MILD TRAUMATIC BRAIN INJURY(mTBI)

TOPIC REPORT

An Updated Review

Independent Medical Expert Group

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Contents

Key Points

1. This Report follows and updates the extensive review of traumatic brain injury (TBI) published in IMEG's Fourth Report in December 2017. In that report we paid particular attention to mild TBI (mTBI). Since then, there have been advances in research in the field of functional neuroimaging with magnetoencephalography (MEG), and in several other areas of clinical science relevant to mTBI. We review these advances in this Report, with special emphasis on MEG.

2. IMEG was tasked by Min (DPV) in June 2019 to review mTBI, with particular reference to the clinical utility of MEG. This coincided with a request from the Surgeon General for a report on MEG. An Interim Report was submitted on behalf of IMEG in September 2019 and subsequently approved by IMEG. This was circulated in military medical circles and presented as one of the papers considered at an international meeting convened by the Surgeon General in January 2020 at Imperial College London (ICL), chaired by Professor Anthony Bull, Director of the Centre for Blast Injury Studies at ICL. In the interests of clarity and transparency, both the IMEG Interim Report and the Consensus Statement arising from the ICL meeting are annexed to this Report.

3. The purpose of this Report is to review the research advances and interpret them in the context of mTBI in the military. mTBI and post-traumatic stress disorder (PTSD) are frequently comorbid conditions. This Report re-examines the relationship between the two conditions in the light of MEG research.

4. There are currently 12 MEG scanners in the UK, all based in research facilities. Each scanner costs in the region of £2m, with high annual maintenance costs. MEG scan results need to be co-registered with high-field magnetic resonance scans (MRI). Thus, the total investigation costs are considerable. MEG scanning is not routinely available in the NHS.

5. The currently established clinical applications of MEG are in the pre-surgical assessment of highly selected patients with epilepsy, and in determining cerebral dominance prior to neurosurgery in some patients with cerebral tumours.

6. The published scientific literature on MEG reveals a lack of agreement about optimal methods of analysis of the data acquired by the MEG scanners, and limited agreement concerning research investigation protocols. The Consensus statement from the ICL meeting referred to above includes a call for greater collaboration between the MEG research groups in the UK which are active in mTBI research, and IMEG supports this.

7. We conclude that MEG research has not yet reached sufficient sensitivity and specificity for

application to mTBI or PTSD in routine clinical practice. MEG remains a research investigation which should be offered only in the context of research ethics committee-approved studies. This is in line with the Consensus Statement from the ICL meeting.

8. The evidence that TBI can cause not only direct cerebral damage in the short term but is also associated with longer term increased rates of neurodegenerative disease, notably Alzheimer's and Parkinson's diseases, is now substantial, especially for moderate and severe TBI, but much further research is needed to establish the risk with mTBI and to understand the evolving neuropathology, mechanisms and symptoms and signs developing over time. Cognitive symptoms, including problems in attention and executive function, are common after mTBI and are usually transient. However, in some individuals, cognitive problems first present long after the index injury. Recent advances in neuroimaging and neuropathology are shedding light on possible mechanisms, including the occurrence and clinical effects of diffuse axonal injury and subsequent chemical changes in the brain.

9. Chronic traumatic encephalopathy (CTE), due to repeated concussive and sub-concussive blows to the head, may take many years to develop and although this diagnosis may be suspected in life, is reliably diagnosed only with post-mortem examination of the brain.

10. Given that TBI, and particularly mTBI, is very common worldwide, trauma to the head may prove to be an important contributory factor in the causation of a proportion of all dementias. Current evidence does not permit definite conclusions to be reached concerning the magnitude of this in relation to mTBI. Emerging neuroimaging techniques and discovery of other biomarkers including brain atrophy rates, and neurofilament light protein levels in cerebrospinal fluid (CSF) and blood, seem promising for assisting in differentiating the underlying neurobiology of psychiatric and neurological conditions, understanding mechanisms and the pathogenesis of neurodegeneration, and in time, having a role in evaluating treatments to slow or prevent progression.

11. We emphasise that both mTBI and PTSD remain defined in the UK and internationally solely on the basis of clinical criteria. There may be strong clinical indications for neuroimaging with CT or MRI scans in the management of selected patients with mTBI, but imaging is not currently a requirement for making the diagnosis.

12. In relation to compensation under AFCS, no affected individual should feel disadvantaged by not having had a head scan. The diagnosis of mTBI can be confidently made on clinical grounds in the great majority of individuals, with an assessment for compensation being made accordingly. However, it should be noted that traumatic vestibular syndromes may result in identical presentations to mTBI and will be overlooked without appropriate objective vestibular investigation.

13. IMEG has reviewed the current Descriptors and Tariffs for mTBI and finds no indication to change these now.

14. It is important to reiterate here that the level of AFCS compensation is based on the severity of loss of functional capacity, particularly for future civilian employment, resulting from attributable physical injury or other disease, irrespective of specific diagnosis.

15. IMEG will continue to monitor research developments in mTBI and related areas, recognising the important contribution MEG is likely to make, not only in understanding the nature and mechanisms of mTBI and PTSD, but also in a wide range of other neurological and psychiatric conditions.

16. IMEG's examination of MEG and mTBI presented here builds on the Interim Report (Annex 1). A Summary and Key Points of this current report were presented to Min (DPV) and the Central Advisory Committee (CAC) on Compensation in January 2021. The full Report, now approved by IMEG in February 2021, is to be made available publicly in electronic format. With appropriate updating and revision, the report will be included in IMEG's Sixth Report, due to be published early in 2022.

17. Although this report pays particular attention to the place of advances in neuroimaging in the assessment of mTBI, an understanding of related recent scientific evidence is essential, to set this in a comprehensible broader clinical context. The report therefore re-examines a wide range of clinical, investigative , neuroimaging and pathological aspects related to both acute and possible long-term sequelae of mTBI. This field of scientific study is evolving rapidly and is complex. This complexity is reflected in the text of the report, and IMEG recognises that until the full clinical implications of new evidence become clear, some of the content of this report is inevitably challenging for a non-medical readership. Wherever possible, we have attempted to provide explanations that are accessible to a wide readership.

Introduction

18. Traumatic Brain Injury (TBI) is a common problem in both military and civilian populations worldwide. In the UK there are approximately 1.3 million attendances at accident and emergency departments annually (1). Severe TBI accounts for 3% of all TBI, moderate for 22% and mild TBI (mTBI) for 75%. Severe TBI is a leading cause of death in young adults. mTBI is not fatal, and although overall recovery is good, a minority of those affected experience persistent symptoms and functional disability (2). Head injury of all severities, and in similar proportions, is an issue in the UK armed forces. The previous IMEG reports focused on mTBI, with the most recent comprehensive 2017 report recording many gaps in our understanding of mTBI (3). Attention was drawn to variations in definitions, classification and nomenclature of severity within the clinical range currently embraced by the diagnosis of mTBI. Current definitions agree that the diagnosis is made entirely on the basis of

history and clinical features, which distinguish mTBI from moderate and severe TBI, in which standard imaging tests are usually abnormal. However, clinical examination will not identify the presence of a primary vestibular disorder, as distinct from mTBI. Conventional brain imaging with CT scanning is normal in mTBI, though may be helpful in identifying unsuspected cerebral abnormalities, such as small intracerebral haemorrhages, indicating more severe forms of injury. However, as discussed in the 2017 Report, research studies with advanced non-routine methods of MRI scanning can sometimes demonstrate subtle changes in mTBI. Furthermore, a new type of functional brain imaging, magnetoencephalography (MEG) frequently demonstrates abnormalities in subjects with mTBI. MEG has attracted a great deal of interest in the last few years in the investigation of brain function resulting from trauma, and from a wide range of other neurological and psychiatric conditions, including PTSD. It is particularly the recent developments in MEG that have prompted the current review of mTBI. Other issues considered in the extensive 2017 IMEG Report included epidemiological aspects, pathophysiology, the relationship of mTBI and concussion, investigation and management, the distinction between, and overlap of, primary traumatic labyrinthine pathology and, audio-vestibular features of mTBI, mental health and TBI, and the comorbidity of mTBI and PTSD. It is worth emphasising here that patients with mTBI frequently experience a wide range of symptoms, including physical, audio-vestibular, cognitive, emotional and behavioural, occurring in different proportions, with all these symptoms contributing to overall morbidity following mTBI. Many persistent symptoms are not specific to mTBI but may also occur following traumatic injury to other body structures, in relation to mental health disorders, such as PTSD and depressive disorder, and indeed, in otherwise apparently healthy individuals (4)(5)(6). Trauma to the inner ear, resulting in labyrinthine concussion, decompensation from an earlier vestibular disturbance, post-traumatic vestibular migraine presenting with vestibular, auditory, or neurological symptoms (including headache, visual blurring or double vision), psychological symptoms (anxiety, panic attacks and depression), or cognitive symptoms, and in the absence of any brain injury and normal brain imaging, may exactly mimic the symptoms of mTBI. Specialist vestibular assessment should be routine in such circumstance.

19. mTBI and mental health disorders may co-exist, with overlap of symptoms and difficulty in clinical differentiation. We recommend reading the 2017 IMEG Report, which discusses these issues in depth, alongside the present Report. The present Report again examines mTBI and related psychiatric morbidity, notably post-traumatic stress disorder (PTSD).

20. Since the 2017 IMEG report, in addition to developments in neuroimaging, there have been research advances in mTBI in the fields of genomics, computational biology, neuropathology, and serum biomarkers, with many publications in the mainstream peer-reviewed scientific literature. In time they promise improved disease characterisation, understanding of mechanisms and the relation between mTBI and later development of neurodegenerative disorders, and will hopefully also inform best practice treatments.

21. This review will consider key recent research on mTBI including diagnosis, early predictors of persistent post-concussion symptoms, prognosis and long-term risk of neurodegenerative disorders, biomarkers, differentiation of mTBI from comorbid mental health disorders, and mTBI treatment evaluation and current best practice. An objective specific biomarker for mTBI would be helpful and the role of functional neuroimaging, particularly magnetoencephalography (MEG) will be discussed. The Interim IMEG Report from September 2019 is at Annex 1 (7).

mTBI in Military Populations

22. Five years from the end of the conflict in Afghanistan it is appropriate to summarise mTBI findings so far. In the same theatres and at the same dates, the reported rates of mTBI in US and UK military personnel in Iraq and Afghanistan were markedly different. Studies of clinician-confirmed injury in deployed US military personnel found that about 23% sustained mTBI, with higher rates amongst combat personnel, and substantially higher rates (59%) in those with combat injury (8) (9)(10). For UK troops on return from deployment, equivalent prevalence rates were 4.4% among those deployed, with 9.5% in combat personnel. Pre-deployment alcohol misuse and PTSD symptoms were associated with subsequent mTBI in UK servicemen (11).The difference between US and UK data may be either a real effect, resulting from longer deployment, for example, or be artefactual, due to either different mTBI definition or different approaches to screening. In a later UK study that was conducted in theatre in the fifth month of a six-month deployment in Afghanistan, looking at self-reported undocumented mTBI in 1363 deployed personnel (96% response rate), 6% reported one or more potential mTBI exposures ('…any injuries as a consequence of the following: fragmentation, round (bullet), fall, blast, direct head injury and motor vehicle accident') during the deployment, and 1.6% reported injury followed by one or more mTBI symptoms (2). Only six individuals reported loss of consciousness, all for less than five minutes. Higher PTSD symptom scores were significantly associated with reporting blast exposures and symptomatic mTBI. Data collected during deployment for this study revealed a substantially lower incidence of mTBI than that recalled post deployment. Similar inflation is seen in history taking of remote events in US studies (12).

23. The most recent UK study of mTBI and post-concussion symptoms (PCS) was longitudinal, conducted by asking Iraq and Afghanistan veterans whether mTBI reported in 2007-2009 was associated with PCS 7 or eight years later (13). The symptoms were headache, dizziness, fatigue, sleeping difficulties, irritability, double or blurred vision, forgetfulness, ringing in the ears and loss of concentration. The study was by questionnaire, with about half those surveyed responding (2,318 out of 4,601). Females, higher rank and education, reserve service, being older and serving in the RAF were linked with completing the follow-up questionnaire. Those who at baseline in 2007-9 met the criteria for mTBI or had alcohol misuse problems were less likely to respond in 2014-16, while those who reported PCS in 2007-9 were more likely to respond at follow-up. When adjusted for baseline social, military and demographic factors, in those responding at follow-up, there was no longer an

association of likelihood of response with baseline alcohol misuse, reporting one or two post-concussion symptoms, or mTBI. Of the symptoms followed up, continuing dizziness and loss of concentration were again reported more frequently seven to nine years later in those originally reporting mTBI, compared with the two control groups, "no injury“ and “other injury” individuals. This was regardless of adjustments, including for social and demographic factors, PTSD and further mTBI occurring between 2009 and 2014. With adjustment, the risk of long-term loss of concentration became borderline significant (prevalence ratio 1.29; 95% CI 0.98-1.71). The study also found that in 2014-16, in the fully adjusted models in both the mTBI and control groups, the prevalence of seven of the nine post-concussion symptoms, but not headache or irritability, increased over time, suggesting they were not directly related to the original mTBI. There were some limitations to the study. The response rate was only 50%, absolute numbers reporting the various symptoms were small and the effect of some unknown confounders may have been overlooked. The symptoms of the index mTBI event in these studies were not exclusively due to blast or bullet injury, but included fragmentation injury, falls, motor vehicle accidents and some events described only as "other exposures”.

Early Predictors of Persistent Post-Concussion Symptoms

24. Prognosis in mTBI and predictors of long-term disabling symptoms were considered in the 2017 IMEG report, when it was concluded that findings across different studies were inconsistent, mainly owing to different definitions of mTBI, variations in patient age groups and comorbidities, the presence of other traumatic injuries from the incident and in some studies, inclusion of different levels of TBI severity without clinical stratification. Other differences included variations in treatment interventions and study outcomes, and assessment at different intervals from the index injury. Since the UPFRONT prognosis study (14) , discussed in the 2017 IMEG Report, the focus has been on development of prognostic models where patient characteristics are combined in a mathematical formula and can be used to provide information on expected outcome in individual patients, adjust for differences in case-mix in studies, and standardise outcome measures and rates to improve design of clinical trials and benchmark care quality (15). Although not yet routinely used clinically, robust models have been developed for moderate and severe TBI but are not yet available for mTBI (16) (17) (18) (19).

Biomarkers

25. Biomarkers are biological markers that can be objectively measured and evaluated and serve as specific indicators of normal or pathological processes or responses to therapeutic interventions. Specific biomarkers will aid understanding of prediction of disease onset, causation, diagnosis, progression, prognosis, and outcome of disease treatment. Potentially relevant to our understanding of neurological damage caused by mTBI, are measurements of certain blood or cerebrospinal fluid (CSF) constituents, and the emerging imaging techniques which provide insights into both structural alterations and brain function.

Neuroimaging

Magnetic Resonance Diffusion Tensor Imaging in mTBI

26. The role of conventional imaging with CT and MRI scanning in the investigation of individuals with mTBI was discussed in the 2017 IMEG Report, and reference was also made to research concerning newer neuroimaging techniques not yet widely available in routine clinical practice. These included more sophisticated approaches to magnetic resonance imaging (MRI) and specifically diffusion tensor imaging (DTI), and MEG.

27. The molecular pathology of mTBI was also considered in the 2017 IMEG Report. Molecular changes are recognised to occur in the absence of cellular pathology. These changes include abnormalities in chemical neurotransmission, ionic changes, increased energy demands, and changes in cellular metabolism, and excitotoxicity, which are all acute and potentially reversible changes, which possibly explain transient cognitive and mood changes in the majority of individuals with mTBI who make a rapid and complete recovery; see Iverson for a full review (20).

28. Research has demonstrated that mTBI causes axonal (nerve fibre) stretching, inflammatory changes, disruption and separation of nerve fibres, together comprising diffuse axonal injury (DAI), although complete severance of nerve fibres (axotomy) is apparently unusual (21). Damage which is less severe than axotomy may prevent electrical nerve impulse transmission (conduction block), leading to functional disconnection, often referred to in this context as deafferentation. This is potentially reversible.

