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Magnetoencephalography abnormalities in adult mild traumatic brain injury: a systematic review

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PII: S2213-1582(21)00141-8
DOI: <https://doi.org/10.1016/j.nicl.2021.102697>
Reference: YNICL 102697



To appear in: *NeuroImage: Clinical*

Received Date: 16 March 2021
Revised Date: 28 April 2021
Accepted Date: 6 May 2021

Please cite this article as: C.M. Allen, L. Halsey, G. Topcu, L. Rier, L.E. Gascoyne, J.W. Scadding, P.L. Furlong, B.T. Dunkley, R. das Nair, M.J. Brookes, N. Evangelou, Magnetoencephalography abnormalities in adult mild traumatic brain injury: a systematic review, *NeuroImage: Clinical* (2021), doi: <https://doi.org/10.1016/j.nicl.2021.102697>

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Title: Magnetoencephalography abnormalities in adult mild traumatic brain injury: a systematic review

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Article type: Systematic Review

Word count: 5388

Keywords: Magnetoencephalography, mild traumatic brain injury, systematic review

Highlights:

- Magnetoencephalography appears to have a higher sensitivity than existing clinical imaging techniques to detect abnormalities in mild traumatic brain injury
- Excess resting state low frequency power is consistently detected following mild traumatic brain injury
- There are widespread magnetoencephalography connectivity changes following mild traumatic brain injury
- Machine learning techniques generate high classification accuracy when analysing magnetoencephalography data
- However, currently there is not enough evidence to support routine clinical use of magnetoencephalography in mild traumatic brain injury

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Abstract

Background: The global incidence of traumatic brain injuries is rising, with at least 80% being classified as mild. These mild injuries are not visible on routine clinical imaging. The potential clinical role of a specific imaging biomarker be it diagnostic, prognostic or directing and monitoring progress of personalised treatment and rehabilitation has driven the exploration of several new neuroimaging modalities. This systematic review examined the evidence for magnetoencephalography (MEG) to provide an imaging biomarker in mild traumatic brain injury (mTBI).

Methods: Our review was prospectively registered on PROSPERO: CRD42019151387. We searched EMBASE, MEDLINE, trial registers, PsycINFO, Cochrane Library and conference abstracts and identified 37 papers describing MEG changes in mTBI eligible for inclusion. Since meta-analysis was not possible, based on the heterogeneity of reported outcomes, we provide a narrative synthesis of results.

Results: The two most promising MEG biomarkers are excess resting state low frequency power, and widespread connectivity changes in all frequency bands. These may represent a potential role of offering clinically relevant prognostic information. In addition, the rich data that MEG produces are well-suited to new methods of machine learning analysis, which is now being actively explored.

Interpretation: MEG reveals several promising biomarkers, in the absence of structural abnormalities demonstrable with either computerised tomography or magnetic resonance imaging. This review has not identified sufficient evidence to support routine clinical use of MEG in mTBI currently. However, verifying MEG's potential would help meet an urgent clinical need within civilian, sports and military medicine.

Abbreviations

MEG, magnetoencephalography; mTBI, mild traumatic brain injury; PCS, post-concussion symptoms; PTSD, post-traumatic stress disorder; EEG, electroencephalography; LFA, low frequency activity; PCL-M, Post Traumatic Stress Disorder Checklist-Military; DKEFS, Delis Kaplan Executive Function Score

1. Introduction

Traumatic brain injury has an estimated worldwide incidence of 27 million cases annually and causes a substantial healthcare burden.(1) At least 80% of injuries presenting to hospital are currently classified as mild traumatic brain injury (mTBI).(2) The global incidence of TBI is increasing, possibly due to increases in population density, population ageing, and increasing use of motor vehicles. The American Congress of Rehabilitation Medicine and later the World Health Organisation produced definitions of mTBI that are in widespread use.(3, 4) Common features include symptoms suggesting disruption of brain function following transfer of mechanical energy to the head by external forces. The severity is limited by post-traumatic amnesia of <24 hours, loss of consciousness <30 minutes, and Glasgow Coma Score of 13-15 on assessment in hospital. The commonest causes of mTBI worldwide are falls and road traffic injuries.(1) Additional causes that have attracted increasing interest in the research literature include military deployment-related blast or non-blast injuries, and sports related injuries – commonly known as concussion. The acute pathophysiology of mTBI has been shown to include axonal injury and clusters of microglial proliferation.(5) The resultant biochemical and immunological cascade is hypothesised to leave the brain vulnerable to additional insults, pending physiological recovery.(6)

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Post-concussion symptoms (PCS) include headache, dizziness or balance disorders, and cognitive impairments including attention, concentration, memory and speed of information processing problems. Symptoms can also include sleep disturbances, blurred vision, photosensitivity, tinnitus and neuropsychiatric symptoms including personality change, irritability, anxiety, and depression that can develop following mTBI.(7) Whether these symptoms comprise a specific syndrome is questionable, because of their subjective nature, and that individually, some of the symptoms can occur in the healthy population or overlap with other conditions. These include anxiety, depression, and post-traumatic stress disorder (PTSD). Systematic reviews suggest group level neuropsychological cognitive testing differences disappear by three months post-mTBI.(8) This contrasts with large, prospective cohort studies, that report 50% of participants were still symptomatic on subjective measures (including cognitive complaints) at one year post-mTBI.(9-11)

Magnetoencephalography (MEG) is a functional neuroimaging technique that measures the magnetic induction produced by electrochemical current flows within the brain.(12) Currently sensory arrays must be cooled by liquid helium to operate, representing a significant cost; therefore, only around 200 MEG scanners were operational worldwide as of 2017.(13) However, technical innovations have allowed the development of prototype MEG sensory arrays that can operate at room temperature.(14) The advantage of MEG lies in a much higher temporal resolution than functional MRI, with technical developments aimed at matching the former's spatial resolution. The key components of the MEG signal are its amplitude and frequency. Frequency bands with clinical relevance, first defined by electroencephalography (EEG) studies are: delta 0.2 – 3 Hz, theta 4 – 7 Hz, alpha 8 – 13 Hz, beta 14 – 31 Hz, and gamma 32 – 100 Hz.(15) There are numerous analysis methods for interpreting MEG data, which can be recorded with the participant at rest, or performing a task. Reviewing the recorded data constitutes sensor space analysis. The overall brain signal has a peak spectral power, which at rest falls in the high alpha band over the occiput for the healthy population. Mapping the recorded signals on to an anatomical image of the brain requires inverse modelling, called source space analysis. Connectivity analysis can then be performed. This is based on the theory that spatially separate brain regions use synchronous firing of neuronal assemblies to facilitate long-range communication and the creation of a transient and dynamic task-specific network, or communication through coherence.(16) Oscillatory amplitude envelope connectivity analysis can be used to establish the location and strength of synchronously firing neuronal populations, within and between brain regions.(17) Other network metrics seek to measure global network properties using graph theory to monitor for changes in health and disease states.(18) Given the complexity of the recorded MEG data, a novel approach is to use machine-learning algorithms to classify participants, without having prior knowledge of the key discriminatory components of the MEG data.(19) Consensus guidelines on methodology and reporting of MEG studies exist,(13, 20) alongside guidelines for research concerning mTBI.(4, 21)

