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Prefrontal Gray Matter Volume Predicts Metacognitive Accuracy Following Traumatic Brain Injury

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Abstract

Objective—To examine metacognitive ability (MC) following moderate to severe traumatic brain injury (TBI) using an empirical assessment approach and to determine the relationship between alterations in gray matter volume (GMV) and MC.

Method—A sample of 62 individuals (TBI n=34; HC n=28) were included in the study. Neuroimaging and neuropsychological data were collected for all participants during the same visit. MC was quantified using an approach borrowed from signal detection theory (Type II AUROC calculation) to evaluate judgments during a modified version of the WAIS-III, Matrix Reasoning subtest where half of the items were presented randomly and half were presented in the order of increasing difficulty. Retrospective confidence judgments were collected on an item-by-item basis. Brain volumetric analyses were conducted using FreeSurfer software.

Results—Analyses of the modified Matrix Reasoning task data demonstrated that HCs significantly outperformed TBIs [ordered: $d = 0.63$; random: $d = 0.58$]. There was a significant difference between groups for MC for the randomly presented stimuli ($d = 0.54$) but not the ordered stimuli. There was an association between GMV and MC in the TBI group between the right orbital region and MC ($R^2 = 0.11$). In the HC group, there were associations between the left posterior ($R^2 = 0.17$), left orbital ($R^2 = 0.29$), and left dorsolateral regions ($R^2 = 0.21$) and MC.

Conclusions—These results are consistent with previous research on MC in the cognitive neurosciences, but this study demonstrates that injury may moderate the regional contributions to MC.

Public Significance Statement—TBI is a great public health concern, as millions of people sustain head injuries each year. This study examines whether individuals who have a TBI also have deficits in monitoring their mental processes (i.e. MC), which has important implications for functional outcome after injury.

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Keywords

traumatic brain injury (TBI); metacognition; FreeSurfer; Type II AUROC

Metacognition, defined as the ability of an individual to evaluate his or her own cognitive processes, is commonly disrupted after traumatic brain injury (Kennedy, 2001; Chiou & Hillary, 2012). This skill may be particularly important for those who have sustained an injury that causes deficits in daily life functioning because it allows for the reflection on one's present condition, as well as a greater understanding of the depth of possible deficits in various domains due to the injury (Chiou, Carlson, Arnett, Cosentino, & Hillary, 2011). Disruption in the ability to evaluate and reflect on one's own condition has implications for the trajectory of recovery, relationships with friends and family, and rehabilitation (Evans, Sherer, Nick, Nakase-Richardson, & Yablon, 2005; Flashman & McAllister, 2002; Ownsworth & Fleming, 2005; Trahan, Pépin, & Hopps, 2006). The inability to identify disrupted cognitive domains or problematic daily life situations could lead to a frustrating recovery process, as well as strained relationships with family or caregivers who are aware of these deficits. Understanding how and why metacognitive processes are disrupted in individuals with TBI can lead to developments in rehabilitation techniques to help these individuals understand their own cognitions and condition. It is the goal in this study to objectively measure metacognition in a group of individuals with moderate and severe TBI and to examine changes in gray matter volume associated with injury to determine how changes in brain volume may predict metacognitive outcomes.

Assessment of Metacognitive Ability

Commonly, metacognitive deficits have been assessed through the use of self-report questionnaires (Akturk & Sahin, 2011). Some commonly used questionnaires for the assessment of metacognitive abilities are the Thought Control Questionnaire (TCQ), Anxious Thoughts Inventory (AnTI), and the Metacognitions Questionnaire (MCQ). All of these scales are often used in relation to psychopathology and metacognitive deficits (Wells & Cartwright-Hatton, 2004). Questionnaires are popular, as they are easy and inexpensive to administer, but may be inexact, as they can be biased by the respondent's unawareness of his or her own capacities (Akturk & Sahin, 2011).

In the study of TBI, metacognitive deficits assessed through questionnaires have reported mixed findings and this is perhaps more evident in milder forms of TBI. For example, Zargar and colleagues (2015) did not find any deficits in individuals with mild TBI on the Cognitive Failures Questionnaire (CFQ) or the Metacognitions Questionnaire (MCQ-30). Conversely, Martinez and Davalos (2016) found that college students with mild TBI had higher scores, indicating higher frequency of dysexecutive behaviors, on the Dysexecutive Questionnaire (DEX) overall, as well as on all three subscales. In severe TBI, Bivona and colleagues found that decreased metacognitive awareness as measured by the Awareness Questionnaire (AQ) was associated with decreased performance on the Wisconsin Card Sorting Test, but not other neuropsychological measures of executive functioning or other cognitive domains (Bivona et al., 2008). Lastly, results from a mixed sample of mild to severe TBI participants

demonstrated that participants in the TBI group had significantly worse overall metacognitive awareness than healthy controls, as measured by the Patient Competency Rating scale (PCRS), Frontal Systems Behavioral Scale (FSBS), and the Cognitive Failures Questionnaire (CFQ) (O'Keeffe, Docktree, Moloney, Carton, & Robertson, 2007). These mixed findings demonstrate that questions remain in the field regarding metacognitive dysfunction following TBI and the utility of self-report measures to assess metacognition.

More exacting approaches have been used to assess metacognition, including online item-by-item judgments of performance while engaged in the task. For example, retrospective confidence judgments are collected when participants judge in real time how sure or unsure they are of their responses during tasks (Nelson & Narens, 1990). Surprisingly, few studies have used this approach to measure metacognitive accuracy in TBI. In an important work by Kennedy, findings revealed that TBI and healthy control participants were equally accurate when judging the correctness of one item compared to another, but the TBI group was generally overconfident when unsure of an answer, whereas under the same circumstances, the healthy control participants were under-confident (Kennedy, 2001). Similarly, Chiou and colleagues (2011) used retrospective confidence judgments for both memory and abstract reasoning tasks within a TBI population and found that metacognitive accuracy was not the same for the different tasks. Their findings of greater metacognitive accuracy for memory tasks compared to abstract reasoning performance suggests that metacognitive ability may be differentiated between cognitive domains (Chiou et al., 2011). Metacognitive accuracy also appears to be a function of anchoring difficulty on task items. Confidence judgments have been found to be more accurate on a task in which the difficulty of items increased from easy to challenging, rather than when the items were randomized in terms of their difficulty (Chiou & Hillary, 2012). These results demonstrate the difficulty in studying metacognition, as metacognitive ability appears to depend on variables that may differ across situations and domains.

