The Post-traumatic Confusional State: A Case Definition and Diagnostic Criteria

Mark Sherer, Ph.D. 1, Douglas I. Katz, MD 2, Yelena G. Bodien, Ph.D. 3, David B. Arciniegas, MD 4, Cady Block, Ph.D. 5, Sonja Blum, MD 6, Matt Doiron 7, Kim Frey 8, Joseph T. Giacino, Ph.D. 9, Min Jeong P. Graf, MD 10, Brian Greenwald, MD 11, Flora M. Hammond, MD 12, Kathleen Kalmar, Ph.D. 13, Jacob Kean, Ph.D. 14, Marilyn F Kraus, MD 15, Risa Nakase- Richardson, Ph.D. 16, Shital Pavawalla, Ph.D. 17, Amy Rosenbaum, Ph.D. 18, Donald T. Stuss, Ph.D. 19, Stuart A. Yablon, MD 20

Affiliations: 1 TIRR Memorial Hermann, 2 Department of Neurology Boston University School of Medicine, 3 Department of Neurology Massachusetts General Hospital, Harvard Medical School, 4 Marcus Institute for Brain Health University of Colorado School of Medicine, 5 Ohio State University Wexner Medical Center, 6 New York University Langone Department of Neurology, 7 Spaulding Rehabilitation Hospital, 8 Department of Speech-Language Pathology Craig Hospital, 9 Spaulding Rehabilitation Hospital, 10 Hennepin Healthcare, 11 JFK Johnson Rehabilitation Institute, 12 Department of Physical Medicine and Rehabilitation Indiana University School of Medicine, 13 JFK Johnson Rehabilitation Institute, 14 Department of Population Health University of Utah, 15 George Washington University Medical Center, 16 Mental Health and Behavioral Sciences James A. Haley Veterans Hospital, 17 Department of Neurology University of California Los Angeles, 18 Park Terrace Care Center, 19 Rotman Research Institute, 20 Mary Free Bed Rehabilitation Hospital

This is the author's manuscript of the article published in final edited form as:

PTCS Case Definition

None have of the authors have any financial conflicts of interest to report for this work.

Corresponding Author: Mark Sherer, Ph.D., ABPP, Associate Vice President for Research, TIRR Memorial Hermann, 1333 Moursund, Houston TX77030. Mark.Sherer@memorialhermann.org.

Acknowledgement
This case definition was developed under the ACRM Evidence and Practice Committee (ACRM EPC), which is supported by unrestricted grants from CARF International and Paradigm. Neither CARF International nor Paradigm were involved in any phase of the development of this case definition.

Preparation of this manuscript was partially supported by National Institute of Disability, Independent Living, and Rehabilitation Research grant # 90DPTB0016. NIDILRR is a Center within the Administration for Community Living (ACL), Department of Health and Human Services (HHS). The contents of this publication do not necessarily represent the policy of NIDILRR, ACL, or HHS, and you should not assume endorsement by the Federal Government.

Portions of this manuscript were presented at the annual meetings of the ACRM (2015-2019) and the 4th Federal Interagency Conference on Traumatic Brain Injury (2018).

This special article was approved by the ACRM EPC on June 19, 2020 and by the American Congress of Rehabilitation Medicine Board of Governors on July 2, 2020 and published in the Archives of Physical Medical Rehabilitation. The Archives of Physical Medicine and Rehabilitation was responsible for the peer review of this article.
PTCS Case Definition

This Case Definition is in the public domain: it may be copied, published, or shared without permission from ACRM.

The authors wish to give special acknowledgement to our coauthor Donald T. Stuss, PhD, OC, OOnt, FRSC, FCAHS, 1941-2019, for his contribution, wisdom and guidance on this paper. His previous work served as a foundation for research on PTCS and he was such an important inspiration and mentor to so many in neuroscience and neuropsychology.

Please use the following attribution when republishing it: This case definition was written by Mark Sherer, Ph.D., Douglas I. Katz, MD, Yelena G. Bodien, Ph.D., David B. Arciniegas, MD, Cady Block, Ph.D., Sonja Blum, MD, Matt Doiron, MS, Kim Frey, Ph.D., Joseph T. Giacino, Ph.D., Min Jeong P. Graf, MD, Brian Greenwald, MD, Flora M. Hammond, MD, Kathleen Kalmar, Ph.D., Jacob Kean, Ph.D., Marilyn F. Kraus, MD, Risa Nakase-Richardson, Ph.D., Shital Pavawalla, Ph.D., Amy Rosenbaum, Ph.D., Donald T. Stuss, Ph.D., Stuart A. Yablon, MD under the guidance of the ACRM EPC, which is supported by CARF International and Paradigm and was published online and in print in the Archives of Physical Medicine and Rehabilitation on (Date).