Earlier neurophysiological research in mTBI comes from EEG studies. They demonstrated focal abnormalities in the delta and theta frequency bands as well as posterior alpha peak slowing; however, there is little evidence for correlation of either routine or quantitative EEG with clinical features of mTBI.(22) There is an increasing incidence of civilian mTBI, growing awareness of the possible long-term consequences of sports-related concussion, and focus on optimum treatment of mTBI in the military services. Biomarkers visible on CT and standard structural MRI that can aid diagnosis or prognostication in moderate and severe injury are absent or infrequent in mTBI. Therefore, this review will focus on: 1. What changes are evident on MEG in adult mTBI? 2. Are MEG changes related to PCS in mTBI? 3. Are MEG changes related to neuropsychological test abnormalities in mTBI? 4. Are any changes related to time post-injury? 5. Do MEG changes differ according to the injury mechanism in mTBI?

2. Methodology

A systematic review of the literature was conducted with planned narrative synthesis, and possible meta-analysis dependent on data availability. The protocol was prospectively registered on PROSPERO CRD42019151387. A literature search of the electronic databases EMBASE, MEDLINE and PsycINFO via Ovid was conducted on 4th December 2020. The complete search strategies are listed in the supplementary material. All relevant papers published prior to the search date were included. References were screened for additional papers and searches of grey literature were conducted on Web of Science, ProQuest, World Health Organisation clinical trials registry, ISCRTN clinical trials registry and the US National Library of Medicine clinical trials registry.

After de-duplication two authors screened the 466 abstracts independently. The inclusion criteria were human research, in adults aged over 16 years, who were clinically diagnosed with mTBI according to recognised criteria with post-traumatic amnesia \leq 24 hours, Glasgow Coma Scale \geq 13, and loss of consciousness \leq 30 minutes. MEG was used as an imaging modality and comparison was made between the mTBI participants and either a normative database or a case control design was used. Outcome assessments included symptom scores, neuropsychological test scores, or clinical diagnosis. The exclusion criteria were papers not available in English, mTBI was not diagnosed by recognised criteria, paper examining pharmacological interventions, mixed diagnoses with mTBI results not published as a subgroup analysis, mixed ages with adult results not published as a subgroup analysis, and review articles, single case reports, and duplicate papers. All disagreements were resolved by discussion and 383 abstracts were rejected, leaving 83 remaining. Two authors then conducted a full text screen independently, 46 papers were rejected, leaving 37 for final inclusion in the narrative synthesis. The Scottish Intercollegiate Guidelines Network critical appraisal checklists for either case-control or cohort study designs were used to appraise risk of bias and quality of individual studies.(23) After review of the available data meta-analyses were not performed.