The metacognitive work to date in TBI has largely employed a gamma coefficient to calculate a value for metacognitive accuracy from a task that uses retrospective confidence judgments. This value ranges from −1 to 1 and gives meaning to the concordance between performance on the task and the individual's confidence of their answer (Kennedy, 2001; Chiou et al., 2011). The gamma coefficient has been commonly used in the metacognitive literature due to its ease in implementation, but it has some limitations. The greatest weakness of this statistic is that it does not incorporate information about whether an individual is consistently responding in an under- or over-confident manner (Fleming & Lau, 2014). In order to retain information about an individual's pattern of responding, an area under the receiver operating characteristic curve (AUROC) value can be calculated from a Type II receiver operating characteristic (ROC) curve, which represents metacognitive accuracy. This method, based on signal detection theory, incorporates both metacognitive sensitivity, which is defined as the capacity to classify correct and incorrect responses based on one's reported confidence level, and metacognitive bias, the respondent's overall level of confidence (Fleming & Lau, 2014). Another benefit to this statistic is that it can calculate the value based on multiple confidence ratings (e.g., "completely confident", "confident", "unconfident", and "completely unconfident."), rather than simply "confident" or

"unconfident." This permits greater dimensionality to the subject response as opposed to the typical binary response criteria.

Neural correlates of Metacognitive Ability

There is an appreciable cognitive neuroscience literature examining the neural substrates associated with metacognition. For example, individual variation in metacognitive ability has been found to positively correlate with gray matter volume of the anterior prefrontal cortex and the frontal pole (Fleming & Dolan, 2012; McCurdy et al., 2013; Fleming, 2010). Similarly, metacognitive accuracy has also been found to have a positive correlation with gray matter volume in the right prefrontal cortex, right anterior insula, and right fusiform gyrus (Sinanaj, Cojan, & Vuilleumier, 2015). Cortical thickness in the right medial prefrontal and anterior cingulate cortices has also been shown to be greater in individuals with better metacognitive accuracy on a perceptual reasoning task (Valk et al., 2016). Additionally, participants who demonstrated greater metacognitive accuracy in their retrospective confidence judgments also had greater white matter integrity in an area of the corpus callosum that projects to the anterior prefrontal cortex (Fleming & Dolan, 2012). Rounis and colleagues used transcranial magnetic stimulation (TMS) to disrupt the dorsolateral prefrontal cortex (DLPFC) processing, revealing decreased metacognitive accuracy while still maintaining the same level of task performance (2010). These results indicate that areas of the DLPFC involved in the judgment of the quality of one's own responses are distinct from performance during the response.

These volumetric findings are also consistent with functional imaging data, where increased activation in the right anterior prefrontal cortex was associated with making subjective confidence ratings, and increased functional connectivity was found between the ventromedial prefrontal cortex and the anterior prefrontal cortex when relating confidence judgments to decision making (DeMartino, Fleming, Garrett, & Dolan, 2012). Activation in other areas including temporal lobe, angular gyrus, and the posterior cingulate cortex (PCC) have been associated with metacognition (Paul et al., 2015). Moreover, the brain response in orbitomedial prefrontal cortex has been associated with self-referential behaviors (Northoff & Bermpohl, 2004). The medial orbital cortex response has been correlated with self-evaluation in a task where participants thought about and assessed their own abilities (Schmitz, Kawahara-Baccus, & Johnson, 2004). These last two findings provide important related support for the role of orbital and medial frontal regions in self-referential processing consistent with the maturing literature in default mode networks in brain functioning (Fox, Snyder, Vincent, Corbetta, & Van Essen, 2005; Raichle, MacLeod, Snyder, Powers, Gusnard, & Shulman, 2001; van de Heuvel & Pol, 2010).

The relationship between prefrontal cortex functioning and metacognition established in healthy adults has been extended to neurologically impaired populations with some consistency. A group of patients with lesions in the prefrontal cortex following tumor resection or epilepsy treatment demonstrated lower perceptual metacognitive accuracy than patients with temporal lobe lesions and healthy control participants (Fleming, Ryu, Golfinos, & Blackmon, 2014). Others have shown that cortical lesions due to early brain damage in the medial and orbital areas are associated with problems in judgment, self-regulation, and

self-awareness, all of which are similar constructs to metacognition (Eslinger, Dennis, Moore, Antani, Hauk, & Grossman, 2005). These lesion studies reveal that loss in metacognitive functioning may be tied to specific lesion constellations, but it is unclear if loss of metacognitive ability in a diffuse injury such as TBI is based upon similar network disruption.

While these prefrontal areas have been shown to be associated with metacognitive ability in healthy control individuals, this association has not been directly investigated in a TBI sample. The present study aims to advance the study of metacognition in TBI by using whole-brain and targeted regional gray matter volume measurements using a method that permits incorporation of the directionality of response bias into the metacognitive metric (Type II AUROC, described below).

Goals of the proposed study—The goals of this study are to examine metacognitive ability after moderate and severe TBI with the objective of determining the structural brain changes that occur post injury and also predict diminished metacognitive accuracy. To do so, we take a novel approach to identifying metacognitive deficits by utilizing the AUROC metacognitive accuracy statistic in conjunction with gray matter volume in a TBI population, thereby integrating an empirical and nuanced measurement of metacognitive ability in order to examine the influence of brain trauma on cognitive performance.

Hypotheses

Hypothesis 1. Individuals with TBI would demonstrate relatively poorer metacognitive accuracy and neuropsychological task performance when compared to an age and education matched control sample.

Hypothesis 2. There would be a significant difference in whole brain gray matter volume between TBI and healthy control participants, in that healthy control participants would have greater whole brain gray matter volume than the TBI participants, but whole brain gray matter volume would not be a strong predictor of metacognitive accuracy.

Hypothesis 3. Based upon a literature established in healthy adults, we predicted that gray matter volume in the dorsolateral and orbitofrontal regions of the frontal lobe would be positively correlated with metacognitive accuracy in the TBI sample.

Method

Participants

This study included 34 participants who have sustained moderate or severe traumatic brain injury and 28 healthy control (HC) participants to serve as a comparison group. Participants in the TBI group were diagnosed with moderate to severe traumatic brain injuries, as defined by a Glasgow Coma Scale (GCS) score of 3–12, and/or by having positive neuroimaging findings during acute brain scanning during treatment (complicated mild TBI). Individuals with complicated mild TBI have demonstrated similar long-term cognitive deficits to those with moderate to severe TBI (Tayim, Flashman, Wright, Roth, & McAllister, 2016). This

study included five participants who had a GCS score of 14 or 15, all with documented hemorrhages, contusions, or both. Participants in the two groups were matched on demographic variables, including age, education, and gender. See Table 1 for the participant demographic information.

The sample included in this study was part of a larger longitudinal study of recovery in TBI. These data were compiled from two studies conducted by the Brain and Behavior Lab at The Pennsylvania State University in collaboration with The Pennsylvania State University Hershey Medical Center Departments of Neurology and Physical Medicine and Rehabilitation. The current analysis combined datasets from longitudinal and cross-sectional studies, but the data for all participants represented the initial exposure to the stimuli only. From this combined database, TBI and healthy control participants were selected for inclusion in this particular study if they had T1-weighted structural images, as well as scores and confidence judgments for the Matrix Reasoning task (the metacognitive task, detailed below). Regarding participants from the longitudinal study, the chosen time point was determined by the first time the participant was administered the metacognitive Matrix Reasoning.

