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Review

Transcranial Magnetic Stimulation: A Tool for Quantifying Neurophysiological Changes in the Brain Following Concussion Injury in Sports

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Abstract

***Background*:** Sport-related concussion is a growing public health concern. Defined as a injury that disturbs neurological functions, concussion is characterised by a constellation of signs and symptoms. However, clinical imaging methods do not reveal any structural damage. Recently, neurophysiological techniques such as single and paired-pulse transcranial magnetic stimulation (TMS) are being applied to quantify neurophysiological changes (specifically corticospinal and intracortical excitation and intracortical inhibition) following concussion; both from an acute perspective, but also to investigate chronic changes associated with concussion injuries. The aim of this review paper is to present a systematic review and qualitative review on studies using TMS to assess concussion. Specifically, questions addressed refer to the efficacy of single and paired-pulse TMS on quantifying changes in neurophysiology following acute concussion and long-term changes in those with a history of repeated head trauma.

***Methods*:** Systematic searching of relevant databases for peer-reviewed literature between 1985 to present day. A qualitative synthesis of studies attaining the inclusion criteria was conducted.

***Results*:** Twenty-two studies met the inclusion criteria. TMS study checklist rated studies of moderate to high methodological quality, with all but five studies being observational between-group design. Nine studies reported short-term data following concussion, with seven of the nine studies reporting alterations in intracortical inhibition. Thirteen studies reported long-term changes in those with persistent symptoms or chronic changes with history of head trauma. Six of 11 studies presented changes in intracortical inhibition with single pulse. Eleven studies presented paired-pulse data; intracortical facilitation was reported in two studies, while one study reporting short-interval intracotrical facilitation. All but one study reported intracortical inhibition measures, with the majority of these studies showing differences in long-interval intracortical inhibition differences between older individuals with a history of head trauma compared to age-matched controls.

***Conclusions*:** This review demonstrates that TMS is a reliable and sophisticated technique to measure the neurophysiology of concussion. While further studies are required to establish effectiveness TMS as a clinical tool for mild brain injury, the potential of TMS to reliably quantify cortical activity offers exciting opportunities to provide objective measures for concussion diagnosis and prognosis.

Keywords

Concussion; neurophysiology; transcranial magnetic stimulation; motor evoked potential; cortical inhibition

1. Introduction

Induced by biomechanical forces, concussion is a brain injury that is usually caused by a direct blow to the head, face, or neck. Concussion can also result from an impact received elsewhere on the body that transmits the force to the head [1]. Currently defined as a 'functional injury' [2], a concussion reflects a complex pathophysiological process that affects brain function [1, 3] characterized by a rapid onset of neurological signs and symptoms that can include, but is not limited, to the following: dizziness, blurred vision, slow or slurred speech, postural instability, headaches, nausea, irritability, confusion, anxiety or emotional labiality, and/or transient amnesia [1, 4]. However, signs and symptoms differ in the number presented, but also the severity between individuals. Loss of consciousness only occurs in 10-20% of concussion injuries [5]. Concussion is also considered an 'evolving injury' whereby delayed symptom onset, or changes in symptom severity over time, ranging from minutes to hours, is not considered unusual [2]. Other noticeable signs in the following days may be sleep disturbance and fatigue [1, 5].

Data from animal studies have suggested that concussion is the result of a transient electrophysiological interruption of the reticular activating system in the upper midbrain following an impact causing rotational movement of the cerebral hemispheres on the relatively fixed brainstem [4]. As described by Giza and Hovda [3], physiological dysfunction results from an undiscerning release of neurotransmitters creating increased depolarization of neurons. In parallel, unchecked ionic changes alter cellular physiological functioning. Together, with lactic acid generation from increased metabolism, reduced intracellular magnesium, free radical production

and inflammation, these contribute to altered neurotransmission affecting overall brain function [3]. Further, animal studies have demonstrated that cerebral blood flow (CBF) may be reduced to 50% of pre injury levels [6, 7]. While this decrease in CBF does not reach critical levels reported in frank ischemia (85%) [8], it is nevertheless an important factor for consideration given the anaerobic environment neurons are working in. As Giza and Hovda posit, this mismatch in reduced blood supply and increased metabolic demand creates a potentially serious energy predicament [3], affecting brain function and recovery.

Human studies are much more limited in terms of understanding the scope of concussion injury and recovery. As such, clinical diagnoses rely on symptom presentation, and medical clearance for athletes to return to full contact is based upon symptom resolution. Whilst the model proposed by Giza and Hovda [3] illustrate a time-course recovery of neurotransmitter, ionic fluxes and cerebral blood flow returning to baseline levels of up to 10 days, it is generally accepted that the majority of concussions in humans will follow a similar time-course for recovery. However, emerging evidence suggests that symptom and neurophysiology time-course recoveries may actually be disparate [9-11]. Recent studies have also shown that in the short term, a sports concussion injury increases risks of further concussion [12] or greater risk of musculo-skeletal injuries [13, 14]. While causality is not implied, physiological studies are required to determine when an individual's brain functioning returns to pre-concussion functioning, particularly in apparently asymptomatic athletes who are medically cleared to return to play and competition.

