

Long-Term Motor Recovery After Severe Traumatic Brain Injury: Beyond Established Limits

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Objective: To report neural plasticity changes after severe traumatic brain injury. **Setting:** Case-control study. **Participants:** Canadian soldier, Captain Trevor Greene survived a severe open-traumatic brain injury during a 2006 combat tour in Afghanistan. **Design:** Longitudinal follow-up for more than 6 years. **Main Measures:** Twelve longitudinal functional magnetic imaging (fMRI) examinations were conducted to investigate lower limb activation changes in association with clinical examination. Trevor Greene's lower limb fMRI activation was compared with control fMRI activation of (1) mental imagery of similar movement and (2) matched control subject data. **Results:** Trevor Greene's motor recovery and corresponding fMRI activation increased significantly over time ($F = 32.54, P < .001$). Clinical measures of functional recovery correlated strongly with fMRI motor activation changes ($r = 0.81, P = .001$). By comparison, while Trevor Greene's mental imagery activated similar motor regions, there was no evidence of fMRI activation change over time. While comparable, control motor activation did not change over time and there was no significant mental imagery activation. **Conclusion:** Motor function recovery can occur beyond 6 years after severe traumatic brain injury, both in neural plasticity and clinical outcome. This demonstrates that continued benefits in physical function due to rehabilitative efforts can be achieved for many years following injury. The finding challenges current practices and assumptions in rehabilitation following traumatic brain injury. **Key words:** functional MRI, neuroplasticity, recovery of motor function, rehabilitation, traumatic brain injury

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The research has been funded by The National Research Council of Canada (NRC), the Natural Sciences and Engineering Research Council (NSERC), the BC Leading Edge Endowment Fund, and the Surrey Memorial Hospital Foundation.

Author contributions are as follows: Conceptualize the study and secure the funding: RD. Study design: RD, SL, DG, LM, JM, and TG. Literature search: RD, XS, SL, JG, and CM. Data collection: RD, SL, DG, LM, JM, and TG. Data analysis: XS, JG, CM, and SH. Result presentation: XS, JG, CM, and SH. Analysis outcome verification: RD, SL, XS, and JG. Result interpretation: All authors. Writing the first draft: RD, SL, XS, JG, and CM. Editing versions of the manuscript and approving the submission: All authors.

The National Research Council of Canada (NRC), the Natural Sciences and Engineering Research Council (NSERC), the BC Leading Edge Endowment Fund, and the Surrey Memorial Hospital Foundation supported this study. The authors acknowledge Sue Rideout, Dr Francis Rolleston, Cathy Jardine, and staff at the Halvar Jonson Centre for Brain Injury for valuable support, assistance, and feedback in the preparation of this study. The authors also

RECENT US ESTIMATES for traumatic brain injury (TBI) report prevalence at 2.5 million, and more than 53,000 people die from the injury each year.^{1,2} The estimated healthcare cost is more than \$48.3 billion annually.¹ Traumatic brain injury is also a significant risk factor for long-term disability,³ such as long-term disability relevant to motor dysfunction. The dramatic increase in survival following TBI in war has emphasized the need for improved recovery.⁴ However, the focus of the field is commonly on early rehabilitation after TBI,⁵ which may not provide the optimal outcome. Although the "common wisdom" is that the majority of motor recovery occurs in the first 6 months,⁵ the possibility that environmental

Acknowledge Dr Aaron Newman for critical comments on the manuscript and Parveen Sangha for proofreading the final version of the paper.

The authors declare no conflicts of interest.

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DOI: 10.1097/HTR.000000000000185

factors, particularly limited rehabilitation access, are important mediators of poor outcome has been raised.⁶ Current clinical assumptions and expected levels of recovery are often mentioned but seldom defined. A striking demonstration of longer-term recovery is Canadian TBI survivor, Captain Trevor Greene (TG), who survived a severe open-head injury and has since shown remarkable success in rehabilitation and functional recovery.⁷

The capacity of the brain to recover from TBI is frequently underestimated, there is little biomedical research on long-term neural plasticity in TBI (for a review, see Kou and Iraj).⁸⁻¹¹ In recent years, researchers have increasingly utilized noninvasive neuroimaging technologies, such as functional magnetic resonance imaging (fMRI), for clinical applications.^{12,13} While most clinical fMRI studies examine brain functional activity at a single examination time point, repeat fMRI provides useful additional insight to monitor ongoing functional changes during recovery.¹⁴ To date, repeat fMRI studies have been applied mostly to detect brain plasticity,^{15,16} especially on tracking the recovery of motor function following stroke.¹⁷⁻²⁰ Only a few studies have examined motor recovery in TBI,²¹⁻²³ and none, to our knowledge, have measured recovery over a multiyear period beyond the conventional 1- to 2-year window.