Recruitment was initiated with a phone screen for both the healthy control and TBI groups to ensure that they met all of the study inclusion and exclusion criteria. Exclusion criteria for both healthy control and TBI participants included left-handedness, colorblindness, history of psychiatric illness or neurodegenerative disease, and alcohol or substance abuse that required inpatient treatment. A screening questionnaire was also administered to individuals in both groups to ensure that there were no contraindications for entry into the MRI scanner.

Informed consent was obtained for all participants. The Penn State IRB approved the informed consent form that was used in this study. Additionally, participants were compensated for participating in this study.

Procedure

Testing Session—Study procedure was consistent for all participants across all portions of the study, including University-approved informed consent, the neuroimaging protocol, and the paper-and-pencil neuropsychological test battery. Total time in the MRI environment was typically 90 minutes. A brief neuropsychological battery was administered for the last hour and a half of the study session, containing measures of premorbid intelligence, memory, attention, and executive functioning.

The primary measure from the neuropsychological battery that was used for this study was a modified version of the Matrix Reasoning task adapted from the Wechsler Adult Intelligence Scale-3rd Edition (WAIS-III) (Wechsler, 1997). The Matrix Reasoning task involves the selection of an image for pattern completion. The traditional version of this task is anchored, beginning with the easiest items and ending with the most difficult items. For our purposes, this 26-item task was divided into two 13-item lists. One list, the ordered list, retained the anchors for item difficulty (easiest to hardest). The second list, the random list, was presented in an order based upon random selection of the items (consistent with Chiou et al, 2011). For both the ordered and random Matrix Reasoning tasks, participants were provided

with identical standardized instructions from the WAIS-III manual (Wechsler, 1997). Following the response for each item on the 13-item task lists, participants were asked, "How confident are you of your choice?" and asked to respond on a 6-point Likert scale that ranged from "completely certain" to "completely uncertain" (see Figure 1). Exact responses were: "completely certain", "certain", "somewhat certain", "somewhat uncertain", "uncertain", and "completely uncertain" (see Chiou et al., 2011). The Modified Matrix Reasoning task was administered to participants twice during the testing session so that each participant received both the ordered and random lists. Administration was counterbalanced with respect to initial exposure to the lists (ordered/random).

MRI Acquisition—MRI data were collected between three scanners. Participants were either scanned at Penn State Hershey Medical Center Department of Radiology on a Philips Achieve 3T scanner or a Siemens Magnetom Trio 3T scanner, or on an identical Siemens Magnetom Trio 3T scanner at Penn State University in the Social, Life, and Engineering Sciences Imaging Center (SLEIC).

During the MRI scan, structural and functional data were collected. Data were collected consistent with two prior studies in our laboratory (Roy, Campbell, Bernier, & Hillary, 2016; Roy et al., 2017). Briefly, anatomical structural scans were collected using an MPRAGE sequence at a spatial resolution of 1.0 × 1.0 × 1.0 mm voxels, 2300ms repetition time, echo time of 2.98, flip angle of 9 degrees, and slices were collected interleaved. The MRI protocol included data collection for diffusion, inverse recovery and functional MRI data, but for the purposes of this paper, analyses are limited to structural imaging data.

Gray matter volume mapping—In order to examine the relationship between metacognitive ability and regional changes in gray matter volume, a whole-brain voxelwise analysis of brain structure was conducted in FreeSurfer for each subject (FreeSurfer Analysis Pipeline Overview, http://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferAnalysisPipelineOverview). These data were then concatenated to examine group-level differences in gray matter volume.

FreeSurfer Analysis Pipeline—The "recon-all" pipeline in FreeSurfer was used to calculate the gray matter volumes and cortical thickness values (see Figure 2). Only the values for gray matter volume were used in this analysis. This pipeline produces values for brain areas from three different atlases: Desikan-Killiany, DKT, and Destrieux. The Desikan-Killiany and DKT atlases are both gyral-based, while the Destrieux atlas is gyral- and sulcal-based (FreeSurfer Analysis Pipeline Overview, http://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferAnalysisPipelineOverview). The Destrieux atlas was used for all subsequent analyses in this study. Using a T1-weighted image from each subject, the processing stream performs skull stripping, volumetric labeling, intensity normalization, white matter segmentation, surface atlas registration, surface extraction, and gyral labeling (FreeSurfer Analysis Pipeline Overview; http://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferAnalysisPipelineOverview). Each participant's image was examined for misalignment or other gross distortions after completion of the processing stream.

Volumetric Parcellation—Figure 3 represents the whole brain parcellated areas using the Destrieux atlas in FreeSurfer. Images such as this were generated from each participant's T1-weighted image using the recon-all pipeline in FreeSurfer.

Frontal parcellation—Using the Destrieux atlas, the parcellations were collapsed into four broader regions that have previously been associated with metacognition: orbital region, dorsolateral region, posterior region, and frontopolar region. See Table 2 for the region classifications.

Temporal Parcellation—The temporal pole was chosen as a control region, as it is an area that is commonly impacted by traumatic brain injury (Mcallister, 2008), but it has not been shown to be associated with metacognition.

Occipital Parcellation—The occipital pole was chosen as a second control region, as it is not commonly injured after a traumatic brain injury and also should not be associated with metacognition.

AUROC Calculation—The AUROC values for metacognitive accuracy were calculated twice for each participant, once for the ordered Matrix Reasoning task and once for the random version. The calculations were completed using the Type II AUROC code from Fleming and Lau (2014) in Matlab (see appendix for code). The algorithm computes a bias-free value of metacognitive ability from a non-parametric Type II AUROC analysis. Because our test stimuli had six confidence ratings for participants to choose from, this statistic is able to incorporate all of them into the calculation, as opposed to the gamma coefficient, which can only use two confidence ratings in its calculation. Moreover, this AUROC analysis calibrates responses based upon response bias (e.g., response bias toward "highly confident" or "unconfident").

Data Analysis

Hypothesis 1

Independent sample t-tests were used to determine group differences in metacognitive test performance, metacognitive accuracy, and other neuropsychological test performances between the TBI and healthy control groups.

Hypothesis 2

Independent sample t-tests were used to determine group differences in total gray matter volume between the TBI and healthy control group. A Pearson's correlation was used to determine if there was a relationship between total gray matter volume and metacognitive accuracy overall and for each of these groups (TBI and healthy control).

Hypothesis 3

Linear regression, controlling for estimated total intracranial volume, determined if there was a relationship between parcellated frontal lobe areas and metacognitive accuracy overall.