At the other end of the spectrum, there is concern regarding the long-term sequelae following a history of repeated concussions and sub-concussive head trauma. Whilst evidence reporting associations and increased risk of brain pathology in boxers dates back to 1928 [15], concern increased following the publication of the seminal 2005 case study by Omalu et al [16] demonstrating that outside of combative sports such as boxing, repetitive brain trauma in collision sports may result in neurodegeneration. Studies into long term risk of multiple concussions and repeated head traumas (also known as sub-concussion) now include chronic neurological impairments such as diminished cognitive ability and/or movement disorders [17]. Neurodegenerative diseases, including Parkinson's disease, amyotrophic lateral sclerosis, dementias including Alzheimer's disease, and chronic traumatic encephalopathy (CTE) have also been reported as a result of repeated head trauma and concussion injuries [18, 19].

Collectively, the increased interest and awareness of concussion in sport, from both the acute and chronic perspectives has generated research from a variety of areas beyond pathological studies. One area that is emerging within this area of research interest is the acute and chronic neurophysiological changes in the brain with concussion. Rationale for measuring neurophysiological responses allows for the understanding of mechanisms but can also potentially assist the clinical assessment via objective biomarkers.

One technique, well established in neurology [20, 21], but only recently recognised as a technique for understanding the effects of concussion is single and paired-pulse transcranial magnetic stimulation (TMS) [2]. While TMS has been utilized in brain injury studies since the late 1990s [22], studies specifically focussing on concussion injuries has only been conducted since 2007 [23, 24]. In a 2015 review, Major et al [23] showed that single pulse TMS was the predominant TMS technique to measure cortical affects in both short and long-term concussion injuries. However the last three to five years have seen an increase in measuring the neurophysiology of not only concussive but also sub-concussive impacts (for example Di Virgillio et

al [25]). Moreover, there has also been an increase in utilizing paired-pulse TMS to understand intracortical neurophysiological changes post injury and the long-term manifestations of multiple concussions. As a result, the most recent consensus statement is now including TMS as an appropriate research tool in understanding the physiology of concussion [2]. The review will initially overview the technique of TMS and key variables quantified by TMS. A systematic review will then present relevant TMS-specific concussion research, with the results and discussion sections providing a qualitative synthesis of TMS concussion studies published to date, and future directions for research and clinical practice. This review differs from previous work [23] by including more recently published paired-pulse TMS studies.

1.1 The Technique of TMS

First developed in 1985 by Barker et al [26, 27], by extending on the initial work of transcranial electrical stimulation (TES) five years prior [28], TMS works by non-invasively stimulating neural and brain tissue to produce an evoked potential response. However, unlike TES that can be painful when applied over the scalp, TMS causes little to no pain [20, 27], providing an opportunity to study the central nervous system.

In the proceeding years, TMS has been used to understand the neurophysiology of the brain involving different protocol techniques, such as interruption of brain activity to study attention [29], intention and cognition [30], and reaction time [31]; brain mapping of muscle representation in highly skilled athletes but also those with injury [32-35]; neuroplasticity of motor training [36-38]; and cortical physiology in healthy individuals, and those suffering various brain disorders [39-41]. While different protocol techniques may be used, the foundation of TMS is to generate an evoked potential. When TMS is placed over the motor cortex, the response is known as the motor evoked potential (MEP).

1.1.1 Quantifying the MEP

Stimulation of the primary motor cortex, above an individual's motor threshold (MT), produces a relatively synchronous muscle twitch known as the MEP. The MEP waveform response (Figure 1) reflects a number of parameters, including latency, evoked potential waveform and the cortical silent period that proceeds the waveform (see Figure 1 for an example). Measured from the time of stimulation to the onset of the MEP waveform, the latency of the MEP is a reproducible measure reflecting corticomotor conduction time [20, 42, 43]. For example, it is well known that conduction time from stimulation to a hand muscle is approximately 20 ms of which Hess et al [44] estimate that approximately just over half the time (~13 ms) is from peripheral mechanisms with the remaining time comprising central conduction, synaptic delay at the motoneuron and conduction down a short intradural segment of the motor root [44]. Latency has been used to quantify progression of neurological and neuromuscular diseases including amyotrophic lateral sclerosis (motor neurone disease), multiple sclerosis and stroke [21, 45].

The MEP waveform (Figure 1) is usually quantified by measuring the peak-to-peak amplitude of the biphasic waveform [46], providing a measure of the fraction of corticomotor neurons activated by TMS [47]. The absolute amplitude of the MEP reflects both upper and lower motor neuron activity and can be altered under experimental conditions, or affected by nervous system disorders or brain injury [21].

