Neuroscience Letters 612 (2016) 238–244

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research paper

Gray matter volume and executive functioning correlate with time since injury following mild traumatic brain injury

William D.S. Killgore [a,b,*], Prabhjyot Singh [a], Maia Kipman [c], Derek Pisner [a], Andrew Fridman [a], Mareen Weber [d]

[a] Social, Cognitive and Affective Neuroscience Lab, University of Arizona College of Medicine, United States
[b] McLean Hospital, Harvard Medical School, United States
[c] Tufts University School of Medicine, United States
[d] Stanford Concussion and Brain Performance Center, Stanford University School of Medicine, United States

HIGHLIGHTS

- A voxel based morphometric study in people with mild traumatic brain injury.
- Longer duration of time since injury was associated with larger gray matter volume.
- Particularly in ventromedial prefrontal cortex and fusiform gyrus regions.
- Compensatory remodeling of cortical regions might be the reason for these findings.

ARTICLE INFO

Article history:
Received 13 November 2015
Received in revised form
14 December 2015
Accepted 15 December 2015
Available online 19 December 2015

Keywords:
mTBI
Mild traumatic brain injury
Concussion
VBM
Voxel-based morphometry
SPM8
Gray matter
Emotion regulation
Motor speed
Psychomotor vigilance

ABSTRACT

Most people who sustain a mild traumatic brain injury (mTBI) will recover to baseline functioning within a period of several days to weeks. A substantial minority of patients, however, will show persistent symptoms and mild cognitive complaints for much longer. To more clearly delineate how the duration of time since injury (TSI) is associated with neuroplastic cortical volume changes and cognitive recovery, we employed voxel-based morphometry (VBM) and select neuropsychological measures in a cross-sectional sample of 26 patients with mTBI assessed at either two-weeks, one-month, three-months, six-months, or one-year post injury, and a sample of 12 healthy controls. Longer duration of TSI was associated with larger gray matter volume (GMV) within the ventromedial prefrontal cortex (vmPFC) and right fusiform gyrus, and better neurocognitive performance on measures of visuospatial design fluency and emotional functioning. In particular, volume within the vmPFC was positively correlated with design fluency and negatively correlated with symptoms of anxiety, whereas GMV of the fusiform gyrus was associated with greater design fluency and sustained visual psychomotor vigilance performance. Moreover, the larger GMV seen among the more chronic individuals was significantly greater than healthy controls, suggesting possible enlargement of these regions with time since injury. These findings are interpreted in light of burgeoning evidence suggesting that cortical regions often exhibit structural changes following experience or practice, and suggest that with greater time since an mTBI, the brain displays compensatory remodeling of cortical regions involved in emotional regulation, which may reduce distractibility during attention demanding visuo-motor tasks.

1. Introduction

Traumatic brain injury (TBI) affects approximately 1.5 million individuals each year [27]. While TBI can be classified as mild, moderate, or severe, the vast majority of these injuries are in the mild range [33]. In contrast to moderate or severe TBI, mild traumatic brain injury (mTBI) is diagnosed following a blow or other insult to the head that leads to transient alterations in cognitive, sensory, or motor functioning, and may or may not involve brief loss of consciousness (i.e., no more than 30 min), and is usually not associated with identifiable abnormalities on standard clinical neuroimaging [2]. Common post-concussive symptoms include reduced attention, memory, and information processing speed [4,21]. Psychiatric

* Corresponding author at: Social, Cognitive, and Affective Neuroscience Lab Department of Psychiatry University of Arizona College of Medicine 1501N Campbell Ave Tucson, AZ 85724, United States. Fax: +1 520 626 6050.
E-mail address: killgore@psychiatry.arizona.edu (W.D.S. Killgore).

http://dx.doi.org/10.1016/j.neulet.2015.12.033
0304-3940/

mood disturbances, including anxiety, depression, post-traumatic stress, and phobic symptoms, are often elevated among those with mTBI compared to healthy controls [3]. For most individuals who have sustained an mTBI, the associated cognitive and affective symptoms reduce with longer time since injury (TSI), typically resolving to baseline levels within the first few days or weeks post-injury [21] and full recovery within 90 days [14]. However, some evidence suggests that nearly 50% of patients with mTBI show some persistent deficits at three months [26], and a smaller proportion will continue to have chronic post-concussive symptoms or cognitive deficits that persist for at least a year or longer [29]. Despite the rapid advancement of powerful neuroimaging techniques, little is known about the structural brain changes that are associated with the recovery process.