29. Standard MRI scanning in mTBI is usually normal. Magnetic resonance DTI quantifies the diffusion characteristics of water, which are altered by changes in tissue microstructure, acting as a sensitive marker of white matter damage. MR DTI findings in a series of 63 military personnel with a clinical diagnosis of mTBI have been reported from the USA (22). All had suffered primary blast exposure, but also another, non-blast-related mechanism of injury including a fall, motor vehicle crash or other blunt head injury. They were compared with 21 military personnel who had experienced blast exposure and other injuries, but who did not have a clinical diagnosis of mTBI. All were scanned within 90 days of the mTBI event. As a group, compared to the controls, 18 of 63 (29%) with blast-related mTBI showed marked changes in several brain sites, a significantly greater number of abnormalities than expected by chance ($p<0.001$). Re-scanning in 47 subjects with mTBI, 6-12 months later, revealed persistent abnormalities, judged to be consistent with evolving injuries. However, many of the mTBI subjects did not have abnormalities on DTI, questioning the sensitivity of DTI in mTBI. This led the authors to conclude that mTBI remains a clinical diagnosis, not dependent

on the results of brain imaging. They further concluded that the observed DTI abnormalities were evidence of axonal injury. However, because all those with blast injury had also suffered additional blunt head injury, the authors cautioned against assuming that the blast injury event was responsible for all the abnormalities shown on DTI. Finally, attention was drawn to the high rate of post-traumatic stress disorder (PTSD) in those with blast-related mTBI (further discussed in the 2011 systematic review of Carlson et al (8).

30. Standard brain imaging, including CT and MRI scanning using routine signal analysis, does not detect the subtle changes that may occur in mTBI. However, MR DTI demonstrates white matter damage, as discussed above, due to diffusion characteristics of water indicative of axonal damage, in between 29 and 70% of patients (22, 23). This evidence was discussed in the 2017 IMEG Report. The fact that, although more sensitive than positron emission tomography (PET) and standard MRI, changes are found in 29-70% of those with mTBI (22, 23, 24) indicates that DTI sensitivity is insufficient to regard it as a gold standard diagnostic test in mTBI. The degree of white matter damage in mTBI demonstrated by DTI is associated with the severity of cognitive impairment (25)(26)(27)(28). DTI has thus proved to be a valuable research tool in mTBI, providing insights into the structural damage and neurological consequences. In addition, another means of magnetic signal analysis, Susceptibility Weighted Imaging (SWI), has a role in identifying the presence of very small haemorrhages (microbleeds).

31. A systematic review of DTI findings in 86 adult civilian, military and sport-related mTBI studies took account of mTBI category, (based on time interval between injury and assessment, acute, subacute, chronic, remote and repetitive), socioeconomic factors and psychiatric disorders known to affect changes in brain structure, as well as injury mechanism (29). It was anticipated that the stratified mTBI study groups might provide different white matter diffusivity metrics, but the variations recorded were inconsistent. Since the effects of mTBI can be modified by comorbid medical and socioeconomic factors, studies were also reviewed which considered socioeconomic status (SES), major depressive disorder (MDD) and attention deficit hyperactivity disorder (ADHD). The authors concluded that DTI is sensitive to a wide range of mTBI group differences in diffusion metrics and in patients affected by MDD, ADHD and socioeconomic factors, and was therefore not specific enough for routine clinical use (29). Difficulties in data comparisons include control group variability and different analytic and reporting techniques. To be useful clinically, studies must include appropriate controls, be longitudinal in design and use standard functional outcomes. Additional MRI research studies are cited in Annex 1, paragraph 5.

Positron Emission Tomography

32. Positron emission tomography (PET) is used to study proteinopathies (disorders resulting from accumulation of abnormal proteins) including neurodegenerative disorders, by detecting markers such

as tau protein in neurofibrillary tangles, and beta amyloid aggregates (30). Short half-life radioactive tracers are injected intravenously, and the gamma radiation emitted is detected by gamma camera arrays arranged to produce a three dimensional image. PET is providing insights into the mechanisms of TBI, such as inflammation and metabolic disturbances, and changes relating to neurodegeneration (31), and the function of cellular organelles such as mitochondria and activated microglial cells (32). These remain research investigations, and PET does not currently have an established role in routine assessment of these disorders.

MEG: Basic Considerations

33. Magnetoencephalography (MEG) is a brain imaging method for recording magnetic fields produced by electrical activity in the brain, using sensitive magnetometers. Its records brain function with high temporal and spatial resolution. The results of MEG always need to be co-registered with detailed images obtained by MRI to produce a detailed 'map' of the different regions of the brain active both at rest and in the performance of cognitive tasks. The recording of the very small magnetic fields generated by electrical activity in the outermost part of the brain, the cerebral cortex, presents major technological problems. Environmental magnetic fields, including the earth's magnetic field, need to be excluded, by making recordings in a magnetically shielded room. The cost of a MEG scanner is currently in the region of £2m. There are currently 12 MEG scanners in the UK, though it is likely that more will be established in the next few years.

34. The physics of recording and the accurate localisation of magnetic fields generated from the cerebral cortex is complex (33)(34). MEG does not record magnetic fields from deeper structures in the brain, but, as with electroencephalography (EEG), such abnormalities may be reflected in the recorded cortical magnetic fields. In addition, removal of confounding magnetic signals from blinking, eye and facial movements, and from the heart is an important issue (35).

35. The unique properties of MEG, with its high spatial and temporal resolution, explain why it is proving to be a useful research tool in neurological and psychiatric disease, in combination with existing functional imaging techniques including functional MRI (fMRI) and single photon emission computed tomography (SPECT). MEG has a sub-millisecond temporal resolution and is far superior in this respect to fMRI which is dependent upon changes in blood flow and has a temporal resolution of hundreds of milliseconds; and to SPECT which has a temporal resolution of minutes. EEG also has a high temporal resolution, but the advantage of MEG over EEG is that magnetic fields are not distorted by the skull and scalp in the way that EEG electrical signals are. This results in a spatial resolution of millimetres for MEG, in contrast to centimetres for EEG (36). Thus, MEG can provide sensitive real-time information about the functioning of the brain.

36. The analysis of MEG data presents another major technological challenge, evident from the range and complexity of the methods described in the research literature (37)(38)(39). The variety of analytical methods used in different published studies to date indicates the need to adopt a cautious interpretation of MEG in research papers. It also demonstrates that MEG is a rapidly developing research technique for investigating brain function, but with limited consensus concerning routine clinical utility.

Current Clinical Applications of MEG

37. The most advanced clinical application of MEG is the pre-surgical assessment of patients with epilepsy, with its ability to localise epileptic activity to within a few millimetres (40)(41)(42). MEG is also establishing a role in determining cerebral dominance for language function in other conditions, including cerebral tumours. MEG is a functional imaging technique, allowing recordings to be made during the performance of cognitive tasks and in response to visual and auditory stimulation. MEG is revealing exciting insights into the relationship between brain activity, cognition and behaviour, and there are research reports of its application to a wide range of conditions including schizophrenia, stroke, Alzheimer's disease, chronic alcoholism, facial pain, multiple sclerosis, and autism (43) (44) (45) (46).

MEG and mTBI

38. MEG identifies abnormalities of the electrical activity in nerve cells in the cerebral cortex and their injured nerve fibres. As with EEG, damaged cerebral tissue gives rise to ongoing electrical activity of lower frequency, detectable by MEG. Recordings from normal cerebral cortex show activity predominantly with frequencies above 8Hz, while injured neurons generate delta (1-4Hz) or theta (5-7Hz) activity. Localisation of such abnormal activity using MEG was demonstrated more than 20 years ago (47) .

39. The sensitivity of MEG has been demonstrated in two further studies. In the first (48), MEG was compared with EEG and standard MRI in subjects who were symptomatic following concussion (mTBI). MEG detected slow wave abnormalities in 65%, whereas EEG was abnormal in 20-25% and MRI in 20%. In a later study (49), a series of 30 mTBI patients with persistent symptoms of more than one year's duration were compared using investigation with MEG, SPECT and MRI. MEG proved to be more sensitive than MRI or SPECT and correlated with cognitive deficits; temporal lobe abnormalities were associated with memory problems, frontal lobe with executive deficits, and parietal lobe with attention deficits.

40. In recent studies, the most consistent MEG findings in mTBI patients, while awake and resting, are increased delta and theta slow wave activity at the site of injury and in the contre coup area of the brain. This was seen in a multi-modal study in 87% of 45 patients with mTBI and persistent post-concussion symptoms (PCS) at 1-46 months post-injury (50). This high detection rate for MEG in mTBI should be compared with EEG, MRI, SPECT, and DTI, which detected only 20%, 2-25%, 40%

and 29-70% of cases respectively (22, 23, 24). MEG can also locate areas of brain affected when other symptoms are present, for example memory impairment (temporal lobe) and attention deficit (parietal lobe). Slow wave activity, demonstrated by either EEG or MEG, is not unique to mTBI but is also seen in many other conditions including, for example, Alzheimer's disease, brain tumour, bipolar disorder, epilepsy, and stroke. Unlike normal resting state MEG data, where neuronal activity is typically recorded at frequencies over 8Hz, damaged neuronal tissues in these conditions generate abnormal signals at low frequency, in the delta (1-4 Hz) or theta (5-7 Hz) range (51)(52) (53) (48) (54)(55) (56). MEG is also affected by therapeutic and recreational drugs. Thus, the type of abnormal MEG activity found in mTBI is not specific to this condition. Furthermore, in the absence of longitudinal studies involving sufficient numbers of patients with symptomatic mTBI, it is not possible to date the MEG findings and be certain that they relate to a recent rather than a past event, nor to what extent evidence of previous injury is detectable by MEG in asymptomatic subjects. Without MEG recordings in appropriate control subjects with mTBI but without symptoms, it is not possible to know whether similar changes occur also in asymptomatic subjects following mTBI. A recent review concluded that MEG offers the most sensitive marker available for detection of disturbed function resulting from mTBI. However, further investigation within the range of clinical severity of mTBI and over time from injury (longitudinal study) is needed before MEG can be applied and reliably interpreted in routine clinical practice (24).

41. As noted above, with refinement of data processing and analysis, the sensitivity of MEG can be increased to 87% in subjects with mTBI and persistent symptoms (50). Of those included in this study, half had mTBI due to blast injury and half due to other causes. In mTBI, multiple cortical areas may be affected in an unpredictable pattern, in contrast to studies of MEG findings in patients with some other neurological conditions (46). This finding raises as yet unanswered questions about specificity and the nature of the injury.

42. Importantly, MEG is a functional brain imaging technique, but to date there have been few studies of altered function in response to the performance of cognitive tasks (cognitive loading). In one study (57), MEG recordings were made in civilian subjects with mTBI from a variety of causes, during performance of a comprehensive battery of cognitive tests. Half of the mTBI subjects were studied at six days to two months following the mTBI event, and half at six months after the mTBI event. MEG abnormalities were found in the left parieto-temporal cortex, left superior frontal gyrus and right parietal regions. The authors concluded that the observed alterations in cortical activity during cognitive loading may provide measurable neurophysiological correlates of cognitive difficulties in subjects with mTBI, even at the individual level. This could potentially have important practical application for individual patients, but the research finding requires confirmation.

MEG and PTSD

43. MEG studies in PTSD are limited in number, and interpretation is challenging, largely due to the differing methods of computational analysis which, as with mTBI studies, are complex. This subject is further elaborated in the Interim IMEG Report (7). Clinically, matters are complicated by the fact that mTBI with persistent symptoms and PTSD are frequently comorbid. Functional MRI (fMRI) has played a pivotal role in revealing aspects of disturbances of cerebral processing in psychiatric illness (58), including the model of PTSD which proposes that behaviour and cognitive phenotypes of PTSD arise from abnormal interactions involving the amygdala, prefrontal cortex and hippocampus (59). The 2019 Interim Report discussed the evidence on MEG and PTSD, citing particularly a study which included an overview of the complex advanced computer principles and approaches used to detect and map MEG signals, needed to investigate neural circuit function via neural oscillations and their connections across different brain regions (38). Unsurprisingly, given the different study conditions, results from the various research studies reviewed were mixed, but the overall conclusion was that compared with normal subjects, there is a reduction in network efficiency and increased randomness in PTSD, while in mTBI there is an increased degree of structure and high levels of clustering co-efficients. These abnormalities were shown in brain regions relevant to core behavioural PTSD phenotypes including disturbances of memory, attention and impulsivity. It was proposed that these MEG changes might prove to be useful markers for PTSD in support of a clinical diagnosis (38). We have reached the conclusion that further research is needed to clarify understanding of brain function in PTSD, and that it is premature to regard MEG as having utility in routine clinical practice in PTSD.

Advanced EEG Studies on Brain Connectivity

44. A recent research report raises the possibility that refined analysis of EEG data may provide another means of looking at brain connectivity in health and disease (61). As mentioned already, EEG has high temporal resolution, but relatively poor spatial resolution, and importantly, much lower than MEG. This is due to electrical properties within the brain and the transmission through the skull and scalp which lead to distortion of the electrical signal and the potential for identifying functional connectivity within the brain where it does not in fact exist.

45. A new method addressing this volume effect is orthogonalized power envelope correlation, which is a method of assessing apparent connectivity from different brain regions. It does this by detecting the signal from two separate brain areas and looking for synchrony in their different signal envelopes. The orthogonalization process means that only true connectivity remains. This finding was validated in a recent paper on EEG profiling in PTSD (61). When network patterns, using a theta carrier frequency and ‘eyes open while resting’ method, were established in a group of demographically homogeneous US combat veterans with PTSD, or sub-threshold PTSD, and compared with civilians without PTSD or any other psychiatric diagnosis, hypoconnectivity was detected between 74 areas of

the brain in the PTSD group (particularly those of the anterior middle frontal and orbital cortices), similar in location to that seen with fMRI. The researchers went on to seek correlations of these changes with cognitive functions and symptoms. The hypoconnectivity also related to digit span impairment but not to other cognitive deficits, symptoms, comorbid depression or taking psychotropic therapeutic drug medication. Importantly, these differences were a group, not individual, effect and were not seen when orthogonalized power envelope correlation was not used.

46. An issue raised by the authors was how far possible interference known to occur with MEG and EEG from eye movements and blinking was taken into account as an explanation for the findings. Frontal lobe connectivity in the theta frequency, as observed in this study, is a potential issue with blinking and eye movements. This will require further study. Further research on band connectivity in PTSD is a promising approach, perhaps particularly in relation to treatment effects and evaluation. The refined EEG analysis described in this study represents yet another means of assessing cognition and brain connectivity and has the advantage of being relatively inexpensive. We mention it here for the sake of completeness, but for the moment, the technique does not have clinical utility at the level of the individual patient. Sophisticated EEG analysis of this sort, if shown to have clinical utility, would be much less expensive than MEG, but the likelihood is that the techniques will become complementary in clinical practice.

Meeting at Imperial College London (ICL) to set a National Consensus for managing mTBI

47. Reference has already been made to the meeting at ICL, held on 15 January 2020, and the Meeting Consensus report is at Annex 2 (62). The first part of this meeting focused on research and the clinical utility of neuroimaging in mTBI, and in particular the use of MEG. The second part considered the neuroendocrine consequences of TBI, their investigation and treatment. From this emerged a consensus statement, which we summarise below:-

i) mTBI due to blunt head injury and blast related mTBI may co-exist in armed forces personnel. Separate work, notably in animals suggests that blast and blunt mTBI may not be pathologically identical, but MEG studies of the issue are scarce (only two to date) and, while suggesting the two are different pathologically, research studies did not always include appropriate controls.

ii) There is overlap in symptoms between mTBI and mental health disorders including PTSD.

iii) There is currently no diagnostic test for mTBI based on a "signature" imaging or other abnormality.

iv) Present treatment of suspected co-existing mTBI and PTSD in armed forces personnel and veterans are not informed by imaging, but rather based on symptoms and disability.

v) More research on military blast induced mTBI is needed to include:-
i) those exposed to blast but with no reported long-term effects,
ii) those exposed to blast and reporting persistent symptoms /long-term sequelae, and
iii) those at risk of future blast exposure.