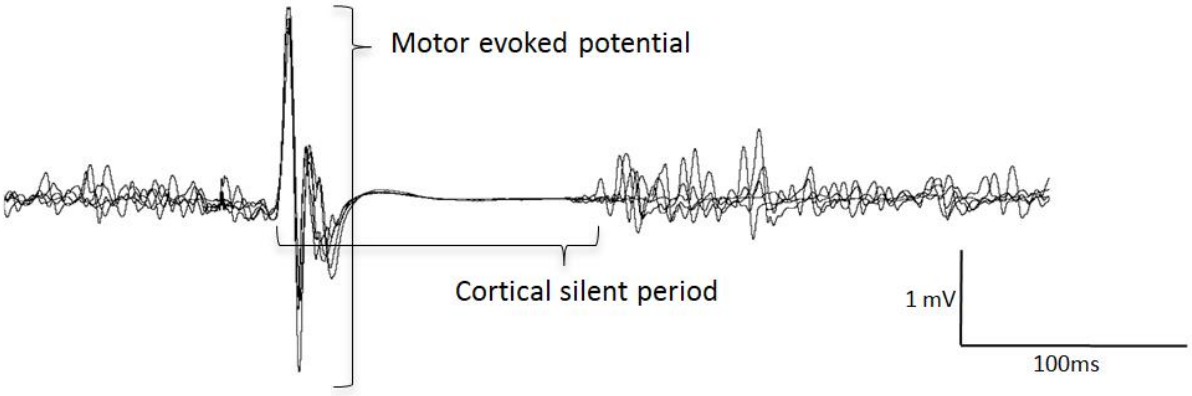

Figure 1 Example of the MEP and cSP during a low-level contraction of the target muscle. To demonstrate reliablity, this is an example of overlayed 10 sweeps, obtained from the first dorsal interosseous (FDI) muscle following TMS over the contralateral motor cortex. (From Author's own collection).

However inter- and intra-individual variability in the MEP is a concern. Studies will aim to reduce this variability by instructing research participants to lightly contract the muscle, which has shown to improve reliability of the MEP [48, 49]. Studies will also normalize the MEP waveform to the compound muscle action potential (CMAP) and present the amplitude as a ratio of the MEP/CMAP. Normalization of the MEP can be undertaken with the MEP taken with the muscle at rest, or alternatively during a sub-maximal tonic contraction.

During a tonic contraction, the waveform response is followed by a characteristic suppression of the EMG signal, known as the 'cortical silent period' (cSP) [39, 50]. First reported with TES by Marsden et al [51] and TMS by Calancie et al [52] the silent period represents inhibitory mechanisms at the spinal, but more so at supraspinal levels. With single pulse TMS the duration of the cSP is thought to reflect mediated inhibitory processes from *γ*-aminobutyric acid receptor b ($GABA_B$) activity [53].

Within the TMS technique MEPs can also be obtained using rapidly applied pairs of stimuli [54]. Known as paired-pulse TMS (Figure 2), this technique provides a greater insight into intracortical circuits. The first of the paired pulses is termed the *conditioning stimulus* (CS), followed by the second pulse termed the *test stimulus* (TS). Dependent upon the intensities of CS and TS, as well as the timing of the interstimulus interval (ISI) between pairs of stimuli, inhibition or facilitation of the TS occurs. For example, when the CS is below the individuals MT to evoke a MEP, and the intensity of the TS is at a suprathreshold intensity for a MEP of ~1 mV amplitude, and the ISI is between 1-5 ms, the CS suppresses the TS and is known as short-interval intracortical inhibition (SICI; Figure 2a) [54]. Conversely, when the paired stimuli ISI is at 10-15 ms, the test MEP is facilitated, and is known as intracortical facilitation (ICF). When two suprathreshold stimuli (~1 mV) are delivered at intervals from 100, 150 or 200 ms, the TS is also inhibited and is termed long-interval intracortical inhibition (LICI). For further general discussion of single and paired-pulse MEPs, the reader is suggested to Hanajima and Ugawa [54].