Voxel-based morphometry (VBM) is a neuroimaging technique that enables quantification of regional gray matter volume (GMV) throughout the cortex. A number of studies suggest that GMV may be reduced in patients with mTBI compared to healthy controls in the semi-acute to post-acute stages [12,19]. Others have shown that GMV often remains decreased in various areas of the cortex when assessed for up to a year after injury [11,39]. The research to date, however, has not examined whether and how GMV differs at various time-points following an injury nor investigated whether there are regions of increased GMV with longer recovery time, and whether this correlates with possible recovery of cognitive capacities. This latter question is important, as numerous studies have suggested that regional GMV can be increased through training or practice in particular cognitive and motor domains [20,32]. This remodeling process is known as experience-dependent cortical plasticity [15], and involves increases in dendritic arborization or neuronal spine density as a result of frequent neuronal stimulation or use (i.e., practice) [5,16]. This raises the possibility that individuals who repeatedly engage in particular cognitive or emotional strategies to compensate for their deficits might show increased experience-dependent cortical remodeling of relevant cortical structures, which over time, might be expressed as increased GMV within those structures.

The goal of the present study was to examine regional GMV within individuals following mTBI at various time-points post-injury and correlate GMV with neuropsychological and emotional functioning. Based on the aforementioned rationale of compensation through experience-dependent cortical plasticity, we hypothesized that greater TSI would be associated with increased GMV within prefrontal regions involved in regulating attention, emotion, and behavior (e.g., dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, medial/ventromedial prefrontal cortex), and that greater volume in such regions would correlate with better speed of information processing, greater vigilance, and reduced neuropsychiatric symptom expression.

2. Methods

2.1. Participants

Twenty-six right-handed, native English speaking, individuals (age range 20–45 years, mean age 23.38 ± 5.23, 11 males, 15 females) with a history of mTBI experienced within the preceding 12 months took part in this study (two-weeks [n = 2], one-month [n = 6], three-months [n = 5], six-months [n = 10], one-year [n = 3]). All participants were recruited from the Boston metropolitan area using advertisements on the Internet, public transportation billboards, newspaper, radio, and posted flyers. Eligible participants were required to have sustained a documented injury involving head impact, followed by some alteration in mental status (e.g., confusion, “seeing stars”, disorientation, post-traumatic amnesia not more than 24 h) or loss of consciousness lasting no more than 30 min. To be eligible, participants had to provide written documentation from an impartial but professionally responsible witness to the head injury (e.g., coach, sports trainer, police officer) or its immediate medical aftermath (e.g., physician, nurse, ambulance driver, medical record, neuropsychologist). In addition, 12 healthy control participants (age range 20–43 years, mean age 25.00 ± 6.55, 4 males, 8 females), without history of head injury or loss of consciousness were also recruited for comparison. Participants were compensated for their time. All study procedures were conducted in accordance with the 1964 declaration of Helsinki and were approved by the McLean Hospital Institutional Review Board. Furthermore, because the study was funded by the US Army Medical Research and Materiel Command (USMRMC), all procedures were also approved by the US Army Human Research Protections Office.

2.2. Materials and procedure

Based on the timing of their injury, mTBI participants were scheduled for an evaluation at one of six different time-points following their mTBI: 2-weeks, 1-month, 3-months, 6-months, or 12-months post injury (all sessions were scheduled within 3 days of the respective anniversary date). Participants underwent a morning assessment session that involved completing several questionnaires and cognitive tasks, followed by a series of neuroimaging scans. Healthy control participants underwent the same structural scanning sequence.

2.3. Neuropsychological assessments

2.3.1. Delis–Kaplan Executive Function System (D–KEFS)

Participants with mTBI were administered the Delis–Kaplan Executive Function System (D–KEFS), a widely used metric of higher order executive functions with established psychometric properties [6,34]. The D–KEFS provides methods for delineating underlying cognitive processes that may contribute to executive functioning. For the present analyses, we focused on two ‘matched fluency’ subtasks of the D–KEFS, (1) the verbal fluency (VF) subtest to measure verbally mediated executive control, and (2) the Design Fluency (DF) subtest to measure visuospatial executive control. For VF, four subtests were collected, including VF1 (letter fluency: number of items correct), VF2 (category fluency: number of items correct), VF3 (switching: number of items correct regardless of whether switching rule was correct), and VF3-A (switching accuracy: number of correct category switches). VF1 required the examinee to say as many words that they could think of in 60 s that began with a particular letter. VF2 required the examinee to name as many animals that they could think of in 60 s. VF3 required the examinee to name as many fruits and furniture as possible in 60 s, alternating between categories for each item. VF3-A is derived from the number of correct across-category switches from the VF3 trial. This procedure allows determination of whether deficits are due to more fundamental executive processes (VF1 and VF2) or higher level executive processes involved in switching (VF3 and VF3-A). For DF, a task that requires the examinee to connect pre-printed circles together using straight lines to make as many uniquely different designs as possible in 60 s, the following three related subtests were evaluated: DF1 (filled dots: number of correctly connected black circles), DF2 (empty dots: number of correctly connected empty circles), and DF3 (switching: number of correct designs where the examinee alternated between filled and empty circles). DF1 required the examinee to generate as many different designs as possible by connecting sets comprised of filled black circles using only 4 straight lines per design. DF2 is nearly identical to DF1, except that the pre-printed sets include both empty and filled circles, requiring the examinee to inhibit the prepotent response