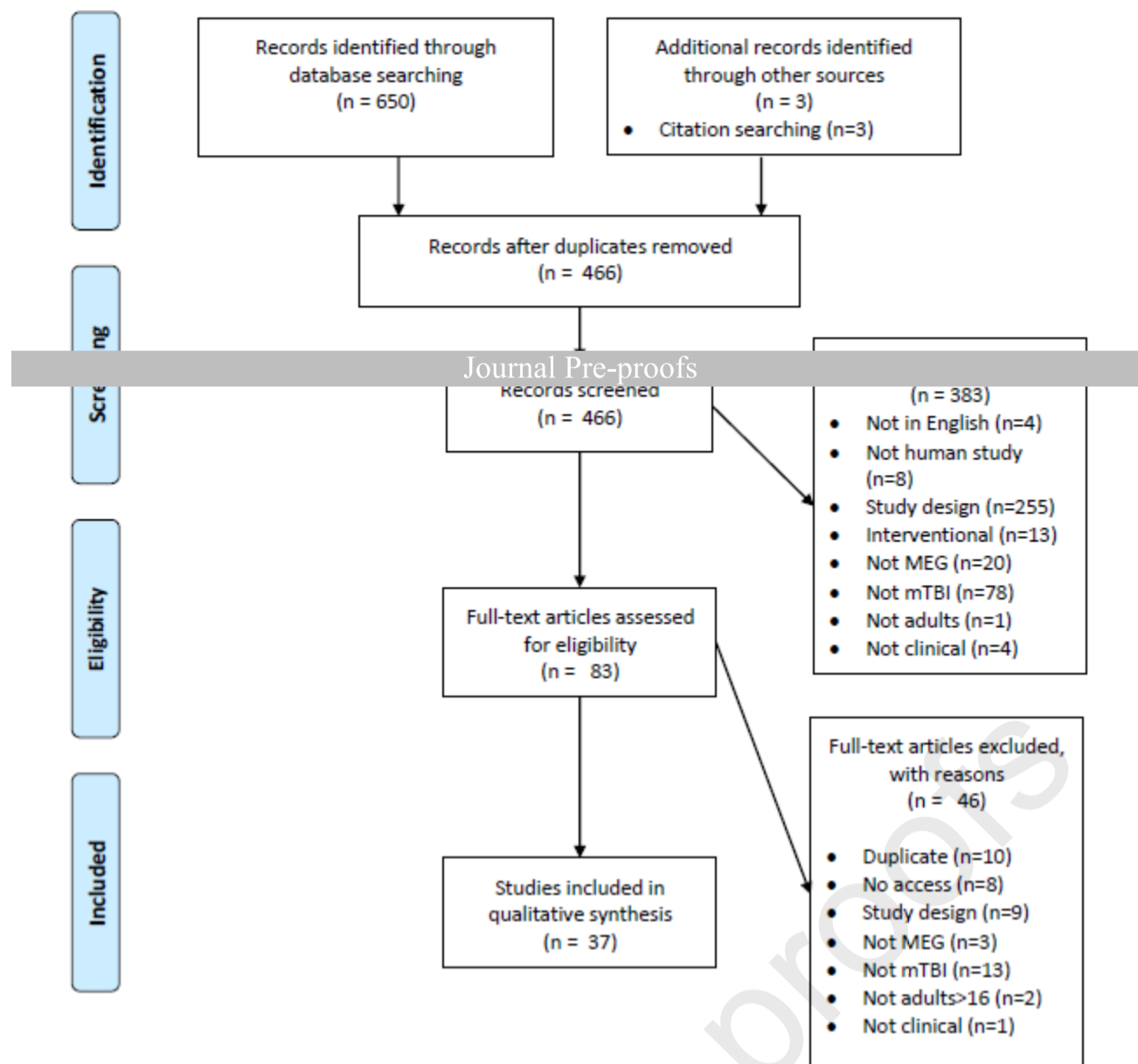


Figure 1: PRISMA flowchart of systematic review process

3. Results

3.1 Characteristics of included papers

In total, 37 papers were identified through text searching, detailed in Figure 1. A summary of extracted study characteristics is shown in Table 2. Thirty-three papers reported a case-control design and four a cohort design. Five of the 33 case-control papers featured longitudinal MEG assessment, 13 matched participants and controls for handedness, only one reported a consecutive recruitment strategy, and none reported being prospectively registered. Orthopaedic controls were used in two of the papers, veterans or active-duty military personnel in six, healthy controls in 25, and a mix in three studies. Fifteen papers reported baseline clinical measures and 16 reported baseline years of education or estimated pre-morbid IQ.

Twenty-five papers examined a civilian population with mixed mechanisms of injury, in five papers the population recruited from was unclear. Five papers examined a military population with two of these specifically focussed on blast injury. Two papers include both military personnel and civilians. Ten of the papers recruited only patients with mTBI and persisting PCS. The study sizes ranged from six to 84 participants with mTBI. Mean time between injury and MEG assessment ranged from six days to 13 years but was unreported in nine papers. There was a male bias in the mTBI population of all included papers, with 17 reporting exclusively male participants. The mean mTBI sample age ranged from 25 to 42 years. Year of publication spanned 1999 to 2020.

Ten papers reported sensor space analyses while the remaining 27 reported findings after source reconstruction. Fourteen papers presented analysis of resting state spectral power. Seventeen papers presented connectivity analyses or report network metrics. Nine papers presented analyses of task-based MEG recordings. Symptom severity was correlated with MEG findings in twelve papers, and neuropsychological test scores in five papers. Thirteen papers attempted classification metrics, most of these being machine-learning algorithms. Several papers reported multi-modal imaging, but only two presented associations between MRI abnormalities and their MEG findings.

3.2 Spectral power analysis

MEG demonstrated improved ability to detect spectral power differences over EEG when utilising multimodal imaging.(24) The most common finding was increased power in the delta frequency band of the MEG signal in mTBI participants relative to controls, reported in eight of the 14 papers that described spectral power analysis, as shown in Table 1.(24-31) The location of this abnormal delta frequency band activity was variable. The most likely sites were within the temporal, frontal, and parietal lobes. Huang et al. used a voxel-based analysis to show that any individual cortical voxel had a low (5-15%) likelihood of abnormal delta generation, but the commonest areas affected in their study were bilateral dorsolateral and ventral pre-frontal cortices, frontal poles, inferior temporal lobes, and the cerebellum.(28) The occipital lobes were noted to be least likely to have excess delta power in mTBI participants compared to controls in three papers.(24, 28, 32) Antonakakis et al. was the only paper to report that controls had increased power in the delta frequency band over the frontal region compared to mTBI participants.(33) They calculated relative power in sensor space, and instead showed that theta and alpha frequency bands had higher power in mTBI participants compared to controls over the frontal region. Four papers reported mTBI participants had an increased power in the theta frequency band relative to controls,(24, 25, 33, 34) and the most likely sites were the temporal lobes and subcortical areas. Some studies combined delta and theta to assess for excess low frequency activity (LFA) in mTBI.(34) This review did not assess the specificity of these changes; there is evidence that other conditions, e.g. Alzheimer's disease demonstrate excess LFA on EEG.(35)

The alpha frequency band was reported to show increased power in mTBI participants compared to controls in three papers(24, 33, 36) and the opposite relationship in two papers.(25, 37) The latter two papers suggest that an increased power in LFA and a decrease in alpha frequency band power represents a slowing of alpha activity in mTBI. However, Mišić et al. noted an increased power in the alpha frequency band and decreased power in the gamma frequency band in civilian mTBI versus both civilian controls and military personnel, some of whom had PTSD.(36) Only one paper reported significant differences in the beta frequency band. Dunkley et al. found beta power to be significantly reduced in mTBI compared to controls in the frontal and temporal lobes.(38) Huang et al. reported that in military mTBI participants with chronic PCS there was widespread increased power in the gamma frequency band relative to military controls.(39)

Kaltainen et al. noted that only MRI T2 hyperintense lesions within 3cm of the cortex were associated with aberrant theta frequency band activity.(34) Similarly, Huang et al. showed in 10 mTBI patients with persistent post-concussive symptoms that aberrant gamma frequency band activity was associated with nearby non-major white matter tract damage, identified by decreased fractional anisotropy with DTI.(40)

Table 1

Summary of spectral power analysis, with number of mTBI participants (n), and risk of bias assessment

Frequency band	Reduced in mTBI relative to controls	Neutral	Increased in mTBI relative to controls
Delta	Antonakakis et al. 2016(33) (30 – highest)	Zhang et al. 2020(38) (27 – intermediate)	Lewine et al. 1999(31) (30 – highest) Lewine et al. 2007(30) (30 – highest)
			(10 – highest) Huang et al. 2012(27) (45 – intermediate) Huang et al. 2014(28) (84 – highest) Dunkley et al. 2015(25) (45 – intermediate) Li et al. 2015(24) (31 – intermediate) Swan et al. 2015(26) (31 – intermediate)
Theta		Zhang et al. 2020(38) (27 – intermediate)	Antonakakis et al. 2016(33) (30 – highest) Dunkley et al. 2015(25) (45 – intermediate) Kaltainen et al. 2018(34) (26 – highest) Li et al. 2015(24) (31 – intermediate)
Alpha	Dunkley et al. 2015(25) (45 – intermediate) Popescu et al. 2016(37) (32 – highest)		Antonakakis et al. 2016(33) (30 – highest) Li et al. 2015(24) (31 – intermediate) Mišić et al. 2016(36) (20 – intermediate)
Beta	Zhang et al. 2020(38) (27 – intermediate)		
Gamma	Mišić et al. 2016(36) (20 – intermediate)		Huang et al. 2019(41) (25 – highest)