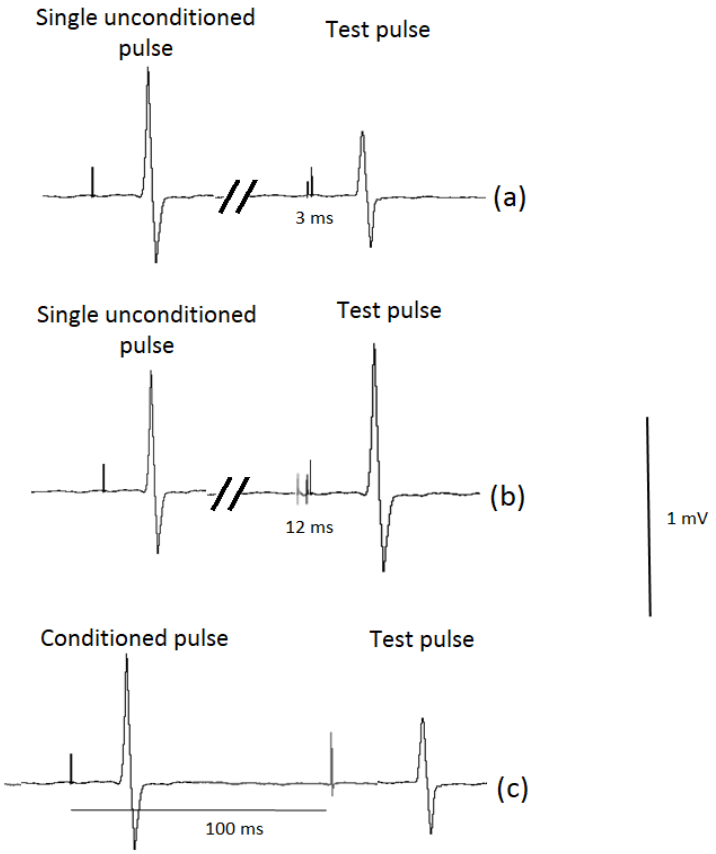

Figure 2 Example of the paired pulse MEPs. (a) Illustration of short interval intracortical inhibition (SICI). A 3 ms paired pulse the inhibited test pulse (right) is quantified as a ratio of the unconditioned pulse (~1 mV) recorded separately (left). (b) Illustration of intracortical facilitation (ICF) where the test pulse (right) is quantified as a ratio of the unconditioned single pulse (~1 mV) recorded separately (left). (c) Illustration of long intracortical inhibition (LICI) where the conditioning pulse followed by the test pulse, spaced between 50-200 ms (100 ms illustrated), are delivered with the ratio of test pulse expressed as a ratio of the conditioning pulse. (From Author's own collection).

2. Materials and Methods

Key questions were identified for the systematic review of the literature specifically addressing the role of TMS in concussion research:

1. Can the technique TMS (single or paired-pulse) quantify the acute and long-term effects of concussion and repeated head trauma?
2. In acute TMS concussion studies
   2.1. What changes occur using single pulse TMS in motor threshold, MEP amplitude and cortical silent period?
   2.2. What changes occur using paired-pulse TMS protocols: SICI, LICI and ICF?
3. In long-term TMS concussion studies
   3.1. What changes occur using single pulse TMS in motor threshold, MEP amplitude and cortical silent period?
   3.2. What changes occur using paired-pulse TMS protocols: SICI, LICI and ICF?

2.1. Search Strategy

The following electronic databases were searched during May 2019: PubMed, SportsDiscus, Cinahl, PsychINFO, Web of Science, Scopus and Google Scholar. Databases were searched for human studies, published in English, dating between 1 January 1985 to the present, using combination and/or variations of the following terms (Table 1) based upon, but modified from, terms previously published by Kamins et al [55].

Table 1 Keywords for search string.

Head injury and relevant sports	**Brain neurophysiology**
('Brain Injuries' [MESH] OR brain injur*[text word] OR concussion*[text word] OR postconcuss*[text word] OR sub-concussion [text word] OR sub-concuss* [text word] or subconcuss* [text word] OR commotio cerebri*[text word] OR post traumatic encephalopath*[text word] OR (post commotion [text word] OR post head injury [text word]) AND syndrome*[text word]) OR brain trauma*[text word] OR TBI [text word] OR MTBI [text word]) AND ('Athletes'[Mesh] OR 'Sports'[Mesh] OR sports[text word] OR sport [text word] OR sporting[text word] OR athleti*[text word] OR athlete*[text word] OR 'recreation'[Mesh] OR recreat*[text word] OR baseball [text word] OR bicycling[text word] OR boxing [text word] OR cycling[text word] OR diving [text word] OR equestrian[text word] OR equine [text word] OR football [text word] OR hockey [text word] OR lacrosse [text word] OR martial arts [text word] OR karate [text word] OR judo [text word] OR tae kwon do [text word] OR aikido [text word] OR OR racquet sports [text word] OR tennis [text word] OR rugby [text word] OR skating [text word] OR skiing [text word] OR snow sports [text word] OR soccer [text word] OR wrestling [text word] OR 'Athletic Injuries' [Mesh]).	'Transcranial magnetic stimulation' (MeSH) OR 'Brain/physiology'(MeSH) OR 'Brain/physiopathology'(MeSH) OR brain physiolog*(text word) OR brain pathophysiol*(text word) OR brain physiopathol*(text word) OR 'Electrophysiology'(Mesh) OR 'Evoked Potentials'(MeSH) OR electrophysiol*(text word) OR Event-related potential*(text word) OR evoked potential*(text word).

Limits: English language, 1985–present, exclude animal only studies.

2.1.1 Criteria for Inclusion

Each database search was limited to peer reviewed, full text publications printed in English between years 1985 to present. Exclusion criteria were applied to each search (1) Non-peer or limited review conference proceedings, (2) Conference abstracts, (3) Books, and (4) Theses (PhD, Masters, Honours). Only studies conducted on humans aged over 18 years were included. Two

studies [56, 57] were excluded because exact TMS data were duplicated [58, 59]. Studies investigating both mTBI and sports concussions were included for review. As repetitive TMS (rTMS) differs in that it is used as a neuromodulation technique for therapeutic interventions,[60] rather than as a prognostic method to assess corticomotor excitability which was the aim of this review, rTMS studies were excluded.

