White and gray matter contributions to executive function recovery after traumatic brain injury

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ABSTRACT

Objective: We investigated the association between regional white and gray matter volume loss and performance on executive functions (EFs) in patients with penetrating traumatic brain injury (pTBI).

Methods: We studied 164 pTBI patients and 43 healthy controls from the Vietnam Head Injury Study. We acquired CT scans for pTBI patients and divided them according to lesion localization (left and right prefrontal cortex [PFC]). We administered EF tests (Verbal Fluency, Trail Making, Twenty Questions) and used voxel-based lesion symptom mapping (VLSM) and group-based correlational and multiple regression analyses to examine the relative influence of gray and white matter lesions on EF recovery.

Results: The VLSM analysis revealed that white and gray white matter lesions were associated with impaired EFs. In the left PFC lesion group, damage to the PFC gray matter, anterior corona radiata, and superior longitudinal fasciculus (SLF) were most correlated with functional recovery. Verbal Fluency, which involves a broad fronto-temporo-parietal network, was best predicted by SLF lesion volume. Trail Making and Twenty Questions, which is associated with more focal left frontal damage, was better predicted by PFC lesions.

Conclusions: Our results indicated that white matter volume loss can be a superior predictor of recovery and a crucial factor driving clinical outcome in functions involving a broad network such as Verbal Fluency. White matter damage may place additional burden on recovery by deteriorating signal transmission between cortical areas within a functional network. *Neurology*® 2015;84:1394-1401

GLOSSARY

ACR = anterior corona radiata; **ANOVA** = analysis of variance; **D-KEFS** = Delis-Kaplan Executive Function System; **EF** = executive function; **HC** = healthy control; **IFG** = inferior frontal gyrus; **IPG** = inferior parietal gyrus; **LACR** = left anterior corona radiata; **LPFC** = left prefrontal cortex lesions; **LSLF** = left superior longitudinal fasciculus; **MFG** = middle frontal gyrus; **PFC** = prefrontal cortex; **pTBI** = penetrating traumatic brain injury; **RPFC** = right prefrontal cortex lesions; **SCR** = superior corona radiata; **SFG** = superior frontal gyrus; **SLF** = superior longitudinal fasciculus; **SPG** = superior parietal gyrus; **TBI** = traumatic brain injury; **VLSM** = voxel-based lesion system mapping.

Traumatic brain injury (TBI) is a major public health problem worldwide.¹ While physical deficits following TBI generally improve over time, cognitive impairments can persist^{2,3} and cause permanent disability.^{1,4}

Some of the most persistent deficits after TBI involve executive functions (EFs), resulting in impaired mental flexibility and planning.^{5,6} Extensive functional neuroimaging and lesion-mapping evidence indicates that the prefrontal cortex (PFC) plays a central role in EFs.⁶⁻⁸ EFs also involve interactions between frontal and posterior brain regions.^{9,10}

To date, the majority of lesion-mapping studies have focused on the cortical gray matter correlates of functional impairment, yet white matter involvement has rarely been quantified. Thus, the relative role of white matter compared to gray matter damage in mediating plasticity and recovery of function remains unclear. The development of stereotaxic white matter atlases based on high-resolution DTI data¹¹ enables quantification of white matter tract damage in TBI patients.¹²

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White matter integrity after brain damage may have an important influence on recovery. Deep lesions that reached white matter were associated with worse language outcome years after penetrating TBI (pTBI).¹³ White matter tract integrity and volume contralateral to injury can predict aphasia recovery in stroke patients.¹⁴ A more precise understanding of the relative role of gray and white matter loss for impairing functional recovery would be useful to clinicians planning and charting therapeutic interventions.

This study aimed to quantitatively examine the relative contributions of gray and white matter damage in predicting functional recovery of EFs in a well-characterized pTBI sample.

METHODS **Participants and behavioral evaluation.** Participants were drawn from Phase 3 of the Vietnam Head Injury Study, which is a longitudinal study of American male combat veterans with focal pTBI and matched combat veterans without brain injury.¹⁵ For this study, we selected all right-handed male veterans who participated in Phase 3 (164 pTBI and 43 healthy controls [HC]). For more detailed analyses, 2 subgroups were selected from the pTBI sample: one group with pure left PFC lesions (LPFC, $n = 34$) and one with pure right PFC lesions (RPFC, $n = 46$).