Correspondence to ACRM info@ACRM.org
The Post-traumatic Confusional State: A Case Definition and Diagnostic Criteria

Abstract

In response to the need to better define the natural history of emerging consciousness after traumatic brain injury (TBI) and to better describe the characteristics of the condition commonly labeled Post-traumatic Amnesia, a case definition and diagnostic criteria for the Post-traumatic Confusional State (PTCS) were developed. This project was completed by the Confusion Workgroup of the American Congress of Rehabilitation Medicine Brain Injury Interdisciplinary Special Interest group. The case definition was informed by an exhaustive literature review and expert opinion of workgroup members from multiple disciplines. The workgroup reviewed 2,466 abstracts and extracted evidence from 44 articles. Consensus was reached through teleconferences, face-to-face meetings, and three rounds of modified Delphi voting. The case definition provides detailed description of PTCS (1) core neurobehavioral features, (2) associated neurobehavioral features, (3) functional implications, (4) exclusion criteria, (5) lower boundary, and (6) criteria for emergence. Core neurobehavioral features include disturbances of attention, orientation, and memory as well as excessive fluctuation. Associated neurobehavioral features include emotional and behavioral disturbances, sleep-wake cycle disturbance, delusions, perceptual disturbances and confabulation. The lower boundary distinguishes PTCS from the minimally conscious state while upper boundary is marked by significant improvement in the four core and five associated features. Key research goals are establishment of cut-offs on assessment instruments and determination of levels of behavioral function that distinguish persons in PTCS from those who have emerged to the period of continued recovery.
Keywords: Traumatic Brain Injury, Post-traumatic Confusional State, Post-traumatic Amnesia, Confusion, Delirium, evidence-based, Delphi process, case definition

Abbreviations:
- DoC – Disorders of Consciousness
- CAP – Confusion Assessment Protocol
- DRS-98 – Disability Rating Scale
- MCS – Minimally Conscious State
- TBI – Traumatic Brain Injury
- VS – Vegetative State
- PTA – Post-traumatic Amnesia
- PTCS – Post-traumatic Confusional State
- UWS – Unresponsive Wakefulness Syndrome
The Post-traumatic Confusional State: A Case Definition and Diagnostic Criteria

Introduction

Traumatic brain injury (TBI) is characterized by disturbed consciousness.\(^1\) The degree of disturbance of consciousness and the time course of recovery can vary, depending on the type and severity of the injury. Those with mild injuries may have brief alterations of consciousness that may or may not involve complete loss of consciousness. Patients who survive severe TBI and recover consciousness, typically continue to improve to states of more intact awareness. A nomenclature has been established to designate the clinical conditions that can occur as consciousness recovers, including coma, vegetative state (VS) (also termed unresponsive wakefulness syndrome [UWS]\(^2\)), and minimally conscious state (MCS).\(^3\) \(^4\) The clinical signs and criteria that define these conditions have been established.\(^3\) This information is summarized in Table 1. Conversely, the clinical condition observed as patients with disorders of consciousness (DoC) transition to a level of consciousness higher than MCS is less well-defined and has various labels including emerged from MCS, Post-traumatic Amnesia (PTA),\(^5\) traumatic delirium,\(^6\) and Post-traumatic Confusional State (PTCS).\(^7\) Depending on severity of injury or differing pathophysiology, this same clinical condition may be observed in patients with various patterns of recovery after TBI. For example, it may occur immediately after injury, without a period of unconsciousness or minimal consciousness, or in the setting of deteriorating consciousness after a lucid interval.\(^8\)

What is the clinical state of patients who have emerged from MCS? Clinical observation of these patients indicates that they are not fully recovered either cognitively or
behaviorally. While these patients respond in a manner that indicates increased awareness of self and the environment compared to MCS, it is apparent that consciousness remains compromised, as indicated by impaired cognition, decreased social and physical awareness, misinterpretation of social and environmental context, and inappropriate or unsafe behaviors.\textsuperscript{9-11}