The author screened the titles and abstract of search results, excluding duplicate articles, or articles that did not meet the inclusion criteria. All references of included articles were screened. Full text PDFs of articles were obtained and exported with their citations into Endnote (X8, Thompson Reuters), with no further modification of references.

Figure 3 outlines the process of article selection following application of criteria according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [61]. Although no meta-analyses were completed in this study, it was important to outline the steps completed in this systematic review to determine studies for quantitative analysis.

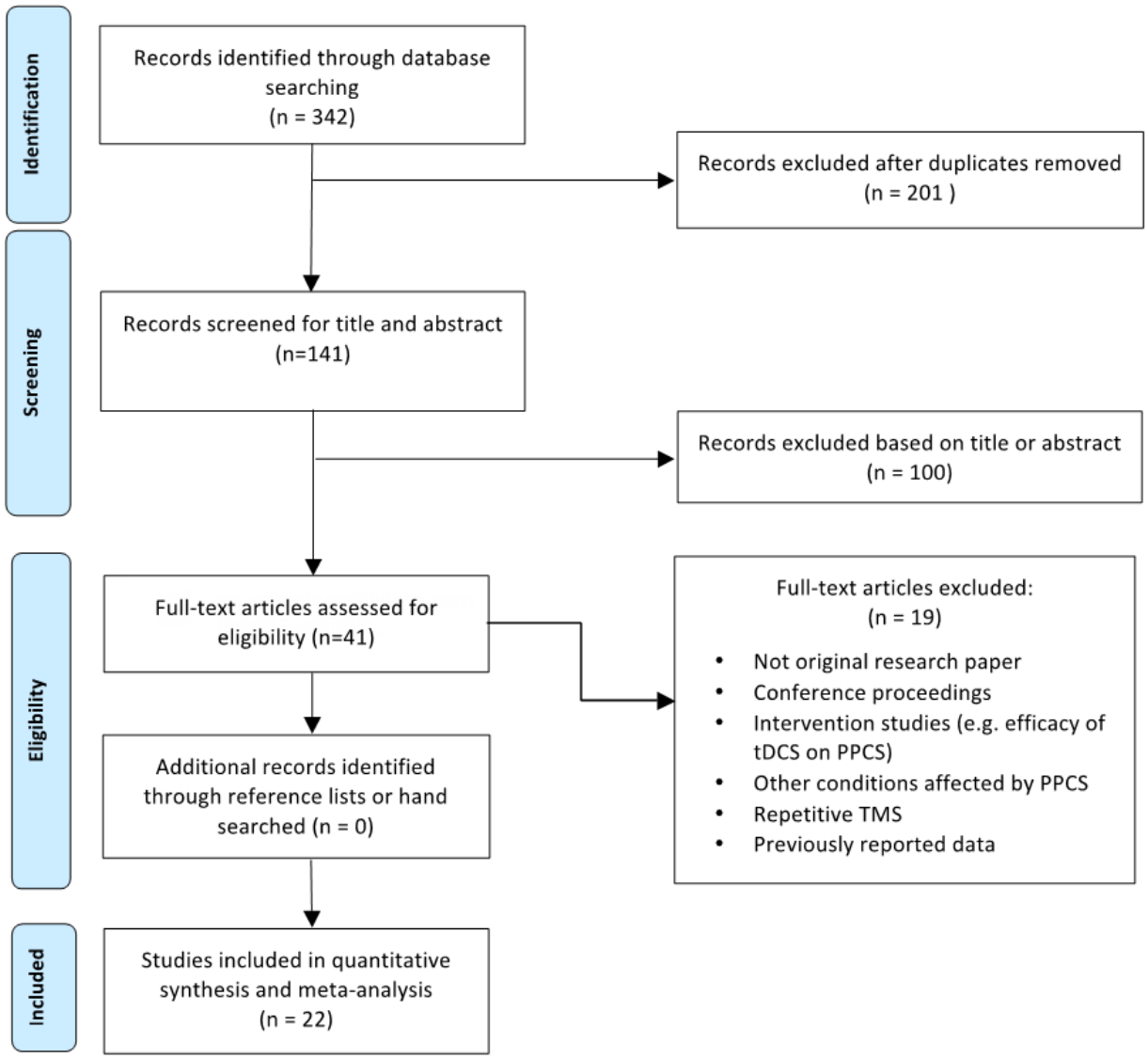

Figure 3 Flow of identification, screening, eligibility and study inclusion of previously published studies using the PRISMA guidelines [61] guidelines.

2.1.2 Allocation of Studies

Studies were categorised into short-term (less than three months) or long-term (greater than three months). Categories were created to differentiate between concussion injury and recovery, as seen in short term studies [11]. Conversely long-term studies sort to understanding the physiology of persistent post-concussion symptoms [62], or the physiology of those with chronic changes years or decades later [63-65].

