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Review Article

Neuroimaging Correlates of Syndromal Anxiety Following Traumatic Brain Injury: A Systematic Review of the Literature

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Background: *Traumatic brain injury (TBI) can precipitate new-onset psychiatric symptoms or worsen existing psychiatric conditions. To elucidate specific mechanisms for this interaction, neuroimaging is often used to study both psychiatric conditions and TBI. This systematic review aims to synthesize the existing literature of neuroimaging findings among patients with anxiety after TBI.* **Methods:** *We conducted a Preferred Reporting Items for Systematic Review and Meta-Analyses–compliant literature search via PubMed (MEDLINE), PsychINFO, EMBASE, and Scopus databases before May, 2019. We included studies that clearly defined TBI, measured syndromal anxiety as a primary outcome, and statistically analyzed the relationship between neuroimaging findings and anxiety symptoms.* **Results:** *A total of 5982 articles were retrieved from the systematic search, of which 65 studied anxiety and 13 met eligibility criteria. These studies were published between 2004 and 2017, collectively analyzing 764 participants comprised of 470 patients with TBI and 294 non-TBI controls. Imaging modalities used included magnetic resonance imaging, functional magnetic resonance imaging, diffusion tensor imaging, electroencephalogram, magnetic resonance spectrometry, and magnetoencephalography. Eight of 13 studies presented at least one significant finding and together reflect a complex set of changes that lead to anxiety in the setting of TBI. The left cingulate gyrus in particular was found to be significant in 2 studies using different imaging modalities. Two studies also revealed perturbances in functional connectivity within the default mode network.* **Conclusions:** *This is the first systemic review of neuroimaging changes associated with anxiety after TBI, which implicated multiple brain structures and circuits, such as the default mode network. Future research with consistent, rigorous measurements of TBI and syndromal anxiety, as well as attention to control groups, previous TBIs, and time interval between TBI and neuroimaging, are warranted. By understanding neuroimaging correlates of psychiatric symptoms, this work could inform future post-TBI screening and surveillance, preventative efforts, and early interventions to improve neuropsychiatric outcomes.*

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Key words: traumatic brain injury, anxiety, neuroimaging, neuropsychiatric symptoms.

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INTRODUCTION

Traumatic brain injury (TBI) can be defined as a physical force to the head that disturbs normal brain function,[1] often precipitating neuropsychiatric changes.[2,3] In some, TBI is not only an acute event but also the start of a chronic disease process. Both the emergence of new psychiatric symptoms and worsening of preexisting conditions can be associated with TBI. Neuroimaging is commonly used in the investigation of psychiatric conditions or in assessing TBI; however, there is less work comparing psychiatric symptoms in the setting of TBI. Studies that utilize brain imaging to explore neuropsychiatric symptoms (NPS) seen in TBI can shed light on their neuroanatomical origins, paving the way for further research and targeted therapies.

In 2014, there were 2.87 million TBI-related emergency department visits, hospitalizations, and deaths.[4] An estimated 5.3 million Americans are currently living with TBI-related disability.[4,5] NPS after TBI are common and include cognitive impairments, mood and anxiety disorders, psychosis, and behavioral disturbances. However, NPS such as anxiety have traditionally been understudied in the setting of TBI relative to topics such as cognitive and functional performance. This remains a crucial field of study, as early diagnosis and treatment of psychiatric disorders after TBI may improve outcomes and functionality.[6]

Within the domain of post-TBI NPS, there is a significant degree of comorbidity between depression and anxiety syndromes: two-thirds of these patients with TBI with major depression also meet criteria for generalized anxiety disorder.[7] Post-TBI anxiety disorders frequently occur in isolation as well, typically presenting earlier than other post-TBI psychiatric disorders.[8,9] In a study of 96,881 Medicare beneficiaries who met criteria for TBI, 17% of patients met criteria for anxiety. Of these patients, 42% had a prior diagnosis and 58% emerged after the injury.[10]

Brain imaging sheds light on the neuroanatomical manifestations of TBI by elucidating potential neurobiological bases for TBI-related disease. Broadly, TBI may induce loss of brain volume via parenchymal degeneration, continuing from the acute to chronic stages.[11–13] For instance, among a civilian population with mild TBI, significant reductions in global brain volume were noted at one month and one year after injury.[14] Professional boxers appear to have a dose-dependent loss of caudate volume, with increased volume loss correlated to years of participation in the sport.[15] Moreover, functional magnetic resonance imaging (fMRI) has been utilized among patients with TBI to identify task-specific brain activation changes in the dorsolateral prefrontal cortex (PFC), ventrolateral PFC, and basal ganglia.[12,16–19]

