Neuroimaging correlates of syndromal depression following traumatic brain injury: A systematic review of the literature

Lisa N. Richey1, Barry R. Bryant1, Akshay Krieg1, Michael J. C. Bray1, Aaron I. Esagoff1, Tejus Pradeep1, Sahar Jahed1, Licia P. Luna2, Nicholas T. Trapp3, Jaxon Adkins4, Melissa B. Jones5, Andrew Bledsoe1, Daniel A. Stevens1, Carrie Roper6,7,8, Eric L. Goldwaser3, LiAnn Morris1, Emily Berich-Anastasio7, Alexandra Pletnikova1, Katie Lobner9, Daniel J. Lee10, Margo Lauterbach7,8, Simon Ducharme11,12, Haris I. Sair2 and Matthew E. Peters1

Abstract
Objective: To complete a systematic review of the literature examining neuroimaging findings unique to co-occurring syndromal depression in the setting of TBI.

Methods: A PRISMA compliant literature search was conducted in PubMed (MEDLINE), PsychINFO, EMBASE, and Scopus databases for articles published prior to April of 2022. The database query yielded 4447 unique articles. These articles were narrowed based on specific inclusion criteria (e.g., clear TBI definition, clear depression construct commenting on the syndrome of major depressive disorder, conducted empirical analyses comparing neuroimaging correlates in TBI subjects with depression versus TBI subjects without depression, controlled for the time interval between TBI occurrence and acquisition of neuroimaging).

Results: A final cohort of 10 articles resulted, comprising the findings from 423 civilians with brain injury, 129 of which developed post-TBI depression. Four articles studied mild TBI, three mild/moderate, one moderate/severe, and two all-comers, with nine articles focusing on single TBI and one including both single and recurrent injuries. Spatially convergent structural abnormalities in individuals with TBI and co-occurring syndromal depression were identified primarily in bilateral frontal regions, particularly in those with damage to the left frontal lobe and prefrontal cortices, as well as temporal regions including bilateral temporal lobes, the left superior temporal gyrus, and bilateral hippocampi. Various parietal regions and the nucleus accumbens were also implicated. EEG studies showed supporting evidence of functional changes in frontal regions.

Conclusion: Additional inquiry with attention to TBI without depression control groups, consistent TBI definitions, previous TBI, clinically diagnosed syndromal depression, imaging timing post-injury, acute prospective design, functional

1Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
2Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
3Department of Psychiatry, University of Iowa Carver College of Medicine
4Louisiana State University, Baton Rouge, Louisiana, USA
5Michael E. DeBakey VA Medical Center & Baylor College of Medicine, Menninger Department of Psychiatry and Behavioral Sciences, Houston, Texas, USA
6VA Maryland Healthcare System, Baltimore, Maryland, USA
7Sheppard Pratt Health System, Baltimore, Maryland, USA
8University of Maryland School of Medicine, Baltimore, Maryland, USA
9Johns Hopkins University, Welch Medical Library, Baltimore, Maryland, USA
10Mesulam Center for Cognitive Neurology and Alzheimer’s Disease & Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA
11Department of Psychiatry, Douglas Mental Health University Institute, McGill University, Montreal, Canada
12Montreal Neurological Institute, McConnell Brain Imaging Centre, Montreal, Canada

Corresponding author: Lisa N. Richey, Johns Hopkins University School of Medicine, Department of Psychiatry & Behavioral Sciences, 5300 Alpha Commons Drive, room 446, Baltimore, MD, 21224, USA.
Email: Lrichey2@jh.edu

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neuroimaging, and well-defined neuroanatomical regions of interest is crucial to extrapolating finer discrepancies between primary and TBI-related depression.

**Keywords**
Traumatic brain injury, depression, neuroimaging, neuropsychiatric symptoms

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**Introduction**

The conceptualization of traumatic brain injury (TBI) as a disease process with potential for consequential downstream effects, rather than a singular isolated event, is becoming an increasingly validated viewpoint amongst clinical scientists. TBI is an incompletely understood precursor to often under-reported neuropsychiatric disruption. It has been linked to a variety of new-onset psychiatric complications and is a risk factor for decompensation of previously well-controlled conditions. There may be utility in ascertaining how the clinical expression of psychiatric disorders in the context of TBI might compare to their idiopathic counterparts, especially as it relates to neuroanatomical underpinnings. Such ideas represent the premise of the current systematic review, which has the objective of synthesizing the existing literature that examines neuroimaging findings related to co-occurring syndromal depression in the setting of TBI.

Prevalence of depression following traumatic brain injury is quite common. It has been shown that 17–53% of TBI patients experience depressive symptoms during the first year post-injury. Studies have also found that 27–29% of TBI patients meet criteria for major depressive disorder. Studies that have followed individuals with TBI for one year or more post-injury found depression and anxiety to be the most commonly reported neuropsychiatric symptoms. There is also evidence that depression portends worse TBI recovery trajectories.

Mood-related neuropsychiatric symptoms (NPS), including symptoms of depression, have not traditionally been at the center of TBI outcomes research. Instead, cognition-related NPS and functional ability have been the primary investigational foci. Despite this, NPS have a variety of characteristics that warrant their study in the setting of TBI. For example, the clinical profile of depression that occurs in patients with TBI is distinct from that of idiopathic depression. Individuals with TBI are at greater risk for developing more isolated depressive symptoms characterized by increased apathy and irritability, as well as greater social isolation, hostility, and more cognitive deficits. The tendency for brain injury to manifest phenotypic expressions in a more isolated manner could provide key insights into the brain networks implicated in depression. TBI supplies an etiology, a key component of the disease triad, which is largely missing in idiopathic depression.