3.3 Connectivity analysis

Combining both intra and cross-frequency analyses the most frequently reported band specific connectivity analysis was in the delta frequency band, in nine of the 17 papers. Of these, three reported an increase in delta frequency band connectivity in participants with mTBI relative to controls,(25, 42, 43) and two reported a decrease.(33, 44) Four papers reported their findings using an alternative network metric, such as complexity and these will be discussed at the end of this section.(45-48) The three papers reporting a relative increase in mTBI participants each noted this change in different regions of the frontal and temporal lobes. The putamen was noted to be implicated in two of the papers. None reported an increased connectivity in the occipital lobes. Of the two papers reporting decreased delta frequency band connectivity, one reported this over bilateral frontal areas in sensor space.(33) The other reported decreased connectivity to and from the occipital lobe in mTBI participants relative to controls.(44) Four papers reported an increase in the theta frequency band connectivity,(25, 42, 49, 50) while none reported a decrease. This includes three papers that also reported an increase in the delta frequency band connectivity, with similar brain locations found to be responsible for both.

Alpha frequency band connectivity analysis was reported in seven papers. Four papers from the same group reported an increase in mTBI participants relative to controls.(25, 36, 44, 51) One paper showed a non-significant decrease,(42) and two used alternative network metrics.(46, 52) The most frequent locations to detect an increased connectivity were the frontal and then temporal lobes. Dunkley et al. examined both the default mode and motor networks in the resting state and found an increased connectivity in these networks in mTBI participants.(51)

Beta frequency band connectivity was reported in five papers. Three reported an increase,(33, 43, 51) in the frontal and temporal lobes of mTBI participants relative to controls and one paper noted this was due to significant cross frequency coupling between the beta and high gamma frequency bands.(33) One paper reported a reduction in beta frequency band connectivity in mTBI participants relative to controls, with the most marked reduction in the bilateral somatosensory and motor cortices.(38) One paper reported alternative network metrics.(45) Gamma frequency band connectivity was reported in six papers, with three reporting an increased connectivity, mostly in the frontal lobes in mTBI participants relative to controls.(33, 43, 51) Two papers reported the opposite, with one finding that it was an increased high gamma functional network that most accurately distinguished mTBI participants from both controls and participants with PTSD.(36, 44) One paper reported alternative network metrics in isolation.(45)

Alternative network metrics included calculating coefficients of: small-worldness,(45, 49) rich club nodes,(45-47) efficiency,(33, 47, 52, 53) and complexity.(48, 50) Summarising these results is challenging, given the variability of analysis methods, and given few findings were replicated. Many used a data driven machine-learning approach to define differences between participants with mTBI and controls and quoted high precision within their own training datasets. Three papers from the same research group described a hypersynchronised delta frequency band modulated rich club network and lower global efficiency in mTBI participants relative to controls.(45-47)

3.4 Task-based analysis

Of the nine papers that included task-based analyses; three assessed working memory,(54-56) two set-shifting,(57, 58) and one visual attention,(59) visual tracking,(60) picture naming,(61) and auditory information processing.(62) These tasks were performed during the MEG recording, while the analyses above only used resting state data. Only one paper performed a connectivity analysis,(58) while the rest performed spectral power analyses. The working memory tasks showed left lingual gyrus hyperactivation, as well as asymmetry of hippocampal activation,(54) and bilateral frontal pole hyperactivation, in all

frequency bands in mTBI participants relative to controls.(56) However, Popescu et al. found a relative reduction in alpha frequency band power in the left rostral middle frontal region was correlated with task performance.(55) This was more strongly associated with PTSD symptom severity evaluated using the Post Traumatic Stress Disorder Checklist-Military (PCL-M), than the severity of mTBI in their cohort study.

In the set-shifting tasks, mTBI participants had longer reaction times and poorer performance in the extradimensional shift condition compared to controls. However, both set-shifting conditions showed mTBI participants had an aberrant sequence of brain area activation. This was significant in the right frontal and bilateral parietal lobes.(57) The same group showed that connectivity between the occipital lobes and the rest of the brain in the alpha frequency band was reduced in mTBI participants compared to controls.(58) Petley et al. showed reduced global field strength and delayed reaction times in a small sample of mTBI participants compared to controls during a visual attention task.(59) Visual tracking of an intermittently obscured target showed lower performance in mTBI participants and was associated with widespread relative changes in beta frequency band power compared to controls.(60) During picture naming there was a reduction in the amplitude of the event-related MEG signal in the dominant hemisphere association areas in those of the cohort whose memory test results were poorest.(61) Kaltainen et al. found altered activation globally in the alpha frequency band during a paced auditory serial addition test in mTBI participants compared to

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3.5 Clinical outcome and MEG results

Five papers reported the correlation between their MEG results and clinical interview results or symptom questionnaire scores, as a surrogate for clinical outcome. Two papers reported the sum of all regions with excess LFA positively correlated with symptom score on the Head Injury Symptom Checklist and symptom severity in a structured clinical interview, respectively.(27, 31) On the contrary, two papers commented specifically that they did not find a significant correlation between MEG abnormalities and mTBI symptoms. This included resting state LFA not correlating with symptoms as recorded by the European Brain Injury Questionnaire.(30) and theta frequency band activity not correlating with symptom score on the Rivermead Post-Concussion Symptom Questionnaire.(34) Dunkley et al. reported increased connectivity in the alpha and gamma frequency bands within the default mode network positively correlated with symptom score on the Sports Concussion Assessment Tool 2.(51)

