per subject. Subjects took all medications as prescribed by their clinical providers. All tests were performed between 9 AM and 5 PM in private, quiet, well-lighted rooms. All examiners were blinded to other clinical information and imaging results, although in the course of the interviews, it often became clear whether the subjects were in the TBI or control group. All examiners were clinicians who underwent standardized training in administering the assessments.

The neuropsychological test battery consisted of the Conners Continuous Performance Test II,[31] a computer-based assessment of attention, impulsivity, reaction time, and vigilance; the Wisconsin Card Sorting Test,[32] an assessment concept formation and mental

TABLE 2. NEUROPSYCHOLOGICAL TEST PERFORMANCE

Test	Control (n=18)	TBI (n=47)	p value	TBI GOS-E 7–8 (n=6)	TBI GOS-E <7 (n=41)	p value	TBI No PTSD (n=18)	TBI+PTSD (n=29)	p value
25-foot walk (sec) (motor strength, balance, coordination)	5.2±2.1	4.7±1.0	0.37 (U)	4.2±1.2	4.8±1.0	0.18 (U)	4.6±0.9	4.7±1.0	0.41 (t)
Conners Continuous Performance Test II									
Omission errors: (attention lapses)	−0.45±2.1	−0.14±1.3	0.47 (U)	0.36±0.4	−0.21±1.3	0.15 (t)	0.32±0.6	−0.42±1.5	0.04 (U)
Commission errors: (impulsivity)	−0.1±1.1	−0.17±1.0	0.38 (t)	−0.09±1.0	−0.19±1.0	0.41 (t)	0.11±0.9	−0.35±1.0	0.06 (t)
Hit rate: (reaction time)	0.06±1.1	0.23±0.9	0.26 (t)	0.10±1.4	0.25±0.8	0.36 (t)	−0.06±0.9	0.41±0.9	0.04 (t)
Hit rate block change: (sustained vigilance)	−0.26±1.0	−0.22±1.1	0.33 (U)	0.06±0.5	−0.26±1.1	0.34 (U)	−0.12±1.1	−0.28±1.1	0.20 (U)
Wisconsin Card Sorting Test: total errors (concept formation, mental flexibility)	0.58±0.8	0.66±0.9	0.38 (t)	0.62±0.6	0.66±1.0	0.46 (t)	0.63±0.7	0.67±1.1	0.43 (t)
Rey-Osterrieth Complex Figure Test: Delayed recall (visual memory)	0.03±1.3	−0.55±1.7	0.10 (t)	−0.32±1.5	−0.58±1.7	0.36 (t)	−0.84±2.0	−0.37±1.5	0.18 (t)
Wechsler Test of Adult Reading (estimate of pre-injury verbal intelligence)	−0.24±1.3	−0.18±1.2	0.40 (U)	0.07±1.4	−0.22±1.1	0.27 (t)	−0.36±1.5	−0.07±0.9	0.26 (U)
California Verbal Learning Test II									
Long-delay free recall (Verbal memory)	0.0±0.9	−0.13±0.9	0.35 (U)	−0.7±1.0	−0.05±0.9	0.13 (U)	−0.11±0.9	−0.14±1.0	0.46 (t)
Total intrusions (falsely recalled items)	−0.44±1.5	−0.15±1.0	0.31 (U)	−0.42±0.5	−0.11±1.1	0.15 (U)	0.00±0.8	−0.24±1.1	0.32 (U)
List B vs. Trial 1 List A (proactive memory interference)	0.11±1.1	−0.34±1.1	0.07 (t)	−0.08±0.9	−0.39±1.1	0.26 (t)	−0.36±1.0	−0.33±1.2	0.46 (t)
Grooved pegboard (motor speed & coordination)									
Dominant hand time	−1.4±0.6	−1.1±0.8	0.10 (t)	−1.35±0.5	−1.06±0.9	0.22 (t)	−1.27±0.7	−0.99±0.9	0.13 (U)
Non-dominant hand time	−1.3±0.8	−1.0±0.8	0.16 (t)	−0.68±0.6	−1.07±0.8	0.15 (t)	−1.12±0.8	−0.96±0.8	0.26 (t)
Trail making test									
Trails A time (visual scanning, coordination)	−0.09±0.9	−0.29±1.1	0.25 (t)	−0.02±1.3	−0.33±1.0	0.25 (t)	−0.01±1.1	−0.46±1.0	0.08 (t)
Trails B time (Trails A+mental flexibility)	0.02±0.9	−0.23±1.1	0.20 (t)	−0.02±0.9	−0.26±1.1	0.30 (t)	0.00±1.13	−0.38±1.0	0.12 (t)
Symbol digit modalities test (working memory)	0.14±1.0	−0.22±0.8	0.04 (U)	0.08±0.5	−0.27±0.8	0.24 (U)	−0.17±0.7	−0.26±0.9	0.46 (U)
Controlled oral word association Total score: (verbal fluency)	−1.08±0.7	−0.80±0.9	0.12 (t)	−0.75±1.0	−0.81±0.9	0.44 (t)	−0.77±0.9	−0.82±1.0	0.42 (t)

Timed walk is reported in seconds. All other test results have been converted to Z-scores with higher scores representing better performance in all cases. The mean Z-scores for the US age and education-matched general male population are 0, and standard deviations are 1. Means±standard deviations are reported. All assessors were blinded to clinical and radiological information. GOS-E: Glasgow Outcome Scale-Extended. Scores of 7–8 represent good overall outcome, and scores <7 represent moderate to severe overall disability. PTSD: Post-traumatic stress disorder. PTSD was defined as meeting all criteria on the Clinician Administered PTSD Scale for *DSM-IV*. Note that many subjects in the "TBI no PTSD" group still have a substantial burden of PTSD symptoms, but did not meet all criteria for a categorical diagnosis of PTSD. The *p* values represent results of one-sided *t* tests (t) or one-sided Mann–Whitney *U*-tests (U); the prespecified hypotheses were that patients with traumatic brain injury (TBI) would perform worse than controls, subjects with poor overall outcome would perform worse than those with good overall outcome, and subjects with TBI+PTSD would perform worse than those with TBI and no PTSD. Results have not been corrected for multiple comparisons. None were significant after Bonferroni correction for 17 variables.

flexibility; the Rey-Osterrieth Complex Figure Test,[33] a paper and pencil test of visual memory; the California Verbal Learning Test II,[34] an assessment of verbal declarative memory; the 25 hole grooved Peg-Board test,[35] an assessment of upper extremity motor speed and coordination; a timed 25 foot walk; the Trail Making test,[36] an assessment of visual scanning, coordination, and mental flexibility; the symbol digit modalities test,[37] an assessment of working memory and processing speed; the controlled oral word association test,[38] an assessment of verbal fluency; and the Wechsler Test of Adult Reading,[39] as an estimate of pre-injury verbal intelligence. A relatively easy forced choice test embedded in the California Verbal Learning Test was used to assess adequacy of effort.

Safety and data monitoring

Subjects were assigned a random four-digit code number to protect confidentiality, and all research data were identified by code number only. A board-certified psychiatrist (ECN) was immediately available in case the CAPS examination exacerbated PTSD symptoms. No exacerbations necessitating medical intervention occurred, although additional support from study staff was needed on several occasions.

For clinical evaluations, the principal investigator audited 1 in 10 randomly selected subjects' data sets to ensure that data were scored and entered correctly. These audits revealed only minor discrepancies in scoring criteria that were then corrected across the entire cohort of subjects.

Statistical analyses

All data was analyzed using Statistica 6.0 (Statsoft Inc). Chi-square analyses were used to assess the relationships between categorical variables. Continuous variables have been summarized as mean ± standard deviation unless otherwise specified. The nor-

mal distribution of each continuous variable was assessed using the Shapiro-Wilk test. For normally distributed variables, unpaired Student t tests were used to compare groups. For non-normally distributed variables, Mann-Whitney U tests were used. We pre-specified that subjects with TBI would have worse outcomes than controls. One-sided tests were used when hypotheses were pre-specified, and two-sided tests were used otherwise. For correlations between continuous variables, Pearson product moment correlations were used when correlations were approximately linear and residuals were normally distributed based on Shapiro-Wilk testing. When these criteria were not met, Spearman non-parametric correlations were used. Uncorrected p values have been reported, but only considered significant if $p < 0.05$ after Bonferroni correction for multiple comparisons within each class of variables.

Clinical trials identifier

The study was registered at clinicaltrials.gov (NCT00785304).

Results

At LRMC, the MACE scores in the subjects with TBI (Fig. 2A) indicated that 19/47 (40.4%) fell below a score of 25 of 30 points, often used as a cutoff for an abnormal score.[23] The MACE was not performed on the control subjects. MACE testing was part of clinical care for patients with TBI at LRMC and was not a pre-specified part of the research protocol.

Global clinical outcomes were worse in subjects with TBI than controls (Fig. 2B). GOS-E scores 6–12 months after enrollment were significantly lower in the subjects with TBI ($p = 0.011$, one-tailed Mann-Whitney U test). More subjects with TBI (41/47, 87%) than controls (11/18, 61%) had moderate to severe overall disability ($p = 0.019$, chi-square), defined as a GOS-E score of 6 or
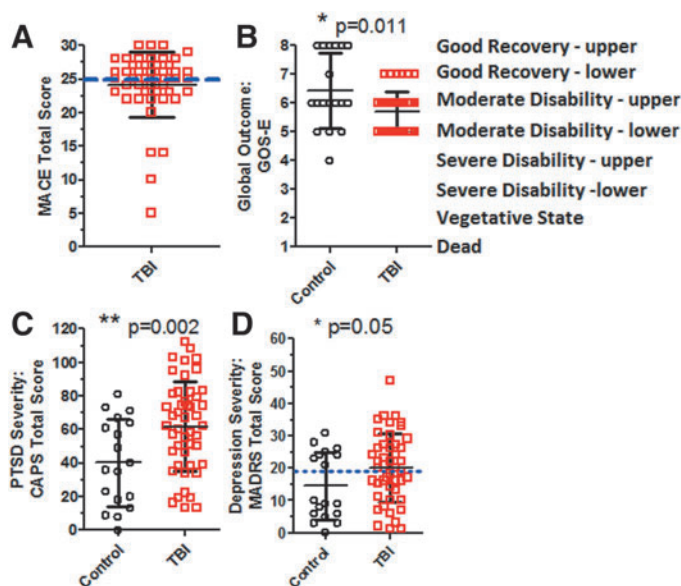
FIG. 2. Clinical assessments in US military personnel with concussive "blast-plus" traumatic brain injury (TBI). (**A**) Military Acute Concussion Evaluation (MACE) scores in subjects with TBI 1–90 days after injury at Landstuhl Regional Medical Center. Maximum score is 30. Higher scores indicate better performance. A cutoff of below 25 (blue dashed line) is considered to represent poor performance. (**B**) Global clinical outcomes assessed using the Glasgow Outcome Scale-Extended (GOS-E) scores 6–12 months after enrollment. *Indicates one-tailed Mann-Whitney U test. (**C**) Post-traumatic stress disorder (PTSD) severity, based on the Clinician Administered PTSD scale (CAPS). Higher scores represent more severe PTSD; maximum score is 132. **Indicates two-sided Student t test. (**D**) Depression severity assessed based on the Montgomery-Asberg Depression Rating Scale (MADRS) structured interview. Dashed blue line indicated cutoff score of 19: >19 reflects moderate to severe depression. *Indicates one-sided Mann-Whitney U test. Color image is available online at www.liebertpub.com/neu

less. Only one subject had severe disability; most subjects had moderate disability. The high rate of moderate disability in both groups is not typically observed in civilian polytrauma cases with concussive (mild) TBI (see Discussion).

Neuropsychological test results did not indicate substantial differences between the subjects with TBI and the controls; both groups generally performed within expectation for age and educational level on most tests (Table 2). All subjects performed well on a test of effort embedded in the California Verbal Learning Test. The psychometricians reported good apparent effort during testing. Likewise, performance did not differ between subjects with TBI with good outcomes (GOS-E = 7–8) versus those with moderate to severe disability (GOS-E < 7). This suggests that cognitive performance impairments may not account for the overall disability observed.

Performance on a standardized neurological interview and examination, the Neurobehavioral Rating Scale, similarly did not reveal major abnormalities, although subjects with TBI were slightly more impaired than controls (Table 3). Blast-plus subjects with TBI overall had marginally more severe neurobehavioral symptoms and deficits than control patients ($p = 0.03$, one-sided Mann Whitney U test). The largest contributing sub-score was mood/affect abnormalities ($p = 0.03$). Blast-plus subjects with TBI who met all criteria for PTSD had worse positive symptoms ($p = 0.005$) and mood/affect abnormalities ($p = 0.02$) compared with subjects with TBI who did not meet full PTSD criteria.

No subjects had focal neurological deficits detected during the neurological examination, performed by a board-certified neurologist (DLB). Specifically, none of the patients with TBI had impairing dysarthria, aphasia, neglect, hemianopsia, cranial nerve deficits, hemiparesis, parkinsonism, ataxia, dystonia, sensory loss, or neurological gait disorders.

Psychiatric assessments revealed substantially more frequent and more severe PTSD in the subjects with TBI. Specifically, 61% (29/47) of subjects with TBI and 28% (5/18) of controls met *DSM-IV* criteria for PTSD ($p = 0.0143$, chi-square) as assessed using the CAPS. The severity of PTSD was also significantly greater in the TBI group (Fig. 2C, $p = 0.002$, t test). All evaluated subjects with TBI and 17/18 controls met PTSD criterion A: ''one or more traumatic events that involved actual or threatened death or serious injury and a reaction that included intense fear, helplessness or horror.'' PTSD severity was significantly increased in the subjects with TBI across all three major sub-domains (Fig. 3A–C): ''Reexperiencing'' (CAPS B), ''Avoidance and Numbing'' (CAPS C), and ''Increased Arousal'' (CAPS D). The largest difference between TBI and control subjects was in reexperiencing (CAPS B),

and the greatest overall burden of PTSD symptoms was in increased arousal (CAPS D).

Symptoms of depression were also more severe in subjects with TBI compared with controls (Fig. 2D). Depression severity based on Montgomery-Asberg Depression Rating Scale scores were 19 ± 11 in subjects with TBI and 14 ± 10 in controls ($p = 0.05$, one-sided Mann-Whitney U test). Depression, however, did not differentiate as strongly as PTSD between TBI and control subjects. Using a total score > 19 on the Montgomery-Asberg Depression Rating Scale as the criterion, significant depression was present in 24/47 (51%) of subjects with TBI and 8/18 (44%) of controls ($p = 0.63$).

Montgomery-Asberg Depression Rating Scale scores were highly correlated with CAPS total scores for PTSD in the entire cohort (Pearson $r = 0.86$, $p < 0.001$), in the subjects with TBI (Pearson $r = 0.82$, $p < 0.001$), and in the control subjects (Pearson $r = 0.95$, $p < 0.001$).

PTSD was strongly associated with overall adverse outcomes. Across both TBI and control groups, 33/34 (97%) of subjects who met all criteria for PTSD had moderate to severe overall disability versus 19/31 (61%) who did not meet full PTSD criteria ($p = 0.0003$, chi-square). A similar relationship held for the TBI subjects in isolation (28/29 vs. 13/19, $p = 0.015$). CAPS scores were 62 ± 25 in subjects with moderate to severe disability versus 31 ± 24 in subjects with good outcomes ($p = 0.0001$, t test). Depression was also strongly associated with overall adverse outcomes: 31/32 (97%) of subjects with depression versus 21/33 (64%) of subjects without depression had moderate to severe overall disability ($p = 0.0008$, chi-square).

There were no differences in neuropsychological test performance in subjects with TBI with PTSD versus subjects with TBI who did not meet all criteria for PTSD (Table 2). Likewise, there were no apparent demographic differences between TBI study participants with versus without PTSD (Table 4). Subjects with PTSD had higher positive symptoms ($p = 0.005$) and mood/affect abnormalities ($p = 0.02$) on the neurobehavioral rating scale (Table 3). Neurobehavioral Rating Scale was performed by a different investigator than the CAPS interview, and these two measures were scored blinded to the other results.

There was a modest negative correlation between self-reported level of education and overall PTSD severity (Spearman $r = -0.29$, $p = 0.02$, Fig. 3D). The tight clustering of educational between 12–14 years made this difficult to fully interpret, however.

Sleep deprivation was correlated with Neurobehavioral Rating Scale scores (Fig. 4) and performance on several neuropsychological test measures (Fig. 4B–D). Sleep deprivation was self-reported as
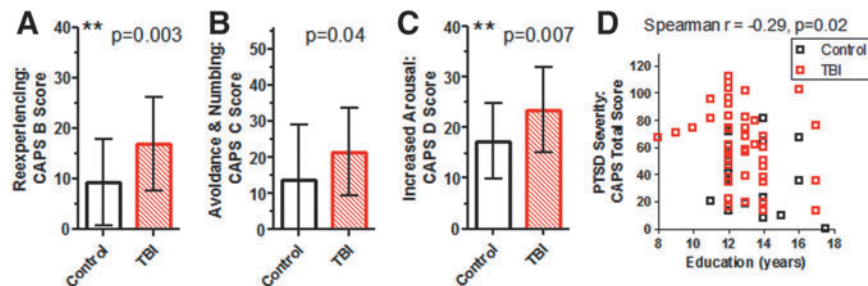
FIG. 3. Post-traumatic stress disorder (PTSD) severity assessed using Clinician Administered PTSD scale (CAPS subscales **A–C**). Subjects with traumatic brain injury (TBI) had more severe PTSD symptoms in all three sub-domains. The sub-domains were based on the *DSM-IV* criteria for PTSD. The maximum scores are CAPS B: 40, CAPS C: 56, CAPS D: 40. Bars represent mean and standard deviation. **Indicates one-sided Student t tests < 0.017 after Bonferroni correction for multiple comparisons. Inverse correlation between self-reported years of formal education and PSTD severity (**D**). Color image is available online at www.liebertpub.com/neu

TABLE 3. NEUROBEHAVIORAL RATING SCALE RESULTS

Rating	Control (n=18)	TBI (n=47)	p	TBI GOS-E 7–8 (n=6)	TBI GOS-E<7 (n=41)	p	TBI no PTSD (n=18)	TBI+PTSD (n=29)	p
Total score (max 87, higher scores worse)	7.9±6.8	11.6±7	0.03*	8.7±5.5	12.0±7.5	0.18	7.8±4.3	13.9±7.8	0.10
Executive/cognitive dysfunction (max 24)	3.1±2.6	3.8±2.8	0.23	2.5±1.8	4.0±2.9	0.11	3.1±1.9	4.3±3.2	0.10
Positive symptoms (max 21)	1.1±1.8	1.4±1.6	0.11	0.8±0.4	1.5±1.7	0.31	0.6±0.7	2.0±1.8	0.005*
Negative symptoms (max 12)	0.8±1.0	1.1±1.3	0.23	1.3±1.6	1.1±1.2	0.43	0.8±0.9	1.4±1.4	0.09
Mood/affect abnormalities (max 15)	2.1±2.2	3.4±2.6	0.03	3.2±1.9	3.5±2.7	0.46	2.3±1.7	4.1±2.9	0.02
Oral/motor dysfunction (max 12)	0.1±0.3	0.7±1.0	0.02	0.5±0.5	0.7±1.0	0.50	0.4±0.6	0.8±1.1	0.13
Worst single domain score (max 3)	1.4±0.8	1.8±0.6	0.04	1.7±0.5	1.9±0.6	0.25	1.7±0.5	1.9±0.7	0.18

The Neurobehavioral Rating Scale score is based on a structured interview and neurological examination followed by clinician ratings across 29 domains. Each domain is rated 0 (no abnormalities) through 3 (severe, disabling abnormalities). The total score is the sum of the ratings across all 29 domains. The five sub-scores are based on previously published principal component analyses from a large group of civilian patients with TBI.[28] Each sub-score is the sum of scores from 4–8 domains. The ''worst single domain score'' was also assessed because the total scores are not necessarily ordinal—i.e., a single high score (2 or 3) in one domain can represent impairing or disabling symptoms and deficits, while several scores of 1 in multiple domains may not represent as much overall impairment. The p values represent results of one-sided Mann-Whitney U tests. *Indicates statistical significance for the total score at $p < 0.05$, or after Bonferroni correction for multiple comparisons at $p < 0.01$ for the subscores. Means±standard deviations are reported.
TBI, traumatic brain injury; GOS-E, Glasgow Outcome Scale-Extended; PTSD, post-traumatic stress disorder.

part of CAPS item D-1 and defined as desired number of hours of sleep per night minus total number of hours of sleep per night. Within the Neurobehavioral Rating Scale, the strongest correlations were with the mood/affect (Spearman r=0.31) and executive/cognitive subscales (Spearman r=0.28).

Discussion

We found that overall disability 6–12 months after concussive blast-plus TBI in US military personnel evacuated to LRMC was surprisingly high. Overall outcomes based on the GOS-E were considerably worse than have been reported in civilian cohorts with concussive (mild) TBI,[40–46] and higher even than civilian polytrauma patients with concussive (mild) TBI.[40,41] The most directly

comparable civilian studies[40,41] reported that 33–36% of polytrauma patients with concussive (mild) TBI had GOS-E scores of <7, indicating moderate to severe disability. In contrast, 87% of subjects in our cohort had GOS-E scores of <7.

Importantly, while outcomes were worse in the subjects with TBI than in the controls, moderate disability was common in the control group as well. This suggests that common aspects experienced by US military personnel injured or ill enough to be evacuated from theater also contributed substantially to outcomes. This is not surprising, because subjects with less substantial health concerns were typically treated in theater and not evacuated to LRMC.

We found that cognitive performance, however, as assessed using standardized neuropsychological testing was generally

TABLE 4. CHARACTERISTICS OF TRAUMATIC BRAIN INJURY STUDY PARTICIPANTS WITH AND WITHOUT POST-TRAUMATIC STRESS DISORDER

Characteristic	TBI No PTSD (n=18)	TBI+PTSD (n=29)	p value
Age in years: median (range)	23.5 (21–58)	27 (19–45)	0.44 (U)
Education in years: median (range)	13 (10–17)	12 (8–17)	0.25 (U)
Race/ethnicity* – no (%)			0.49 (C)
White	12 (66.7%)	22 (75.9%)	
African American	3 (16.6%)	2 (6.9%)	
Hispanic/Latino	2 (11.1%)	4 (13.8%)	
Asian	1 (5.6%)	1 (3.4%)	
Branch of Service – no (%)			0.04 (C)
US Army	14 (77.8%)	28 (95.6%)	
US Air Force	0	0	
US Marine Corps	4 (22.2%)	1 (3.4%)	
US Navy	0	0	
Military rank – no (%)			0.30 (C)
Enlisted	16 (88.9)	28 (95.6)	
Officer	2 (11.1)	1 (3.4)	
Theater of operation – no (%)			0.98 (C)
Iraq	8 (44.4%)	13 (44.9%)	
Afghanistan	10 (55.5%)	16 (55.1%)	

TBI, traumatic brain injury; PTSD, post-traumatic stress disorder; (U), Mann-Whitney U test, (C) chi square. For race/ethnicity, this comparison was for white versus other.
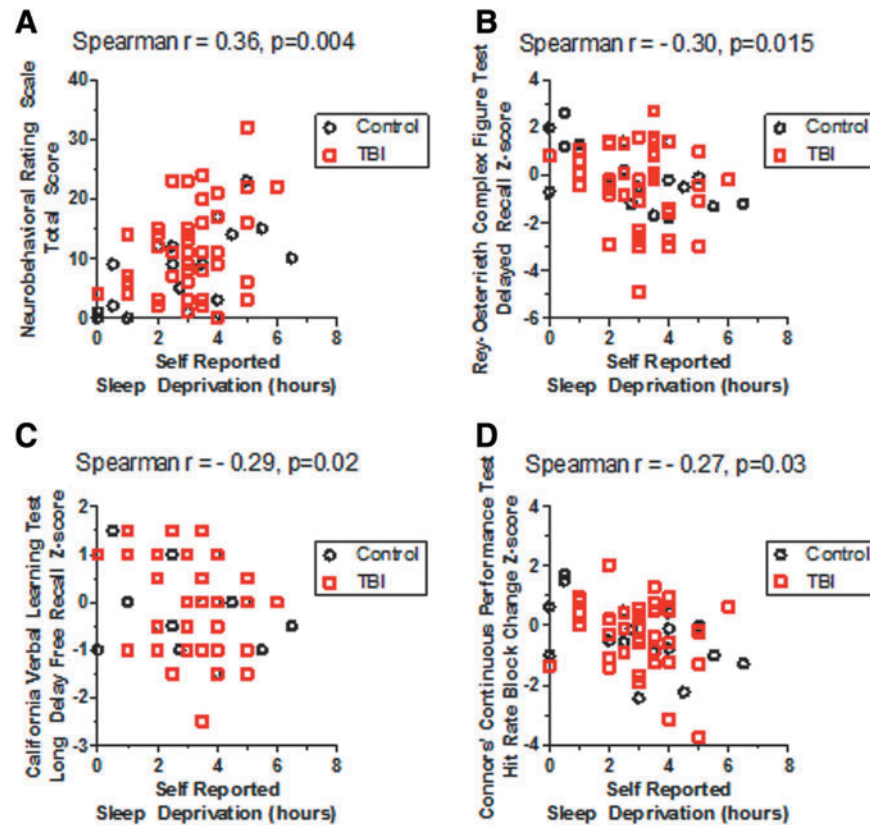
FIG 4. Correlations between self-reported sleep deprivation and test performance. (**A**) Positive correlation with Neurobehavioral Rating Scale total score, where higher scores indicate worse performance. (**B**) Negative correlation with visual memory performance on the delayed recall portion of the Rey-Osterrieth Complex Figure Test, where lower Z-scores indicate worse performance. (**C**) Negative correlation with verbal memory performance on the long delay free recall portion of the California Verbal Learning Test, where again lower Z-scores indicate worse performance. (**D**) Negative correlation with sustained vigilance, assessed using the hit rate block change measure from the Conners Continuous Performance Test, where similarly lower Z-scores indicate worse performance. TBI, traumatic brain injury. Color image is available online at www.liebertpub.com/neu

normal. Control subjects, subjects with TBI without PTSD, and subjects with TBI with PTSD all performed equally well, and all three groups performed essentially as expected for their ages and educational levels. Likewise, none had focal neurological deficits.

Performance on the grooved Peg-Board, a test of motor speed and coordination, was borderline to mildly deficient in both TBI and control subjects. This did not differ between groups and did not differ as a function of global outcome (Table 2). Also, there was low average performance in both TBI and control subjects on the Controlled Oral Word Association test, an assessment of verbal fluency (Table 2). It was not clear why performance on the grooved Peg-Board and Controlled Oral Word Association were worse than expected in both groups. The subjects did not have focal neurological deficits, and neither grooved Peg-Board nor Controlled Oral Word Association scores were correlated with PTSD measures, depression, or self-reported sleep loss.

The modest correlations of self-reported sleep deprivation with cognitive performance are not surprising. Future investigations with larger samples sizes will be needed to determine whether there is an interaction between TBI and sleep deprivation, such that, for example, patients with TBI might be more sensitive to the effects of sleep deprivation than controls. Further, objective measurements of sleep quantity and quality would likely improve the accuracy of these correlations.

The disability appeared to be most closely related to PTSD and depression. Most subjects who reported being unable to work at all (GOS-E of 5), work at reduced capacity (GOS-E of 6), or reported significant impairments in social or family life (GOS-E of 6) also had substantial PTSD, depression, or both. As noted above, no cognitive impairments or focal neurological deficits that could account for this level of disability were detected. It was clearly understood by the subjects that the clinical assessors and research staff had no role in any disability determinations and none of the research data would become part of their medical records. Thus, secondary gain issues were unlikely to have played a role. In general, validity ratings for all assessments were quite high. Because of the close correlation between PTSD and depression severities, the relative contribution of PTSD versus depression could not be determined.

Strengths of this study include prospective identification of a relatively homogenous cohort of subjects and standardized, blinded, clinician evaluations of outcomes. Limitations include a modest sample size, all male subjects, no predeployment testing,[16] no direct comparison with identically assessed non–blast-related subjects with TBI, no formal assessment of combat exposure intensity, and absence of genetic data. We cannot rule out deficits in cognitive or behavioral domains not tested,[47,48] nor early cognitive impairments that resolved before follow-up evaluation. Likewise,

we did not address the question of pure blast-related TBI versus blast plus other mechanisms. All of our subjects had blast plus another injury mechanism indicating that the incidence of pure blast-related TBI[47,49,50] may be low in US military personnel injured seriously enough to be evacuated to LRMC. It should also be noted that this cohort, although representative of medically evacuated personnel, may not be generalizable to those sustaining injuries who remain in theater. Further, the diagnoses of TBI were largely based on self-report; thus, we cannot rule out the possibility that some patients with TBI and controls were miscategorized. At present, there are no validated objective tests for concussive TBI, so this reflects a limitation not just of these results but of the entire field of concussive (mild) TBI research.

We did not systematically assess all potential factors contributing to depression and PTSD other than TBI. Based on three lines of evidence, however, major physical disabilities did not appear to play a substantial role in the greater severity of depression and PTSD in the subjects with TBI compared with the controls: First, analysis of timed 25 foot walk performance (Table 2) revealed no difference between TBI and control groups, no difference between subjects with TBI with good outcomes versus poor outcomes, and no difference between subjects with TBI with PTSD versus without PTSD. All subjects completed the 25 foot walk. Second, oral/motor dysfunction as assessed by the Neurobehavioral Rating Scale (Table 3) was the least substantially affected sub-score, and again did not differ by group, by outcome, or by PTSD status. Third, there were no substantial differences in the extent of self-reported sleep deprivation in the two groups of subjects, as can be seen from the scatter plots in Figure 4. We did not collect Injury Severity Scores, however, nor did we systematically assess pain or medications to treat pain in this study.

Further research will be needed to determine the underlying explanation for the higher rate of PTSD and depression in the concussive subjects with TBI than in controls and whether this directly translates to patients who are not medically evacuated from combat. Possibilities include more intense combat experiences, intrinsic genetic or environmental factors leading to both higher risk of TBI and vulnerability to PTSD and depression, blast-related hormonal abnormalities,[51] and blast-related injuries to specific parts of the brain causing impaired emotional resilience and thereby increasing the incidence or severity of disorders of mood regulation. Of note, repetitive blast injuries in anesthetized rats caused chronic PTSD-like behavioral traits.[52] Ongoing human imaging and genetic studies will be needed to begin to address these possibilities. It remains to be determined whether specific treatments for PTSD and depression will effectively improve outcomes in blast-related concussive subjects with TBI.

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Author Disclosure Statement

No competing financial interests exist.

References

1. Tanielian, T.L., and Jaycox, L.H. (2008). Invisible Wounds of War: Psychological and Cognitive Injuries, Their Consequences, and Services to Assist Recovery. RAND Corporation: Santa Monica, CA.
2. Hoge, C.W., McGurk, D., Thomas, J.L., Cox, A.L., Engel, C.C., and Castro, C.A. (2008). Mild traumatic brain injury in U.S. Soldiers returning from Iraq. N. Engl. J. Med. 358, 453–463.
3. Luethcke, C.A., Bryan, C.J., Morrow, C.E., and Isler, W.C. (2011). Comparison of concussive symptoms, cognitive performance, and psychological symptoms between acute blast-versus nonblast-induced mild traumatic brain injury. J. Int. Neuropsychol. Soc. 17, 36–45.
4. Wilk, J.E., Bliese, P.D., Kim, P.Y., Thomas, J.L., McGurk, D., and Hoge, C.W. (2010). Relationship of combat experiences to alcohol misuse among U.S. soldiers returning from the Iraq war. Drug Alcohol Depend. 108, 115–121.
5. Wilk, J.E., Herrell, R.K., Wynn, G.H., Riviere, L.A., and Hoge, C.W. (2012). Mild traumatic brain injury (concussion), posttraumatic stress disorder, and depression in U.S. soldiers involved in combat deployments: association with postdeployment symptoms. Psychosom. Med. 74, 249–257.
6. Lippa, S.M., Pastorek, N.J., Benge, J.F., and Thornton, G.M. (2010). Postconcussive symptoms after blast and nonblast-related mild traumatic brain injuries in Afghanistan and Iraq war veterans. J. Int. Neuropsychol. Soc. 16, 856–866.
7. Scheibel, R.S., Newsome, M.R., Troyanskaya, M., Lin, X., Steinberg, J.L., Radaideh, M., and Levin, H.S. (2012). Altered brain activation in military personnel with one or more traumatic brain injuries following blast. J. Int. Neuropsychol. Soc. 18, 89–100.
8. Verfaellie, M., Lafleche, G., Spiro, A., 3rd, Tun, C., and Bousquet, K. (2013). Chronic postconcussion symptoms and functional outcomes in OEF/OIF veterans with self-report of blast exposure. J. Int. Neuropsychol. Soc. 19, 1–10.
9. Polusny, M.A., Kehle, S.M., Nelson, N.W., Erbes, C.R., Arbisi, P.A., and Thuras, P. (2011). Longitudinal effects of mild traumatic brain injury and posttraumatic stress disorder comorbidity on postdeployment outcomes in national guard soldiers deployed to Iraq. Arch. Gen. Psychiatry 68, 79–89.
10. Terrio, H., Brenner, L.A., Ivins, B.J., Cho, J.M., Helmick, K., Schwab, K., Scally, K., Bretthauer, R., and Warden, D. (2009). Traumatic brain injury screening: preliminary findings in a US Army Brigade Combat Team. J. Head Trauma Rehabil. 24, 14–23.
11. Kontos, A.P., Kotwal, R.S., Elbin, R.J., Lutz, R.H., Forsten, R.D., Benson, P.J., and Guskiewicz, K.M. (2013). Residual effects of combat-related mild traumatic brain injury. J. Neurotrauma 30, 680–686.
12. Brenner, L.A., Terrio, H., Homaifar, B.Y., Gutierrez, P.M., Staves, P.J., Harwood, J.E., Reeves, D., Adler, L.E., Ivins, B.J., Helmick, K., and Warden, D. (2010). Neuropsychological test performance in soldiers with blast-related mild TBI. Neuropsychology 24, 160–167.
13. Belanger, H.G., Kretzmer, T., Yoash-Gantz, R., Pickett, T., and Tupler, L.A. (2009). Cognitive sequelae of blast-related versus other mechanisms of brain trauma. J. Int. Neuropsychol. Soc. 15, 1–8.
14. Brenner, L.A., Ladley-O'Brien, S.E., Harwood, J.E., Filley, C.M., Kelly, J.P., Homaifar, B.Y. and Adler, L.E. (2009). An exploratory study of neuroimaging, neurologic, and neuropsychological findings in veterans with traumatic brain injury and/or posttraumatic stress disorder. Mil. Med. 174, 347–352.
15. Drag, L.L., Spencer, R.J., Walker, S.J., Pangilinan, P.H., and Bieliauskas, L.A. (2012). The contributions of self-reported injury characteristics and psychiatric symptoms to cognitive functioning in OEF/OIF veterans with mild traumatic brain injury. J. Int. Neuropsychol. Soc. Society 18, 576–584.
16. Vasterling, J.J., Brailey, K., Proctor, S.P., Kane, R., Heeren, T., and Franz, M. (2012). Neuropsychological outcomes of mild traumatic

brain injury, post-traumatic stress disorder and depression in Iraq-deployed US Army soldiers. Br. J. Psychiatry 201, 186–192.