Such research should satisfy several criteria, including adequate study size; randomised controlled trials of treatment, longitudinal research, including, in some instances, neuropsychological and neuroendocrine testing according to standard protocols over time; and there should be suitable controls including personnel with traumatic injuries other than TBI.

vi) Since one possible influence on the varied incidence of blast-related TBI (bTBI), reported in different countries and militaries, is the time interval of reporting symptoms after the blast incident, care should be taken to assess index injury severity and numbers of exposures as objectively as possible.

vii) Multimodal imaging including standard MRI, DTI and SWI, as well as MEG, offer opportunities to investigate and clinically manage patients with mTBI and blast mTBI, but ahead of findings becoming more robust, and adoption of MEG for clinical use, research based on agreed standard technologies, protocols and data analysis will be needed.

viii) For the future, neuroendocrine testing with standard protocols should also be further explored.

48. The meeting also made a clinical recommendation for implementation of TBI screening in various circumstances and following further research:

i) Since a high percentage of military personnel at recruitment have had at least one blunt mTBI or concussion episode (not necessarily reported), as blast and blunt injury mTBI may arise from the same combat related blast event, and since blunt sport related injury mTBI may occur in service, introduction of screening at recruitment, pre-deployment and for those likely to have been exposed in service to blast or a blunt mTBI is recommended.

ii) Neuroendocrine testing for diagnosis should also be further investigated by expert groups including members from universities and practising NHS clinicians.

49. There are three important caveats to bear in mind in the interpretation of the currently published research on MEG studies in subjects with mTBI. First, that MEG has not yet been sufficiently studied in other neurological disorders to be able to conclude that the reported findings are reliably specific to mTBI. Second, that in the absence of MEG recording prior to the incident mTBI event, it is not possible to be certain that the mTBI event in question is the cause of the recorded abnormality. Third, that no prospective longitudinal study has yet been reported, and it is possible that there are subjects exposed to blast injury and other causes of mTBI who show similar MEG abnormalities but who are asymptomatic.

50. In preparing this Report, IMEG has carried out further scrutiny of the literature, mainly from 2015 onwards, and had discussion with experts on MEG and TBI. Professor Matthew Brookes, of Nottingham University, is one of a handful of UK scientists at the cutting edge of computational biology and MEG in mTBI and mental health disorders. In October 2020, IMEG was fortunate to discuss these issues with him. Professor Brookes gave a presentation entitled:
"Magnetoencephalography: principles, applications and use in mTBI".
The Key points included:-.

i) As yet there is neither MEG evidence nor other valid objective method to detect mTBI in the acute phase, nor in those who have had a single mTBI injury but recover completely without persistent PCS.

ii) Most MEG recordings have been resting state examinations and at a single time point following mTBI. Longitudinal studies, with cognitive loading, are a priority.

iii) Whether blast and blunt injury mTBI are the same pathologically is of great interest in military populations but the issue is not yet resolved. It is hoped MEG will provide insight.

iv) Given that MEG seems able to identify changes in those with psychiatric diagnoses, a particular interest in the military context is the objective diagnosis of PTSD and its differentiation from mTBI.

v) Symptoms of PTSD and mTBI overlap. The research work of Dunkley and Zhang in Toronto, classifying PTSD and differentiating it from mTBI, using MEG neural synchrony, is promising (59). Other planned topics of investigation include functional connectivity in mTBI, results to date having yielded inconsistent findings. More work is needed on cognitive task-based MEG in mTBI. To date, both hypoactivation and hyperactivation have been reported.

vi) Longitudinal assessment of mTBI with MEG in acute, subacute and chronic phases will throw

light on recovery from mTBI and help to predict development of PCS and cognitive deficits.

51. Professor Brookes then confirmed that most MEG studies to date have been conducted on small numbers of subjects, with often inconsistent results. There are many challenges and limits to consistent findings in such studies. A major issue is the diversity of computational analytical techniques used. As well as study design, matters such as use of different scanner types and the timing of investigation relative to the injury are important and incompletely studied. Some research groups are now investigating patients in the immediate aftermath of the injury (within two weeks), while others investigate at longer intervals (two months or longer). The presence or absence of PCS needs to be identified. Finally, the recognition that age has a marked effect on MEG recorded activity means that those with mTBI and controls should be carefully age matched. It has been observed that delta (low frequency) oscillations characteristic of mTBI decline with age (63).

52. In relation to the suggestion that MEG can be regarded as a diagnostic test for mTBI, we conclude that:

- MEG is providing important insights into functional alterations in the brain in mTBI and PTSD but has not reached levels of sensitivity and specificity to be regarded or used as an investigation in routine clinical practice.
- Differences in published MEG research findings indicate that there are important methodological differences between research groups that need to be resolved.
- As recommended in the Consensus Statement arising from the ICL meeting held in January 2020, IMEG supports the need for collaborative research on MEG in mTBI.
- The diagnosis of mTBI and PTSD remain clinical, dependent upon the history of the event(s) and clinical examination, in the case of mTBI, supported by CT or MRI scans in a minority of individuals, according to specialist opinion.
- IMEG recognises that these conclusions will need to be reviewed regularly in the light of research advances.

Other Biomarkers of mTBI - Neuroendocrine and Metabolic

53. As stated, the agreed diagnostic criteria for mTBI are exclusively clinical, both in the UK and elsewhere, but there is increasing interest in the possibility that, in addition to neuroimaging techniques, specific and sensitive biomarkers of mTBI in body fluids might prove to have clinical utility in routine practice. There are now research reports of putative biomarkers of brain damage, including blood, cerebrospinal fluid (CSF) and salivary markers of axonal injury, which might inform underlying pathology, prognosis, potential therapeutic targets and treatment evaluation.

54. For many years, moderate and severe TBI have been recognised as causes of hypopituitarism (deficiency of pituitary gland function). The underlying mechanisms are not yet established, but genetic predisposition, autoimmunity and neuroinflammatory changes may all be involved (64). There is evidence that hormone replacement, most commonly with growth hormone (GH) can at least partially reverse the clinical manifestations, including psychological and cognitive deficits (65). The 2013 UK Biosap study (66) investigated the prevalence and consequence of pituitary dysfunction in 19 military personnel who survived a moderate to severe blast-induced TBI (bTBI) due to improvised explosive devices (IED) in Afghanistan between December 2009 and March 2012. The controls were 39 age and gender-matched civilians with moderate to severe non-blast induced TBI (nbTBI). Some of the nbTBI group had had previous TBI due to RTAs, falls, assault or sporting injury. Cases and controls all had full dynamic endocrine assessment 2-48 months after injury, MRI and DTI, and cognitive assessment by neuropsychological testing. Exclusion criteria for both groups included the presence of PTSD diagnosed by psychologist interview, diabetes, previous craniotomy (neurosurgery), current drug or alcohol use and reverse sleep cycle. nbTBI injuries were RTAs (43%), assaults (32%), falls (23%) and sporting injuries (2%). The military personnel also had routine MRI, DTI and susceptibility-weighted imaging, to detect structural changes which might be associated with pituitary gland deficiencies. Six of the 19 soldiers had anterior pituitary dysfunction, compared to only one of 39 nbTBI controls. Two soldiers had GH deficiency, one had adrenocorticotrophic hormone (ACTH) deficiency, as well as GH/ACTH/gonadotrophin deficiency.

55. Amongst the nbTBI controls only one had pituitary dysfunction, manifested by isolated GH deficiency. Neuroimaging results showed more cerebral contusions and skull or facial fractures in the soldiers with pituitary dysfunction and DTI showed greater white matter damage in the blast injured soldiers. No structure-specific hypothalamic-pituitary hormone abnormalities were seen in soldiers with pituitary dysfunction. Soldiers with pituitary dysfunction after blast damage had worse fatigue, emotional symptoms, social problems and mood disturbances.

56. These may relate to GH deficiency, but the basis for this is presently unclear. The findings led to the recommendation that all patients with moderate or severe bTBI should have detailed endocrine function assessment including dynamic stimulation testing. This was an initial research study and unanswered questions remain. The position with mTBI is still less clear. Repeated mTBI may exacerbate pre-existing neurological deficits (67) and a single study suggests that repeated mTBI can produce endocrine disturbance (68). In the aftermath of TBI, endocrine abnormalities are common but often resolve spontaneously. The frequency and severity of neuroendocrine abnormalities following mTBI remain under investigation. While there are as yet no clear clinical guidelines, current UK best practice indicates that investigations, including dynamic function tests, should be carried out at an interval after the acute event, preferably in a specialist unit, in patients with mTBI who have persistent and unexplained PCS, refractory to treatment (see Annex 2) .

57. Total tau protein and neurofilament light protein (NFL), present in cerebrospinal fluid (CSF) (69), are markers of neuronal damage, with levels being elevated acutely in CSF after mTBI (70)(71). For mTBI, practical and ethical considerations exclude routine CSF examination, which requires lumbar puncture. A recent prospective study of acute blood-based biomarkers in sports related concussion followed up 106 concussed American football players, controls comprising 84 uninjured football players and 50 non-contact sports athletes (72). Blood was collected at pre-injury baseline, within six and then 48 hours post-concussion. Levels of glial fibrillary acidic protein, ubiquitin, S100 calcium binding protein, interleukin six and one receptor antagonists and C-reactive protein were measured in blood. All proteins, except glial fibrillary acidic protein and C-reactive protein were elevated at six hours compared with baseline and the control groups. While individually the proteins showed varied ability to differentiate concussed and uninjured controls, when combined they showed good to excellent discrimination. The study had several limitations. The best discriminator of "concussed" versus the two "normal control "groups was symptom severity score. The study was not adjusted for multiple comparisons and nothing was known about possible previous concussions in any of the groups. Inclusion of additional control groups, for example people with acute non-neurological medical disorders, would have enhanced the study.

58. An issue with chemical biomarkers is that they may be present in multiple tissues and so, in polytrauma, raised levels may not be specific to brain injury. Neurofilament light protein (NFL) is a neurone-specific protein shown in multiple studies to be elevated in blood and CSF in the first 15 days after acute mTBI (73). Further longitudinal studies on timing of investigations relative to injury, correlation with clinical progress and neuroimaging are required (74)(75).

Differentiating Blunt and Blast TBI

59. The question as to whether blunt and blast induced mTBI are different in relation to pathological changes in the brain remains unresolved. Much investigation has been done in animal models. Human studies are few and observations and conclusions have been inconsistent, influenced by different protocols, including enquiry into previous TBI, baseline timing, and lack of verifiable clinical details. Blunt and blast mTBI types may co-exist in military populations, with a high percentage of personnel having sustained concussion pre-service, mainly due to sport, often unrecorded at the time and unreported at recruitment, while military service carries the risk of blunt TBI from sports injury, road traffic accidents (RTAs), assault, falls and other accidents.

60. Primary blast injuries are due to a sudden increase in air pressure following an explosion. If casualties are close to detonations, primary blast injury has high mortality, with severe damage to air-containing organs and structures, including the chest, abdomen, middle ear and nasal sinuses with rupture into the cranial cavity in severe cases. Secondary blast damage occurs when bomb fragments or debris cause penetrating injury. Tertiary blast damage causes rapid displacement of the person

within the blast environment, who is then injured by collision with objects and structures in their path. This results in blast and blunt brain injury often being sustained at the same time, making it difficult to identify those with 'pure' blast injury. Quaternary blast injury is due to thermal injury and inhalational effects (76). These mechanisms and effects occur to greater or lesser extent in military blast-related TBI, dependent on factors such as blast energy, distance from the blast, body position, use of body armour and helmets, whether blast was sustained in a closed environment or an open space, and number of exposures. Primary blast injury may cause TBI of any severity while secondary, tertiary and quaternary blast injuries are associated with moderate or severe TBI.

Neuropathological Changes over time in mTBI

61. A post-mortem human study has added to understanding of TBI pathology (77). Brain specimens from five military male cases of chronic blast exposure, and three who had died shortly after acute severe blast exposure, were compared with five male civilian cases with no history of blast exposure but with multiple impact TBI, five civilian cases with chronic exposure to opiates and three uninjured civilians with no known neurological problems. Limited case histories including for psychological symptoms were available for all participants. The military chronic blast cases had astroglial scarring involving the sub-glial plate, cortical blood vessels, grey-white matter junctions and structures lining the ventricles, while the acute blast cases showed early astroglial scarring in the same distribution. All five chronic blast cases had a diagnosis in life of PTSD. None of the civilian cases had astroglial scarring. The researchers concluded that interface astroglial scarring could indicate specific areas of blast damage occurring at brain tissues of different density or adjacent to vascular or cerebrospinal fluids, such a pattern being consistent with the understanding of blast wave biophysics. An important limitation of the study, related to the limited case histories available, was the absence of a record of lifetime TBI event exposures experienced by the military subjects, including sports-related concussion. It is also impossible to be sure that the pathological and clinical changes were due to blast primary pressure and not the secondary or tertiary blunt injury elements, and since mTBI itself is not fatal, it is more likely that the military TBIs were moderate or severe in nature, rather than being mild, though there may have been inclusion of individuals with mTBI who died from their other injuries. A further consideration in relation to this neuropathological study is that in mTBI associated with multiple injuries, a mild brain injury may be exacerbated by systemic factors resulting from the other injuries, including lack of oxygen supply to the brain and metabolic disturbances (78). These additional factors might affect later post-mortem changes observed in the brain. This work needs to be confirmed.

Long-Term Cognitive Impairment in mTBI

62. A major issue of medical and public concern is the possibility that mTBI might predispose to later degenerative change, only becoming evident many years later, manifested by the development of dementia.

63. Worldwide, the numbers of older people, including those living with dementia, is rising. At the same time, in many countries the age-specific incidence of dementia has fallen, probably related to better education, healthcare, nutrition and healthier lifestyles. Nine potentially modifiable risk factors for dementia have been identified (79). These include limited education, high blood pressure, smoking, obesity, deafness, physical inactivity, depression and social isolation. Recently, three additional factors have emerged, including alcohol consumption, air pollution and TBI (80). Together, these are thought to account for about 40% of those who develop dementia.

64. Memory disturbance, slow mental processing and executive dysfunction are common acutely after TBI of all severities and usually improve, but there is increasing evidence of long-term cognitive decline, and, following moderate and severe TBI, an increased risk of developing Alzheimer's disease (AD) or Parkinson's disease (PD). The case is much less convincing for mTBI. Many published studies do not differentiate TBI severity or whether there has been single or repetitive injury, and for mTBI are reliant on self or family report, recognised only at an interval after the index incident. The studies are often cross-sectional, small, and so underpowered.

65. Another complication is the definition of dementia, which differs amongst clinicians, and in the current and proposed international disease classifications, the WHO International Classification of Diseases (ICD, 11th edition) (81), and the American Psychiatric Association (APA) Diagnostic and Statistical Manual (DSM5, 2013)(82). Most clinicians understand dementia to describe global cognitive decline due to an underlying progressive neurodegenerative or neurometabolic process. However, in the different classifications, dementia covers both acute post-injury, often static non-progressive cognitive impairment, as well as progressive cognitive decline due to an underlying continuing neuropathological process.

66. There are at least five possible interpretations of these definitions of dementia in relation to TBI. The first refers to a deficit presenting shortly after the injury, due to a primary TBI, which may remit or remain stable over time. Second, after the primary injury there may be a slow further decline over many years. Third, there may be individuals in whom there is initial good recovery, followed by the development of a dementing illness, unrelated to the previous mTBI, many years later. Fourth, there may be confounding by lifestyle factors such as alcohol use. And fifth, there may be reverse causality, in that those with early dementia may be prone to falls leading to TBI and later confirmation of dementia, rather than the causal association being in the opposite direction.

67. A 2018 Swedish nationwide cohort study considered three factors. First, whether risk of dementia decreased over time from acute injury; second, whether risk differed with injury type; and third, whether risk was influenced by familial factors (83). The potential study population was all 3,329,360 individuals in Sweden aged 50 years or over in 2005. Diagnoses of TBI and dementia, taken from a

national database of hospital records, were tracked from 1964 until 2012 and three cohorts were assembled. In the first, 164,334 individuals with TBI but no dementia at baseline were each matched with up to two controls. The second comprised 46,970 full sibling pairs with discordant TBI status. The third comprised all subjects diagnosed with dementia during follow-up, and again, each subject matched with up to two controls. The follow-up period ranged from 0-49 years with a mean of 15.3 years. The risk of dementia was analysed using multivariable conditional logistic regression. Odds ratios (OR, the odds of dementia occurring in those exposed to TBI divided by the odds of it occurring in controls) were adjusted for age, civil status, education, early retirement pension, and baseline diagnosis.