Results

Behavioral Analyses

There were significant differences between the TBI group and the healthy control group on accuracy of the Matrix Reasoning task. Differences between groups were evident for both the ordered list, TBI (M = 9.09; SD = 2.53) and HC (M = 10.46; SD = 1.73), $t(57) = -2.50$, $p = 0.015$, $d = 0.63$, 95% CI [−2.47, −0.27], and the random list, TBI (M = 8.33; SD = 2.26) and HC (M = 9.46; SD = 1.57), $t(57) = -2.29$, $p = 0.026$, $d = 0.58$, 95% CI [−2.12, −0.14]. When testing the order of presentation within the counter-balanced design, the order (ordered vs. random list) did not impact performance on either Matrix Reasoning task for TBI participants [Ordered: $t(29) = 0.75$, $p = 0.457$, 95% CI [−1.15, 2.50], Random: $t(25) = -0.65$, $p = 0.520$, 95% CI [−2.18, 1.13]] or healthy control participants [Ordered: $t(26) = -0.32$, $p = 0.749$, 95% CI [−1.53, 1.11], Random: $t(22) = -1.85$, $p = 0.078$, 95% CI [−2.30, 0.13]]. In contrast, there were no significant differences between the TBI group and the healthy control group on metacognitive accuracy of the ordered list, TBI (M = 0.70; SD = 0.10) and HC (M = 0.71; SD = 0.09), $t(59) = -0.66$, p = 0.513, $d = 0.11$, 95% CI [−0.06, 0.03]. There was a non-significant difference showing medium effect size between the TBI group and the healthy control group on metacognitive accuracy of the random list, TBI (M = 0.65; SD = 0.13) and HC (M = 0.71; SD = 0.09), $t(57) = -1.81$, p = 0.076, $d = 0.54$, 95% CI [−0.10, 0.01] (see Table 3). Interestingly, individuals in the TBI group who received the random list first had better metacognitive accuracy on the random list than those who received the random list second, $t(20) = -2.31$, $p = 0.032$, 95% CI [−0.19, −0.01]. There was no affect of order of list presentation on metacognitive accuracy on the random list in the healthy control group, $t(20) = 1.10$, $p = 0.285$, 95% CI [−0.03, −0.11].

In examining the association between metacognitive accuracy and matrix reasoning performance, there was no association between metacognitive accuracy on the ordered list and matrix reasoning performance on the ordered list, $r = 0.25$, $p = 0.553$. There was a medium association between metacognitive accuracy on the random list and matrix reasoning performance on the random list, $r = 0.45$, $p < 0.001$.

In order to determine if there was an overall cognitive deficit in the TBI group compared to the healthy control group, multiple tests from the neuropsychological battery were examined. The healthy control group outperformed the TBI group on Trails A and Digit Span Forward, two tests that are commonly used to assess brain injury (Demery, Larson, Dixit, Bauerand, & Perlstein, 2010; Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005). See Table 4 for a full summary of the neuropsychological tests.

Structural Imaging Analyses

There was a significant difference in total gray matter volume between TBI (M = 611771.9 mm^3; SD = 73791.13) and HC (M = 676214.1 mm^3; SD = 89463.56) groups, $t(52) = -3.04$, $p = 0.004$, $d = 0.33$, 95% CI [−107041.54, −21842.78]. As predicted, however, total gray matter volume was not a predictor of metacognitive accuracy on the ordered ($r = 0.20$, $p = 0.120$) or random ($r = 0.17$, $p = 0.196$) lists.

Two-sample t-tests examined differences in gray matter volume of the four grouped brain regions (orbital, dorsolateral, posterior, and frontopolar) between the healthy control and TBI groups. In both the left and right hemispheres, there were significant differences in gray matter volume between the healthy control and TBI groups in the orbital region and dorsolateral region. The following differences were apparent in the left and right hemispheres. In the left hemisphere, there was a significant difference in gray matter volume of the orbital region between the TBI group (M = 3945.58 mm^3; SD = 685.51) and the healthy control group (M = 4465.70 mm^3; SD = 578.63), $t(58) = -3.19$, p = 0.001, $d = 0.82$, 95% CI [−846,86, −193.38], as well as a statistically non-significant difference in gray matter volume of the dorsolateral region between the TBI (M = 9778.96 mm^3; SD = 1432.52) and healthy control (M = 10547.94 mm^3; SD = 1755.77) groups, $t(52) = -1.84$, $p = 0.071$, $d = 0.48$, 95% CI [−1606.49, 68.53]. In the right hemisphere, there was a significant difference in gray matter volume of the orbital region between the TBI group (M = 4197.73 mm^3; SD = 568.02) and the healthy control group (M = 4746.39 mm^3; SD = 661.88), $t(54) = -3.44$, $p = 0.001$, $d = 0.89$, 95% CI [−868.39, −228.94], as well as a significant difference in gray matter volume of the dorsolateral region between the TBI (M = 9357.03 mm^3; SD = 1191.16) and healthy control (M = 10344.89 mm^3; SD = 1878.12) groups, $t(44) = -2.40$, $p = 0.021$, $d = 0.63$, 95% CI [−1816.18, −159.54].

Behavior x Volume Analysis

When examining both the TBI and healthy control groups together and controlling for total intracranial volume, there was a small positive association between the left dorsolateral region and metacognitive accuracy on the random list, [$t(57) = 2.00$, $p = 0.051$, $R^2 = 0.07$]. There were no other significant associations between the other three brain regions and metacognitive accuracy in the left or right hemisphere.

To identify changes in gray matter volume that predicted the primary TBI deficits in metacognition, we correlated frontal volumes with metacognitive accuracy for the random list solely within the TBI group. Within the right hemisphere for the TBI group, orbital region volume predicted 11% of the variance in metacognitive accuracy on the random list after controlling for total intracranial volume, [$t(30) = -1.85$, $p = 0.075$, $R^2 = 0.11$], see Figure 4. No additional areas in the right or left hemisphere were predictive of metacognitive accuracy. Within the healthy control group, there was a significant positive association between the left posterior region and metacognitive accuracy on the random list when controlling for total intracranial volume, [$t(25) = 2.09$, $p = 0.047$, $R^2 = 0.17$], see Figure 5. There was also a significant association between the left orbital region and metacognitive accuracy on the random list when controlling for total intracranial volume, [$t(25) = 3.18$, $p = 0.004$, $R^2 = 0.29$], see Figure 4. Lastly, there was a significant positive association between the left dorsolateral region and metacognitive accuracy on the random list when controlling for total intracranial volume, [$t(25) = 2.50$, $p = 0.019$, $R^2 = 0.21$], see Figure 6. There were no significant associations between metacognitive accuracy and gray matter volume within the right hemisphere for the healthy control group.

The temporal pole and occipital pole were used as control regions. Contrary to literature indicating that temporal pole volumes would be reduced in individuals with TBI (Bigler,

2001), there were no significant differences in gray matter volume for the temporal poles between the TBI and healthy control groups, [left hemisphere: TBI (M = 5525.38 mm^3; SD = 1056.69) and HC (M = 5757.50 mm^3; SD = 978.57), $t(58) = -0.90$, $p = 0.373$, $d = 0.23$, 95% CI [−749.07, 284.82]; right hemisphere: TBI (M = 5579.97 mm^3; SD = 718.42) and HC (M = 5869.89 mm^3; SD = 616.14), $t(59) = -1.69$, $p = 0.097$, $d = 0.43$, 95% CI [−633.56, 53.61]]. Expectedly, there were no significant differences in gray matter volume for the occipital poles (the "control" region in the analysis) between the TBI and healthy control groups, [left hemisphere: TBI (M = 3234.47 mm^3; SD = 631.01) and HC (M = 3357.93 mm^3; SD = 630.38), $t(57) = -0.76$, $p = 0.452$, $d = 0.20$, 95% CI [−449.76, 202.84]; right hemisphere: TBI (M = 4868.12 mm^3; SD = 743.12) and the healthy control (M = 5069.50 mm^3; SD = 904.23) groups, $t(51) = -0.93$, $p = 0.354$, $d = 0.24$, 95% CI [−633.72, 230.96]]. Importantly, these control regions did not predict metacognitive accuracy [temporal left hemisphere: r = 0.22, $p = 0.997$; temporal right hemisphere: $r = 0.21$, $p = 0.738$], [occipital left hemisphere: $r = 0.04$, $p = 0.971$; occipital right hemisphere: $r = 0.03$, $p = 0.813$].