Neuroimaging studies on idiopathic depression have broadly suggested frontal lobe involvement including functional hypoactivation in the left dorsolateral PFC, functional hyperactivity of the ventromedial PFC, and decreased volume in the PFC, hippocampi, amygdala, and basal ganglia. Imaging correlates of idiopathic depression have received ample research attention, producing a multitude of systematic reviews and meta-analytic studies, with some even focusing on a single imaging modality. Imaging correlates of TBI-related depression, however, have not achieved such large-scale focus. Existing systematic reviews on post-TBI depression do not primarily focus on imaging findings.

This systematic review summarizes the neuroimaging literature investigating syndromal depressive disorder in TBI. The aim of this review is to determine if there is an area of the brain which when damaged, as demonstrated by neuroimaging, seems to be associated with the diagnosis of a depressive disorder after TBI. We posit that this effort may prove useful for future work regarding TBI screening and surveillance, bolstering preventative research efforts in neuropsychiatry, distinguishing specifiers in heterogeneous populations, and identifying neuroimaging markers for improvement in TBI patients.

**Methods**

**Search strategy**

A structured literature search strategy was designed to garner articles with neuroimaging and syndromal depression components in human TBI samples. Articles published up to April, 2022 were extracted from PubMed (MEDLINE), PsychINFO, EMBASE, and Scopus databases. Boolean searches were kept broad in the interest of reflecting all neuroimaging modalities and in order to capture broad domains of neuropsychiatric symptomatology. A more general approach was also necessitated by the current state of the TBI literature, which comprises many disparate approaches to definition, severity, population, and timing of assessment. We employed 1 imaging-, 35 neuropsychiatric symptom-, and 15 TBI-related keywords. Exact search phrases and MeSH search field qualifiers are outlined in Appendix 1.
**Review protocol**

This review adhered to PRISMA guidelines for implementation and reporting of systematic reviews. A summary of the review protocol, including the number of articles included and excluded in each step, can be found in Figure 1. In the first level of the screening process, titles and abstracts were reviewed in parallel for determination of inclusion or exclusion. Individuals in dyads, each with at least one senior TBI researcher, were blind to each other’s determinations. An

*Figure 1. Article selection process*
Figure 2a. Brain mapping by article of approximate structural ROI overlays implicated in TBI-related depression. Note: for each study, reported regions of interest (ROIs) with statistically significant associations were extracted from a brain parcellation map in the Montreal national institute (MNI) space using MATLAB (MATLAB R2021b, the mathWorks). Color overlays of segmented brain structures were displayed on a representative T1-weighted MP-RAGE image using MRcron visualization software.

Figure 2b. Brain map representing the approximate locations of replicated structural neuroimaging findings in TBI-related depression. Note: A statistical analysis tool in MRcron was used to extract region overlaps across studies. Color overlays representing the extracted overlaps of 2 and 3 studies were displayed on a T1-weighted MP-RAGE image. Study counts denote the number of studies with a finding in the highlighted brain region. A single study may be counted in more than one highlighted region.
identical data extraction sheet was utilized by all reviewers (authors LNR, BRB, AK, MJCB, TP, SJ, NTT, JA, MBJ, AB, DAS, CR, ELG, LM, EBA, AP, DJL, ML, MEP). Discrepancies and cases in which a reviewer was unsure were routed to a third-party reviewer for a final decision. All included articles were then subjected to a full-text review by dyads, again followed by a reappraisal if necessary. The resulting article cohort was then split up into six neuropsychiatric domains: depression, anxiety, post-traumatic stress disorder, sleep disturbance, behavior/personality change, and psychosis. The present review focuses on syndromal depression. A series of subsequent reviews focused on the other neuropsychiatric domains will be published from these same efforts.

**Inclusion and exclusion criteria**

For both title/abstract and full-text reviews, a standardized set of inclusion and exclusion criteria were applied. Articles were excluded if they: (1) Lacked any one of the three key elements (i.e., neuroimaging, NPS, and TBI); (2) Were of an undesirable study type (i.e., case reports/case series with n < 5, editorials, commentary letters, replies to editor, book reviews, non-peer-reviewed articles, conference proceedings, poster abstracts, dissertations); (3) Were not written in English; and/or (4) The study population had no human subjects or adult data (≤18 years). Articles were not excluded on the basis of TBI severity, singularity or reoccurrence of TBI, acuity or chronicity of neuropsychiatric symptoms, neuroimaging modality, or if neuroimaging was conducted in the acute (≤ 48 h), subacute (2 days − 2 weeks), intermediate (2 weeks − 6 months), or chronic (> 6 months) time-span post-TBI. This information was, however, collected on all articles.

Final articles selected for the present syndromal depression-centric review include those that met all of the following additional criteria: (1) Conducted empirical analyses comparing neuroimaging correlates in TBI subjects with depression versus TBI subjects without depression; (2) Had a clear TBI definition for participants included in the study (i.e., formalized or study-specific criteria with any combination of Glasgow Coma Scale score, loss/alteration in consciousness, and/or post-traumatic amnesia); (3) TBI was clinician diagnosed, (e.g., a hospitalization-requiring injury that yielded confirmatory medical records and was not based on self-report); (4) Quantified and controlled for the time interval between TBI occurrence and acquisition of neuroimaging; (5) Had a clear depression construct (i.e., used DSM criteria/a structured diagnostic interview to comment on syndromal depressive disorder, not only depressive symptoms; was not broadly studying “affect”, which could include mood pathology other than depression, such as anxiety or mania).