Participants underwent 5–7 days of neuropsychological testing between 2003 and 2006 at the National Naval Medical Center in Bethesda, Maryland. We examined performance on 3 tests from the Delis-Kaplan Executive Function System (D-KEFS)¹⁶ as EF measures: Verbal Fluency, Trail Making, and Twenty Questions. Details of the D-KEFS tests and other control neuropsychological tests can be found in e-Methods on the *Neurology*[®] Web site at Neurology.org (tables 1 and 2).

Standard protocol approvals, registrations, and patient consents. Written informed consent was obtained from all participants. The National Naval Medical Center and the National Institute of Health institutional review board approved all the study procedures.

CT scan acquisition and lesion mapping. Axial CT scans were acquired as described in e-Methods. Since metal was retained in the brain due to penetrating wounds or surgical materials, MRI scans could not be acquired. Lesion density overlap maps were created for all pTBI patients and selected LPFC and RPFC groups. Voxel-based lesion system mapping (VLSM) was applied to the whole brain for each EF measure as described in e-Methods. The anatomic location of significant clusters was identified using the automated anatomical labeling atlas for gray matter¹⁷ and the ICBM-DTI-81 atlas for white matter.¹¹ We used percentage of volume loss in selected regions of interest (e-Methods) to establish the extent of damage used in subsequent analyses.

Statistical analysis. Behavioral analyses were conducted using IBM (Armonk, NY) SPSS 21.0 with significance levels set to 0.05 (2-tailed) for all analyses. Parametric tests (independent samples t test and one-way analysis of variance [ANOVA]) were performed on normally distributed data, and nonparametric tests (Mann-Whitney U tests and Kruskal-Wallis test) on non-normally distributed data. Bivariate Spearman correlations were calculated between test scores and lesion size in gray matter (PFC) and white matter (anterior corona radiata [ACR] or superior longitudinal fasciculus [SLF]) for all pTBI patients, and LPFC and RPFC subgroups. We only conducted analysis on white matter tracts that are involved in EF, had sufficient statistical power given our sample size, and had sufficient variation in distribution of lesion size within our sample.

Using the group median score for each test, LPFC and RPFC participants were split into higher and lower performing subgroups. We constructed lesion maps for each subgroup for each test and compared differences in lesion volume in white matter (ACR, SLF) or gray matter (PFC, parietal or temporal lobes) structures between each pair of subgroups.

Table 1 Demographics, neuropsychological control measures, and EF tests (mean $\pm$ SD) for pTBI patients and HC

Measure	pTBI (n = 164)	HC (n = 43)	Statistics
Age, y	58.3 $\pm$ 3.0	59.2 $\pm$ 3.7	$U = 2912$, $Z = -1.83$, $p = 0.07$
Education, y	14.9 $\pm$ 2.5	15.1 $\pm$ 2.4	$U = 3380$, $Z = -0.36$, $p = 0.72$
Preinjury intelligence (AFQT)	61.1 $\pm$ 25.2	67.3 $\pm$ 22.3	$U = 1785$, $Z = -1.17$, $p = 0.24$
Postinjury intelligence (AFQT)	53.1 $\pm$ 25.0	66.0 $\pm$ 21.8	$U = 2405$, $Z = -3.07$, $p < 0.01$
Word naming (BNT)	53.5 $\pm$ 7.4	55.4 $\pm$ 3.8	$U = 3007$, $Z = -1.10$, $p = 0.27$
Verbal comprehension (TT)	97.6 $\pm$ 5.7	98.7 $\pm$ 1.7	$U = 3171$, $Z = -0.64$, $p = 0.53$
Object perception (VOSP)	19.8 $\pm$ 0.6	19.7 $\pm$ 1.5	$U = 3136$, $Z = -1.66$, $p = 0.10$
Verbal Fluency (D-KEFS)	9.0 $\pm$ 3.8	10.3 $\pm$ 3.3	$t = -2.02$, $p = 0.04$
Trail Making (D-KEFS)	8.5 $\pm$ 3.8	9.4 $\pm$ 3.3	$U = 2938$, $Z = -1.20$, $p = 0.22$
Twenty Questions (D-KEFS)	9.7 $\pm$ 3.2	10.0 $\pm$ 3.5	$U = 2987$, $Z = -1.05$, $p = 0.29$

Abbreviations: AFQT = Armed Forces Qualification Test for preinjury and postinjury general intelligence; BNT = Boston Naming Test for object naming; D-KEFS = Delis-Kaplan Executive Function System; EF = executive function; HC = healthy controls; pTBI = penetrating traumatic brain injury; TT = Token Test for basic verbal comprehension; VOSP = Visual Object and Space Perception battery for object and space perception.