Discussion

The goal of this paper was to identify the relationships between regional cortical changes after TBI and metacognitive accuracy using a novel approach based on signal detection theory to define metacognitive accuracy. It was also a goal to vary the presentation with regard to item difficulty to determine this influence on metacognition, thus examining the conditions that most directly influence metacognitive accuracy (i.e. with and without task difficulty anchors).

We predicted that the TBI group would perform worse on the Matrix Reasoning task compared to the healthy control group and show similar deficits in metacognitive accuracy that would be increased by using task anchors. With regard to task performance, findings supported the hypotheses for both the ordered and random lists of Matrix Reasoning. Interestingly, for metacognitive accuracy, there were no significant differences between the TBI and healthy control groups for the ordered list, but differences emerged for the random stimulus presentation, with the TBI sample showing reduced metacognitive accuracy to the HC group. Additionally, there was a list-presentation effect so that the TBI participants who received the random Matrix Reasoning list first had better metacognitive accuracy for the random stimuli than those who received the random list second (i.e., the ordered list first). This list-presentation effect was not apparent in the healthy control group and indicates that for individuals predisposed to metacognitive deficit, ordered presentation at the outset of the task may set an expectation that is preserved even when stimuli no longer follow this pattern, or a perseveration in the anchoring effect. Future work could design additional manipulations to determine the contextual circumstances where metacognitive deficit in TBI is ameliorated or accentuated.

The second goal of this study sought to determine whether there was a whole brain gray matter volume difference between the TBI and healthy control group, and whether total gray matter volume was significantly associated with metacognitive accuracy. If total gray matter volume had a significant relationship with metacognitive accuracy, we could assume that differences between individuals with TBI and healthy controls were due to generalized

cortical atrophy and not due to regional disruption of specific circuits post injury. The data supported our hypothesis that individuals with TBI had less total gray matter volume than healthy controls, but that total gray matter volume was not an important predictor of metacognition. This finding indicates that perhaps the differences in metacognitive accuracy were due to regional gray matter volume changes, rather than overall volume loss or total number of brain lesions, as previously examined Sherer and colleagues (2005) and Prigatano and Altman (1990).

The third goal was then to determine if there was a regional contribution to metacognitive awareness and dysfunction after TBI. When the TBI and healthy control groups were analyzed together, the left dorsolateral region was significantly associated with metacognitive accuracy on the random list. Interestingly, the regional contributions of PFC to metacognitive accuracy varied by group. Within the healthy control group, gray matter volume within the left hemisphere was associated with metacognitive accuracy. Specifically, gray matter in the previously defined regions of the left orbital area, left posterior area, and left dorsolateral area were all significantly associated with metacognitive accuracy. Within the TBI group, only gray matter volume in the right orbital area was associated with metacognitive accuracy. These results for the healthy control and TBI groups are consistent with previous research revealing that the PFC has been associated with metacognitive accuracy, in particular the anterior PFC (Fleming & Dolan, 2012; McCurdy et al., 2013; Fleming, 2010; DeMartino et al., 2012). Specifically, the dorsolateral regions sampled in this study were comprised of the superior and middle frontal gyri and sulci (see Table 2), which have been linked to self-evaluative processes involved in performance in healthy adults (Schmitz et al., 2004). This is also consistent with findings from studies in healthy adults documenting activation of the right orbitofrontal region during completion of a metacognitive task (Chua, Schacter, Rand-Giovannetti, & Sperling, 2006). Other studies have shown that the orbitomedial prefrontal cortex is associated with self-referential behaviors and judgments of one's own qualities (Northoff & Bermpohl, 2004; Johnson et al., 2002). Perhaps the act of reflecting on one's own correctness is a similar process to reflecting on one's personal traits and qualities. In addition, posterior medial cortical regions, particularly the posterior cingulate cortex (PCC), have been shown to be associated with metacognition (Paul et al., 2015) and metamemory (Chua, Pergolizzi, & Weintraub, 2014). The between-group differences demonstrated might be attributed to overall gray matter volume loss in the TBI group, or the prominence of prefrontal cortex injuries, which in turn alter the regional contribution to metacognition.

In summary, the current findings reveal that TBI results in metacognitive deficits and these deficits are more likely to be evident when important anchors, or indicators of task expectancy, are removed. These findings provide greater specificity to the situations where we would expect to observe metacognitive deficit after TBI. Moreover, the findings here refute generalist hypotheses that metacognition is a function of whole-brain processes and that lesion volume, as opposed to location, should be a predictor of deficits in metacognition. Finally, these data provide continued and more nuanced support for the role in PFC in metacognition; the data did not reveal significant relationships between posterior default mode regions purported to be involved in self-referential functioning, but

relationships were revealed between orbital regions and metacognitive ability in the TBI sample, specifically.

Study Limitations and Future Directions

There are several limitations to this study. First, the sample size is modest, even for a structural imaging study in moderate and severe TBI, and greater power and the opportunity to examine the split-half reliability of these findings would be afforded with a larger sample. Another consideration for this TBI sample is the heterogeneity in time post injury. Because this study included data from both longitudinal and cross-sectional studies, the variability in time-post-injury for participants in this study was quite high. In post-hoc analyses, there was no difference in metacognitive accuracy between TBI participants who were in the early phases of head injury (i.e. about 4 months) versus individuals who were several years post injury at the time of measurement ($p = 0.634$) and time-post-injury was not a predictor of metacognitive accuracy ($r = 0.08$). However, there may be more subtle and unknown ways that time post injury is interacting with the current findings. Also, it is known that all of the participants in this study received rehabilitation services, but the differences in types and lengths of time of these services was not available. Information about the effects of these services on gray matter volume and metacognitive accuracy is unknown. Finally, we note that participant effort was not monitored with validity tests within the neuropsychological battery but we do not expect that this omission has significant impact on the interpretation of the results for several reasons. First, this is a moderate-severe TBI sample with identifiable injury demonstrating cognitive deficit in areas of functioning consistent with the literature (e.g., speed, working memory). Second, this sample was recruited as part of a research protocol and not a clinical assessment, and therefore the possible secondary gain in this sample, compared to forensic or disability cases, is less intuitive and unlikely to be systematic (Committee on Psychological Testing, Including Validity Testing, for Social Security Administration Disability Determinations; Board on the Health of Select Populations; Institute of Medicine, 2015). Even so, when considering an embedded measure of effort such as reliable digit span, all individuals in the study demonstrated sufficient effort with a score of 7 or higher (Mathias, Greve, Bianchini, Houston, & Crouch, 2002). Performance on neuropsychological measures in this study is therefore thought to be an accurate reflection of cognitive functioning.

