

Retrospective Identification and Characterization of Traumatic Brain Injury

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Bottom Line Up Front

- Self/proxy-report, whether via standardized instruments or survey methodologies, is essential for clinical, research and surveillance applications, providing information that cannot be obtained via other methods.
- Medical record extraction is an invaluable tool for identification of past history of *medically attended* TBI.
- Imaging or fluid-based biomarkers as well as performance-based assessments lack sufficient evidence of both sensitivity and specificity in detecting remote histories of TBI to be recommended for this use at this time.
- There is not a common definition of “repetitive head impacts” (RHI).

Recommendations

- There has been sufficient study of both standardized instruments and survey methodologies for self/proxy-report that whenever possible clinicians and researchers should employ elicitation protocols that have been studied and found valid.
- Two-tiered self/proxy-report elicitation approaches that separately identify events involving external forces and the effects of the events on brain function are superior to approaches that use diagnostic terms like “traumatic brain injury” or “concussion” to elicit recall.
- There is an immediate need for consensus on which ICD codes should be included in a case definition for medical record extraction.
- Imaging methods, particularly MRI, are specific but not sensitive to detection of prior TBIs. The prognostic value of imaging of remote TBIs has not been established.

- Blood-biomarkers of remote TBI are in a nascent stage of investigation and cannot yet be used for detection of remote TBI.
- Performance-based methods in isolation do not have sensitivity and specificity to detect *prior history* of TBI but are useful for characterizing the effects of prior injuries.
- Establishment of a consensus case definition of RHI should be pursued as a precursor to development or refinement of valid and standardized measures.

Future Directions

- Continued development and validation of self/proxy-report should be directed to unique populations, elicitation settings, non-English speaking respondents, and diverse cultural contexts.
- More research is needed to (1) understand the limits on accuracy of self/proxy-report due to age at injury, remoteness of the event, TBI severity, and characteristics of the reporter (e.g. proxy or self-report, current cognitive or emotional status); and (2) better characterize the prognostic value of exposure history when elicited via self/proxy-report.
- Coding schemes for medical record extraction should be elaborated to better detect follow-up care, late effects of TBI, and multiple TBIs. International agreement on coding is needed.
- Training and guidance for providers and coders should be expanded to improve the quality of medical record documentation.
- Research and development will be needed to inform best practices for the retrospective identification of RHI.
- More research is needed on the ability to detect remote TBI(s), including residual effects and prognostic value using imaging, blood-based biomarkers, performance tests and other available methods.

Retrospective Classification Work Group Summary

Being able to identify and classify a remote history of traumatic brain injury (TBI) is essential for clinical, research and surveillance purposes. In clinical settings, identification, and classification of prior TBI exposure may inform care management and minimize symptom misattribution. Studies of persons who have a prior history TBI, including those being served in community-based programs, advances understanding of the late effects of injury. Research using biomarkers or neuropathology to understand the biological correlates of TBI also requires accurate classification of TBI history. In surveillance, having a method for capturing TBI history is critical for accurately measuring the public health burden of these injuries. The Retrospective Identification Work Group evaluated the current state of the science when using a broad array of methodologies (self/proxy-report, medical record extraction, and diverse biomarkers) to detect and characterize prior exposure to TBI. For each methodology, we addressed the extent to which it can validly (1) detect a history of prior exposure to TBI; (2) characterize whether/how

that exposure affected past and current functioning; and (3) predict risk for future consequences of past exposure.

For each methodology evaluated, the Work Group also sought to address exposure to repetitive head impacts (RHI). We defined RHI as an environmental exposure to repeated hits, impacts, blows, or forces to the head regardless of whether a TBI occurred. Exposure to RHI can be assessed by querying an individual's history of participation in specific activities such as contact and collision sports or military duties, regardless of the effect on brain function. Sub-concussive injuries are often discussed in the context of RHI; however, consensus definition of these injuries, as well as methods for their accurate estimation, are nascent.

Self/Proxy-report via Standardized Instruments

There are several standardized instruments that have demonstrated criterion-related and construct validity¹⁻⁹; though only some have been tested for reliability^{1,2,4,5,8,10-12}. Capturing lifetime history of TBI exposure employing self-report instruments should use these standardized and validated instruments for either clinical or research purposes. Most instruments use a two-tiered approach of first identifying events that may have resulted in an external force applied to the brain, followed by elicitation of the nature of altered brain function (e.g., being dazed, having a gap in memory, loss of consciousness) arising from that event. It is strongly recommended that respondents should not be asked to self-diagnose by using terms like "concussion" or "traumatic brain injury" in elicitation, as this approach is more prone to bias based on respondents' differing knowledge and understanding of these terms^{4,13}.