Early characterizations of this clinical state described a broad range of deficits in attention, memory, orientation, and judgment, along with irritability, perceptual disturbances, and agitation.\textsuperscript{1} Some clinicians and researchers use the term PTA for the clinical state characterized by these various neurobehavioral signs.\textsuperscript{5} Others define PTA by emphasizing the anterograde amnesia observed in early recovery from TBI over the other cognitive and behavioral findings. Indeed, assessment of PTA has primarily focused on disorientation to time, place, and situation along with impairment of recognition memory as indicated by the Galveston Orientation and Amnesia Test and the Westmead Post-traumatic Amnesia Scale, measures frequently used to evaluate PTA.\textsuperscript{12-14} Inconsistency in the definition of PTA used by clinicians and investigators may lead to confusion while, uniform nomenclature with greater clarity of diagnostic criteria will improve clinical understanding and research.

Here, we present a case definition for this condition that was developed by synthesizing empirical evidence and expert opinion. We also describe the key clinical features. We have chosen the term, \textit{Post-traumatic Confusional State (PTCS)} over Post-traumatic Amnesia (PTA) to emphasize the wide range of neurobehavioral features associated
with this condition. In 1999, Stuss et al. introduced the term PTCS and proposed that PTCS was a more descriptive label than PTA for this period of recovery following TBI. Stuss et al. proposed that impaired attention was the key cognitive deficit seen in PTA/PTCS rather than anterograde amnesia and that in the less severe TBI patients, disturbed attention may be the primary cause of the memory disturbance. These investigators noted the similarity between PTCS and acute confusion or delirium.

To establish a case definition of PTCS and to distinguish the terms PTA and PTCS, the Confusion Workgroup of the American Congress of Rehabilitation Medicine Brain Injury Interdisciplinary Special Interest Group conducted a comprehensive review of the empirical literature on PTA and PTCS and integrated these findings with a broad survey of expert opinion. We believe that a case definition will contribute to several goals: (1) improved understanding of the natural history of recovery from TBI, (2) improved classification and uniformity of nomenclature for clinical and research purposes (3) improved prognostication with better characterization of the recovery of the neurobehavioral manifestations of PTCS, (4) development of structured assessments that fully address the phenomenology of PTCS, (5) pursuit of a research agenda including determining functional implications of PTCS, defining clinical subtypes of PTCS, understanding the pathophysiologic underpinnings of PTCS, improving rehabilitation management and evaluating potential treatments, and (6) comparison of confusion resulting from TBI to delirium resulting from other causes.

With these goals in mind, we developed a case definition to achieve four objectives:
(1) Clinical Features/Case Ascertainment. The case definition provides a description of the observable elements of PTCS that is sufficiently detailed to support diagnosis based on clinical evaluation while also informing selection of existing measures that are most useful in assessing patients at risk for PTCS. Ideally, this degree of detail supports development of improved measures that provide reliable and reproducible diagnosis and clinical characterization.

(2) Description of the Pattern of Resolution of Signs of PTCS. Previous findings suggest that some signs of PTCS may resolve before others while some signs are related so that resolution of one occurs close in time to resolution of the other. Improved understanding regarding these patterns of recovery may inform prognosis and treatment.

(3) Description of Functional Status. Just as the transition from MCS to emerged from MCS is described in terms of functional abilities (consistent and correct yes/no answers to simple questions, correct demonstration of use of a functional object), there should be functional capabilities shown by those whose confusion is resolved as compared to those who remain in PTCS. Clear determination of how non-confused patients are more functional than confused patients will support consistent classification, indicate ability to benefit from continued therapies, and have implications for supervision needs.
Comparison of PTCS to Delirium caused by other Etiologies. Delirium is a relatively common occurrence in hospitalized patients. Deliria resulting from etiologies other than TBI differ from PTCS in phenomenology, duration, pattern of recovery, and implications for long-term prognosis. A detailed case definition of PTCS will facilitate comparison of confusion in recovery from TBI to deliria of various causes.

Below, we describe our approach to developing the case definition of PTCS and present the clinical features, upper and lower boundaries, patterns of recovery, and functional implications of this syndrome. We also describe how PTCS differs from deliria resulting from other etiologies.