The objectives were to (1) investigate the potential of functional neuroimaging to provide physiological, objective evidence in support of decision making and strategies during rehabilitation and (2) further substantiate the role of neuroplasticity in brain injury recovery. We hypothesized that fMRI would demonstrate increased extent of motor activation corresponding to recovery of motor function. In turn, that finding would provide evidence in support of monitoring neural plasticity during longer-term rehabilitation treatment.

METHODS

Nature of the injury

Trevor Greene was 41 years of age at the time of injury (45 years of age at the beginning of the study) and is a right-handed, university-educated journalist/writer with no history of neurological injury or illness. The National Research Council's Research Ethics Board and the Joint University of Victoria/Vancouver Island Health Authority approved the study, and informed consent was obtained. Captain Greene and his wife Debbie Greene participated as full investigators in the design, data collection, results presentation, and manuscript preparation.

On March 4, 2006, 41-year-old TG was struck in the head with a crude axe. As a sign of respect, he and the other soldiers removed their helmets and laid down their weapons during a goodwill meeting with elders in the vil-

lage of Shinkay, Kandahar, Afghanistan. A male youth approached TG from behind, raised an axe, and brought it down into the crown of his head with full strength. The attack resulted in immediate loss of consciousness. Trevor Greene received emergency care on a helicopter, his vital signs remained stable, and he survived. It took approximately 1 hour for medivac to reach Kandahar Air Field for advanced care. Trevor Greene was then transferred to the US Army Landstuhl Regional Medical Centre in Germany for neurosurgical treatment. Medical coma was induced to reduce swelling. With intracranial pressure well above the upper limit of 25 mm Hg, decompressive craniectomy was performed to remove 2 sections of skull. Ten days after the attack, TG was medically stable and transported home to Vancouver General Hospital (British Columbia, Canada), where he underwent bilateral cranioplasty to repair his skull. Initial prognosis was poor, with TG expected to be in a permanent vegetative state. Even so, TG emerged from coma and recovered full consciousness. See reference Greene and Greene⁷ for a moving first person account of this difficult journey of recovery.

During acute care, TG overcame significant medical complications and demonstrated an unexpected level of functional recovery. Consequently, he was admitted to an intensive inpatient rehabilitation program at the Halvar Jonson Centre for Brain Injury for 14 months (Alberta, Canada). After discharge, TG continued daily home-based rehabilitation with the main long-term objective of recovering ambulatory walking abilities. From 2009 to 2012, TG progressed from being completely unable to stand to being able to stand with assistance and support to practicing walk movements with a 3-person assist (see Table 1). Importantly, considerable functional progress continued well beyond established expectations. The current report focused on TG's long-term rehabilitation outcomes related to recovery of walking.

The axe penetrated TG's skull along the long axis of the midsagittal plane. Relative to bregma, the skull fracture extended mainly anterior into the frontal bone and also posteriorly along the sagittal suture. There was a slight angle from cardinal frontal to posterior axis, deviating approximately 13 mm from midline in the extreme anterior frontal margin and 24 mm from midline at the left parietal bone margin. The injury continued into the underlying brain tissue (gray and white matter). The nature of the injury was consistent with both penetration and rotational impact, with lateral damage extending 19 mm in the right frontal lobe and 32 mm in the left parietal lobe (away from the midline). Neuroanatomically, the primary area of impact was generally in the frontal lobes but extended along the sagittal sinus posterior to the left parietal lobe. In the frontal lobes, both the primary motor and premotor areas of the superior frontal gyri were damaged. In the left parietal lobe, the medial

TABLE 1 Rating of Trevor Greene's physical rehabilitation progress between the first and last scans^a

Year	Time	Date	Mean movement score	Progress to date
1	1	May 2010	1.0	Stands at wall-mounted bar without safety harness
	2	August 2010	1.0	Takes steps inside parallel bar with harness and assistance
	3	November 2010	1.5	No longer used lift during brain scan
	4	February 2011	1.5	Stands and pivots with assistance
2	5	May 2011	1.8	Stands for 2 min with knee blocks
	6	August 2011	1.9	Stands for 6 min with knee blocks and assistance
	7	November 2011	1.9	Stands for 10 min with knee blocks assistance
	8	February 2012	1.9	Stands for 30 s without knee blocks or assistance
3	9	May 2012	2.0	Sits without support
	10	August 2012	2.0	Stands with walker
	11	November 2012	2.5	Takes steps inside parallel bar with assistance
	12	February 2013	2.5	Takes steps with walker with assistance

^aMean movement scores and progress to date were assessed by Trevor Greene's occupational therapist.

postcentral gyrus and anterior aspect of the left superior parietal lobule were damaged. The depth of injury involved the anterior cingulate gyri along with the body and genu of the corpus callosum, extending to the lateral ventricles and involving surrounding white matter.

For control comparison, matched fMRI activation data were obtained from a coinvestigator (DSL) during the study midpoint (year 2, time points 5-8). DSL was 53 years of age at test time and is right-handed, university-educated, with no evident motor impairment.