The differential influence of distinct pathophysiologies, (e.g., diffuse axonal injury) on the current findings was not quantified but could hold important implications for metacognitive ability. In post-hoc analyses, total white matter volume and total gray matter volume (set as ratios to intracranial volume) were highly correlated, ($r = 0.74$, $p < 0.001$) and neither predicted metacognitive accuracy (white matter ratio: $r = 0.21$, $p = 0.102$; gray matter ratio: $r = 0.22$, $p = 0.090$). While global measures of white matter disruption appear insensitive as determinants of metacognition, future studies could further examine regional alterations in white matter that might be related to metacognition.

Future research in this area should integrate additional imaging modalities to target regional brain changes and metacognitive accuracy after TBI. For example, functional and structural connectivity methods would provide novel insights into the patterns of structural change and

functional network plasticity associated with metacognitive functioning. Integration of connectivity approaches could improve our understanding of the distributed nature of metacognition and systemic plasticity post injury.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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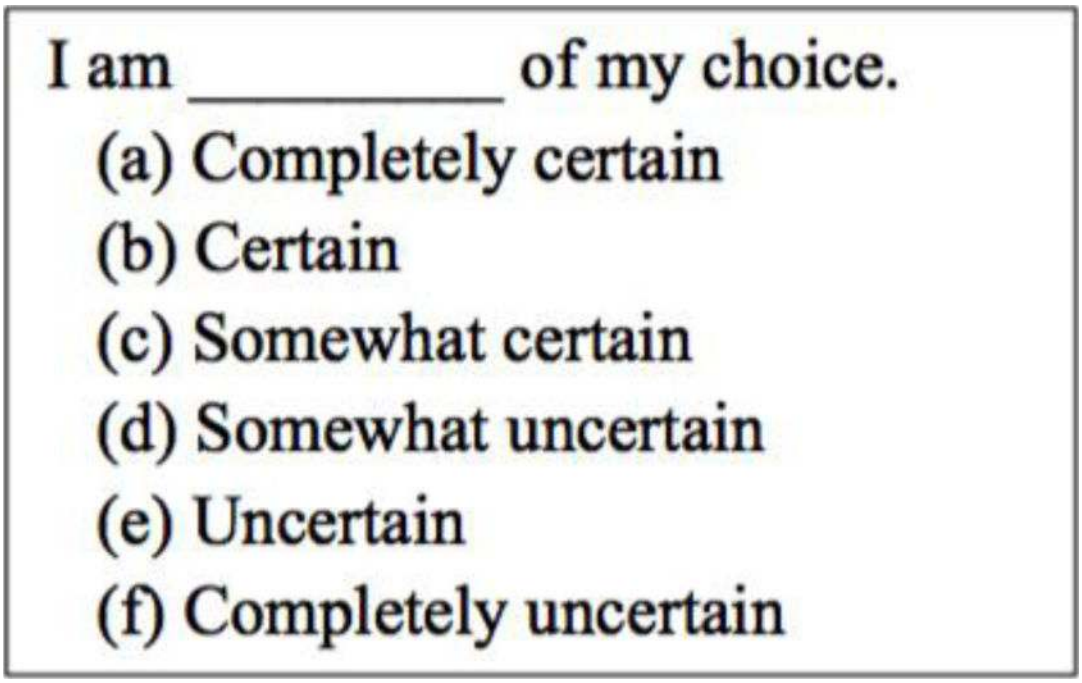


Figure 1.
Additional stimuli card from modified Matrix Reasoning WAIS-III task. Participants were shown this card and asked to respond after each Matrix Reasoning trial with the letter that best fit how certain or uncertain they felt of their previous choice.

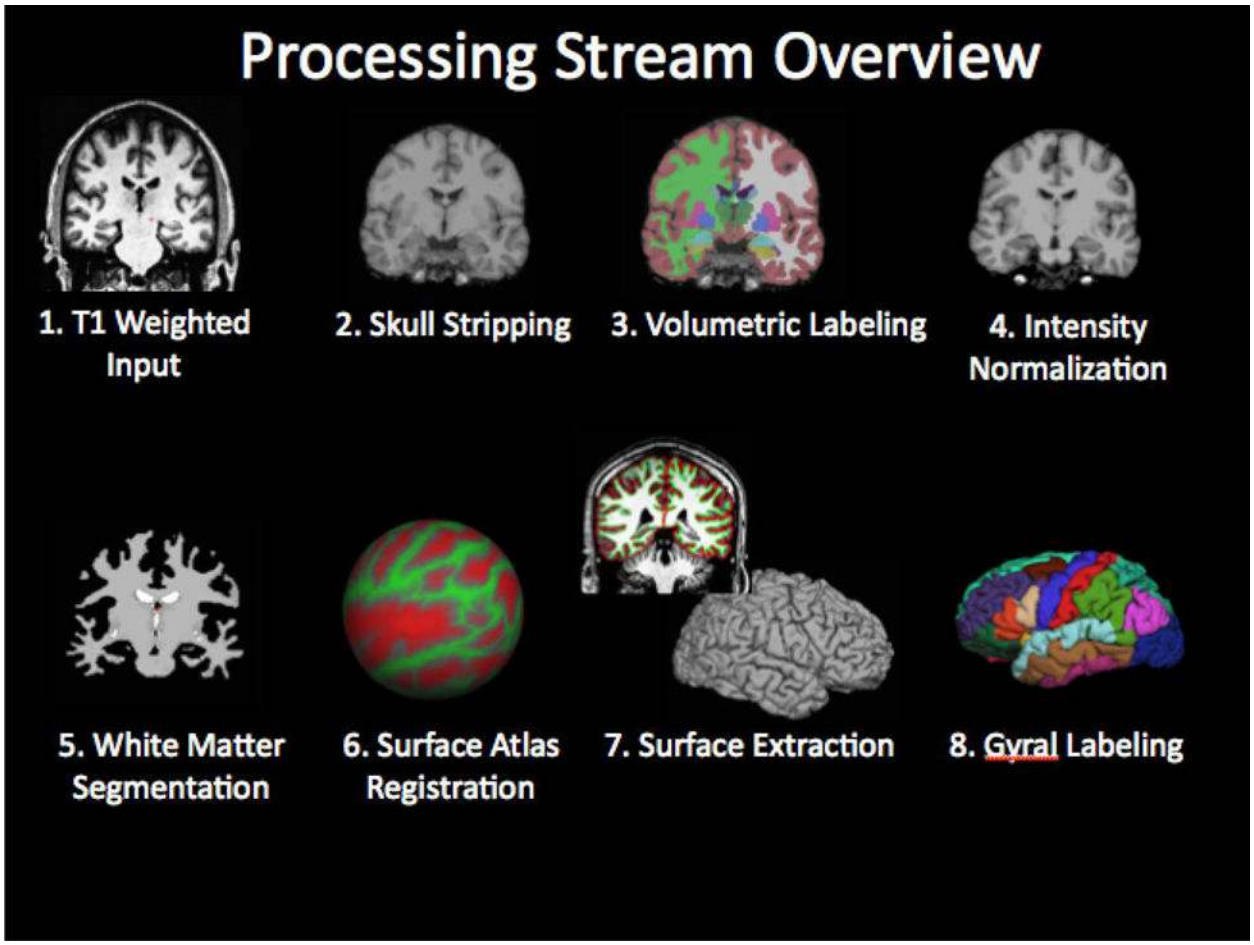


Figure 2.