68. 21,963 individuals were diagnosed as having dementia during follow-up. Of these 6.3% had had TBI and 3.6% no TBI, giving an adjusted OR of 1.81 (1.75-1.86), the association being strongest in the first year after TBI with OR 3.52 (3.23 -3.84). Single mTBI showed a weaker association, OR 1.63 (1.57-1.70) than more severe TBI, OR 2.06 (1.95-2.19) and multiple TBIs, OR 2.81 (2.51-3.15). In the sibling pairs, TBI was also associated with increased dementia, OR 1.89 (1.62-2.21) and followed a similar time course with risk highest soon after the TBI and then declining, but still significantly raised more than ten years after TBI. It may be that in this study the early peak represented a direct acute post-injury effect or reverse causality, while the later "tail" was due to progressive underlying neurodegeneration.

69. The study is unusual in having a long follow-up time (mean 15 years for those with TBI and up to 50 years follow-up overall). Short follow-up studies can be at risk of reverse causality, meaning that an elderly person with the early stages of dementia is liable to TBI due to falls (84).With significant risk observed more than 30 years after TBI, reverse causality is unlikely to be the full explanation here, although it may account for some cases diagnosed soon after the TBI. The study also showed the influence of familial factors and a clear dose response between TBI severity and the development of dementia. Diagnoses were made by hospital doctors, although register-based and so the researchers were unable to confirm the basis of diagnosis. Another possible bias is that in the aftermath of a TBI, subsequent healthcare and follow-up may be especially rigorous. Finally, despite the strong suggestion of an association between TBI and subsequent dementia, as an observational study it cannot prove causation, due to potential confounding factors, so that having a TBI may be more common in those with other risk factors for the development of dementia.

70. A recent US retrospective cohort study involved 325,870 nationwide US military veterans enrolled in the Veterans' Health Administration (VHA) healthcare service, average age 46.9 +/- 17.4 years, of whom half had TBI (defined as mild or moderate to severe) and the remainder no recorded TBI diagnoses. The primary outcome was a diagnosis of Parkinson's disease (PD) a year or more after the first TBI diagnosis, or selection for the study for those without TBI. The veterans were followed for an average of 4.6 years, by which time 1462 had been diagnosed with PD. PD and TBI exposure and

severity were determined via physician assessment. Among those diagnosed with PD, those with prior TBI did not differ significantly on education, income incidence or time to death, but were diagnosed at a younger age, had higher prevalence of PD and of nearly all medical and psychiatric co-morbidities compared with those without recorded TBI, suggesting this might be due to ascertainment bias. Of those with prior documented TBI of any severity, 0.58% developed PD compared with 0.31% of those without recorded TBI; while for mTBI the comparable figure was 0.47%. In adjusted models increased risk of PD in TBI of all severities was statistically significant. There were some limitations, particularly the fact that some TBIs may have gone unrecorded and the short follow-up time, but advantages included physician diagnosis of TBI and PD, the large nation - wide sample size and the longitudinal design. Most of the TBIs occurred during civilian life either before or after military service so the findings may have wider societal implications (85).

71. A second study of US veterans looked at the association of mTBI, with and without loss of consciousness (LOC), and subsequent diagnosis of dementia (86). It was a large cohort study of all veterans diagnosed with TBI in the VHA healthcare system between October 2001 and September 2014 and a suitably matched comparison group. Diagnoses were part of a comprehensive TBI evaluation by a neurologist or allied health professional. For study purposes severity was based on the most severe injury recorded on the databases. 178,779 veterans were diagnosed with a TBI in the VHA database and there were a similar number of controls selected from the database without TBI. TBI severity varied. Differences in age and gender between those with and without TBI were small. Incident dementia was diagnosed by a neurologist using the VA Steering Committee ICD 9 codes. Following adjustment for demographics and medical and psychiatric diagnoses 4,698 (2.6%) veterans without TBI developed dementia compared with 10,835 (6.1%) with TBI.

72. The risk of dementia rose with the severity of TBI; the adjusted hazard ratio (HR) for mTBI was 2.36 (95% CI, 2.10-2.66), (adjusted for demographic characteristics, medical conditions, and psychiatric disorders), for mild TBI without LOC, going up to 3.77 (3.63-3.91) in those with moderate or severe TBI. This apparent dose response relationship with severity of TBI supports the association between TBI and later dementia. While results of prior studies of the association between mTBI and dementia have been mixed, the Barnes study, which was large, longitudinal in design and adjusted for a range of confounders, adds to the weight of evidence suggesting that mild TBI is also associated with increased dementia diagnosis risk (86). Its limitations are the propensity matching design and the uncertainty regarding unmeasured confounders.

73. As discussed in the 2017 IMEG report, since the 1920s and the first description of dementia pugilistica, there have been suggestions that sports such as boxing, leading to repeated blunt brain injury, may be associated with a distinctive progressive neuropathological change, usually called chronic traumatic encephalopathy (CTE). A study of former soccer players, playing on average for 26 years, all skilled headers of the ball and dying in their seventies, and with progressive cognitive

impairment of average duration 10 years, included six individuals with previous identifiable concussion (mTBI) (87). Six had post-mortem brain examination, which showed cavum septum pellucidum (CSP). The septum pellucidum is a thin triangular membrane lying between the cerebral hemispheres, immediately below the corpus callosum, the large band of nerve fibres connecting the right and left hemispheres. CSP occurs during foetal life, closure occurring in 85 percent, but persisting into post-natal life in 15 percent of normal infants (88). It is thus a normal variant, but also shows an association with traumatic brain injury (89). Four brains examined post-mortem showed CTE, and other pathological changes were apparent in six cases, including Alzheimer's disease, cerebral amyloid, hippocampal sclerosis and Lewy body disease. The authors concluded that further work, particularly longitudinal study, was needed (87).

74. Since then, interest in a causal link between contact sport, mTBI and development of neurodegenerative disease has remained high. A 2019 data-matching retrospective cohort mortality study of former Scottish professional football players, with 7,376 former players and 23,028 controls from the general population matched on age, gender and social deprivation, found that during 18 years' follow-up, all-cause mortality up to age 70 was lower in the footballers (15.4%) than the matched general community (16.5%); deaths from ischaemic heart disease were 20% lower in players and 50% lower from lung cancer (90). Mortality from neurodegenerative disease, listed as a primary or contributory cause on the death certificate occurred in 1.6% of former players compared to 0.5% of population controls. When adjusted for competing risk of death from heart disease or any cancer, it was still higher amongst players than controls. Mortality was highest for Alzheimer's disease (AD) with hazard ratio of 5.07 (CI 2.92-8.82) compared with controls, while deaths from Parkinson's disease (PD), had a hazard ratio of 2.15 (CI 1.17-3.96). Dementia-related medications were prescribed more frequently to footballers (but not goalkeepers) compared with controls. However, in this study death from neurodegenerative disease was not related to field position played, comparing goalkeepers with outfield players (90). This finding casts doubt on whether heading the ball is indeed a factor in the development of later dementia. Again, prospective matched cohort studies are needed, bearing in mind that leather footballs, which become heavier in wet conditions, were replaced by non-absorbent material balls some years ago. In addition to the direct head trauma in sports such as soccer and rugby, where frequent sub-concussive and sometimes concussive blows directly to the head are well-recognised, there is increasing concern that indirect head trauma, caused by repetitive deceleration injury, as for example in the winter sports of luge and skeleton, might lead to the development of cognitive impairment at an interval. Published studies in the medical literature have yet to appear.

75. A 2020 systematic review of evidence on concussion and long-term cognitive impairment among professional or elite sports persons was carried out on 14 studies across a range of sports (91). Three comparisons were made:

i) athletes within the same sport - concussed and non-concussed;

ii) between sport comparison (contact vs non-contact sport); and
iii) athletes compared with the general population.

From a total of 3,783 studies screened, 14 were selected as meeting the inclusion criteria. The evidence overall suggested an association between a sport-related concussion and poorer cognitive function later in life in rugby, American football and boxing. However, the authors concluded that overall, the quality of the evidence was poor. Limitations in the selected studies included selection bias, with many subjects being volunteers. Controls met varied definitions, concussion had different definitions across the studies and was almost always diagnosed by self-report. Cognitive decline used different assessment methods and there was poor adjustment for potential confounders. The authors recommended urgent high quality well-designed, appropriately powered epidemiological studies.

76. Neuro-pathological research, from post-mortem human examination and from experimental animal studies, is throwing light on the mechanism of the evolution of changes in the brain resulting from TBI over time, including diffuse axonal injury (DAI). Very rapid axonal stretching, as in TBI, leads to the axon becoming stiffer, probably due to micro-tubule stabilising protein, tau protein accumulation and breakage of the microtubules (92). This then interrupts axonal transport leading to amyloid precursor protein accumulation at sites of injury, and beta amyloid deposition. The majority of injured axons appear normal after TBI but quite likely with impaired conduction of action potentials due to these changes, and ultimately, some axonal degeneration and loss.

77. A single moderate to severe TBI can cause marked cerebral atrophy at 6 months post-injury. This may progress over many years; measured by serial MRI (serial T1 volumetric MRI), cerebral atrophy can track TBI or neurodegenerative disorder progression. Volumetric MRI can identify damaged areas of brain and has an association with cognitive and functional outcomes. Variations in brain volume can provide normative data on expected brain appearance at different chronological ages, allowing comparisons with observed brain age. After moderate or severe TBI, brains appear older than chronological age, an effect that increases over time, with older patients at the time of injury being more at risk (93).

78. A 2015 neuro-imaging study applied an established model of normal brain ageing to 99 TBI patients and 113 healthy controls. The mean (+/-standard deviation) age of cerebral grey matter in TBI patients was 4.66 (+/-10.8) years older than chronological age, while for cerebral white matter it was 5.97 (+/-11.22) years older. This correlated with time since injury, suggesting a progressive process through the post-injury period and not a one-off effect at the time of injury. The effect was seen only in severe and moderate injuries, not in mTBI. Outcome did not depend on the mechanism of injury but did predict cognitive impairment (94).

79. By contrast, a 2016 examination of the association of TBI and late-life neurodegenerative conditions and neuropathological findings considered three prospective cohort studies with 7,130 participants divided into two groups (95). In one, TBI was associated with loss of consciousness (LOC) of less than an hour, while in the other LOC was more than an hour. All were free of dementia at the outset. Followed up for 45,190 person years, no association was found between TBI and LOC of any duration and dementia or Alzheimer's disease, but an association was found with incidence and progression of Parkinson's disease and the development of Lewy bodies, but not neuritic plaques or neurofibrillary tangles. Conflicting outcomes reflect study limitations including study size, bias, absence of matched controls, TBI heterogeneity and diagnostic criteria, as well as reliance on self-report or from relative's reports.

80. In summary, as recorded in the 2017 IMEG report, a relationship has been documented between moderate and severe TBI in the presence of certain genotypes and increased risk of neurodegenerative disorders, including APOE-epsilon 4 and Alzheimer's disease (96), and Alpha-synuclein Rep 1 and Parkinson's disease (97). The position with mTBI is less clear. Studies have yielded conflicting results and while neuroimaging has led to better understanding of neuropathology over time from the initial TBI, the associated clinical phenotype at the various stages remains undefined. Understanding of this issue is critical for prevention, early treatment and compensation. IMEG will continue to be guided by the evolving published evidence on the issue.

Comorbid mTBI and Mental Health Disorders

81. The prevalence of mental health disorders is increased after mTBI (3). These may pre-date and predispose to TBI, (such as alcohol misuse), be caused by the TBI, or occur independently. Traumatic injury of any type including due to combat occurs in psychologically stressful circumstances, which may cause a transient symptomatic stress reaction or develop into discrete diagnosable disorders.

Distinguishing mTBI and Post-Traumatic Stress Disorder (PTSD)

82. PTSD was common in relation to reported mTBI in the recent conflicts with high prevalence of PTSD in some US mTBI series affecting, along with depression, a third of cases (98). Separation of symptoms due to mTBI from those due to a stress reaction is a challenge. Where there is a documented mTBI and a preponderance of physical and neurological symptoms, such as visual problems, headache, balance problems, or confirmed cognitive impairment, the conclusion would favour mTBI as the primary disorder. However, if nightmares, flashbacks, hyperarousal and avoidance are the primary symptoms, PTSD is likely to be considered the main diagnosis (3). In these contexts, objectively verifiable biomarkers to differentiate the diagnoses would be useful. In terms of treatment, certain symptoms such as anxiety and sleep disturbance may be treated without regard to aetiology, but evidence-based interventions for comorbid psychiatric disorders such as

PTSD depend on the role played by the exposure to trauma. Both medication and psychotherapeutic interventions are used to treat psychiatric disorders. Eye movement desensitisation reprocessing (EMDR) and trauma based cognitive behaviour therapy (CBT) are effective treatments for PTSD (99)(100). CBT is also effective in treating other trauma related disorders such as depression, anxiety and somatoform disorders. The presence of either PTSD or depressive illness, comorbid with mTBI in military patients, may be associated with a worse prognosis and quality of life (101), so effective clinical management of these comorbid disorders is important.

83. Two systematic reviews on effectiveness of mental health treatments on mental health disorders comorbid with mTBI in military and civilian populations have appeared since the 2017 IMEG report. One review did not find any randomised controlled trials (RCT) but suggested that the presence of mTBI in military patients does not necessarily reduce the effectiveness of psychotherapies for comorbid psychiatric disorders (102). The second review (systematic) considered 23 longitudinal studies and 26 comparator case studies on treatment for PTSD in patients with TBI of mixed severity published between 1980 and 2019; only four of the studies were RCTs (103). CBT was the most common intervention, notably prolonged exposure (PE) and cognitive processing (CP). One RCT supported multidisciplinary interventions and another CBT for reducing PTSD; a third found no difference comparing two cognitive processing therapies, and a fourth found a significant benefit with hyperbaric oxygen. Non-RCT results broadly support the present accepted use of CBT as best practice intervention for PTSD alone. Evidence has not emerged of a relationship between TBI severity and the magnitude of treatment gains. The review recommended further work through well-controlled studies, preferably randomised controlled trials, with more female civilian and military patients and cases of different severity of mTBI considered separately.

Treatment of Psychiatric Disorders associated with TBI

84. Having a psychiatric disorder preceding TBI or occurring simultaneously or in its aftermath is common with mTBI, and if untreated may impact not only functional outcomes but possibly also the effectiveness of mTBI treatment. PTSD is seen in civilian and military patients with mTBI, and symptoms and signs associated with both disorders such as executive dysfunction, memory impairment, word-finding difficulty and processing speed deficits show substantial overlap. Together PTSD and mTBI may be thought of as being mutually exacerbating (24). Another study suggested that the increased risk of post-concussion symptoms in soldiers with mTBI almost disappeared when studies were adjusted for the effects of comorbid depression and PTSD (4). The 2018 Kulas study investigated mTBI and PTSD separately and together in US veterans of Iraq and Afghanistan, who were treated in the US DVA Veterans' Health Services (VHS), considering socio-demographic factors, psychiatric and medical comorbidities (104). 164,884 veterans took part, diagnosed with both mTBI and PTSD, mTBI or PTSD alone. 23,063 (14%) had both PTSD and mTBI, 9,253 (6%) had mTBI and 132,568 (80%) had PTSD. The PTSD group were at high risk of comorbid psychiatric conditions,

regardless of the co-existence of mTBI. The psychiatric disorders included personality disorder, substance misuse, major depression and bipolar disorder. Conversely, although uncommon, those with mTBI were more likely than those with PTSD to have a diagnosed physical disorder. mTBI on its own or together with PTSD did not increase risk of other psychiatric conditions, with the one exception of organic brain syndrome, which although rare, was more common after mTBI than PTSD. Unfortunately, organic brain syndrome was not further defined in the paper.

85. Interpretation of these findings is difficult. On the one hand, we could conclude that PTSD, not mTBI is the most common "signature" injury of Iraq and Afghanistan and a greater driver of health care demand. On the other, we might simply be looking at overdiagnosis of both PTSD and mTBI, given that they are clinical diagnoses based mainly on patient self-report. The major limitation of this study is that those in the sample were all seeking treatment. While the study throws light on VHA practice, and so patterns of care, more work with other patient groups is needed.