Experimental design

A longitudinal study design was used to examine changes in motor activation over time. Data were acquired on 12 occasions every 3 months (ie, T1-T12) from May 2010 until February 2013, each time using the same parameters for image acquisition, postprocessing, and analysis.

The tasks of interest remained constant across all time points. The tasks involved lower limb movement (experimental condition: basic walking motion) and mental imagery of comparable movement (control condition: visualization of rowing). During each scanning session, TG's upper limb movement activity and resting state scans were also collected, but for brevity, these results will be discussed in future articles. The lower limb experimental condition was chosen to best approximate basic walking motion within the confines of magnetic resonance imaging (MRI) and TG's functional capabilities. Mental imagery of rowing was selected for the control task to combine both lower and upper limb motor tasks. (1) Lower limb task: With assistance, TG pulled his knee toward chest and then extended his leg back out at a consistent pace (4-5 repetitions during each 20-second active block; 7 rest and 6 active blocks). Left and right legs

were alternated for each new active block (ie, rest-left-rest-right-rest-left, etc). Trevor Greene was instructed to do his best to execute all components of the movement. (2) Mental imagery: TG imagined competitive rowing, a sport in which he formerly excelled, which involved generally comparable lower limb movement. There was similar cueing but no physical movement during mental imagery. Movement or mental imagery was cued to begin and end each active block. The total time was 4 minutes and 20 seconds per task.

The lower limb task and mental imagery tasks were repeated to optimize data quality. Head movement was monitored during scanning, accepting only sessions with motion minimized within the predefined acceptance range.²⁴ The motion artifact cutoff was based on the global estimation of the rigid body movement parameters for averaged movement during each session. The root-mean-square deviation value of the translation and rotation estimate parameters was set to less than 0.3 mm and was further processed and analyzed (see later).

Clinical movement scores

To link fMRI findings with clinical outcomes, regular occupation therapy assessments were conducted over the course of the study (conducted by the same rater throughout). Trevor Greene's physical performance of movements similar to those performed during fMRI was assessed every 3 months by an occupational therapist and rated from 0 (no indication of any activation), 1 (activation but little movement), 2 (very weak/slow incomplete movement), 3 (weak/slow/incomplete movement), 4 (slightly weak/slow/incomplete), 5 (near-full function) to 6 (full function). At the beginning of the study (May 2010, over 4 years postinjury), a lift was used to transfer TG onto the MRI. By the end of the study

(February 2013), TG was able to stand with minimal assistance, support himself in a walker, and walk distances with assistance to move each foot forward.

Imaging protocol

Data were collected at the Royal Jubilee Hospital in Victoria, British Columbia, Canada, using a 1.5 Tesla whole-body clinical GE Signa HDx MR system. Functional MRI data were acquired using GRE-EPI sequence (TR/TE = 2000/35 ms, flip angle = 70°); axial slices were acquired to cover the whole brain (4-mm thickness, 0.4-mm gap; FOV = 24 mm², 64 × 64 matrix). For structural registration purposes, whole-brain anatomical images were collected during each session. The structural MRI used a T1-weighted MPRAGE sequence (SPGR BRAVO, TR/TE = 7.9/3.1 ms, flip angle 12°, 160 contiguous axial slices of 1.2-mm thickness with no gap, covering the whole brain [256 × 256 matrix; 0.94 × 0.94 in-plane resolution, FOV = 24 mm²]).

Data analysis

Functional MRI data processing and analysis were performed using the FMRIB Software Library (FSL, version 5.98). After reconstruction with the application of field-map and navigator correction, data acquired during the initial 10 seconds of each fMRI run were removed for signal stabilization. The data were then de-noised applying MELODIC (Model-free analysis using the probabilistic Independent Component Analysis), which automatically estimates the number of components expressing signal sources in the data.²⁵ Components representing significant artifacts (eg, scan-specific signal drops, eddy current variations, susceptibility, and head motions) were removed, using both spatial probability and frequency distribution patterns. De-noising across time points was verified for consistency and noise detection was limited to approximately 20% of the total components.

Preprocessing included head motion correction, non-brain removal,²⁶ spatial smoothing (5-mm Gaussian kernel FWHM), grand-mean intensity normalization of the data set by a single multiplicative factor, and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting sigma = 30.0 s). Motion artifact across time points was verified for consistency (global motion <0.3 mm). Time series statistical analysis was performed with local autocorrelation correction.²⁷ A canonical hemodynamic response function, with time and dispersion derivations, and outlier weighting, was convolved with the boxcar time series (γ function) waveform to model each task onset and duration against the rest phase. Contrasts were calculated to statistically compare active conditions (ie, lower limb movement or mental imagery) to rest. Z statistic images were de-

veloped using a threshold for clusters determined by Z value greater than 2.3 and a (corrected) cluster significance threshold of P value of .05.^{28,29}