2.1.3 Data Extraction and Quality Assessment

Results were qualitatively synthesized and descriptively summarized using previously published methods [66]. A checklist was used to assess the TMS methodological quality of studies [67]. Items contained in the checklist addressed specific items in studies across broad areas:

a) Participant factors (age, gender, handedness);
b) Clinical factors (reporting, if applicable, of medical conditions or neurological/psychiatric conditions; or medications participants were currently prescribed;
c) TMS protocol factors (such as position of electromyography electrodes, contraction intensity during stimulation, TMS coil type, location over scalp, orientation of coil, stimulation intensity, time between MEP pulse, and pulse type);
d) Single and paired-pulse MEP measures (such as normalization of MEP amplitude between participants; and for paired-pulse, the intensity of the conditioning and test pulses, and inter-stimulus intervals for SICI, ICF and LICI).

3. Results

Figure 3 illustrates the flow of studies through the systematic review process returning an initial yield of 342 citations. Of these, 201 duplicates were removed. Following title and abstract screening of the remaining 141 studies, 100 were removed as they failed to meet the inclusion criteria (see Section 2.1.1). Examination of 41 full-text articles revealed 22 studies met the inclusion criteria and were retained for review. No further citations were found through hand searching of reference lists, making the final total of included papers of 22.

3.1 Study Characteristics

All studies meeting inclusion criteria are shown in Table 2. TMS study checklist ranged between 15 and 25, making studies of moderate to high methodological quality [67]. All but five studies were between groups with Bashir et al [68] being a case study; and Pearce et al [11], Livingston et al [59], Miller et al [69] and Di Virgillio et al [25] presenting repeated measures designs.

3.2 Transcranial Magnetic Stimulation

3.2.1 Acute TMS Concussion Studies

Nine studies investigated short-term (< three months as defined by DSM-V definition for persistent post concussion symptoms [70]) responses following sub-concussion [25] and concussion injury [11, 22, 59, 68, 69, 71-73]. Six studies presented MT data with five studies

showing no difference between groups or over time [11, 22, 59, 69, 72]. One study showed difference in MT between groups, but not over time [71]. Latency was reported in three studies [11, 59, 69] with only Livingston et al [59] observing increased latency. MEP amplitude showed mixed results with two studies presenting decreased MEP amplitude [22, 59], one study showing increased resting MEP amplitude [71], and two studies showing no change [11, 25].

Seven of nine studies reported cSP inhibition duration. Six of these seven studies observed an increase in cSP duration following concussion and sub-concussion [11, 22, 25, 69, 71, 73]. One study reported a reduction in cSP duration but this was not reported as significant [72]. Paired pulse measures were conducted in three studies [11, 68]. Three studies [11, 68, 72] found no difference in SICI. One study showed absent LICI in their case study at two weeks, returning to baseline, and no different to the control group, by six weeks [68]. Conversely no differences in LICI were observed by Powers et al [72]. Two studies reported ICF. Bashir et al found increased facilitation, compared to baseline and control group, at both two and six weeks [68]. Conversely Powers et al observed greater ICF in the control group compared to the concussed group [72].

3.2.2 Long-Term TMS Concussion Studies

Thirteen studies presented long-term data, with group mean time post concussion ranging from 17 months [74] to 34.7 years [63]. MT data was presented in eight studies [24, 58, 63, 64, 74-77] with only one study reporting significantly increased MT in both symptomatic and asymptomatic concussed groups, compared to control [56]. Three studies reported latency data, with no difference between groups [65, 74, 78]. MEP amplitude presented in eight studies [24, 62-65, 74, 76] showed no differences between groups. ICF (12 and 15 ms ISI) was reported in two studies [24, 63], and one study presented short intracortical facilitation (SICF) at 1.4 and 2.8 ms ISI with no differences reported between groups for ICF or SICF.

Intracortical inhibition was reported in all but one study [56]. Eleven studies presented cSP duration [24, 62-65, 74-80]. Six studies reported significant lengthening of the cSP [24, 62, 63, 77-79], two studies reported significant shortening of the cSP [64, 65], and three studies presented no change or mixed data [74, 75, 80]. Eleven studies included paired-pulse inhibitory measures [24, 62-65, 75-80]. Three of seven studies showed significant difference in SICI ratio between concussed and non-concussed controls [62, 64, 76]. Seven of eight studies showed significant differences in LICI ratio between groups [62, 64, 65, 75, 77-79].

Table 2a Descriptive data and TMS study score [68] of studies included in qualitative review.