17. Maguen, S., Madden, E., Lau, K.M., and Seal, K. (2012). The impact of head injury mechanism on mental health symptoms in veterans: Do number and type of exposures matter? J. Trauma. 25, 3–9.

18. Bryant, R. (2011). Post-traumatic stress disorder vs traumatic brain injury. Dialogues Clin. Neurosci. 13, 251–262.

19. Ruff, R.L., Riechers, R.G., 2nd, Wang, X.F., Piero, T., and Ruff, S.S. (2012). A case-control study examining whether neurological deficits and PTSD in combat veterans are related to episodes of mild TBI. BMJ Open 2, e000312.

20. Vanderploeg, R.D., Belanger, H.G., Horner, R.D., Spehar, A.M., Powell-Cope, G., Luther, S.L., and Scott, S.G. (2012). Health outcomes associated with military deployment: mild traumatic brain injury, blast, trauma, and combat associations in the Florida National Guard. Arch. Phys. Med. Rehabil. 93, 1887–1895.

21. Eskridge, S.L., Macera, C.A., Galarneau, M.R., Holbrook, T.L., Woodruff, S.I., Macgregor, A.J., Morton, D.J., and Shaffer, R.A. (2013). Influence of combat blast-related mild traumatic brain injury acute symptoms on mental health and service discharge outcomes. J. Neurotrauma 30, 1391–1397.

22. Casscells, S. (2007). Traumatic Brain Injury: Definition and Reporting, in: Defense, A.S.o. (ed). Department of Defense.

23. Dempsey, K.E., Dorlac, W.C., Martin, K., Fang, R., Fox, C., Bennett, B., Williams, K., and Flaherty, S. (2009). Landstuhl Regional Medical Center: traumatic brain injury screening program. J. Trauma Nurs. 16, 6–7, 10–12.

24. Mac Donald, C.L., Johnson, A.M., Cooper, D., Nelson, E.C., Werner, N.J., Shimony, J.S., Snyder, A.Z., Raichle, M.E., Witherow, J.R., Fang, R., Flaherty, S.F., and Brody, D.L. (2011). Detection of blast-related traumatic brain injury in U.S. military personnel. N. Engl. J. Med. 364, 2091–2100.

25. Wilson, J.T., Pettigrew, L.E., and Teasdale, G.M. (1998). Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. Journal of neurotrauma 15, 573–585.

26. Pettigrew, L.E., Wilson, J.T. and Teasdale, G.M. (2003). Reliability of ratings on the Glasgow Outcome Scales from in-person and telephone structured interviews. J. Head Trauma Rehabil. 18, 252–258.

27. Levin, H.S., High, W.M., Goethe, K.E., Sisson, R.A., Overall, J.E., Rhoades, H.M., Eisenberg, H.M., Kalisky, Z., and Gary, H.E. (1987). The neurobehavioural rating scale: assessment of the behavioural sequelae of head injury by the clinician. J. Neurol. Neurosurg. Psychiatry 50, 183–193.

28. McCauley, S.R., Levin, H.S., Vanier, M., Mazaux, J.M., Boake, C., Goldfader, P.R., Rockers, D., Butters, M., Kareken, D.A., Lambert, J., and Clifton, G.L. (2001). The neurobehavioural rating scale-revised: sensitivity and validity in closed head injury assessment. J. Neurol. Neurosurg. Psychiatry 71, 643–651.

29. Weathers, F.W., Keane, T.M., and Davidson, J.R. (2001). Clinician-administered PTSD scale: a review of the first ten years of research. Depress. Anxiety 13, 132–156.

30. Montgomery, S.A., and Asberg, M. (1979). A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.

31. Conners, C., and Staff, M. (2000). Conners' Continuous Performance Test II: Computer Program for Windows Technical Guide and Software Manual. Multi-Health Systems: North Tonwanda, NY.

32. Heaton, R., Chelune, G., Talley, J., Kay, G., and Curtiss, G. (1993). Wisconsin Card Sorting Test Manual Revised and Expanded. Pychological Assessment Resources: Odessa, Fl.

33. Taylor, L. (1991). Scoring criteria for the ROCF, in: A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. O. Spreen, E. Strauss (eds). Oxford: New York.

34. Delis D, Kramer J, Kaplan E and B, O. (2000). California Verbal Learning Test Manual: Second Edition, Adult Version. Psychological Corporation: San Antonio, TX.

35. Matthews C, and Kløve, H. (1964). Instruction Manual for the Adult Neuropsychology Test Battery. University of Wisconsin Medical School: Madison, WI.

36. Reitan, R. (1992). Trail Making Test Manual for Administration and Scoring. Reitan Neuropsychology Laboratory: Tuscon, AZ.

37. Smith, A. (1991). Symbol Digit Modalities Test. Western Psychological Services: Los Angeles.

38. Benton A, Hamsher, K., and Sivan, A.B. (1983). Multilingual Aphasia Examination (3rd ed.). AJA Associates: Iowa City, Ia.

39. Wechsler, D. (2001). Wechsler Test of Adult Reading (WTAR) Manual. Psychological Corporation: New York.

40. Jacobs, B., Beems, T., Stulemeijer, M., van Vugt, A.B., van der Vliet, T.M., Borm, G.F., and Vos, P.E. (2010). Outcome prediction in mild traumatic brain injury: age and clinical variables are stronger predictors than CT abnormalities. J. Neurotrauma 27, 655–668.

41. Stulemeijer, M., van der Werf, S.P., Jacobs, B., Biert, J., van Vugt, A.B., Brauer, J.M.. and Vos, P.E. (2006). Impact of additional extracranial injuries on outcome after mild traumatic brain injury. J. Neurotrauma 23, 1561–1569.

42. Mosenthal, A.C., Livingston, D.H., Lavery, R.F., Knudson, M.M., Lee, S., Morabito, D., Manley, G.T., Nathens, A., Jurkovich, G., Hoyt, D.B., and Coimbra, R. (2004). The effect of age on functional outcome in mild traumatic brain injury: 6-month report of a prospective multicenter trial. J. Trauma 56, 1042–1048.

43. Thornhill, S., Teasdale, G.M., Murray, G.D., McEwen, J., Roy, C.W., and Penny, K.I. (2000). Disability in young people and adults one year after head injury: prospective cohort study. BMJ 320, 1631–1635.

44. Alexander, M.P. (1995). Mild traumatic brain injury: pathophysiology, natural history, and clinical management. Neurology 45, 1253–1260.

45. Benedictus, M.R., Spikman, J.M., and van der Naalt, J. (2010). Cognitive and behavioral impairment in traumatic brain injury related to outcome and return to work. Arch. Phys. Med. Rehabil. 91, 1436–1441.

46. Sigurdardottir, S., Andelic, N., Roe, C., and Schanke, A.K. (2009). Cognitive recovery and predictors of functional outcome 1 year after traumatic brain injury. J. Int. Neuropsychol. Soc. 15, 740–750.

47. Mendez, M.F., Owens, E.M., Jimenez, E.E., Peppers, D., and Licht, E.A. (2013). Changes in personality after mild traumatic brain injury from primary blast vs. blunt forces. Brain Inj. 27, 10–18.

48. Mendez, M.F., Owens, E.M., Reza Berenji, G., Peppers, D.C., Liang, L.J., and Licht, E.A. (2013). Mild traumatic brain injury from primary blast vs. blunt forces: post-concussion consequences and functional neuroimaging. NeuroRehabilitation 32, 397–407.

49. Mac Donald, C., Johnson, A., Cooper, D., Malone, T., Sorrell, J., Shimony, J., Parsons, M., Snyder, A., Raichle, M., Fang, R., Flaherty, S., Russell, M., and Brody, D.L. (2013). Cerebellar white matter abnormalities following primary blast injury in US military personnel. PloS One 8, e55823.

50. Warden, D.L., French, L.M., Shupenko, L., Fargus, J., Riedy, G., Erickson, M.E., Jaffee, M.S., and Moore, D.F. (2009). Case report of a soldier with primary blast brain injury. NeuroImage 47, Suppl 2, T152–T153.

51. Wilkinson, C.W., Pagulayan, K.F., Petrie, E.C., Mayer, C.L., Colasurdo, E.A., Shofer, J.B., Hart, K.L., Hoff, D., Tarabochia, M.A., and Peskind, E.R. (2012). High prevalence of chronic pituitary and target-organ hormone abnormalities after blast-related mild traumatic brain injury. Front. Neurol. 3, 11.

52. Elder, G.A., Dorr, N.P., De Gasperi, R., Gama Sosa, M.A., Shaughness, M.C., Maudlin-Jeronimo, E., Hall, A.A., McCarron, R.M., and Ahlers, S.T. (2012). Blast exposure induces post-traumatic stress disorder-related traits in a rat model of mild traumatic brain injury. J. Neurotrauma 29, 2564–2575.

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1   CLINICAL, COGNITIVE AND DIFFUSION TENSOR IMAGING ASSESSMENT OF

2   ACUTE BLAST-RELATED MILD TRAUMATIC BRAIN INJURY IN SERVICE MEMBERS

3   IN AFGHANISTAN

4

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ABSTRACT

IMPORTANCE: Mild traumatic brain injury (mTBI) has been a leading cause of combat-related injury among deployed service members.

OBJECTIVE: To evaluate whether diffusion tensor imaging (DTI) will noninvasively reveal white matter changes that are not present on conventional MRI in acute blast-related mTBI and to determine whether imaging abnormalities correlate with specific clinical measures and recovery.

DESIGN, SETTING AND PARTICIPANTS: Prospective observational study of 95 mTBI and 101 healthy control US military service members enrolled within 7 days from injury in Afghanistan between March and September 2012.

EXPOSURE: Acute blast-related mTBI with diagnoses based on history, examination, and review of field medical records.

MAIN OUTCOME MEASURES: Assessments included Rivermead Post-Concussive Symptom Questionnaire (RPCSQ), Post-Traumatic Stress Disorder Checklist Military (PCLM), Beck Depression Inventory (BDI), Balance Error Scoring System (BESS), Automated Neurocognitive Assessment Metric (ANAM), conventional MRI and DTI. DTI fractional anisotropy was calculated for specific regions of interest in a blinded and automated fashion.

RESULTS: Significantly greater impairment was observed in mTBI participants versus controls on all clinical measures, including RPCSQ (19.7 ± 12.9 vs. 3.6 ± 7.1, $p<0.001$), PCLM (32 ± 13.2 vs. 20.9 ± 7.1, $p<0.001$), BDI (7.4 ± 6.8 vs. 2.5 ± 4.9, $p<0.001$), and BESS (18.2 ± 8.4 vs. 15.1 ± 8.3, $p=0.01$). Decline in ANAM performance compared to individual predeployment baseline was

3

56   significantly larger in mTBI participants compared to controls, with largest effect size for simple

57   reaction time (74.5 ± 148.4 vs. -11 ± 46.6 ms, $p<0.001$). Fractional anisotropy was significantly

58   reduced in mTBI compared to controls in the right superior longitudinal fasciculus (0.393 ± 0.022

59   vs. 0.405 ± 0.023, $p<0.001$) and left middle cerebellar peduncle (0.412 ± 0.024 vs. 0.422 ± 0.028,

60   $p=0.003$) whereas no abnormalities were detected with conventional MRI. Time to return-to-duty

61   correlated with RPCSQ ($r=0.53$, $p<0.001$), decline in ANAM simple reaction time ($r=0.49$,

62   $p<0.0001$), PCLM ($r=0.47$, $p<0.0001$), and BDI ($r=0.36$ $p=0.0005$. No correlations between

63   clinical measures and imaging abnormalities were found.

64   CONCLUSIONS AND RELEVANCE: Somatic, behavioral and cognitive symptoms and

65   performance deficits are substantially elevated in acute blast-related mTBI. Post-concussive

66   symptoms and performance on measures of post-traumatic stress disorder, depression and

67   neurocognitive performance at initial presentation correlate with return-to-duty time. DTI is

68   more sensitive than conventional MRI in imaging white matter integrity in blast-related mTBI

69   acutely, although changes are of unclear clinical significance.

70

INTRODUCTION

Mild traumatic brain injury (mTBI) has emerged as one of the most prevalent war injury sustained by service members in the conflicts in Afghanistan and Iraq[1]. The most common mechanism is exposure to explosive blasts [2].

Unique features to combat mTBI, such as blast-exposure, fear of imminent death, witnessing death, moral injuries, survivor's guilt, combat stress, sleep deprivation, post-traumatic stress disorder (PTSD) and depression[3] have been increasingly recognized as significant components with potential impact on what has been considered a mild injury. As such, traditional ratings of mTBI severity including alteration and/or loss of consciousness (LOC) and posttraumatic amnesia (PTA)[4-7] may not reliably predict recovery of blast-related combat mTBI.

Diffusion tensor imaging (DTI) is an advanced MRI technique acquired on standard MRI scanners that measures the diffusion water in many directions[8]. Abnormalities on DTI are thought to reflect loss of white matter microstructural integrity, such as due to traumatic axonal injury[9-13] . DTI allows the *in vivo* evaluation of some aspects of brain white matter integrity by measuring the diffusion anisotropy of water molecules within coherently organized white matter tracts[8,14]. Water diffusion is fastest along the longitudinal axis of intact axons, while axonal microstructure, including the myelin sheath, membranes and cytoskeleton, causes water diffusion to be more restricted perpendicular to the longitudinal axis of the axons[15,16].

Three MRI scanners were deployed to Kandahar Air Field (KAF), Bagram Air Force base (BAF) and Bastion/Camp Leatherneck (LNK) in Afghanistan between October 2011 and February 2013. The presence of MRI capabilities in the combat theater provided an unprecedented opportunity to study the presence and degree of white matter injury acutely in an important and

93   understudied mTBI patient population – service members with mild blast-related injuries who

94   recover quickly and return to duty. These mildly injured service members represent the

95   overwhelming majority of mTBI casualties. We hypothesized that DTI would reveal

96   abnormalities not present on head CT and conventional MRI acutely following blast-related

97   mTBI and that specific pattern of injuries detected using DTI would correlate with neurological

98   and neurocognitive deficits and time to recovery.

99

METHODS

PARTICIPANTS

Screening of 230 U.S active duty military service members was performed between March 2012 and September 2012 at KAF and LNK (**Figure 1**). mTBI subjects were eligible if they met the diagnostic criteria for mTBI as defined by the American Congress of Rehabilitation Medicine[17] and sustained a blast exposure event within 7-days preceding enrollment. Controls were recruited from healthy, uninjured service members or service members receiving care for minor non-blast related musculoskeletal injuries. Controls were eligible if they had no history of any severity TBI in the preceding 12 months. The demographic characteristics of the study participants are summarized in **Table 1**. Reports of wartime stressors experienced by combatants were measured using the Combat Exposure Scale (CES)[18].

All participants provided written informed consent before enrolment. None of the participants received monetary compensation for participating. This study was conducted under a protocol reviewed and approved by the US Army Medical Research and Materiel Command Institutional Review Board and in accordance with the approved protocol.

CLINICAL ASSESSMENTS

The mean time from injury to clinical testing was 3.0 ± 1.5 days. All clinical assessments were conducted in a quiet, private room. Level of effort was measured using the Test of Memory Malingering (TOMM)[19]. Participants with TOMM score lower than 45 on two consecutive TOMM trials were excluded from analysis for poor testing effort (**Figure 1**).

120   Post-concussive symptom severity was measured using the Rivermead Post-Concussion

121   Symptom Questionnaire (RPCSQ)[20]. Symptoms of PTSD and depression were assessed using the

122   Post-traumatic Stress Disorder Check List Military (PCLM)[21], and Beck Depression Inventory

123   (BDI)[22,23].

124   The neurological examination was conducted by research staff (JD, DR, TM, OA).

125   Severity of balance impairment was tested using the Balance Error Scoring System (BESS)[24].

126   Cognitive testing was conducted using the ANAM – Traumatic Brain Injury Military

127   Version 4[25] and results were compared with subjects pre-deployment baseline performance.

128   Recovery time, defined as days from injury to final disposition (e.g. return to duty), was

129   used as a surrogate for outcome.

130   MRI ASSESSMENTS

131   The mean time from injury to MRI was 3.8±1.7 days. All subjects in both groups underwent

132   MRI without the administration of sedation beyond that required as part of routine clinical care

133   on Phillips 1.5T Achieva scanners at KAF and LNK. DTI was acquired using a 15 direction

134   sequence at b=1,000 with 1 b-zero image and spatial resolution of 2.5x2.5x2.5 mm. To improve

135   signal-to-noise ratio, two acquisitions were taken and averaged, each approximately 4:38

136   minutes. Conventional MR sequences included T1- (1x1x1mm) and T2- (0.5x0.5x0.5mm)

137   weighted images, fluid-attenuated inversion recovery (FLAIR) (0.8x0.8x5mm slices) and T2*-

138   weighted images (1.7x1.7x5mm slices). The total scan duration for each participant was

139   approximately 29 minutes. MRI scan data was transferred through a 4-5 relay server system via

140   KAF and Landstuhl Regional Medical Center (LRMC), Germany to Washington University, St

141   Louis for DTI post-processing and analysis. The specifics of processing have been previously

142   published[26,27]. Whole brain multiple region of interest (ROI) analysis was conducted in a semi-

143   automated fashion using DTI Studio software[28]. Single subject images were aligned to a template

144   atlas as previously published in a fully automated fashion[29]. DTI metrics were sampled for 130

145   ROIs covering the entire brain. Only white matter was compared between groups; 56 white-

146   matter ROIs were analyzed (**Supplementary Table S1**). Fornix and cingulum (cingulate gyrus,

147   hippocampus) were excluded due to insufficient spatial resolution. In addition to pure white

148   matter structures, four areas of mixed white-gray matter (superior frontal gyrus, middle frontal

149   gyrus, inferior frontal gyrus, middle fronto-orbial gyrus) were included in the analysis because of

150   their previously observed vulnerability to blast-related trauma[27]. In regions of mixed grey and

151   white matter, white matter was segmented using a fractional anisotropy (FA) threshold of 0.20.

152   STATISTICAL METHODS

153   All analysis was completed with Statistica 12 (Statsoft, Inc). Continuous data was screened for

154   normality using the Shapiro-Wilk test. For normally distributed data, unpaired Student's t-tests

155   were utilized. Non-parametric data was compared using Mann-Whitney-U tests. Correlations

156   were determined by Pearson Product Moment or Spearman-Rank depending on the distribution

157   of the residuals. Chi-square or Fisher Exact test was used depending on the group size to

158   compare categorical data. Correction for multiple comparisons was determined by Bonferroni or

159   false-discovery rate (FDR). Multivariate models were constructed using the generalized linear

160   models tool.

161

162 **RESULTS**

163 PARTICIPANTS

164 Alteration of consciousness was reported by 92 (97%) mTBI participants. Although 53 (56%)

165 sustained LOC, the duration was less than five minutes in the majority (96%). PTA (anterograde,

166 retrograde or both) was experienced by 35 (37%). Only two mTBI participants required medical

167 evacuation to LRMC. None of the mTBI participants sustained severe injuries and only 22 (23%)

168 reported other minor injuries (musculoskeletal, soft tissue). No trauma-related abnormalities

169 were identified on head CT in the 68 mTBI participants who underwent imaging as part of

170 routine medical care. Women, officers and older individuals were better represented in the

171 control group (**Table 1**). Group comparisons by age, rank, gender distribution, injury-to-MRI

172 scan days, did not show any statistically significant differences between the two recruiting sites

173 (**Supplementary Table S2**)

174 SYMPTOMS

175 The mTBI group reported significantly more intense symptoms on the RPCSQ compared to the

176 control group (**Figure 2A**, p=0.0000001, Mann-Whitney U). Significant group differences were

177 found across 15 of 16 individual RPCSQ symptoms (**Supplementary Table S3**). The largest

178 effect sizes were recorded for specific somatic symptoms (headache, dizziness, phonophobia,

179 fatigue and sleep disturbance) and cognitive symptoms (taking longer to think and poor

180 concentration). Since officers, women and older participants were better represented in the

181 control group, the results were validated by performing demographically matched subgroup

182 analysis using enlisted men only (87 mTBI and 67 controls, mean age 26 and 27 respectively,

183 Chi-square p=0.08). The results remained statistically significant (**Supplementary Table S4**).

10

184   NEUROLOGICAL EXAMINATION AND BALANCE

185   The neurological examination was normal in all subjects. Balance was significantly more

186   affected in the mTBI group compared to controls (**Figure 2B**, p=0.01, Student's t-test) with a

187   relatively small effect size (Cohen's *d* 0.37, effect size *r* 0.18). However, the difference lost

188   statistical significance when analysis was restricted to subgroups of age-matched enlisted men

189   (**Supplementary Table S5**).

190   BEHAVIORAL ASSESSMENTS

191   The mTBI group reported significantly more intense symptoms on measures of PTSD (**Figure

192   2C**, p=0.0000001, Mann-Whitney U), and depression (**Figure 2D**, p=0.0000001, Mann-Whitney

193   U). These results also maintained statistical significance on subgroup analysis of age-matched

194   enlisted men only (**Supplementary Table S5**).

195   NEUROCOGNITIVE TESTING

196   Changes in cognitive performance assessed using post-injury ANAM scores relative to pre-

197   deployment baseline (delta ANAM) were significantly larger in the mTBI compared to the

198   control group (**Figure 2F-L**). Higher positive delta ANAM means in the mTBI group compared

199   to controls were indicative of worse performance for simple reaction time (74.5±148.4 vs -11

200   ±46.6 ms, p=0.0000001, **Figure 2F**) and repeat simple reaction time (91.6±205.4 vs.

201   14.3±118.2ms, p=0.000002, **Figure 2G**). Lower negative delta ANAM means in the mTBI

202   groups compared to controls were indicative of worse performance for processing speed (-

203   11.4±18.4 vs. -0.1±15.6, p=0.00004, **Figure 2H**), associative learning (-3.8±10 vs. 4.6±9.7,

204   p=0.0000001, **Figure 2I**), delayed memory (-7 ±14.6 vs. 4.4±13.3 p=0.000002, **Figure 2J**),

205   working memory (-2.5±6.2 vs. 2.2±5.7 p=0.0000001, **Figure 2K**) and visual spatial memory (-

206   6.6±14 vs 2.2±10, p=0.000007, **Figure 2K,** all Mann-Whitney U tests). ANAM sleep index

207   mean reflecting changes from baseline showed that controls felt significantly more alert than

208   mTBI participants at the time of testing (-0.24±1.05 and 0.76±1.31 respectively) (**Figure 2E**).

209   These results maintained strong statistical significance on subgroup analysis of age-matched

210   enlisted men (**Supplementary Table S6**).

211   Controls and mTBI participants were neurocognitively similar at baseline; predeployment

212   ANAM data, available for 84 controls and 87 mTBI subjects, showed no significant differences

213   between the two groups (**Supplementary Tables S7 and S8**).

214   CONVENTIONAL MRI AND DTI FINDINGS

215   Conventional MRI images reviewed by board certified neuroradiologist (JR) and radiologist

216   (DA, BD) identified no brain trauma related abnormalities. Analyses of DTI data revealed

217   univariate statistically significant reduction in FA between the injured and control groups in nine

218   ROIs (**Supplementary Table S9**). After FDR correction for multiple comparisons, only the right

219   superior longitudinal fasciculus (SLF) and the left middle cerebellar peduncle (MCP) differed

220   significantly between groups (**Figure 3**). Analysis at the single individual level demonstrated

221   DTI abnormalities, defined as FA reductions two standard deviations below mean for controls, in

222   seven (7%) mTBI subjects in the SLF and two (2%) mTBI subjects in MCP. Subgroup analysis

223   using age-matched enlisted men (DTI data available for 87 mTBI and 65 control participants)

224   showed that both the SLF and the MCP remained statistically significant (Mann-Whitney U,

225   p=0.002 and 0.01 respectively), with a trend toward significance after FDR correction for

226   multiple comparisons, likely due to the reduction in sample size. Analyses of mean diffusivity,

227   axial diffusivity and radial diffusivity detected no significant group differences for any ROI after

228   correction for multiple comparisons. Analysis of DTI data collected on a single individual

229   scanned at both sites did not show any machine dependent differences in acquisition between

230   KAF and LNK (**Supplementary Figure S1**).

231   CORRELATES OF RETURN TO DUTY TIME

232   Clinical measures but not imaging results correlated with recovery time, defined as days required

233   to return to duty (**Figure 4**). Subjects who reported having lost consciousness returned to duty

234   slightly later than those who did not report loss of consciousness (**Figure 4A**, p=0.02).

235   Significant additional correlations with time to recovery were found for total symptom severity

236   assessed by the RPCSQ score (**Figure 4B**, r=0.53, p<0.0001), change in reaction time measured

237   by the delta ANAM SRT (**Figure 4C**, r=0.49, p<0.0001), severity on measures of PTSD

238   assessed by the PCLM (**Figure 4D**, r=0.47, p<0.0001) and depression assessed by the BDI

239   (**Figure 4E**, r=0.36, p=0.0005). A multivariate model including all 5 of these factors predicted

240   return to duty time only modestly better than any single factor (**Figure 4F**, r=0.56, p=0.00001).

241   Alteration in consciousness, retrograde amnesia and anterograde amnesia were not related to

242   recovery time in mTBI participants (**Supplementary Figure S2**). No significant correlations

243   were found between DTI FA in any of the examined ROI and recovery time, nor with clinical

244   variables evaluated including RPCSQ, BDI, CES, BESS, and ANAM modules.

DISCUSSION

In summary, we performed a prospective, acute phase study of US service members exposed to blast in combat who sustained mild, uncomplicated TBI. The mTBI participants reported significantly more severe concussive symptoms than controls, performed substantially worse on measures of depression and PTSD, and had impaired cognitive abilities in many domains. Nonetheless, the majority made a quick symptomatic recovery (mean of 7 days), and had favorable disposition (97% returned to combat duty). None of the mTBI subjects had abnormalities on head CT or conventional brain MRI scans, whereas diffusion tensor imaging revealed abnormalities at a group level suggestive of loss of brain white matter integrity in two anatomical areas, the superior longitudinal fasciculus and middle cerebellar peduncle. However, no correlations were found between DTI and acute clinical measures. Recovery time correlated modestly with loss of consciousness, initial symptom severity, reaction time and scores on measures of PTSD and depression. However, recovery time correlated poorly with alteration of consciousness and amnesia, which are traditionally used for mTBI severity ratings.

To our knowledge, this is the first study that used MRI to prospectively acquire brain imaging data in service members with mTBI acutely in a combat zone. The absence of trauma related changes on conventional brain MRI is likely attributed to the very mild injuries in our cohort. Nonetheless, the study demonstrates the feasibility of MRI-based research in a combat zone, despite substantial logistical challenges. Subtle drops in DTI FA in two of 56 brain ROI, the SLF and the MCP, are suggestive of disruption of white matter integrity. The MCP has been hypothesized to be particularly vulnerable to blast exposure[30,31]. It has also been previously found to be affected in blast-related mTBI in the subacute post-injury stages in service members who were medically evacuated from combat to LRMC, Germany[27]. The presence of

14

268   abnormalities in the MCP in both these independent cohorts of different severities imaged at

269   different points in time suggests that the MCP is an area of particular vulnerability across the

270   spectrum of severity of blast-related mTBI. The SLF has also been previously found to be

271   affected in chronic[32-34] as well as subacute mTBI[35,36]. One study however reported that SLF

272   changes may be associated with comorbid depression independent of mTBI in this patient

273   population[37].

274   The main strength of this study is the enrollment of a unique patient population of service

275   members exposed to concussive intensity blast in combat and a control population recruited in

276   the same environment. Prior small sample human blast-related mTBI studies used participants

277   exposed to subconcussive intensity blasts as part of military training[38]. The large sample size

278   compared to most studies examining DTI changes in mTBI was powered to detect anticipated

279   small differences considering the very mild severity of these injuries. This study is one of the

280   few[39,40] that prospectively and systematically analyzed post-concussive symptoms and cognition

281   and the only one that used MR imaging in blast-related mTBI acutely, in the combat

282   environment, close to the point of injury where the recovery takes place.

283   Nonetheless, this study has important limitations. First, the injured and control cohorts

284   were not perfectly matched demographically, with a higher proportion of older participants,

285   officers and women in the control group. However, demographically matched subgroup analyses

286   indicated that the main results maintained statistical significance or trended towards statistical

287   significance and thus were unlikely to have resulted from effects restricted to certain specific

288   subgroups of participants. Even in matched subgroups, combat exposure was substantially higher

289   in the TBI group compared to the controls and this may have affected our results. Unfortunately,

290   it was not logistically feasible to enroll a control group with matched levels of combat exposure,

291   and so the exact contribution of combat-related blast mTBI *per se* vs. combat exposure as a

292   whole cannot be resolved directly. However, in another study completed recently, combat

293   exposure was substantially higher in US military personnel with blast-related TBI than in

294   otherwise similar personnel with non-blast-related TBI, yet clinical outcomes were

295   indistinguishable[41]. Thus, combat exposure may not be the main driver of outcomes.

296   A second limitation was the spatial and angular resolution of the DTI scans performed,

297   which were well below recommended standards[42]. Future studies of this kind may be

298   substantially more sensitive, especially if high resolution scans of the type being developed for

299   the Human Connectome Project can be acquired[43]. Thus, the lack of correlations between DTI

300   findings and clinical results should not be interpreted as lack of white matter structural injury in

301   these subjects.

302   A final limitation is that our study did not use direct outcome measures for clinical

303   correlations but instead used time to return to duty as a surrogate. Although mTBI treatment

304   protocols and return to duty decision making in Afghanistan are well standardized, variability in

305   patient symptom reporting and individual provider treatment styles may have distorted recovery

306   time data.

307   Future longitudinal studies are needed to identify the predictive value of specific clinical,

308   behavioral and neurocognitive assessments conducted in the early stages of mTBI for the

309   subsequent development of PTSD, post-concussion syndrome and disability. The identification

310   of such predictive markers may help to better stratify patients early and to refine the concept of

311   mTBI severity beyond traditional symptoms such as alteration or loss of consciousness and PTA.

312   Future studies are also needed to optimize DTI parameter protocols and post-processing

313   methodology for the enhanced sensitivity needed to detect subtle white matter changes in the

314   mildest forms of mTBI. The reversibility and clinical significance of these white matter changes

315   will also need to be addressed in follow up studies.

316   **CONCLUSIONS**

317   This study underscores the value of behavioral and neurocognitive assessments in

318   addition to changes in consciousness, amnesia and somatic symptoms when evaluating mTBI in

319   its acute stages. This study provides important proof of concept data indicating that diffusion

320   tensor imaging has the potential to reveal disruptions of white matter integrity in specifically

321   vulnerable brain regions. Furthermore, this study serves as a demonstration that prospective

322   studies requiring advanced imaging dependent on complex infrastructure and technology plus

323   close military-civilian cooperation are feasible even in the most remote, austere and harsh

324   environments. The clinical significance of such advanced imaging assessments remains to be

325   fully investigated.

326

Acknowledgments

378

REFERENCES

1. Hayward P. Traumatic brain injury: the signature of modern conflicts. *Lancet neurology.* Mar 2008;7(3):200-201.
2. Warden D. Military TBI during the Iraq and Afghanistan wars. *The Journal of head trauma rehabilitation.* Sep-Oct 2006;21(5):398-402.
3. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *The New England journal of medicine.* Jan 31 2008;358(5):453-463.
4. Practice parameter: the management of concussion in sports (summary statement). Report of the Quality Standards Subcommittee. *Neurology.* Mar 1997;48(3):581-585.
5. Cantu RC. Return to play guidelines after a head injury. *Clinics in sports medicine.* Jan 1998;17(1):45-60.
6. Harmon KG. Assessment and management of concussion in sports. *American family physician.* Sep 1 1999;60(3):887-892, 894.
7. Giza CC, Kutcher JS, Ashwal S, et al. Summary of evidence-based guideline update: Evaluation and management of concussion in sports: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* Jun 11 2013;80(24):2250-2257.
8. Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G. Diffusion tensor MR imaging of the human brain. *Radiology.* Dec 1996;201(3):637-648.
9. Blumbergs PC, Scott G, Manavis J, Wainwright H, Simpson DA, McLean AJ. Staining of amyloid precursor protein to study axonal damage in mild head injury. *Lancet.* Oct 15 1994;344(8929):1055-1056.
10. Mac Donald CL, Dikranian K, Bayly P, Holtzman D, Brody D. Diffusion tensor imaging reliably detects experimental traumatic axonal injury and indicates approximate time of injury. *J Neurosci.* Oct 31 2007;27(44):11869-11876.
11. Mac Donald CL, Dikranian K, Song SK, Bayly PV, Holtzman DM, Brody DL. Detection of traumatic axonal injury with diffusion tensor imaging in a mouse model of traumatic brain injury. *Experimental neurology.* May 2007;205(1):116-131.
12. Niogi SN, Mukherjee P. Diffusion tensor imaging of mild traumatic brain injury. *The Journal of head trauma rehabilitation.* Jul-Aug 2010;25(4):241-255.
13. Blumbergs PC, Scott G, Manavis J, Wainwright H, Simpson DA, McLean AJ. Topography of axonal injury as defined by amyloid precursor protein and the sector scoring method in mild and severe closed head injury. *Journal of neurotrauma.* Aug 1995;12(4):565-572.
14. Hunter JV, Wilde EA, Tong KA, Holshouser BA. Emerging imaging tools for use with traumatic brain injury research. *Journal of neurotrauma.* Mar 1 2012;29(4):654-671.
15. Newcombe VF, Williams GB, Nortje J, et al. Analysis of acute traumatic axonal injury using diffusion tensor imaging. *British journal of neurosurgery.* Aug 2007;21(4):340-348.
16. Arfanakis K, Haughton VM, Carew JD, Rogers BP, Dempsey RJ, Meyerand ME. Diffusion tensor MR imaging in diffuse axonal injury. *AJNR. American journal of neuroradiology.* May 2002;23(5):794-802.
17. Ruff RM, Iverson GL, Barth JT, et al. Recommendations for diagnosing a mild traumatic brain injury: a National Academy of Neuropsychology education paper. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists.* Feb 2009;24(1):3-10.
18. Keane T, Fairbank J, Caddell J, Zimering R, Taylor K, Mora C. Clinical evaluation of a measure to assess combat exposure. *Psychological Assessment.* 1989(1):53-55.
19. Tombough T. The Test of Memory Malingering. *Multi-Health Systems.* 1996.