Images were registered to the high-resolution T1-weighted anatomical image.³⁰ The anatomical image at each successive time point was coregistered to that of the first time point. Analyses were performed independently for each task collected during each of the sessions. For each fMRI scan/task, percent signal change and activated voxels passing the threshold within the region of interest (ROI) were calculated postthreshold from the query outcomes on the basis of the filtered time series and percentage of activated voxels within the ROI (see Appendix Figure 1). The motor ROI representing the bilateral primary motor cortices (execution of movement) and the bilateral prefrontal supplementary motor area (movement preparation) adjusted to individual's brain anatomy. The numbers of activated voxels and the percent signal changes were statistically compared across scan times for each task condition using SPSS v19. A T test was used to compare the mean activation values between TG and control over time points 5 through 8.

RESULTS

fMRI activation

Functional MRI tasks evoked activation in the motor ROI in TG ($Z > 2.3$, $P_{\text{corr}} < .05$; see Figures 1A and B), which extended beyond the leg motor regions. During the lower limb task, motor activation increased significantly from the first to last scan (see Figure 1A). The yearly mean activated voxels increased significantly across 3 years ($F = 32.54$, $P < .001$), from year 1 (mean \pm SD = 4.8 \pm 2.2 for T1-T4 average) to year 2 (16.8 \pm 3.2 for T5-T8 average; $|t| = 6.16$, $P < .001$), and from year 2 to year 3 (20.0 \pm 2.9 for T9-T12; $|t| = 8.36$, $P < .001$; see Figure 2A). In contrast, in the mental imagery task, motor activation remained stable over time (see Figure 1B), with no significant change in the yearly average levels (mean \pm SD year 1: 9.5 \pm 6.5, year 2: 8.6 \pm 5.3, and year 3: 6.5 \pm 5.5; $F = 0.28$, $P = .76$; see Figure 2B).

Compared with TG's lower limb fMRI results, the control subject's activation corresponded with similar regions but was stable over time (from T5 to T8; $Z > 2.3$, $P_{\text{corr}} < .05$; $F = 1.73$, $P = .32$; see Figure 2A). Similar to TG, control activation during mental imagery did not change statistically across time ($Z > 2.3$, $P_{\text{corr}} < .05$; $F = 4.96$, $P = .16$). Of note, TG showed greater mental imagery activation relative to control as averaged for T5-T8 ($Z > 2.3$, $P_{\text{corr}} < .05$; see Figure 2B). Moreover, activation averaged across all time points for TG (T1-T12) and for the control (T5-T8) showed similar patterns during the lower limb task ($Z > 2.3$, $P_{\text{corr}} < .05$; see Figure 3A), whereas during mental imagery, such