TBI and Suicide

86. The sixth IMEG report will include a comprehensive report on suicide and relevant risk factors, looking both at the military and wider society. There is a substantial international literature on suicidal ideation, self-harm and suicide in people with TBI. Overall, studies, while heterogeneous in quality, suggest that those with TBI in military and civilian populations are at increased risk of death by suicide, but there remain conflicting results, with some studies finding an association (105)(106)(107), but others no relation between TBI and suicide (108). Data issues include biases related to either retrospective or case-control studies. Often the military population of interest, is compared with general population data which are not age and gender matched. A further limitation is that so many mTBI events are never recorded or, when they are, the means of diagnosis - whether by self-report or objectively verified - is unknown. Suicide is a rare event in both military and civilian populations, and so results from small studies must be viewed with caution.

87. In a 2013 systematic review of 16 relevant studies, on suicidal ideation and behaviours after TBI five suggested that there probably was an increased risk of suicide in those who had suffered a previous TBI, in both civilian and military populations (109). The study rated as having the highest quality supported the finding that those with TBI of all severities are at raised risk of death by suicide (105). This was an investigation of US military veterans receiving healthcare through the US Veterans' Health Administration (VHA) health care services between 2001 and 2006. It identified those with TBI who died by suicide. A total of 49,626 patients had a history of TBI and of those, 105 died by suicide. Models were adjusted for demographic and psychiatric co-variates. Those with a TBI history were 1.55 (CI 1.24-1.92) times more likely to die by suicide than those without.

88. Analysis by TBI severity suggested that compared with no TBI, those with concussion, with or without cranial fracture, were 1.98 (CI 1.39-2.82) times more likely to die by suicide, while for cerebral contusion or intracranial haemorrhage the figure was 1.34 (CI 1.09-1.64). Suicide in those with TBI was associated with psychiatric disorders, such as major depressive disorder (MDD) (105).

89. A 2016 Swedish register-based study identified 104,290 (9%) of the 1973-1985 national birth cohort of 1,143,470 individuals, who had had at least one TBI in childhood or adolescence (to age 25 years). The comparator group was their unaffected siblings (n= 68,268). Using logistic and Cox regression models, these individuals were linked through other national registers to information on receipt of disability pension and means-tested benefits, specialist diagnosis of psychiatric disorders and in-patient care, mortality before age 41 years and low educational attainment. At median follow-up of eight years from age 26 years, TBI was associated with raised risk of all these measures with absolute risk of 10% for specialist diagnosis of psychiatric disorder and low educational achievement, 5% for receipt of disability pension and 2% for premature mortality. These risks were only slightly attenuated compared with the siblings, implying that TBI was likely to be causal. The risk for all outcomes increased with age at first TBI and showed a dose response relationship with TBI severity and recurrent TBI (110).

90. An important study used nationwide registers in a retrospective cohort study of 7,418,391 people living in Denmark for ten or more years between 1980 and 2014 and with study follow-up of 164,265,624 person years (111). This found that 567,823 (8%) people had had a medical contact for TBI. Data were analysed against the general Danish population who did not have TBI, using Poisson regression adjusted for co-variates including fractures other than skull, psychiatric diagnoses and self-harm, compared to the general Danish population who did not have a record of TBI. TBIs were divided into mTBI, skull fracture without documented TBI, and severe TBI, defined as having evidence of structural brain damage. The study outcome was suicide recorded in the Danish Cause of Death register to 31 December 2014. Altogether, 34,259 had died by suicide, with an absolute rate of 21 per 100,000 person years. 3,536 (10%) had had a medical contact for TBI; 2,701 with mild TBI, 174 with skull fracture without documented TBI and 661 with severe TBI. The absolute suicide rate in those with TBI of all severities was 40.6 (CI 39.2-41.9) per 100,000 compared with 19.9 (CI 19.7-20.1) per 100,000 for those with no diagnosis of TBI. Adjusting for age, sex and calendar period provided an incidence rate ratio (IRR) of 2.64 (CI 2.55-2.74). When fully adjusted for age, sex, marital and cohabitation status, education, socioeconomic status, other injuries, epilepsy, the Charlson comorbidity index for other chronic disorders, pre-TBI psychiatric diagnosis and self-harm, the incidence rate ratio (IRR) fell to 1.90 (CI 1.83-1.97).

91. Those diagnosed with psychiatric disorder after their TBI had a higher risk of suicide (IRR 4.90 (CI 4.55-5.29) as did those with a psychiatric diagnosis before their TBI (IRR 2.32 CI 2.10-2.55). Interaction analysis showed that those with a pre-existing psychiatric diagnosis, or who had self-

harmed before TBI, were at lower risk of suicide than those who had a psychiatric diagnosis or self-harm episode but did not experience a TBI. Severe TBI had an adjusted IRR of 2.38 (CI 2.20-2.58) compared with no TBI, while for mild TBI and skull fracture without documented TBI, IRRs were 1.88 (CI 1.74-188) and 2.01 (CI 1.73-2.34). Suicide risk was associated with the number of medical contacts for distinct TBI events and with time since last medical contact for TBI. Compared with the general population, IRR was 3.67 (CI 3.33-4.04) within the first six months of last contact for TBI and 1.76 (CI 1.67-1.86) for contact after seven years of last medical contact.

92. This study had strengths in its size and long follow-up (35 years), its adjustment for many risk factors for suicide and that it included only suicide deaths not uncertain deaths, as outcome. It also had some limitations. Not all mTBI events would come to medical attention; prior to 1995, mTBI out-patient contacts and self-harm episodes were not recorded and similarly some people in the cohort might have had a pre-1977 TBI incident, the date when the national register was set up. The importance of this study is related to its size and nationwide sample, which shows the important role of psychiatric comorbidity in mediating the risk of suicide in those with TBI. With the growing evidence of a positive association between TBI of all severities and suicide rates overall, further studies on suicide risk factors, screening, prevention strategies and effective support interventions are awaited.

Management of mTBI

93. While general principles for pre-hospital and acute TBI management have emerged, including indications for CT scanning and the use of specialist centres, there are as yet no internationally accepted guidelines for management of TBIs of specific severities, and across the world there are significant disparities, particularly in long-term rehabilitation care plans. Future approaches must take account of the context and heterogeneity of TBI, and care pathways should reflect patient and family priorities and preferences including quality of life and disability. The present progress in specialist imaging and investigation, neuroinformatics and discovery of genomic factors that influence long term outcomes, including the risk of development of neurodegenerative disorders, permitting patient stratification, is poised to support future precision medicine care plans (112)(113).

94. A holistic approach informed by evidence-based guidelines, such as NICE Head Injury CG 176 (last updated Sept 2019) (114)), delivered by a multidisciplinary team in a specialist unit, seems best able to meet requirements. For mTBI, both military and civilian, in the UK, management is community based, multidisciplinary and stepped care in design, beginning with patient education and information about PCS and expected progress. Where symptoms persist beyond about three months, specialist assessment is appropriate. PCS are diverse, and where there are cognitive problems, difficulty with information processing, multi-tasking and/or executive function, neurorehabilitation may be required.

95. Referral for neurological assessment allows, as required, objective deficits to be identified by further examination including psychometric testing, specialist neuroimaging, endocrine and audio-vestibular assessment. For cognitive deficits, compensation techniques in which the patient uses residual cognitive abilities are helpful. Since long-term residual symptoms of mTBI are predicted by emotional distress and maladaptive coping (114), and poor function is associated with comorbid depression and PTSD anger, irritability, PTSD and depressive illness should be treated according to current mental health best practice. CBT with training to use retained abilities is reported to benefit isolated tasks in a hospital or clinic setting, but evidence of positive impact on day-to-day function is less compelling (115). A more recent systematic review of 14 RCTs on therapy and rehabilitation identified significant positive results for CBT in six trials, similarly in four digital or video feedback studies and in one physical therapy trial (116). Headache is common after TBIs of all severities, of variable duration and not directly related to injury severity. It should be treated symptomatically. Headache pathogenesis is not well understood, but, in individual patients, muscular tension, cervicogenic and migrainous headaches occur (117). Sleep problems related to pain or depression occur frequently and may respond to a brief course of CBT (118). Rarely, obstructive sleep apnoea may present, which requires specialist assessment.

96. As discussed in the 2017 IMEG report, dizziness affects a high proportion of patients in the acute aftermath of mTBI and may persist, with one study suggesting up to 20% of affected patients are still symptomatic at five years (119). Most causes of dizziness and associated symptoms are treatable. Expert audio-vestibular assessment is important. Underlying pathologies include migraine, central vestibular damage and most commonly, benign paroxysmal positional vertigo (BPPV), which has similar prognosis to BPPV not due to mTBI occurring in the civilian population. A recent systematic review of vestibular rehabilitation identified two RCTs and eight non-randomised studies (120). Results were inconsistent but a majority confirmed that vestibular treatment was successful, while one small RCT found that out of 15 patients, 11 (73%) of the treated group and 1 of 14 controls (7%) had recovered within eight weeks of starting treatment (121).

97. Overall, the individual studies on the effects of treatment and rehabilitation of mTBI share the limitations highlighted in the 2017 IMEG Report (3). These include use of different definitions for mTBI, limited patient matching in terms of age, sex, socio-economic group, and cases of different TBI severity. Interventions in studies may not be standard and are often multiple, with effects of the component parts not assessed and use of many different outcomes, with few including return to work. All these factors limit pooling of studies for systematic review or meta-analysis.

Return to Work after mTBI

98. Concerning return to work, most studies relate to civilian injury and work (122). A prospective cohort study of 151 Norwegian patients with mTBI seen consecutively at outpatient clinics, considered

predictors of return to work at 12 months for patients sick-listed at six to eight weeks after the TBI, with persistent PCS. Information on injury characteristics, demographic data, and sick leave data from one year pre-injury to one year post-injury was gathered. There was a significant negative association between being back at work at 12 months and psychological distress, functioning post-injury and being on sick leave during the year prior to the injury and at two months post-injury (123). Despite the small study size, such findings support the importance of addressing psychiatric morbidity in rehabilitation programmes. A high quality larger recent systematic review and meta-analysis on return to work in civilian patients with definite mTBI identified 14 eligible studies. More than half the patients had returned to work at one month post-injury and more than 80% at six months (124). This is reassuring.

99. A recent Danish thematic analysis looked at facilitators and barriers to return to work after mTBI in civilians. The study was qualitative and used semi-structured in-depth interviews with 22 adults 2-5 years after injury. While support services are not precisely as in the UK, the three themes identified as most adversely influencing return to work were relevant in the UK context. These included worker-employer relationships, including support for job access, tasks and hours worked. This was especially referenced as a problem if, before injury, workers had high work capacity and so there were high expectations. In addition, co-workers were reported as not always being sympathetic. General practitioners were recognised as potentially having a key role in rehabilitation options for mTBI, but in this group most patients felt their knowledge was limited and they had some scepticism about the reported associated degree of functional compromise. Lastly, local authority social workers and state benefit administrators were seen overall as focused only on return to work and not on improving symptoms or the well-being and quality of life of patients (125).

Compensation Aspects

100. From April 2005 until 31 March 2020, a total of 335 awards at levels 11 and 13 were made for mTBI. While the descriptors do not allow differentiation of mode of injury, the majority were related to combat-related blast incidents in Iraq and Afghanistan and had been clinically diagnosed using the Defence HQ SG definition. We have considered claims made since the 2017 IMEG report and conclude that, in relation to mTBI compensation under AFCS, clinical diagnoses and assessment based on the severity and duration of functional compromise, particularly for civilian employability, have been robust. We have also reviewed the current Descriptors and Tariffs for mTBI and find no indication to change these now.

Diversity and Inclusivity

101. IMEG regards issues of equality and diversity as core values and aims to avoid unjustified discrimination on equality grounds whether age, disability, gender, gender reassignment, marriage

and civil partnership, pregnancy, maternity, race, religion or belief and sexual orientation. During this updated review no diversity and equality issues emerged.

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Glossary

Absolute number: actual total number, not qualified in any way.

Adjusted rate: a summary rate statistically adjusted to remove the effect of a variable (eg age or gender) allowing unbiased comparison between groups having different composition with respect to these two variables.

Algorithm: in mathematics and computer science, an algorithm is a plan set out in step-by-step, ordered instructions to solve a problem.

Bias: a systematic error in measurement that leads to a conclusion that deviates from the truth.

Biomarker: a characteristic that is objectively measured and evaluated as an indicator of a normal biological process, a pathogenic process or a response to a therapeutic intervention.

Cognitive Behavioural Therapy (CBT): a 'talking' therapy that can help manage problems by changing the way an individual thinks and behaves. CBT is used in anxiety, depression and PTSD, and for some cases where pain or fatigue are prominent.

Computational Biology: includes many aspects of bioinformatics, the science of using biological data to develop models to understand biological systems and their relationships.

Confidence Interval (CI): a range of values within which the true value lies. For example, a 95% CI means we can be 95% certain that the true value is contained within that range. As the study sample size increases the CI narrows.

Covariates or covariables: characteristics of the participants of a study other than that of primary interest.

Cross-sectional study (survey): an observational study which is a snap-shot of a group of people at a given point in time.

EMDR: Eye Movement Desensitisation and Re-processing is a form of psychotherapy invented in 1988. It does not use 'talking' therapy or medication but the patient's own rapid eye movements which reflect emotionally charged memories of traumatic events. EMDR is used in the treatment of PTSD.

Genomics: the study of all (rather than single) genes in complex disorders caused by both genetic and environmental factors.

Incidence: a measure of the probability of a given medical condition occurring in a population within a specified period of time; it is expressed as a proportion or rate.

Incidence Rate Ratio (IRR): the ratio between two incidence rates.

Longitudinal Study: an observational study that follows a group of people over a period of time .

MRI: a medical imaging technique for studying the anatomy and physiological processes of the body. MRI scanners use strong magnetic field gradients and radio waves to generate images of the organs in the body; MRI does not use X-Rays or ionising radiation.

MRI DTI: a specialised MRI technique (using Diffusion Tensor Imaging) used to examine the white matter of the brain.

Odds Ratio (OR): a measure of risk or 'effect size' used in observational studies. An OR of 1.0 implies no increase in risk; values above 1.0 indicate an increase, and those below 1.0, a decrease in risk.

Parameter: a measurable, quantifiable characteristic of an individual.

Positron Emission Tomography (PET): a functional imaging technique that uses radioactive substances known as radioisotopes to visualize and measure change in metabolic processes and in other physiological activities including blood flow, regional chemical composition and absorption.

Poisson Distribution: a discrete frequency distribution which gives the probability of a number of rare events in a fixed time.

Prevalence: the proportion of a particular population affected by a medical condition at a particular time point (= 'point' prevalence) or over a period of time (= 'period' prevalence).

Randomised Controlled Trial (RCT): an experiment that reduces bias by randomly allocating subjects to two or more groups, treating them differently and then comparing them with respect to a measured response. Commonly there is a treatment group who receive the intervention being tested and a control group who receive either no intervention or a placebo. The trial may be 'blinded' to the participants including subjects, researchers and statisticians to reduce sources of bias.

Retrospective Study: an observational study that looks back at a patient's history, lifestyle etc.

Sensitivity: the ability of a test to correctly identify those with a disease.

Specificity: the ability of a test to correctly identify those without a disease.

Standardised Mortality Ratio (SMR): the ratio of the observed numbers of deaths in a study population and the numbers of deaths 'expected', based on age- and sex-specific rates in a studied reference population. An SMR of 1.0 (or 100) implies no difference in risk of death from that expected. An SMR above 1.0 (or 100) indicates an excess of deaths; if the 95% CI of the SMR value does not include 1.0 (or 100) then the excess rate is considered to be statistically 'significant' and unlikely to have occurred by chance. SMR vales below 1.0 (or 100) imply fewer deaths than would be expected.

Variable: in research studies, the outcome under study is known as the 'dependent' variable; the variables (such as age, sex, treatment) that may determine this outcome are known as 'independent' variables'.