Focusing on idiopathic anxiety disorders, functional abnormalities of the amygdala and its interactions with the frontal cortex, hippocampus, and striatum have been identified.[20] During emotional reactivity and regulation, individuals with generalized anxiety disorder (GAD) exhibit abnormalities in limbic and prefrontal regions.[21] One study of thirty individuals with GAD demonstrated overengagement of the amygdala and frontal regions when viewing negative images as compared with controls.[22] Taken together, these findings suggest a complex interplay between multiple brain regions. Systematic reviews of GAD imaging reveal this complexity, although they highlight the PFC and anterior cingulate cortex as major players.[23] A number of these regions are components of the default mode network (DMN), a neural circuit that has been implicated in psychiatric disorders such as anxiety and depression as well as shown to be damaged after TBI.[24–26] Of note, key DMN structures include the medial PFC, posterior cingulate cortex (PCC), inferior parietal lobe, temporal cortex, hippocampus, and precuneus.[26] Studies such as these have generated interest in utilizing imaging to predict responses to both therapy and pharmaceuticals among patients with anxiety.[27] Despite this progress, the neuroanatomical underpinnings of anxiety disorders after TBI remain less clear.

The objectives of this systematic review are to synthesize the existing neuroimaging literature of anxiety after TBI to 1) enhance the understanding of neuroanatomical and functional changes in idiopathic versus TBI-related anxiety, 2) reveal trends in the literature according to imaging modality, and 3) highlight the current literature's limitations to strengthen future research. We believe that this work will inform future TBI research with regard to postinjury screening and surveillance, preventative efforts and early interventions in neuropsychiatry, identification of neuroimaging correlates to psychiatric symptoms, and ultimately targeted therapies to improve NPS outcomes.

METHODS

Search Strategy

A literature search was conducted to extract articles with neuroimaging and NPS among human patients with TBI. PubMed (MEDLINE), PsychINFO, EMBASE, and Scopus databases were used to obtain relevant articles. Boolean searches were kept broad in the interest of reflecting all neuroimaging modalities and to capture broad domains of neuropsychiatric symptomatology. TBI literature takes many different approaches to definition, severity, population, and timing of assessment, necessitating a relatively general approach to the literature search. We used 41 imaging-, 35 NPS-, and 15 TBI-related keywords. Exact search phrases and Medical Subject Headings search field qualifiers are outlined in Appendix 1.

Review Protocol

This review adhered to Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines for implementation and reporting of systematic reviews.[28] 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 were blind to each other's determinations, and an identical data extraction sheet was used by all reviewers. 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 6 NPS domains: depression, anxiety, post-traumatic stress disorder, sleep disturbance, behavior/personality change, and psychosis. The present review focuses on the NPS domain of anxiety. A series of subsequent reviews focused on the other NPS domains will be published from these same efforts.

Inclusion and Exclusion Criteria

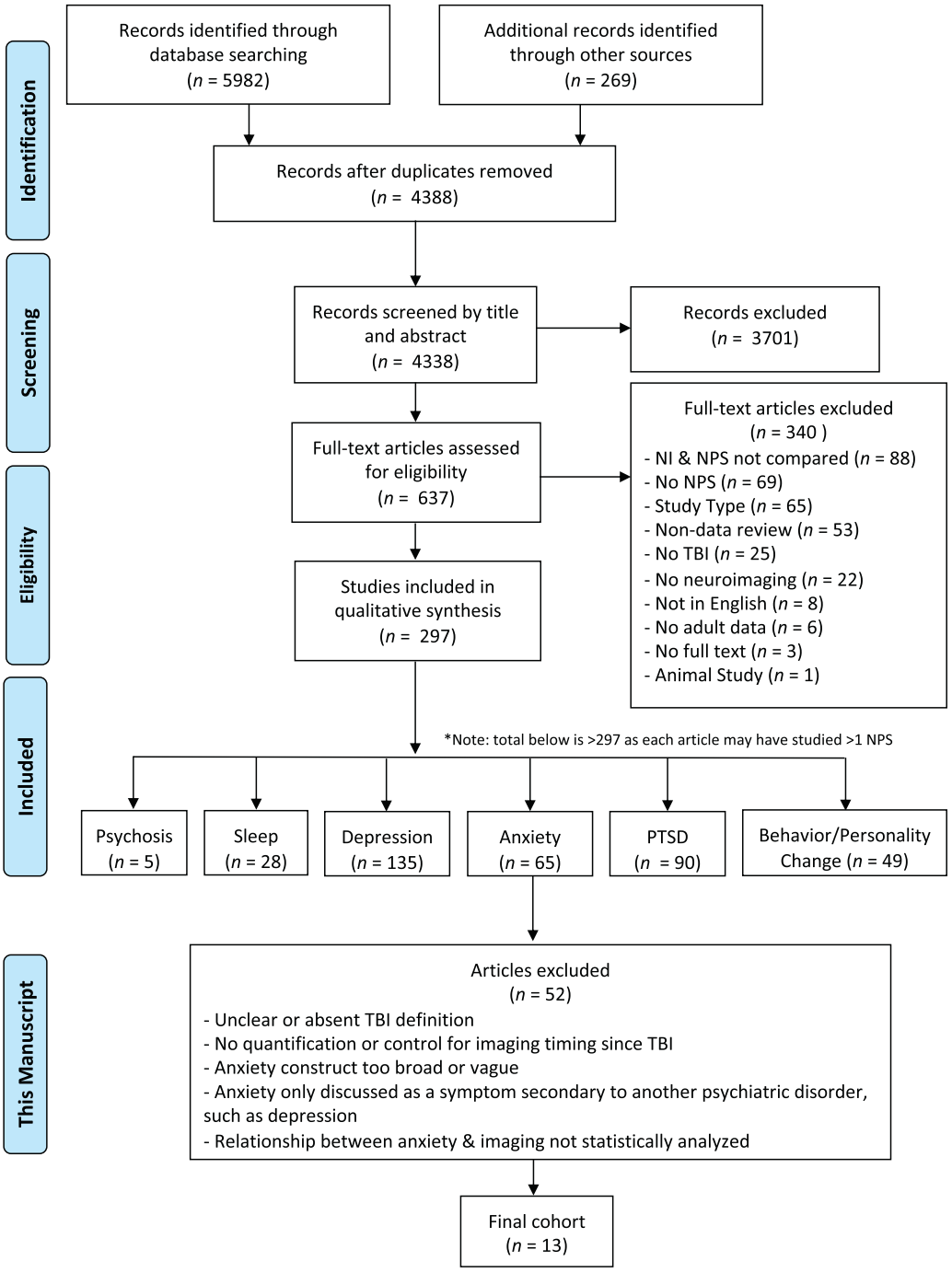
For both title/abstract and full-text reviews, a standardized set of inclusion and exclusion criteria were applied. Articles were excluded if 1) they lacked any one of the 3 key elements (i.e., neuroimaging, NPS, and TBI); 2) they were of an undesirable study type (i.e., case reports/case series with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