425 20. King NS, Crawford S, Wenden FJ, Moss NE, Wade DT. The Rivermead Post Concussion Symptoms
426   Questionnaire: a measure of symptoms commonly experienced after head injury and its
427   reliability. *Journal of neurology.* Sep 1995;242(9):587-592.
428 21. Yeager DE, Magruder KM, Knapp RG, Nicholas JS, Frueh BC. Performance characteristics of the
429   posttraumatic stress disorder checklist and SPAN in Veterans Affairs primary care settings.
430   *General hospital psychiatry.* Jul-Aug 2007;29(4):294-301.
431 22. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression.
432   *Archives of general psychiatry.* Jun 1961;4:561-571.
433 23. Homaifar BY, Brenner LA, Gutierrez PM, et al. Sensitivity and specificity of the Beck Depression
434   Inventory-II in persons with traumatic brain injury. *Archives of physical medicine and
435   rehabilitation.* Apr 2009;90(4):652-656.
436 24. Guskiewicz KM, Ross SE, Marshall SW. Postural Stability and Neuropsychological Deficits After
437   Concussion in Collegiate Athletes. *Journal of athletic training.* Sep 2001;36(3):263-273.
438 25. Cernich A, Reeves D, Sun W, Bleiberg J. Automated Neuropsychological Assessment Metrics
439   sports medicine battery. *Archives of clinical neuropsychology : the official journal of the National
440   Academy of Neuropsychologists.* Feb 2007;22 Suppl 1:S101-114.
441 26. Mac Donald C, Johnson A, Cooper D, et al. Cerebellar white matter abnormalities following
442   primary blast injury in US military personnel. *PloS one.* 2013;8(2):e55823.
443 27. Mac Donald CL, Johnson AM, Cooper D, et al. Detection of blast-related traumatic brain injury in
444   U.S. military personnel. *The New England journal of medicine.* Jun 2 2011;364(22):2091-2100.
445 28. Mori S, Oishi K, Faria AV. White matter atlases based on diffusion tensor imaging. *Current
446   opinion in neurology.* Aug 2009;22(4):362-369.
447 29. Zhang Y, Zhang J, Oishi K, et al. Atlas-guided tract reconstruction for automated and
448   comprehensive examination of the white matter anatomy. *NeuroImage.* Oct 1 2010;52(4):1289-
449   1301.
450 30. Chafi MS, Karami G, Ziejewski M. Biomechanical assessment of brain dynamic responses due to
451   blast pressure waves. *Annals of biomedical engineering.* Feb 2010;38(2):490-504.
452 31. Taylor PA, Ford CC. Simulation of blast-induced early-time intracranial wave physics leading to
453   traumatic brain injury. *Journal of biomechanical engineering.* Jun 2009;131(6):061007.
454 32. Cubon VA, Putukian M, Boyer C, Dettwiler A. A diffusion tensor imaging study on the white
455   matter skeleton in individuals with sports-related concussion. *Journal of neurotrauma.* Feb
456   2011;28(2):189-201.
457 33. Geary EK, Kraus MF, Pliskin NH, Little DM. Verbal learning differences in chronic mild traumatic
458   brain injury. *J Int Neuropsychol Soc.* May 2010;16(3):506-516.
459 34. Kraus MF, Susmaras T, Caughlin BP, Walker CJ, Sweeney JA, Little DM. White matter integrity
460   and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain : a journal
461   of neurology.* Oct 2007;130(Pt 10):2508-2519.
462 35. Messe A, Caplain S, Paradot G, et al. Diffusion tensor imaging and white matter lesions at the
463   subacute stage in mild traumatic brain injury with persistent neurobehavioral impairment.
464   *Human brain mapping.* Jun 2011;32(6):999-1011.
465 36. Smits M, Houston GC, Dippel DW, et al. Microstructural brain injury in post-concussion
466   syndrome after minor head injury. *Neuroradiology.* Aug 2011;53(8):553-563.
467 37. Matthews SC, Strigo IA, Simmons AN, O'Connell RM, Reinhardt LE, Moseley SA. A multimodal
468   imaging study in U.S. veterans of Operations Iraqi and Enduring Freedom with and without
469   major depression after blast-related concussion. *NeuroImage.* Jan 2011;54 Suppl 1:S69-75.
470 38. Tate CM, Wang KK, Eonta S, et al. Serum brain biomarker level, neurocognitive performance,
471   and self-reported symptom changes in soldiers repeatedly exposed to low-level blast: a
472   breacher pilot study. *Journal of neurotrauma.* Oct 1 2013;30(19):1620-1630.

473   39.   Luethcke CA, Bryan CJ, Morrow CE, Isler WC. Comparison of concussive symptoms, cognitive
474   performance, and psychological symptoms between acute blast-versus nonblast-induced mild
475   traumatic brain injury. *J Int Neuropsychol Soc.* Jan 2011;17(1):36-45.
476   40.   Coldren RL, Russell ML, Parish RV, Dretsch M, Kelly MP. The ANAM lacks utility as a diagnostic or
477   screening tool for concussion more than 10 days following injury. *Military medicine.* Feb
478   2012;177(2):179-183.
479   41.   Mac Donald C, Johnson A, Wierzechowski L, et al. Prospectively Assessed Clinical Outcomes in
480   Concussive Blast vs. Non-blast Traumatic Brain Injury in Evacuated US Military Personnel. *JAMA*
481   *Neurology.* 2014;*In Press*.
482   42.   NINDS Common Data Elements, Traumatic Brain Injury.
483   http://www.commondataelements.ninds.nih.gov/tbi.aspx#tab=Data_Standards. Accessed
484   February 9th, 2014.
485   43.   Van Essen DC, al. E. Diffusion MRI 2nd Edition. 2013.

486

487

FIGURE LEGENDS

489 **Figure 1: Subject Screening and Enrollment.** A total of 230 US Military Service members
490 were screened from March through September 2012 at two sites in Afghanistan; 212 participated
491 and complete data was obtained from 196 subjects.

492 **Figure 2**. **More Severe Concussive Symptoms, Depression, Post-traumatic Stress Disorder**
493 **Impaired Balance, and Cognitive Dysfunction in mTBI subjects. A**. Rivermeade Post-
494 Concussion Symptom Questionnaire - RPCSQ (N=101 CTL, 95 mTBI, Mann-Whitney U). **B**.
495 Balance Error Scoring System - BESS (N=99 CTL, 89 mTBI: two CTL and six mTBI
496 participants did not complete BESS because of musculoskeletal injuries, Student's t-test). **C.**
497 Beck Depression Inventory - BDI (N=101 CTL, 95 mTBI, Mann-Whitney U). **D**. Post-
498 Traumatic Stress Disorder Checklist Military - PCLM (N=101 CTL, 95 mTBI, Mann-Whitney
499 U). **E-L:** Change in ANAM measures, where Deltas are defined as study ANAM scores minus
500 baseline ANAM scores (N=87 CTL, 84 mTBI). **E**: Sleep index; **F**: Simple Reaction Time
501 (SRT); **G**: Repeat Simple Reaction Time (2SRT); **H**: Processing speed, assessed with Procedural
502 Reaction Time (PRT); **I**: Associative learning assessed by Code Substitution Learning (CSL); **J**:
503 Delayed memory assessed Code Substitution Delayed (CSD); **K**: Working memory assessed by
504 Mathematical Processing (MTP); **L**: Visual-spatial memory assessed by Matching to Sample
505 (MTS). All were significant after Bonferroni correction for multiple comparisons Dotted lines
506 represent maximum scores. Solid horizontal lines represent means and vertical bars indicate
507 standard deviations (SD).

508 **Figure 3. Reduced Fractional Anisotropy on Diffusion Tensor Imaging in Two Brain**
509 **Regions in mTBI Subjects. A**: Right Superior Longitudinal Fasciculus (Student's t test), **B**: Left
510 Middle Cerebellar Peduncle (Mann-Whitney U). Solid horizontal lines represent the means and
511 the vertical bars indicate standard deviations (SD). The dashed horizontal line marks 2SD below
512 the mean for CTL. Solid symbol points (triangles for mTBI, squares for CTL) represent subjects
513 below this level. **C-D**: DTI Fractional Anisotropy images displaying signal loss in a mTBI
514 subject compared to control in the right Superior Longitudinal Fasciculus (C) and left Middle
515 Cerebellar Peduncle (D). Images are displayed in anatomical convention.

516 **Figure 4. Correlates of Time to Return to Duty. A.** Loss of consciousness. **B.** Total post-
517 concussive symptom severity scored with the RPCSQ. **C.** Change from baseline in simple
518 reaction time on ANAM testing. **D.** PTSD symptom severity scored using the PCLM. **E.**
519 Depression symptom severity scored using the Beck Depression Inventory. **F.** Overall prediction
520 of return to duty time using a multivariate linear model including LOC, RPCSQ, ANAM, PCLM,
521 and BDI.

522

Table 1. Subject Characteristics			
CHARACTERISTIC	mTBI (N=95)	CONTROLS (N = 101)	p VALUE
Age (years)			
Median	26	28	p=0.0002[U]
Range	19-41	19-48	
Male gender, no (%)	93 (98%)	79 (78%)	p=0.00001[C]
Branch of Service, no (%)			
Army	79 (83%)	39 (39%)	p=0.00001[C]
Marine Corps	15 (16%)	11 (11%)	
Navy	1 (1%)	39 (39%)	
Air Force	0 (0%)	12 (12%)	
Rank, no (%)			
Enlisted	89 (94%)	78 (77%)	p=0.001[C]
Officer	6 (6%)	23 (23%)	
Number of deployments$	2.11 ± 1.67	1.81 ± 1.26	p=0.24[U]
Returned to duty, no (%)	93 (97%)		
Return to duty time (days)			
Mean	7		
Range	2-26		
Combat Exposure Scale$$	18.41±9.13	5.28±8.63	p=0.0000001 [U]
History of Attention Deficit Disorder$$$	4	5	p=0.90[C]
History of Learning Disability$$$$	4	0	p=0.06[C]

mTBI mild traumatic brain injury;

[C] Chi-square, [U] Two-tailed Mann Whitney U.

$ CTL N=100 (data not available for one participant)

$$ mTBI N=94 (data not available for one participant)

$$$ mTBI N=87, CTL N= 100 (data not available for two mTBI and one CTL participants)

$$$$ mTBI N=88, CTL N= 100 (data not available for one mTBI and one CTL participants)

Figure 1

```
                    ┌──────────────────────────────────────┐
                    │  230 Total Service Members Screened   │
                    └──────────────────────────────────────┘
                                    │
                                    │        ┌──────────────────────────────────────────┐
                                    │        │  •   3 MRI contraindicated               │
                                    │        │        •   2 shrapnel                    │
                                    │        │        •   1 history of welding          │
                                    │        │  •   6 Screening failure                 │
                                    ├────────│        •   3 non-blast mechanism         │
                                    │        │        •   1 history of severe TBI       │
                                    │        │        •   1 outside enrolment window    │
                                    │        │            1 blast exposure without      │
                                    │        │            concussion                    │
                                    │        │  •   1 Subject withdrawal                │
                                    │        └──────────────────────────────────────────┘
                                    │
                    ┌──────────────────────────────────────┐
                    │   220 Total Service Members Enrolled  │
                    └──────────────────────────────────────┘
                                    │        ┌──────────────────────────────────┐
                                    ├────────│   Subjects lost for follow up: 8 │
                                    │        └──────────────────────────────────┘
                    ┌──────────────────────────────────────┐
                    │   Total Service Members scanned: 212  │
                    └──────────────────────────────────────┘
```
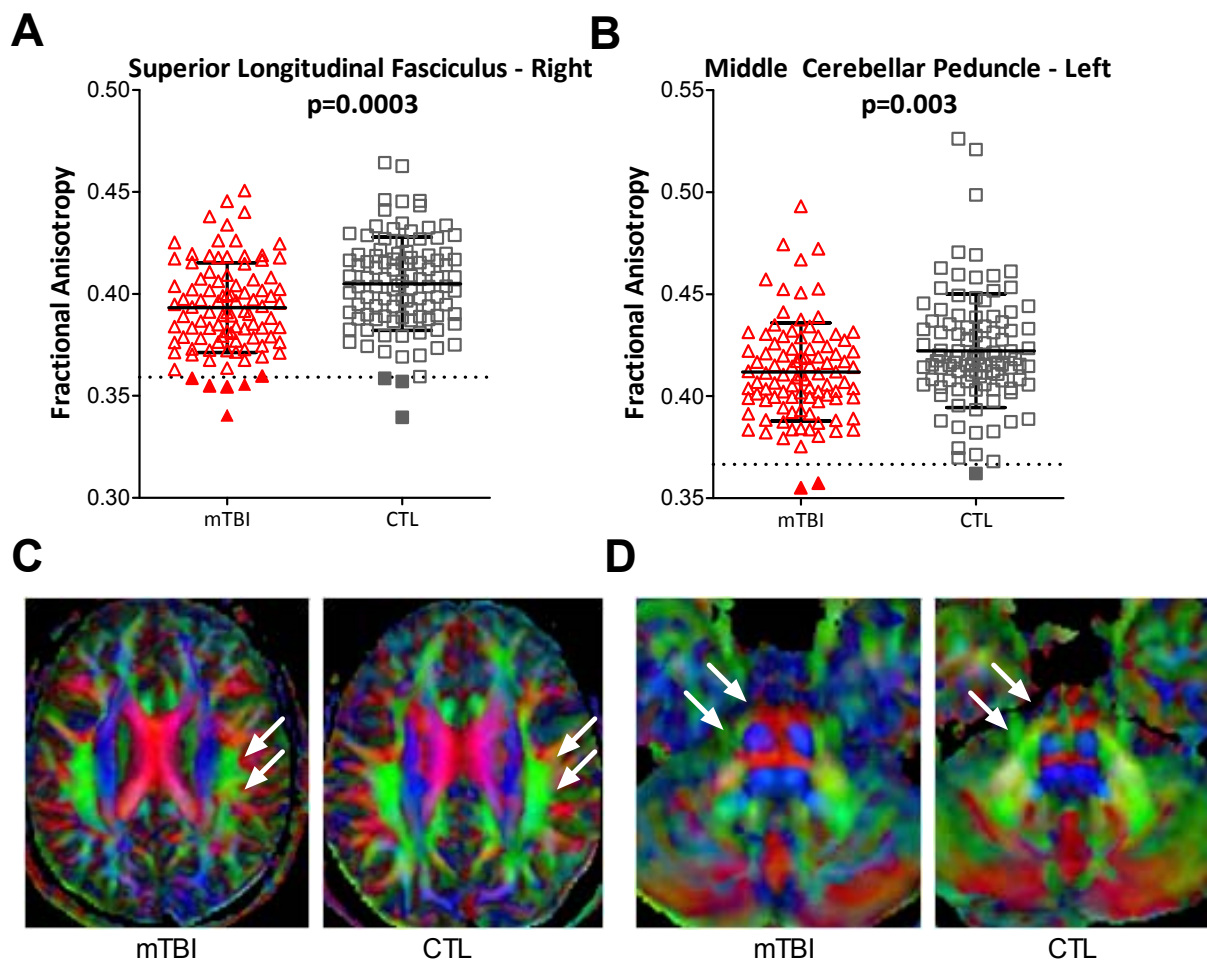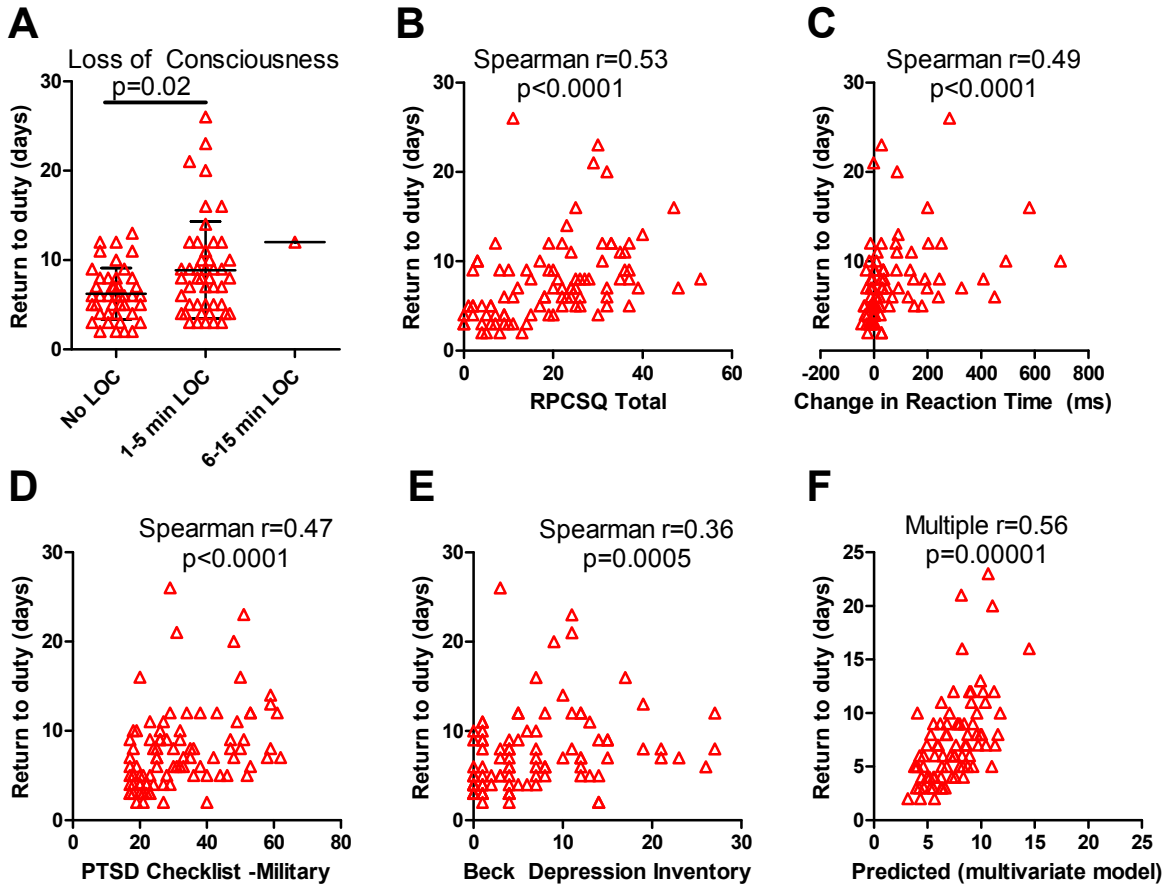
| Kandahar Air Field (KAF): 172 | Camp Leatherneck (LNK): 40 |

| CTL: 94 | TBI: 78 | CTL: 12 | TBI: 28 |

5 Excluded for poor MRI image quality

5 Excluded for TOMM <45
1 for poor MRI image quality

3 Excluded for TOMM <45
2 poor MRI image quality

| CTL: 89 | TBI: 72 | CTL: 12 | TBI: 23 |

Figure 2

A Superior Longitudinal Fasciculus - Right
p=0.0003

B Middle Cerebellar Peduncle - Left
p=0.003

C mTBI   CTL

D mTBI   CTL

Figure 3

Figure 4

1   CLINICAL, COGNITIVE AND DIFFUSION TENSOR IMAGING ASSESSMENT OF

2   ACUTE BLAST-RELATED MILD TRAUMATIC BRAIN INJURY IN SERVICE MEMBERS

3   IN AFGHANISTAN

4   Octavian Adam, MD[*], Christine L. Mac Donald, PhD[*], Dennis Rivet, MD, John Ritter, MD,

5   Todd May, DO, Maria Barefield OT, Josh Duckworth, MD, Donald LaBarge, MD, Dean Asher,

6   MD, Benjamin Drinkwine, MD, Yvette Woods, PhD, Michael Connor, PsyD, David L. Brody,

7   MD, PhD

8   **SUPPLEMENTAL INFORMATION**

Supplemental Methods

All mTBI participants had a Glasgow Coma Scale of 15 at the time of consent and were interviewed and examined by the research staff (JD, DR, TM, OA), who also reviewed available field medical records. Control or mTBI participants were excluded if they had a lifetime history of severe TBI or conditions that are known to or could reasonably be expected to alter DTI signal characteristics, including cerebrovascular disease, multiple sclerosis, hypoxic/ischemic brain injury, HIV, severe electrolyte disturbance, liver failure, renal failure, heart failure, alcohol abuse or longstanding psychiatric disease. Additional inclusion criteria for both groups were willingness to participate in the study, ability to communicate and comply with the study protocol and ability to provide consent. Both mTBI and control subjects were excluded if they had contraindications to MRI, such as claustrophobia, retained metallic foreign objects or inability to lie still in a supine position for the duration of the scan.

RPCSQ[1] is a self-administered questionnaire assessing 16 common post-concussive symptoms on a scale of 0 (none) to 4 (severe) covering three domains: cognitive ("forgetfulness, poor memory", "poor concentration", "taking longer to think"), emotional ("being irritable, easily angered", "feeling depressed or tearful", "feeling frustrated or inpatient") and somatic ("headache", "feeling of dizziness", "nausea and/or vomiting", "noise sensitivity, easily upset by loud noise", which many patients also equate to tinnitus, "sleep disturbance", "fatigue, tiring more easily", "blurred vision", "light sensitivity, easily upset by bright light", "double vision", "restlessness").

The PCLM[2] is a 17 item self-administered questionnaire tying symptom ratings to events experienced during military service, using a scale of 1 (not at all) to 5 (extremely).

The BDI[3,4] is a self-administered 21 item questionnaire corresponding to symptoms of depression rated on a severity scale of 0 (no symptoms) to 3 (severe symptoms).

The Combat Exposures Scale[5] (CES) measures the self-reported frequency of selected wartime dangerous situations such as combat patrols, being under enemy fire, being surrounded by the enemy, number of soldiers killed in action (KIA) or missing in action (MIA) in one's unit, firing rounds at the enemy, witnessing someone hit by incoming or outgoing rounds and being in danger of being killed or injured. The CES measures each of the 7 items using a 5 point scale (1

53 is "no", 2 is "1 to 3 times", 3 is "4 to 12 times", 4 is "13 to 50 times", and 5 is "51+ times").

54 Each item is weighted differently based on the severity of the experience, the total scores ranging

55 from 0−41.

56 The neurological examination consisted of cranial nerve, motor, sensory, coordination,

57 deep tendon reflex, posture and gait assessments.

58 The ANAM[6] is sanctioned by the Department of Defense for baseline neurocognitive

59 assessment in all deploying troops. It is also available in deployed setting. The ANAM includes a

60 collection of cognitive modules. The first (SRT) and repeat (2SRT) simple reaction time for

61 basic neural processing are expressed in milliseconds, lower scores indicating a faster reaction

62 time. The code substitution – learning (CSL) for associative learning, procedural reaction time

63 (PRT) for processing speed, mathematical processing (MTP) for working memory, matching to

64 sample (MTS) for visual spatial memory and code substitution – delayed (CSD) for delayed

65 memory are expressed as throughput, which is derived from percent correct answers divided by

66 mean reaction time, reflecting performance across both dependent variables. Higher scores

67 indicate better performance. Throughput has been shown to have greater sensitivity and reduced

68 variability compared to reaction time or accuracy alone[7]. The cognitive modules are preceded by

69 a sleepiness and general level of alertness scale, , a self-rated one to seven score, one

70 representing the maximum level of alertness. Post-injury cognitive performance group

71 comparisons were measured relative to predeployment baselines rather than comparing absolute

72 ANAM scores. Using individual baseline neurocognitive scores minimizes potential false-

73 positive errors[8].

74 The TOMM is a clinician administered tool of effort to discern malingerers from bona

75 fide cognitively impaired individuals[9]. The testing paradigm involved a single TOMM trial for

76 subjects with a score higher or equal to 45 and a second trial for subjects with a first TOMM

77 score lower than 45.

78 The BESS[10] is a clinician administered balance test which includes single, double and

79 tandem stance assessment on firm and foam (unstable) surfaces, each held for 20 seconds, with

80 the participant's hands on the hips and eyes closed. The score is a representation of cumulative

81 errors.

82   Data regarding immediate effects of injury were collected as follows: loss of

83 consciousness was scored as none, <5 minutes, 6-15 minutes, or 16-30 minutes. No subject

84 reported loss of consciousness >15 minutes. Alteration of consciousness was scored as none, <5

85 minutes, 6-59 minutes, or 1-24 hours. No subject reported alteration of consciousness greater

86 than 24 hours. Anterograde and retrograde amnesia were scored separately as none, <5 minutes,

87 6-59 minutes, or 1-24 hours. No subject reported amnesia of either type greater than 24 hours.

88   The specific acquisition DTI parameters were set to accommodate limitations on patient

89 scanning time and imaging data file size, taking into account the available infrastructure and the

90 logistics of transferring such large data files from Afghanistan to the United States. Unique

91 sources of artifact represented by the effects of wind gusts and vibration from high speed aircraft

92 take off on the MRI machines located in trailers on the combat hospital compounds further

93 restricted scan duration. The geographical distance between the acquisition and analysis study

94 sites posed challenges for the quick feedback needed on each individual scan quality. It required

95 considerable coordination efforts between the five relay server sites involved in the imaging data

96 file transfer across 12 time zones. One server site (Germany) required manually operated data

97 file transfers as part of the interacting interface between the Department of Defense (DoD) and a

98 civilian institution. Nonetheless, processing and analysis was completed within 24 hours of

99 acquisition in all cases.

100   Recovery time, defined as days from injury to final disposition (e.g. return to duty), was

101 used as a surrogate for outcome. Service members who sustained a blast-related mTBI were

102 prescribed rest and symptomatic treatment until they became asymptomatic at rest and during a

103 final exertion test. Treatment and return to duty decision making was conducted by the clinicians

104 involved in patient care and followed a standardized algorithm based on the Department of

105 Defense directive-type memorandum "Policy Guidance for Management of Concussion/Mild

106 Traumatic Brain Injury in the Deployed Setting[11]. Treating clinicians were not aware of MRI

107 results and based decisions largely on symptom resolution, independent of initial test

108 performance.

109   All participants provided written informed consent before enrolment. None of the

110 participants received monetary compensation for participating in this study. This research was

111 approved by the Department of Defense Central Command Medical Research and Materiel

112 Command Institutional Review Board and complied with human research ethics regulations.

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120   Supplemental Tables

Table S1. Regions of interest considered for analysis of DTI Data (Numbering, nomenclature and parenthetical notes from Zhang et al., 2010[12])			
3	Superior frontal gyrus right	68	Superior frontal gyrus left
4	Middle frontal gyrus right	69	Middle frontal gyrus left
5	Inferior frontal gyrus right	70	Inferior frontal gyrus left
22	Middle fronto-orbital gyrus right	87	Middle fronto-orbital gyrus left
29	Corticospinal tract right	94	Corticospinal tract left
30	Inferior cerebellar peduncle right	95	Inferior cerebellar peduncle left
31	Medial lemniscus right	96	Medial lemniscus left
32	Superior cerebellar peduncle right	97	Superior cerebellar peduncle left
33	Cerebral peduncle right	98	Cerebral peduncle left
34	Anterior limb of internal capsule right	99	Anterior limb of internal capsule left
35	Posterior limb of internal capsule right	100	Posterior limb of internal capsule left
36	Posterior thalamic radiation (include optic radiation) right	101	Posterior thalamic radiation (include optic radiation) left
37	Anterior corona radiata right	102	Anterior corona radiata left
38	Superior corona radiata right	103	Superior corona radiata left
39	Posterior corona radiata right	104	Posterior corona radiata left
40	Cingulum (cingulate gyrus) right	105	Cingulum (cingulate gyrus) left
43	Superior longitudinal fasciculus right	108	Superior longitudinal fasciculus left
44	Superior fronto-occipital fasciculus (could be a part of anterior internal capsule) right	109	Superior fronto-occipital fasciculus (could be a part of anterior internal capsule) left
45	Inferior fronto-occipital fasciculus right	110	Inferior fronto-occipital fasciculus left
46	Sagittal stratum (include inferior longitidinal fasciculus and inferior fronto-occipital fasciculus) right	111	Sagittal stratum (include inferior longitidinal fasciculus and inferior fronto-occipital fasciculus) left
47	External capsule right	112	External capsule left
48	Uncinate fasciculus right	113	Uncinate fasciculus left
49	Pontine crossing tract (a part of middle cerebellar peduncle) right	114	Pontine crossing tract (a part of middle cerebellar peduncle) left
50	Middle cerebellar peduncle right	115	Middle cerebellar peduncle left
52	Genu of corpus callosum right	117	Genu of corpus callosum left
53	Body of corpus callosum right	118	Body of corpus callosum left
54	Splenium of corpus callosum right	119	Splenium of corpus callosum left
55	Retrolenticular part of internal capsule right	120	Retrolenticular part of internal capsule left

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Table S2. Enrolment site comparisons (Demographics, time from injury to MRI scan)						
	mTBI			CONTROLS		
	KAF (N=72)	LNK (N=23)	P Value	KAF (N=89)	LNK (N=12)	P Value
Age						
Median (years)	25	25	0.42^U	28	28	0.35^U
Range (years)	19-41	20-32		19-48	21-32	
Enlisted	67	22	1.00^F	66	12	0.06^F
Officer	5	1		23	0	
Male	72	21	0.06^F	69	10	1.00^F
Female	0	2		20	2	
Time from injury to MRI scan						
Mean±SD (days)	3.69±1.63	3.96±2.06	0.7605^U	N/A	N/A	
Range (days)	1.0-8.0	1.0-8.0		N/A	N/A	

KAF Kandahar Air Field; LNK Camp Leatherneck;
^{U} Mann Whitney U test; ^{F} Fisher's exact test;
mTBI mild traumatic brain injury

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Table S3. Rivermeade Post-Concussion Symptom Questionnaire (RPCSQ),

Group comparisons by individual symptoms

RPCSQ Symptom	mTBI mean±SD N=95	CTL mean±SD N=101	p Value (Mann Whitney U)	Cohen's d	Effect-size r
Headache	2.07 ± 1.03	0.27 ± 0.66	p=0.0000001	2.08	0.72
Noise sensitivity, easily upset by loud noise	1.81 ± 1.44	0.25 ± 0.74	p=0.0000001	1.41	0.58
Taking longer to think	1.56 ± 1.28	0.24 ± 0.64	p=0.0000001	1.30	0.55
Dizziness	1.06 ± 1.09	0.06 ± 0.24	p=0.0000001[F]	1.27	0.54
Fatigue, tiring more easily	1.64 ± 1.32	0.34 ± 0.78	p=0.0000001	1.20	0.51
Poor concentration	1.49 ± 1.32	0.29 ± 0.70	p=0.0000001	1.14	0.49
Sleep disturbance	1.62 ± 1.45	0.40 ± 0.92	p=0.0000001	1.00	0.45
Restlessness	1.17 ± 1.22	0.23 ± 0.66	p=0.0000001	0.99	0.44
Nausea and/or Vomiting	0.75 ± 1.00	0.05 ± 0.33	p=0.0000001[F]	0.94	0.43
Irritable, easily angered	1.28 ± 1.25	0.31 ± 0.76	p=0.0000001	0.94	0.42
Forgetfulness, poor memory	1.38 ± 1.25	0.37 ± 0.90	p=0.0000001	0.93	0.42
Light sensitivity, easily upset by bright light	1.08 ± 1.15	0.22 ± 0.70	p=0.0000001[F]	0.90	0.41
Frustrated, Impatient	1.19 ± 1.25	0.29 ± 0.70	p=0.0000001	0.89	0.41
Depressed, Tearful	0.82 ± 1.06	0.11 ± 0.44	p=0.00006[F]	0.87	0.40
Blurred vision	0.52 ± 0.94	0.07 ± 0.64	p=0.0005[F]	0.68	0.32
Double vision	0.20 ± 0.59	0.02 ± 0.20	p=0.12[F]	0.41	0.20
RPCSQ Total score	19.77 ± 12.92	3.62 ± 7.13	P=0.0000001	1.55	0.61

mTBI mild traumatic brain injury; CTL control; [F] Fisher's exact test

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Table S4. Rivermeade Post-Concussion Symptom Questionnaire (RPCSQ), *Subgroup comparisons of enlisted men only*					
RPCSQ Symptom	**mTBI mean±SD N=87**	**CTL mean±SD N=65**	**p Value (Mann Whitney U)**	**Cohen's d**	**Effect-size r**
Headache	2.08 ± 1.05	0.32 ± 0.73	p=0.000001	1.95	0.70
Noise sensitivity, easily upset by loud noise	1.85 ± 1.46	0.26 ± 0.80	p=0.0000001	1.35	0.56
Dizziness	1.10 ± 1.11	0.09 ± 0.29	p=0.0000001[F]	1.25	0.53
Taking longer to think	1.60 ± 1.26	0.32 ± 0.73	p=0.0000001	1.24	0.53
Fatigue, tiring more easily	1.69 ± 1.31	0.38 ± 0.88	p=0.0000001	1.17	0.51
Poor concentration	1.55 ± 1.32	0.40 ± 0.81	p=0.0000001	1.05	0.46
Sleep disturbance	1.68 ± 1.44	0.43 ± 1.00	p=0.0000001	1.01	0.45
Restlessness	1.20 ± 1.22	0.26 ± 0.73	p=0.0000002	0.94	0.42
Nausea and/or Vomiting	0.78 ± 1.02	0.06 ± 0.39	p=0.0000001[F]	0.93	0.42
Forgetfulness, poor memory	1.43 ± 1.24	0.4 ± 1.05	p=0.000002	0.90	0.41
Light sensitivity, easily upset by bright light	1.09 ± 1.14	0.28 ± 0.82	p=0.000002[F]	0.82	0.38
Frustrated, Impatient	1.20 ± 1.23	0.35 ± 0.78	p=0.000023	0.83	0.38
Irritable, easily angered	1.33 ± 1.25	0.40 ± 0.86	p=0.000003	0.82	0.38
Depressed, Tearful	0.76 ± 1.10	0.14 ± 0.53	p=0.000046[F]	0.72	0.34
Blurred vision	0.53 ± 0.97	0.08 ± 0.32	p=0.000444[F]	0.62	0.30
Double vision	0.21 ± 0.61	0.03 ± 0.25	p=0.03[F]	0.39	0.19
RPCSQ Total score	20.18 ± 12.80	4.28 ± 7.93	0.0000001	1.50	0.60

mTBI mild traumatic brain injury; CTL control; [F] Fisher's exact test

Table S5. PCLM, BDI, CES and BESS
Subgroup comparisons of enlisted men only

TEST	mTBI N	CTL N	mTBI Mean ± SD	CTL Mean ± SD	P value (Mann-Whitney U)	Cohen's *d*	Effect size *r*
BESS	81	64	17.94 ± 8.34	15.42 ± 8.89	0.08[t]	0.29	0.14
BDI	87	65	7.34 ± 6.57	2.73 ± 5.12	0.000001	0.78	0.36
PCLM	87	65	32.36 ± 13.11	20.95 ± 7.01	0.000001	2.79	0.81
CES	86	65	19.08 ±9.05	6.42 ± 9.15	0.000001	1.39	0.57

[t]Student's t-test; BESS Balance Error Scoring System, BDI Beck Depression Inventory, PCLM Post-traumatic Stress Disorder Checklist Military, CES Combat Experience Scale, mTBI mild traumatic brain injury, CTL control

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Table S6. Delta ANAM (change from pre-deployment baseline to post-injury performance) *Subgroup comparisons of enlisted men only*					
ANAM modules	mTBI (N=81) mean ± SD	CTL (N=57) mean ± SD	P values (Mann-Whitney U)	Cohen's *d*	Effect size *r*
Sleep index	0.83 ± 1.34	-0.16 ± 1.11	0.000032	0.80	0.37
Simple Reaction Time	77.19 ± 151.22	-13.26 ± 53.11	0.000003	0.80	0.37
Simple Reaction Time Repeat	95.62 ± 211.98	3.49 ± 44.29	0.000109	0.60	0.29
Procedural Reaction Time	-12.32 ± 18.87	-0.70 ± 16.70	0.000170	-0.65	-0.31
Code Substitution Learning	-4.01 ± 10.25	3.30 ± 9.71	0.000092	-0.73	-0.34
Code Substitution Delayed	-7.75 ± 16.68	3.84 ± 14.05	0.000021	-0.75	-0.35
Mathematical Processing	-3.02 ± 6.65	1.58 ± 6.44	0.000060	-0.70	-0.33
Matching to Sample	-7.17 ± 14.42	2.67 ± 9.23	0.000007	-0.81	-0.38

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Table S7. Baseline Automated Neurocognitive Assessment Metrics (ANAM)

ANAM module	mTBI (N=87) mean±SD	CTL (N=84) mean±SD	P value (Mann Whitney U)
Sleep index	2.15 ± 1.15	1.97 ± 0.95	0.39
Simple Reaction Time	247.7 ± 20.73	257.5 ± 48.8	0.21
Simple Reaction Time Repeat	257.2 ± 32.23	260 ± 40.31	0.71
Procedural Reaction Time	103 ± 12.94	104.2 ± 13.65	0.58
Code Substitution Learning	56.21 ± 11.97	56.57 ± 10.67	0.89
Code Substitution Delayed	49.18 ± 14.17	46.14 ± 17	0.25
Mathematical Processing	21.03 ± 6..33	20.43 ± 5.84	0.43
Matching to Sample	38.92 ± 12.41	36.45 ± 11.56	0.17

Table S8. Baseline Automated Neurocognitive Assessment Metrics (ANAM)
Subgroup comparisons of enlisted men only

ANAM module	mTBI (N=81) mean±SD	CTL (N=57) mean±SD	P value (Mann Whitney U)
Sleep index	2.16 ± 1.16	1.95 ± 0.97	0.35
Simple Reaction Time	247.16 ± 20.54	257.30 ± 55.65	0.46
Simple Reaction Time Repeat	256.93 ± 33.08	258.93 ± 40.23	0.74
Procedural Reaction Time	103.75 ± 12.76	103.61 ± 13.85	0.91
Code Substitution Learning	56.78 ± 11.86	56.67 ± 10.60	0.87
Code Substitution Delayed	50.00 ± 14.62	45.82 ± 16.43	0.16
Mathematical Processing	21.17 ± 6.40	19.56 ± 5.40	0.06
Matching to Sample	39.38 ± 12.48	35.40 ± 10.05	0.04*

*univariate statistical significance but not significant after correction for multiple comparisons.