All standardized instruments were developed for use as a contemporaneous interview, though the Ohio State University TBI Identification Method^{2,14,15} and the Brain Injury Screening Questionnaire^{3,7} also have self-administered versions. It is presumed that self-report can be used with adults and adolescents who are capable of understanding the questions though there has been no reported testing of the youngest age at time of interview for which use is valid. For children and younger adolescents, proxy-report by a parent or other adult who has a thorough knowledge of their exposure history should be employed. While most instruments address lifetime exposure to TBI, some have a narrower scope that focuses on a particular population (e.g., military service members or victims of domestic violence), type of exposure (e.g., blast-related) or intended use (e.g., symptomology that may become the target of treatment). Instruments should be used for the purpose for which they were developed and validated.

Many studies using standardized instruments indicate that injury severity as manifested by the extent of altered brain function at time of injury has the greatest predictive and prognostic value^{7,16-21}. Self-reported loss of consciousness, especially with longer duration, is associated with greater deficits in neurobehavioral function²²⁻²⁵. There is also support for a history of multiple TBIs, regardless of the severity, to confer greater neurobehavioral consequences^{16,26-28}. There is some indication that age at injury and injury characteristics may interact, specifically childhood injuries with less severe altered brain function manifesting in adult neurobehavioral consequences^{29,30}.

Finally, exposure to RHI from contact and collision sports and other sources captured via self-report instruments has been associated with long-term neurological and neuropsychiatric outcomes³¹. However, most of the literature is based on male former, elite, contact sports participants. Considerably more research is needed for all causes of RHI on the ability for standardized instruments to characterize past effects, current functioning, and/or future prognosis.

Self/Proxy-report via Survey Methods

Self/proxy-report incorporated into survey methodologies provide a less time-consuming alternative to using standardized instruments and are particularly useful for estimating TBI incidence and prevalence. These methodologies also provide an alternative to healthcare administrative datasets for population estimates by capturing those who sustained a TBI but did not seek care³² or sought care but did not receive a diagnosis³³⁻³⁶. In recent years, researchers have used a wide variety of approaches to add questions to national surveys to better quantify the burden of TBI. Each approach has benefits and drawbacks.

Self-reporting is preferred over proxy-reporting when there is a choice^{37,38}. Generally, individuals are able to report more accurately on their own experiences. However, in the case of children or severely impaired adults, it is necessary to rely on proxy-reporting. Due to issues with recall bias and telescoping, eliciting reports of more recent events will likely be more accurate than reporting on lifetime experiences. However, surveys may need to ascertain lifetime prevalence in order to capture respondents' full exposure to TBI or attain sufficient numbers for analysis. Utilizing a series of questions, versus a single question, allows for a more inclusive elicitation of TBI and for the possibility of categorizing injuries based on the certainty that they constituted a TBI (e.g., probable vs possible or diagnosed or suspected TBI)³⁹⁻⁴¹. Using multiple questions also allows survey administrators to better frame the injury, either by defining TBI or spurring recall by providing examples of how the respondent might have been injured. Requiring a specific diagnosis to be reported (e.g., "has a doctor ever told you that you had a TBI?") will result in under-identification and is not recommended on self-report surveys. Researchers need to be thoughtful about the terminology used in self-report surveys; asking about a "head injury" will likely elicit a different response than a "traumatic brain injury." Using the term "concussion" or "TBI" will be limited by the accuracy of respondents' knowledge of these terms as well as the actual terminology used by medical professionals^{13,42}, which could vary by region or country.

Future research is needed to determine the accuracy of incidence and prevalence estimates derived from self-report in survey methodologies. There is currently no gold standard method to use as a comparator⁴³. With few exceptions, most of the research on self-reporting has been limited to English-speaking respondents—international and cross-cultural studies should be undertaken to assure generalizability of these methods. RHI is not routinely assessed in self-report surveys—effort should be made to establish best practices for eliciting RHI via survey methodologies.

Medical Record Extraction

Medical record extraction is an invaluable tool in population research for identification of a past history of *medically attended* TBI. Methods for abstracting a documented occurrence of TBI in an electronic medical record (EMR) typically rely on International Classification of Diseases, tenth revision, clinical modification (ICD-10-CM) coding, but may include documented clinical signs, acute symptoms of TBI, or, when available, abnormal findings from contemporaneously captured biomarkers^{44,45}. In addition to knowing that many do not seek medical attention for TBI, potential weaknesses of medical record extraction include absent or inaccurate documentation, lack of specificity of symptoms, loss of information due to change of residence or health insurance, and limitations to proper coding of the injury^{34,46-49}.