**Table 1. Summary of article characteristics (n = 10)**

| Variable                        | Number of Articles |
|---------------------------------|--------------------|
| Population                      |                    |
| Civilian                        | 10                 |
| Military                        | 0                  |
| Sport                           | 0                  |
| TBI Severity                    |                    |
| Mild                            | 4                  |
| Mild & Moderate                 | 3                  |
| Moderate & Severe               | 1                  |
| All-comers                      | 2                  |
| TBI Occurrence                  |                    |
| Single                          | 9                  |
| Single & Recurrent              | 1                  |
| Imaging Timing Post-TBI *       |                    |
| Acute                           | 0                  |
| Acute & Subacute                | 1                  |
| Intermediate                    | 3                  |
| Intermediate & Chronic          | 5                  |
| Chronic                         | 1                  |
| Neuroimaging Modality**         |                    |
| MRI                             | 4                  |
| DTI                             | 3                  |
| EEG                             | 3                  |
| PET                             | 1                  |
| Neuroimaging Analysis           |                    |
| ROI                             | 5                  |
| Whole Brain                     | 5                  |

Note: * Acute ≤ 48 h, subacute 2 days − 2 weeks, intermediate 2 weeks − 6 months, and chronic > 6 months. ** Numbers do not summate to 10 because an article had more than one imaging modality. MRI = magnetic resonance imaging, CT = computed tomography, DTI = diffusion tensor imaging, EEG = electroencephalogram, PET = positron emission tomography, ROI = region of interest.

**Article quality review**

Included articles were reviewed for methodological quality and sources of potential bias (Supplemental Figures 1a and 1b) using the Newcastle-Ottawa Scale.33 Broadly, this scale evaluates the risk of selection bias, comparability of comparison groups (e.g., risk of potential confounds), and the validity of outcome/exposure ascertainment for observational, non-randomized investigations (including distinct evaluation criteria for case-control and cohort studies). Articles were sorted based on the appropriate study type (i.e., case-control or cohort), and the corresponding Newcastle-Ottawa schematic was applied. Articles were determined to be case-control or cohort based on the outcome of interest to the systematic review, not necessarily the articles’ primary outcome. Each article was analyzed by a dyad of reviewers (LNR & BRB or AK & MJCB) followed by a consensus process, during which any discrepancies were addressed. Quality assessment data are presented, however, articles were not excluded from the systematic review based on quality outcomes.
Brain mapping

Approximate regions of interest (ROIs) reported by each study as having statistically significant associations with depression were extracted from a brain parcellation map in the Montreal National Institute (MNI) space \(^{34}\) (JHU MNI Type II) \(^{35}\) using MATLAB \(^{36}\) (MATLAB R2021b, The MathWorks). In JHU MNI type II parcellation map, the entire gray matter and the white matter are parcellated. Color overlays of segmented brain structures were displayed on a representative T1-weighted MP-RAGE image (Figure 2(a)) using MRICron visualization \(^{37}\) software. Subsequently, a statistical analysis tool in MRICron was used to extract region overlaps across studies. Finally, color overlays representing the extracted overlaps of 2 and 3 studies were displayed on a T1-weighted MP-RAGE image (Figure 2(b)).

Results

Application of inclusion and exclusion criteria produced a final cohort of 10 articles (Table 2). Not including duplicate sample populations, these articles comprised the findings of 129 civilian subjects who developed post-TBI depression, and 294 who did not develop post-TBI depression. No studies with military or sport populations survived to the final article cohort. Two articles did not exclude for pre-TBI depressive disorders, \(^{12,38}\) three articles did not exclude for co-occurring anxiety disorders, \(^{39-41}\) and two articles excluded for previous TBIs. \(^{39,42}\) Only one article conducted a formal power analysis \(^{43}\) and three studies reported effect size statistics. \(^{43-45}\) For details regarding article population, TBI severity, TBI occurrence, timing of imaging post-TBI, and neuroimaging modality, refer to Table 1. For limitations of the literature base and recommendations for future studies, see Table 3. For technical data on imaging parameters, see Supplemental Table 1.

Findings by imaging modality

MRI volumetrics. Structural findings visualized by neuroanatomical regions of interest (ROI) via brain mapping are displayed in Figure 2(a) and 2(b). Of the three articles with structural findings related to MRI volumetrics, all had significant findings associating onset of depression with decreased volume/cortical thinning in subjects who developed post-TBI depression compared to TBI subjects who did not. \(^{12,38,44}\) Areas implicated were left frontal grey matter, dorsolateral PFC, ventrolateral PFC, middle/superior/inferior gyri, \(^{12}\) left frontal grey matter, bilateral hippocampal volume, \(^{38}\) temporal, left inferior parietal, and right lingual regions as well as left and right nucleus accumbens. \(^{44}\)

Susceptibility-weighted imaging. There was one article that utilized susceptibility-weighted imaging \(^{42}\) which found the number and volume of microbleed lesions to be higher in the depressed TBI group when compared to the non-depressed TBI group referencing the frontal lobe, temporal lobe, parietal lobe, and whole brain. \(^{16}\)

Diffuse tensor imaging (DTI). Three articles conducted diffusion tensor imaging (DTI) analyses. Two of these articles found decreased fractional anisotropy to be associated with presence of depression in subjects with mild TBI when compared to mild TBI with absence of depression. \(^{43,45}\) These findings corresponded to the right nucleus accumbens, right anterior limb of the internal capsule and right superior longitudinal fasciculus, as well as the left superior temporal gyrus. The third article did not find significant differences in fractional anisotropy of the uncinate fasciculus and cingulum between TBI subjects with depression and TBI subjects without depression. \(^{46}\)

Positron emission tomography (PET). One article featured the PET modality, specifically focusing on dopamine D2/D3 receptor availability following TBI. \(^{46}\) There were no significant differences in \(^{11}\)C]PHNO BPND binding in the amygdala, nucleus accumbens, caudate, hypothalamus, pallidum, putamen, thalamus, or substantia nigra between TBI subjects with depression and TBI subjects without depression.