There can be diagnostic uncertainty when attempting to differentiate PCS and PTSD. While not the focus of this review, four of the included papers reported correlations between their MEG results, predominantly in the alpha frequency band and co-morbid PTSD symptoms.(28, 37, 55, 63) Popescu et al. reported lower power frontally in the resting state alpha frequency band, in those who screened positive for PTSD with the PCL-M, compared to those who did not, as well as those who had loss of consciousness associated with their mTBI.(37) During a working memory task frontal alpha frequency band power negatively correlated with symptom score.(55) Rowland et al. did not find a correlation with symptom scores; however, they did show a shift in connectivity from the alpha to theta frequency bands in both mTBI and PTSD.(49) There were few network-level differences between the mTBI, PTSD and dual diagnosis groups in this study in the alpha frequency band, however when considering all frequency bands, the mTBI group had increased small-worldness and the PTSD group had reduced small-worldness. The same group replicated their findings of increased small-worldness when participants had PTSD detected using the Clinician-Administered PTSD Scale 5 in addition to mTBI.(63)

Three of the included papers reported on the correlation between MEG findings and symptoms of depression or anxiety.(25, 28, 61) Huang et al. reported that delta frequency power in the anterior cingulate cortex correlated with depressive symptoms recorded using a modified Head Injury Symptoms Checklist.(28) Dunkley et al. reported alpha frequency connectivity between left occipital and bilateral temporal and subcortical regions was positively correlated with Patient Health Questionnaire 9 and Generalised Anxiety Disorder 7 score.(25) Yet, Popescu et al. reported no correlation between global spectral power and either of these scores.(61) Major depressive disorder, independent of mTBI, has been associated with a global excess of LFA in EEG studies.(64, 65) Huang et al. reported trouble concentrating was associated with increased delta frequency power in the right orbitofrontal cortex and Dunkley et al. reported a positive correlation between low frequency connectivity and inattention scores on Conner's Comprehensive Behaviour Rating Scale.(25, 28)

3.6 Neuropsychological testing and MEG results

There was marked variability in approach when correlating MEG data with neuropsychological testing data. Some papers used resting state data, while others used task specific data, e.g., from an N-back working memory task and both spectral power and connectivity analyses were used. The most reported neuropsychological assessments were the Trail Making Test Part B within the Delis Kaplan Executive Function Score (DKEFS), and the Digit Symbol Coding task within the Wechsler Adult Intelligence Scale. Four papers reported correlations between these test scores and either power or connectivity of specific frequency bands in the frontal MEG results.(26, 41, 43, 56) For the Trail Making Test Part B the right dorsolateral prefrontal cortex power in all frequency bands,(56) and left ventrolateral prefrontal cortex beta frequency band functional connectivity,(43) were negatively correlated with test performance. LFA power in the frontal poles and right precentral gyrus were also reported to be negatively correlated with test performance.(26) Finally, power in the gamma frequency band in the right supplementary motor area was negatively correlated with test performance and distinguished between mTBI participants and controls.(41)

For the Digit Symbol Coding task, the right prefrontal cortex power in all frequency bands and low frequency power in right temporal gyri were negatively correlated with test performance.(26, 56) Huang et al. found widespread negative correlations between gamma frequency band power and test performance.(41) While the left superior parietal lobe, right precentral gyrus and left frontal pole LFA were positively correlated with test performance.(26) Left ventrolateral prefrontal cortex beta band connectivity was also positively correlated with test performance.(43) Spectral power in the frontal poles, left superior parietal lobe gamma frequency band power and functional connectivity of the beta frequency band in the left ventrolateral prefrontal cortex were negatively correlated with performance of the letter fluency subtest within the DKEFS by the same author.(41, 43, 56)

3.7 Diagnostic application

Fifteen papers described methods to determine participant classification between mTBI participants and controls. From the reports, it is unclear if any of these used methods that were set prospectively, prior to data collection. Four of these used resting state LFA.(27, 28, 31, 34) Lewine et al. demonstrated the potential role of MEG in 1999 when they reported a sensitivity of 65% for excess LFA in mTBI participants with persistent PCS. This test had a false positive rate of 5% in healthy controls, and 10% of mTBI participants without persistent PCS tested positive.(31) Kaltainen et al. more recently showed a sensitivity of 30% in a symptomatic subacute mTBI sample, with a false positive rate in healthy controls of 1%.(34) Huang et al. reported a significant increase in sensitivity by considering normalised power on an individual voxel, not whole brain basis. They reported sensitivities of 85% and 87% in symptomatic mTBI participants with specificities of 100%.(27, 28) The cut-off threshold was set after data processing to achieve this maximum specificity for both papers.

Ten papers applied a machine learning approach to distinguish the connectivity analysis of mTBI participants from controls.(33, 38, 44-48, 52, 53, 66) Most papers did not split their data into model training and test sets, and subsequently reported extremely high, possibly over-fitted performance. Diwakar et al. used a novel approach, combining MEG features with task performance and neuropsychological testing results to achieve a 94% classification accuracy in a chronic symptomatic mTBI cohort compared to healthy controls.(60)

3.8 Time post-injury and MEG results

While the mean time between MEG assessment and injury ranged from six days to 11 years in the papers incorporated in this systematic review, five papers included repeat MEG imaging sessions.(31, 34, 42, 59, 62) Three papers showed the incidence of abnormal LFA dropped as the interval between MEG imaging and injury increased, suggesting this represents an acute to subacute marker of injury that may also be linked to recovery.(31, 34, 42) However, when considering all papers that reported LFA as able to differentiate mTBI participants from controls, the mean time to scanning ranges from one week to 33

months. Given this discrepancy between longitudinal and cross-sectional study designs, it is not possible to ascertain whether excess LFA resolution is associated with symptomatic recovery from mTBI. Two of the papers with serial MEG imaging found that differences in task-based alpha frequency band power and event related potentials differentiated mTBI participants and controls acutely and 3-6 months later, suggesting the MEG abnormalities persist.(59, 62) Both papers noted that only small subsets of their samples returned for serial MEG sessions, which may have biased their results.

3.9 Mechanism of injury and MEG results

Individual studies did not report the ability to detect differing MEG abnormalities dependant on the mechanism of injury. The mechanisms were divided into sports-related concussion, any other civilian injury, or those suffered by military personnel, which could be further split into blast (from explosive blast waves) and non-blast trauma. In total 16 papers reported mTBI participants from more than one of these groups, though small sample sizes may have led to underpowered comparison.