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Table S9. Regions of Interest with significant FA group differences			
Region of Interest	FA mTBI (mean ± SD) N=95	FA CTL (mean ± SD) N=101	P Value (Student's t)
Superior Longitudinal Fasciculus Right	0.3933±0.0220	0.4050±0.0229	0.0003 *
Middle Cerebellar Peduncle Left	0.4119±0.0240	0.4222±0.0279	0.0026[U] *
Superior Cerebellar Peduncle Left	0.4549±0.0231	0.4628±0.0263	0.0258
Middle Fronto-orbital gyrus Right	0.3071±0.0139	0.3132±0.0186	0.0102
Superior Corona Radiata Right	0.3546±0.0237	0.3637±0.0228	0.0071
Superior Corona Radiata Left	0.3875±0.0232	0.3944±0.0224	0.0358
Posterior Corona Radiata Left	0.3715±0.0264	0.3794±0.0267	0.0379
Posterior Limb Internal Capsule Right	0.5682±0.0224	0.5762±0.0238	0.0170
Posterior Limb Internal Capsule Left	0.5284±0.0228	0.5354±0.0259	0.0485

[U] Mann Whitney U; FA Fractional Anisotropy; mTBI mild traumatic brain injury; CTL control

P values indicate univariate results

*Statistically significant after false discovery rate correction for multiple comparisons across 56 regions of interest.

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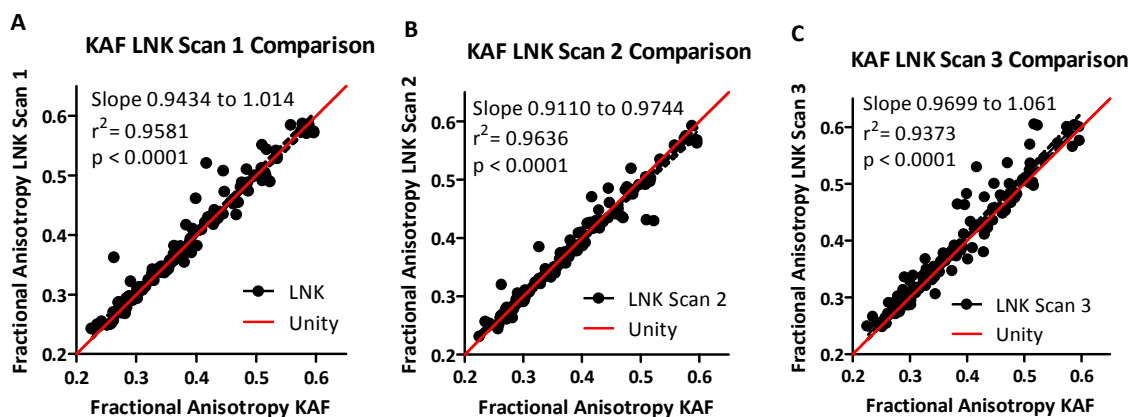
Figure S1. Fractional Anisotropy Site Comparisons: Three MRI-DTI scans (A, B, C) acquired at LNK compared to a single scan acquired at KAF using the same healthy control show that FA comparisons are fairly centered on the line of unity, indicating no significant site effect on DTI acquisition across 56 regions of interest.

A Alteration of Consciousness

B Anterograde Amnesia

C Retrograde Amnesia

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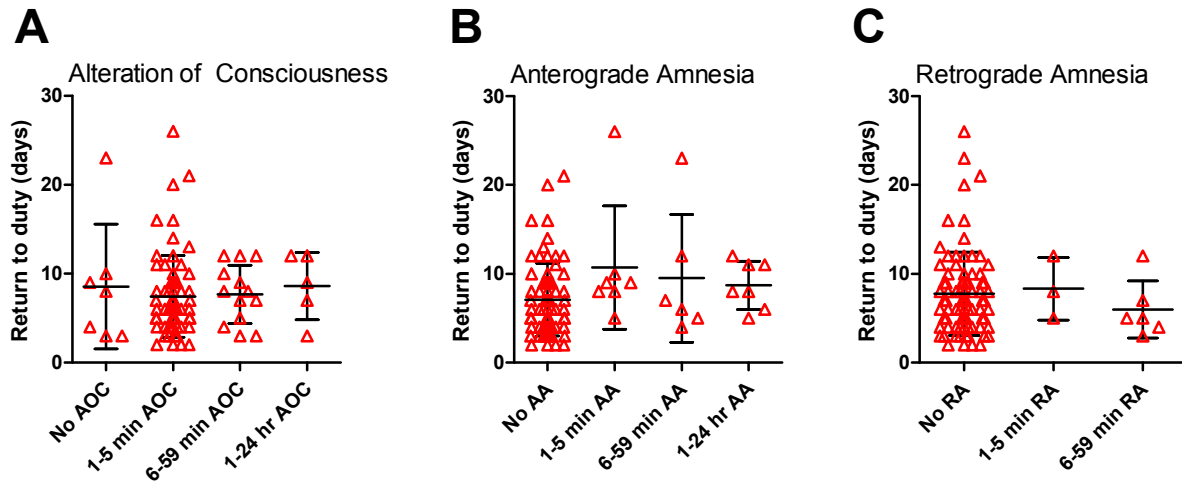
Figure S2. No Relationship Between Return to Duty Time and Self-Reported Alteration of Consciousness or Amnesia. A. No relationship with alteration of consciousness (AOC). 1-way ANOVA $F_{(3,88)}=0.21$, p=0.89. **B.** No relationship with anterograde amnesia (AA: for events after the injury). 1-way ANOVA $F_{(3,87)}=1.9$, p=0.13. Data was not available for 1 subject. No relationship with retrograde amnesia (RA: for events before the injury). 1-way ANOVA $F_{(2,88)}=0.44$, p=0.64. Bars shown indicate means and standard deviations.

158

159 **SUPPLEMENTAL DISCUSSION** There are several aspects of this study that warrant further

160 discussion in relation to the previous literature and to inform future investigations.

161 <u>Subject Characteristics</u>

162 The exact mechanism of injury is difficult to ascertain in a chaotic combat environment.

163 Thus, we cannot determine with certainty whether the subjects in the study sustained blast only

164 or blast+impact TBI. Nonetheless, 42 mTBI participants reported a pure blast injury, 53 reported

165 an associated head impact (e.g. motor vehicle rollover, being struck or striking an object) and 22

166 could not recall a possible compounding mechanism. A total of 40 mTBI participants sustained

167 dismounted blast exposures (e.g. on foot patrol) while 55 were mounted (inside a tactical

168 vehicle).

169 <u>Additional Limitations</u>

170 Level of education, which may impact performance on neurocognitive testing and

171 vulnerability to mood disorders following TBI, was not collected in our study. The effects of age

172 and gender on ANAM performance are well documented[13] while the influence of education is

173 less well studied. Although SRT and PRT reflect reaction time with little cognitive processing,

174 other ANAM cognitive modules may be more heavily influenced by education level. In order to

175 account for this potential demographic confounder, we used individualized ANAM baselines as

176 opposed to reference group normative data and replicated the results by conducting

177 demographically matched subgroup comparisons using only enlisted men. The effect of

178 education on ANAM performance appears to be minimal once age is controlled[8].

179 The injured cohort may not be representative of the combat mTBI service members at

180 large because recruitment was restricted to the two highest level medical treatment facilities in

181 Afghanistan. However, the demographic characteristics are similar to those of other studies of

182 combat mTBI[14,15]. The mean recovery time is comparable to those reported by other concussion

183 care centers in Afghanistan[16] (O Adam, D Rivet; unpublished data). The majority of mTBI

184 patients treated at KAF and LNK were transported directly from point of injury, and therefore

185 comparable to the patient population of other concussion care centers in Afghanistan. The most

186 refractory mTBI patients referred from lower level concussion care centers in Afghanistan would

187 not have been eligible for this study based on the time lapsed from their injury of over 7 days.

16

188   The collection of accurate data regarding loss or alteration of consciousness and PTA

189   presents challenges when head injuries occur in a chaotic combat environment, impacting data

190   reliability. Efforts were made to minimize such recall and documentation errors. The information

191   was extracted directly from participants within days from injury by study staff experienced in the

192   evaluation of mTBI, corroborated by third party accounts (combat medics or fellow service

193   members present at the site of injury) and verified using combat records whenever possible.

194   Our conventional MRI protocol included GRE. The more sensitive susceptibility

195   weighted imaging has gradually become the norm in clinical MR imaging in mTBI. However,

196   data file sizes too large for transfers out of Afghanistan and scan duration were the main limiting

197   factors taken into consideration in the decision to favor one blood-sensitive sequence over the

198   other.

199

200   <u>Relationship to Previous Imaging Studies</u>

201   Neuroimaging has long played an important role in TBI. Computer tomography (CT) is

202   widely available, including at combat hospitals in Afghanistan, and has short scan times. While it

203   is very useful in screening out more severe head injuries that require medical evacuation and

204   possible neurosurgical intervention, it is of limited utility in mTBI. Magnetic Resonance Imaging

205   (MRI) is less widely available and involves longer scan times. In civilian settings, conventional

206   brain MRI in the acute and subacute stages of mTBI can detect infrequent but clinically pertinent

207   abnormalities with prognostic significance such as brain contusions and hemorrhagic axonal

208   injury[17]. However, our findings are in line with numerous other studies of normal conventional

209   MR imaging in mTBI[18], suggesting its limited clinical utility in this mildly injured patient

210   population

211   In a previous military study performed at LRMC[19], 18/63 injured participants were found

212   to have DTI changes on a single subject basis. In contrast, none of the subjects in this study

213   could be determined unambiguously to have been injured based on DTI. The difference between

214   the two studies is likely attributable to dissimilarities in mTBI injury severity and possibly

215   timing. The LRMC cohort consisted entirely of service members injured severely enough to be

216   medically evacuated out of combat, whereas the subjects in this study had a 97% return to duty

217 rate. Furthermore, the LRMC subjects were imaged within a median time of 14 days post-injury

218 (range of one to 90 days), whereas in this study the time to imaging from injury was on average 3

219 days. Animal studies and theoretical considerations indicated that DTI should be similarly

220 sensitive at a range of acute time points[20,21] but this has not been definitively established in

221 human mTBI patients. While both studies used similar imaging protocols (MRI 1.5T, isometric

222 voxel sizes of 2.5mm), the Avanto scanners used at LRMC may have had greater stability than

223 the Achieva scanners in mobile trailers employed in this study.

224 The extent to which the MCP is specifically vulnerable to blast related brain injuries is

225 not entirely clear. While most DTI studies have not reported abnormalities in this region, one

226 study reported that cerebellar white matter DTI changes correlated modestly with impact severity

227 in sports-related mTBI[22].

228

229 Relationship to Previous Clinical Studies

230 There is a paucity of studies examining symptoms systematically and prospectively

231 across multiple domains (somatic, cognitive, behavioral) in the acute stages of combat mTBI. In

232 our study, the mTBI participants reported significantly more severe concussive symptoms,

233 primarily somatic symptoms including headache, sensitivity to noise and dizziness. These results

234 are consistent with prior findings of the most frequently endorsed symptoms acutely after injury

235 of headache, dizziness, tinnitus and auditory symptoms[15,23]. The frequency of LOC and alteration

236 of consciousness in our cohort was higher than prior studies[15,23] likely explained by

237 dissimilarities in the study cohorts as well as methodology. LOC, alteration of consciousness and

238 PTA are the most commonly used symptoms in the diagnosis and grading of mTBI[24-26]. They are

239 also used by the Department of Defense in determining eligibility of service members for

240 military awards such as Purple Heart. However, controversy exists regarding their reliability as

241 predictors of recovery or future post-concussive syndrome (PCS) and disability. Our findings,

242 contrary to other studies of mTBI in military veterans of wars in Iraq and Afghanistan[23,27] found

243 no or weak correlations between loss or alteration of consciousness and recovery time. In sports

244 mTBI, a greater number and severity of symptoms acutely after trauma are predictors of a

245 prolonged recovery[28]. In our study, the total RPCSQ score correlated well with recovery time.

18

246 This correlation may be construed to be the result of circular logic considering that the decision
247 of return to duty was based on patient symptom reporting. However, the return to duty decision
248 was based not on the initial RPCSQ score, but on symptom resolution, independent of initial
249 symptom severity. A quantitative approach to symptom recording using standardized symptom
250 inventories in the acute stages of combat mTBI may help predict recovery in blast-related mTBI.
251 Also, traditional measures of loss or alteration of consciousness and amnesia may not be
252 sufficient in addressing mTBI severity, specifically related to length of recovery.

253   When somatic, cognitive and behavioral symptoms were tested together using a general
254 symptom inventory (RPCSQ), behavioral symptom group comparisons recorded smaller effect
255 sizes relative to somatic and cognitive symptoms acutely following the injury. A heightened
256 perception of somatic relative to behavioral symptoms is consistent with findings of prior
257 studies[23,27]. When behavioral symptoms were assessed independently on measures of acute stress
258 disorder/PTSD and depression/anxiety, group differences were sizable and significant.
259 Unaccounted premorbid group differences in the level of combat intensity, prior history of
260 unreported mTBIs and undiagnosed or unreported preexisting mental health conditions may have
261 been contributors. However, an independent effect of mTBI cannot be excluded. There is a
262 rapidly growing body of evidence supporting a strong association between combat mTBI and
263 subsequent development of mental health symptoms, including PTSD, depression and high
264 combat stress in veterans of the conflicts in Iraq and Afghanistan[23,29]. Even when accounting for
265 other factors, such as a predeployment history of TBI, PTSD and combat intensity, TBI suffered
266 during a most recent deployment remains the strongest predictor for post-deployment PTSD
267 symptoms[30]. However, not all mTBI patients develop PTSD and it is unclear which specific early
268 aspects of mTBI contribute to this increased risk. In our study, the PCLM and to a lesser extent
269 the BDI correlated with recovery time. Quantitative behavioral assessments such as the PCLM
270 performed in the acute stages of mTBI, might prove valuable tools for better stratifying these
271 patients early for risk of future PTSD. Interestingly, despite robust and significant differences in
272 PCLM and BDI scores between mTBI and controls, means fell below threshold scores for PTSD
273 and major depression disorder screening recommended in TBI patients[4,31]. These findings
274 suggest that lower cut-point values may be clinically meaningful when used as predictive
275 markers for mTBI recovery acutely.

276   Cognitive deterioration compared to individual baselines acutely following trauma are in

277   line with prior studies of computerized neurocognitive assessment validity in mTBI screening in

278   the first week after injury[14,16,27]. The largest effect size was demonstrated for SRT, which also

279   correlated with mTBI recovery time, lending support to findings of prior studies that found SRT

280   to be a sensitive tool for mTBI screening and recovery tracking[16,27,32]. Computerized

281   neurocognitive assessment tools, specifically tasks that measure or incorporate reaction time,

282   appear to be valuable tools that can be used by clinicians to predict recovery acutely in mTBI

283   patients.

284

SUPPLEMENT REFERENCES

285   **SUPPLEMENT REFERENCES**

286   1.   King NS, Crawford S, Wenden FJ, Moss NE, Wade DT. The Rivermead Post Concussion Symptoms
287   Questionnaire: a measure of symptoms commonly experienced after head injury and its
288   reliability. *Journal of neurology.* Sep 1995;242(9):587-592.

289   2.   Yeager DE, Magruder KM, Knapp RG, Nicholas JS, Frueh BC. Performance characteristics of the
290   posttraumatic stress disorder checklist and SPAN in Veterans Affairs primary care settings.
291   *General hospital psychiatry.* Jul-Aug 2007;29(4):294-301.

292   3.   Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression.
293   *Archives of general psychiatry.* Jun 1961;4:561-571.

294   4.   Homaifar BY, Brenner LA, Gutierrez PM, et al. Sensitivity and specificity of the Beck Depression
295   Inventory-II in persons with traumatic brain injury. *Archives of physical medicine and*
296   *rehabilitation.* Apr 2009;90(4):652-656.

297   5.   Keane T, Fairbank J, Caddell J, Zimering R, Taylor K, Mora C. Clinical evaluation of a measure to
298   assess combat exposure. *Psychological Assessment.* 1989(1):53-55.

299   6.   Cernich A, Reeves D, Sun W, Bleiberg J. Automated Neuropsychological Assessment Metrics
300   sports medicine battery. *Archives of clinical neuropsychology : the official journal of the National*
301   *Academy of Neuropsychologists.* Feb 2007;22 Suppl 1:S101-114.

302   7.   Thorne DR. Throughput: a simple performance index with desirable characteristics. *Behavior*
303   *research methods.* Nov 2006;38(4):569-573.

304   8.   Roebuck-Spencer TM, Vincent AS, Schlegel RE, Gilliland K. Evidence for added value of baseline
305   testing in computer-based cognitive assessment. *Journal of athletic training.* Jul-Aug
306   2013;48(4):499-505.

307   9.   Tombough T. The Test of Memory Malingering. *Multi-Health Systems.* 1996.

308   10.   Guskiewicz KM, Ross SE, Marshall SW. Postural Stability and Neuropsychological Deficits After
309   Concussion in Collegiate Athletes. *Journal of athletic training.* Sep 2001;36(3):263-273.

310   11.   Lynn WJ. Policy Guidance for Management of Concussion/Mild Traumatic Brain Injury in the
311   Deployed Setting. In: Readiness USoDfPa, ed: Department of Defence; 2010.

312   12.   Zhang Y, Zhang J, Oishi K, et al. Atlas-guided tract reconstruction for automated and
313   comprehensive examination of the white matter anatomy. *NeuroImage.* Oct 1 2010;52(4):1289-
314   1301.

315   13.   Vincent AS, Roebuck-Spencer T, Gilliland K, Schlegel R. Automated Neuropsychological
316   Assessment Metrics (v4) Traumatic Brain Injury Battery: military normative data. *Military*
317   *medicine.* Mar 2012;177(3):256-269.

318   14.   Coldren RL, Russell ML, Parish RV, Dretsch M, Kelly MP. The ANAM lacks utility as a diagnostic or
319   screening tool for concussion more than 10 days following injury. *Military medicine.* Feb
320   2012;177(2):179-183.

321   15.   Luethcke CA, Bryan CJ, Morrow CE, Isler WC. Comparison of concussive symptoms, cognitive
322   performance, and psychological symptoms between acute blast-versus nonblast-induced mild
323   traumatic brain injury. *J Int Neuropsychol Soc.* Jan 2011;17(1):36-45.

324   16.   Norris JN, Carr W, Herzig T, Labrie DW, Sams R. ANAM4 TBI reaction time-based tests have
325   prognostic utility for acute concussion. *Military medicine.* Jul 2013;178(7):767-774.

326   17.   Yuh EL, Mukherjee P, Lingsma HF, et al. Magnetic resonance imaging improves 3-month
327   outcome prediction in mild traumatic brain injury. *Annals of neurology.* Feb 2013;73(2):224-235.

328   18.   Shenton ME, Hamoda HM, Schneiderman JS, et al. A review of magnetic resonance imaging and
329   diffusion tensor imaging findings in mild traumatic brain injury. *Brain imaging and behavior.* Jun
330   2012;6(2):137-192.

331 19. Mac Donald CL, Johnson AM, Cooper D, et al. Detection of blast-related traumatic brain injury in
332   U.S. military personnel. *The New England journal of medicine.* Jun 2 2011;364(22):2091-2100.
333 20. Mac Donald CL, Dikranian K, Bayly P, Holtzman D, Brody D. Diffusion tensor imaging reliably
334   detects experimental traumatic axonal injury and indicates approximate time of injury. *J*
335   *Neurosci.* Oct 31 2007;27(44):11869-11876.
336 21. Mac Donald CL, Dikranian K, Song SK, Bayly PV, Holtzman DM, Brody DL. Detection of traumatic
337   axonal injury with diffusion tensor imaging in a mouse model of traumatic brain injury.
338   *Experimental neurology.* May 2007;205(1):116-131.
339 22. McAllister TW, Ford JC, Flashman LA, et al. Effect of head impacts on diffusivity measures in a
340   cohort of collegiate contact sport athletes. *Neurology.* Jan 7 2014;82(1):63-69.
341 23. Eskridge SL, Macera CA, Galarneau MR, et al. Influence of combat blast-related mild traumatic
342   brain injury acute symptoms on mental health and service discharge outcomes. *Journal of*
343   *neurotrauma.* Aug 15 2013;30(16):1391-1397.
344 24. Cantu RC. Return to play guidelines after a head injury. *Clinics in sports medicine.* Jan
345   1998;17(1):45-60.
346 25. Harmon KG. Assessment and management of concussion in sports. *American family physician.*
347   Sep 1 1999;60(3):887-892, 894.
348 26. Practice parameter: the management of concussion in sports (summary statement). Report of
349   the Quality Standards Subcommittee. *Neurology.* Mar 1997;48(3):581-585.
350 27. Kelly MP, Coldren RL, Parish RV, Dretsch MN, Russell ML. Assessment of acute concussion in the
351   combat environment. *Archives of clinical neuropsychology : the official journal of the National*
352   *Academy of Neuropsychologists.* Jun 2012;27(4):375-388.
353 28. Harmon KG, Drezner J, Gammons M, et al. American Medical Society for Sports Medicine
354   position statement: concussion in sport. *Clinical journal of sport medicine : official journal of the*
355   *Canadian Academy of Sport Medicine.* Jan 2013;23(1):1-18.
356 29. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S.
357   Soldiers returning from Iraq. *The New England journal of medicine.* Jan 31 2008;358(5):453-463.
358 30. Yurgil KA, Barkauskas DA, Vasterling JJ, et al. Association Between Traumatic Brain Injury and
359   Risk of Posttraumatic Stress Disorder in Active-Duty Marines. *JAMA psychiatry.* Dec 11 2013.
360 31. PTSD NCf. PTSD: National Center for PTSD. http://www.ptsd.va.gov/, 2014.
361 32. Hugenholtz H, Stuss DT, Stethem LL, Richard MT. How long does it take to recover from a mild
362   concussion? *Neurosurgery.* May 1988;22(5):853-858.

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Acute Post-Traumatic Stress Symptoms and Age Predict Outcome in Military Blast Concussion

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Title: Acute Post-Traumatic Stress Symptoms and Age Predict Outcome in Military Blast Concussion

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ABSTRACT

High rates of adverse outcomes have been reported following blast-related concussive traumatic brain injury (TBI) in US Military personnel, but the extent to which such adverse outcomes can be predicted acutely after injury is unknown.   We performed a prospective, observational study of US Military personnel with blast-related concussive TBI (n=38) and controls (n=34) enrolled between March and September 2012. Importantly all subjects returned to duty and did not require evacuation. Subjects were evaluated acutely 0-7 days after injury at two sites in Afghanistan and again 6-12 months later in the United States. Acute assessments revealed heightened post-concussive, post-traumatic stress, and depressive symptoms along with worse cognitive performance in TBI subjects. At 6-12 month follow up, 63% of TBI subjects and 20% of controls had moderate overall disability. TBI subjects showed more severe neurobehavioral, post-traumatic stress, and depression symptoms along with more frequent cognitive performance deficits and more substantial headache impairment than controls. Logistic regression modeling utilizing only acute measures identified that a diagnosis of TBI, older age, and more severe post-traumatic stress symptoms provided a good prediction of later adverse global outcomes (area under the receiver-operating characteristic curve = 0.84). Thus, US military personnel with concussive blast-related TBI in Afghanistan who returned to duty still fared quite poorly on many clinical outcome measures 6-12 months following injury. Poor global outcome appears to be largely driven by psychological health measures, age, and TBI status. The effects of early interventions and longer term implications of these findings are unknown.

Keywords: Traumatic Brian Injury, Post-traumatic Stress, Clinical Outcome, Concussion

INTRODUCTION

In the US military, it is estimated that roughly 20% of the deployed force suffered a head injury(Taniellian and Jaycox, 2008) in the wars in Iraq and Afghanistan. Of these, 83.3% endured a mild, uncomplicated TBI or concussion(Casscells, 2007, DVBIC, 2013), the long term impact of which is just beginning to be appreciated. Previous studies have reported that 78% of all combat casualties can be accounted for by explosive mechanisms(Owens *et al.*, 2008) and 88% of all patients referred to second echelon treatment centers for further care were due to blast exposure(Warden, 2006).

Prior work has attempted to understand the sequelae of these blast-related "mild"/concussive brain injuries but it has been predominantly limited to later stage evaluations(Verfaellie *et al.*, 2013, Fischer *et al.*, 2014), retrospective review(Galarneau *et al.*, 2008, Cooper *et al.*, 2011, Eskridge *et al.*, 2013, Kontos *et al.*, 2013) or biased towards patients requiring medical evacuation(Mac Donald *et al.*, 2014, Macdonald *et al.*, 2014) which may not be representative of the larger population of concussive TBI patients treated directly in the combat theater. Few studies have prospectively examined patients acutely in theater(Luethcke *et al.*, 2011, Coldren *et al.*, 2012, Norris *et al.*, 2013), but none to our knowledge, have completed longitudinal evaluations to elucidate the relationship between acute characteristics and long-term outcomes. The objective of the current study was to clinically assess service members from the point of injury in Afghanistan and follow them to 6-12 month outcome back in the United States in order to determine if acute clinical measures could be used to predict brain injury sequelae and overall outcome.

MATERIALS and METHODS

Participants were initially enrolled at Kandahar Air Field (KAF) and Camp Leatherneck (LNK) in Afghanistan between March and September 2012 as part of a prospective, observational, research study. Through this ongoing collaborative effort, a subset of these subjects were also enrolled in a 6-12 month follow up at Washington University in Saint Louis, Missouri (PI: D. Brody). This group was randomly selected from the larger cohort enrolled in Afghanistan from those who consented to participate in a long term follow up examination back in the United States. In total, 72 subjects, 34 control, and 38 TBI subjects completed both the initial study in Afghanistan and the follow up evaluation at Washington University in Saint Louis 6-12 months later. Demographic characteristics were similar but not identical between groups. (**Table 1**). Within each group, there were no significant differences in demographic information comparing those who followed up to those who only completed the initial study (**Supplementary Table 1**).

Subjects: Inclusion criteria for the TBI group were as follows: 1) clinical diagnosis of "mild"/concussive TBI from a blast exposure within the past 7 days made by a trained, board-certified Neurologist or Neurosurgeon based on the criteria from the American Congress of Rehabilitation Medicine 1993, 2) injury from blast exposure within 7 days of enrollment, 3) US military, 4) ability to provide informed consent in person, 5) no contraindications to MRI such as retained metallic fragments, 6) no prior history of moderate to severe TBI based on Department of Defense criteria, 7) agreement to communicate by telephone or email and then travel to Washington University in Saint Louis for in-person follow-up. Inclusion criteria for the control group were the same except for a negative assessment for TBI and no history of blast exposure.

The research protocol was approved by the Human Research Protection Office at Washington University. This study was conducted under a protocol reviewed and approved by the US Army Medical Research and Materiel Command Institutional Review Board and in accordance with the approved protocol.

Written informed consent was obtained from all subjects in person at KAF or LNK; no surrogate consent was allowed. All subjects had a Glasgow Coma Scale of 15 at the time of consent and competence to provide informed consent was assessed in a standardized fashion based on responses to questions regarding the purpose of the study, expected requirements for participation, and potential risks. Additional written consent was obtained from the subjects at the time of follow-up at Washington University. Active duty military subjects were not paid for participation, though travel expenses to St Louis were covered. Subjects not on active military duty status at the time of follow-up in St Louis were paid $240 plus travel expenses for participation.

For the TBI group, no intracranial abnormalities were detected on non-contrast head CT. All TBI subjects met the DoD criteria for uncomplicated 'mild' TBI. All clinical histories were verified by study personnel taking additional clinical history and reviewing medical records. None that screened positive for TBI at initial enrolment in Afghanistan were determined not to have had a TBI at follow up. Mean time from injury to enrolment was 3.76 ± 1.74 days with a total range of 0-7 days.

Initial Clinical Assessments: At the time of enrollment in Afghanistan, the following battery of assessments were completed: TBI subjects completed the military acute concussion evaluation (MACE) (Dempsey *et al.*, 2009) which is a brief cognitive test to evaluate orientation, immediate verbal memory, concentration, and short term delayed verbal memory. Both TBI and control participants also completed the Rivermead Post-Concussion Symptom Questionnaire (RPCSQ)(King *et al.*, 1995), Post-traumatic Stress Disorder Check List Military (PCL-M)(Yeager *et al.*, 2007), Beck Depression Inventory (BDI)(Beck *et al.*, 1961, Homaifar *et al.*, 2009), Combat Exposures Scale (CES)(Keane *et al.*, 1989), Balance Error Scoring System (BESS)(Guskiewicz *et al.*, 2001), Automated Neurocognitive Assessment Metrics – Traumatic Brain Injury Military Version 4 (ANAM)(Cernich *et al.*, 2007) and the Test of Memory Malingering (TOMM)(Tombough, 1996).

The severity of post-concussive symptoms was measured by the Rivermead Post-Concussion Symptom Questionnaire (RPCSQ)(King *et al.*, 1995), a self-administered questionnaire assessing 16 post-concussive symptoms on a scale of 0 (none) to 4 (severe) covering three domains: cognitive (cognitive and concentration difficulties), emotional (anxiety, restlessness and depression) and somatic (fatigue, headache, dizziness, nausea, sleep disturbance and changes in vision).

Symptoms of post-traumatic stress disorder (PTSD), anxiety and mood changes were assessed using the Post-traumatic Stress Disorder Check List-Military (PCL-M)(Yeager *et al.*, 2007) and Beck Depression Inventory (BDI)(Homaifar *et al.*, 2009). The PCL-M is a 17 item self-administered questionnaire tying symptom ratings to events experienced during military service, using a scale of 1 (not at all) to 5 (extremely). The BDI is a self-administered 21 item questionnaire corresponding to symptoms of depression rated on a severity scale of 0 (no symptoms) to 3 (severe symptoms).

Reports of wartime stressors experienced by combatants were measured using the Combat Exposure Scale (CES)(Keane *et al.*, 1989), a 7-item scale with 5-response points (1 is "no", 2 is "1 to 3 times", 3 is "4 to 12 times", 4 is "13 to 50 times", and 5 is "51+ times"), each item being weighted differently based on the severity of the experience, the total scores ranging from 0−41.

Severity of balance impairment was tested using the Balance Error Scoring System (BESS)(Guskiewicz *et al.*, 2001). The BESS is a clinician administered balance test which includes single, double and tandem stance assessment on firm and foam (unstable) surfaces, each held for 20 seconds, with the participant's hands on the hips and eyes closed. The final score is a representation of cumulative errors.

The Automated Neurocognitive Assessment Metrics – Traumatic Brain Injury Military Version 4 (ANAM)(Cernich *et al.*, 2007) is sanctioned by the Department of Defense for baseline neurocognitive assessment in all deploying troops and it is also available in the deployed setting. The ANAM includes a

collection of cognitive modules. The simple reaction time (SRT) and repeat simple reaction time (SRTR) for basic neural processing are expressed in milliseconds, lower scores indicating a faster reaction time. Code substitution learning (CSL) for associative learning, procedural reaction time (PRT) for processing speed, mathematical processing (MTP) for working memory, matching to sample (MTS) for visual spatial memory and code substitution delayed (CSD) for delayed memory are expressed as percentage of correct answers in 60 seconds, higher scores indicating better performance. The cognitive modules are preceded by sleepiness and mood scales.

Level of examination effort was measured using the Test of Memory Malingering (TOMM)(Tombough, 1996), which is a clinician administered tool designed to assist in determining effort(Tombough, 1996). The testing paradigm involved a single TOMM trial for subjects with a score higher or equal to 45 and a second trial for subjects with a first TOMM score lower than 45. Subjects with TOMM score lower than 45 on both consecutive TOMM trials were excluded from analysis for possible poor effort during testing.

All exams and questionnaires were administered in a quiet, private room. Total examination time took approximately 1 hour and 15 minutes.

Follow Up Clinical Assessments: The in-person clinical evaluations at Washington University included a standardized neurological exam, neuropsychological test battery, and psychiatric evaluation. Both control and TBI subjects were screened at follow up for interim head injuries or blast exposure associated with alteration or loss of consciousness or amnesia. None of the participants in either group were found to have suffered additional TBI between the initial enrolment and follow up visit. Overall clinical outcome was assessed using the Glasgow outcome scale extended (GOS-E)(Wilson *et al.*, 1998, Pettigrew *et al.*, 2003). The GOS-E is scored from 1-8: 1=dead, 2=vegetative, 3-4=severe disability, 5-6=moderate disability, 7-8=good recovery. Moderate disability (GOS-E = 5-6) is defined as one or more of the following: 1) inability to work to previous capacity 2) inability to resume the majority of regular social and leisure activities outside the home 3)

psychological problems which have frequently resulted in ongoing family disruption or disruption of friendships. Severe disability is defined as reduced ability to perform activities of daily living such that supervision is required. Standardized, structured interviews were performed according to published guidelines (Wilson *et al.*, 1998).