Annex 1

Magnetoencephalography (MEG) and Mild Traumatic Brain Injury

Interim Report, on behalf of IMEG, September 2019

Key Points

1. MEG is a relatively new functional neuroimaging technique, which relies on detection of magnetic fields induced by electrical activity in the cerebral cortex. It is providing research insights into brain function in a variety of neurological and psychiatric disorders. MEG's place in routine clinical practice is not yet established, except perhaps in epilepsy.

2. There are probably currently no more than 10 MEG scanners in the UK.

3. MEG has yielded insights into localisation and pathophysiology in both mild traumatic brain injury (mTBI) and post-traumatic stress disorder (PTSD). However, published research results are not entirely consistent.

4. There are ongoing methodological problems, particularly related to MEG data processing.

5. While MEG shows great promise as an investigation in mTBI and possibly also in PTSD, it is concluded on current evidence that it is premature to regard MEG as a specific diagnostic test in either disorder.

6. Both mTBI and PTSD remain clinical diagnoses.

7. It is important to note that the results of imaging studies of any type are not required for the assessment of military personnel for compensation under AFCS of either mTBI or PTSD.

8. The level of AFCS compensation is awarded in relation to the severity of loss of functional capacity, particularly for future civilian employment, as the consequence of attributable injury/disease, irrespective of specific diagnosis.

9. Furthermore, MEG currently has no role in informing clinical management of either mTBI or PTSD.

10. IMEG is currently undertaking a comprehensive review of MEG, due to be published in 2020.

Introduction

I. This short paper has been prepared in response to a request from Minister (DPV) for IMEG to examine evidence concerning the clinical utility of magnetoencephalography (MEG) in the investigation and assessment of military personnel with mild traumatic brain injury (mTBI) and post-traumatic stress disorder (PTSD). Further to that request, Brigadier Tim Hodgetts (Army Personnel Senior Health Adviser) and Air Vice Marshall Alastair Reid (Surgeon General), have informed IMEG of plans to convene an urgent high-level meeting on the role of MEG in mTBI and PTSD during October 2019. This paper addresses some key issues and published evidence, in order to assist that meeting. It is presented as a preliminary review of a complex topic in which detailed understanding of basic physics and computer-based analysis is key to the interpretation of the emerging research evidence. The paper has been prepared solely to inform the planned meeting in October and should be viewed as an interim preliminary assessment of MEG, a technologically complex new imaging modality.

II. This paper should be read in conjunction with the chapter on Traumatic Brain Injury (TBI) in the fourth IMEG Report published in December 2017 (IMEG, 2017 pp65-96, attached). The Report presented an extensive evidence-based account of many issues relating to TBI, including definitions, epidemiology, TBI severity, pathophysiology, clinical aspects, diagnosis of mild traumatic brain injury (mTBI), the relationship of mTBI and concussion, investigation and management of mTBI, functional outcomes and prognosis of mTBI, audiovestibular features of TBI, mental health and TBI, and distinguishing mTBI and PTSD. It is recommended that the reader reads that review before proceeding further with this paper.

MEG: Basic Considerations

I. Magnetoencephalography (MEG) is a functional imaging method for recording magnetic fields produced by electrical activity in the brain, using sensitive magnetometers. The weak magnetic fields generated are recorded by arrays of SQUIDS (superconducting quantum interference devices). An alternative recording method with SERF (spin exchange relaxation-free) recording devices is under development (Boto et al, 2018). Although MEG signals were first reported 51 years ago (Cohen, 1968; Cohen, 1972), the technical challenges of reliably recording the very small magnetic fields generated by cerebral cortex electrical activity are considerable. Synchronised neuronal electrical currents in the brain produce magnetic fields which measure in the region of 10 femtotesla (fT), and the larger amplitude alpha rhythm, 10^3 fT. Because the average ambient environmental magnetic field, including the Earth's magnetic field, is of the order of 10^8 fT, MEG recordings need to be made in a magnetically shielded room, which itself is elaborate and costly. The cost of a MEG scanner is currently approximately two million US$. Information available via the internet indicates that there are currently ten MEG scanners in the UK, though it is likely that more will be established in clinical neuroscience centres in the near future.

II. The physics of recording and the accurate localisation of cortically-generated magnetic fields is complex (Hauk et al, 2011; Sheltraw and Cousins, 2013). MEG signals are produced from the net effect of ionic currents in the dendrites of neurons, generated during synaptic transmission (produced by action potentials in neurons). The synchronised discharge of some 50,000 neurons in similar spatial orientation in the cortex is required to generate a detectable signal (Okada, 1983). As a result, it is predominantly electrical discharge of pyramidal neurons, lying perpendicular to the surface of the brain (cerebral cortex), that give rise to detectable MEG signals. MEG does not record magnetic fields from deeper structures in the brain though as with EEG, pathology in sub-cortical regions of the brain may be reflected to some extent in recorded cortical activity.

III. MEG is a functional imaging technique with high sub-millisecond temporal resolution, and is far superior in this respect to functional magnetic resonance imaging (fMRI), which is dependent upon changes in blood flow and

has a temporal resolution of hundreds of milliseconds, and single photon emission tomography (SPECT) which has a resolution of minutes. Electroencephalography (EEG) also has a high temporal resolution, but the advantage of MEG over EEG is that magnetic fields are not distorted by human tissue in the way that scalp-recorded EEG electrical signals are. This results in a spatial resolution for MEG of millimetres, in contrast to centimetres for EEG (Leahy et al, 1998).

IV. Computational analysis and modelling in order to produce MEG-based images presents another major challenge, and a wide variety of methods have been described. The published research literature on MEG is characterised by lengthy descriptions of different computer models, which for those not working in the field are not easy to grasp (see for example Alhourani et al, 2016; Rowland et al, 2017; Huang et al, 2019a).The variety of computational methods used in different studies is an important factor in the need to adopt a cautious interpretation of published MEG research papers, and is indicative of a new technique with potential clinical application but one which is still under development. Indeed, discussion of the limitations and caveats of interpretation of their results by the authors of the research studies cited in this short paper is a consistent and notable feature. Removal of contaminating artefact signals, for example from blinking, eye and facial movements, and of cardiac origin is another important issue in data interpretation (Jung et al, 2000).

Clinical Uses of MEG

I. The most advanced clinical application of MEG is in the pre-surgical assessment of patients with epilepsy. The high temporal and spatial resolution of MEG has proved valuable in the localisation of inter-ictal spike activity to within a few millimetres (Cohen and Cuffin, 1983; Sutherling et al, 2008).

II. The relatively unconstrained space available in MEG scanners (in contrast to MRI) means that evoked MEG activity can be measured in response to visual and auditory stimulation, and in response to cognitive tasks. MEG has an established role in determining hemispheric language dominance, important in the presurgical assessment of patients with epilepsy (Simos et al, 2000) and potentially in a variety of other conditions including the pre-surgical assessment of patients with cerebral tumours. MEG is providing insights into the relationship between brain activity and cognition and behaviour, and there are research reports of application in a number of conditions including schizophrenia, stroke, Alzheimer's disease, chronic alcoholism, facial pain, multiple sclerosis and autism (Georgopoulos et al, 2007; Montez et al, 2009; Hirano et al, 2010; Ihara et al, 2012; Lee and Huang, 2014).

Magnetic Resonance Diffusion Tensor Imaging (DTI) in mTBI

I. The role of conventional imaging with CT and MRI scanning in the investigation of individuals with mTBI was discussed in the fourth IMEG Report (IMEG, 2017), and brief reference was also made to recent research concerning new neuroimaging techniques not yet widely available in routine clinical practice. These included magnetic resonance diffusion tensor imaging (DTI) and MEG (denoted mEEG in the IMEG Report, but now widely referred to as MEG).

II. The molecular pathology of mTBI was considered in the fourth IMEG Report (IMEG, 2017); this has been investigated principally in animal models of mTBI. Molecular changes can occur in the absence of cellular pathology. Molecular changes include abnormalities in neurotransmission, ionic changes, increased energy demands, changes in cellular metabolism, and excitotoxicity, which are all acute potentially reversible changes (see Iverson, 2005 for review), possibly explaining transient cognitive and mood changes in individuals with mTBI

who make a rapid and complete recovery. However, a mismatch between increased oxygen demand and decreased cerebral blood flow, even in mTBI may be severe enough to lead to cell death (Arciniegas et al, 2005).

III. Studies in man have demonstrated that mTBI causes axonal stretching, inflammatory changes, disruption and separation of nerve fibres, together comprising diffuse axonal injury (DAI), although complete axotomy is apparently unusual (Adams et al, 1989). However, damage less severe than axotomy may prevent nerve impulse transmission (conduction block), leading to functional disconnection, often referred to in this context as deafferentation.

IV. Standard MRI scanning in mTBI is usually normal. Magnetic resonance diffusion tensor imaging (DTI) quantifies the diffusion characteristics of water, which are altered by changes in tissue microstructure, acting as a sensitive marker of white matter damage. The extent of DTI abnormality in mTBI correlates with cognitive impairment and is a useful guide to prognosis (see Sharp and Jenkins, 2015 for review).

V. Macdonald et al (2011) reported DTI findings in a large series of 63 military personnel with a clinical diagnosis of traumatic brain injury. All had suffered primary blast exposure plus another, non-blast-related mechanism of injury including a fall, motor vehicle crash or other blunt head injury. Controls consisted of 21 military personnel who had experienced blast exposure and other injuries but who did not have a clinical diagnosis of traumatic brain injury. All those with a clinical diagnosis of TBI fulfilled the diagnostic criteria for mTBI. All were scanned within 90 days of the mTBI event. As a group, compared to the controls, those with mTBI showed marked changes in the middle cerebellar peduncles, the cingulum and in the right orbitofrontal white matter. Re-scanning with DTI in 47 subjects with mTBI 6-12 months later revealed persistent abnormalities, judged to be consistent with evolving injuries. However, many of the mTBI subjects did not have abnormalities on DTI, questioning the sensitivity of DTI in mTBI and leading the authors to conclude that mTBI remains a clinical diagnosis. They further concluded that the observed DTI abnormalities were evidence of axonal injury. However, because all those with blast injury had also suffered other forms of head injury, the authors cautioned against making the assumption that the blast injury event was responsible for all the abnormalities shown on DTI. Finally, attention was drawn to the high rate of post-traumatic stress disorder (PTSD) in those with blast-related mTBI (see systematic review of Carlson et al, 2011).

MEG in mTBI

I. MEG reflects abnormalities of the electrical activity in cortical neurons and their injured axons. As with EEG, damaged cerebral tissue gives rise to ongoing electrical activity of lower frequency. Recordings from normal cerebral cortex show activity predominantly with frequencies above 8Hz, while injured neurons generate delta (1-4Hz) or theta (5-7Hz) activity. This occurs with damage of any kind, including stroke, tumour, infection, inflammation or tumour. Localisation of such abnormal activity using MEG was demonstrated more than 20 years ago (Veith et al, 1998; Lewine et al, 1999).

II. The sensitivity of MEG has been demonstrated in two further studies. In the first (Lewine et al, 1999), MEG was compared with EEG and standard MRI in subjects who were symptomatic following concussion (mTBI). MEG detected slow wave abnormalities in 65%, whereas EEG was abnormal in 20-25% and MRI in 20%. In a later study, Lewine et al (2007) reported a series of 30 mTBI patients with persistent symptoms of more than one year's duration, comparing investigation with MEG, SPECT and MRI. Abnormal slow wave activity was demonstrated in

63% of patients, compared with abnormalities with SPECT in 40% and in 13% with MRI. In those subjects with psychiatric symptoms, MEG was abnormal in 86%, compared with 40% for SPECT and 18% for MRI. Regional abnormalities on MEG showed associations with cognitive deficits, temporal lobe abnormalities being associated with memory problems, frontal lobe with executive deficits, and parietal lobe with attention deficits.

III. Huang et al (2009) correlated MEG and DTI abnormalities in ten subjects with persistent mTBI symptoms, concluding that abnormal MEG was detected from cortical areas with abnormal axons in the underlying white matter, as demonstrated by DTI. All ten patients had abnormal MEG scans; of these, seven had abnormalities on DTI.

IV. With refinement of data processing using a specialised high-resolution time-domain MEG imaging solution programme (VESTAL), Huang et al (2012) increased the sensitivity of MEG in detecting abnormalities in 87% of 45 subjects with persistent mTBI symptoms, half due to blast injury and half due to other causes.

V. Lee and Huang (2014) drew attention to the fact that in mTBI, multiple cortical areas may be affected in mTBI in an unpredictable pattern, in contrast to studies of MEG findings in patients with Alzheimer's disease (predominantly temporoparietal).

VI. Two further recently published studies deserve mention. In the first, Huang et al (2019a) demonstrated an increase in gamma band activity (30-80Hz) in subjects with combat-related mTBI throughout frontal, parietal, temporal and occipital areas. Drawing on evidence from animal experiments, they suggested that this might result from damage to GABA-ergic interneuron dysfunction. Furthermore, the presence of increased gamma activity correlated with cognitive impairments.

VII. In the second study (Huang et al, 2019b), MEG source-magnitude images were obtained for alpha (8-12Hz), beta (15-30 Hz), gamma (30-80Hz) and low frequency (1-7 Hz) bands before and during tests of working memory. Compared with healthy combat controls, those with mTBI showed increased MEG signals in all frequency bands in the frontal pole, ventromedial prefrontal cortex, orbitofrontal cortex and anterior dorsolateral prefrontal cortex, but decreased MEG signals in anterior cingulate cortex. Hyperactivations in most of these areas of frontal cortex were associated with slower reaction times on tests of working memory, and hyperactivation of the frontal pole, in particular, suggested that this part of the frontal lobe might be particularly vulnerable to damage and dysfunction in combat-related mTBI. However, the authors drew attention to an important potential limitation of this study: the lack of control for previous non-combat-related mTBI, including falls and sports injuries.

VIII. In keeping with the findings of Huang et al (2019b), Kaltiainen et al (2019) recorded MEG in subjects with mTBI (civilians, with a variety of causes) and control subjects, during performance of a comprehensive battery of cognitive tests of attention, working memory, reasoning, visual perception, visual memory, naming, verbal memory, word fluency and executive functions. Half the mTBI subjects were studied at six days to two months following the mTBI event, and half at six months after the mTBI event. Handedness was not recorded, but it is safe to assume that the great majority were right-handed and thus that they were left cerebral hemisphere dominant. MEG abnormalities were found in the left parieto-temporal cortex, left superior frontal gyrus and right parietal regions. The authors concluded that the observed alterations in cortical activity during cognitive load may provide measurable neurophysiological correlates of cognitive difficulties in subjects with mTBI, even at the individual level.

IX. There are four important caveats to bear in mind in the interpretation of these MEG studies in subjects with mTBI. First, that slow wave activity is not specific to mTBI, but as outlined above, can be due to multiple other types of cerebral pathology. Second, in the absence of MEG recording prior to the incident mTBI event, it is not possible to be certain that the mTBI event in question is the cause of the recorded abnormality. Third, no prospective longitudinal study has yet been reported. It is possible that there are subjects exposed to blast injury and other causes of mTBI who show similar MEG abnormalities but who are asymptomatic. This would necessitate a reconsideration of the significance of the results of the published studies. And fourth, MEG has not yet been sufficiently studied in other neurological disorders to be able to conclude that the reported findings are reliably specific to mTBI. This could be the case but has not yet been conclusively demonstrated.

X. Finally, in relation to the suggestion that MEG can be regarded as a diagnostic test for mTBI, the point should be made that imaging of any modality, including CT and MRI, is rarely 100% specific regarding causation for any neurological disorder. The diagnosis of mTBI is in the history, supported by clinical examination features (notably cognitive, and assessment of mood and other psychiatric features), and then potentially supported by special investigations such as DTI and MEG. Regarding MEG as a specific and sensitive diagnostic test for mTBI leads to the awkward and illogical conclusion that individuals exposed to blast or another potential cause of mTBI in whom the purported 'specific' changes are not demonstrated by MEG, might be denied correct diagnosis and the subsequent benefits of appropriate care and, indeed, compensation under AFCS.

MEG and Post-Traumatic Stress Disorder (PTSD)

I. Interpretation of the published studies on MEG studies in PTSD is challenging, largely due to the differing methods employed in computer processing and analysis of MEG signals. Research publications up to 2017 are reviewed by Rowland et al (2017). A detailed appraisal of the published papers on this topic demands advanced technical knowledge of, and familiarity with, some highly complex computer-based principles and processing of raw MEG signal data. The following two paragraphs are intended to provide an indication of this complexity.