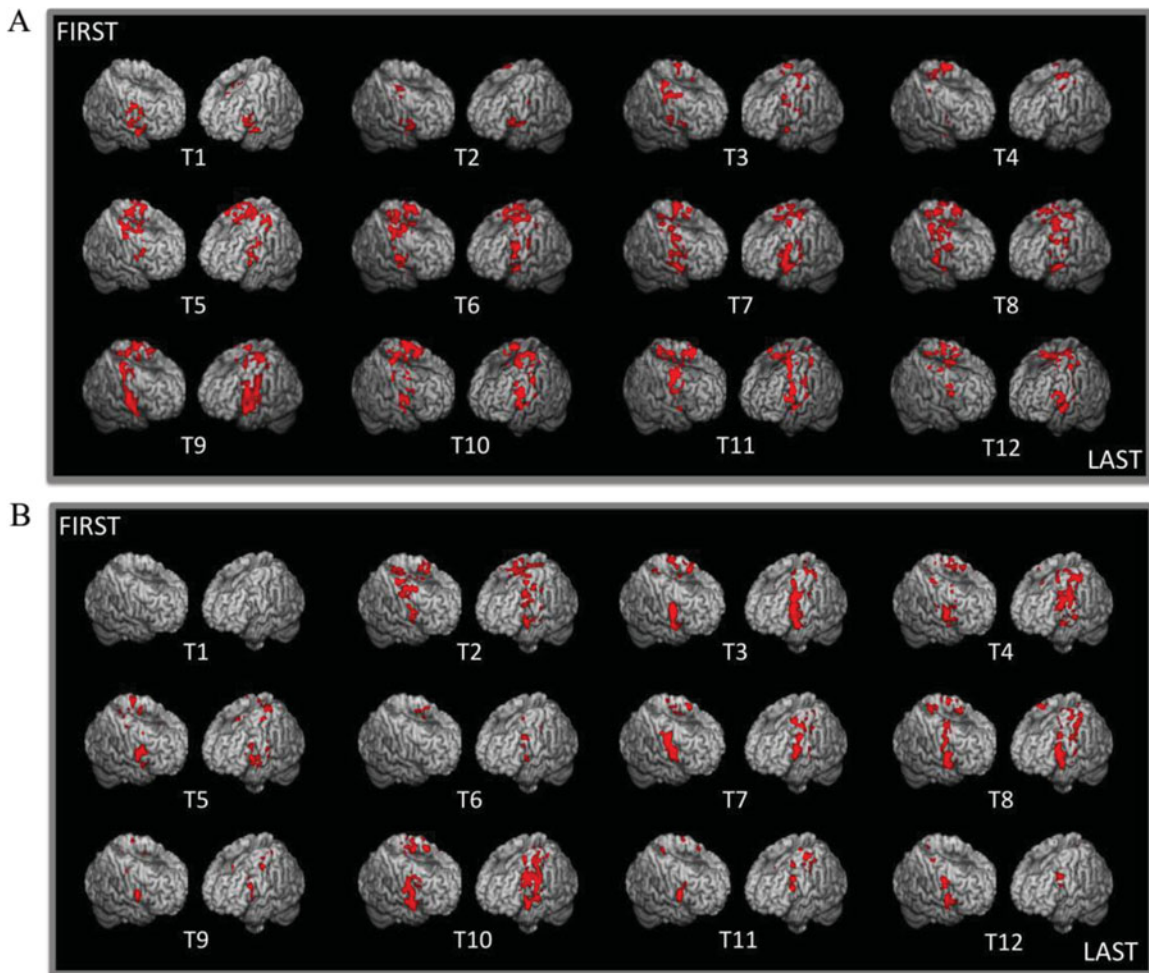


Figure 1. Trevor Greene's lower limb motor activation (panel A) and mental imagery activation (panel B) across all time points (T1-T12, 33 months). All analysis parameters equal for comparison ($Z > 2.3$, $P_{\text{corr}} < .05$).

activation was seen only in TG but not in the control (see Figure 3B).

fMRI activation in relation to clinical assessment

Trevor Greene's rehabilitation progressed considerably over the study period, as shown by increases in the clinical rating scores (see Table 1). More importantly, the increase of the clinical rating scores on the mean lower limb movement correlated positively with that of the fMRI motor activation during the lower limb task ($r = 0.81$, $P = .001$; see Figure 4A). The rating scores were not significantly associated with mental imagery activation ($r = 0.19$, $P = .56$; see Figure 4B).

DISCUSSION

The present study followed functional motor recovery of Canadian soldier Captain TG during rehabilitation to walk. Recovery has continued for more than 6 years after severe TBI from an axe attack in Afghanistan (see Table 1). We tracked changes in motor region activa-

tion over a 3-year period (extending to >6 years after the injury). During this time, TG's motor function recovered significantly to the point in which he was able to practice walking using a walker with assistance. He was able to support himself standing but required assistance to move each foot forward. The brain imaging results showed significant plasticity-related neural activation gains, which have the potential to inform treatment rehabilitation strategies.

As predicted, lower limb movement activation increased in close correspondence with recovering the ability to walk (see Figures 1A and 2A). Motor activation, averaged across all time points, was comparable to that observed in the control (see Figure 3A). However, the control did not show any change over time (see Figure 2A). Importantly, TG's activation changes correlated significantly with recovery scores during rehabilitation (see Figure 4A).

When doing mental imagery for comparable movements, TG showed significant activation in the same motor regions over the study period (see Figure 2B).