The final articles selected for the present review focusing on anxiety met all of the following additional criteria: 1) statistically analyzed the relationship between neuroimaging findings and anxiety symptoms in individuals with TBI; 2) presented and discussed anxiety as a primary outcome (e.g., not only as a symptom associated with depression); 3) had a clear TBI definition for participants included in the study (formalized or study-specific criteria with any combination of Glasgow Coma Scale score, loss/alteration in consciousness, and/or post-traumatic amnesia); 4) had a clear, rigorous construct for syndromal anxiety, meaning a clinician diagnosis or validated anxiety measurement scale (e.g., not a single dichotomous variable or symptom of another psychiatric diagnosis such as depression); and 5) quantified and controlled for the time interval between TBI occurrence and acquisition of neuroimaging. Articles that satisfied these additional criteria were then reviewed for individual analyses, both statistically significant and nonsignificant, between syndromal anxiety and neuroimaging.

Article Quality

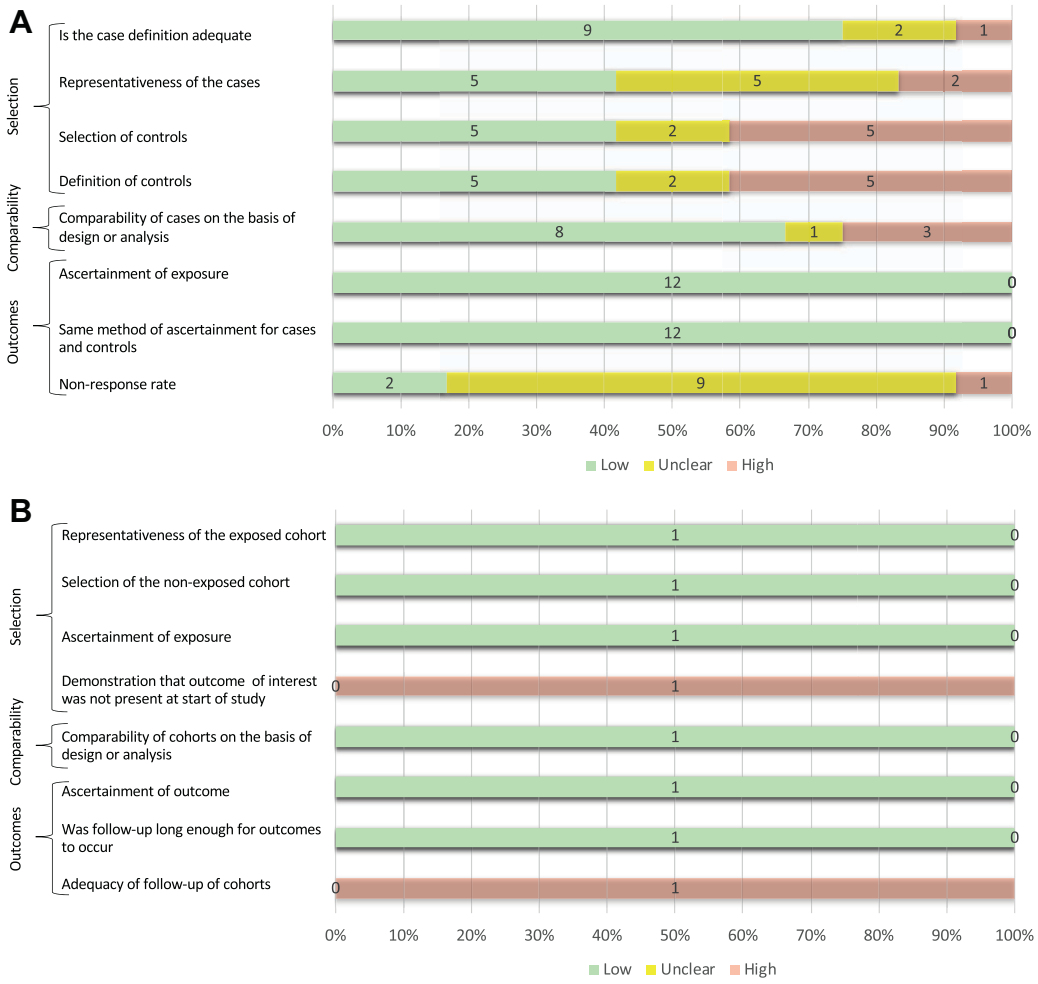
Included articles were reviewed for methodological quality and sources of potential bias (Figure 2) using the Newcastle-Ottawa Scale.[29] Broadly, this scale evaluates the risk of selection bias, comparability of comparison groups (e.g., risk of potential confounders), and the validity of outcome/exposure ascertainment for observational, nonrandomized investigation, including distinct evaluations criteria for case-control and cohort studies. Articles were determined to be case-control or cohort studies based on