The neurological evaluation included Neurobehavioral Rating Scale-Revised (NRS) (Levin *et al.*, 1987), a structured interview designed for TBI patients, two headache interviews to capture recent headache frequency and intensity, Migraine Disability Assessment (MIDAS) and Headache Impact Test (HIT-6)(Stewart *et al.*, 1999, Kosinski *et al.*, 2003) , and the Neurological Outcome Scale for TBI (NOS) (McCauley *et al.*, 2010, Wilde *et al.*, 2010, Wilde *et al.*, 2010), a structured neurological examination targeting deficits frequently experienced by TBI patients. The Neurobehavioral Rating Scale – Revised was scored using a previously published 5 sub-domain model(McCauley *et al.*, 2001).

The neuropsychological test battery consisted of the Conner's Continuous Performance Test II (Conners and Staff., 2000), a computer-based assessment of attention, impulsivity, reaction time, and vigilance; the California Verbal Learning Test II (Delis D *et al.*, 2000), an assessment of verbal declarative memory; the 25 hole grooved pegboard test (Matthews C and Kløve, 1964), an assessment of upper extremity motor speed and coordination; a timed 25 foot walk; the Trail Making test (Reitan, 1992), an assessment of visual scanning, coordination and mental flexibility; the Controlled Oral Word Association test (Benton A *et al.*, 1983), an assessment of verbal fluency; the Wechsler Test of Adult Reading (Wechsler, 2001) as an estimate of pre-injury verbal intelligence; the Iowa Gambling Test(Bechara *et al.*, 1994), a computer-based assessment of impulsivity and decision making; the D-KEFS Color-Word Interference Test (Delis, 2001), an multi-domain assessment of executive function similar to the Stroop test; and the Ruff-Light Trail Learning Test(Ruff *et al.*, 1996), an assessment of visual-spatial learning and memory. A relatively easy forced choice test embedded in the California Verbal Learning Test was used to assess adequacy of effort.

The psychiatric evaluation included the Clinician-Administered PTSD Scale for DSM-IV (CAPS) (Weathers *et al.*, 2001), Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979, Snaith *et al.*, 1986), Combat Exposure Scale (CES)(Keane *et al.*, 1989), and the Michigan Alcohol Screening Test(Selzer, 1971). The CAPS was scored using standard scoring rules from the Blake et al, National Center for Post-traumatic Stress Disorder, July 1998 revision.

The standardized neurological evaluation required approximately 1 hour per subject. The psychiatric assessments required approximately 2 hours per subject, and the neuropsychological battery required approximately 2 hours per subject. Subjects took all medications as prescribed by their clinical providers. All tests were performed between 9 am and 5 pm in private, quiet, well-lighted rooms. All examiners were blinded to other clinical information and imaging results, though in the course of the interviews it often became clear whether the subjects were in the TBI or control group based off their endorsements of prior events. All examiners were clinicians who underwent standardized training in administering the assessments.

Safety and Data Monitoring: Subjects were assigned a random 4 digit code number to protect confidentiality and all research data was identified by code number only. A board certified psychiatrist (Dr. Nelson) was immediately available in case the CAPS examination exacerbated PTSD symptoms. No exacerbations requiring medical intervention occurred, though additional support from study staff was required on several occasions.

Statistical Analyses: All data was analyzed using Statistica 10.0 (Statsoft Inc). Continuous variables have been summarized as mean ± standard deviation unless otherwise specified. The normal distribution of each continuous variable was assessed using the Shapiro-Wilk test. For normally distributed variables, student's t tests were used to compare groups. For non-normally distributed variables, Mann-Whitney U (MWU) tests were used. Although we pre-specified the hypothesis that TBI subjects would have worse outcomes than controls, we have reported results of two-sided tests throughout to be conservative. Nominal p-values have been reported,

but only considered significant using a Bonferroni correction for multiple comparisons with a significance level of 0.05. The number of tests within each domain of assessment was used to calculate the Bonferroni correction.

Data from neuropsychological testing was further analyzed for the expected occurrence by chance that a subject would have multiple abnormal evaluations. The binomial distribution was used with p=0.02275 for the (n=18) neuropsychological variables examined. Prior to this analysis, all neuropsychological variables were confirmed to be statistically independent as is required by the assumptions of this approach.

Correlation analysis was employed to investigate the relationship between initial and follow up data. Nonparametric rank-based Spearman correlations were utilized. Pearson correlations were attempted, but the residuals were not normally distributed as determined by the Shapiro Wilk test.

Logistic regression analysis were utilized to explore the relationship between a dichotomized measure of clinical outcome (GOS-E), clinical measures 6-12 months post injury, and acute clinical data collected at 0-7 days. The Statistica 10.0 'generalized linear/nonlinear model building' algorithm was used with the selection of the 'logit' link function for logistic regression. The algorithm generated a distinct model for each possible subset of quantitative measures of specific symptoms and impairments. Models were then ranked by Akaike information criterion. Receiver-operating characteristic (ROC) curves were generated for the top ranked models.

RESULTS

Acute Clinical Measures

Assessments performed 0-7 days post-injury indicated more severe symptoms and worse performance in the TBI group than in controls (**Fig 1, Supplementary Fig 1**). TBI subjects had significantly higher scores on the Rivermead Post Concussion Symptoms Questionnaire (**Fig 1A**) than controls (p=0.0000002, Mann-Whitney U). In contrast, there were no significant differences in performance on the Balance Error Scoring System assessment (**Fig 1B**), a test of postural stability (p=0.36, Mann-Whitney U). Both groups, control and TBI subjects, performed worse than the normative performance score of college varsity athletes (dashed line, **Fig 1B**). TBI subjects also endorsed significantly worse symptoms on measures of PTSD (p=0.000002, Mann-Whitney U) and depression (p=0.0006, Mann-Whitney U) during this acute phase following injury (**Fig 1C to D**).

In addition, TBI subjects generally performed worse than controls on the Automated Neurocognitive Assessment Metrics (ANAM) test.after exposure to brain injury in Afghanistan compared to their individual pre-deployment baseline (**Supplementary Fig 1**). This assessment was completed before they deployed to combat theater and then repeated in theater 0-7 days post-injury or at the point of enrollment for the control subjects. Scores represent the 'delta' of each subject's performance compared to his or her own baseline testing before deployment. Specifically, performance on simple reaction time (p=0.002, **Supplementary Fig 1A**), procedural reaction time (p=0.004, **Supplementary Fig 1D**), ode substitution learning (p=0.0012, **Supplementary Fig 1E**), mathematical processing (p=0.002, **Supplementary Fig 1G**) and match to sample (p=0.0006, **Supplementary Fig 1H**) were significantly worse in TBI subjects 0-7 days post-injury (Mann-Whitney U). The acute clinical symptoms and deficits in this subgroup of subjects who participated in the complete longitudinal study were similar to those in the entire cohort. Self-reported sleep deprivation was also substantially worse in the TBI subjects than controls (p=0.01, **Supplementary Fig 1C**).

Other injuries sustained at the time of mTBI were all very minimal and all subjects were returned to duty. Median time to return to duty was 7 days (range 2-23). All subjects had an Injury Severity Score (Baker *et al.*, 1974) (ISS) of zero meaning there were no injuries to the head and neck, face, chest, abdomen, extremity or external as scored by the clinicians who recorded the ISS..

Chronic Clinical Measures

At 6-12 months post-injury, global outcomes as measured by the Glasgow Outcome Scale-Extended (GOSE) were significantly worse in TBI subjects than in controls (p=0.0001, Mann-Whitney U, **Fig 2**). The majority of TBI subjects had moderate disability (GOS-E = 5-6). This was surprising given the relatively mild TBI sustained in these non-medically evacuated service members, but in line with previous work reporting GOS-E disability in service members medically evacuated from the combat theater for blast plus impact complex concussive TBI (Macdonald *et al.*, 2014). In a similar fashion, TBI subjects were found to have worse impairment than controls on the NRS (p=0.00006, Mann-Whitney U, **Fig 3A**). Significant impairments were observed in the executive/cognitive (p=0.001, **Fig 3B**) and mood/affect (p=0.002, **Fig 3C**) sub-domains of the NRS. In contrast, there were no significant differences in neurological examination by the NOS-TBI (p=0.81, Chi-square 0 vs. 1 or more, **Supplementary Fig 2**). Most subjects in both groups (25 of 34 controls and 27 of 38 TBI subjects) had no abnormalities on neurological examination. In controls, 6 subjects had olfactory deficits, 1 had a partial visual field deficit, 1 had a partial gaze deficit, and 1 had partial sensory loss of a lower limb. In TBI subjects 6 had olfactory deficits and 5 had partial hearing loss, one of whom also had a partial gaze deficit.

TBI subjects had significantly worse impact of headache in comparison to controls, as identified by two measures, the MIDAS and HIT-6. Headache impairment as assessed by the MIDAS (**Supplementary Fig 3**) was significantly worse for TBI subjects on total impact (**Supplementary Fig 3A**, p=0.0001), overall severity (**Supplementary Fig 3B,** p=0.00012), and frequency (**Supplementary Fig 3C,** p=0.000002) (all Mann-

Whitney U). HIT-6 results (**Supplementary Fig 4**) also indicated overall worse impairment based on the total score (**Supplementary Fig 4A,** p=0.00004), and frequency of severe headache pain (**Supplementary Fig 4B,** p=0.004), frequency of limitations of abilities due to headache (**Supplementary Fig 4C**, p=0.001), frequency of being tired because of headache (**Supplementary Fig 4D**, p=0.0008), frequency of being irritated because of headache (**Supplementary Fig 4E,** p=0.0000002), and frequency of having reduced concentration due to headache (**Supplementary Fig 4F,** p=0.000008) (all Mann-Whitney U).

Examination of neuropsychological test results identified trends towards worse performance in the TBI group 6-12 months post-injury in comparison to controls although none that were significant after correction for multiple comparisons (**Supplementary Table 2**). There was concern that these results may have been skewed by the disproportionate number of controls who were older and had higher education (**Table 1**). Secondary analysis restricted to enlisted service members only from each group revealed that these trends in neurocognitive test performance were likely due to subject mismatch as most of the differences were not present in this sub-group analysis (**Supplementary Table 3**). The only exception was the California Verbal Learning Test long-delay free recall assessment of delayed verbal memory, where performance remained significantly worse in the TBI group (p=0.004, Mann-Whitney U test). There was no significant difference between groups (p=0.46, Mann-Whitney U test) on a forced choice test embedded in the California Verbal Learning Test that was used to assess adequacy of effort; all subjects performed adequately on this measure.

However, evaluation at the single-subject level revealed subsets of TBI subjects with impaired cognitive test battery performance (**Fig 4**). Abnormal performance on each individual assessment was defined as a subject's score that fell 2 standard deviations worse than the mean of the control group for that exam. For each subject, the number of tests with abnormal performance was then summed. The number of subjects per group was then compared to what would be expected by chance. For 18 variables, 66% of subjects per group would be expected to have abnormal performance on 0 exams, 28% on 1 exam, and 5% on 2 or more exams. The TBI

group had a greater number of subjects with 2 or more abnormal exams than what would have been expected by chance for the group size, with 15 out of the 38 performing abnormally on 2 or more tests (**Fig 4A**, p = 0.0003, Chi-Square). No significant difference was observed in the control group compared to what would have been expected by chance (p=0.3925, Chi-square). Secondary evaluation of enlisted subjects only (**Fig 4B**) confirmed this finding in a better matched sample (TBI: p=0.0012, CTL: p=0.2543, Chi-Square). There was a heterogeneous distribution of which assessments were found to be abnormal for each subject. These findings are in line with previously published work on medically-evacuated "mild"/ concussive TBI subjects(Mac Donald *et al.*, 2014, Macdonald *et al.*, 2014).

Clinical evaluations for PTSD and depression revealed a greater severity of symptoms in TBI subjects than in controls 6-12 months post-injury (**Fig 5**). Symptoms of depression as measured by the MADRS were more severe in TBI subjects (p=0.001, Mann-Whitney U, **Fig 5A**). 24% of TBI subjects and 6% of controls were found to have moderate to severe depression(Snaith *et al.*, 1986). Total PTSD symptom severity was also significantly worse in TBI subjects than in controls as determined by the CAPS for DSM-IV (p=0.00014, Mann-Whitney U, **Fig 5B**). 21% of TBI subjects were found to have moderate to severe PTSD while no control subjects exceeded this threshold(Weathers *et al.*, 2001). CAPS sub-domain B which quantifies symptoms of re-experiencing or re-living traumatic events (**Fig 5C**, p=0.0004) and CAPS sub-domain D which quantifies feelings of hyper-arousal or hyper-vigilance (**Fig 5E**, p=0.0008) were also significantly worse in TBI subjects than in controls. Importantly, there was no significant difference in the poor sleep index, a sub-measure of CAPS-D which assesses the difference between the number of hours of sleep desired vs. the number of hours of sleep reported. This is in contrast to previous reports of medically-evacuated blast plus impact complex concussive TBI in which TBI subjects were found to have worse self-reported sleep than controls on this assessment(Macdonald *et al.*, 2014).

Self-reported alcohol use was not significantly different across groups as evidenced by the Michigan Alcohol Screening Test (**Supplementary Fig 5**) suggesting that alcohol abuse at follow up did not contribute to the disability observed in these TBI subjects.

Relationship between Acute and Chronic Clinical Measures

Only very modest correlations were observed between clinical data acquired 0-7 days post-injury and comparable measures collected at 6-12 month follow up (**Fig 6**). Correlations between acute self-report symptom measures of depression (**Fig 6A**) and PTSD (**Fig 6B**) modestly correlated with results from structured interviews administered for the comparable measure in the chronic phase post-injury. This modest correlation was observed for both controls (r=0.31, p=0.07 for depression measures; r=0.34, p=0.04 for PTSD measures) and TBI subjects (r=0.37, p=0.02 for depression measures; r=0.38, p=0.02 for PTSD measures).

In addition, comparisons of early and chronic cognitive performance measures were explored. Only measures of reaction time were found to be significantly correlated in TBI subjects (**Fig 6C**). No correlation was observed in control subjects across any of the neuropsychological test measures.

Of interest, there were no correlations between the acute military acute concussion evaluation (MACE) scores and any chronic clinical outcome measure.

Acute and Chronic Multivariate Predictors of Dichotomized Global Outcome

Predictors of dichotomized global outcome were examined using the acute clinical data only, chronic clinical data only, and combined acute and chronic clinical data. Global outcome was defined by the dichotomized GOS-E, with scores of 7 or 8 categorized as good outcome, and scores of 6 or below defined as disabled. Candidate variables for the model using acute data only included total scores on the PTSD Checklist-Military version (PCL-M), Beck Depression Inventory (BDI), Balance Error Scoring System (BESS),

Rivermead Post-Concussion Symptoms Questionnaire (RPCSQ), the 'delta' scores from the 8 domains of the Automated Neurocognitive Assessment Metrics – Traumatic Brain Injury Military Version 4 (ANAM), combat exposure scale (CES), number of previous deployments, age, education, and group distinction (Control. vs TBI). Acute PTSD symptoms as assessed by the PCL-M, group distinction (Control vs TBI), and age were the variables in the best fit logistic regression model. Higher likelihood of disability was observed in older TBI subjects with more severe PTSD symptoms (**Fig 7**). The receiver-operator curve (**Fig 7A**) indicated a good prediction of dichotomized GOS-E with a receiver-operating characteristic area under the curve (AUC) of 0.8426. This multivariate model performed substantially better than any single variable; the AUC for PCL-M alone was 0.76, for control vs TBI alone was 0.72, and for age alone was 0.56. There was also no apparent relationship between time to return to duty and 6-12 month global outcome. In addition, there was no relationship between a dichotomized measure of the GOSE defined as good outcome (GOSE 7-8) or moderate disability (GOSE 6 or less) and the mTBI subject's concussion history or history of previous blast exposure (p=0.56 blast history vs. no blast history, p=0.39 previous concussions (0-1) vs. previous concussions (2 or more), Chi-Square).

Candidate variables for the model using chronic clinical data only included total scores on the Clinician Administered PTSD Scale for DSM IV (CAPS), Montgomery-Asberg Rating Scale (MADRS), Michigan Alcohol Screening Test (MAST), Migraine Disability Scale (MIDAS), Headache Impact Test (HIT-6), neurological outcome scale for TBI (NOS-TBI), group distinction (Control vs TBI), combat exposure scale (CES), age, education, and the number of neuropsychological abnormalities. Using chronic clinical measures only, the best fit logistic regression model contained the CAPS, MADRS, CES, and age (**Fig 7B**). The chronic model provided an excellent reflection of global outcome with an AUC of 0.9551.

Using combined acute and chronic measures, the best fit model from logistic regression contained the PTSD Checklist, Military version (PCL-M), Clinician Administered PTSD Scale for DSM IV (CAPS),

Montgomery-Asberg Rating Scale for Depression (MADRS), Combat Exposure Scale (CES) and age (**Fig 7C**).

This model performed comparably to the chronic only model with an AUC of 0.9378.

DISCUSSION

In summary, non-medically evacuated concussive blast-related TBI subjects fared more poorly than controls in the chronic (6-12 months) phase following injury. Early clinical assessments revealed heightened PTSD and depression symptoms along with worse cognitive performance on the ANAM in comparison to pre-" deployment baseline testing. At 6-12 month follow up, TBI subjects showed persistent and more severe neurobehavioral, PTSD, and depression symptoms along with more significant headache impairment in comparison to controls. Worse performance on neurocognitive exams largely resolved at the group level, however analysis at the single-subject level revealed subsets of TBI subjects with lasting abnormal test performance in 2 or more assessments.

Interestingly, results from logistic regression utilizing either acute measures or chronic data identified that a diagnosis of TBI, age, and measures of psychological health contributed most strongly to the best predictive models of adverse 6-12 month overall outcomes. Of no surprise, the model generated by the acute data left a larger amount of the variance in 6-12 month outcome unaccounted for in comparison to the best model generated from chronic data. This could be due to many factors including the validity of the self-report measures (BDI, PCL-M) used acutely versus structured interviews (MADRS, CAPS) used at the chronic time point, the consideration of both 'current' and 'lifetime' psychological trauma on the CAPS versus only 'current-military' trauma on the PCL-M, or other factors. Balance, neurological deficits, headache impact, cognitive performance, and alcohol use did not appear to contribute substantially to prediction of overall outcomes.

It is important to point out that the acute measures captured less of the determinants of global outcome than the specific chronic assessments, and that acute and chronic measures of the same domains correlated only modestly. This lends support to the need for new measures to be used in the early evaluation of these patients that could better predict the long term impact of concussive brain injuries. However, irrespective of the

measures tested, poor global outcome as evidenced by the GOS-E in this population appears to be largely driven by psychological health measures, TBI status, and age. This finding adds to the growing body of literature underscoring the very high risk of disability in patients with both psychological health impairments and traumatic brain injury in the military(Hoge *et al.*, 2008, Lippa *et al.*, 2010, Polusny *et al.*, 2011, Drag *et al.*, 2012, Maguen *et al.*, 2012, Ruff *et al.*, 2012, Scheibel *et al.*, 2012, Vanderploeg *et al.*, 2012, Eskridge *et al.*, 2013, Kontos *et al.*, 2013, Verfaellie *et al.*, 2013, Yurgil *et al.*, 2013, Mac Donald *et al.*, 2014, Macdonald *et al.*, 2014).

This study is the first to our knowledge to provide longitudinal assessments that include both acute clinical information collected 0-7 days in the combat theater and chronic data collected 6-12 months in the United States. Limitations include a modest sample size, mismatch in age and education across the groups, no information collected regarding treatment during the interval between injury and evaluation, enrollment of subjects only from two concussion care center treatment facilities in Afghanistan and lack of matched assessments completed at both 0-7 days and 6-12 months. None of the participants had a known history of PTSD, depression or other mental health disorders, which would have precluded them from being deployed to a war zone based on pre-deployment health screening. However, pre-deployment medical records were not accessible at the time of enrollment for confirmation. In addition, the evaluations collected at 0-7 days and 6-12 months were designed to assess many relevant domains in an efficient manner so that subject test fatigue would not be a major problem. Nonetheless, it is possible that increased fatigue in the mTBI subjects relative to controls could have contributed to the results. A notable strength is that evaluation and treatment of service members with concussion acutely in theater was conducted based on established, standardized Department of Defense protocols (DTM 09-033).

Since this study did not include a comparable cohort of non-blast-related brain injured participants, no conclusions can be drawn regarding any specificity that may be present due to injury mechanism. However,

recent findings in medically-evacuated blast and non-blast service members suggest that clinical outcome may

not be differentially related to injury mechanism (Mac Donald *et al.*, 2014).

In conclusion, this study found that US military personnel with concussive blast-related TBI mild

enough to remain in theater still fared quite poorly on clinical outcome measures acquired 6-12 months

following injury. It was surprising that these concussive injuries, perceived by many as trivial, appeared to

result in significantly worse global outcomes and psychological health symptoms. Most notably, the percentage

of subjects with poor global outcome was much higher than what has been previously reported in comparable

 civilian studies of "mild" traumatic brain injury or sports concussion(Alexander, 1995, Thornhill *et al.*, 2000,

 Mosenthal *et al.*, 2004, Sigurdardottir *et al.*, 2009, Benedictus *et al.*, 2010, Jacobs *et al.*, 2010, Lannsjo *et al.*,

 2013, Yuh *et al.*, 2013, McMahon *et al.*, 2014) and much more in line with recent studies of service members

with "mild"/concussive TBI that required medical evacuation from the combat theater(Mac Donald *et al.*, 2014,

Macdonald *et al.*, 2014). **The incongruity between time to return to duty and the outcome measures is**

likely the result of the fact that the return to duty decision is based on overall clinical assessments. These

are performed acutely and may not be an accurate reflection of subsequent disability associated with

mTBI, which may be better predicted by poor psychological health. Most importantly, the observation that

the best predictive models utilizing acute data provided a good but incomplete account of global outcome

suggests that further research will be necessary to identify additional determinants of adverse outcomes.

Identification of these determinants of outcome may in turn allow a rational approach to revising protocols for

the care and management of these patients(Conaton, 2012). It remains to be determined whether early

interventions focused on psychological health symptoms in high risk subjects will improve outcomes.

Likewise, the longer term implications of concussive blast

related military TBI are currently unknown and are an active area of ongoing research.

MANUSCRIPT TABLES, FIGURES, AND FIGURE LEGENDS

Table 1. Participant Characteristics			
Characteristic	Control (n=34)	TBI (n=38)	P-Value
Age in years:			
median (range)	28 (19-44)	26 (20-41)	0.02 MWU
Education in years:			
median (range)	15 (12-24)	13 (12-18)	0.0003 MWU
Gender no (%)			
Male	27 (79%)	36 (95%)	0.05 Fisher's Exact
Female	7 (21%)	2 (5%)	
Race/ethnicity no (%)			
White	22 (65%)	29 (77%)	0.28 Chi-Square
African American	5 (15%)	2 (5%)	
Hispanic/Latino	7 (20%)	7 (18%)	
Asian	0	0	
Branch of Service no (%)			
US Army	13 (38%)	32 (84%)	0.0001 Chi-Square
US Air Force	2 (6%)	0	
US Marine Corps	3 (9%)	6 (16%)	
US Navy	16 (47%)	0	
Military Rank no (%)			
Enlisted	24 (71%)	35 (92%)	0.018 Fisher's Exact
Officer	10 (29%)	3 (8%)	
Enrollment Site (%)			
Kandahar Airfield	31 (91%)	30(79%)	0.15 Fisher's Exact
Camp Leatherneck	3 (7%)	8 (21%)	
Previous Deployments			
median (range)	2 (0-7)	2 (0-8)	0.99 MWU
Previous Blast Exposures			
median (range)	0 (0-2)	0 (0-6)	0.0031 MWU
Previous Concussions			
median (range)	N/A	2 (0-11)	
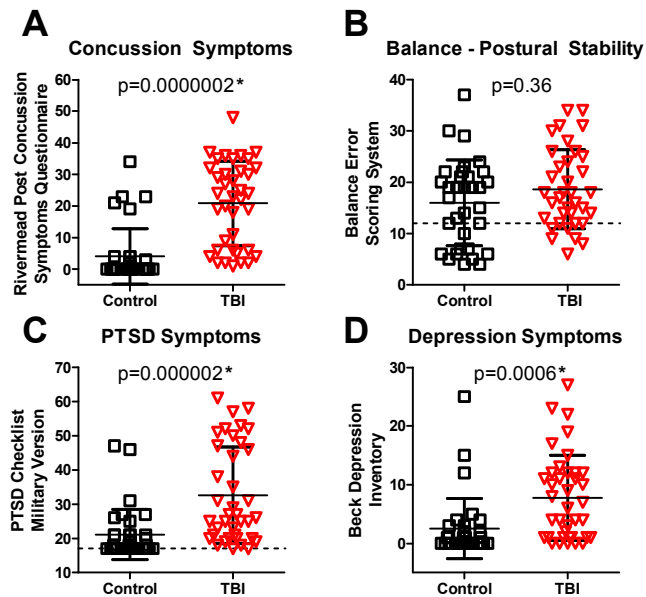
Figure 1. Initial Clinical Assessments Indicate More Severe Concussion Symptoms, PTSD Symptoms and Depression Symptoms in TBI patients vs. Controls. **A.** Rivermead Post-Concussion Symptoms Questionnaire (Max 64). **B.** Balance Error Scoring System (Max 60), an assessment of balance and postural stability. Dashed line indicates average score of normal performance by college varsity athletes. **C.** PTSD Check List for Military (PCL-M) (Max 85). Dashed line indicates minimum score of 17 on questionnaire. **D.** Beck Depression Inventory (Max 63). Uncorrected p-values reported. *indicates significance after Bonferroni correction for multiple comparisons at p < 0.05/4 = 0.0125.
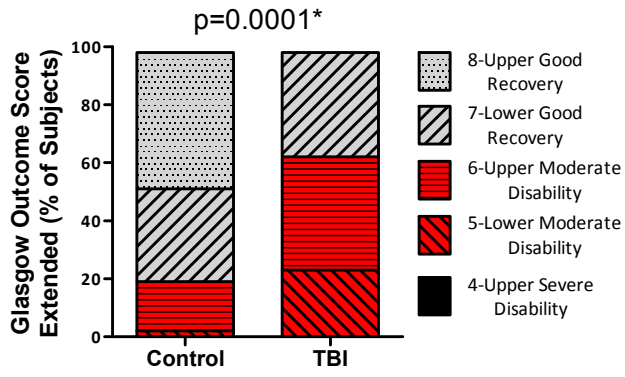
**Figure 2. Global Measure of Outcome 6-12 Months After Enrollment Indicate Worse Outcomes in TBI**

Subjects vs. Controls. Glasgow Outcome Scale – Extended (GOS-E). Mann-Whitney U test .
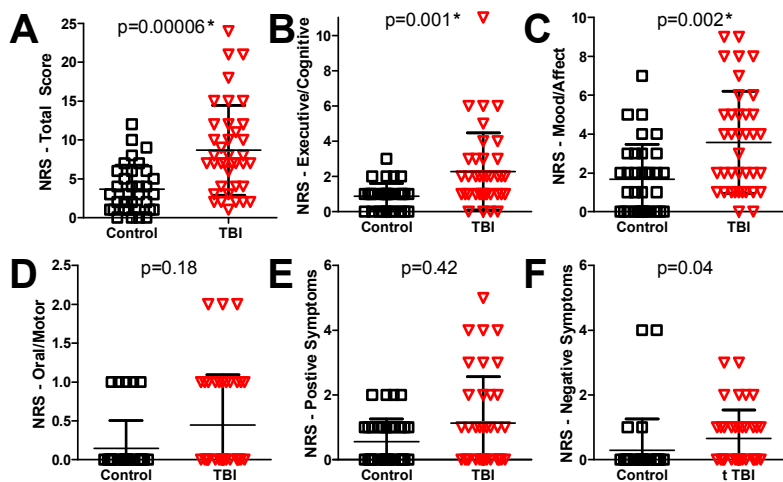
Figure 3. Neurobehavioral Outcome Indicate Worse Outcomes in TBI Subjects vs. Controls A. Total Neurobehavioral Rating Scale (NRS) Total Score (Max 87). **B.** Executive/Cognitive domain (Max 24). **C.** Mood/affect domain (Max 15). **D.** Oral/motor domain (Max 12). **E.** Positive Symptoms domain (Max 21). **F.** Negative Symptoms domain (Max 12). Higher scores on all of the measures indicate worse impairment. Uncorrected p-values reported. *indicates significance after Bonferroni correction for multiple comparisons at p<0.05/6 = 0.0083.
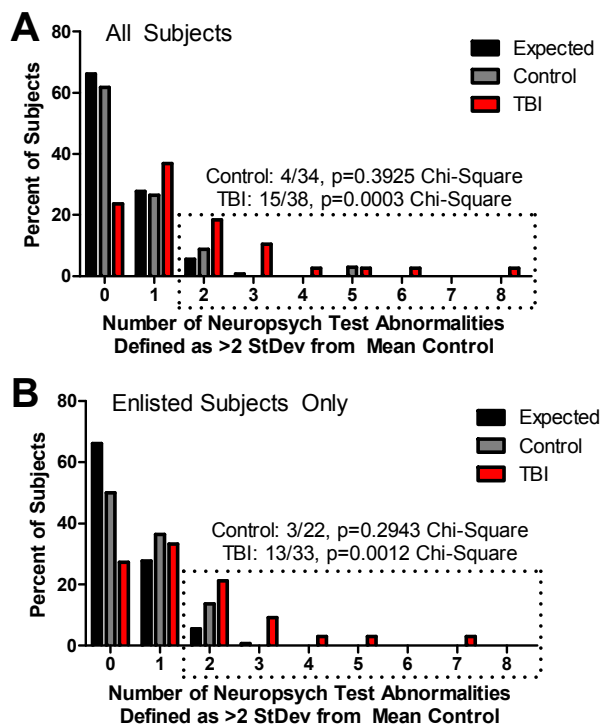
Figure 4. Larger Numbers of TBI Subjects than Controls with 2 or More Neuropsychological Performance Abnormalities at Follow Up. A. All subjects. **B.** Enlisted subjects only. The number of subjects with neuropsychological test abnormalities are displayed by group in comparison to what would be expected by chance (black bars). Percent of subjects is displayed to account for the differences in the number of subjects in each group. Dotted box indicates the group of subjects who had poor performance on 2 or more of the 18 neuropsychological assessments. Poor performance is defined as a score that is greater than 2 standard deviations away from the mean of the control group in the direction of worse performance. P-value calculated using the chi-square test by group in comparison to the expected distribution for that group size.
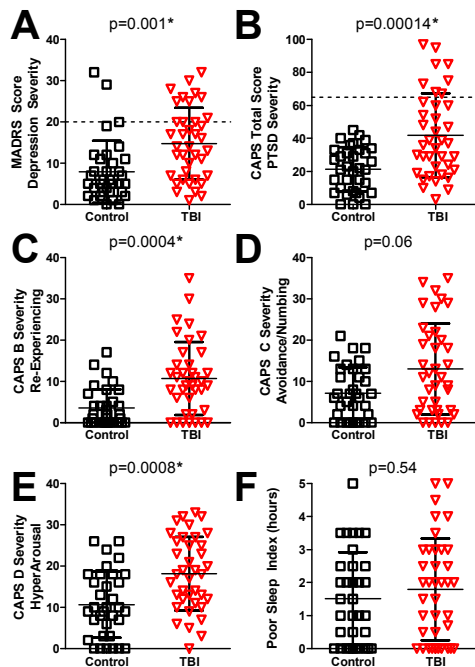
Figure 5. Greater Depression and PTSD Severity in TBI Subjects vs Controls at Follow-up. A. Depression severity assessed by the Montgomery Asberg depression rating scale (MADRS) (Max 60). Dashed line indicates cutoff for moderate to severe symptoms(Snaith *et al.*, 1986). **B.** PTSD severity assessed by the Clinician administered PTSD scale for DSM IV (CAPS) (Max 136). Dashed line indicates cutoff for moderate to severe symptoms(Weathers *et al.*, 2001). **C.** CAPS B Severity – Re-experiencing (Max 40). **D.** CAPS C Severity – Avoidance and Numbing (Max 56). **E.** CAPS D Severity – Increased Arousal and hypervigilance (Max 40). **F.** Poor sleep index, taken from CAPS D1, defined as the self-reported number of desired hours of sleep minus the number of hours reported. Higher scores on all of the measures indicate worse impairment. Uncorrected p-values reported. *indicates significance after Bonferroni correction for multiple comparisons for the 3 CAPS subdomains at p<0.05/3=0.0167.
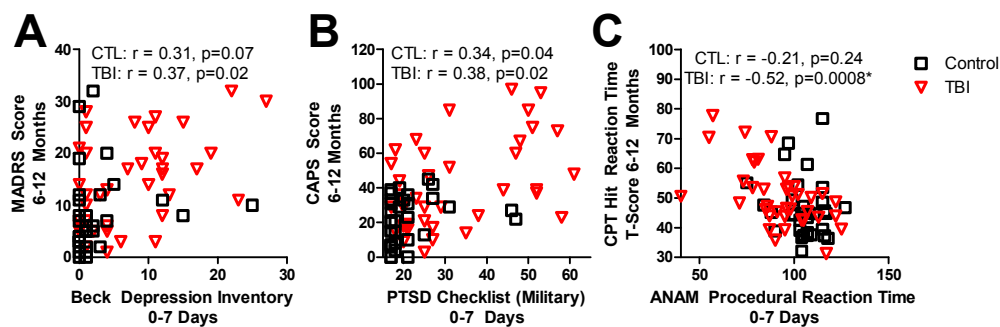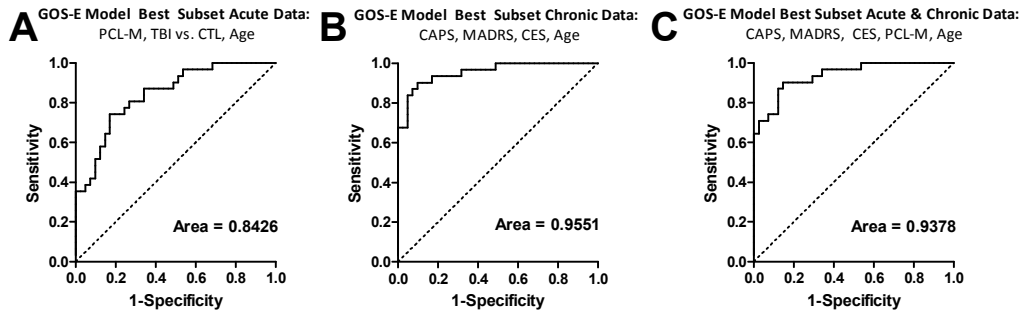
Figure 6. Modest correlations observed between acute and chronic measures of Depression, PTSD, and Neuropsychological Test Performance-Reaction Time. A. Very modest correlations for both control and TBI subjects were observed between the self-report symptom checklist for depression collected 0-7 days post-injury and a structured interview administered by trained research staff at 6-12 month follow up. **B.** Similar modest correlations were observed for controls and TBI subjects comparing acute self-report to chronic structured interview data for PTSD symptoms. **C.** Metrics of reaction time collected as part of the neuropsychological examination in both the acute (ANAM Procedural Reaction Time) and chronic phase (Conners' Continuous Performance Test II Reaction Time) significantly correlated in TBI subjects but not in controls using the Bonferonni corrected criterion of p<0.05/6 = 0.0083.