3.10 Risk of bias

Three papers were sufficiently detailed to complete at least two thirds of the relevant Scottish Intercollegiate Guidelines Network critical appraisal checklist and judged to be at the lowest risk of bias.(44, 51, 56) Seven papers were judged at intermediate risk of bias,(25-27, 36, 38, 54, 62) and the remaining 18 at high risk of bias. Frequent concerns for potential bias in the 32 case control studies were lack of clinical description of participants and adequate screening of controls to avoid inclusion of cases with many papers not reporting exclusion criteria. In addition, there was often inadequate controlling for potential confounders, and lack of a clearly defined prospective research question. Within the five cohort studies, areas of potential bias included a lack of clearly defined pre-specified outcomes and not reporting on blinding when performing the analysis. Another potential concern is the possibility of overlapping clinical samples, or unacknowledged re-analysis of previous datasets, which may lessen the impact of the entire field.

4. Discussion

This review has identified that while MEG has demonstrated clear promise as a functional neuroimaging modality, it is not yet a diagnostic or prognostic clinical tool in mTBI of sufficient sensitivity and specificity. However, MEG is one of the most sensitive imaging modalities for the evaluation of mTBI, considering the very low sensitivity of CT, structural MRI and EEG. There is growing consensus around key features such as an increase in LFA power and widespread connectivity changes following mTBI. The consistently high prevalence of MEG abnormalities across several studies, and the initial successes of AI algorithms to classify participants, implies that MEG is one of the most sensitive neuroimaging modalities to investigate this condition. Future work should concentrate on harmonising biomarkers and data analysis methods, so that different groups can generate a robust evidence base quickly. Harmonisation should also aim to build on the current published longitudinal studies to establish the natural history of these changes in the weeks, months and years following injury. Current evidence indicates that task-based MEG data, with cognitive loading, are also an important tool to improve our understanding of the impact of mTBI on neural activity and could possibly play a role in guiding therapeutic interventions.

Increases in LFA power have been reported with a frontal predilection. This correlates with acute changes in mTBI in the corpus callosum seen using DTI. In addition, when abnormal LFA and MRI lesions appear to co-localise, it suggests that LFA may arise from partial cortical deafferentation.(67) Despite this, LFA is known to be non-specific, occurring in other conditions such as depression or secondary to medication use.(65) Differences in measurement techniques may explain the variation in reported prevalence of the abnormal LFA, so despite two studies suggesting it can resolve with time, and some evidence of association with symptoms or neuropsychology test results, its role as a diagnostic or prognostic marker is yet to be determined. The heterogeneity of available neuropsychological tests and symptom scoring tools additionally limits the robustness of this conclusion. The findings reported in this systematic review are often the result of group level comparisons, but two papers of intermediate risk of bias differentiated between their chronic PCS participants and controls on a single participant level with high accuracy. However, none of the included studies met the criteria of a high quality prospective clinical diagnostic test accuracy study.

Many papers have examined the role of network metrics, connectivity, and machine learning. There is a lack of methodological homogeneity across papers, and studies have not addressed the direction of observed effects. However, an increase in delta and theta connectivity is reported, including in four of the papers at minimum or intermediate risk of bias. Authors have suggested that these effects are reflective of plasticity in recovery, and symptoms may be related to an inability to deactivate the default mode network. Network metric studies often used machine learning to report high levels of classification accuracy, but frequently used convenience samples of unmatched controls, making them vulnerable to spectrum bias. While not yet being clinically useful, this shows a potential role for machine learning, which should be explored further.

The most common risks of bias identified in this review related to clarity of outcome measures, likely retrospective unblinded analysis and a lack of clinical description of participants, leading to the possibility of confounding. Most studies were small, the largest included 84 participants with mTBI. Additionally, the analysis performed was heterogeneous, with the most common type of analysis (a connectivity analysis) being performed in only 17 of the 37 included papers. There was a wide intra-study and inter-study range of time interval between injury and MEG scanning, which may mask some of the temporal evolution of MEG changes following mTBI.

For future studies, collaboration across sites should be encouraged. This will increase sample size and power, and prospective registration with clear quantifiable outcome measures would limit bias. These should align with recommended core outcome sets for mTBI research.(4, 21) An appropriately matched trauma-exposed control group should be used. This is especially important if the intention is to apply machine learning techniques. This would be more representative of the population that mTBI participants are drawn from, ensure machine learning only detects features related to mTBI, and will reveal pragmatic false positive rates, which would be more applicable to clinical settings. To further limit bias, the baseline characteristics of both control and case samples should be clearly stated and ideally matched, given that this is known to influence MEG findings. Exclusion criteria should be well defined, dropout rates stated, and impact on results considered. Regarding the application of machine learning within these studies, training and test populations should be separate to avoid over-fitting. More importance should be given to repeatability, ideally across different scanners and clinical settings.

5. Limitations

The major limitations of this review were being unable to resolve its broad questions into quantitative measures and the inability to perform a meta-analysis of MEG data, based on the available literature. For example, different mechanisms of injury could not be differentiated by MEG within individual studies. If this data could be pooled, and assessed with a pre-specified analysis method, we could definitively answer this question. This issue arises because of the broad definition of mTBI, the complex nature of the MEG datasets and variety of analysis methods available and reported. It is likely that a pooling of original study datasets will be required to overcome this, but this was beyond the scope of this review. The review's strengths include the prospectively registered systematic design and independent rating of papers, which should limit the risk of bias in its conclusions. Additionally, this review has identified and made recommendations to improve study methodology, frequently judged suboptimal by clinical critical appraisal tools.

6. Conclusion

To the best of the authors' knowledge, this is the first prospectively registered systematic review of MEG studies focused on adult mTBI. This review has not identified sufficient evidence to support routine clinical use of MEG in mTBI currently. This is due to study heterogeneity, a lack of diagnostic test accuracy studies, and underpowered longitudinal studies of low quality. Despite this, some key areas of progress have been identified. These include the two most promising biomarkers of excess resting state low frequency power, and connectivity changes in all frequency bands. These may represent biomarkers, with

potential for diagnostic application, which reflect time-sensitive changes, or may be capable of offering clinically relevant prognostic information. Verifying these findings would help meet an urgent clinical need within civilian, sports and military medicine to identify and characterise mTBI, and to allocate neurorehabilitation resources of differing nature, complexity and cost. This is best done with prospective clinical studies, using pre-defined protocols and drawing on the research guidelines highlighted in this review. Collaboration across sites would help standardise analysis methods and reporting, allowing quantitative comparison of findings across studies.

Funding

No external funding or other support was received for this systematic review.