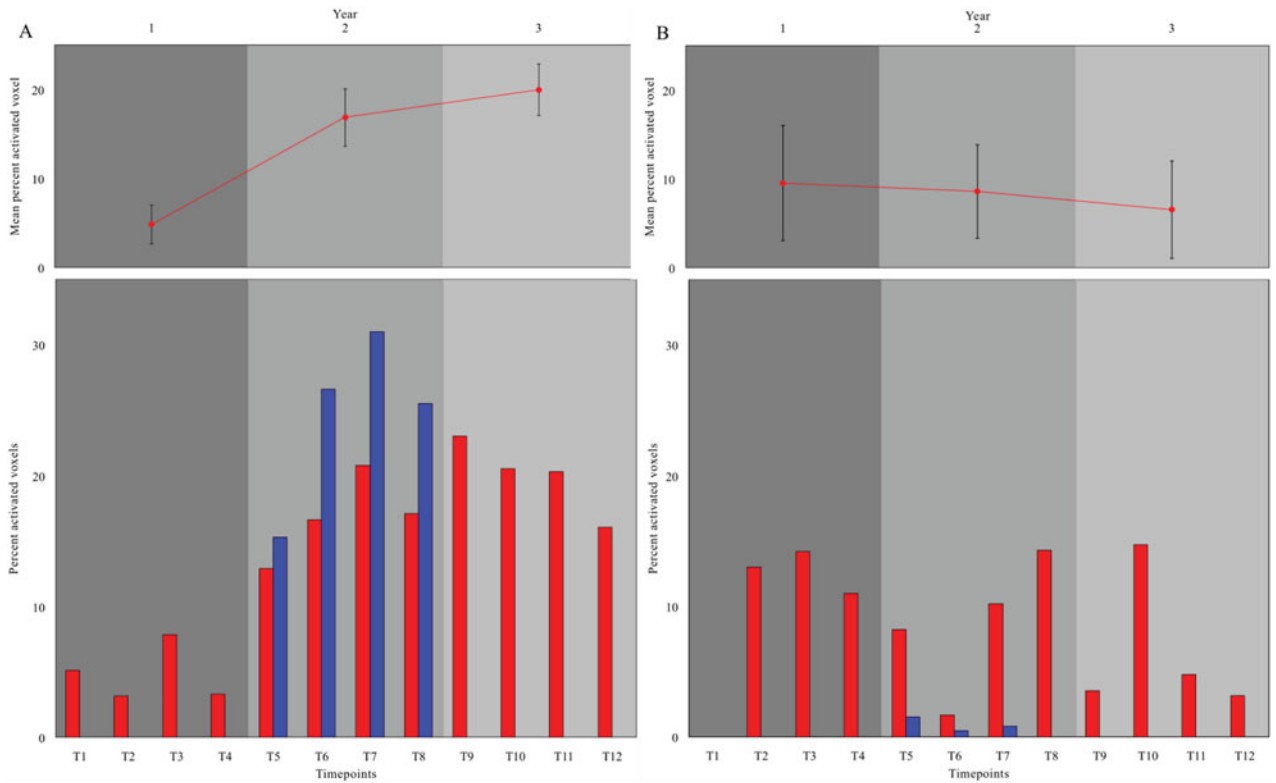


Figure 2. Percent activated voxels in the motor ROI for the lower limb task (panel A) and mental imagery task (panel B) in Trevor Greene (red; T1-T12, 33 months) and the control (blue; T5-T8, 10 months), with yearly mean levels (top sections).

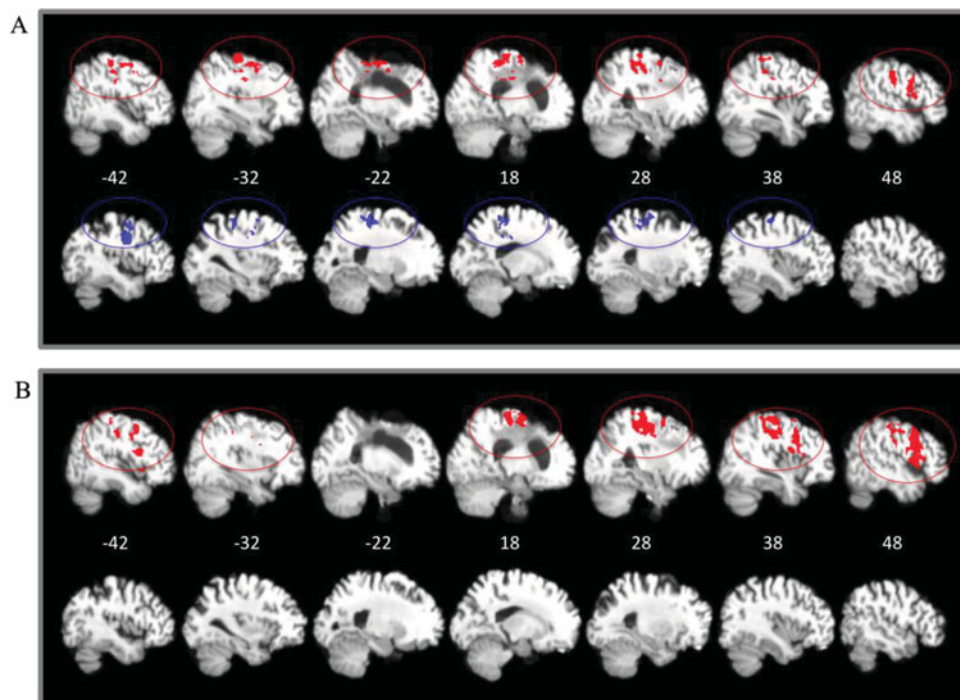


Figure 3. Sagittal view of mean lower limb motor activation (panel A) and mental imagery activation (panel B) averaged across all time points in Trevor Greene (red; T1-T12, 33 months) and the control (blue; T5-T8, 10 months). Numbers indicate the x coordinate for each slice ($Z > 2.3$, $P_{\text{corr}} < .05$).