A GOS-E Model Best Subset Acute Data: PCL-M, TBI vs. CTL, Age — Area = 0.8426

B GOS-E Model Best Subset Chronic Data: CAPS, MADRS, CES, Age — Area = 0.9551

C GOS-E Model Best Subset Acute & Chronic Data: CAPS, MADRS, CES, PCL-M, Age — Area = 0.9378

Logistic Regression for Global Outcome Best Fit Models of Acute and Chronic Clinical Data			
Model 1 (Acute Data) - GOSE: PCL-M, CTL/TBI, Age			
Overall model : AIC 73.34, Likelihood ratio Chi square: 27.45			
Parameter	**Estimate**	**95% Confidence Interval**	**P-value**
Intercept	-6.5626	(-10.4579 :-2.6672)	0.00096
PCL-M (PTSD Symptoms)	0.0827	(0.0247 : 0.1408)	0.00521
Control vs. TBI	0.9139	(0.2418 : 1.5862)	0.00770
Age	0.1399	(0.0275 : 0.2521)	0.01473
Model 2 (Chronic Data) - GOSE: CAPS, MADRS, CES, Age			
Overall model : AIC 56.29, Likelihood ratio Chi square: 52.13			
Parameter	**Estimate**	**95% Confidence Interval**	**P-value**
Intercept	-3.5502	(-5.2967 :-1.8039)	0.00034
CAPS (PTSD Symptoms)	0.0714	(0.0063 : 0.1365)	0.03167
MADRS (Depression)	0.1117	(0.0017 : 0.2216)	0.04648
CES (Combat Exposure)	0.1179	(0.0288 : 0.2069)	0.00947
Age	0.1893	(0.0384 : 0.3402)	0.00139
Model 3 (Acute & Chronic Data) - GOSE: CAPS, MADRS, CES, PCL-M, Age			
Overall model : AIC 55.80, Likelihood ratio Chi square: 52.62			
Parameter	**Estimate**	**95% Confidence Interval**	**P-value**
Intercept	-12.1446	(-18.5902 :--5.6991)	0.00022
CAPS (PTSD Symptoms)	0.0679	(-0.0022 : 0.1381)	0.05781
MADRS (Depression)	0.1081	(-0.0033 : 0.2195)	0.05715
CES (Combat Exposure)	0.1068	(0.0148 : 0.1988)	0.02286
PCL-M (PTSD Symptoms)	0.0444	(-0.0282 : 0.1171)	0.23061
Age	0.2013	(0.0477 : 0.3549)	0.01020

Figure 7. Logistic Regression Models Predict Global Outcome Moderately Based on Acute Data and Strongly Based on Chronic Data. A. Receiver-operator curve for best fit model of overall disability defined as the dichotomized GOS-E of 7 or 8 – good outcome, and 6 or below – disabled using acute clinical data. The

best model included the PTSD Checklist, Military version (PCL-M), Group distinction of Control vs TBI, and

Age. **B.** Receiver-operator curve for model of overall disability using chronic clinical data. The best fit model

consisted of the Clinician Administered PTSD Scale for DSM IV (CAPS), Montgomery-Asberg Rating Scale

for Depression (MADRS), Combat Exposure Scale (CES) and Age. This model showed improvement over the

acute data best fit model. **C.** Receiver-operator curve for best fit model of overall disability using both acute and

chronic clinical data. The model consisted of PTSD Checklist, Military version (PCL-M), Clinician

Administered PTSD Scale for DSM IV (CAPS), Montgomery-Asberg Rating Scale for Depression (MADRS),

Combat Exposure Scale (CES) and age.

SUPPLEMENTARY MATERIALS

TABLES AND FIGURES

Supplementary Table 1. Comparison of Participant Characteristics Follow Up vs. No Follow Up						
Characteristic	Control Follow Up (n=34)	Control No Follow Up (n=67)	P-Value	TBI Follow Up (n=38)	TBI No Follow Up (n=57)	P-Value
Age in years:						
median (range)	28 (19-44)	27 (20-48)	0.09 MWU	26 (20-41)	25 (20-41)	0.26 MWU
Gender no (%)						
Male	27 (79%)	52 (78%)	0.84 Chi-Square	36 (95%)	57 (100%)	0.08 Fisher's Exact
Female	7 (21%)	15 (22%)		2 (5%)	0	
Branch of Service no (%)						
US Army	13 (38%)	26 (39%)	0.96 Chi-Square	32 (84%)	47 (82%)	0.82 Chi-Square
US Air Force	2 (6%)	10 (15%)		0	0	
US Marine Corps	3 (9%)	8 (12%)		6 (16%)	9 (16%)	
US Navy	16 (47%)	23 (34%)		0	1 (2%)	
Military Rank no (%)						
Enlisted	24 (71%)	54 (81%)	0.23 Chi-Square	35 (92%)	54 (95%)	0.61 Fisher's Exact
Officer	10 (29%)	13 (19%)		3 (8%)	3 (5%)	
Enrollment Site (%)						
Kandahar Airfield	31 (91%)	58 (87%)	0.49 Chi-Square	30(79%)	42 (74%)	0.56 Chi-Square
Camp Leatherneck	3 (7%)	9 (13%)		8 (21%)	15 (26%)	
Previous Deployments						
median (range)	2 (0-7)	1 (0-6)	0.18 MWU	2 (0-8)	2 (0-11)	0.79 MWU
Combat Exposure Scale	5 ± 9	5 ± 8	0.93 MWU	18 ± 9	19 ± 9	0.52 MWU
MACE Exam Score	n/a	n/a	n/a	24 ± 5	24 ± 4	0.77 MWU
Return to Duty Time (days)						
Median (Range)	n/a	n/a	n/a	7 (2-23)	7 (2-26)	0.62 MWU

Supplementary Table 2. Neuropsychological Test Performance			
Test	Control (n=34)	TBI (n=38)	P-Value Test
25-Foot Walk (seconds)			
(Motor Strength, Balance, Coordination)	3.78 ± 0.60	4.23 ± 0.68	p=0.004 Student's t
Conners' Continuous Performance Test II			
Omission Errors (T-score):			
(Attention Lapses)	48.85 ± 10.51	60.41 ± 28.13	p=0.22 MWU
Commission Errors (T-score):			
(Impulsivity)	53.83 ± 11.03	54.69 ± 10.16	p=0.73 Student's t
Hit Rate (T-score):			
(Reaction Time)	46.06 ± 9.88	50.81 ± 10.33	p=0.018 MWU
Hit Rate Block Change (T-score):			
(Sustained Vigilance)	48.67 ± 5.56	54.69 ± 13.43	p=0.018 Student's t
Iowa Gambling Test (T-score)			
(Impulsivity)	48.21 ± 10.8	51.34 ± 11.4	p=0.24 Student's t
Ruff-Light Trail Learning Test (T-score)			
Trials Correct *(Visual Memory)*	52.62 ± 10.41	50.11 ± 9.30	p=0.02 MWU
Wechsler Test of Adult Reading (Standard Score)			
(Estimate of Pre-injury Verbal Intelligence)	105.41 ± 10.58	99.03 ± 12.50	p=0.023 Student's t
California Verbal Learning Test II			
Long-Delay Free Recall (Standard Score)			
(Verbal Memory)	0.15 ± 1.28	-0.57 ± 0.92	p=0.013 MWU
Total Intrusions (Standard Score)			
(Falsely Recalled Items)	0.14 ± 0.84	0.50 ± 1.22	p=0.20 MWU
List B vs. Trial 1 List A (Standard Score)			
(Proactive Memory Interference)	0.00 ± 1.05	-0.12 ± 0.90	p=0.48 MWU
Grooved Pegboard			
(Motor Speed & Coordination)			
Average Dom & Non-Dom Time (seconds)	67.68 ± 10.34	71.63 ± 7.44	p=0.03 MWU
Trail Making Test			
Trails A time (seconds)			
(Visual Scanning, Coordination)	23.24 ± 7.65	23.6 ± 7.08	p=0.84 Student's t
Trails B time (seconds)			
(Trails A + Mental Flexibility)	55.38 ± 18.65	64.43 ± 23.89	p=0.09 Student's t
Controlled Oral Word Association			
Total Score: *(Verbal Fluency)*	42.82 ± 9.61	41.45 ± 11.47	p=0.59 Student's t
D-KFES Color-Word Interference Test			
(Executive Function)			
Color & Word Naming (summed scaled score)	20.85 ± 4.95	20.5 ± 4.15	p=0.46 Student's t
Inhibition (scaled score)	10.79 ± 2.43	9.55 ± 2.82	p=0.05 Student's t
Inhibition/Switching (scaled score)	10.18 ± 2.42	8.92 ± 3.59	p=0.06 Student's t

Bonferroni Correction for Multiple Comparisons (p=0.05/18 = 0.00278)

Supplementary Table 3. Neuropsychological Test Performance – Enlisted Subjects Only			
Test	Control (n=22)	TBI (n=33)	P-Value Test
25-Foot Walk (seconds) *(Motor Strength, Balance, Coordination)*	3.97±0.65	4.05±0.63	p=0.02 Student's t
Conners' Continuous Performance Test II			
Omission Errors (T-score): *(Attention Lapses)*	50.09±27.52	59.10±18.05	p=0.47 MWU
Commission Errors (T-score): *(Impulsivity)*	54.57±9.90	54.34±9.63	p=0.93 Student's t
Hit Rate (T-score): *(Reaction Time)*	45.08±10.45	50.06±9.46	p=0.03 MWU
Hit Rate Block Change (T-score): *(Sustained Vigilance)*	48.33±12.68	53.85±9.06	p=0.06 Student's t
Iowa Gambling Test (T-score) *(Impulsivity)*	49.86±9.87	51.36±12.10	p=0.64 Student's t
Ruff-Light Trail Learning Test (T-score) Trials Correct *(Visual Memory)*	53.45±10.45	51.06±7.03	p=0.04 MWU
Wechsler Test of Adult Reading (Standard Score) *(Estimate of Pre-injury Verbal Intelligence)*	103.77±9.38	98.67±12.11	p=0.10 Student's t
California Verbal Learning Test II			
Long-Delay Free Recall (Standard Score) *(Verbal Memory)*	0.25±0.83	-0.61±1.13	p=0.002 MWU*
Total Intrusions (Standard Score) *(Falsely Recalled Items)*	0.20±0.74	0.58±1.33	p=0.25 MWU
List B vs. Trial 1 List A (Standard Score) *(Proactive Memory Interference)*	0.02±1.02	-0.05±0.80	p=0.68 MWU
Grooved Pegboard *(Motor Speed & Coordination)* Average Dom & Non-Dom Time (seconds)	70.59±9.97	71.13±8.52	p=0.71 MWU
Trail Making Test			
Trails A time (seconds) *(Visual Scanning, Coordination)*	24.97±8.38	23.96±6.84	p=0.63 Student's t
Trails B time (seconds) *(Trails A + Mental Flexibility)*	54.58±21.26	64.07±23.37	p=0.12 Student's t
Controlled Oral Word Association Total Score: *(Verbal Fluency)*	41.23±10.74	42.33±10.35	p=0.71 Student's t
D-KFES Color-Word Interference Test *(Executive Function)*			
Color & Word Naming (summed scaled score)	20.41±4.64	20.27±4.35	p=0.91 Student's t
Inhibition (scaled score)	10.55±2.40	9.79±2.85	p=0.31 Student's t
Inhibition/Switching (scaled score)	9.77±4.64	9.00±3.59	p=0.34 Student's t

Bonferroni Correction for Multiple Comparisons (p=0.05/18 = 0.00278)
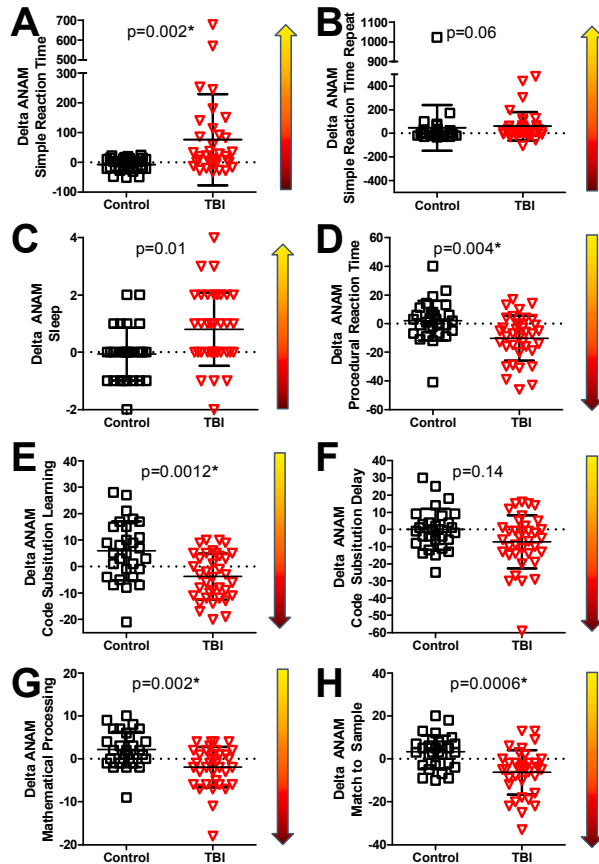
Supplementary Figure 1. Comparison of ANAM scores 0-7 days post-injury to Baseline Performance Indicate Evidence of Worsening Performance in TBI Subjects vs. Controls. Each data point is reported as the 'Delta,' defined as subject performance in theater minus subject performance at baseline collected as part of pre-deployment evaluation. Shaded arrows indicate direction of worse performance. **A.** Simple reaction time. **B.** Simple reaction time repeated. **C.** Sleep deprivation by self-report (hours). **D.** Procedural reaction time. **E.** Code substitution learning. **F.** Code substitution delay. **G.** Mathematical Processing. **H.** Match to sample.

Uncorrected p-values reported. *indicates significance after Bonferroni correction for multiple comparisons at p<0.05/8=0.00625.
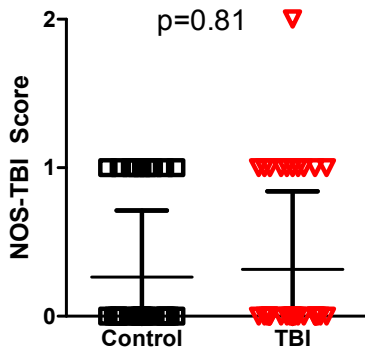
Supplementary Figure 2. No Difference Between Groups in Focal Neurological Deficits. Focal neurological deficits were assessed using the Neurological Outcome Scale for Traumatic Brain Injury (NOS-TBI).
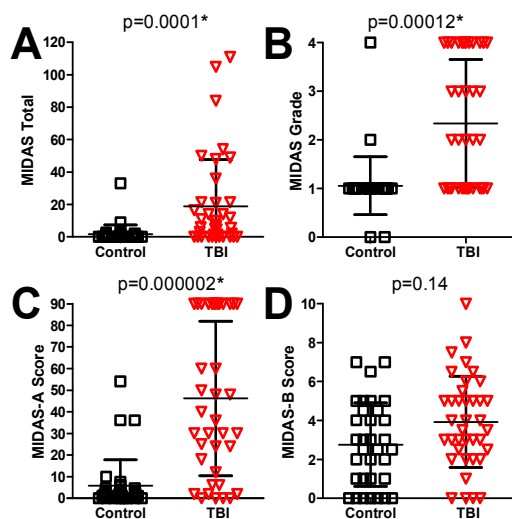
Supplementary Figure 3. TBI Subjects Had Greater Headache-Related Disability at Follow Up Than Controls. A. Overall headache impairment assessed by the Migraine Disability Assessment Test (MIDAS) total score (Max 180). **B.** Total headache grade score for headache impact severity (Max 4). **C.** MIDAS-A assessment for headache frequency (Max 90). **D.** MIDAS-B assessment for headache pain intensity (Max 10). Higher scores on all of the measures indicate worse impairment. Uncorrected p-values reported. *indicates significance after Bonferroni correction for multiple comparisons at p<0.05/4=0.0125.
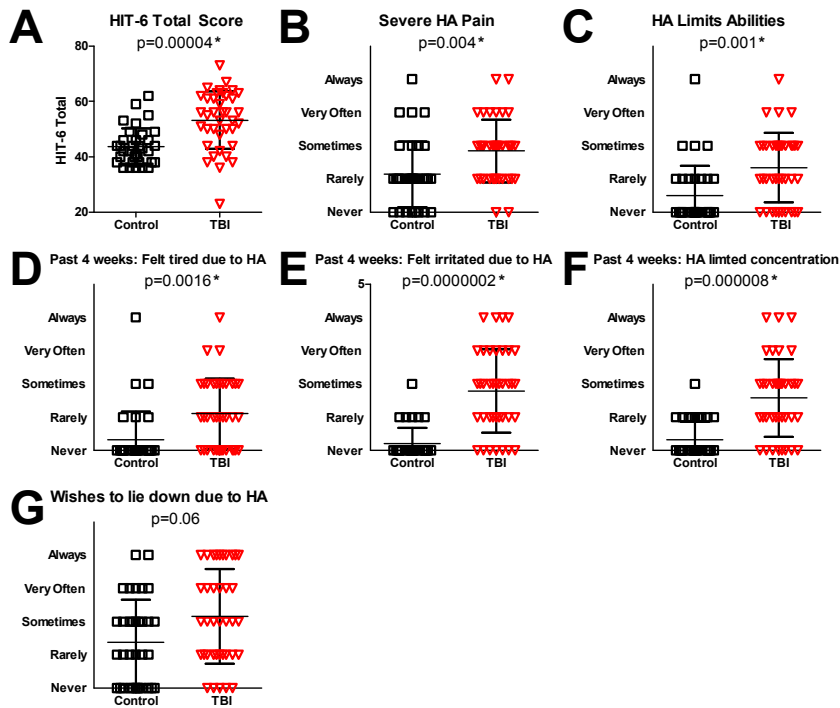
Supplementary Figure 4. An Alternate Measure of Headache Impact Also Indicated Greater Effects of Headache in TBI Subjects vs Controls A. Headache impairment assessed by the headache impact test (HIT-6) (Max 78). **B.** Frequency of severe headache pain. **C.** Frequency of headaches limiting ability to complete daily activities. **D.** Impact of headache in the past 4 weeks on how often a subject felt tired. **E.** Impact of headache in the past 4 weeks on how often a subject felt fed up or irritated. **F**. Impact of headache in the past 4 weeks on how often a subject was limited in their concentration at work. **G**. Impact of headache determined by how often a subject wishes to lie down. Uncorrected p-values reported. *indicates significance after Bonferroni correction for multiple comparisons at p<0.05/7=0.0071.

Supplementary Figure 5. No Difference Between Groups in Self-Reported Alcohol Use at Follow Up.

Alcohol use was assessed using the Michigan Alcohol Screening Test (MAST).

REFERENCES

Alexander MP. Mild traumatic brain injury: pathophysiology, natural history, and clinical management. Neurology. 1995;45(7):1253-60.

Baker SP, O'Neill B, Haddon W, Jr., Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. The Journal of trauma. 1974;14(3):187-96.

Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition. 1994;50(1-3):7-15.

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Archives of general psychiatry. 1961;4:561-71.

Benedictus MR, Spikman JM, van der Naalt J. Cognitive and behavioral impairment in traumatic brain injury related to outcome and return to work. Archives of physical medicine and rehabilitation. 2010;91(9):1436-41.

Benton A, Hamsher K, A S. Multilingual Aphasia Examination (3rd ed.). Iowa City, Ia: AJA Associates; 1983.

Casscells S. Traumatic Brain Injury: Definition and Reporting. In: Defense Aso, ed: Department of Defense. 2007.

Cernich A, Reeves D, Sun W, Bleiberg J. Automated Neuropsychological Assessment Metrics sports medicine battery. Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists. 2007;22 Suppl 1:S101-14.

Coldren RL, Russell ML, Parish RV, Dretsch M, Kelly MP. The ANAM lacks utility as a diagnostic or screening tool for concussion more than 10 days following injury. Military medicine. 2012;177(2):179-83.

Conaton E. DoD Policy Guidance for Management of Mild Traumatic Brain Injury/Concussion

in the Deployed Setting: Department of Defense; 2012.

Conners C, Staff. M. Conners' Continuous Performance Test II: Computer program for Windows technical guide and software manual. North Tonwanda, NY: Multi-Health Systems; 2000.

Cooper DB, Kennedy JE, Cullen MA, Critchfield E, Amador RR, Bowles AO. Association between combat stress and post-concussive symptom reporting in OEF/OIF service members with mild traumatic brain injuries. Brain injury : [BI]. 2011;25(1):1-7.

Delis D, Kramer J, Kaplan E, B O. California Verbal Learning Test Manual: Second Edition, Adult Version. San Antonio, Tx: Psychological Corporation; 2000.

Delis DC, Kaplan, E. & Kramer, J.H. Delis-Kaplan Executive Function System (D-KEFS): *Examiner's manual*. San Antonio, TX: The Psychological Corporation; 2001.

Dempsey KE, Dorlac WC, Martin K, Fang R, Fox C, Bennett B, et al. Landstuhl Regional Medical Center: traumatic brain injury screening program. Journal of trauma nursing : the official journal of the Society of Trauma Nurses. 2009;16(1):6-7, 10-2.

Drag LL, Spencer RJ, Walker SJ, Pangilinan PH, Bieliauskas LA. The contributions of self-reported injury characteristics and psychiatric symptoms to cognitive functioning in OEF/OIF veterans with mild traumatic brain injury. J Int Neuropsychol Soc. 2012;18(3):576-84.

DVBIC. DoD Numbers for Traumatic Brain Injury, Worldwide - Totals, 2000-2012 (Q1-Q3). 2013 [cited 2013 12/10/13]; Available from: http://www.dvbic.org/sites/default/files/uploads/dod-tbi-worldwide-2000-2013-Q3-as-of-05%20Nov-2013.pdf

Eskridge SL, Macera CA, Galarneau MR, Holbrook TL, Woodruff SI, MacGregor AJ, et al. Influence of combat blast-related mild traumatic brain injury acute symptoms on mental health and service discharge outcomes. Journal of neurotrauma. 2013;30(16):1391-7.

Fischer BL, Parsons M, Durgerian S, Reece C, Mourany L, Lowe MJ, et al. Neural Activation during Response Inhibition Differentiates Blast from Mechanical Causes of Mild to Moderate Traumatic Brain Injury. Journal of neurotrauma. 2014;31(2):169-79.

Galarneau MR, Woodruff SI, Dye JL, Mohrle CR, Wade AL. Traumatic brain injury during Operation Iraqi Freedom: findings from the United States Navy-Marine Corps Combat Trauma Registry. Journal of neurosurgery. 2008;108(5):950-7.

Guskiewicz KM, Ross SE, Marshall SW. Postural Stability and Neuropsychological Deficits After Concussion in Collegiate Athletes. Journal of athletic training. 2001;36(3):263-73.

Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. The New England journal of medicine. 2008;358(5):453-63.

Homaifar BY, Brenner LA, Gutierrez PM, Harwood JF, Thompson C, Filley CM, et al. Sensitivity and specificity of the Beck Depression Inventory-II in persons with traumatic brain injury. Archives of physical medicine and rehabilitation. 2009;90(4):652-6.

Jacobs B, Beems T, Stulemeijer M, van Vugt AB, van der Vliet TM, Borm GF, et al. Outcome prediction in mild traumatic brain injury: age and clinical variables are stronger predictors than CT abnormalities. Journal of neurotrauma. 2010;27(4):655-68.

Keane T, Fairbank J, Caddell J, Zimering R, Taylor K, Mora C. Clinical evaluation of a measure to assess combat exposure. Psychological Assessment. 1989(1):53-5.

King NS, Crawford S, Wenden FJ, Moss NE, Wade DT. The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. Journal of neurology. 1995;242(9):587-92.

Kontos AP, Kotwal RS, Elbin RJ, Lutz RH, Forsten RD, Benson PJ, et al. Residual effects of combat-related mild traumatic brain injury. Journal of neurotrauma. 2013;30(8):680-6.

Kosinski M, Bayliss MS, Bjorner JB, Ware JE, Jr., Garber WH, Batenhorst A, et al. A six-item short-form survey for measuring headache impact: the HIT-6. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2003;12(8):963-74.

Lannsjo M, Raininko R, Bustamante M, von Seth C, Borg J. Brain pathology after mild traumatic brain injury: an exploratory study by repeated magnetic resonance examination. Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine. 2013;45(8):721-8.

Levin HS, High WM, Goethe KE, Sisson RA, Overall JE, Rhoades HM, et al. The neurobehavioural rating scale: assessment of the behavioural sequelae of head injury by the clinician. Journal of neurology, neurosurgery, and psychiatry. 1987;50(2):183-93.

Lippa SM, Pastorek NJ, Benge JF, Thornton GM. Postconcussive symptoms after blast and nonblast-related mild traumatic brain injuries in Afghanistan and Iraq war veterans. J Int Neuropsychol Soc. 2010;16(5):856-66.

Luethcke CA, Bryan CJ, Morrow CE, Isler WC. Comparison of concussive symptoms, cognitive performance, and psychological symptoms between acute blast-versus nonblast-induced mild traumatic brain injury. J Int Neuropsychol Soc. 2011;17(1):36-45.

Mac Donald CL, Johnson AM, Wierzechowski L, Kassner E, Stewart T, Nelson EC, et al. Prospectively Assessed Clinical Outcomes in Concussive Blast vs Nonblast Traumatic Brain Injury Among Evacuated US Military Personnel. JAMA Neurol. 2014.

Macdonald CL, Johnson AM, Nelson EC, Werner NJ, Fang R, Flaherty SF, et al. Functional status after blast-plus-impact complex concussive traumatic brain injury in evacuated United States military personnel. Journal of neurotrauma. 2014;31(10):889-98.

Maguen S, Madden E, Lau KM, Seal K. The impact of head injury mechanism on mental health symptoms in veterans: do number and type of exposures matter? Journal of traumatic stress. 2012;25(1):3-9.

Matthews C, Kløve H. Instruction manual for the Adult Neuropsychology Test Battery. Madison, WI: University of Wisconsin Medical School; 1964.

McCauley SR, Levin HS, Vanier M, Mazaux JM, Boake C, Goldfader PR, et al. The neurobehavioural rating scale-revised: sensitivity and validity in closed head injury assessment. Journal of neurology, neurosurgery, and psychiatry. 2001;71(5):643-51.

McCauley SR, Wilde EA, Kelly TM, Weyand AM, Yallampalli R, Waldron EJ, et al. The Neurological Outcome Scale for Traumatic Brain Injury (NOS-TBI): II. Reliability and convergent validity. Journal of neurotrauma. 2010;27(6):991-7.

McMahon P, Hricik A, Yue JK, Puccio AM, Inoue T, Lingsma HF, et al. Symptomatology and Functional Outcome in Mild Traumatic Brain Injury: Results from the Prospective TRACK-TBI Study. Journal of neurotrauma. 2014;31(1):26-33.

Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. The British journal of psychiatry : the journal of mental science. 1979;134:382-9.

Mosenthal AC, Livingston DH, Lavery RF, Knudson MM, Lee S, Morabito D, et al. The effect of age on functional outcome in mild traumatic brain injury: 6-month report of a prospective multicenter trial. The Journal of trauma. 2004;56(5):1042-8.

Norris JN, Carr W, Herzig T, Labrie DW, Sams R. ANAM4 TBI reaction time-based tests have prognostic utility for acute concussion. Military medicine. 2013;178(7):767-74.

Owens BD, Kragh JF, Jr., Wenke JC, Macaitis J, Wade CE, Holcomb JB. Combat wounds in operation Iraqi Freedom and operation Enduring Freedom. The Journal of trauma. 2008;64(2):295-9.

Pettigrew LE, Wilson JT, Teasdale GM. Reliability of ratings on the Glasgow Outcome Scales from in-person and telephone structured interviews. The Journal of head trauma rehabilitation. 2003;18(3):252-8.

Polusny MA, Kehle SM, Nelson NW, Erbes CR, Arbisi PA, Thuras P. Longitudinal effects of mild traumatic brain injury and posttraumatic stress disorder comorbidity on postdeployment outcomes in national guard soldiers deployed to Iraq. Archives of general psychiatry. 2011;68(1):79-89.

Reitan R. Trail Making Test manual for administration and scoring. Tuscon, AZ: Reitan Neuropsychology Laboratory; 1992.

Ruff R, Light R, Parker S. Visuospatial learning: Ruff Light Trail Learning Test. Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists. 1996;11(4):313-27.

Ruff RL, Riechers RG, 2nd, Wang XF, Piero T, Ruff SS. A case-control study examining whether neurological deficits and PTSD in combat veterans are related to episodes of mild TBI. BMJ open. 2012;2(2):e000312.

Scheibel RS, Newsome MR, Troyanskaya M, Lin X, Steinberg JL, Radaideh M, et al. Altered brain activation in military personnel with one or more traumatic brain injuries following blast. J Int Neuropsychol Soc. 2012;18(1):89-100.

Selzer ML. The Michigan Alcoholism Screening Test (MAST): The quest for a new diagnostic instrument. American Journal of Psychiatry. 1971(127):1653-8.

Sigurdardottir S, Andelic N, Roe C, Schanke AK. Cognitive recovery and predictors of functional outcome 1 year after traumatic brain injury. J Int Neuropsychol Soc. 2009;15(5):740-50.

Snaith RP, Harrop FM, Newby DA, Teale C. Grade scores of the Montgomery-Asberg Depression and the Clinical Anxiety Scales. The British journal of psychiatry : the journal of mental science. 1986;148:599-601.

Stewart WF, Lipton RB, Whyte J, Dowson A, Kolodner K, Liberman JN, et al. An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. Neurology. 1999;53(5):988-94.

Taniellian T, Jaycox L. Invisible Wounds of War: Psychological and Cognitive Injuries, Their Consequences, and Services to Assist Recovery. RAND Corporation. 2008.

Thornhill S, Teasdale GM, Murray GD, McEwen J, Roy CW, Penny KI. Disability in young people and adults one year after head injury: prospective cohort study. BMJ. 2000;320(7250):1631-5.

Tombough T. The Test of Memory Malingering. Multi-Health Systems. 1996.

Vanderploeg RD, Belanger HG, Horner RD, Spehar AM, Powell-Cope G, Luther SL, et al. Health outcomes associated with military deployment: mild traumatic brain injury, blast, trauma, and combat associations in the Florida National Guard. Archives of physical medicine and rehabilitation. 2012;93(11):1887-95.

Verfaellie M, Lafleche G, Spiro A, 3rd, Tun C, Bousquet K. Chronic postconcussion symptoms and functional outcomes in OEF/OIF veterans with self-report of blast exposure. J Int Neuropsychol Soc. 2013;19(1):1-10.

Warden D. Military TBI during the Iraq and Afghanistan wars. The Journal of head trauma rehabilitation. 2006;21(5):398-402.

Weathers FW, Keane TM, Davidson JR. Clinician-administered PTSD scale: a review of the first ten years of research. Depression and anxiety. 2001;13(3):132-56.

Wechsler D. Wechsler Test of Adult Reading (WTAR) Manual. New York: Psychological Corporation; 2001.

Wilde EA, McCauley SR, Kelly TM, Levin HS, Pedroza C, Clifton GL, et al. Feasibility of the Neurological Outcome Scale for Traumatic Brain Injury (NOS-TBI) in adults. Journal of neurotrauma. 2010;27(6):975-81.

Wilde EA, McCauley SR, Kelly TM, Weyand AM, Pedroza C, Levin HS, et al. The Neurological Outcome Scale for Traumatic Brain Injury (NOS-TBI): I. Construct validity. Journal of neurotrauma. 2010;27(6):983-9.

Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. Journal of neurotrauma. 1998;15(8):573-85.

Yeager DE, Magruder KM, Knapp RG, Nicholas JS, Frueh BC. Performance characteristics of the posttraumatic stress disorder checklist and SPAN in Veterans Affairs primary care settings. General hospital psychiatry. 2007;29(4):294-301.

Yuh EL, Mukherjee P, Lingsma HF, Yue JK, Ferguson AR, Gordon WA, et al. Magnetic resonance imaging improves 3-month outcome prediction in mild traumatic brain injury. Annals of neurology. 2013;73(2):224-35.

Yurgil KA, Barkauskas DA, Vasterling JJ, Nievergelt CM, Larson GE, Schork NJ, et al. Association Between Traumatic Brain Injury and Risk of Posttraumatic Stress Disorder in Active-Duty Marines. JAMA psychiatry. 2013.

Outcome Trends Following US Military Concussive Traumatic Brain Injury

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ABSTRACT (<mark>250 words MAX-Currently</mark> 250

BACKGROUND

Care for military personnel with combat-related concussive traumatic brain injury (TBI) has substantially changed in recent years, yet the trends in clinical outcomes remain largely unknown.

METHODS

We prospectively assessed clinical outcomes 6-12 months after TBI in four cohorts of active-duty US Military personnel injured in theater along with military controls. Enrollment occurred from 2008-2013 at Landstuhl Regional Medical Center in Landstuhl, Germany and 2 sites in Afghanistan.

RESULTS

Global disability, neurobehavioral impairment, depression severity, and post-traumatic stress disorder (PTSD) severity were worse in all concussive TBI groups in comparison to controls ($p<0.0001$). There was a modest but statistically significant trend towards improved PTSD in later cohorts relative to earlier cohorts. Blast–exposed controls without apparent TBI also exhibited significantly worse global disability ($p=0.004$), neurobehavioral impairment ($p=0.001$), depression ($p=0.006$) and PTSD severity ($p<0.0001$) than non-blast-exposed controls. Most subjects had normal neuropsychological performance, but subsets of subjects with TBI and blast-exposed controls had impaired neuropsychological performance. Overall disability was largely driven by TBI diagnoses, evacuation status, depression, and PTSD severity, but not by neuropsychological performance, age, education, self-reported sleep deprivation, or injury mechanism.

CONCLUSIONS

Despite changes in care for US military personnel with blast-related concussive TBI, 6-12 month outcomes have improved only modestly and are often poor. Future focus on mental health treatment after concussive TBI and after blast exposure without apparent TBI appears warranted. However, adverse outcomes are incompletely explained, and additional domains of assessment will be required to fully address the causes of disability after wartime injury.

INTRODUCTION

There are more than 2.5 million veterans of the recent conflicts in Iraq and Afghanistan with more than a third completing multiple deployments[1]. It is estimated that roughly 20% of this deployed force suffered a head injury[2] in these wars; 83.3% of whom endured a mild, uncomplicated traumatic brain injury (TBI) or concussion[3,4]. The long term impact of these war time injuries is still largely unknown. Previous studies in active-duty US military and veterans have been restricted to single cohort evaluations[5-22] often involving retrospective record review[5,6,8,9] or self-report[12-19].

Furthermore, on June 21, 2010 the US Military issued a Directive Type Memorandum (DTM 09-033) with the objective to "identify, track and ensure the appropriate protection of Service members exposed to potential concussive events, including blast events, to the maximum extent possible."[23] Prior to June 2010, TBI screening was not routinely implemented in Afghanistan or Iraq and there were no standardized provisions for recurrent TBI prevention or treatment. There were accounts of strong disincentives to report symptoms plus a near universal desire of service members to remain with their units. Return-to-duty decisions were generally left to line commanders, not medical providers. Thus, many injuries were not immediately reported.[2] However, there have been no reports to our knowledge directly comparing military concussive TBI outcomes before and after the implementation of the DTM.