FIGURE 1. Article Selection Process.



the outcome of interest to the present systematic review, not necessarily the articles' primary outcome. Each article was subsequently independently analyzed by a dyad of reviewers (N.O.D. and B.R.B.) followed by a consensus process to address any discrepancies. For each item of the Newcastle-Ottawa Scale, bias was determined to be high, low, or unclear. Quality assessment data are presented; however, articles were not excluded from the review based on quality outcomes.

FIGURE 2. **(A) Sources of Bias in Case-Control Studies (n = 12). (B) Sources of Bias in Cohort Studies (n = 1).**



RESULTS

Application of inclusion and exclusion criteria generated a final set of 13 articles, published between 2004 and 2017 (Table 1). These articles collectively comprised the findings of 764 participants: 470 with TBI and 294 normal controls. Only one article did not include a control group. Twelve articles had case-control designs, and one was a cohort study. The 13 articles included various imaging modalities with the following frequencies: 4 magnetic resonance imaging (MRI), 4 functional MRI (fMRI), 2 diffusion tensor imaging (DTI), 1 electroencephalogram (EEG), 1 magnetic resonance spectroscopy (MRS), and 1 magnetoencephalogram (MEG). Eight articles presented at least one significant anxiety-related finding. Details regarding article percentages by study design type, population, TBI severity, TBI occurrence, timing of imaging after TBI, and neuroimaging modality are presented in Table 2.

Findings by Imaging Modality

Structural findings visualized by neuroanatomical region of interest via brain mapping are displayed in Figures 3A and 3B.

Cortical Structure (Structural CT and MRI)

Four studies conducted structural imaging analyses, all of which utilized MRI. Of these 4 structural studies, 3 yielded statistically significant findings, each reporting unique results.

TABLE 1. Summary of Article Characteristics (n = 13)

Variable	% (n)
Study type	
Case-control	92.3 (12)
Cohort	7.69 (1)
Population	
Civilian	76.9 (10)
Military	7.69 (1)
Sport	15.4 (2)
TBI severity	
Mild	61.5 (8)
Moderate to severe	15.4 (2)
Any severity	23.1 (3)
TBI occurrence	
Single	76.9 (10)
Single & recurrent	23.1 (3)
Imaging timing after TBI*	
Acute/subacute	30.8 (4)
Acute/subacute & intermediate	0 (0)
Intermediate	0 (0)
Intermediate & chronic	23.1 (3)
Chronic	15.4 (2)
Acute/subacute, intermediate, & chronic	30.8 (4)

TBI =traumatic brain injury.

* Note: Acute/subacute = 0 hours−2 weeks, intermediate = 2 weeks−6 months, and chronic ≥ 6 months.