Electroencephalography (EEG). Three articles contained EEG analyses, all of which were in the chronic/intermediate time frame for when imaging was conducted relative to injury occurrence. Two studies focused on frontal regions and found less fronto-central negativity, less N2 global field power, an altered N2b window, reduced frontal positivity, a more posterior distribution of positivity, and an altered pattern of averaged activity during the Pe window in depressed TBI subjects compared to non-depressed TBI subjects. \(^{39,40}\) The third study found that TBI subjects without depression showed increased left temporal/inferior frontal to right parieto-occipital and fronto-central connectivity whereas TBI subjects with depression showed increased bilateral temporal to parieto-occipital connectivity. \(^{41}\) All three of the EEG modality articles were out of the same research group.

Article quality. Bias amongst cohort studies (n = 3) solely resulted from comparability of cohorts on the basis of design or analysis (Supplemental Figure 1a). Bias in case-control studies (n = 7) was mainly due to definition of controls, comparability of cases and controls on the basis of design or analysis, representativeness of the cases, and to a lesser degree selection of controls (Supplemental Figure 1b). Additionally, assessment of article quality revealed a widespread absence of methodologically controlling for previous TBI(s).
Table 2. Articles with neuroimaging findings comparing traumatic brain injury patients with and without syndromal depression (n = 10)

| Article          | Sample Size* | Population | TBI Diagnostic Criteria ** | TBI Severity; Occurrence | Timing of Neuroimaging Since TBI | Neuroimaging Modality | Neuropsychiatric Outcome Measure(s) and Description of Depression Construct | Findings Comparing TBI Patients With Depression and TBI Patients Without Depression*** |
|------------------|--------------|------------|---------------------------|--------------------------|----------------------------------|----------------------|------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Alhilali et al., 201543 | n = 65 (TBI-D = 13, TBI+ D = 32) | Civilian | LOC < 1 min, PTA < 30 min, unremarkable CT | Mild; Single, recurrent | Median = 20 days, Range = 0–506 days | DTI | DSM-V criteria for a depressive disorder due to another medical condition (mTBI). History of a neuropsychiatric illness prior to TBI was an exclusion criterion. | Significantly decreased fractional anisotropy within the right nucleus accumbens, right anterior limb of the internal capsule, and right superior longitudinal fasciculus in TBI subjects with depression compared to TBI subjects without depression. |
| Bailey et al., 201440 | n = 35 (TBI-D = 20, TBI+ D = 15) | Civilian | LOC ≥ 1 min, PTA ≥ 30 min, neuroradiological evidence suggesting TBI. Severity determined by GCS (mild = 13–15, moderate = 9–12 or 12–15 with intracranial surgery/focal lesions, severe = 3–8). | Mild, moderate; Single | ≥ 6 weeks | EEG | MDD diagnosis assessed by the MINI for DSM-IV. Severity was assessed with the BDI-II and MDARS. Participants with comorbid axis I psychiatric disorders were excluded, with the exception of anxiety. Anti-depressant medications were continued during the study. Depression prior to the TBI was an exclusion criterion. | TBI subjects with depression had significantly less fronto-central negativity, less N2 global field power, and an altered N2b window compared to TBI subjects without depression. |
| Bailey et al., 201539† | n = 28 (TBI-D = 16, TBI+ D = 12) | Civilian | GCS ≥ 9 and PTA or LOC ≥ 10 min, but less than 24 h | Mild, moderate; Single | ≥ 6 weeks (TBI-D mean = 32.63 months, TBI+ D mean = 188.05 months) | EEG | Current depressive episode assessed with the MINI for DSM-IV. Excluded if met criteria for any axis I psychiatric disorder (with the exception of depression and generalized anxiety disorder). Depression severity had to be in the moderate to severe range (≥20) on the MDARS to be included. Those taking a single anti-depressant medication were allowed in the study. Depression prior to the TBI was an exclusion criterion. | TBI subjects with depression had an altered topographical distribution of activity during the Pe window, with reduced frontal positivity compared to TBI subjects without depression. TBI subjects with depression showed a more posterior distribution of positivity compared to TBI subjects without depression. Topographical ANOVA showed a significant difference between TBI subjects with and without depression for averaged activity during the Pe window. There were no significant differences in neural response strength. |
| Bailey et al., 201741† | n = 35 (TBI-D = 20, TBI+ D = 15) | Civilian | Mild/moderate injury severity was determined by LOC < 24 h and an initial GCS > 9. To ensure injuries were at mild/moderate severity, LOC was < 24 h and an initial GCS > 9. | Mild, moderate; Single | ≥ 6 weeks (TBI mean = 22.89 months, TBI+ D mean = 188.05 months) | EEG | MDD diagnosis assessed with the MINI for DSM-IV. Included if MDD was deemed to be causally related to the TBI by the study | TBI subjects without depression showed increased left temporal/ inferior frontal to right parieto-occipital and (continued)
| Article | Sample Size | Population | TBI Diagnostic Criteria ** | TBI Severity; Occurrence | Timing of Neuroimaging Since TBI | Neuroimaging Modality | Neuropsychiatric Outcome Measure(s) and Description of Depression Construct | Findings Comparing TBI Patients With Depression and TBI Patients Without Depression*** |
|---------|-------------|------------|---------------------------|--------------------------|---------------------------------|----------------------|-----------------------------------------------------------------|---------------------------------------------------------------------------------|
| D = 15) |             |            | least mild, a LOC or PTA ≥ 10 min. or an initial GCS of < 15 was required. | TBI + D mean = 176.77 months | PET, DTI                      | Moderate, severe: Median = 44 months, Range = 15–372 months | Psychiatrist Severity assessed with BDI-II and MDARS (>19 to be included, which is moderate to severe). Comorbid psychiatric diagnoses detected with the MINI were excluded (with the exception of anxiety disorder). Depression prior to TBI was an exclusion criterion. | There were no significant differences in [11C]PHNO BPND binding in the amygdala, nucleus accumbens, caudate, hypothalamus, pallidum, putamen, thalamus, or substantia nigra between TBI subjects with depression and TBI subjects without depression. There were no significant differences in fractional anisotropy in the uncinate fasciculus and cingulum between TBI subjects with depression and TBI subjects without depression. Decreased frontal grey matter volume with decreased left frontal gray matter in TBI subjects with depression as opposed to TBI subjects without depression. TBI subjects with depression had significantly decreased cortical volume in the dorsolateral and ventrolateral PFC, and middle/superior/ inferior gyri. Total brain volume, white matter volume, and grey matter volume did not significantly differ between groups. Occipital and temporal grey matter volume was not associated with depression. |
| Jolly et al., 2019 | n = 12 (TBI-D = 6, TBI + D = 6) | Civilian | Moderate-severe severity was determined using the Mayo TBI Severity Classification System (one or more of the following criteria apply: 1. death due to TBI, 2. LOC ≥ 30 min., 3. anterograde PTA ≥ 24 h, 4. Worst 24 h GCS ≤ 13, 5. One or more traumatic neuroimaging finding). | Moderate, severe: Single | PET, DTI | MDD diagnosis made by a qualified psychiatrist using the SCID for DSM-IV-TR Axis I disorders. Severity of depressive symptoms assessed with the BDI. Depression prior to TBI, having other current DSM-IV diagnoses, and being on medication known to affect dopaminergic function were exclusion criteria. | |
| Jorge et al., 2004 | n = 91 (TBI-D = 61, TBI + D = 30) | Civilian | Mild = GCS 13–15, moderate = 9–12, severe = 3–8. GCS of 12–15 with focal lesions were considered moderate. | All: Single | 3 months | MRI | MDD diagnosed using two semi-structured interviews, the PSE and SCID for DSM-IV. Depression severity assessed with the HAM-D. | |