All tests were completed postinjury except for the preinjury AFQT. Although HC did not sustain brain injuries, they underwent neuropsychological assessments during the same period as pTBI patients in phase 3. Normal ranges for tests: AFQT, 31–99 percentile; BNT, 47–60; TT, 50–100; VOSP, 18–20; D-KEFS subtests, 7–20.

Table 2 Demographics, neuropsychological control measures, and EF tests (mean $\pm$ SD) for pTBI patients with either LPFC or RPFC lesions

Measure	LPFC (n = 34)	RPFC (n = 46)	Statistics
Age, y	58.0 $\pm$ 2.5	58.6 $\pm$ 4.1	$U = 755, Z = -0.27, p = 0.79$
Education, y	14.7 $\pm$ 2.6	14.8 $\pm$ 2.5	$U = 703, Z = -0.78, p = 0.44$
Percent volume loss	3.8 $\pm$ 5.0	3.0 $\pm$ 3.8	$U = 740, Z = -0.41, p = 0.68$
Preinjury intelligence (AFQT)	60.8 $\pm$ 22.8	56.9 $\pm$ 24.8	$t = 0.70, p = 0.49$
Postinjury intelligence (AFQT)	49.7 $\pm$ 27.5	51.0 $\pm$ 24.5	$U = 735, Z = -0.13, p = 0.90$
Word naming (BNT)	50.4 $\pm$ 10.5	54.8 $\pm$ 3.3	$U = 642, Z = -0.76, p = 0.45$
Verbal comprehension (TT)	95.2 $\pm$ 10.9	98.1 $\pm$ 2.4	$U = 689, Z = -0.28, p = 0.78$
Object perception (VOSP)	19.7 $\pm$ 0.6	19.7 $\pm$ 0.8	$U = 723, Z = -0.36, p = 0.72$
Verbal fluency (D-KEFS)	7.9 $\pm$ 4.1	9.5 $\pm$ 3.3	$t = -1.92, p = 0.06$
Trail making (D-KEFS)	8.1 $\pm$ 4.1	8.8 $\pm$ 3.9	$U = 650, Z = -0.84, p = 0.40$
Twenty questions (D-KEFS)	9.7 $\pm$ 3.5	9.8 $\pm$ 3.0	$U = 722, Z = -0.27, p = 0.80$

Abbreviations: AFQT = Armed Forces Qualification Test for preinjury and postinjury general intelligence; BNT = Boston Naming Test for object naming; D-KEFS = Delis-Kaplan Executive Function System; EF = executive function; LPFC = left prefrontal cortex lesions; pTBI = penetrating traumatic brain injury; RPFC = right prefrontal cortex lesions; TT = Token Test for basic verbal comprehension; VOSP = Visual Object and Space Perception battery for object and space perception. All tests were completed postinjury except for the preinjury AFQT.

In the LPFC group, which was most impaired in EF, we performed multiple linear regressions for each EF test after adjusting for preinjury intelligence (AFQT), entering gray matter (left prefrontal, parietal, or temporal cortex) and white matter tract (left ACR [LACR] or left SLF [LSLF]) lesion volumes as regressors.

RESULTS Behavioral results. The pTBI and HC groups did not differ on demographic or most of the neuropsychological measures (table 1). The pTBI group had a lower postinjury intelligence score than HC, although their scores were within the normal range. The LPFC and RPFC subgroups did not differ on demographic and neuropsychological measures (table 2).

The pTBI and HC groups differed on Verbal Fluency but not on Trail Making or Twenty Questions (table 1). One-way ANOVA between LPFC, RPFC, and HC groups revealed a between-group effect ($F_{2,119} = 4.65, p = 0.015$) on Verbal Fluency. Post hoc comparisons with Bonferroni correction indicated that the LPFC group had lower scores than the HC group while the RPFC group did not perform differently from the other groups. There were no differences in performance among the 3 groups on Trail Making ($p = 0.39$) or Twenty Questions ($p = 0.79$) (table 2). The 3 groups (LPFC, RPFC, and HC) did not differ in preinjury intelligence scores ($\chi^2 = 3.40, p = 0.18$).

VLSM results. Lesion overlap maps are shown in figure e-1. In the pTBI group, the maximum overlap within 29 patients occurred in frontotemporal regions and underlying white matter tracts.