One cross-sectional study (n = 38) found that decreased volume within the ventromedial prefrontal cortex (vmPFC) was associated with increased symptoms of anxiety.[30] Examining time since injury across subjects, there was a statistically significant reduction in anxiety with corresponding increased grey matter volume within the vmPFC. In another study (n = 80), higher anxiety scores at 5 and 12 months after moderate to severe TBI predicted significant unilateral volume loss of the right hippocampal head and complex.[31] However, right total hippocampal and right hippocampal head volumes were not predictive of changes in anxiety scores, suggesting a unidirectional effect of anxiety symptoms to decreased volumes. A third study (n = 50) demonstrated that atrophy in the white matter volume of the left cingulate gyrus isthmus correlated with higher anxiety scores at 1 year after injury.[14]

White Matter Microstructural Integrity (DTI)

Two articles examined associations between post-TBI anxiety symptoms and neuroimaging data obtained via DTI. DTI studies fiber orientation of microstructural components within brain parenchyma, most commonly housed within white matter tracts. In one study (n = 74), patients with anxiety exhibited diminished fractional anisotropy (a composite measure of the direction of water diffusion, used to infer microstructural integrity, where greater values indicate healthier, intact white matter) in the cerebellar vermis relative to TBI controls without anxiety.[32]

Networks (Functional Imaging)

Six of 13 articles utilized functional imaging techniques in localizing post-TBI anxiety. Of this group, 4 used fMRI, 1 EEG, and 1 MEG.

Among the 4 studies that used fMRI, 2 presented statistically significant findings. First, analysis of a military population with TBI (n = 27) correlated increase anxiety with abnormal functional connectivity of the default mode network (DMN) in the anterior left supramarginal gyrus and regions I-IV of the left cerebellum.[33] A second study (n = 74) found that higher anxiety scores correlated with lower static functional connectivity in the executive network within the medial prefrontal areas of the bilateral frontal network and PCC and precuneus within the left frontoparietal network.[34]

The single EEG study examined athletes (n = 81) and found that those with TBI exhibited a significant correlation between anxiety and frontal lobe alpha asymmetry.[35] The study analyzing participants with mild TBI using MEG (n = 41) reported significant associations between anxiety and increased network connectivity in the alpha bands of the left occipital cortex connecting to the bilateral temporal and subcortical regions.[36]

Article Quality

Results of bias analyses via the Newcastle-Ottawa Scale are shown in Figure 2. Bias among case-control studies (n = 12) was widespread on the bases of selection and definition of healthy controls (Figure 2A). Seventy-five percent of these studies were also deemed unclear in regard to their nonresponse rates. Analysis of the single cohort study demonstrated potential bias in that the outcome of interest (i.e., anxiety) was not present at the start of the study and that a significant percentage of the cohort was lost to follow-up (Figure 2B).

TABLE 2. Articles Comparing Neuroimaging and Neuropsychiatric Symptoms of Anxiety in Traumatic Brain Injury (n = 13)

Article	Study type	Sample size	Population	TBI diagnostic criteria	TBI severity; occurrence	Timing of neuroimaging since TBI	Neuroimaging modality	Neuropsychiatric outcome measure(s)	Key findings*
Bergeson et al., 2004[43]	Case-control	150 (75 TBI, 75 NC)	Civilian	Model Systems TBI Database diagnostic criteria (Dahmer et al., 1993)	Moderate, severe; single	M = 33.4 months	MRI	BAI	BAI scores were elevated to a level indicating endorsement of at least mild symptoms of anxiety, although ratings did not significantly correlate to lobular atrophy in the right, left, or total anterior frontal, anterior temporal, or midparietal lobes.
Killgore et al., 2016[30]	Case-control	38 (26 TBI, 12 NC)	Civilian	Sustained an injury with written documentation by sports official or clinician involving head impact followed by AOC (e.g., confusion, "seeing stars", disorientation), PTA ≤24 hours, or LOC ≤30 min.	Mild; Single	Within 1 year	MRI	PAI anxiety related disorders scale	Reduction in anxiety symptoms was significantly associated with longer time since injury and larger grey matter volume within the ventromedial prefrontal cortex.
Terpstra et al., 2017[31]	Cohort	80	Civilian	GCS score of ≤12 and/or PTA ≥24 hours, resolution of PTA by 3 months post-injury	Moderate, severe; single	At least 2 time points (M = 5.1, 12.7 and/or 30.3 months)	MRI	BAI	Higher anxiety scores at 5 months predicted total right hippocampal and right hippocampal head atrophy from 5–12 months after TBI. The same was true for higher anxiety scores at 12 months predicting total right hippocampal and right hippocampal head atrophy from 12–30 months after TBI. Right hippocampal volume and volume change did not predict subsequent anxiety scores or anxiety change scores.