II. Using graph-based network analysis, Lei et al. (2015) studied patients with PTSD resulting from an earthquake event, finding that PTSD was associated with higher values of clustering coefficient, global and local efficiency, with lower values of path length, but without a significant difference in Small-worldness (a mathematical concept that measures connections through the number of steps necessary to establish connectivity). In contrast, using the network-based statistic (NBS), Zalesky et al (2010) identified a subnetwork in which connectivity was reduced in those with PTSD. Using NBS to analyse resting state MEG, Dunkley et al (2014) identified a subnetwork in the high gamma bandwidth located primarily in the left hemisphere with increased connectivity in patients with PTSD. However, in several studies using both resting state MEG and fMRI, reductions in functional connectivity have been demonstrated in patients with PTSD. These studies are detailed by Rowland et al (2017), who comment that the findings are mixed concerning the effect of PTSD on the resting state network as measured with MEG, but that the most consistent finding is reduced functional connectivity in PTSD. Two studies in patients with both mTBI and PTSD, using fMRI with graph theory-based network analysis, have also produced mixed results (Messe et al. 2013; Han et al, 2014).

III. Against this confusing background, Rowland et al. (2017) determined to investigate how mTBI and/or a diagnosis of PTSD altered the whole-brain resting state network, as measured with MEG, in post-deployment veterans. As with many other MEG research investigations, details of the analysis of MEG signals described by Rowland et al (2017) are complex and dense. The calculation of Small-worldness, Rich Club (a measure of the extent to which well-connected nodes also connect to each other) and Modularity (a measure of the degree to which a system's components may be separated and recombined, often with the benefit of flexibility and variety of use), is essential

to the understanding of the data analysis presented. However, this is not easily accessible to those not working in this field. Notwithstanding this reviewer's limited understanding of the data analysis methodology and its limitations, the findings of Rowland et al (2017) appear to be striking. First, in PTSD, particularly in the absence of a history of mTBI, there were lower values of network metrics, indicative of reduced functional structure and increased randomness, suggesting a shift away from local connectivity and hierarchical network structure towards larger more inclusive modules. Second, mTBI was associated with an increase in Small-worldness in the wideband network but was not associated with alterations in alpha network metrics. And third, differing results were obtained when restricting connectivity within the alpha bandwidth, causing important network connections to be missed at other frequencies.

IV. In essence, interpretation of these results seems to be as follows: the reduction in network efficiency and increased randomness found in PTSD might relate to the poorer cognitive performance associated with this condition. By contrast, in mTBI, networks showed a greater degree of structure and less resemblance to random networks, as evidenced by higher levels of clustering coefficient and Small-worldness.

V. Rowland et al (2017) stated that this is the first study to evaluate wideband connectivity using a purely phase-based metric, allowing connectivity to be determined anywhere in the frequency range. In a wide-ranging discussion, they drew attention to the limitations of their study, including the lack of premorbid studies in the subjects investigated, and the possibility that some of the altered connectivity demonstrated in patients with PTSD might have represented risk factors for the development of PTSD rather than consequences of the disorder. In addition, the majority of those with PTSD were taking psychotropic medication, and the effects of these drugs on network metrics is currently not known. The authors concluded that their results demonstrated differing effects on brain function in mTBI and PTSD, as determined by graph-based network analysis of resting-state MEG data.

VI. Overall, this study represents an important contribution, indicating that there are differences in MEG activity in mTBI and PTSD. Intuitively, this is perhaps not surprising. As a research tool to better understand brain function and its relationship to symptoms including cognitive, mood and psychiatric morbidity, MEG is likely to continue to make additional contributions. However, there are clearly many unresolved technical issues, notably concerning the selection and analysis of MEG signals. This is manifest by the sometimes widely variable results of different studies, employing different methods of analysis.

MEG and DTI in Relation to Compensation for mTBI and PTSD under AFCS

I. The fourth Report of IMEG (IMEG, 2017) set out revised descriptors and tariffs for traumatic brain injury, including mTBI. Within the last year, a new descriptor for Complex PTSD, with an enhanced tariff, has been added to the Mental Health descriptors, in recognition of increasing evidence of the persistence of severe symptoms of PTSD in a small minority of those who develop this condition as a result of military service. Results of investigations such as neuroimaging (including CT, MRI, fMRI, SPECT or MEG) are not required in order to either make the diagnosis or to assess the severity of these conditions. Diagnosis is based on clinical assessment of history and examination, including physical examination and examination of the mental state. Compensation is awarded in relation to the severity and loss of functional capacity, particularly for future civilian employment, irrespective of specific diagnosis.

II. The broad concept of mTBI, argued and recommended by IMEG in 2017, remains appropriate, judged on current evidence. Affected individuals present with a variable mix of persistent physical, mood and psychiatric symptoms. They are all included within the diagnosis of mTBI. Some individuals will also have symptoms that fulfil the diagnostic criteria for PTSD. Compensation under AFCS does not require a sharp distinction between these frequently co-morbid conditions.

III. This preliminary review of the recent evidence concerning newer neuroimaging techniques, including DTI and MEG, leads to the conclusion that while these techniques are beginning to provide important insights into the pathological basis for mTBI and PTSD, they should not be regarded as specific diagnostic tests. It may be appropriate in individual patients for one or both these investigations to be performed, based upon expert opinion and recommendation, and importantly, as part of approved research studies, but the results will not currently affect the assessment of compensation under AFCS.

IV. IMEG is embarking on an in-depth evaluation of MEG in its next programme of work, extending into 2020. In line with its established practices, this will involve a thorough literature review and consultation with specialists experienced in MEG both in clinical practice and research, in order to gain understanding and insight into methods and the benefits and limitations of the technique. IMEG will include MEG as a topic in its sixth Report.

V. Finally, it is worth reiterating that IMEG adopts an objective evidence-based approach to all the conditions it considers in relation to AFCS, while at the same time striving to understand, respect and consider the impact on patients and their families in a compassionate way.

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29th September 2019

Annex 2

Setting a National Consensus for Managing Mild and Blast Traumatic Brain Injury: Post-Meeting Consensus Report - August 2020

Foreword

I am grateful that so many came together to help address this important topic. The United Kingdom Ministry of Defence was pleased to support this event as part of our duty of care to Service personnel, yet I recognise this subject is of national and international importance to our allies and across many fields of healthcare, employment and sporting activity.

It goes without saying that people, and specifically patients and their families, are the priority. The aim was a consensus that will help direct our further research and clinical innovation in mTBI prevention, detection and treatment pathways. The focus was to address diagnostic imaging modalities, but the discussion ranged much wider and deeper. It was important to me that all stakeholders had a voice. Moreover, it was critical that we could reach enough consensus on which to act, understanding where evidence is contested or at equipoise and that consensus may not mean unanimous acceptance.

I witnessed genuinely new knowledge being appreciated amongst the attendees, which was a success measure in itself, reflecting the value of bringing together national and international expertise. I also witnessed debate and challenge, those essential components for due diligence on the evidence presented. With the follow-up exchange of discussion and clarification, the summit has reached a series of consensus statements that provide a framework to align behind and drive forward the next steps.

I commend the consensus statements to you. I look forward to translating the summit outcomes into tangible actions that ultimately improve our patient outcomes, safety or experience.

Air Vice-Marshal Alastair N C Reid CB QHP
Surgeon General

Setting a National Consensus for Managing Mild and Blast Traumatic Brain Injury: Post-Meeting Consensus Report

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* The opinions and assertions expressed herein are those of Dr David Brody and Dr Daniel Perl and do not necessarily reflect the official policy or position of the Uniformed Services University or the Department of Defence.

Summary of Recommendations

1. **The military should consider the implementation of recruitment or pre-deployment screening as part of an independent research study**. Recruitment or pre-deployment screening of selected military personnel would allow for a comparison within the individual post-deployment and/or post-blast exposure or non-blast TBI event.
2. **The military should employ pre-emptive medical assessment for those experiencing an event likely to have caused m/bTBI.** This is rather than waiting for individuals to present later with symptoms.
3. **A diagnostic suite of tests incorporating imaging and neuroendocrine testing should be introduced within a 'one-stop research clinic' approach**. Expertise and resources would need to be carefully focussed. The one-stop research clinic should form part of a multi-modal clinical research protocol and the data collected should feed into a longitudinal research study.
4. **Regional Hubs are required** across the country with access to a one-stop research clinic. Hubs could be located in the South, the Midlands and Scotland based on research expertise and access to appropriate imaging facilities.
5. **Establish imaging and neuroendocrinology sub-groups for implementation**. Two sub-groups of experts will be established to help implement the recommendations from this Consensus Report, agree on protocols and/or technology to use, and ensure integration of research protocols within clinical settings. Joint coordination will facilitate collaboration and coherence.

Introduction

The purpose of the meeting held on Wednesday 15 January 2020 was to examine the current evidence for non-routine imaging and for neuroendocrine screening in the management of military personnel with brain injury and overlapping symptom domains. The Summit aimed to specifically address the relative utility of magnetoencephalography (MEG), diffusion tensor imaging (DTI) and susceptibility weighted imaging (SWI) in the UK context.

Those in attendance at the meeting represented the following organisations/expertise:

- Defence Medical Services;
- Scientists from the United Kingdom, Unites States of America and Canada – many of whom work with the military;
- The UK National Health Service (NHS) – which would be responsible for implementing any new assessment protocols shown by research to have clinical utility in routine practice;
- The Chair of the Independent Medical Expert Group – the group which advises on medical aspects of the Armed Forces Compensation Scheme; and
- Clinicians who treat brain injury.

The approach during the day split the discussions into those about imaging and diagnosis first, followed by discussions about neuroendocrine testing. Both sessions started with a veteran's personal experience of mild traumatic brain injury to help inform the clinical context for discussions. These were then followed by presentations about the current science and clinical practice in the fields of clinical diagnosis, imaging, and neuroendocrine testing in the context of the current understanding of mTBI. The presentations led to discussions and debate which helped to establish the points of consensus outlined below, identified divergence of opinion and highlighted major uncertainties and gaps in knowledge.

Following the meeting, a brief Summary Report was produced and circulated to all attendees. Comments were then solicited for inclusion in this Consensus Report. The Consensus Report has been drafted with input from the attendees named as authors on this report.

Points of Consensus

Mild impact/acceleration TBI (mTBI) due to blunt head injury and blast-related TBI (bTBI) may not be pathologically identical. mTBI due to impact or acceleration is a well-recognised problem both in military and civilian populations, and many of the injury causations are similar between bTBI and mTBI. The majority of overall TBI are in the mild category. The military are more likely to be exposed to blast injury during conflict, and therefore this Consensus Report deals with bTBI as well as

military-related mTBI (from non-blast events). Blast exposure appears to result in a different pathophysiological entity. Repeated mTBI or bTBI may also have cumulative effects that may be different to a single exposure to a blast or non-blast cause.

Overlap in symptoms between TBI and mental health conditions. The mental health conditions include Post-Traumatic Stress Disorder (PTSD), depression, anxiety and functional neurological disorders. TBI and mental health conditions (including PTSD) are leading causes of morbidity in service personnel and veterans. The disorders are complex, and the underlying pathophysiology is incompletely understood.

Currently there is no consensus or adoption of a diagnostic test that provides a 'signature' abnormality for m/bTBI. Severity of TBI from mild to moderate-severe can be defined using different categorisations that include factors such as acute level of consciousness (e.g. Glasgow Coma Scale), duration of post-traumatic amnesia (PTA) and acute neuroimaging findings (e.g. the Mayo classification). Currently there is no diagnostic test for m/bTBI that has been adopted. The MOD currently use a combination of the WHO and DoD definitions which are based solely on clinical criteria to diagnose mTBI in UK military personnel. Advanced imaging and formal neurocognitive testing are also used in some individuals, but not in a routine way.

Treat and diagnose the patient's symptoms rather than the suspected diagnosis or imaging results. At the current time, there is no biomarker to distinguish m/bTBI as distinct from PTSD. The two conditions often co-exist. Diagnosis is based on a history of one or more m/bTBI events, and treatment depends on the nature of the symptoms in individual patients, rather than imaging results. PTSD also remains a diagnosis made on purely clinical grounds. Baseline data (both imaging and neuroendocrinology) should be acquired in both these domains as part of future research (see Recommendations section).

Consideration of different cohorts for bTBI. There are three different military groups affected by blast-related TBI which require investigation:

1.Those currently presenting with symptoms compatible with a diagnosis of long-term sequelae of previous blast-related TBI and/or PTSD:

This cohort requires the development of an evidence-based management protocol/pathway which is agnostic of injury sequelae, and which acknowledges that both blast-related TBI and mental health conditions may be present. This cohort could also be involved in the investigation of the longer term structural, functional and neuroendocrine changes which can be assessed against controls and other groups.

2.Those exposed to blast but with no long-term symptoms.

3.Population at risk of future blast-related TBI and who require enhanced mitigation strategies.

For this cohort it is important to better understand blast injury, particularly in terms of load, biomechanical effects, physiological responses and assessment of mitigation proposals.

Assessing the severity of the initial blast injury is difficult. A greater length of time since deployment may render it more difficult to recall the specific details related to blast exposure. Any future studies and clinical research protocols in this area should focus on serving military as well as veterans, with careful consideration of the severity of injury, and number and intensity of blast exposures.

Multi-modal imaging potentially offers new opportunities for the investigation and management of patients with military-related mTBI or bTBI.

1. Magnetic resonance imaging (MRI) is routinely used to assess the structural and functional impact of TBI.
    - Standard MRI approaches can identify many types of brain injury in both the acute and chronic phase. However, diffuse axonal injury and diffuse vascular injury are often missed unless more advanced MRI techniques are used.
    - Diffusion MRI has been widely applied to the study of diffuse axonal injury produced by civilian and military TBI. Diffusion tensor imaging (DTI) can identify subtle but important signatures of diffuse axonal injury, which can inform clinical management and outcome prediction.
    - Susceptibility weighted imaging (another type of MRI) is a sensitive way to identify diffuse vascular injury.
    - MRI scanners are available in almost all hospitals and protocols for advanced MRI acquisition are available on modern MRI scanners.
2. MEG appears to offer the potential to:
    - aid in diagnosis and in differentiating the pathophysiological consequences of m/bTBI from PTSD through 'signature' MEG abnormalities (noting however that TBI and PTSD often co-exist);

- predict recovery outcomes and stratify patients e.g. those who will make a full recovery versus those who will continue to experience ongoing problems;
- better understand the pathophysiology of these disorders; and
- correlate with neuro-behavioural measures, e.g. symptom and neurophysiological scores.

3. MEG data acquisition and analysis techniques should be standardised, but MEG data acquisition is straightforward when acquiring resting-state data.
4. The importance of acting now and not waiting for the imaging technology to mature further was agreed.
5. MEG scans performed on those in the military affected by mTBI or bTBI should be undertaken as part of ethics committee-approved research studies and compared with advanced MRI.

There are deficiencies in the current imaging literature. Whilst the imaging field is progressing (both in terms of research and clinical use), there are discrepancies and deficiencies in the existing literature:

1. Many of the imaging studies are performed on varying versions of technologies without standardisation of data analysis methodologies. Technologies have evolved rapidly over recent years making some of the previously published data difficult to compare with recent studies.
2. Significant variability of protocol and scanner capabilities complicates sound meta-analysis being reliably performed. Harmonisation methods are being developed by many groups globally, but there is currently no consensus as to the most appropriate methods of data analysis.
3. There is a lack of longitudinal data, particularly for MEG studies.
4. In some studies, images have been interpreted by non-specialists, putting the reliability of the conclusions into question.

There is potential to incorporate neuroendocrine testing in a multimodal clinical research pathway. Further discussion is required about how best to incorporate evidence-based neuroendocrine testing within the potential multimodal clinical research programme that will be taken forward.

Points for Further Discussion/Points of Equipoise

The following points were established as requiring further discussions or investigation.

Study measures and study size. Imaging and neuroendocrine research studies in the literature have often included small patient groups, and rarely have been combined together in the same study. Global efforts to scan and test more individuals, with clearly defined clinical characteristics, with standardised protocols, and with pooling of data need to be pursued further.