(continued)
| Article | Sample Size* | Population | TBI Diagnostic Criteria ** | TBI Severity; Occurrence | Timing of Neuroimaging Since TBI | Neuroimaging Modality | Neuropsychiatric Outcome Measure(s) and Description of Depression Construct | Findings Comparing TBI Patients With Depression and TBI Patients Without Depression*** |
|---------|--------------|------------|---------------------------|-------------------------|---------------------------------|----------------------|---------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Jorge et al., 200738 | n = 37 (TBI-D = 18, TBI+ D = 19) | Civilian Mild = GCS 13–15, moderate = 9–12, severe = 3–8. Patients with a GCS 13–15 with a history of intracranial surgery or focal lesions greater than 15 cc were considered moderate. | All; Single | 3 months | MRI | Mood disorders due to TBI with major depressed or mixed features assessed with the PSE and SCID for DSM-IV. Depression severity assessed with the HAM-D. | There was no volume-depression association for the parietal lobe, lateral frontal lobe, orbitofrontal, or medial frontal PFC. Left frontal grey matter volume decrease in TBI subjects with depression as opposed to TBI subjects without depression. Decreased bilateral hippocampal volume in TBI plus depression group as opposed to TBI only group, most amplified in moderate/severe TBI. There was no difference between groups in frontal lobe lesion frequency or whole:left:right volume. Total brain volume and frequency of focal lesions did not significantly differ between groups. |
| Maller et al., 201444 | n = 26 (TBI-D = 12, TBI+ D = 14) | Civilian Field GCS = 13–14, LOC 15 min. to 2 h, PTA 0 min to 48 h | Mild; Single | CT in acute phase, MRI range = 6 weeks to 12 months | MRI | MDD diagnosis made by a treating psychiatrist and confirmed with the MINI for DSM-IV as well as a score of at least 16 on the MADRS. TBI patients were required to have no history of pre-TBI depression. TBI-related major depression patients were required to have developed MDD between 6 weeks and 12 months post-TBI. | TBI subjects with depression had reduced volume in temporal, left inferior parietal, and right lingual regions compared to TBI subjects without depression. The left and right nucleus accumbens were also decreased in size. Higher depression severity in those with TBI and major depression significantly correlated with reduced volume in anterior cingulate, bilateral entorhinal cortex, left hippocampus, right insula, right temporal gyrus, and temporal lobe (not significant after multiple corrections). |
| Rao et al., 201245 | n = 14 (TBI-D = 10, TBI+ D = 4) | Civilian GCS ≥ 13, ACRM criteria | Mild; Single | ≤ 1 month | DTI | Mood Disorder Due to General Medical Condition assessed by the SCID for DSM-IV with subtypes of 1) major depressive-like episode (if the full | TBI subjects with depression had significantly decreased fractional anisotropy in the left superior temporal gyrus compared to TBI subjects without depression. |