As part of our efforts to assess the role of advanced MRI methods in the identification and assessment of the effects of concussive TBI in US military personnel[24,25], we obtained standardized, prospective, clinician rating-based outcome information 6-12 months after injury in four distinct cohorts of US Military personnel between 2008 and 2013 using essentially identical methods across studies[21,22]. This provided the opportunity to assess the results of the 'natural experiment' initiated with the issuance of the DTM in 2010.

MATERIALS and METHODS

Subjects: We enrolled a total of 591 subjects between 2008 and 2013 across the cohorts, 347 of which completed follow up 6-12 months later at Washington University in Saint Louis (**Fig. 1**). The first 3 cohorts were enrolled at Landstuhl Region Medical Center (LRMC) following medical evacuation from theater (Study 1-3). LRMC is the primary triage facility for all medically evacuated casualties originating from Iraq and Afghanistan. Study 1 cohort was enrolled from November 2008 to August 2009 and accepted patients 0-90 days post-injury. Study 2 cohort was enrolled from September 2010 to March 2011 and accepted patients 0-30 days post-injury. Study 3 cohort was enrolled from October 2010 to May 2013 and accepted patients 0-30 days post-injury. Study 4 cohort was enrolled at Kandahar Air Field and Camp Leatherneck in Afghanistan from March to September 2012 and accepted patients 0-7 days post-injury who remained in theater. Subjects with military-related blast exposure but without clinical evidence of recent TBI were referred to as 'blast controls.' Subjects without blast exposure or TBI were referred to as 'non-blast controls.' Subjects with blast-plus-impact concussive TBI were referred to as 'Blast+impact TBI.' Subjects with non-blast-related concussive TBI (i.e. TBI from mechanisms other than blast) were referred to as 'non-blast TBI'.

Inclusion criteria across cohorts for the concussive TBI group were as follows: 1A) a positive screen for TBI at LRMC based on standard US military clinical criteria[26] including self-report of blast exposure or non-blast mechanism such as blunt trauma resulting in loss of consciousness, amnesia for the event, or change in neurological status (for studies 1-3) or, 1B) a clinical diagnosis of TBI in Afghanistan based on the criteria from the American Congress of Rehabilitation 1993, (for study 4) 2) TBI from blast or non-blast mechanisms of injury within the specified time of enrollment, 3) US military, 4) ability to provide informed consent in person, 5) no contraindications to MRI such as retained metallic fragments, 6) no prior history of moderate to severe TBI based on Department of Defense criteria, 7) no prior history of major psychiatric disorder, 8) agreement to communicate by telephone or email monthly for 6-12 months and then travel to Washington University for in-

person follow-up. Inclusion criteria for the control groups were the same except for a negative diagnosis of TBI.

Protocol: The research protocol was approved by the Human Research Protection Office at Washington University, the Institutional Review Board at Brooke Army Medical Center, the Clinical Investigation Regulatory and Human Research Protection Offices of the U.S. Army Medical Research and Materiel Command and the Department of Defense Central Command Medical Research and Materiel Command Institutional Review Board. Written informed consent was obtained from all subjects in person at the time of enrollment; no surrogate consent was allowed. Competence to provide informed consent was assessed in a standardized fashion based on responses to questions regarding the purpose of the study, expected requirements for participation, and potential risks. Additional written consent was obtained from the subjects at the time of follow-up at Washington University.

Clinical Assessments: Overall clinical outcome was assessed using the Glasgow outcome scale extended (GOS-E)[27,28]. The GOS-E is scored from 1-8: 1=dead, 2=vegetative, 3-4=severe disability, 5-6=moderate disability, 7-8=good recovery. Moderate disability (GOS-E = 5-6) is defined as one or more of the following: 1) inability to work to previous capacity 2) inability to resume the majority of regular social and leisure activities outside the home 3) psychological problems which have frequently resulted in ongoing family disruption or disruption of friendships. Severe disability is defined as reduced ability to perform activities of daily living such that supervision is required. Standardized, structured interviews were performed according to published guidelines[27].

In-person clinical evaluations at Washington University included a neurobehavioral assessment, neuropsychological test battery, and psychiatric evaluation. The neurobehavioral assessment involved a structured exam and interview designed for TBI patients (Neurobehavioral Rating Scale-Revised),[29] scored using a previously published 5 sub-domain model[30]. The neuropsychological test battery consisted of the Conner's Continuous Performance Test II[31], a computer-based assessment of attention, impulsivity, reaction time, and vigilance; the California Verbal Learning Test II[32], an assessment of verbal declarative memory; the

25 hole grooved pegboard test[33], an assessment of upper extremity motor speed and coordination; a timed 25 foot walk; the Trail Making test[34], an assessment of visual scanning, coordination and mental flexibility; the Controlled Oral Word Association test[35], an assessment of verbal fluency; the Wechsler Test of Adult Reading[36], an estimate of pre-injury verbal intelligence. The psychiatric evaluation included the Clinician-Administered PTSD Scale for DSM-IV (CAPS)[37] and the Montgomery-Asberg Depression Rating Scale (MADRS)[38].

Statistical Analyses: Data was analyzed using Statistica 12.0 (Statsoft Inc). The normal distribution of each continuous variable was assessed using the Shapiro-Wilk test. For normally distributed variables, Analysis of Variance, Analysis of Covariance and Student's t tests were used to compare groups. For non-normally distributed variables, Kruskal-Wallis Tests and Mann-Whitney U tests were used. We pre-specified the hypothesis that concussive TBI subjects would have worse outcomes than controls. One-sided tests were used when hypotheses were pre-specified, and two-sided tests were used otherwise. Uncorrected p-values have been reported, but only considered significant if $p < 0.05$ after correction for multiple comparisons. For trends over time, linear regression and generalized linear models were used. Logistic regression modeling was utilized to explore the relationship between a dichotomized measure of clinical outcome (GOS-E), and the demographic and clinical measures collected 6-12 months post injury. Models were ranked by Akaike information criterion.

RESULTS

Demographics of the subjects were consistent across the cohorts from 2008-2013. Most subjects were young, high-school educated, male, enlisted members of the US Army (**Supplementary Table S1**).

Scores on the military acute concussion evaluation (MACE) completed after medical evacuation to LRMC or directly following injury in Afghanistan did not significantly differ across studies within concussive TBI groups (**Supplemental Fig. S1A**, $p=0.87$ Kruskal Wallis ANOVA). Furthermore, there were no trends in MACE as a function of date of injury (**Supplemental Fig. S1A**, $p=0.52$ linear regression).

Global Outcomes

Global outcomes at 6-12 month follow-up assessed using the Glasgow Outcome Scale-Extended significantly differed by group (**Fig. 2A**, $p<0.0001$ Kruskal-Wallis ANOVA). Concussive TBI subjects had significantly worse outcomes than both the non-blast control subjects ($p<0.0001$) and blast controls ($p<0.0001$, one-sided Mann-Whitney U tests). The blast control subjects exhibited significantly worse outcomes than non-blast control subjects ($p=0.0044$, two-sided Mann-Whitney U). The percentage of subjects who had an overall outcome of moderate to severe disability ranged from 62-96% in the TBI cohorts.

Neurobehavioral Assessment

Neurobehavioral impairment assessed using the Neurobehavioral Rating Scale-Revised also differed significantly by group (**Fig. 2B**, $p<0.0001$ Kruskal Wallis ANOVA). Concussive TBI subjects exhibited significantly worse neurobehavioral impairments than both non-blast controls ($p<0.0001$) and blast controls ($p=0.001$, one-sided Mann-Whitney U tests). Blast controls were more impaired than non-blast controls ($p<0.0001$, two-sided Mann-Whitney U test). Impairments were noted in each of the 5 sub-domains: mood/affect, executive/cognitive function, oral/motor function, positive symptoms, and negative symptoms (**Supplemental Fig. S2**; all $p<0.0001$, Kruskal Wallis ANOVA).

Neurobehavioral impairments among concussive TBI subjects were less severe for those injured after June 21, 2010 than for those injured before the issuance of the DTM (**Fig. 2C**, $p=0.017$, Mann Whitney U test).

The significance was marginal (p=0.057, ANCOVA) when including the following covariates: age, education, branch (army vs. other), race (white vs. other), mechanism of injury (blast vs. non-blast) and evacuation to LRMC vs. treatment in Afghanistan with return to duty. None of the covariates were significantly associated with neurobehavioral impairment. Furthermore, there was a trend towards less severe neurobehavioral impairment after concussive TBI as a function of date of injury (**Fig. 2D**). Average impairments decreased by 1.05 points (out of 87) per year from 2008-2013 (r^2=0.04, p=0.0037, linear regression). However, this trend lost statistical significance when including the covariates in the statistical model (p=0.08, generalized linear model).

Neuropsychological Testing

Across independent cohorts, most concussive TBI patients performed indistinguishably from controls on neuropsychological testing (**Supplemental Table S2**). Evaluation at the single-subject level revealed subsets of concussive TBI subjects with impaired neuropsychological performance (**Fig. 3**). Abnormal performance on each individual assessment was defined as a subject's score that fell outside 2 standard deviations worse than the mean of the pooled non-blast control group for that exam. For each subject, the number of tests with abnormal performance was then summed. The number of subjects per group was then compared to what would be expected by chance. More subjects with abnormal test performance in 2 or more neuropsychological assessments than expected by chance were observed in the evacuated TBI subjects from studies 1-3 (51/161, 31%, p=0.00001), the non-evacuated TBI subjects from study 4 (10/31, 26%, p=0.003), and blast control subjects (10/45. 22%, p=0.01, Chi-square tests). There were no differences between subjects injured before vs. after the issuance of the DTM (p=0.87) and no trends in neuropsychological test abnormalities after concussive TBI as a function of date of injury (p=0.53).

Post-Traumatic Stress Disorder and Depression

Clinician ratings of depression and PTSD severity substantially differed across groups (**Fig. 4,** p<0.0001, Kruskal Wallis ANOVA). Concussive TBI subjects were more depressed than both non-blast control (p<0.0001) and blast control (p=0.0062, one-tailed Mann-Whitney U tests) subjects. Blast controls also had more depression than non-blast controls (p=0.0007 two-tailed Mann-Whitney U test). Similarly, concussive

TBI subjects also more severe PTSD than both non-blast controls (p<0.0001) and blast controls (p=0.0004, one-tailed Student's t tests). Blast controls also had more severe PTSD than non-blast controls (p<0.0001 two-tailed Student's t test). All three PTSD domain sub-scores (re-experiencing, avoidance and numbing, hyperarousal) were found to also be significantly different across groups, as was self-reported sleep deprivation (**Supplemental Figure S3**, p<0.0001 Kruskal-Wallis ANOVAs).

Among concussive TBI subjects, both depression and PTSD were less severe for those injured after the issuance of the DTM than before (**Fig. 4C-D**, p=0.02 for depression p=0.006 for PTSD, Mann Whitney U tests). However, the statistical significance was lost (p=0.12 for depression, p=0.07 for PTSD, ANCOVA) when including the covariates. Evacuated TBI subjects (studies 1-3) had more severe PTSD than non-evacuated (study 4) subjects (p=0.03) in this analysis. There were trends towards less severe depression and PTSD as a function of date of injury (**Fig. 4E-F**). Depression decreased by 1.6 points (out of 60) and PTSD decreased by 5.9 points (out of 156) on average per year from 2008-2013 (r^2=0.035, p=0.012 for depression, r^2=0.069, p=0.00037 for PTSD, linear regression). The trend for depression lost significance (p=0.15) but the trend for PTSD maintained statistical significance when including the covariates (p=0.03, generalized linear models).

Multivariate Predictors of Dichotomized Global Outcome

Dichotomized global outcome was defined as follows: GOS-E scores of 7-8 were categorized as good outcome and scores of ≤6 were defined as disabled. Candidate variables for logistic regression modeling included PTSD severity (CAPS total score), depression severity (MADRS), poor sleep index, group distinction (Control vs. TBI), exposure (blast vs. non-blast), enrollment site distinction (evacuated vs. non-evacuated), age, education, and number of neuropsychological test abnormalities. The best logistic regression contained the CAPS, MADRS, group distinction (control vs. TBI), and enrollment site distinction (evacuated vs. non-evacuated) with a receiver-operating characteristic area under the curve 0.8351 (**Fig. 5**). Higher likelihood of disability was observed in service members with diagnoses of concussive TBI who were evacuated and had more severe PTSD and depression.

DISCUSSION

In summary, there were adverse clinical outcomes 6-12 months after concussive TBI in a substantial majority of US military personnel injured in theater. Outcomes were generally consistent across four cohorts enrolled from 2008-2013, though there were modest improvements in PTSD severity over time. Blast-exposed service members without apparent TBI had outcomes that were intermediate between subjects with concussive TBI and non-blast-exposed military controls. Adverse global outcomes were most strongly associated with concussive TBI, PTSD and depression severity, and requirement for medical evacuation from theater.

The percentage of concussive TBI subjects with poor overall outcome at 6-12 month outcome (62-96%) far exceeds what is routinely reported in the civilian literature for comparable patient populations where reports range from 22-47% [39,40]. Blast-related TBI itself does not appear to be a major contributor, as subjects with non-blast-related TBI fared comparably.[22]

This is the first study to our knowledge to attempt to assess the effects of the issuance of the Department of Defense Directive Type Memorandum (DTM) in 2010 regarding identification and treatment of military concussive TBI in theater.[23] While such an assessment was not our pre-specified purpose, these 4 longitudinal cohorts assessed in a homogenous fashion over 5 years provided a serendipitous opportunity to do so. Strengths of this study include the use of a prospective, observational, longitudinal research design; enrollment of all combat-deployed, active-duty US military; the inclusion of subjects with both blast-related and non-blast-related concussive TBI; the assessment of both blast-exposed and non-blast-exposed combat-deployed controls; the incorporation of both medically-evacuated and non-medically evacuated casualties; and the comparison of four independent cohorts of subjects across all branches of the military.

Nonetheless, there are several limitations that should be acknowledged: 1) diagnostic accuracy, 2) self-report for many of the key outcome measures, 3) heterogeneous treatment across centers in theater and in the US after injury 4) single time point for most assessments 5) incomplete assessment of combat exposure severity 6) no objective markers of the severity of initial injury, 7) possible unmeasured covariates that differ between groups 8) lack of long-term follow-up.

Based on this data, it appears that the severity of PTSD and depression are strongly linked to overall outcomes following concussive TBI in US service members. However, the direction of causality cannot be determined from the current results. In our view, the most likely scenario is that concussive TBI along with the emotional dysregulation that accompanies deployment in a war zone interact supra-additively to worsen outcomes; TBI may damage the brain's emotional regulation circuitry and emotional dysregulation may interfere with recovery from TBI. However, it is also possible that the overall injury severity is the primary driver of both overall outcomes and emotional dysregulation. A third alternative is that the stress of a wartime event labeled as a concussive injury leading to subsequent separation from ones' unit may result in worsening PTSD and depression, which in turn drive disability. Clearly, future studies involving objective measures of primary brain injury severity and careful anatomical delineation of the relevant brain circuitry involved in emotional regulation will be required to address these alternatives.

REFERENCES

1.   Honoring American Wartime Veterans. US Department of Commerce, Economics and Statistics Administration, 2013. at http://www.census.gov/how/pdf/memorial_day.pdf.)

2.   Tanielian TL, Jaycox LH. Invisible Wounds of War: Psychological and Cognitive Injuries, Their Consequences, and Services to Assist Recovery: RAND Corporation 2008.

3.   DoD Numbers for Traumatic Brain Injury, Worldwide - Totals, 2000-2012 (Q1-Q3). 2013. (Accessed 12/10/13, 2013, at http://www.dvbic.org/sites/default/files/uploads/dod-tbi-worldwide-2000-2013-Q3-as-of-05%20Nov-2013.pdf.)

4.   Casscells S. Traumatic Brain Injury: Definition and Reporting. In: Defense Aso, ed: Department of Defense 2007.

5.   Cooper DB, Chau PM, Armistead-Jehle P, Vanderploeg RD, Bowles AO. Relationship between mechanism of injury and neurocognitive functioning in OEF/OIF service members with mild traumatic brain injuries. Military medicine 2012;177:1157-60.

6.   Eskridge SL, Macera CA, Galarneau MR, et al. Influence of combat blast-related mild traumatic brain injury acute symptoms on mental health and service discharge outcomes. Journal of neurotrauma 2013;30:1391-7.

7.   Fischer BL, Parsons M, Durgerian S, et al. Neural Activation during Response Inhibition Differentiates Blast from Mechanical Causes of Mild to Moderate Traumatic Brain Injury. Journal of neurotrauma 2014;31:169-79.

8.   Galarneau MR, Woodruff SI, Dye JL, Mohrle CR, Wade AL. Traumatic brain injury during Operation Iraqi Freedom: findings from the United States Navy-Marine Corps Combat Trauma Registry. Journal of neurosurgery 2008;108:950-7.

9.   Kontos AP, Kotwal RS, Elbin RJ, et al. Residual effects of combat-related mild traumatic brain injury. Journal of neurotrauma 2013;30:680-6.

10.   Petrie EC, Cross DJ, Yarnykh VL, et al. Neuroimaging, behavioral, and psychological sequelae of repetitive combined blast/impact mild traumatic brain injury in Iraq and Afghanistan war veterans. Journal of neurotrauma 2014;31:425-36.

11.   Verfaellie M, Lafleche G, Spiro A, 3rd, Tun C, Bousquet K. Chronic postconcussion symptoms and functional outcomes in OEF/OIF veterans with self-report of blast exposure. J Int Neuropsychol Soc 2013;19:1-10.

12.   Belanger HG, Proctor-Weber Z, Kretzmer T, Kim M, French LM, Vanderploeg RD. Symptom complaints following reports of blast versus non-blast mild TBI: does mechanism of injury matter? The Clinical neuropsychologist 2011;25:702-15.

13.   Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. The New England journal of medicine 2008;358:453-63.

14.   Kennedy JE, Cullen MA, Amador RR, Huey JC, Leal FO. Symptoms in military service members after blast mTBI with and without associated injuries. NeuroRehabilitation 2010;26:191-7.

15.   Polusny MA, Kehle SM, Nelson NW, Erbes CR, Arbisi PA, Thuras P. Longitudinal effects of mild traumatic brain injury and posttraumatic stress disorder comorbidity on postdeployment outcomes in national guard soldiers deployed to Iraq. Archives of general psychiatry 2011;68:79-89.

16.   Schneiderman AI, Braver ER, Kang HK. Understanding sequelae of injury mechanisms and mild traumatic brain injury incurred during the conflicts in Iraq and Afghanistan: persistent postconcussive symptoms and posttraumatic stress disorder. American journal of epidemiology 2008;167:1446-52.

17.   Thomas JL, Wilk JE, Riviere LA, McGurk D, Castro CA, Hoge CW. Prevalence of mental health problems and functional impairment among active component and National Guard soldiers 3 and 12 months following combat in Iraq. Archives of general psychiatry 2010;67:614-23.

18.   Wilk JE, Herrell RK, Wynn GH, Riviere LA, Hoge CW. Mild traumatic brain injury (concussion), posttraumatic stress disorder, and depression in U.S. soldiers involved in combat deployments: association with postdeployment symptoms. Psychosomatic medicine 2012;74:249-57.

19.   Wilk JE, Thomas JL, McGurk DM, Riviere LA, Castro CA, Hoge CW. Mild traumatic brain injury (concussion) during combat: lack of association of blast mechanism with persistent postconcussive symptoms. The Journal of head trauma rehabilitation 2010;25:9-14.

20.   Luethcke CA, Bryan CJ, Morrow CE, Isler WC. Comparison of concussive symptoms, cognitive performance, and psychological symptoms between acute blast-versus nonblast-induced mild traumatic brain injury. J Int Neuropsychol Soc 2011;17:36-45.

21.   Mac Donald CL, Johnson AM, Wierzechowski L, et al. Prospectively assessed clinical outcomes in concussive blast vs nonblast traumatic brain injury among evacuated US military personnel. JAMA neurology 2014;71:994-1002.

22.   Mac Donald CL, Johnson AM, Nelson EC, et al. Functional status after blast-plus-impact complex concussive traumatic brain injury in evacuated United States military personnel. Journal of neurotrauma 2014;31:889-98.

23.   Lynn WJ. Policy Guidance for Management of Concussion/Mild Traumatic Brain Injury in the Deployed Setting. In: DEFENSE DSO, ed.2010.

24.   Mac Donald CL, Johnson AM, Cooper D, et al. Detection of blast-related traumatic brain injury in U.S. military personnel. The New England journal of medicine 2011;364:2091-100.

25.   Han K, Mac Donald CL, Johnson AM, et al. Disrupted modular organization of resting-state cortical functional connectivity in U.S. military personnel following concussive 'mild' blast-related traumatic brain injury. NeuroImage 2014;84:76-96.

26.   Dempsey KE, Dorlac WC, Martin K, et al. Landstuhl Regional Medical Center: traumatic brain injury screening program. Journal of trauma nursing : the official journal of the Society of Trauma Nurses 2009;16:6-7, 10-2.

27.   Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. Journal of neurotrauma 1998;15:573-85.

28.   Pettigrew LE, Wilson JT, Teasdale GM. Reliability of ratings on the Glasgow Outcome Scales from in-person and telephone structured interviews. The Journal of head trauma rehabilitation 2003;18:252-8.

29.   Levin HS, High WM, Goethe KE, et al. The neurobehavioural rating scale: assessment of the behavioural sequelae of head injury by the clinician. Journal of neurology, neurosurgery, and psychiatry 1987;50:183-93.

30.   McCauley SR, Levin HS, Vanier M, et al. The neurobehavioural rating scale-revised: sensitivity and validity in closed head injury assessment. Journal of neurology, neurosurgery, and psychiatry 2001;71:643-51.

31.   Conners C, Staff. M. Conners' Continuous Performance Test II: Computer program for Windows technical guide and software manual. North Tonwanda, NY: Multi-Health Systems; 2000.

32.   Delis D, Kramer J, Kaplan E, B O. California Verbal Learning Test Manual: Second Edition, Adult Version. San Antonio, Tx: Psychological Corporation; 2000.

33.   Matthews C, Kløve H. Instruction manual for the Adult Neuropsychology Test Battery. Madison, WI: University of Wisconsin Medical School; 1964.

34.   Reitan R. Trail Making Test manual for administration and scoring. Tuscon, AZ: Reitan Neuropsychology Laboratory; 1992.

35.   Benton A, Hamsher K, A S. Multilingual Aphasia Examination (3rd ed.). Iowa City, Ia: AJA Associates; 1983.

36.   Wechsler D. Wechsler Test of Adult Reading (WTAR) Manual. New York: Psychological Corporation; 2001.

37.   Weathers FW, Keane TM, Davidson JR. Clinician-administered PTSD scale: a review of the first ten years of research. Depression and anxiety 2001;13:132-56.

38.   Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. The British journal of psychiatry : the journal of mental science 1979;134:382-9.

39.   McMahon P, Hricik A, Yue JK, et al. Symptomatology and Functional Outcome in Mild Traumatic Brain Injury: Results from the Prospective TRACK-TBI Study. Journal of neurotrauma 2014;31:26-33.

40.   Thornhill S, Teasdale GM, Murray GD, McEwen J, Roy CW, Penny KI. Disability in young people and adults one year after head injury: prospective cohort study. BMJ 2000;320:1631-5.
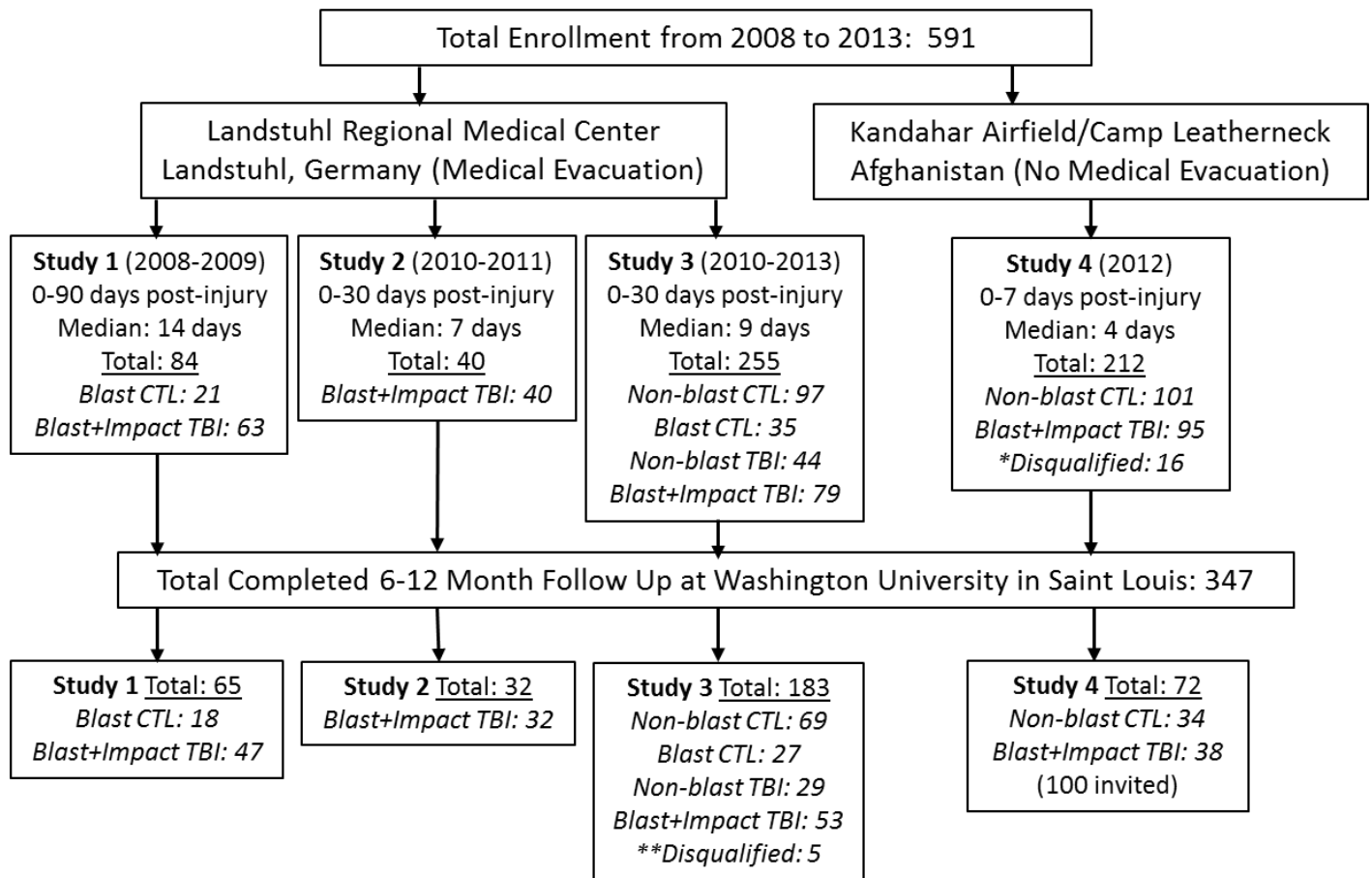
Figure 1. Consort Diagram of Cross Cohort Enrollment.

*Subjects disqualified for poor performance on the Test of Memory Malingering and/or substantial artifacts on MRI; a criteria of the study.

**Subjects disqualified at follow up for clear malingering and/or erratic performance on clinical evaluations.
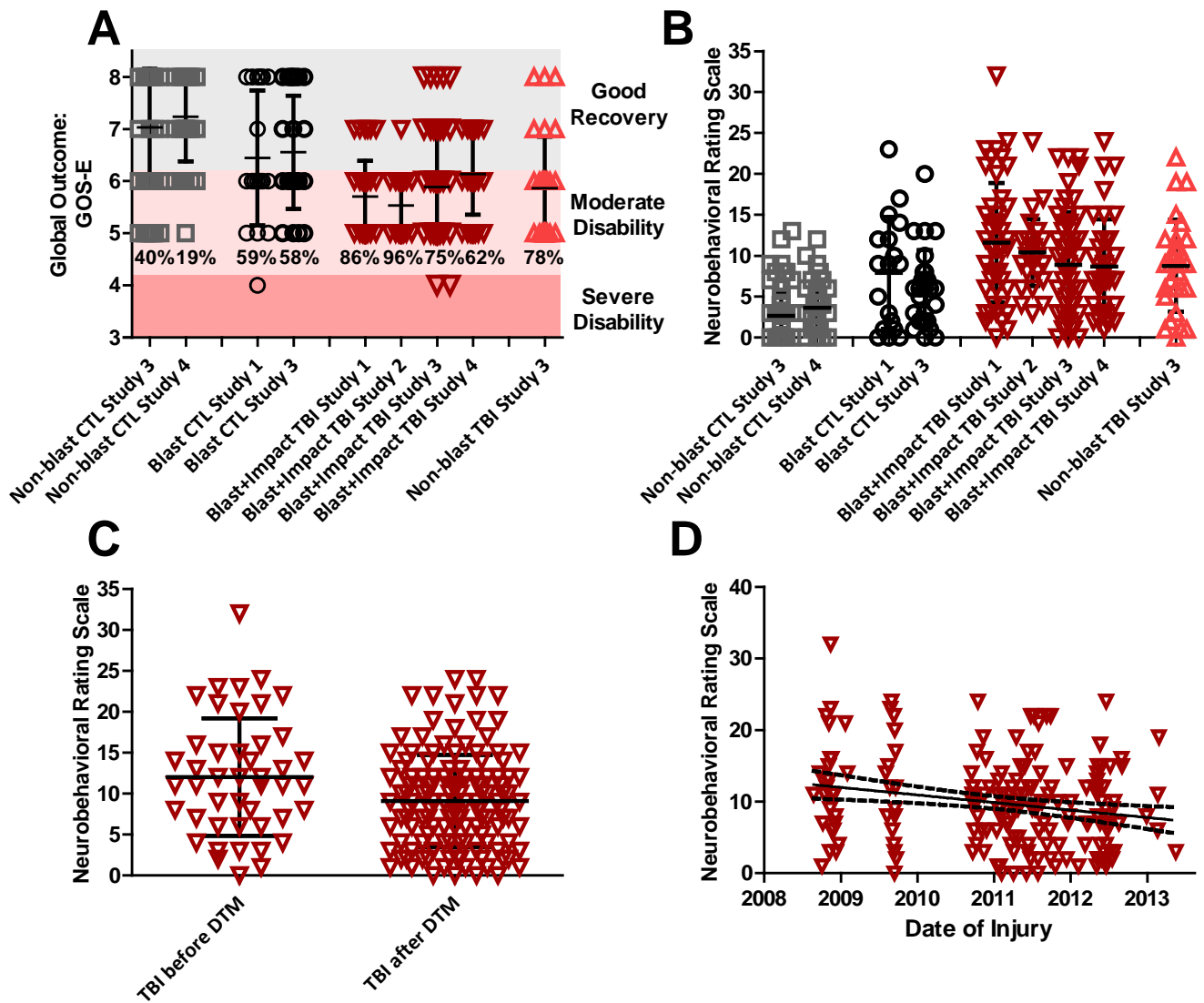
Figure 2. Global Measures of Outcome. A. Glasgow Outcome Scale – Extended (GOS-E). Percent of service members with moderate to severe disability are reported under each study group on the graph. **B.** Neurobehavioral outcome assessed using the Neurological Rating Scale-Revised (NRS) Total Score: (Max 87). Results assessed 6-12 months after enrollment. **C.** Worse neurobehavioral outcomes before the issuance of the DTM on 6/21/10 compared to afterwards (p=0.017, Mann-Whitney U test, p=0.057 ANCOVA). **D.** Trend towards reduced neurobehavioral impairment over time (p=0.0037 linear regression, p=0.08 generalized linear model).
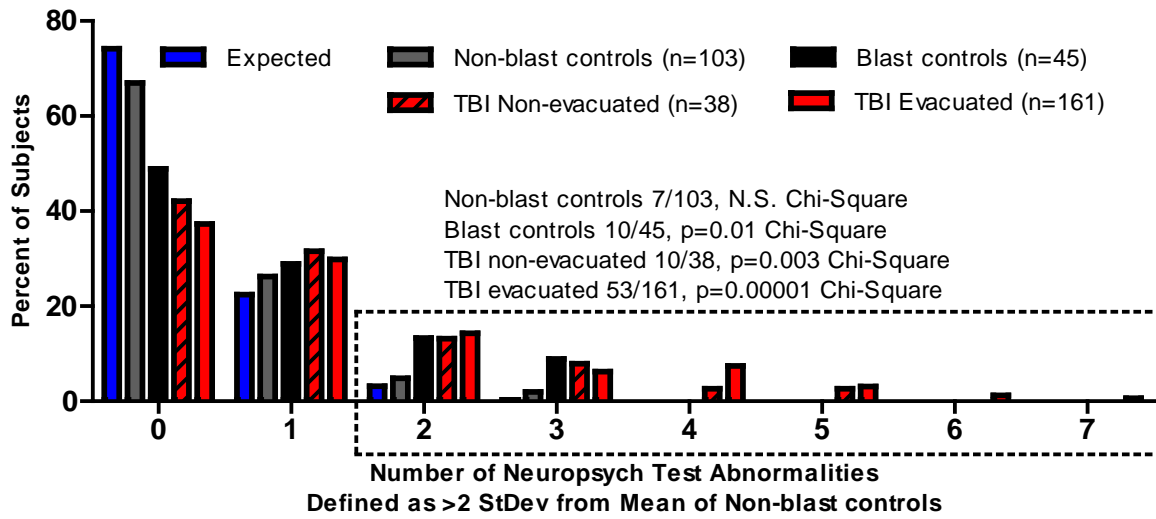
Figure 3. Neuropsychological testing abnormalities. The number of subjects with neuropsychological test abnormalities are displayed by group in comparison to what would be expected by chance (black bars). Percent of subjects is displayed to account for the differences in the number of subjects in each group. Dotted box indicates the group of subjects who had poor performance on 2 or more of the 13 neuropsychological variables.
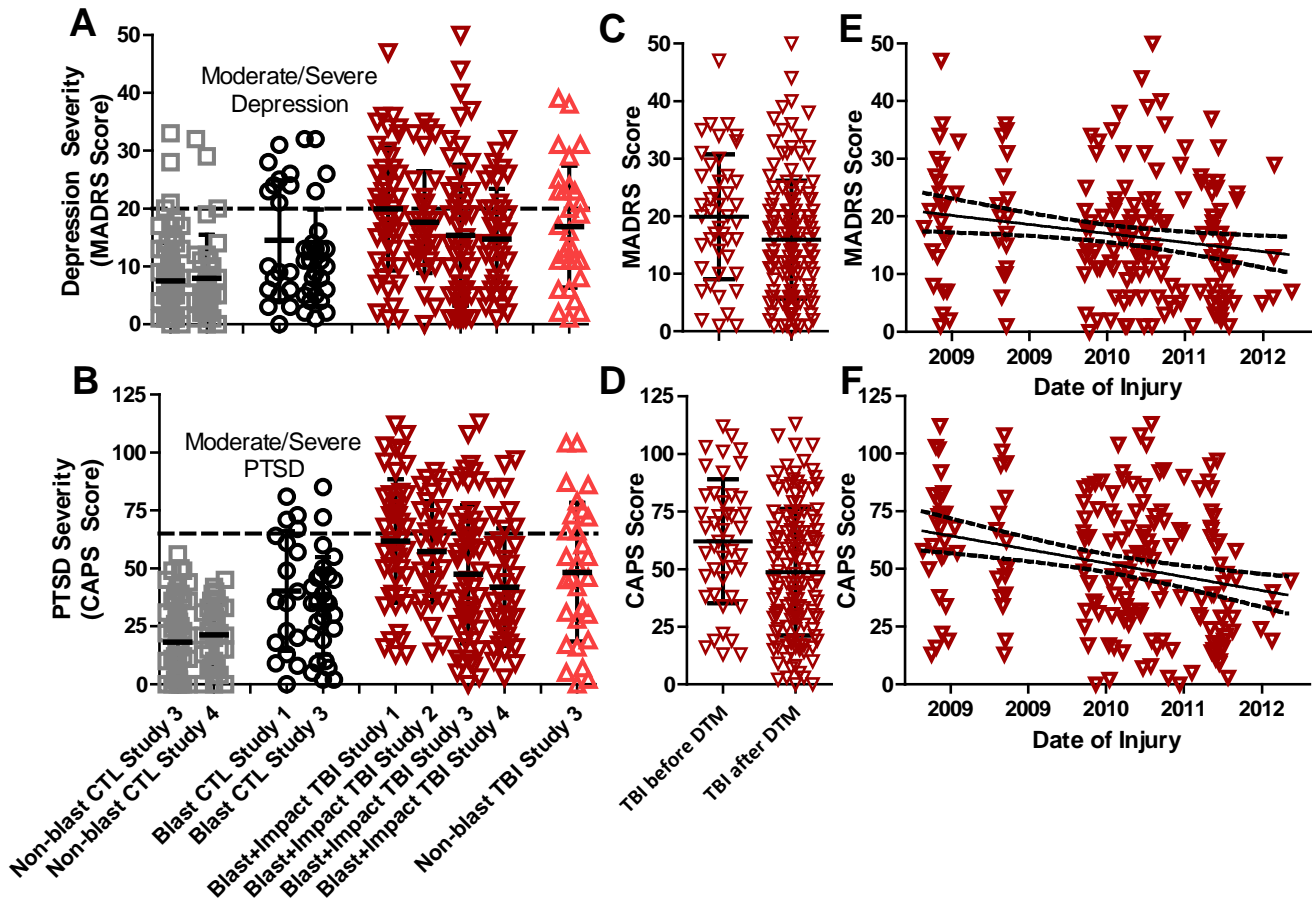
Figure 4. PSTD and Depression Severity. A. Depression severity assessed by the Montgomery Asberg depression rating scale (MADRS) (Max 60). **B.** PTSD severity assessed by the Clinician administered PTSD scale for DSM IV (CAPS) (Max 136). Dotted lines indicate the threshold for moderate to severe symptomatology for each evaluation. **C.** Worse depression before the issuance of the DTM on 6/21/10 compared to afterwards (p=0.02, Mann-Whitney U test, p=0.12 ANCOVA). **D.** Worse PTSD before the issuance of the DTM compared to afterwards (p=0.006, Mann-Whitney U test, p=0.07 ANCOVA). **E.** Trend towards reduced depression over time (p=0.012 linear regression, p=0.15 generalized linear model). **F.** Statistically significant reduction in PTSD over time (p=0.00037 linear regression, p=0.03 generalized linear model).