Reference	TMS score	Group(s)	Population			Recruitment population	Additional assessment (s).
			M	F	Age (yrs)		
Bashir et al. [68]	15	Concussion Control	1 2	5	44 44 ± 14	Case study X	ImPACT, CANTAB, MRI and DTI
Christyakov et al. [22]	23	mTBI Control	9 15	5	33.2 ± 13.2	Hospital	None
Davidson et al. [74]	21	Concussion Control	12 12	4 4	24.3 ± 3.1 24.4 ± 4.8	Sports organizations	ImPACT, Groove pegboard, Multi-Operational Apparatus for Reaction Time (MOART) system
De Beaumont et al. [24]	21	Multiple concussions Single concussion Control	15 15 15		23.4 ± 2.6 22.9 ± 2.8 22.5 ± 2.5	University	NFL neuropsychological testing
De Beaumont et al. [79]	17	Concussion Control	21 15		22.3 ± 3.4	University	Centre of pressure oscillation Centre of pressure displacement Rapid Alternating Movement (RAM) Task
De Beaumont et al. [64]	17	Concussion Control	19 21		60.8 ± 5.2 58.9 ± 9.1	Former University	Mini-mental score RAM Task; Flanker Task
De Beaumont et al. [77]	18	Concussion Control	13 19		23.4 ± 3.1	University	Motor learning task BDNF polymorphism profile
Di Virgilio et al. [26]	21	Athlete	14	5	22 ± 3	Amateur football (soccer)	Cognitive testing battery
Edwards et al. [71]	15	Concussion Control	4 7	5 7	20.8 ± 2.3 20.9 ± 0.9	General	Spelling five-letter words inreverse order Reverse order counting between 70 and 100 by 6s or 7s Months of the year in reverse order
Lewis et al. [75]	23	Concussion – Elite Concussion – Amateur Control	23 28 22		43 ± 7 45 ± 8 44 ±9	Sporting (Rugby, Hockey, Cricket)	Rivermead post concussion questionnaire General health assessment

Livingston et al. [57]	17	Concussion Control	6 6	6 3	20.4 ± 1.3 20 ± 0.9	University	Internet based neurocognitive Concussion resolution index
Meehan et al. [76]	25	Concussion Control	12 8	4 7	20 ± 2.3 21 ± 2.5	University	Motor response tasks
Miller et al. [69]	22	mTBI Control	8 8	7 7	20.8 ± 1.2 21.1 ± 1.3	General	None
Pearce et al. [11]	24	Concussion – Elite Concussion – Amateur Controls	20 20 20		49.7 ± 5.7 48.8 ± 6.9 47.6 ± 6.8	Former recreational & professional football	Fine Dexterity & associated learning Visuomotor reaction time Spatial working memory
Pearce et al. [65]	24	Concussion Control	8 15		25.1± 4.5	Australian football	Fine motor dexterity, reaction time, implicit learning, attention
Pearce et al. [66]	24	Concussion – Elite Control	25 25		48.4 ± 6.9 48.8 ± 7.0	Rugby League	Fine Dexterity & associated learning Visuomotor reaction time Spatial working memory
Pearce et al. [63]	24	Persistent symptoms Recovered Control	15 16 16	5 4 4	36.2 ± 14.0 33.8 ± 6.6 37.7 ± 8.0	General public	Reaction time Visual working memory N-back task Neurosensory vibration
Powers et al. [72]	22	mTBI Control	8 8		20.2 ± 1.2 20.3 ± 1.5	University	Voluntary muscle activation and sensation of force
Tallus et al. [59]	21	mTBI – Symptomatic mTBI – Asymptomatic Controls	64 4 6	7 4 3	43.7 ± 11.6 35.9 ± 15.9 33.6 ± 13.2	X	Magnetic resonance imaging/EEG
Tremblay et al. [78]	23	mTBI Control	12 14		22.4 ± 4.4 23.2 ± 5.9	University	Somatosensory evoked potential/EEG
Tremblay et al. [80]	24	mTBI Control	16 14		22 ± 1.1 22 ± 1	University	Proton magnetic resonance spectroscopy
Yasen et al. [73]	23	mTBI Control	10 10	10 10	21.2 ± 4.4 21.4 ± 4.6	General public	Reaction time, Gait walking speed

Table 2b Concussion data from studies included in qualitative review.

Reference	Time since last concussion	Concussion assessment used	No. of concussions
Bashir et al. [68]	6 weeks n/a	X	4 0
Christyakov et al. [22]	2 weeks X	GCS	1 X
Davidson et al. [74]	17 months n/a	X	2 0
De Beaumont et al. [24]	31 ± 22.1 months 59.1 ± 69.5 months n/a	GCS	2+ 1 0
De Beaumont et al. [79]	19 ± 13.7 months n/a	X	2.6 ± 1.4 0
De Beaumont et al. [64]	30+ Years n/a	GCS & AAN	1 – 5 0
De Beaumont et al. [77]	34.7 ± 6.2 months n/a	Self-report n/a	2.8 ± 1.4 0
Di Virgilio et al. [26]	n/a	n/a	n/a
Edwards et al. [71]	Within 72 hours n/a	SCAT3 n/a	X
Lewis et al. [75]	Minimum 5 years n/a	Self-report n/a	n = 20; >3 n = 23; >3 n = 1; >3
Livingston et al. [57]	< 24 Hours X	Head injury scale	1 n/a
Meehan et al. [76]	4 ± 3 years n/a	Self-report SCAT 3	2 ± 1.2 n/a
Miller et al. [69]	72 hours X	SCAT 3	1 n/a
Pearce et al. [11]	20 + years 20 + years n/a	Self-report	n/a
Pearce et al. [65]	< 24 Hours n/a	X	1 n/a
Pearce et al. [66]	20 + years n/a	Self-report	8.5 n/a
Pearce et al. [63]	15.6 ± 7.6 months 12.5 ± 6.6 months n/a	Self-report Fatigue symptoms	4.0 ± 3.0 4.8 ± 2.6 n/a
Powers et al. [72]	6 – 34 Days X	SCAT 2	1 n/a
Tallus et al. [59]	6.1 ± 5.4 years 3.8 ± 1.1 years n/a 3.8 ± 0.4 years n/a	GCS	1 1 n/a 1 n/a
Tremblay et al. [78]	n/a	AAN & GCS	3.2 ± 1; n/a
Tremblay et al. [80]	3.1 ± 2.1 years X	AAN & GCS	1.9 ± 0.9 n/a
Yasen et al. [73]	72 hours – 8 weeks; n/a	SCAT 3	n/a