Methods

Evidence Review

The Confusion Workgroup consisted of all authors of the case definition. The Workgroup included seven neuropsychologists, six physiatrists, two behavioral neurologists/neuropsychiatrists, two neuroscientists, and two speech language pathologists. These members met in-person and via teleconference from 2012 to 2019. Key in-person meetings were held at American Congress of Rehabilitation Medicine annual conferences from 2013 through 2017 and at the Galveston Brain Injury Conference in 2017 and 2018.

In developing the case definition of PTCS, we focused on areas of impairment (e.g., attention, memory, orientation, fluctuation, sleep disturbance, decreased arousal,
agitation, and psychotic-type symptoms) as well as the lower boundary, upper boundary, functional implications, and patterns of recovery. Given the long history of the use of the term PTA prior to the development of PTCS, we accepted articles about PTA as providing evidence regarding PTCS. We extracted data from articles in three phases. First, we conducted an Ovid Medline literature search beginning in 1946 (the publication date of the earliest articles indexed by OVID Medline) for abstracts published through 2013. We used the search criteria and keywords presented in the Supplementary Materials (Supplementary Table 1). In 2018 we conducted an additional abstract search for articles published from 2013 through 2017. We overlapped these reviews by several months to ensure no articles were missed. Finally, we reviewed articles that were not previously captured by the two abstract searches if they were identified as potentially relevant to the case definition by the review teams based upon the reference sections of articles retained in the first two phases. We followed the following procedure for each abstract and article review:

1. Teams of two independent raters reviewed abstracts and determined whether each abstract met the abstract inclusion criteria outlined in the Supplementary Materials (Supplementary Table 2) and rated the abstracts according to the categories described in the Supplementary Table 3.

2. Once all abstract reviews were completed, each pair of reviewers was unmasked and reconciled their ratings for abstracts.

3. For abstracts marked as “retained” after reviewer reconciliation, teams of two reviewers extracted data from the full-text articles using an online standardized form
(Supplementary Materials).

4. Information from the data extraction forms was compiled into evidence tables by the first three authors (YGB, DIK, MS).

Developing the Case Definition

After the first phase of article review, and following extensive in-person and telephone discussions by the Workgroup regarding the clinical presentation of confusion after TBI, a subgroup (DIK, YGB, MS) of the authors developed the first draft of a six-part PTCS case definition by integrating evidence from the article reviews with expert opinion. Additional input from members of the Workgroup, as well as other thought leaders in brain injury research and clinical care invited to the 2017 Galveston Brain Injury Conference, was incorporated into the draft case definition during a session dedicated to this topic. Utilizing a modified Delphi procedure, each of the six components of the draft case definition was submitted to the entire author group for individual votes. The modified Delphi follows a procedure commonly used to achieve expert group consensus in medical science and other fields using rounds of voting, with summary of comments from each participant provided anonymously back to all participants. Four of the six components were approved on the first vote by receiving endorsement by 80+% of the author group, the threshold agreed at the start of the process. Based on written feedback provided as part of the vote, the other two components were edited and submitted for a second vote. A fifth component received endorsement on the second vote, performed online. The final component was again edited and this remaining component was endorsed by the third vote, performed online. Findings from articles
included in our review that were published after 2013 were reviewed by a subgroup of
the authors and found to support the language approved by the Delphi process; thus no
changes were made to the definition.

Results
Evidence Review
During the first round of abstract and article reviews (published through 2013), the
literature search yielded 1757 abstracts, from which 154 were retained for full-
manuscript review. Of these 154, 53 articles met all inclusion criteria. The second
literature search for 2013-2017, identified 649 additional abstracts. We reviewed 14
articles and retained 6 that met all inclusion criteria. During the final round of review
(i.e., abstracts identified during the review of publication references), 60 abstracts were
reviewed with 13 retained. Full article reviews indicated that 10 articles met all inclusion
criteria. In sum, we reviewed 2,466 abstracts and 181 full text articles. Sixty-nine articles
met all inclusion criteria and, of these, 44 contributed directly to the evidence presented
in Supplementary Materials (Supplementary Tables 4-16). PTCS phenomenology was
best represented with 34 articles addressing various signs of confusion (Figure 1).