TABLE 2. (*Continued*)

Article	Study type	Sample size	Population	TBI diagnostic criteria	TBI severity; occurrence	Timing of neuroimaging since TBI	Neuroimaging modality	Neuropsychiatric outcome measure(s)	Key findings*
Zhou et al., 2013[14]	Case-control	50 (28 TBI, 22 NC)	Civilian	American Congress of Rehabilitation Medicine criteria	Mild; Single	1 month and 1 year	MRI	BAI	At 1-year follow-up, white mater volume in the left cingulate gyrus isthmus correlated inversely with clinical scores of anxiety.
Alhilali et al., 2015[32]	Case-control	74 (13 TBI only, 32 TBI + depression, 29 NC)	Civilian	LOC <1 min., PTA <30 min., unremarkable CT	Mild; both	Median = 20 days, range = 0–506 days	DTI	DSM-5 criteria for an anxiety disorder due to another medical condition	Patients with anxiety had diminished fractional anisotropy in the cerebellar vermis. No significant differences in mean diffusivity, axial diffusivity, or radial diffusivity were seen between patients with TBI who had anxiety and control subjects. There were no regions where control subjects with TBI had lower fractional anisotropy values than patients with anxiety.
Meier et al., 2016[44]	Case-control	86 (40 TBI, 46 NC)	Sport	McCrory et al., (2013) recommended guidelines	Mild; both	1 day, 1 week, and 1 month	DTI	HAM-A	Compared with heathy athletes, concussed athletes had higher scores for the HAM-A at one day, one week, and one month after injury. No correlations between behavioral outcomes and fractional anisotropy were significant.
Nathan et al., 2015[33]	Case-control	27 (15 TBI, 12 NC)	Military	Veterans Affairs/ Department of Defense criteria	Mild; single	2–10 months (M = 147.21–87.19 days)	fMRI	PAI	Significant association between anxiety and default mode network connectivity maps of subjects with TBI in left cerebellar regions 1–4 and the anterior division of the left supramarginal gyrus.

TABLE 2. (*Continued*)

Article	Study type	Sample size	Population	TBI diagnostic criteria	TBI severity; occurrence	Timing of neuroimaging since TBI	Neuroimaging modality	Neuropsychiatric outcome measure(s)	Key findings*
Zhan et al., 2015[45]	Case-control	30 (15 TBI, 15 NC)	Civilian	Field GCS 13–15, LOC <30 min., PTA <24 hours, and closed head injury without focal neurologic deficit on MRI.	Mild; single	2.92 + - 2.73 days	fMRI	HAM-A	No significant correlation was observed between the mean abnormal regional homogeneity values in brain areas and HAM-A scores. However, patients with TBI showed significantly reduced regional homogeneity in the left insula and left precentral, postcentral, and supramarginal gyri.
van der Horn et al., 2016[34]	Case-control	74 (54 TBI, 20 NC)	Civilian	Self-reported complaints on a 19-item post-traumatic questionnaire derived from the Rivermead Post-concussion Symptoms Questionnaire	Mild; single	4 weeks	fMRI	HADS	Higher anxiety scores were related to lower functional connectivity of the posterior cingulate cortex and precuneus within the left frontoparietal network as well as lower connectivity medial prefrontal cortex within the bilateral frontal network. No significant correlations were found between dynamic functional connectivity and anxiety scores.
van der Horn et al., 2017[46]	Case-control	74 (54 TBI, 20 NC)	Civilian	Head Injury Symptoms Checklist, European Federation of Neurological Societies Task Force guidelines, GCS 13–15, and/or LOC <30 min.	Mild; Single	4 weeks	fMRI	HADS	No significant correlations were observed between local graph measures or global network measures and anxiety scores.