4. Discussion

The aim of this review, presenting TMS as a technique to measure the neurophysiological effects of concussion injury, was two-fold: 1) to quantify cortical excitability and inhibition, via single and paired-pulse TMS measures, following a concussion injury; and 2) to evaluate changes in neurophysiological function in those with persistent and chronic manifestations of repeated head trauma using single and paired-pulse TMS. Extending on a previous systematic review in 2015 [23] the main finding from studies published since that paper showed that paired-pulse intracortical inhibition (cSP, SICI and LICI) was most affected variable following concussion in the short and long term. While further research is required to build on the emerging evidence, the data to date suggests that TMS is an appropriate technique to assess concussion injury. Indeed, the latest consensus statement includes TMS as physiological measurement technique [2].

4.1 Single Pulse TMS

While some single pulse studies showed alterations in motor threshold, central motor conduction time, and MEPs, the consistent finding from the majority of investigations showed that cortical inhibition (cSP) is altered post concussion. This suggests that the $GABA_B$ pathways reflect neurological disturbances observed with the injury. It has been suggested that transient increased inhibition (24 hours to 10 days) following head impacts may reflect protective mechanisms against minor injury [11, 25]. However, while respite from contact activities allows for the return of increased inhibition to baseline levels, illustrating the dynamic nature of the corticomotor pathway, a concern is that repeated head trauma may lead towards maladaptive changes longer term reflecting neurological impairment [25]. For example, De Beaumont and colleagues observed increased inhibition, associated with motor and cognitive deficits, in apparently asymptomatic athletes with a history of repeated concussion injuries [24, 79, 81]. Similarly Pearce et al [62] recently presented data showing increased cortical inhibition that was associated with chronic post-concussion fatigue. Long term studies have also shown altered inhibition in retired athletes with a history of multiple concussions [63-65], suggesting a link between functional deficits and possible pathophysiology of cortical inhibitory interneurons [25].

4.2 Paired Pulse TMS

The majority of concussion studies using paired-pulse measures have focussed on SICI and LICI. Interestingly, LICI demonstrated between changes more so than SICI, which showed mixed results. This does not indicate that LICI is a more sensitive measure for concussion, but rather, from the studies in this review, it may be that concussion affects $GABA_B$ pathways, reflected in LICI but also cSP from single pulse TMS, rather than $GABA_A$ pathways as measured by SICI. Further studies are required to explore if this is indeed the case and why certain inhibitory pathways are affected, as well as studies incorporating ICF protocols to investigate if excitability pathways are similarly affected.

4.3 TMS in Context of Concussion Studies

Similar to other areas of neurology, this review has shown that TMS is an effective technique for quantifying the acute and chronic effects of concussion and repeated head trauma. With the

majority of studies finding intracortical inhibitory pathways affected, but also alterations in motor threshold and conduction time, pathophysiology in the brain following concussion is suggested. However, as posited by Kobyashi and Pascual-Leone [21] TMS results need to be interpreted in context of other clinical data. The studies in this review demonstrated that concussed individuals cognitive and motor function was compromised suggesting that alterations (mainly) in intracortical inhibition may explain the mechanism for clinical outcomes found. The TMS data may also be reflecting pathology. Recently two TMS studies reported alterations in intracortical circuits correlating with cognitive impairments in early stage Alzheimer's [82, 83] suggesting synaptic impairments, identified by paired pulse TMS could be used to track progression such as Alzheimer's. However, further TMS studies are required to test diagnostic and prognostic efficacy, particularly for concussion related pathologies such as CTE.

5. Conclusions

Developed nearly 35 years ago, TMS has developed into a reliable and sophisticated technique in neuroscience research. While TMS studies into concussion are emerging, the data to date illustrates that it is a technique that can not only identifies physiological changes following a concussion, but also a tool that can be used for early detection of motor and cognitive impairments in those with a history of concussions and head trauma. However, further studies are required to establish the clinical indication for a systematic application of TMS as a diagnostic tool for mild brain injury. Nonetheless, the potential of TMS to reliably quantify cortical activity offers important opportunities to provide a low-cost, objective biomarker to value-add to existing clinical assessments of concussion.

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Competing Interests

The author has declared that no competing interests exist.

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