(continued)
| Article | Sample Size* | Population | TBI Diagnostic Criteria ** | Timing of Neuroimaging Since TBI | Neuroimaging Modality | Neuropsychiatric Outcome Measure(s) and Description of Depression Construct | Findings Comparing TBI Patients With Depression and TBI Patients Without Depression*** |
|---------|--------------|------------|---------------------------|-------------------------------|------------------------|-----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Wang et al., 2014\(^5\) | \(n = 200\) | Civilian | GCS 13–15, PTA < 24 h, unremarkable CT and MRI | Mild; Single | Range = 2 h to 3 days | MRI (SWI) | As per DSM-IV-TR criteria utilizing the SCID, depressive disorders after TBI were grouped as ‘Mood Disorder Due to General | Patients who had a major depressive episode within one year after TBI had a significantly higher rate of abnormality (microbleeds) at the right superior temporal gyrus/white matter, left/right temporal middle/inferior temporal gyrus/white matter, left/right superior/middle/inferior frontal gyrus and white matter, left/right caudate nucleus, putamen, globus pallidus, or thalamus. Increased mean diffusivity in the temporal and inferior frontal lobes was associated with increased depression over time. Lower fractional anisotropy in superior/middle temporal gyrus associated with depression level at baseline and predictive of higher depressive symptoms over time. Higher mean diffusivity score in the right superior longitudinal fasciculus, inferior frontal white matter, and superior temporal white matter was predictive of increasing HAM-D scores. Higher mean diffusivity in the left side of the superior longitudinal fasciculus was associated with lower Ham-D scores. Mean diffusivity/fractional anisotropy of varied frontal and subcortical regions with respect to depression at multiple time points did not differ. |

\(^{1}\) Table 2. Continued.
| Article | Sample Size* | Population | TBI Diagnostic Criteria ** | TBI Severity; Occurrence | Timing of Neuroimaging Since TBI | Neuroimaging Modality | Neuropsychiatric Outcome Measure(s) and Description of Depression Construct | Findings Comparing TBI Patients With Depression and TBI Patients Without Depression*** |
|---------|--------------|------------|---------------------------|--------------------------|---------------------------------|----------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| D = 28  |              |            |                           |                          |                                 |                      | Medical Condition’ (MDD-GMC), with subtypes of (1) major depressive-like episode (if the full criteria for a major depressive episode were met); or (2) depressive features (prominent depressed mood but full criteria for a major depressive episode were not met). Only those who met criteria for ‘Mood Disorder Due to General Medical Condition’ major depressive-like episode subtype for at least one follow-up visit within 1 year were considered as major depression after TBI. History of depression prior to TBI (having reported depression diagnosis, treatment for depression, depression-related counseling, or a suicide attempt) was an exclusion criterion. | whole-brain level than those without a major depressive episode after TBI. Number and volume of microbleed lesions in frontal, temporal, and parietal lobes was significantly higher in the depressed TBI subjects with depression than TBI subjects without depression. |

Note: * Sample size has been adjusted to reflect only participants with TBI + depression and TBI-depression and does not include other groups such as depression only and normal controls.
** All TBI was diagnosed by a clinician.
*** The findings listed in this table only focus on analyses comparing TBI with depression and TBI without depression. Some articles conducted additional analyses comparing TBI subjects to other groups, such as normal controls or depression only controls.
† Denotes duplicate samples that were not included in the overall N’s calculated by this review
TBI + D = traumatic brain injury with depression, TBI-D = traumatic brain injury without depression, GCS = Glasgow Coma Scale, LOC = loss of consciousness, AOC = alteration of consciousness, PTA = post-traumatic amnesia, ACRM = American Congress of Rehabilitation Medicine, MRI = magnetic resonance imaging, SWI = susceptibility-weighted imaging, DTI = diffusion tensor imaging, EEG = electroencephalogram, PET = positron emission tomography, PSE = Present State Examination, DSM-I V = Diagnostic and Statistical Manual of Mental Disorders 5th Edition, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4th Edition, DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision, MINI for DSM-V = Mini-international Neuropsychiatric Interview, BDI = Beck Depression Inventory, BDI II = Beck Depression Inventory Version 2, MADRS = Montgomery–Åsberg Depression Rating Scale, SCID = Structured Clinical Interview for DSM-5, HAM-D = Hamilton Depression Rating Scale, HRS-D = Hamilton Rating Scale for Depression, CES-D = Center for Epidemiologic Studies Depression Scale, MDD = major depressive disorder, PFC = prefrontal cortex.
### Table 3. Limitations existing among the included studies in the current systematic review and recommendations for future research