GOS-E Model Best Subset:
TBI vs. Control, Enrollment Site, MADRS, CAPS

Area = 0.8351
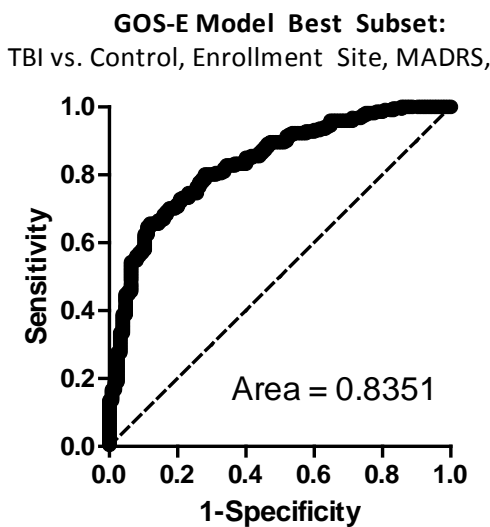
Best Fit Model - Dichotomized GOSE: CAPS, MADRS, CTL/TBI				
Overall model : AIC 337.01, Likelihood ratio Chi square: 125.66				
Parameter	**Estimate**	**95% Confidence Interval**	**P-value**	**Worse Outcome**
Intercept	-1.2832	(-1.8131 :-0.7532)	0.000002	
TBI /Control	0.5474	(0.8291 : 0.2658)	0.0001	TBI
Enrollment Site: Med-Evac vs. Non-Med-Evac	0.5672	(0.2462 : 0.8882)	0.0005	Med-Evac
MADRS (Depression Symptoms)	0.0657	(0.0137 : 0.1176)	0.0133	Higher Score
CAPS (PTSD Symptoms)	0.0229	(0.0033 : 0.0426)	0.0223	Higher Score

Figure 5. Predictors of Global Outcome. A. Receiver-operator curve and parameter table for best fit model of overall disability defined as the dichotomized GOS-E of 7 or 8 – good outcome, and 6 or below – disabled. The best model contained the CAPS PTSD severity score, MADRS Depression severity score, group distinction of Control vs TBI, and enrollment site distinction of patients requiring medical evacuation vs. those that did not require medical evacuation.

Outcome Trends Following US Military Concussive Traumatic Brain Injury

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SUPPLEMENTARY MATERIAL

Supplementary Methods

Active duty military subjects were not paid for participation, though travel expenses to Washington University were covered. Subjects not on active military duty status at the time of follow-up were paid $240 plus travel expenses for participation.

For the control groups in the LRMC cohorts who were medically evacuated, gastrointestinal, dermatological, and women's health reasons were the main diagnoses. Orthopedic injuries from non-combat events such as broken bones resulting from recreational sports on time off or work-related accidents also comprised a subset of this population. The control group from Afghanistan mostly included onsite personnel who volunteered to participate in the study. A small number of controls enrolled in Afghanistan also had minor orthopedic injuries from non-combat events that did not require medical evacuation to LRMC. All clinical histories from the controls indicated no current or previous diagnoses of TBI. The blast control groups endorsed previous history of blast exposure but were found not to have had TBI following a clinical evaluation for possible brain injury at LRMC.

For the blast TBI groups across all of the cohorts, all available clinical histories indicated blast exposure plus another mechanism of head injury such as a fall, motor vehicle crash, or being struck by a blunt object. None suffered an isolated blast injury. The mechanisms of injury for the non-blast TBI group were primarily falls, motor vehicle crashes, or being struck by a blunt object that did not involve blast exposure. For both the blast and non-blast TBI groups, clinical histories indicated a change in the level of consciousness or loss of consciousness for a few minutes and post-traumatic amnesia for less than 24 hours. The requirement for in-person informed consent made more severe TBI patients typically not eligible and none were enrolled. No intracranial abnormalities were detected on non-contrast head CT. Thus, all TBI subjects met the DoD criteria for uncomplicated 'mild'/ concussive TBI.

All clinical histories were verified by study personnel taking additional clinical history and reviewing medical records. None that screened positive for TBI were determined not to have had a TBI upon further

inspection. Initial records of clinical status in TBI subjects using the Military Assessment of Concussion Exam (MACE)[1] were reviewed. This brief cognitive test assesses orientation, immediate verbal memory, concentration, and short term delayed verbal memory.

The standardized neurological exam and interview required approximately 1 hour per subject. The psychiatric assessments required approximately 2 hours per subject, and the neuropsychological battery required approximately 2 hours per subject. Subjects took all medications as prescribed by their clinical providers. All tests were performed between 9 am and 5 pm in private, quiet, well-lighted rooms. All examiners were blinded to other clinical information, though in the course of the interviews it often became clear whether the subjects were in the TBI or control group based off their endorsements of prior events. All examiners were clinicians who underwent standardized training in administering the assessments.

A relatively easy forced choice test embedded in the California Verbal Learning Test was used to assess adequacy of effort. 5 subjects, all from study 3, were disqualified for either poor effort or clear malingering.

The CAPS was scored using standard scoring rules from the Blake et al, National Center for Post-traumatic Stress Disorder, July 1998 revision.

Safety and Data Monitoring: Subjects were assigned a random 4 digit code number to protect confidentiality and all research data was identified by code number only. A board certified psychiatrist (E. Nelson) was immediately available in case the CAPS examination exacerbated PTSD symptoms. No exacerbations requiring medical intervention occurred, though additional support from study staff was required on several occasions.

For clinical evaluations, the principal investigator audited 1 in 10 randomly selected subjects' data sets to ensure that data was scored and entered correctly. These audits revealed only minor discrepancies in scoring criteria which were then corrected across the entire cohort of subjects.

Additional Statistical Analyses:

Following Dunn's correction for multiple comparisons, there were no significant differences in GOS-E within comparable sub-group of subjects across studies. Therefore, the data was combined into the following three groups for additional analysis: Non-blast control, blast control, concussive TBI.

For ANCOVA and generalized linear models there were too few officers (8 total) or females (10 total) for accurate statistical assessment, so the analysis was limited to enlisted males.

To determine the number of neuropsychological tests expected to be abnormal by chance, the binomial distribution was used with $p=0.02275$ for the ($n=13$) neuropsychological variables examined. Prior to this analysis, all neuropsychological variables were confirmed to be statistically independent as is required by the assumptions of this approach.

There were no significant differences in the number of subjects with abnormal neuropsychological test performance in 2 or more neuropsychological assessments between evacuated TBI subjects, non-evacuated TBI subjects, and blast control subjects.

For logistic regression, the Statistica 12.0 'generalized linear/nonlinear model building' algorithm was used with the selection of the 'logit' link function for logistic regression. The algorithm generated a distinct model for each possible subset of demographic data and quantitative measures of specific symptoms and impairments. Models were then ranked by Akaike information criterion.

Supplementary Tables

Supplemental Table S1. Follow Up Participant Characteristics									
	Study 1		**Study 2**		**Study 3**			**Study 4**	
Characteristic	Blast CTL (n=18)	Blast TBI (n=47)	Blast TBI (n=32)	Non-blast CTL (n=69)	Blast CTL (n=27)	Non-blast TBI (n=29)	Blast TBI (n=53)	Non-blast CTL (n=34)	Blast TBI (n=38)
Age in years:									
median (range)	32(20-49)	26 (19-45)	24 (19-44)	31 (21-49)	34 (22-46)	28.5 (20-50)	26 (19-47)	28 (19-44)	26 (20-41)
Education in years:									
median (range)	13 (12-18)	12 (8-17)	12 (9-16)	14 (9-28)	13 (10-19)	14 (9-18)	12 (12-18)	15 (12-24)	13 (12-18)
Gender no (%)									
Male	16 (100%)	47 (100%)	29 (91%)	63 (91%)	25 (92%)	26 (87%)	51 (96%)	27 (79%)	36 (95%)
Female	0	0	3 (9%)	6 (9%)	2 (8%)	3 (13%)	2 (4%)	7 (21%)	2 (5%)
Race/ethnicity no (%)									
White	15 (83%)	35 (74%)	22 (68%)	50 (73%)	20 (77%)	19 (60%)	40 (76%)	22 (65%)	29 (77%)
African American	2 (11%)	5 (11%)	5 (16%)	16 (23%)	4 (12%)	7 (27%)	4 (6%)	5 (15%)	2 (5%)
Hispanic/Latino	1 (6%)	2 (4%)	5 (16%)	3 (4%)	2 (8%)	3 (10%)	7 (14%)	7 (20%)	7 (18%)
Asian	0	5 (11%)	0	0	1 (3%)	1 (3%)	2 (4%)	0	0
Branch of Service no (%)									
US Army	15 (83%)	42 (89%)	26 (81%)	55 (80%)	24 (89%)	26 (90%)	46 (90%)	13 (38%)	32 (84%)
US Air Force	2 (11%)	0	0	11 (16%)	0	2 (7%)	1 (2%)	2 (6%)	0
US Marine Corps	1 (6%)	5 (11%)	5 (16%)	3 (4%)	3 (11%)	1 (3%)	5 (6%)	3 (9%)	6 (16%)
US Navy	0	0	1 (3%)	0	0	0	1 (2%)	16 (47%)	0
Military Rank no (%)									
Enlisted	16 (89%)	45 (96%)	32 (100%)	63 (91%)	24 (89%)	27 (93%)	52 (98%)	24 (71%)	35 (92%)
Officer	2 (11%)	2 (4%)	0	6 (9%)	3 (11%)	2 (7%)	1 (2%)	10 (29%)	3 (8%)
Theatre of Operation no (%)									
Afghanistan	6 (33%)	28 (60%)	27 (84%)	55 (80%)	21 (77%)	18 (60%)	50 (94%)	34 (100%)	38(100%)
Iraq	12 (69%)	19 (40%)	5 (16%)	14 (20%)	6 (23%)	11 (40%)	3 (6%)	0	0

| Supplemental Table S2. Neuropsychological Test Performance								
	Study 1		**Study 2**	**Study 3**				**Study 4**	
Assessment	Blast Control (n=18)	Blast+Impact TBI (n=47)	Blast +Impact TBI (n=32)	Non Blast Control (n=69)	Blast Control (n=27)	Non Blast TBI (n=29)	Blast+Impact TBI (n=53)	Non Blast Control (n=33)	Blast+Impact TBI (n=38)
25-Foot Walk (seconds)*	5.18 ± 2.05	4.96 ± 1.02	4.65 ± 1.37	3.92 ± 0.82	4.22 ± 0.66	4.76 ± 1.16	4.59 ± 1.17	3.78 ± 0.60	4.23 ± 0.68
(Motor Strength, Balance, Coordination)									
Conners' Continuous Performance Test II									
Omission Errors (T-score):	54.49 ± 21.18	51.39 ± 12.56	75.67 ± 64.71	48.29 ± 12.17	47.45 ± 7.51	53.30 ± 15.11	56.06 ± 19.8	48.85 ± 10.51	60.41 ± 28.13
(Attention Lapses)									
Commission Errors (T-score):	50.92 ± 10.54	51.73 ± 9.64	55.36 ± 8.85	50.40 ± 10.60	50.02 ± 8.19	52.46 ± 9.81	54.05 ± 10.6	53.83 ± 11.03	54.69 ± 10.16
(Impulsivity)									
Hit Rate (T-score):	49.4 ± 11.22	47.69 ± 9.04	47.88 ± 12.80	48.94 ± 11.72	48.98 ± 8.67	52.10 ± 12.22	47.83 ± 8.63	46.06 ± 9.88	50.81 ± 10.33
(Reaction Time)									
Hit Rate Block Change (T-score):	52.62 ± 10.29	52.17 ± 10.74	49.92 ± 13.73	52.05 ± 10.62	48.01 ± 8.82	51.64 ± 13.75	48.73 ± 12.0	48.67 ± 5.56	54.69 ± 13.43
(Sustained Vigilance)									
Wechsler Test of Adult Reading (Standard Score)	97.56 ± 12.56	98.3 ± 11.74	100.09 ± 10.48	102.88 ± 14.55	100.56 ± 10.99	98.52 ± 11.10	99.49 ± 11.66	105.41 ± 10.58	99.03 ± 12.50
(Estimate of Pre-injury Verbal Intelligence)									
California Verbal Learning Test II									
Long-Delay Free Recall (Standard Score)	0 ± 0.89	-0.13 ± 0.94	-0.33 ± 1.31	-0.17 ± 1.10	-0.15 ± 0.95	-0.32 ± 1.27	-0.58 ± 1.21	0.15 ± 1.28	-0.57 ± 0.92
(Verbal Memory)									
Total Intrusions (Standard Score)	0.44 ± 1.45	0.15 ± 1.04	0.28 ± 1.10	0.22 ± 1.00	0.22 ± 0.95	0.52 ± 1.42	0.45 ± 1.38	0.14 ± 0.84	0.50 ± 1.22
(Falsely Recalled Items)									
List B vs. Trial 1 List A (Standard Score)	0.11 ± 1.13	-0.34 ± 1.11	-0.23 ± 1.16	0.08 ± 0.87	-0.15 ± 0.89	0.58 ± 1.03	-0.16 ± 1.12	0.00 ± 1.05	-0.12 ± 0.90
(Proactive Memory Interference)									
Grooved Pegboard*									
(Motor Speed & Coordination)									
Average Dom & Non-Dom Time (seconds)	80.94 ± 11.54	77.31 ± 12.65	78.72 ± 14.28	69.03 ± 17.7	69.04 ± 10.56	75.84 ± 15.85	75.54 ± 15.52	67.68 ± 10.34	71.63 ± 7.74
Trail Making Test									
Trails A time (seconds)	24.78 ± 5.86	27.28 ± 10.54	28.02 ± 11.28	22.10 ± 8.61	24.26 ± 7.41	26.57 ± 14.10	28.5 ± 16.69	23.24 ± 7.65	23.6 ± 7.08
(Visual Scanning, Coordination)									
Trails B time (seconds)	59.56 ± 15.80	66.79 ± 22.53	63.06 ± 19.01	57.12 ± 24.77	57.00 ± 14.97	67.52 ± 31.28	61.19 ± 21.40	55.38 ± 18.65	64.43 ± 23.89
(Trails A + Mental Flexibility)									
Controlled Oral Word Association* Total Score: *(Verbal Fluency)*	34.33 ± 7.35	35.91 ± 9.31	34.19 ± 9.53	42.1 ± 10.18	40.37 ± 9.05	37.62 ± 9.98	37.75 ± 9.30	42.82 ± 9.61	41.45 ± 11.47

Supplemental Table S2: * Significant group differences by Kruskal-Wallis ANOVA after Bonferroni correction for multiple comparisons.

Performance on three tests was significantly different across studies by Kruskal Wallis ANOVA after correction for multiple comparisons. This included the 25 hole grooved pegboard test (p=0.00001), an assessment of upper extremity motor speed and coordination; a timed 25 foot walk (p=0.0001), and the Controlled Oral Word Association test (p=0.001), an assessment of verbal fluency. For each assessment the non-blast control subjects from study 3 and 4 outperformed blast control subjects and the medically evacuated concussive TBI groups from studies 1-3. There were no significant differences after Dunn's correction for multiple comparisons between the non-blast controls and non-medically evacuated concussive TBI group from study 4.

A
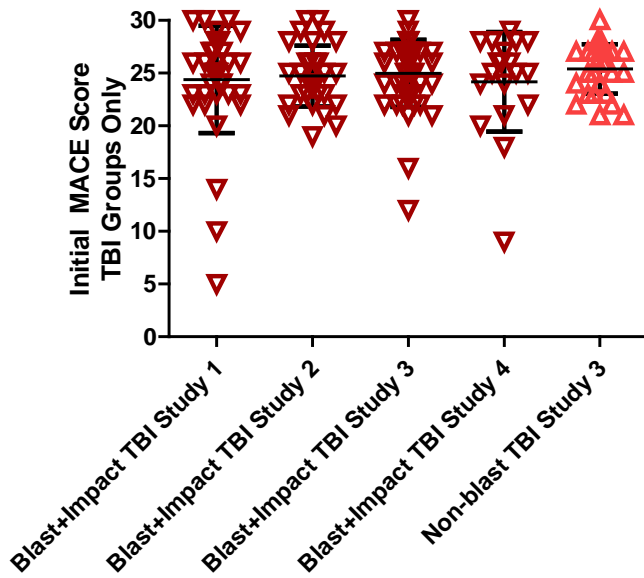
B
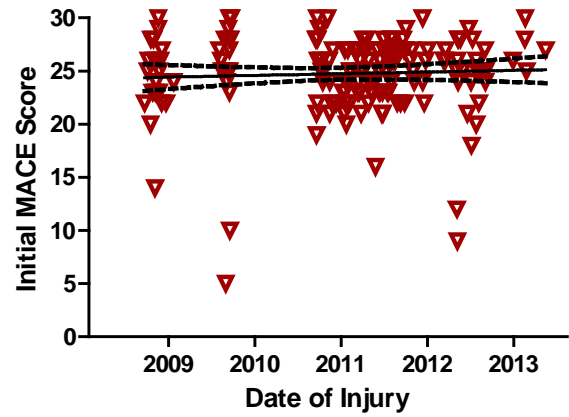
Supplemental Figure S1. Military Assessment of Concussion Evaluation (MACE). Lower scores indicate greater concussion impairment (Max 30, Symptomatic defined as below 25). **A.** No difference in MACE between cohorts (p=0.87 Kruskal Wallis ANOVA). **B.** No trends in MACE as a function of date of injury (p=0.52, linear regression).

Supplement Figure S2. Neurobehavioral Rating Scale Sub-Domains. A. Mood/affect domain (Max 15). **B.** Executive/Cognitive domain (Max 24). **C.** Oral/motor domain (Max 12). **D.** Positive Symptoms domain (Max 21). **E.** Negative Symptoms domain (Max 12). Higher scores on all of the measures indicate worse impairment.
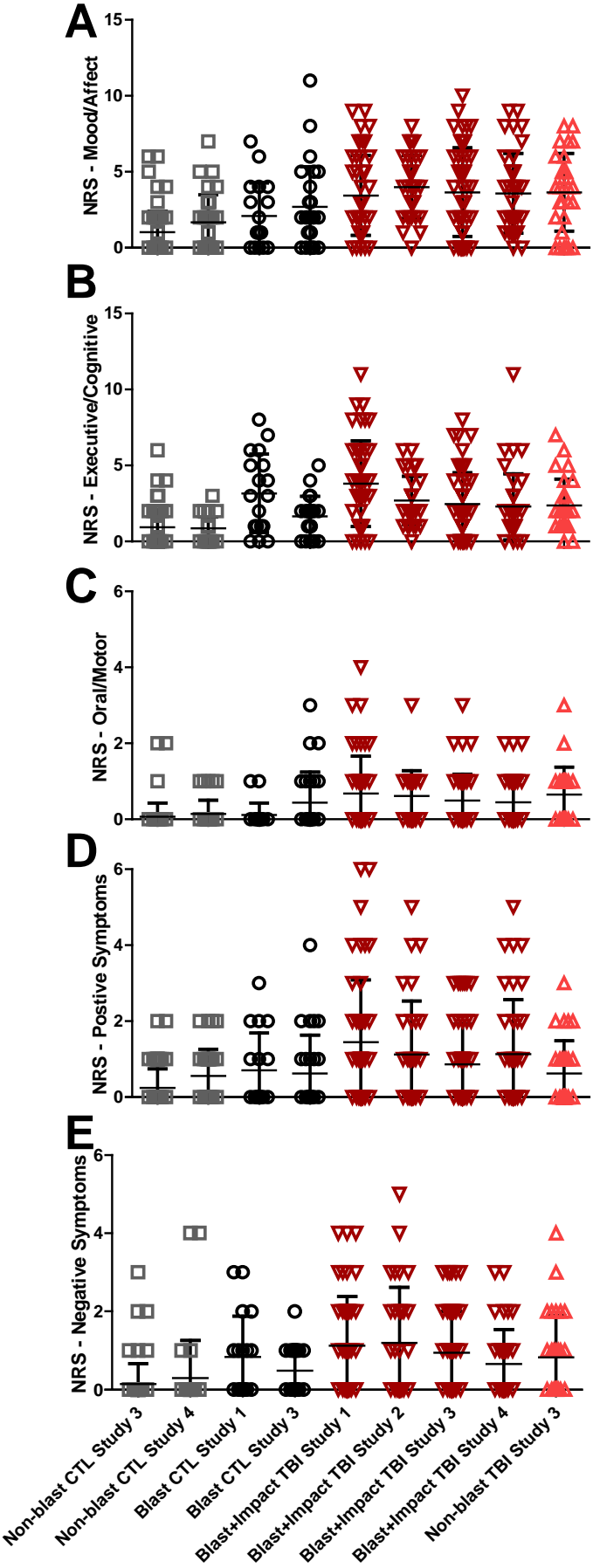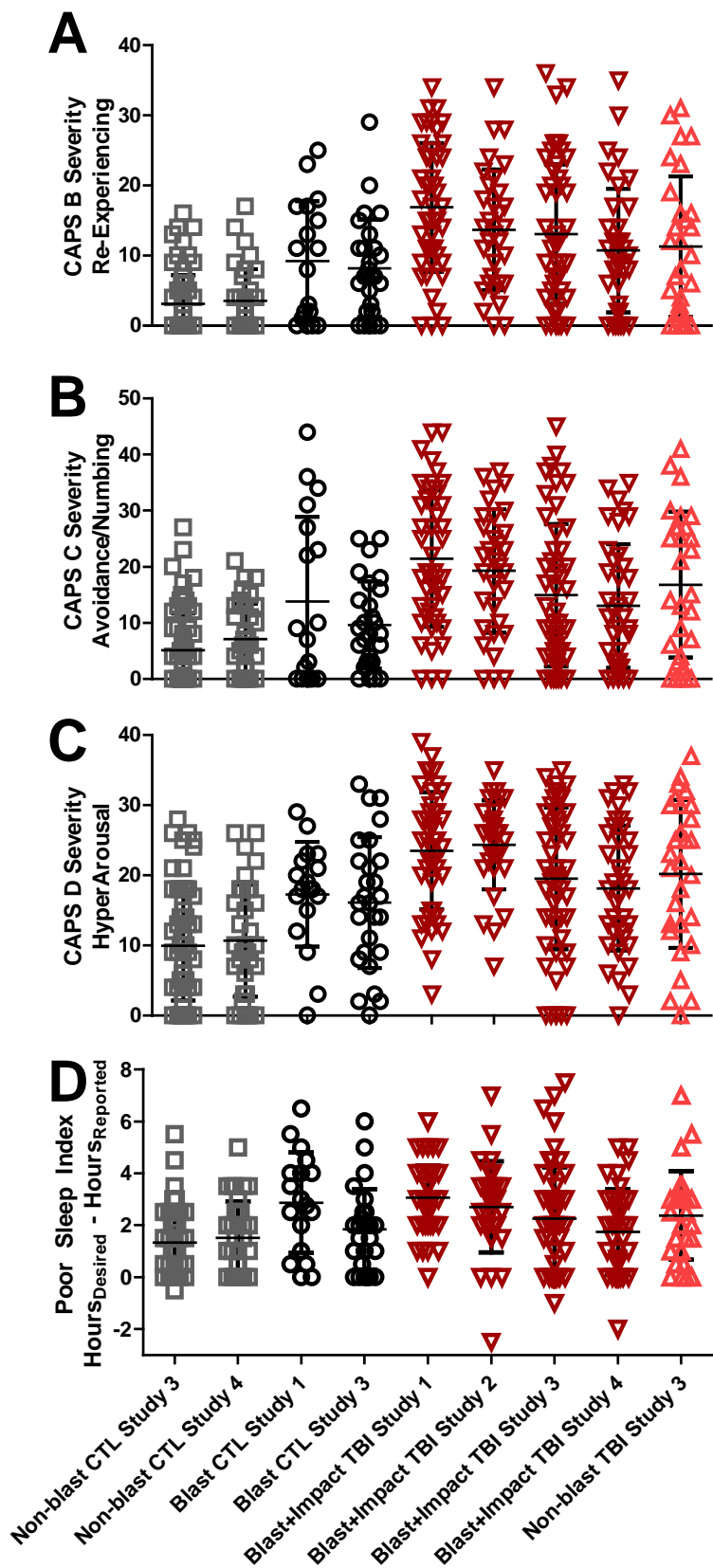
Supplemental Figure S3. Sub-Domains of the Clinician Administered PTSD Scale (CAPS) for DSM IV. A. CAPS B Severity – Re-experiencing (Max 40). **B.** CAPS C Severity – Avoidance and Numbing (Max 56). **C.** CAPS D Severity – Increased Arousal and hypervigilance (Max 40). **D.** Poor sleep index, defined as the self-reported number of desired hours of sleep minus the number of hours reported taken from subsection D-1 of the CAPS. Higher scores on all of the measures indicate worse impairment.

Poor sleep index was found to be significantly different across groups (p=0.00001, Kruskal Wallis ANOVA). For the poor sleep index, we did not collapse all concussive TBI groups the way we did for several of the other measures because blast TBI subjects from study 1 differed significantly from blast TBI subjects in study 4 (p<0.05, Dunn's Multiple Comparison Test). However, both non-blast control groups were pooled and both blast control groups were pooled because these did not differ from each other. With this pooling, we found that the overall ANOVA was again significant (p<0.0001). In post-hoc testing, blast+impact concussive TBI subjects from studies 1 and 2 had higher poor sleep indexes than non-blast controls (p<0.05) but none of the TBI groups differed from the blast controls. The blast control group was not statistically significantly different from the non-blast control group.

Supplementary Discussion

Directive Type Memoranda (DTM) are policy-making documents, and compliance is required throughout the Department of Defense. The key provisions of the DTM[2] on concussion/mild TBI (mTBI) issued in 2010 were the following:

1) Mandatory evaluations for mTBI for any Service member exposed to a potential mechanism of injury such as a blast, vehicle collision, rollover, blow to the head, or loss of consciousness. This included those without apparent injuries, as a major goal was to reduce the incidence of unreported mTBI.

2) Mandatory reporting of both positive and negative mTBI evaluations in Service members' medical records and to the organizations tasked with implementing improved protective strategies.

3) Standardizing treatment of mTBI, including mandatory rest and recovery periods, instructions for medics and corpsmen, and specific clinical algorithms for early symptom management.

4) Mandatory comprehensive evaluations by qualified medical providers for Service members with 3 or more documented mTBI's in a 12 month period. Responsibility for return-to-duty decisions was assigned specifically to medical providers.

Importantly, none of our data directly bear on the question of the extent to which these specific provisions in the DTM were actually followed. Thus, we cannot assess the true effect of full implementation of the changes in care articulated in the DTM. Furthermore, it is unclear whether 6-12 month outcomes are truly representative of long term function or quality of life. [3,4 5 6,7] Studies are currently underway to explore >5 year outcomes in these military concussive TBI cohorts.

One of the most striking findings in this report is that over a 5 year period from 2008 to 2013, the severity of disability, PTSD and depression following concussive TBI in deployed US military personnel improved only marginally. Clearly, more effective interventions to treat PTSD and depression should be considered a top priority. Pre-injury resilience training and interventions starting at very early times following

concussive TBI in high risk individuals, such as US military service members, could be effective strategies. In other contexts, both PTSD and depression are at least partially treatable with a combination of medications[8-10] and psychological interventions such as prolonged exposure[11-13] or cognitive processing therapy [12,14]. No additional clinical care was provided as part of these research studies and we did not collect data on the specific interventions the study participants received. However, recent literature indicates that only a relatively small fraction of US military service members complete a full course of treatment for PTSD and depression. Reasons cited include lack of access, fear of stigma, poor follow-up compliance, and initial worsening of symptoms during the early part of the therapy. Likewise, reasons for less than ideal pharmacotherapy effectiveness include troubling side effects, irregular compliance, and concomitant drug or alcohol use[15-21]. Anecdotal reports obtained from the participants in these studies are in line with the above cited concerns. Alternatively it is possible that the effects of these standard treatments for PTSD and depression are less effective in the context of TBI because of brain circuitry disruption and neurochemical deregulation. Thus, based on the results presented here, a logical direction for future studies would involve assessment of the efficacy of both established and novel therapeutic approaches to PTSD and depression in patients with traumatic brain injury.

Supplemental References

1.	Dempsey KE, Dorlac WC, Martin K, et al. Landstuhl Regional Medical Center: traumatic brain injury screening program. J Trauma Nurs 2009;16:6-7, 10-2.
2.	Lynn WJ. Policy Guidance for Management of Concussion/Mild Traumatic Brain Injury in the Deployed Setting. In: DEFENSE DSO, ed.; 2010.
3.	Isoniemi H, Tenovuo O, Portin R, Himanen L, Kairisto V. Outcome of traumatic brain injury after three decades--relationship to ApoE genotype. J Neurotrauma 2006;23:1600-8.
4.	Rutherford G, Bazarian JJ, Cernak I, et al. IOM (Institute of Medicine) Long-Term Consequences of Traumatic Brain Injury. Washington, DC: The National Academies Press; 2009.
5.	Konrad C, Geburek AJ, Rist F, et al. Long-term cognitive and emotional consequences of mild traumatic brain injury. Psychol Med 2011;41:1197-211.
6.	Lewin W, Marshall TF, Roberts AH. Long-term outcome after severe head injury. Br Med J 1979;2:1533-8.
7.	Wood RL, Rutterford NA. Long-term effect of head trauma on intellectual abilities: a 16-year outcome study. J Neurol Neurosurg Psychiatry 2006;77:1180-4.
8.	Attari A, Rajabi F, Maracy MR. D-cycloserine for treatment of numbing and avoidance in chronic post traumatic stress disorder: A randomized, double blind, clinical trial. J Res Med Sci 2014;19:592-8.
9.	Raskind MA, Peskind ER, Hoff DJ, et al. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. Biol Psychiatry 2007;61:928-34.
10.	Raskind MA, Peskind ER, Kanter ED, et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry 2003;160:371-3.
11.	Foa EB, Davidson JR, Frances A. Treatment of Posttraumatic Stress Disorder. The Journal of Clinical Psychiatry 1999;60:3-76.
12.	Karlin BE, Ruzek JI, Chard KM, et al. Dissemination of evidence-based psychological treatments for posttraumatic stress disorder in the Veterans Health Administration. J Trauma Stress 2010;23:663-73.
13.	Shalev AY, Ankri Y, Israeli-Shalev Y, Peleg T, Adessky R, Freedman S. Prevention of posttraumatic stress disorder by early treatment: results from the Jerusalem Trauma Outreach And Prevention study. Arch Gen Psychiatry 2012;69:166-76.
14.	Zatzick D, Roy-Byrne P, Russo J, et al. A randomized effectiveness trial of stepped collaborative care for acutely injured trauma survivors. Arch Gen Psychiatry 2004;61:498-506.
15.	Tanielian TL, Jaycox LH. Invisible Wounds of War: Psychological and Cognitive Injuries, Their Consequences, and Services to Assist Recovery: RAND Corporation 2008.
16.	Galea S, Basham K, Culpepper L, et al. Treatment for Posttraumatic Stress Disorder in Military and Veteran Populations: Initial Assessment. Washington DC: National Academies Press; 2012.
17.	Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. N Engl J Med 2004;351:13-22.
18.	Milliken CS, Auchterlonie JL, Hoge CW. Longitudinal assessment of mental health problems among active and reserve component soldiers returning from the Iraq war. JAMA 2007;298:2141-8.
19.	Warner CH, Appenzeller GN, Grieger T, et al. Importance of anonymity to encourage honest reporting in mental health screening after combat deployment. Arch Gen Psychiatry 2011;68:1065-71.
20.	Castro CA. The US framework for understanding, preventing, and caring for the mental health needs of service members who served in combat in Afghanistan and Iraq: a brief review of the issues and the research. Eur J Psychotraumatol 2014;5.
21.	Clinician's Guide to Medications for PTSD. PTSD: National Center for PTSD, 2014. (Accessed November 14, 2014, at http://www.ptsd.va.gov/professional/treatment/overview/clinicians-guide-to-medications-for-ptsd.asp.)