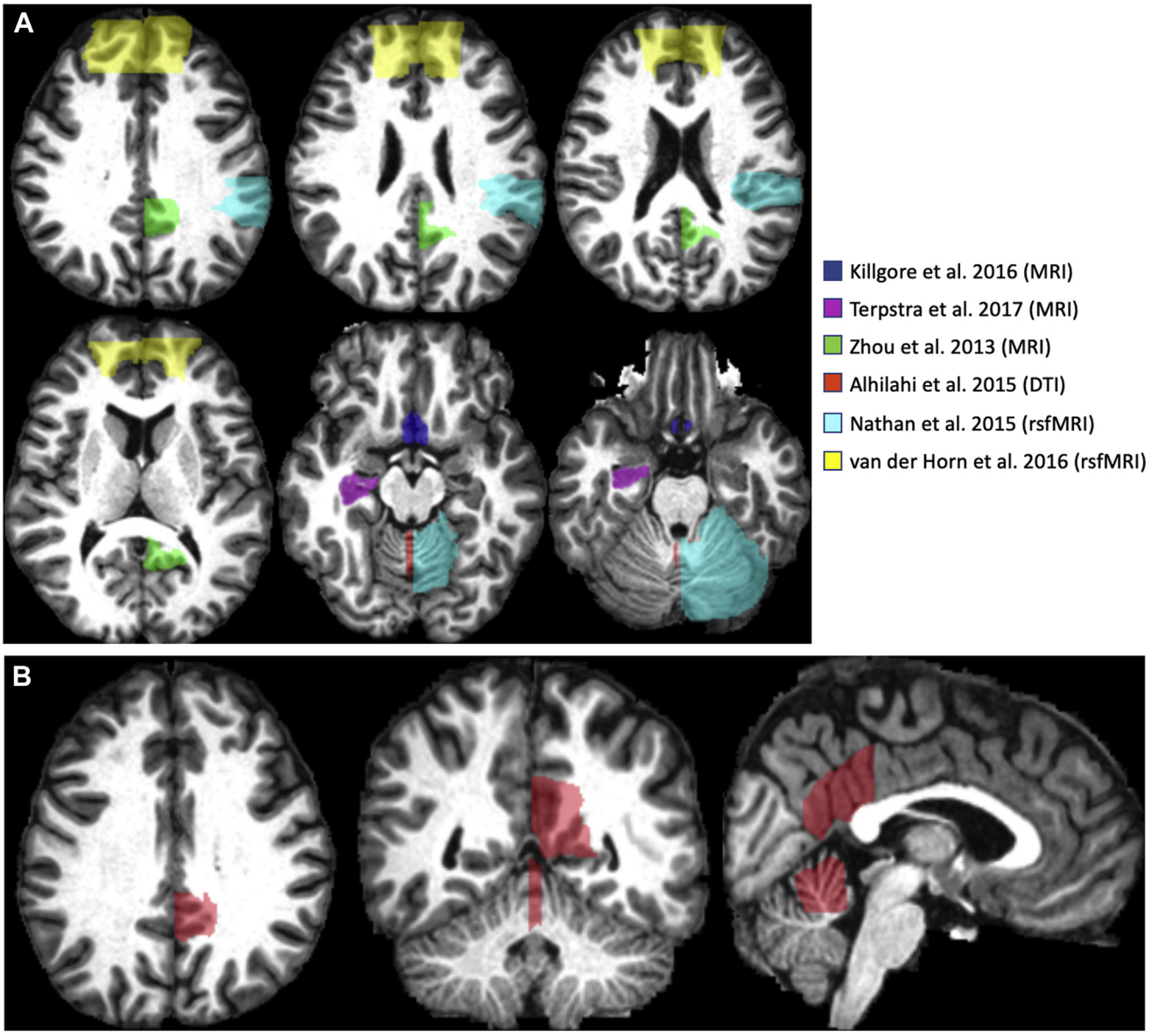
TABLE 2. (*Continued*)

Article	Study type	Sample size	Population	TBI diagnostic criteria	TBI severity; occurrence	Timing of neuroimaging since TBI	Neuroimaging modality	Neuropsychiatric outcome measure(s)	Key findings*
Capizzano et al., 2010[47]	Case-control	33 (20 TBI, 13 NC)	Civilian	CDC Guidelines for Surveillance of CNS Injury	All; single	<1 year or >1 year	MRS	HAM-A	No metabolic abnormalities were recognized between patients with and without a diagnosis of anxiety disorder in studied regions (left or right anterior cingulate cortex, orbitofrontal cortex, inferior or middle frontal gyri, inferior or middle or superior temporal gyri, temporal pole, hippocampus.
Dunkley et al., 2015[36]	Case-control	41 (20 TBI, 21 NC)	Civilian	LOC <30 min., PTA <24 hours, GCS >12 unremarkable CT	Mild; single	3 months	MEG	GAD-7	Associations between increased neurophysiological network connectivity and measures of anxiety were largely absent in the delta and theta bands. Networks appeared similar in spatial extent and distribution, with a high-degree node correlation observed in the left occipital cortex connected with bilateral temporal and subcortical regions.
Moore et al., 2016[35]	Case-control	81 (52 TBI, 29 NC)	Sport	American Academy of Neurology criteria	Mild; both	11–50 months	EEG	POMS	Athletes with a history of concussion exhibited significant correlations between frontal alpha-asymmetry and symptoms of anxiety.

AOC = alteration of consciousness; BAI = Beck Anxiety Inventory; CT = computed tomography; DTI = diffusion tensor imaging; EEG = electroencephalogram; GAD-7 = Generalized Anxiety Disorder 7; GCS = Glasgow Coma Scale; HADS = Hospital Anxiety and Depression Scale; HAM-A = Hamilton Anxiety Scale; LOC = loss of consciousness; M = mean; MEG = magnetoencephalography; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; NC = normal controls; PAI = Personality Assessment Inventory; POMS = Profile of Mood States; PTA = post-traumatic amnesia; TBI = traumatic brain injury.

* Note: Key findings are statistically significant unless otherwise noted.

FIGURE 3. **(A) Brain Mapping by Article of Approximate Structural and Functional Region of Interest Overlays Implicated in TBI-related Anxiety. (B) Brain Map Representing the Approximate Locations of Replicated Structural and Functional Neuroimaging Findings in TBI-related Anxiety (Overlap of 2 Studies).**



DISCUSSION

This systematic review summarized the existing literature reporting on the associations between neuroimaging findings and anxiety in populations with TBI. This review represents the findings from 13 original research articles comprising 764 participants. Although conclusive establishment of structural and functional changes associated with post-TBI anxiety requires further inquiry, the existing data suggest that parts of the cingulate cortex, frontal lobe, and cerebellum may be particularly implicated in mediating the onset of anxiety after TBI. However, numerous other localizations throughout the brain have been presented, suggesting that a complex and dynamic set of neurologic changes could result in post-TBI anxiety. Interestingly, many of the structural and functional changes identified are components of the DMN. Taken together, these

findings suggest that TBI-related anxiety is associated with diffuse changes throughout the brain, accompanied by a host of specific, regional alterations. Continued research is warranted to fully understand the neuroanatomical and neurofunctional correlates of post-TBI anxiety, as this knowledge could ultimately guide postinjury surveillance and targeted therapies.