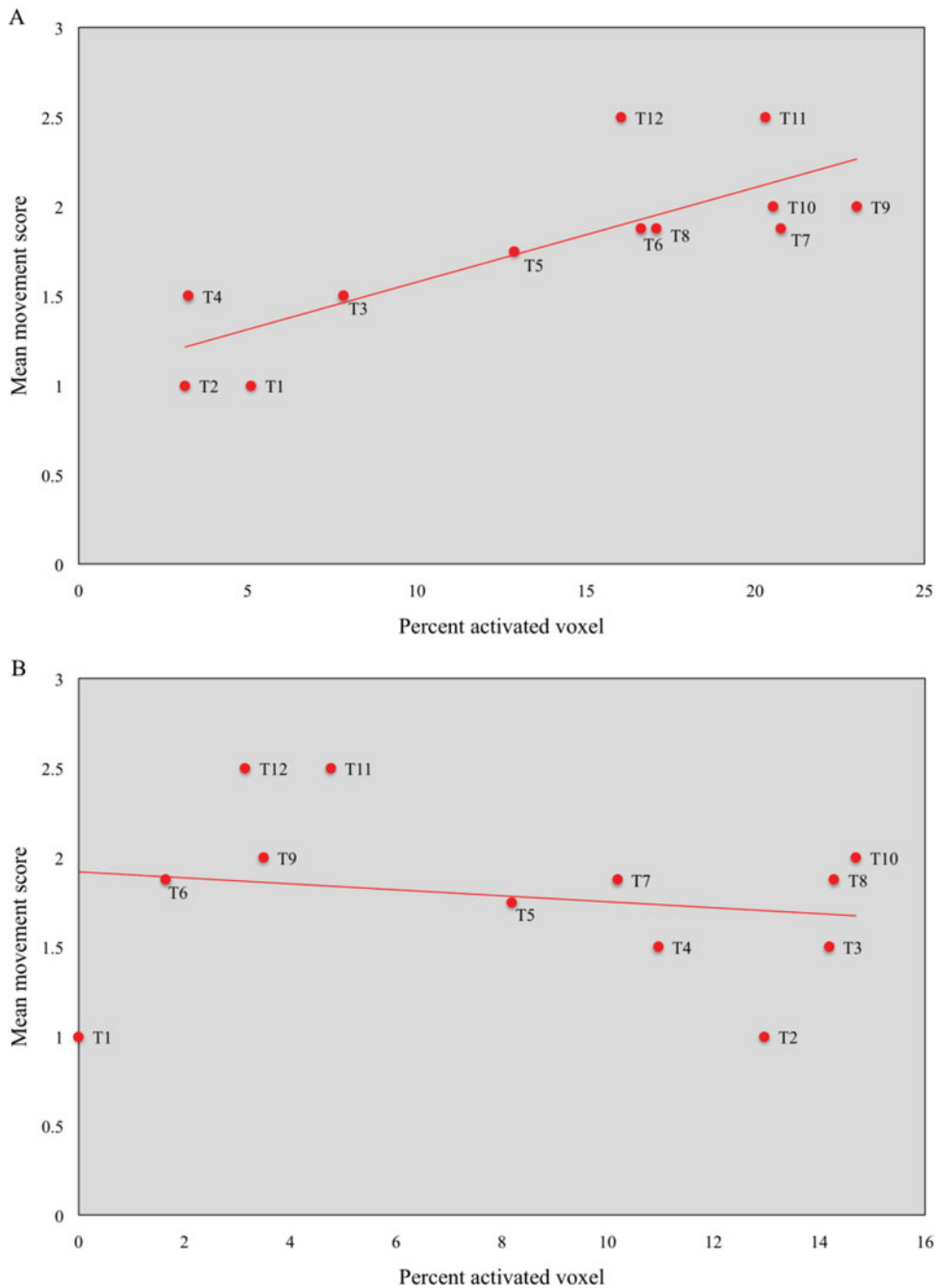


Figure 4. Relationships between Trevor Greene’s mean lower limb movement score assessed by the occupational therapist and the percent activated voxels for the lower limb task (Panel A; $y = 1.06 \pm 0.05x$; $r = 0.81$, $P = .001$) and the mental imagery task (panel B; $y = 1.92 \pm 0.02x$; $r = 0.19$, $P = .56$) across all time points (T1-T12, 33 months).

However, as expected, there was no significant change in mental imagery activation over time (see Figure 3B). Of clinical note, TG had significantly more mental imagery activation than the control—in fact, when averaged across time points, only TG showed mental imagery activation (see Figure 3B). Similar fMRI results have been reported with elite athletes who use mental imagery to rehearse skilled activities prior to execution, where novice

and nonathletes do not demonstrate an as effective translation of imagery into a motor/internal pattern of brain activity.³¹ TG has significantly greater experience in rowing than the control participant. In this respect, the functional task-specific imagery was likely significantly enhanced for TG. Accordingly, mental imagery, especially functionally task-specific imagery, is increasingly attracting interest as a potential tool in rehabilitation.^{32,33}

These results demonstrate that although motor function recovery occurs in the initial years after TBI,³⁴ further clinically meaningful improvements can continue several years after injury. Furthermore, the improvement in clinical function correlates with changes in fMRI results, suggesting that underlying neuroplasticity and functional reorganization are supporting the recovery. It is likely that the frequent, consistent, and diverse rehabilitative effort that TG has undertaken has translated into continuous recovery, demonstrating the impact of improved rehabilitation in the clinical management of TBI.