VLSM results for the 3 EF tests are shown in figure 1. Lesions within a left fronto-temporo-parietal network

impaired Verbal Fluency test scores. This network involved gray matter structures such as the left inferior frontal gyrus (IFG), middle frontal gyrus (MFG), superior frontal gyrus (SFG), middle temporal gyrus, superior temporal gyrus, inferior parietal gyrus (IPG), and superior parietal gyrus (SPG), as well as underlying white matter tracts including the SLF, ACR, and superior corona radiata (SCR).

Lesions within a fronto-parietal network were found to impair Trail Making test scores. This network included gray matter structures such as the left IFG, MFG, SFG, right IPG, SPG, and white matter structures such as the LSLF, ACR, and SCR.

Lesions within a left frontal network were found to impair Twenty Questions test scores. This network comprised the left IFG, MFG, and SFG, as well as white matter tracts including the LSLF, ACR, and SCR. For a complete list of brain regions and Montreal Neurological Institute coordinates, see table e-1.

Group analysis. Lesion overlap figures showed that the LPFC and RPFC groups had a maximum overlap of 15 and 16 patients, respectively (figure e-1).

In the LPFC patients, the lower performing subgroup on all 3 tests had more extensive lesions that extended more dorsally compared to the higher performing subgroups (figure 2).

White matter involvement was more pronounced in the lower performing subgroups. Moreover, the largest amount of lesion overlap corresponded to frontal white matter. For each EF test, the percentage of lesion overlap located in white matter was higher in the lower performing subgroup compared to the higher performing subgroup (Verbal Fluency: lower

Figure 1 Voxel-based lesion system mapping results for the executive function tests

(A) Verbal Fluency, (B) Trail Making, and (C) Twenty Questions. For each test, voxel-based lesion system mapping compares voxel by voxel the performance of penetrating traumatic brain injury with a lesion against those without a lesion in a given voxel. Colored areas indicate a significant association between the presence of a lesion in that location and lower score. The results are overlaid onto an MRI template brain in Montreal Neurological Institute space for visualization purposes. Images are shown in radiologic convention: the right hemisphere is shown on the reader's left side. Color bar indicates Z scores.

group: 11.25%, higher group: 0.57%; Trail Making: lower group: 7%, higher group: 2.14%; Twenty Questions: lower group: 6.47%, higher group: 1.31%).

For the Verbal Fluency test, the lower performing subgroup had greater LSLF damage than the higher performing subgroup ($U = 55$, $Z = -3.61$, $p < 0.01$). Similarly, for the Trail Making test, we found larger lesions to the left SLF in the lower performing subgroup ($U = 85$, $Z = -2.40$, $p = 0.04$). For the Twenty Questions test, the lower performing subgroup tended to have larger left PFC lesions compared to the higher performing subgroup ($U = 90$, $Z = -1.88$, $p = 0.06$). A similar median split analysis performed for the RPFC group revealed no differences (figures 1 and 2).

Correlation analysis. Correlations in all pTBI patients yielded modest results between EF scores and lesion size in left PFC and white matter tracts (table e-2). Since PFC is the main cortical region associated with EF performance, we performed detailed analyses on patients with PFC damage to further investigate gray and white matter contributions to recovery of function. We found moderate to large correlations between lesion extent in certain structures and task performance for the LPFC group, but not for the RPFC group (table e-2). For the LPFC group, we found a large correlation between Verbal Fluency and LSLF lesion ($r_s = -0.698$, $p < 0.01$); a moderate correlation between Trail Making and LSLF lesion ($r_s = -0.405$, $p < 0.05$); and a moderate correlation between Twenty Questions and lesion size in LPFC ($r_s = -0.425$, $p < 0.05$), LACR ($r_s = -0.441$,

$p < 0.01$), and LSLF ($r_s = -0.433$, $p < 0.05$). A Fisher Z test showed that the Verbal Fluency–LSLF correlation was higher than the Verbal Fluency–LPFC ($Z = 3.04$, $p < 0.01$) and Verbal Fluency–LACR ($Z = 2.28$, $p < 0.05$) correlations.

Multiple regression analysis. For the Verbal Fluency test, LSLF lesion predicts test scores ($\beta = -0.88$, $p < 0.02$, R^2 change = 0.12) after controlling for preinjury intelligence, LACR, and gray matter lesions. For the Trail Making test, LPFC lesion marginally predicted test scores ($\beta = -0.41$, $p = 0.076$, R^2 change = 0.06) after controlling for preinjury intelligence, white matter, and other gray matter lesions. For the Twenty Questions test, LPFC lesion marginally predicted test scores ($\beta = -0.38$, $p = 0.055$, R^2 change = 0.05) after controlling for preinjury intelligence, white matter, and other gray matter lesions.