Author contributions

Christopher Martin Allen Journal Pre-proofs & editing. Lloyd Halsey: Data curation; Formal analysis; Writing - original draft; Writing - review & editing. Gogem Topcu: Methodology; Writing - review & editing. Lukas Rier: Writing - review & editing. Lauren Gascoyne: Writing - review & editing. John W Scadding: Writing - review & editing; Paul L Furlong: Writing - review & editing. Benjamin T Dunkley: Writing - review & editing. Roshan Das Nair: Conceptualization; Supervision; Writing - review & editing. Matthew Brookes: Conceptualization; Writing - review & editing. Nikos Evangelou: Conceptualization; Supervision; Writing - review & editing.

Declaration of competing interest

JWS is Chair of the Independent Medical Expert Group, a Non-Departmental Public Body that advises the UK Ministry of Defence on medical aspects of the Armed Forces Compensation Scheme. M.J.B. is a director of and holds founding equity in Cerca Magnetics Limited, a university spin-out company whose aim is to commercialise aspects of OPM-MEG technology. CMA, LH, GT, LR, LEG, PLF, BT, RdN, and NE have nothing to declare.

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Table 2

Characteristics of 37 papers included in review

Reference	Country and study design	Study mTBI population	Mechanism of mTBI	Number of mTBI participants	Mean time post-injury (Days)	Mean age of mTBI participants (Years)	Sex of mTBI participants (% male)	Control type	Analysis type
Delayed and disorganised brain activation detected with magnetoencephalography after mild traumatic brain injury(57)	Canada, case-control	ED department, non-consecutive	Not specified	16	33	31	100	16 HC	Task-based source analysis
Low-frequency connectivity is associated with mild traumatic brain injury(25)	Canada, case-control	ED department, non-consecutive	7 Sports, 13 Civilian	20	32	31	100	21 HC	RS source analysis, RS connectivity analysis
Default mode network oscillatory coupling is increased following concussion(51)	Canada, case-control	ED department, non-consecutive	Not specified	26	32	31	100	24 HC	RS connectivity analysis
Post-Traumatic stress constrains the dynamic repertoire of neural activity(36)	Canada, case-control	ED department, non-consecutive	Not specified	20	32	31	100	20 control soldiers, 20 civilian HC, 23 soldiers with PTSD	RS source analysis, RS connectivity analysis.
Reduced brain connectivity and mental flexibility in mild traumatic brain injury(58)	Canada, case-control	ED department, non-consecutive	Not specified	16	33	31	100	16 HC	Task-based connectivity analysis (sensor space)
Detecting Mild Traumatic Brain Injury Using Resting State Magnetoencephalographic Connectivity(44)	Canada, case-control	ED department, non-consecutive	Not specified	20	32	31	100	21 HC	RS connectivity analysis, machine learning algorithm.
Concussion Alters the Functional Brain Processes of Visual Attention and Working Memory(54)	Canada, case-control	ED department, non-consecutive	4 Sports, 14 Civilian	18	36	30	100	19 HC	Task-based source analysis
Activation of dominant hemisphere association cortex during naming as a function of cognitive performance in mild traumatic brain injury: Insights into mechanisms of lexical access(61)	USA, cohort	PCS outpatient programme	Not specified	57	1920	39	99	None	Task-based source analysis
Reduced prefrontal MEG alpha-band power in mild traumatic brain injury with associated posttraumatic stress disorder symptoms(37)	USA, cohort	PCS outpatient programme	Not specified	32	1590	40	100	None	RS source analysis
Post-traumatic stress disorder is associated with altered modulation of prefrontal alpha band oscillations during working memory(55)	USA, cohort	PCS outpatient programme	Not specified	35	Not specified	42	100	None	Task-based source analysis
Altered cross-frequency coupling in resting-state MEG after mild traumatic brain injury(33)	USA, case-control	Texas trauma centres	2 Sports, 28 Civilian	30	Not specified	29	60	50 HC	Connectivity analysis (sensor space), machine learning algorithm
Altered rich-club and frequency-dependent subnetwork organization in mild traumatic brain injury: A MEG resting-state study(45)	USA, case-control	Texas trauma centres	2 Sports, 28 Civilian	30	Not specified	29	60	50 HC	Connectivity analysis (sensor space), network metrics, machine learning algorithm
Reconfiguration of dominant coupling modes in mild traumatic brain injury mediated by delta-band activity: A resting state MEG study(46)	USA, case-control	Texas trauma centres	2 Sports, 28 Civilian	30	Not specified	29	60	50 HC	Connectivity analysis (sensor space), network metrics, machine learning algorithm
Data-Driven Topological Filtering Based on Orthogonal Minimal Spanning Trees: Application to Multigroup Magnetoencephalography Resting-State Connectivity(47)	USA, case-control	Texas trauma centres	2 Sports, 28 Civilian	30	Not specified	29	60	50 HC	Network metrics, machine learning algorithms
Functional connectivity changes detected with magnetoencephalography after mild traumatic brain injury(52)	USA, case-control	Texas trauma centres	2 Sports, 29 Civilian	31	Not specified	29	58	50 HC	Connectivity analysis (sensor space), network metrics, machine learning algorithm
Improving the Detection of mTBI Via Complexity Analysis in Resting - State Magnetoencephalography(48)	USA, case-control	Texas trauma centres	2 Sports, 28 Civilian	30	Not specified	29	60	50 HC	Network metrics, machine learning algorithm
Functional connectivity changes in mild traumatic brain injury assessed using magnetoencephalography(53)	USA, case-control	Texas trauma centres	Not specified	10	Not specified	31	70	50 HC	Connectivity analysis (sensor space), machine learning algorithm
Magnetoencephalography slow-wave detection in patients with mild traumatic brain injury and ongoing symptoms correlated with long-term neuropsychological outcome(26)	USA, case-control	TBI clinics with persistent PCS >3 months	6 Sports, 20 Blast related, 5 Civilian	31	97	27	90	33 HC	RS source analysis
An automatic MEG low-frequency source imaging approach for detecting injuries in mild and moderate TBI patients with blast and non-blast causes(27)	USA, case-control	Veterans brain injury centre with persistent PCS	23 Military, 22 Civilian	45	250	28	84	44 HC	RS source analysis