Processing stream overview of FreeSurfer recon-all function used to extract gray matter volumes, image adapted from the FreeSurfer Analysis Pipeline Overview (http://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferAnalysisPipelineOverview).

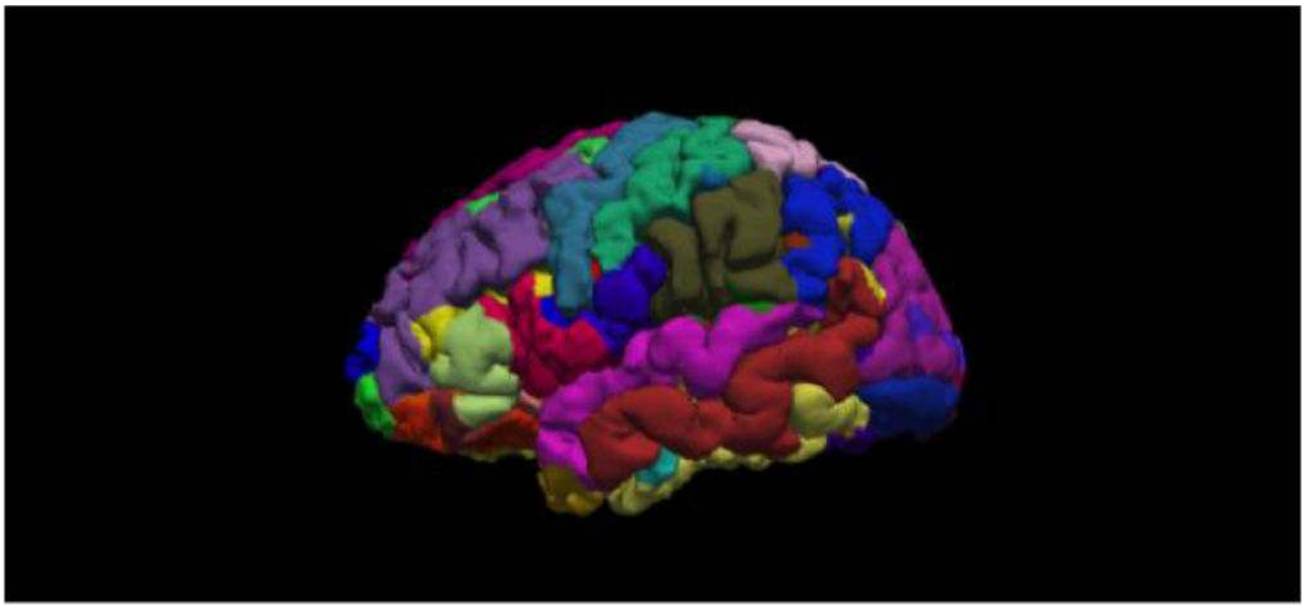


Figure 3.
Left hemisphere of participant in the TBI group parcellated using Destrieux atlas in FreeSurfer.

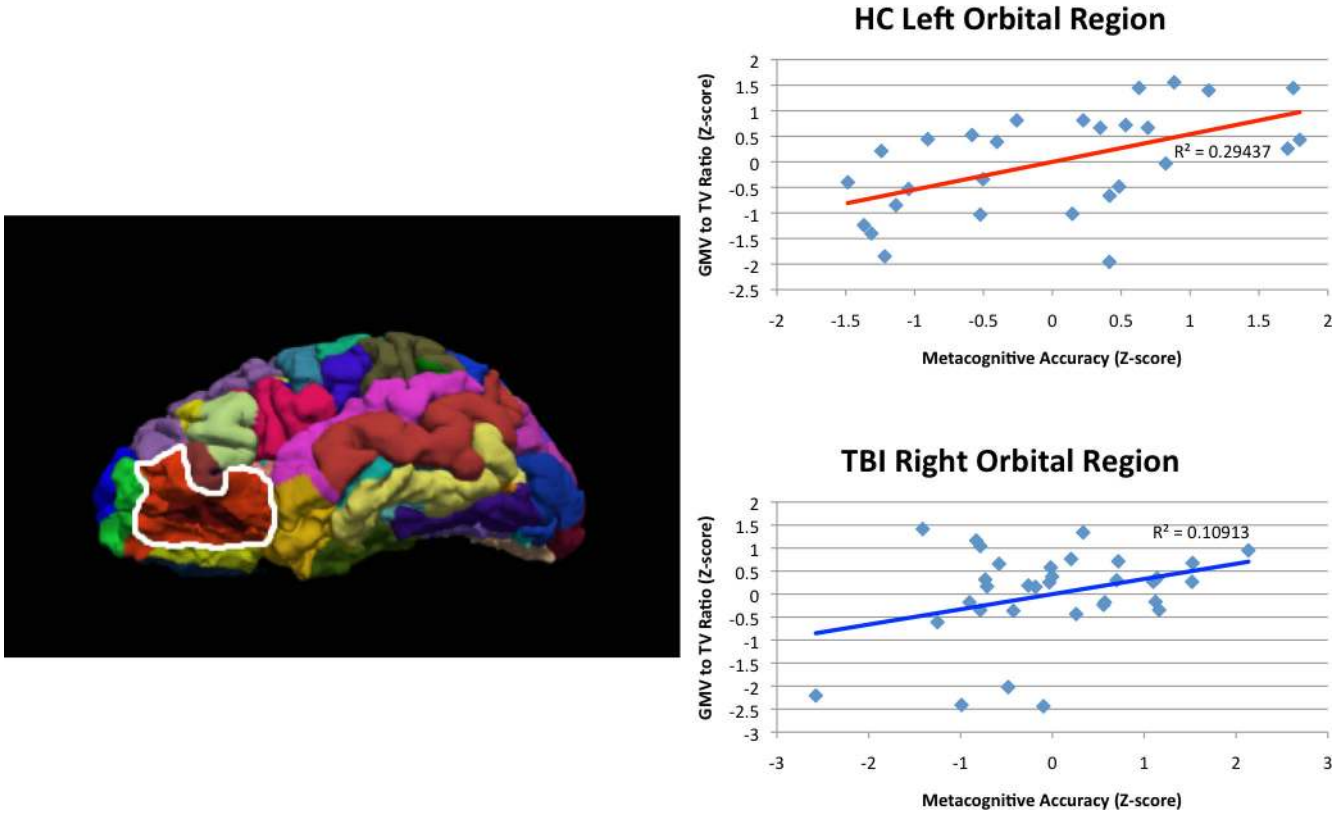


Figure 4.