Several issues affect the validity of TBI diagnoses captured from medical records. The certainty of diagnosis from medical record extraction of more severe TBI is less problematic than for less severe TBI as symptoms for the latter may be unnoticed or nonspecific. A limitation of medical record diagnosis coding is the differentiation of new injuries from previous ones and the inability to capture RHI. The ability to identify the consequences of TBI is difficult as functioning in a variety of domains (e.g., resumption of social roles) is often not documented⁵⁰. Long-term effects, including those based on

assessments like neuropsychological testing, may not be routinely captured in the medical record^{45,50,51}. Without documentation of later effects, it is unlikely information can be extracted from medical records about how prior exposure to TBI affects current functioning⁵².

There are several gaps in knowledge related to the use of medical records to retrospectively identify TBI. First, multiple diagnostic codes are used to denote TBI and there is no consensus on which algorithm(s) constitute best practice. Uncertainty regarding use of S09.90, unspecified injury of head, is an example^{46,49}. Further, the use of multiple algorithms limits comparisons across studies. Second, there is no research showing whether care providers or coders in different medical settings use appropriate or consistent codes for TBI. Third, current coding practices do not enable determination of multiple TBIs (e.g., new injury versus treatment for prior injury), or the presence of RHI. Finally, current practices do not provide information on long-term effects of TBI. Recommendations for future directions include the establishments of expert consensus should be established for the use of diagnostic coding for TBI. Research is warranted on artificial intelligence and machine learning techniques that could retrospectively identify TBI cases in medical records. Additional training of medical care providers and coders is needed. Finally, to limit discrepancies between actual versus diagnosed cases, additional investigation is needed on the documentation of clinical variables used to ascertain TBI.

Imaging

As there is another work group focusing on early imaging, here we discuss imaging in relation to chronic changes. Several neuroimaging modalities are used in clinical care of TBI as well as in ongoing TBI research including computed tomography (CT), magnetic resonance imaging (MRI), transcranial Doppler (TCD), positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional near-infrared spectroscopy⁵³. MRI techniques do not have ionizing radiation and are more readily available for implementation than PET or SPECT that require radiotracers⁵⁴. Cranial CT scanning is primarily used in the acute phase of head injury to diagnose focal injuries and guide neurosurgical interventions. However, CT imaging has less utility in detecting the often subtle changes in chronic stages of TBI and is rarely included in research studies outside of the acute injury⁵⁵.

MRI is widely used in clinical and research applications and is more sensitive to structural injuries in the brain, particularly damage to the white matter^{56,57}. While quantitative MRI findings are not typically used to guide clinical care, various types of MRI have been used to examine brain changes related to both acute and chronic TBI with quantitative analysis of sequences including T1-weighted, diffusion weighted and resting-state functional imaging being particularly useful to understand the longer-term effects over the more clinical sequences⁵⁸⁻⁶². MRI methods may effectively detect remote TBI-related changes in brain structure, function, and neurochemistry that may predict functional outcomes^{63,64}.

MRI findings indicating post-injury neurodegenerative changes that occur because of TBI include progressive atrophy of the brain and reduced white matter integrity^{59,61,62,65}. Interestingly, in the chronic stages of TBI, neural declines have been shown to happen concurrently with behavioral recovery^{62,66,67}, and this may be an important window for interventions⁶⁸⁻⁷⁰. However, little work has been done to understand the recovery processes occurring during this time period. MRI imaging approaches may be useful to parse out beneficial and deleterious brain changes during the chronic stages of TBI and may uncover potential avenues of therapy that minimize deleterious changes while maximizing beneficial ones⁷¹. Interpretation of findings to date should be considered in light of imaging methods and analyses, selection of populations studied (e.g., civilians, military, or athletes), potential co-morbidities including substance use and psychiatric disorders, and age, to name a few⁷².

A wide array of other neuroimaging and neurophysiological approaches, including PET, SPECT, EEG, qEEG and MEG, have also been used to examine chronic post-TBI effects in the brain; however, a review of these methods was beyond the scope of this paper⁵³.

Performance-based Measures

Performance-based evaluations like neuropsychological assessments currently lack specificity to the effects of a remote TBI or RHI⁷³⁻⁷⁷. Self-report or medical record extraction will be necessary for the identification of the occurrence of a remote TBI or RHI. Performance-based evaluations alone are insufficient for the determination that a past TBI or RHI occurred but can be used to assess whether the identified history of TBI or RHI is contributing to current symptoms⁷⁸. To attribute symptoms to a remote TBI, it is necessary to rule out other sources of central nervous system compromise that may be affecting objective findings or subjective reports. Determining the extent to which the results of a performance-based evaluation can be attributed to past TBI or RHI depends in part on the temporal relationship between the event that could cause symptoms, the types of symptoms, and the frequency, severity and/or developmental stage at the time of the TBI exposure, as well as lack/presence of other potential explanations. Confidence in concluding that current symptoms are due to past TBI increases with injury severity and shorter interval between TBI and the performance-based evaluation.