Importantly, a number of caveats related to the findings should be highlighted. The current evidence was derived from a case study and the generalizability of the findings should be determined, as there are many potential factors that can affect motor recovery after brain injury. Even so, the investigation provides clear evidence linking brain activation and behavior, demonstrating that, at least in some patients, continuation of rehabilitation therapy is beneficial. For this study, we merged ROI across key cortical motor regions to use fMRI to track rehabilitation-relevant activation changes over time. Further investigations involving in-depth scope and focused neuroimaging methods need to examine specific regional/voxel level changes over time in order to develop composite maps of activation change over time, which has motivated our current investigations.

The main objective of the study was to directly address a major barrier in the treatment of brain injury: underestimating the brain's potential for recovery. This situation can drastically limit decisions in care and treatment. Recent cases such as that of US Representative Gabrielle Giffords, who recovered considerably after a gunshot wound, underscore the untapped potential of neuroplasticity in clinical applications.³⁵ The current study utilized neuroimaging to provide an objective, physiological measure of neuroplasticity in order to monitor and optimize recovery efforts. Although many studies have used fMRI to examine brain plasticity fol-

lowing stroke,^{15,16,19,20} relatively few have investigated the outer limits functional recovery. Furthermore, only a few studies have tracked possible changes in the brain beyond more than 2 time points,^{17,18} and none to our knowledge have demonstrated continued recovery after 2 years posttrauma. More such evidence is needed to better understand the way to bring functional changes of this magnitude and over this duration to the many individuals who survive brain injury, stroke, and related conditions.³⁶ Additional investigations will also need to examine the neuroanatomical relationship between changes in brain activation and underlying neuroplasticity mechanisms, as understanding the conceptual linkages is critical.³⁷

CONCLUSION

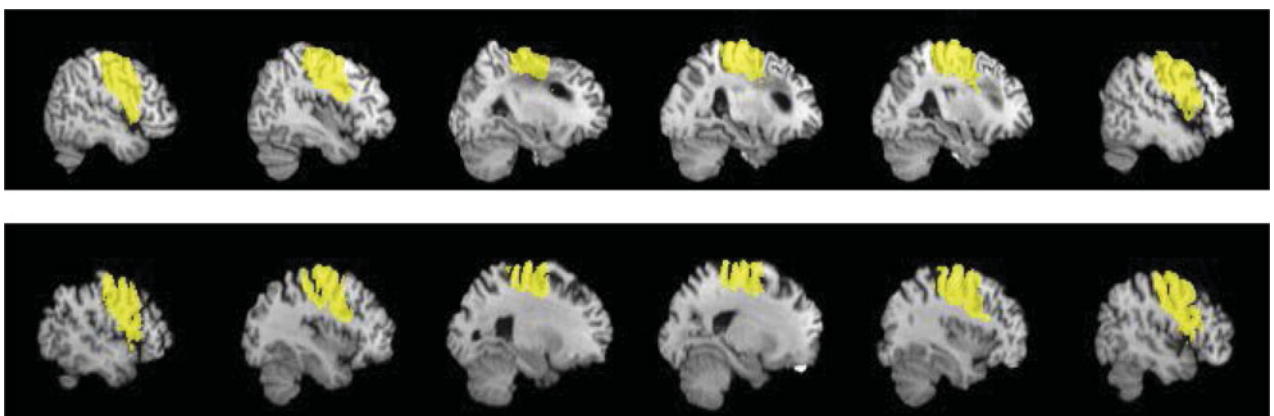
Traumatic brain injury is a priority health problem with significant socioeconomic impact. We conducted a thorough search of the literature on plasticity and recovery after severe TBI. It is suggested that the capacity of the brain to recover from TBI is often underestimated, and there is limited research on long-term neural plasticity-related mechanisms in TBI.⁸⁻¹¹ Although, in recent years, functional MRI has been applied in better understanding recovery after stroke,²¹⁻²³ its potential in monitoring ongoing functional changes over a multi-year period beyond the conventional 1- to 2-year window during long-term motor recovery in TBI is waiting to be fully explored. Here, we showed that clinically meaningful recovery can occur several years after severe TBI, demonstrating the need to improve current decisions in TBI care and treatment. The added value of our study comes from the demonstration of what is possible beyond what is currently assumed in clinical practice. These findings challenge current practices and assumptions in rehabilitation following TBI, demonstrating that continued benefits in physical function due to rehabilitative efforts can be achieved for many years following injury.

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APPENDIX



Appendix Figure 1. The regions of interest (yellow) for the patient (top panel) and the control subject (bottom panel), superimposed onto the anatomical brain images.