| Limitations | Recommendations for Future Research |
|-------------|-------------------------------------|
| **Sample- / Study-related** | | |
| • Sample heterogeneity (e.g., TBI severity, TBI definition, depressive syndrome definition, time since injury) | In addition to below, more selective inclusion criteria (e.g., mild TBI, subacute TBI, new onset depression only). |
| • Insufficient sample sizes | Seeing as how nine out of ten articles did not conduct a formal power analysis, fully-powered and longitudinal cohort studies are a glaring gap in the field, which will be needed for causality and directionality determination. Effect size statistics should be reported to enable future work to be appropriately powered. Future systematic reviews separated by TBI severity, timing of neuroimaging since injury, etc. and a quantifiable meta-analysis should be considered once the literature base in this area is more developed. |
| • High level of bias regarding the comparability of cohorts/cases on the basis of design or analysis | Exposed and non-exposed individuals in cohort studies and cases/controls in case-control studies must be matched in design and/or confounders must be adjusted for in the analysis (e.g., making statements of no differences between groups or that differences were not statistically significant). |
| • Difficulty isolating the direct connections between neuroimaging findings and TBI-associated depressive syndromes | Ensure that studies are properly designed to isolate the neuroimaging findings specific to TBI-related depressive syndromes, such as comparison groups with TBI only and idiopathic depression only. |
| • Lack of acute prospective studies | Design of future studies with initial data/imaging collection in the acute phase of TBI and multiple follow-up data/imaging collection points across time. |
| **TBI-related** | | |
| • Inconsistent TBI definitions | Clearly quantify and report on the established National Institute of Neurological Disorders and Stroke common data elements for TBI (e.g., loss of consciousness and post-traumatic amnesia duration, Glasgow Coma Scale score). Utilize established TBI criteria (e.g., Veterans Affairs/Department of Defense, American Congress of Rehabilitation Medicine) rather than study-specific criteria. |
| • No solely severe TBI samples | Future inquiry into the neuroimaging correlates of post-TBI depression in patients with severe TBI. Some articles in this review looked at participants with multiple severities of TBI (including severe) combined into one sample, however, there were no distinct severe TBI groups. |
| • Lack of military- and sports-related TBI | Although these populations should be considered separately from general civilian populations, they do warrant focused study (exclusion occurred largely due to lack of clinician confirmation of TBI diagnosis). |
| • Not considering the potential impact of post-concussive syndrome and other post-TBI complications on depression | Post-concussive syndrome and other post-TBI complications (e.g., headache, vestibular disorders) may act as a trigger for developing depression after a brain injury. To overcome this potential confound, future studies should consider choosing TBI control subjects that have similar medical comorbidities. |
| **Depression-related** | | |
| • Largely reported data on depressive symptoms as opposed to clinically diagnosed syndromal depressive disorders | Use a structured diagnostic interview tool administered by a clinician, (e.g., SCID for DSM-V, MINI for DSM-V) instead of or in addition to screeners noting depressive symptoms (e.g., PHQ-9, Beck Depression Inventory). |
| • Ability to confirm that post-TBI depression is new onset vs. a recurrence of a pre-injury depressive illness | Report and statistically adjust for data on pre-TBI depression history or exclude for pre-injury depressive disorders as (continued)
Discussion

This systematic review summarized the neuroimaging literature reporting on structural and functional changes associated with syndromal depressive disorder in the setting of TBI. Existing systematic reviews address the imaging correlates of idiopathic depression, and separately the imaging correlates of TBI, however this review aimed to synthesize the imaging findings that integrate depression and TBI. From a final cohort of 10 articles representing the findings from 423 total participants with TBI, we ascertained that syndromal depression developed after a TBI is generally associated with decreased volume or cortical thinning, decreased functional connectivity, decreases in white matter fractional anisotropy, and higher number/volume of microbleeds when compared to TBI subjects who did not develop depression. Regionally, TBI-related depression was associated with a variety of bilateral frontal regions, particularly in those with damage to the left frontal lobe, including the prefrontal, orbitofrontal, and anterior cingulate cortices. Functional findings from EEG studies in this review further supported the beforementioned structural emphasis on frontal regions. These regions have been consistently reported to be part of the biological pathways underpinning heterogeneous mental disorders like major depression. Nevertheless, TBI is more likely to affect frontal areas due to the anatomy of the brain within the skull in the context of TBI mechanics. Thus, there is a degree of uncertainty regarding the precise pathways which could be influenced by those structural products with relevance to the underlying neurobiology of subsets of individuals who develop depression following TBI. More likely, it cannot be fully attributed to a specific frontal brain lesion but should be related to the whole frontal cortex and its interconnections.

Localized frontal lobe findings could be categorized into the three frontal-subcortical circuits implicated in TBI: the dorsolateral prefrontal circuit, orbitomedial frontal circuit,
and anterior cingulate circuit.\textsuperscript{50} These circuits are implicated in corresponding clinical syndromes (i.e., dysexecutive, disinhibition, and apathy syndrome, respectively).\textsuperscript{51} In the current review, regarding differences between TBI subjects with and without depression, the two circuits that were most implicated were the dorsolateral prefrontal circuit (see Jorge et al., 2004 regarding the dorsolateral prefrontal cortex\textsuperscript{13}) and orbitomedial frontal circuit (see Maller et al., 2014 and Alhilali et al., 2015, which both involve the nucleus accumbens\textsuperscript{43,44}). The anterior cingulate circuit did not have as many findings when comparing TBI subjects with and without depression, though Maller et al., 2014 found that higher depression severity in those with TBI and depression significantly correlated with reduced volume in the anterior cingulate.\textsuperscript{44} Many articles in the current review focused on functional activity of the frontal lobes more globally,\textsuperscript{40,41} volumetrics of total frontal white/gray matter,\textsuperscript{12} and microbleeds in frontal regions.\textsuperscript{42}

Amongst the included articles, frontal regions were a main focus and temporal regions were also well represented. The parietal lobes, including occipital/lingual regions, and right nucleus accumbens, are also worthy of mention. Regions of lesser emphasis were the right anterior limb of the internal capsule and right superior longitudinal fasciculus. Global volumetric brain analyses on MRI did not reach significance, which is consistent with systematic review results in idiopathic depression.\textsuperscript{24} In contrast, significant findings from whole-brain analyses have been identified in a systematic review of TBI alone.\textsuperscript{52} It is therefore possible that some of the less consistent findings in this review are related to TBI itself rather than the co-presenting depressive syndrome.