Randomised Controlled Trials (RCTs) of treatments. Some believe that RCTs are required for the field to make progress, precisely because m/bTBI is a complex condition, hard to define, without a diagnostic investigative marker, with multiple co-morbidity, and without a clear pathology. It was noted that the only way to take management/treatment forward is well designed RCTs, preferably using just one treatment approach at the time so that one can be sure that any differences between the two samples are due to the intervention under study.

Longitudinal research is essential. Overall, the prognosis following m/bTBI is good. In a small minority, there can be a persistence and/or progression of symptoms, but there has not yet been an appropriate longitudinal study which follows the progression of abnormalities in the MEG signal, correlated with symptoms and cognitive deficits. The question remains as to whether a multi-modal longitudinal study should be used to assess the following:

1. MEG allied with the use of EEG – there is growing evidence of MEG's utility in the identification and differentiation of the pathophysiological changes found in mTBI and PTSD. Resting state MEG and MEG studies with cognitive loading are needed. Correlation with neuropsychological evaluation is essential (see below). The relative ubiquity of EEG across hospitals may prove advantageous if MEG derived abnormalities could be mirrored in EEG (albeit with perhaps lower sensitivity and vastly reduced spatial precision).
2. There are a number of areas that may prove particularly beneficial for the future assessment of m/bTBI using MRI:
   - The use of AI based software or computer aided diagnosis to assess advanced MRI (SWI and diffusion MRI, plus other novel sequences).
   - The use of high field strength magnets that can be used in clinical research protocols in multiple locations may be evaluated.
   - The use of diffusion MRI to assess white matter microstructure and identify evidence of diffuse axonal injury after m/bTBI.
   - The use of functional MRI to estimate the integrity of brain networks.

3. Assess the utility of neuropsychological testing in m/bTBI:
    - Research to identify the optimal cognitive loading testing required in the evaluation of individuals following m/bTBI.
    - Development and validation of neuropsychological/neurophysiological testing which may be more sensitive to subtle, but clinically meaningful changes in performance and functioning.
    - Assess the use of semi-structured interviews for assessment of mTBI and mental health across the studies to understand the broader neuropsychological symptom complex and relate to pathology.
4. Agree and assess a battery of neuroendocrine testing to measure the incidence and severity of dysfunction.

5. Accurate phenotyping of:
    - Military m/bTBI secondary to blast-related and non-blast-related mechanisms, that often co-occur.
    - Military moderate-severe TBI secondary to blast-related and non-blast-related mechanisms.
    - Military PTSD.
    - Military with both PTSD and m/bTBI (blast- and non-blast-related).
    - Military with blast injury but without symptoms of m/bTBI or PTSD.
    - Civilians with m/bTBI.
    - Civilians with PTSD.
    - Military and civilians with neither m/bTBI nor PTSD.

Test beyond the 'resting state'. Currently most published studies have reported resting state MEG data to assess abnormalities in those with mTBI, PTSD or both. While the recent literature has shifted focus from task-dependent to task-free paradigms, there is still a lot to be gained from the combined use of the two using study designs that are specific to the behavioural phenotype of the individual. Information may be gained, and more sensitive biomarkers found, via the use of cognitive tasks (working memory or attentional tasks) which probe patient symptoms.

Potential clinical research protocols for imaging and neuroendocrine testing. These are some suggestions for clinical research pathways which require further development and discussion:

1. Imaging and neuroendocrine testing undertaken before deployment so baseline data is established and then further testing employed post-deployment. Agreement needs to be reached on which individuals should receive recruitment or pre-deployment screening. Research may be required to provide criteria for selection, and there needs to be clear evidence from the research that markers are stable over time.
    - We need to further understand whether doing post-deployment imaging and neuroendocrine testing without baseline data is valuable. This may be more useful for imaging, as false positive results may often be seen in dynamic neuroendocrine tests depending on test and reference ranges used.
2. Serving military personnel with agreed diagnostic criteria for a particular clinical research protocol (e.g. imaging and neuroendocrine testing).
3. Veterans and civilians with similar entry criteria to an NHS clinical research pathway.

Selection of appropriate control groups. This needs to be considered in relation to the potential use of databases from around the world which contain MEG data from healthy control participants (e.g. Human Connectome Project, Omega, UK-MEG-partnership), which could provide a normative database against which to test for statistical differences in individuals with m/bTBI. This could also be considered in the context of randomised control trials where a comparator group is created by randomisation. Special care must be taken to recruit a military battlefield exposed, non-injured, comparator group.

Recommendations

The military should consider the implementation of recruitment or pre-deployment screening as part of an independent research study. Recruitment or pre-deployment screening of selected military personnel would allow for a comparison within the individual post-deployment and/or post-blast exposure (or non-blast TBI event). The following options should be considered:

1. Pre-recruitment history enquiring about previous m/bTBI.
2. Scanning:
    - Pre first deployment MEG and MRI screening of medium and high-risk servicemen and women. The risk stratification should be operationally based;
    - acutely following exposure to blast and non-blast injuries;
    - at an interval when there are persistent symptoms which could be attributed to m/bTBI; and

- at retirement from active combat service and had exposure (or expected exposure) to blast or known to have had an m/bTBI.

A consideration of recruitment or pre-deployment scanning raises the likely prospect of picking up asymptomatic but potentially serious unknown neuroimaging abnormalities in the recruitment or pre-deployment scan. If such a study were to be undertaken in the UK, we would advise that scans are reviewed by an independent neuroradiologist and neurologist if abnormalities are identified. These independent reviewers would then decide if action should be taken.

Employ pre-emptive medical assessment for those experiencing an event likely to have caused m/bTBI. Based on experience from the United States, this may be preferable to waiting for individuals to present later with symptoms. It would also provide the opportunity to address immediate problems and reassure individuals about the likely good prognosis.

A diagnostic suite of tests incorporating imaging and neuroendocrine testing should be introduced within a 'one-stop research clinic' approach. Expertise and resources would need to be carefully focussed. The one-stop clinic should form part of a clinical research protocol and the data collected should feed into a multi-centre longitudinal research study.

1. Such a multi-modal prospective longitudinal study would help with determining the answers to the following questions:
   - Can m/bTBI and/or PTSD be differentiated from non-head injured controls by measuring brain activity?
   - Can m/bTBI and/or PTSD be pathophysiologically differentiated from non-head injured controls by novel imaging techniques?
   - Can biomarkers provide prognostic information for m/bTBI and/or PTSD?
   - To what extent do MEG, MRI and other imaging abnormalities correlate with symptoms and cognitive deficits?
   - Does analysis of MRI, MEG and EEG recordings allow network modelling to predict seizure risk after mTBI?
   - What is the prevalence of neuroendocrine dysfunction after mild or moderate-severe blast or non-blast TBI in military, what are the risk factors, and can it be predicted by clinical features or multi-modal imaging to enable targeted screening?
2. The following imaging would be conducted: structural imaging including conventional and advanced MRI techniques (including SWI and DTI), as well as functional imaging including the use of fMRI and MEG. Where available, high spatial resolution MRI using high and ultra-high field MRI and high gradient strength microstructure imaging could also be used.
3. The defined multimodal imaging as part of a one-stop clinic approach would standardise the pathway provided whilst minimising the number of interactions for patients.

Regional Hubs are required. To provide benefit across the country, regional hubs should be established for the one-stop research clinic where the suite of imaging and neuroendocrine testing can be carried out. Hubs could be located in the South, the Midlands and Scotland (possibly London, Birmingham, Nottingham, and Glasgow), based on research expertise and access to appropriate imaging facilities.

Establish imaging and neuroendocrinology sub-groups for implementation. Two sub-groups of experts will be established to help implement the recommendations from this Consensus Report, agree on protocols and/or technology to use, and ensure integration of research pathways within clinical settings. It is important that the recommendations from the sub-groups are considered within the context of being able to deploy the research protocols within the NHS and, therefore, NHS participation is recommended. The sub-groups should clearly communicate with each other and coordinate activities for a seamless 'one-stop' experience.

Conclusion

There is an urgent clinical need to address the issues arising out of large numbers of military personnel and veterans with persistent symptoms of m/bTBI/PTSD. The exceptional promise of advanced imaging and new knowledge of neuroendocrine function in this area will only be translated into practice via an integrated, global, multi-modal research effort; acquiring new data, pooling existing data, integrating new experimental paradigms, initiating longitudinal metrics and standardising methods. The UK can achieve the first major step in achieving this translation to clinical practice through an appropriately resourced and supported research effort.

Declaration of Competing Interests

The following authors are employed by the Ministry of Defence: MC, IG, TGH, AM, ANCR, DS, AS, DRW.

AMJB is Director of the Centre for Blast Injury Studies that receives core funding from the Royal British Legion and support from the Ministry of Defence; AMJB serves on the project board of the Armed Services Trauma

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AM is the Chair of the Clinical Reference Group for Complex Rehabilitation and Disability for NHS England.

JWS is Chair of the Independent Medical Expert Group, which makes recommendations concerning the Armed Forces Compensation Scheme.

DJS is a member of the Rugby Football Union Expert Concussion Panel.

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Appendix

Definitions and current status of imaging for TBI

Traumatic Brain Injury

- Traumatic brain injuries (TBIs) can be described as mild, moderate or severe and the mechanism of injury can be from blunt, penetrating or blast forces[1]. The severity, location, type, mechanism and physiological response to injury are also used as classifications of TBI[1].
- Clinical diagnosis of an acute injury is usually based on use of the Glasgow Coma Scale and sometimes the evaluation of neurobehavioural deficits[1,2,3].
- Imaging techniques can be used to help with diagnosis. Each of the below imaging techniques have been used in TBI patients, either individually or in combination. Some of these techniques are also utilised in research.

Computed Tomography Scanning

- Computed Tomography (CT) scanning is the modality of choice when assessing a head injury in the acute setting[3]. It is able to detect haemorrhage, intracranial injury, trauma-related fractures, swelling of the brain tissue and the presence of foreign bodies that are radio-opaque (e.g. shrapnel).
- Patients with mild TBI will have normal CT scans, so this modality is a poor discriminator for the presence or absence of mild TBI[2].

Magnetic Resonance Imaging

- Magnetic Resonance Imaging (MRI) is an imaging method that is non-invasive and allows the imaging of soft tissue and structures within the body[4]. Different tissues and structures have different magnetic properties, allowing clinicians to tell them apart[5].
- MRI is considered superior to CT in terms of sensitivity for identifying haemorrhagic axonal injury and contusions. This includes in patients that have shown normal CT scans[2].
- MRI is more expensive than CT, and is usually less available in acute settings[2] with particular patient safety concerns in the acutely injured patient but provides optimal definition of brain structural anatomy.

Functional MRI

- Functional MRI (fMRI) can identify changes in communication between and within neural networks. It measures the differences in the MR signal between deoxygenated blood and oxygenated blood. When there is increased neural activity in a region, the signal from the local tissue changes as there is an increase in oxygenated blood to the region[6].
- Functional MRI provides information about brain function, which can be used following TBI. It has been

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primarily used to investigate dysfunction seen after TBI at the group level[7].

MRI: Diffusion Tensor Imaging

- Diffusion tensor imaging (DTI) is an advanced type of MRI that produces a measure of white matter structure in the brain[8]. DTI has been extensively used to investigate subtle but important effects of TBI and other types of brain injury. It has been shown to be useful in assessing post-traumatic damage to the structure of white matter connections in the brain.

Diffusion-Weighted Imaging

- Diffusion-Weighted Imaging (DWI) is able to map the complex architecture of fibres within the brain, at the submillimetric level.
- DWI is particularly used to help identify brain tissue that is ischaemic in the early stages of TBI[9].

Susceptibility Weighted Imaging

- Susceptibility-Weighted Imaging (SWI) is a technique which uses the differences in magnetic susceptibility of different compounds, for example iron, calcium and blood, to give contrast images[10,11].
- SWI aids the detection of diffuse axonal injury and microhaemorrhages. Small haemorrhages can be missed when using other MRI sequences[12].
- SWI MRI is a sensitive way to look at blood vessels and iron deposition within the brain[13]. This has been shown to be useful in the evaluation of Traumatic Brain Injury (TBI)[14].

Electroencephalography

- Electroencephalography (EEG) measures the synchronous activity of millions of neurons and allows assessment of electrical activity during different brain states (e.g. sleep, attentive wakefulness) where different frequency bands are often present[15].
- Pathological changes can also be identified, for example because of axonal injury during TBI[15].

Magnetoencephalography

- Magnetoencephalography (MEG) measures the magnetic field which is generated by neuronal electrical activity[16]. It provides high spatial and temporal resolution and is non-invasive[16,17].

Neuroendocrine Testing in TBI

Neuroendocrinology is the field that looks at the nervous system's control of hormonal secretion and the control of the brain via hormones[18]. Neuroendocrine systems control many bodily functions.

Neuroendocrine Dysfunction in TBI

- Many papers have considered neuroendocrine dysfunction after TBI, with the prevalence varying

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between studies. Potential differences are attributed to different sample populations, time since injury, injury severity, differences in the screening tests used, as well as confounding effects of other medications and other diseases[19,20].

- Hormonal screening can confirm significant pituitary hormone dysfunction, but usually needs repeat testing, with multiple dynamic endocrine tests needed for growth hormone and cortisol deficiency, and if a single test is used may in fact result in overdiagnosis[19,21].
- Pituitary dysfunction seen in the non-acute phase of TBI may recover in many patients within the first year after injury[19,22].
- Hypopituitarism in TBI patients may be the result of a number of potential mechanisms such as compression of the pituitary, vascular injury, increased intracranial pressure, direct trauma to the pituitary, and autoimmunity, genetic susceptibility and side effects of medications may play a role[19,20].
- Symptoms of pituitary hormone dysfunction after a TBI overlap with the neurological and psychiatric symptoms of the TBI itself[19].
- Even though pituitary hormone dysfunction may not be common after TBI, their diagnosis and treatment may have an important role in the individual's cognitive, psychological and functional recovery[22].
- Exposure to moderate-severe blast TBI appears to be a particular risk factor for development of pituitary dysfunction[21].

Testing and diagnosis

- TBI-induced hypopituitarism and other pituitary dysfunction is diagnosed in the same way as diagnosis of classical pituitary disease. There are variable patterns of hormone deficiencies/excess in patients with TBI-induced pituitary dysfunction and so each pituitary hormone needs to be tested for.
- Dynamic testing is required for some pituitary hormones - growth hormone, ACTH/cortisol and vasopressin/ADH[22].
- Evaluation of the functioning of the pituitary during the acute phase of injury, i.e. during the admission with TBI, is unnecessary because it is not clear at that stage whether the hormonal changes are because of an adaptive response or a deficiency[21]. Central adrenal insufficiency should only be investigated in the acute phase if it is suspected clinically[23].
- In the non-acute phase after injury, adrenal insufficiency is a priority for testing as although uncommon, it can be life-threatening[19,20,23,24].
- Testing of anterior and posterior pituitary dysfunction, are usually undertaken in the chronic phase of the injury as hypopituitarism can evolve over several months[20,24].

Measurements

- The availability of particular dynamic tests to diagnose growth hormone deficiency and central adrenal insufficiency may vary between countries and centres, and depend on resources available, while cut-off values vary between tests and may vary locally depending on the assays used[22]. Harmonisation of assays to national or international standards e.g. for growth hormone and cortisol helps this process.
- Defining cut-off values for diagnosis of growth hormone deficiency and central adrenal insufficiency is also made difficult because of the influences of other factors such as level of hypothalamic-pituitary damage, age, body mass index, and presence of other diseases such as diabetes mellitus.
- Several peripheral hormones (cortisol, testosterone, IGF-I) have circulating binding proteins whose levels can vary between individuals. While the binding proteins concentrations can be measured (cortisol binding globulin, SHBG, IGFBP3), interpreting their influence on total hormone concentrations can be difficult, and tests for measuring free, biologically active hormones, are technically difficult, expensive and time-consuming[24].
- Basal pituitary hormone levels naturally vary because of circadian, pulsatile and situational changes in secretion of certain hormones e.g. from stress or food intake[22]. This requires rigorous attention to circumstances of sample collection and necessity to avoid making diagnoses based on single samples collected

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