DISCUSSION EF impairments after TBI can become a large source of burden for caregivers. Therefore, understanding the factors crucial to brain plasticity and recovery has important clinical implications. Here, we investigated the relative contribution of white and gray matter brain damage in mediating recovery in focal pTBI patients, using 3 standard tests of EF as outcome measures: Verbal Fluency, Trail Making, and Twenty Questions.

Neuroplastic changes in the brain can facilitate some restoration of function immediately after damage, and long-term outcomes can reflect the extent of recovery. In this study, we used long-term outcomes as a measure of recovery after TBI. Our results

Figure 2 Median split subgroup lesion overlaps in left prefrontal cortex lesions group according to executive function scores

The left prefrontal cortex lesions group subdivided according to their test score on the (A) Verbal Fluency, (B) Trail Making, and (C) Twenty Questions test. The lower performing penetrating traumatic brain injury group had wider network of gray and white matter damage compared to higher performing individuals. Color denotes the number of patients with overlapping lesion at each voxel. Red indicates the highest density of lesion overlap subjects and blue indicates the least density of lesion overlap. The results are overlaid onto an MRI template brain in Montreal Neurological Institute space for visualization purposes. Images are shown in radiologic convention: the right hemisphere is shown on the reader's left side.

show that the relative contribution of white and gray matter depends on the property of the EF tasks. Verbal Fluency performance recruits a large left fronto-temporo-parietal network. Converging evidence from VLSM, group, and regression analyses demonstrated that Verbal Fluency performance can be predicted by the degree of white matter damage

to the LSLF, with poorer performance associated with larger lesions. In fact, LSLF lesion volume predicted functional outcome better than gray matter lesion.

Deficits in the Trail Making test are associated with lesions to a network involving left frontal and right parietal regions, and thus the precise contribution of white matter vs gray matter in functional

outcomes is more complicated, probably due to the multiple cognitive processes recruited by this task. White matter tracts (LSLF) and gray matter regions (LPFC) were associated with Trail Making performance and LPFC trends to be a better predictor of recovery.

Finally, the Twenty Questions test showed more localized left frontal involvement. While underlying white matter tracts, including LACR and LSLF, were also associated with poorer task performance, white matter damage played a smaller role in predicting functional recovery compared to LPFC gray matter.

In our study, 2 white matter tracts, LSLF and LACR, were associated with impaired EF. The SLF is a major association fiber tract that connects the frontal lobe to temporo-parietal regions,¹⁸ and is involved in visuospatial attention,¹⁹ working memory,²⁰ and language articulation.²¹ The ACR is a projection fiber tract that connects frontal and subcortical regions, and has been associated with executive attention.²² The different structural connections and functional relevance of these tracts likely underlie some of the different subprocesses involved in the EF tasks that impact functional outcome when damaged.

Our results shed light on the relative contributions of gray and white matter damage in EF recovery

depending on the network of brain regions recruited (figure 3).

In addition to critical involvement of the frontal lobes, a flexible network that includes posterior regions also contributes to successful EF performance.²³ EF encompasses a variety of complex processes, and the make-up of the network recruited depends on the various demands in different EF tasks, giving rise to varying recovery mechanisms. White matter contribution appears to be crucial in tasks that involve a large network of cortical regions, such as the PFC and temporoparietal network. We propose that when both cortical gray matter (PFC) and associated white matter (SLF) are damaged, performance on the task will inevitably be impaired. When only PFC is damaged, recovery mechanisms can still occur, possibly through compensatory processes dependent on preserved white matter tracts that connect spared PFC regions to posterior regions. However, when deeper white matter tracts are damaged, functional recovery is limited and EF task performance is more severely impaired.