Regarding imaging modality, amongst articles finding significant differences between TBI patients with and without depression, there were four articles on structural MRI concerned with cortical findings (one susceptibility weighted), three articles on DTI concerned with white matter and subcortical findings, and three articles that focused on connectivity with EEG. A recent systematic review was conducted on the characterization of chronic traumatic encephalopathy/TBI using various imaging modalities.\textsuperscript{53} By comparison, there was a far greater proportion of articles in the chronic traumatic encephalopathy/TBI review focused on structural imaging (21 of 25 articles) and fewer that utilized functional imaging (6 of 25 articles). This may suggest discordant approaches to studying emotional syndromes (focus on brain function) vs. brain trauma itself (focus on structure).

It is also an important confound to consider that certain connectivity measures, namely those used in DTI, have demonstrated non-linear brain changes over time post-injury. Two of the three DTI articles included in this review found significantly decreased fractional anisotropy in acute and subacute TBI compared to controls,\textsuperscript{43,45} which is consistent with the literature regarding connectivity measures in TBI longitudinally.\textsuperscript{53} The third article in this review, which looked at chronic TBI, did not note significant differences in fractional anisotropy.\textsuperscript{46}

This review identified notable limitations in the literature base and areas of focus for future research, which are displayed in Table 3. There are also several methodological limitations to consider with the reported findings of this review. The timing of a patient’s depression as it related to their TBI, as well as the timing of imaging data acquisition, was variable across articles and therefore not restricted. Also included in this review were several articles by the same authors that utilized some of the same participants in both studies. This issue of duplicate samples was factored in when calculating the sample size of this review. Three EEG articles were included in this review; the conclusions we can draw from those articles and the comparisons that can be made to MRI, DTI, and PET studies are limited by the spatial localization limitations that are inherent to the EEG modality. Additionally, because publication dates of the final article cohort ranged from 2004 to 2019, articles used both DSM-IV and DSM-5 criteria with their respective structured clinical interviews.

A systematic review was performed to examine neuroimaging correlates of co-occurring syndromal depression in TBI with the aim of utilizing neuropsychiatric illness to improve our understanding of what neuroanatomy to investigate in idiopathic depression. Research examining the nexus of TBI and depression represents an emerging field; additional inquiry with attention to TBI-only control groups, consistent TBI definitions, previous TBI, clinically diagnosed syndromal depression, co-occurring anxiety disorders, imaging timing post-injury, acute prospective design, functional neuroimaging, and well-defined neuroanatomical regions of interest is crucial to extrapolating finer discrepancies between the pathophysiology of idiopathic and TBI-related depression. The impact of TBI on brain abnormalities in individuals with depression requires further study, with continued research focus on structural, functional, and metabolic correlates of the prefrontal cortex, anterior cingulate, and other selected regions.

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Appendix

I. Search Terms

(“Magnetic Resonance Imaging”[mh:noexp] OR “Diffusion Magnetic Resonance Imaging”[mh] OR “Magnetic Resonance Angiography”[mh] OR “magnetic resonance imaging” OR “magnetic resonance imaging” OR “MRI” OR “fMRI” OR “MR imaging” OR “diffusion imaging” OR “diffusion tensor imaging” OR “fDTI” OR “tractography” OR “magnetic resonance angiography” OR “perfusion weighted imaging” OR “perfusion imaging” OR “Tomography, X-Ray Computed”[mh:noexp] OR “Four-Dimensional Computed Tomography”[mh] OR “Tomography, Spiral Computed”[mh] OR “Multidetector Computed Tomography”[mh] OR “computer assisted tomography” OR “computed tomographic angiography” OR “computed tomography” OR “electron beam tomography” OR “computer tomography” OR “optical tomography” OR “susceptibility weighted imaging” OR “SWI” OR “Positron-Emission Tomography”[mh] OR “Positron emission tomography” OR “PET” OR “EEG” OR “electroencephalogram” OR “electroencephalography”[mh] OR “electroencephalography” OR “MEG” OR “magnetoencephalography” OR “magnetoencephalography”[mh] OR “Spectroscopy, Near-Infrared”[mh] OR “infrared imaging” OR “near-infrared spectroscopy” OR “neuroimaging”[mh] OR “neuroimaging” OR “voxel-based morphometry” OR “VBM” OR “SPECT”) AND

(“neuropsychiatric” OR “psychiatric” OR “delusion” OR “hallucination” OR “psychotic Disorders”[mh] OR “affective Disorders, Psychotic”[mh] “psychotic” OR “aggression” OR “agitation” OR “emotional dyscontrol” OR “behavioral dyscontrol” OR “dysphoria” OR “depression”[mh] OR “Depressive disorder”[mh] OR “depressive” OR “Anxiety”[mh] OR “mania” OR “elation” OR “euphoria” OR “apathy”[mh] OR “disinhibition” OR “lability” OR “irritability” OR “stress disorders, Post-Traumatic”[mh] OR “post-traumatic stress disorder” OR “PTSD” OR “Sleep Wake Disorders”[mh] OR “Sleep Disorders, Circadian Rhythm”[mh] OR “sleep disorder”
OR “sleep disorders” OR “Circadian Rhythm” OR “sleep apnea” OR “executive dysfunction” OR “impulsivity” OR “personality”)

AND

(“Brain Injuries”[mesh] OR “Brain Hemorrhage, Traumatic”[mh] OR “Diffuse Axonal Injury”[mh] OR “traumatic brain” OR “cerebral trauma” OR “brain trauma” OR “diffuse axonal injury” OR “brain injury” OR “brain injuries” OR “Brain Concussion”[mh] OR “concussion” OR “concussed” OR “Brain Injury, Chronic”[mh] OR “traumatic brain injury” OR “TBI” OR “head injury”)

NOT

(“animals”[mesh] NOT (“animals”[mesh] AND “humans”[mesh])))