Association between the ratio of gray matter volume (GMV) to total intracranial volume (TV) of the orbital region and metacognitive accuracy on the random list for the healthy control (HC) and traumatic brain injury (TBI) groups. X and Y axes are standardized values (z-scores). A anterior; P posterior.

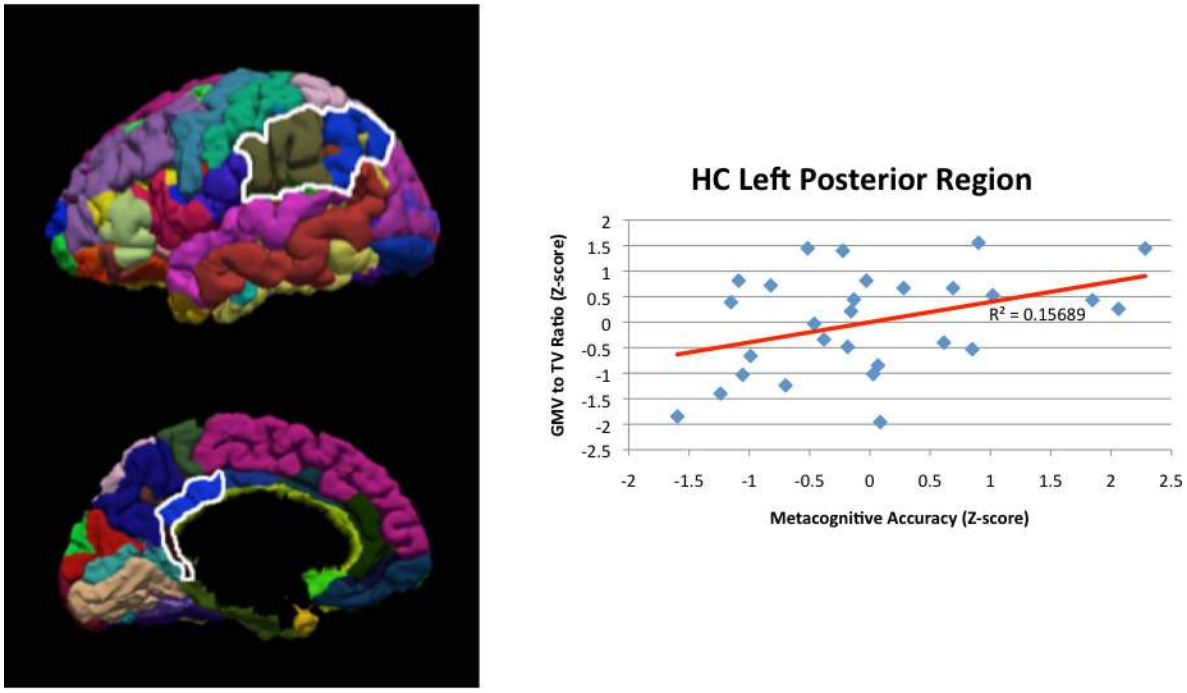
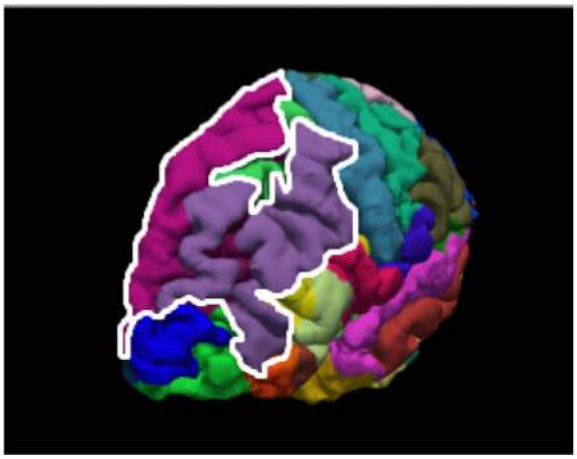


Figure 5.

Association between the ratio of gray matter volume (GMV) to total intracranial volume (TV) of the left posterior region and metacognitive accuracy on the random list in the healthy control (HC) group. X and Y axes are standardized values (z-scores). A anterior; P posterior.



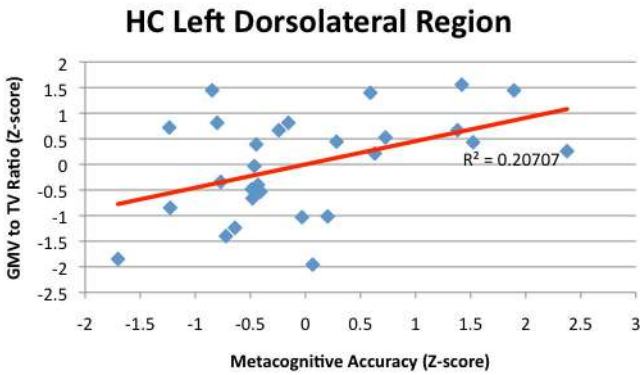


Figure 6.

Association between the ratio of gray matter volume (GMV) to total intracranial volume (TV) of the left dorsolateral region in healthy controls (HCs) with metacognitive accuracy on the random list. X and Y axes are standardized values (z-scores). A anterior; P posterior.

Table 1

Demographic Information

	TBI	HC
Age (in years)	33.39 (13.07)	34.11 (12.57)
Education (in years)	12.97 (1.81)	13.45 (1.73)
Gender	19 M, 15 F	16 M, 12 F
GCS	6.85 (4.69)	----------
Time post injury (in months)	51.73 (85.20)	----------

Table 2

Divisions of important regions related to metacognition.

Orbital Region	**Frontopolar Region**
Orbital gyrus	Transverse frontopolar gyri
Orbital H-shaped sulcus	Transverse frontopolar sulci
Dorsolateral Region	**Posterior Region**
Superior frontal gyrus	Posterior dorsal part of the cingulate cortex
Middle frontal gyrus	Posterior ventral part of the cingulate cortex
Middle frontal sulcus	Angular gyrus
	Supramarginal gyrus

Table 3

Differences between the healthy control and TBI groups on Matrix Reasoning task performance and metacognitive accuracy.

	TBI Mean	**HC Mean**	***p*-value**	***d***
Matrix Reasoning Performance – Ordered	9.09	10.46	0.015*	0.63
Matrix Reasoning Performance – Random	8.33	9.46	0.026*	0.58
Metacognitive Accuracy – Ordered	0.70	0.71	0.513	0.11
Metacognitive Accuracy - Random	0.65	0.71	0.076	0.54

Table 4

Differences between the healthy control and TBI groups other neuropsychological tests included in the test battery.

	TBI Mean	**HC Mean**	***p*-value**	***d***
Digit Span –Forward	10.27	11.30	0.074	0.48
Digit Span –Backward	6.82	7.22	0.482	0.18
Trails A Time	29.63	22.65	0.023*	0.60
Trails B Time	67.81	57.00	0.127	0.41