Since white matter damage reduces connections between the cortical areas in the implicated network, it places additional burden on EF recovery. Adjacent cortical tissue spared from the lesion may be restricted in its ability to receive and respond to signals from

Figure 3 Summary of results

Summary of executive function results that involve (A) cortically distributed network (Verbal Fluency [VF]) and (B) cortically localized regions (Twenty Questions [TQ]). The 2 tests that yielded the clearest results were chosen for illustrative purposes. Top panels: healthy controls (HCs) have no gray matter (GM) or white matter (WM) lesion and normal performance on both tests. Middle panels: penetrating traumatic brain injury (pTBI) with lesions predominantly in the GM, while WM tracts (superior longitudinal fasciculus [SLF] or anterior corona radiata [ACR]) are spared. Their performance on the tests is impaired (single downward arrow). Bottom panels: pTBI with lesions in both GM and WM. The combination of prefrontal cortex (PFC) lesion plus SLF lesion impairs performance on the Verbal Fluency test (double downward arrows), which requires a broad network of brain regions. The combination of PFC lesion plus ACR lesion did not markedly impact performance on the Twenty Questions test.

other brain regions, thus limiting compensatory functioning in other sectors within the network. In this case, the contribution of white matter damage is more important in functional recovery than gray matter lesions. On the other hand, in the case of more localized functions, the contribution of white matter damage appears to be less relevant compared to gray matter, since recovery and plasticity processes can occur within the PFC and are less dependent on a widespread neural network.

Our study is consistent with previous findings examining diffuse low-grade glioma, a rare tumor condition that evolves along associative white matter tracts, where white matter tract damage was shown to play a critical role in language impairments.²⁴

Recovery after TBI can be varied due to the range of genetic, molecular, psychological, and environmental factors that influence functional outcomes. One such factor is individual genetic variation, which can predispose TBI patients to different functional outcomes.^{25,26} For example, brain-derived neurotrophic factor, a neurotrophic factor important to synaptic plasticity,²⁷ is involved in the recovery of EF after pTBI.²⁸ Another predictor of functional recovery is preinjury cognitive ability.¹⁵ People with more cognitive reserve are less susceptible to adverse outcome of brain damage, due to either preexisting neuroprotective processes or postinjury cognitive compensatory mechanisms.^{29,30}

Besides individual variability, environmental influences also play an important role in recovery of function. Support from family members and significant others help facilitate rehabilitation,^{31,32} while a stressful family setting may deter recovery.³³ Cognitive training intervention can also help improve function^{34,35} by affecting brain plasticity.³⁶ It would be useful to understand how these other factors interact with the extent of white matter damage in mediating neuroplasticity and recovery of EF after TBI in order to devise better individual-oriented rehabilitation plans.

A limitation of our study is that the white matter atlas used identifies deep white matter tracts, but not different layers within the tracts as can be identified using more refined white matter atlases.³⁷ Other limitations include the use of an all-male sample and the requirement that only CT scans could be used given the retained metal within the brain as a result of the penetrating brain wounds or surgical materials.

Another promising avenue for future research in white matter involvement in functional recovery is the influence of genetic variation. Interestingly, the Val variant of the *BDNF* gene is associated with reduced white matter integrity in healthy participants,³⁸ while Met allele carriers demonstrate increased structural connectivity,³⁹ despite the greater

association of the Met allele with cognitive impairment and clinical pathology.⁴⁰ It would be interesting to study whether individual genetic variation mediates the contribution of white matter structural integrity in functional outcome after brain injury.

Our results have clinical implications for minimizing the undesirable effects of penetrating brain wounds. A lesion that penetrates deeper and occludes more white matter may have more serious functional consequences than a more superficial lesion comparable in size. This emphasizes the importance of producing helmets that can effectively reduce shrapnel velocity, thus reducing the depth of penetration into the brain. However, helmets do not protect from blast injury, which can affect both gray and white matter; thus, improved forms of wearable shielding would be necessary to reduce the impact of a strong blast on the brain. Our results also suggest that neurosurgeons should be cautious about removing white matter.

Results from the present study indicate an important role of white matter volume loss in predicting recovery of EF after TBI. Particularly in cognitive functions that involve a broadly distributed network of brain regions such as verbal fluency, white matter lesion volume can predict functional outcome above and beyond contributions from gray matter damage. White matter damage may place additional burden on EF recovery by altering and deteriorating signal transmission between cortical areas within a functional network. Thus, white matter lesion volume can be considered as a crucial factor driving clinical outcome in addition to other neural and psychosocial factors.

AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript. I.C., W.Z., F.K., and J.G. designed and performed research. I.C. and W.Z. analyzed the data. I.C., W.Z., and J.G. interpreted the data. I.C., W.Z., A.C., F.K., J.S., and J.G. wrote the paper. F.K. and J.G. acquired the data. J.S. implemented analysis algorithms. J.G. supervised the study. All authors read and approved the final version of the manuscript.

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