Theta-Band Oscillations as an Indicator of Mild Traumatic Brain Injury(34)	Finland, case-control	Not specified	Not specified	26	Longitudinal	41	58	139 HC from previous study dataset	RS source analysis
Mild traumatic brain injury affects cognitive processing and modifies oscillatory brain activity during attentional tasks(62)	Finland, case-control	Not specified	4 Sports, 21 Civilian	25	Longitudinal	42	56	20 HC	Task-based sensor space and source analyses
Source Connectivity Analysis Can Assess Recovery of Acute Mild Traumatic Brain Injury Patients(42)	USA, case-control	Not specified	Not specified	13	Longitudinal	26	54	8 orthopaedic trauma controls	RS connectivity analysis
Brain Activation Profiles in mTBI: Evidence from Combined Resting-State EEG and MEG Activity(24)	USA, case-control	Not specified	Not specified	6	Not specified	28	66	5 orthopaedic trauma controls	RS analysis (sensor space)
Contrasting Effects of Posttraumatic Stress Disorder and Mild Traumatic Brain Injury on the Whole-Brain Resting-State Network: A Magnetoencephalography Study(49)	USA, case-control	Veterans	Military	12	2265	39	100	10 HC	Network metrics
Increased Small-World Network Topology Following Deployment-Acquired Traumatic Brain Injury Associated with the Development of Post-Traumatic Stress Disorder(63)	USA, cohort	Veterans	Military	16	4138	40	100	None	Network metrics
MEG Working Memory N-Back Task Reveals Functional Deficits in Combat-Related Mild Traumatic Brain Injury(56)	USA, case-control	Veterans or active-duty military personnel with persistent PCS	Military	25	315	27	100	20 veterans or active-duty military personnel	Task-based source analysis
Marked Increases in Resting-State MEG Gamma-Band Activity in Combat-Related Mild Traumatic Brain Injury(41)	USA, case-control	Veterans or active-duty military personnel with persistent PCS	Military	25	594	28	100	35 veterans or active-duty military personnel	RS source analysis
Single-subject-based whole-brain MEG slow-wave imaging approach for detecting abnormality in patients with mild traumatic brain injury(28)	USA, case-control	Persistent PCS	36 Military, 48 Civilian	84	265	29	83	11 veterans or active-duty military personnel 68 civilian HC	RS source analysis
Resting-State Magnetoencephalography Reveals Different Patterns of Aberrant Functional Connectivity in Combat-Related Mild Traumatic Brain Injury(43)	USA, case-control	Veterans or active-duty military personnel	26 Military	26	508	28	100	22 veterans or active-duty military personnel	RS connectivity analysis
Integrated imaging approach with MEG and DTI to detect mild traumatic brain injury in military and civilian patients(29)	USA, case-control	Persistent PCS	4 Sports, 4 Military, 2 Civilian	10	353	25	90	14 HC	RS source analysis.
Attentional dysfunction and recovery in concussion: effects on the P300m and contingent magnetic variation(59)	Canada, case-control	Consecutive ED mTBI patients	2 Sports, 11 Civilian	13	Longitudinal	26	31	13 HC	Task-based ERFs
Complexity analysis of resting state magnetoencephalography activity in traumatic brain injury patients(50)	USA, case-control	Not specified	15 Military, 3 Civilian	18	1859	29	100	18 HC	Network metrics
Filling in the gaps: Anticipatory control of eye movements in chronic mild traumatic brain injury(60)	USA, case-control	mTBI clinic or neurology referrals with persistent PCS	13 Sports, 12 Civilian	25	968	33	84	25 HC including from other studies	Task-based source analysis
Objective documentation of traumatic brain injury subsequent to mild head trauma: Multimodal brain imaging with MEG, SPECT, and MRI(30)	USA, cohort	Outpatient clinics with persistent PCS >1 year	30 Civilian	30	1011	38	53	None	RS source analysis
Neuromagnetic assessment of pathophysiologic brain activity induced by minor head trauma(31)	USA, case-control, longitudinal	mTBI with or without PCS	Not specified	30	345	36	60	20 HC	RS source analysis
Aberrant Whole-Brain Transitions and Dynamics of Spontaneous Network Microstates in Mild Traumatic Brain Injury(66)	USA, case-control	Texas trauma centres	2 Sports, 28 various	30	Not specified	29	60	50 HC	Network metrics
Local and large-scale beta oscillatory dysfunction in males with mild traumatic brain injury(38)	Canada, case-control	Non-consecutive ED mTBI patients	12 Sports, 15 Civilian	27	39	30	100	23 HC	RS source analysis, RS connectivity analysis

USA- United States of America, mTBI – mild traumatic brain injury, ED – emergency department, PCS - Post Concussive Symptoms, Sports – sports related concussion, HC – healthy controls, RS – Resting State, ERF – Event Related Fields

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Supplementary InformationOvid Search Strategy (Medline)

- 1.exp Brain Concussion/
- 2.exp Brain Injuries, Traumatic/
- 3.(brain adj4 injur*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 4.(head adj4 injur*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 5.exp Post-Concussion Syndrome/
- 6.Post Concuss* Syndrome.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 7.Postconcuss* Syndrome.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 8.Post-concuss* Syndrome.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 9.Post Concuss* Symptom\$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 10.Postconcuss* Symptom\$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 11.Post-concuss* Symptom\$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 12.exp Magnetoencephalography/
- 13.magnetoencephalogra*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 14.MEG.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 15.1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
- 16.12 or 13 or 14
- 17.15 and 16

Data extracted from each paper

Identification: paper title, reference (DOI), author, year published, country, setting, design, inclusion and exclusion criteria, follow up duration

Baseline participant characteristics: Number of participants by mTBI mechanism, number of controls by type, mean and standard deviation of ages, percentage male, clinical/questionnaire measures used to describe participants and results, time post-injury at recruitment and scanning

MEG scanning: Scanner used, atlas used in analysis, inverse modelling method, artefact elimination method

Outcomes recorded: Resting state spectral and connectivity analysis, analysis of task-based data, machine learning methods, link between MEG data and neuropsychology/clinical measures/questionnaire scores and any statistical tests used

Summary of conclusions

Critical appraisal checklist: Completed relevant SIGN checklist

Highlights:

- Magnetoencephalography appears to have a higher sensitivity than existing clinical imaging techniques to detect abnormalities in mild traumatic brain injury
- Excess resting state low frequency power is consistently detected following mild traumatic brain injury
- There are widespread magnetoencephalography connectivity changes following mild traumatic brain injury
- Machine learning techniques generate high classification accuracy when analysing magnetoencephalography data
- However, currently there is not enough evidence to support routine clinical use of magnetoencephalography in mild traumatic brain injury