The most frequently reported regions of interest (at least 2 studies) with statistically significant neuroimaging alterations in participants with TBI-related anxiety were the left PCC and superior cerebellum (Figure 3B). Other significant independent imaging data sets included the bilateral PFCs (medial and ventromedial), left parietal region (supramarginal gyrus), and right hippocampus. Interestingly, most of the reported structural and functional abnormalities converge in regions that are primarily associated with the DMN. Core areas of the DMN include the medial posterior cortex (specifically the PCC/precuneus), medial PFC (mPFC), and bilateral inferior parietal regions. Hippocampus and adjacent regions in the temporal lobe are also often reported as part of the DMN.[26] The DMN has been found to be altered in several psychopathological conditions such as anxiety and depression.[24,25] Moreover, abnormal DMN connectivity patterns have been reported in patients with TBI.[37,38] Injury of these crucial brain networks could promote aberrant functional connectivity and contribute to the pathophysiology of anxiety after TBI.

In addition, the findings reviewed herein demonstrated impairments in the superior cerebellum. Converging evidence supports the cerebellar implication in some of the brain functions involved in anxiety disorders, such as memory.[39,40] Imaging studies have shown cerebellar functional involvement with fear and anxiety-related brain areas, including the amygdala, midbrain structures, and the prefrontal cortical areas.[40] Damage of the cerebellar cortex or major afferent pathways, including the fronto-cerebellar circuits (which includes the prefrontal cortices),[41] could play a role in the etiology and expression of TBI-related anxiety.

Comparing the conclusions of a recent systematic review of neuroimaging and GAD outside the context of TBI[23] with the findings of our review suggests that both idiopathic GAD and post-TBI anxiety emerge via similar neuroanatomical and functional disturbances, insofar as limbic and frontal lobe anomalies, and to a lesser extent numerous other brain regions, are highly implicated. Further research is necessary to elucidate the nuanced neuroimaging correlates of idiopathic versus post-TBI anxiety.

Several limitations of the existing literature base are presented as follows. First, multiple studies defined TBI without well-recognized criteria, using surrogate markers such as loss of consciousness, Glasgow Coma Scale score, and a self-report questionnaire. Although many projects utilized established criteria (e.g., Centers for Disease Control guidelines), those using study-specific criteria limit validity and comparability. Moreover, none of the articles utilized a control group with idiopathic anxiety, limiting direct comparisons between idiopathic and post-TBI anxiety. This present systematic review also contains methodological limitations. To begin with, this project analyzed "anxiety" as a single entity, despite the use of 7 separate measures of anxiety. Second, the time course of TBI, anxiety, and imaging was not uniform across articles, nor was TBI severity.

In considering the current literature, various areas of continued research are warranted. This review identified multiple isolated neuroimaging findings from different neuroimaging modalities whose role in post-TBI anxiety remains inconclusive. Further exploration of these data, possibly using alternate imaging modalities, could aid in clarifying the contribution of these anatomical structures and functional networks to anxiety after TBI. Additionally, this systematic literature review found no studies using neuronuclear imaging such as positron emission tomography (PET). Given the unique abilities of neuronuclear imaging to assess functional neurobiology, inflammation, metabolism, and tauopathies in patients with TBI,[42] future research with these modalities could broaden and advance current knowledge. Additionally, studies utilizing and overlaying multimodal neuroimaging in the same individual (e.g., PET for neuroinflammation, DTI for white matter integrity, and fMRI for functional connectivity) may lead to advancements in how we understand disorders of mental life in the setting of a pathological etiology.

In conclusion, this study represents the first systematic literature review of neuroimaging correlates to anxiety in the setting of TBI. Although no anatomical or functional changes can be conclusively identified as the hallmark of post-TBI anxiety, parts of the DMN including the cingulate and prefrontal cortices, as well as the cerebellum (possibly in relation to the fronto-cerebellar circuitry), may contribute to the syndrome of anxiety after TBI. As the relationship between TBI and NPS remains a nascent field, further research replicating and expanding on these

findings is vital. Attention to standardized TBI definitions, control groups with idiopathic anxiety, and broad imaging modalities are warranted. We envision that elucidating the neuroanatomical and functional changes of post-TBI anxiety and contrasting them to those of idiopathic anxiety could ultimately guide prevention, surveillance, and targeted therapies.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jaclp.2021.09.001.

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