It possible that a *later life* TBI can be superimposed on an underlying neurodegenerative disease process, worsening or unmasking the disease process even if the individual was asymptomatic prior to the injury (i.e., rather than *causing* the underlying disease per se), or could contribute to variability in age of symptom onset⁷⁹⁻⁸¹, types of symptoms experienced⁸²⁻⁸⁴, or rate of progression⁸⁵. The presence of chronic traumatic encephalopathy (CTE) at autopsy strongly implicates exposure to RHI. However, the specific clinical correlates and profiles of CTE, as well as non-CTE neuropathologies that might arise from RHI remain an area of active investigation. Future research should seek a better understanding of the relative contributions of TBI and RHI to the biological and clinical features of neurodegenerative disease processes. Integrating comprehensive neuropsychological and neurological evaluations with increasingly available multimodal biomarker measurement(s) is expected to rapidly accelerate our understanding of the spectrum of contributions of lifetime TBI and RHI to current and future brain health.

Blood-based Biomarkers

At the current nascent stage of investigation, there is insufficient evidence for the use of blood-based biomarkers to detect remote histories of TBI. However, there are now examples where blood-based biomarkers are rapidly moving toward clinical applications in the diagnostic workup of older adults with cognitive and behavioral concerns. Proteins measurable in blood range from nonspecific indicators of neurodegeneration (e.g., neurofilament light chain, NfL) to disease-specific markers of Alzheimer's disease (AD) like plasma p-tau217^{86,87}. There are currently no blood-based biomarkers that signal neurodegenerative effects specific to prior TBI or RHI, such as CTE or TBI-related forms of neurodegeneration. Nonspecific neurodegenerative proteins like plasma NfL and total tau have been reported in a few studies as modestly elevated in older adults with a history of TBI^{88,89}, and NfL levels in the early chronic phases have been found to correlate with the annual atrophy rate years after injury⁹⁰⁻⁹². Current possible contexts of use for blood-based markers in clinical research of adults with and without TBI include characterizing nonspecific neurodegenerative and potential neuroinflammatory processes (e.g., NfL, glial fibrillary acidic protein) or establishing the presence of AD pathology (p-tau217) to contextualize possible contributors to cognitive or behavioral changes irrespective of the

specific role of prior head trauma. Using available validated biomarkers to rule out AD pathology may also facilitate differential diagnosis from competing neurodegenerative diseases^{87,93,94}.

Conclusions

Self/proxy-report, whether via standardized instruments or survey methodologies, is essential for clinical, research and surveillance applications, providing information that cannot be obtained via other methods. There has been sufficient study of both standardized instruments and survey methodologies that whenever possible clinicians and researchers should employ elicitation protocols that have been studied and found valid. Continued development and validation should be directed to unique populations, elicitation settings, non-English speaking respondents, and diverse cultural contexts. Two-tiered elicitation approaches that separately identify events involving external forces and the effects of the events on brain function are superior to approaches that use the terms “traumatic brain injury” or “concussion” to elicit recall. More research is needed to (1) understand the limits on accuracy of self-report due to age at injury, remoteness of the event, TBI severity, and characteristics of the reporter (e.g. proxy or self-report, current cognitive or emotional status); and (2) better characterize the prognostic value of exposure history when elicited via self/proxy-report.

Medical record extraction is an invaluable tool in population research for identification of past history of *medically attended* TBI. However, there is an immediate need for consensus on a case definition. Coding schemes should be elaborated to better detect follow-up care, late effects of TBI, and multiple TBIs. Training for providers and coders should be expanded to improve the quality of documentation.

Imaging or fluid-based biomarkers as well as performance-based assessments lack sufficient evidence of accuracy in detecting remote histories of TBI to be recommended for this use at this time. Imaging methods, particularly MRI, are specific but not sensitive to detection of prior TBIs. Features described include (but are not exclusive to) gliosis, atrophy (which may be generalized and or in specific areas e.g., hippocampus) and a cavum septum pellucidum. More advanced quantitative methods provide some insight into residual effects but more research is needed. The prognostic value of imaging of remote TBIs has not been established. Blood-biomarkers of remote TBI are in a nascent stage of investigation. We did not attempt to address electrophysiologic-based biomarkers in this summary. The accuracy of performance-based methods is limited by both sensitivity and specificity. There is not a performance-based assessment that is specific to *prior history* of TBI, but they are still important tools for an individual clinical assessment.

Research and development effort will be needed to inform best practices for the retrospective identification of RHI. Establishment of a consensus case definition should be pursued as a precursor to development or refinement of valid and standardized measures. Currently, the concepts of sub-concussive blows to the head and multiple mild TBIs (which by definition do not overlap) are not consistently included or excluded when operationalizing RHI.

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