In the articles that addressed one or more aspects of confusion, the 4 core
neurobehavioral features were evident in most individuals in PTCS. In articles that
addressed at least 6 neurobehavioral features of PTCS, 90% to 100% had impairments
on cognitive measures that primarily assessed attention and some aspects of new
learning. Orientation was impaired in 89% to 95% and fluctuation was observed in 97%
to 100% (Supplementary Tables 4 - 7). Longitudinal data indicate that features of PTCS may be present in patients who no longer meet criteria for PTCS (Supplementary Tables 4-11). The severity of these remaining features may be decreased and no longer sufficient to cause functional limitations at the level present in PTCS. A study using the Confusion Assessment Protocol as a measure of PTCS found that some persons emerged from PTCS remained with some of the 4 core features. However, the occurrence of these feature was markedly reduced; of persons who emerged from PTCS, only 35% remained with attention or memory impairment, 0% with disorientation, and 45% with fluctuation.\textsuperscript{17}

In articles that addressed multiple neurobehavioral features of PTCS, concurrent clinical features were also observed in many patients. Greater impairment of core features of PTCS such as memory and orientation was generally associated with a greater number of additional features such as emotional and/or behavioral disturbances and sleep-wake cycle disturbance. Behavioral and emotional dysregulation was evident in 53% to 72% (Supplementary Table 8). Sleep disturbance and arousal impairment were evident in 58% to 83% (Supplementary Table 9). Delusions, hallucinations, or other perceptual disturbances were observed in 46% to 72% (Supplementary Tables 10, and 11). Notably, no articles addressed confabulation as a sign of confusion. However, the Confusion Workgroup reached consensus that it should be included based on clinical experience.

Only 17 of 34 articles provided evidence for more than one of the 9 features of PTCS
described in our Case Definition. Only 3 articles addressed as many as 6 features and
none addressed all 9. Consequently, conclusions regarding the co-occurrence of
various features depended as much on expert opinion as on evidence.

Five articles provided evidence on the lower boundary of PTCS while 6 provided
evidence regarding the upper boundary. These articles provide a moderate amount of
evidence regarding the upper and lower boundaries of PTCS. However, for almost half
these papers, diagnosis of PTA was accepted as a proxy for PTCS. The lower
boundary for PTCS was largely based on the definition of the upper boundary for MCS\(^3\),
however some evidence suggested that the criteria for emergence from MCS requiring
accurate yes-no responses for all six basic questions might be too stringent.\(^{18}\) The lower
boundary for PTCS was worded to allow some flexibility in determining the return of
basic communication. The upper boundary was based on evidence that the 4 core
neurobehavioral features occurred at a substantially lower frequency in studies that
measured all of these components in individuals who were no longer considered in a
PTCS. Other evidence supported that recognition memory and free recall of newly
learned information can recover after orientation and should be important components
in the defining the upper boundary.\(^7\)

Ten articles provided evidence on the course of recovery of PTCS. These articles
provide preliminary evidence that recovery from PTCS is somewhat systematic with
certain signs more likely to resolve before others. One study tracked multiple clinical
features longitudinally and found that cognitive impairment and fluctuation were most
persistent, while psychotic features and sleep disturbance resolved earliest.\(^{18}\) One study
that measured aspects of attention, orientation and memory found that more demanding attentional tasks, orientation and recognition memory recovered at about the same time but that free recall of words after 24 hour delay recovered later. However, 7 of the 10 articles only assessed PTA so that information regarding the recovery of the broader clinical profile of PTCS is limited (Supplementary Table 15).

Eleven articles provided general evidence that persons emerged from PTCS are more functional, in both physical and cognitive domains, than those who are in PTCS. However, this evidence was primarily regarding general physical and cognitive functioning and did not allow determination of specific functional tasks that could be used to diagnose PTCS or indicate the level of support and supervision needed by individuals who have emerged from PTCS (Supplementary Table 16).

**Case Definition**

Following three rounds of modified Delphi voting, the group approved the six-part definition of PTCS shown in Table 2. Briefly, the case definition defines the clinical presentation of PTCS as requiring four core features while five associated neurobehavioral features may also be present. Functional abilities in multiple domains are impaired. Diagnosis of PTCS requires serial assessment and cannot be attributed to causes other than head trauma. The lower boundary of PTCS is defined by at least basic functional communication and/or simple, meaningful environmental interactions. The upper boundary of PTCS is defined by significant improvement in the 4 core and 5 associated features.
Discussion

PTCS commonly occurs after TBI of all severity levels. This condition often follows emergence from lower levels of consciousness, but also occurs with other patterns of recovery, including those without a period of unconsciousness. While historically, the term PTA has been used by some to label this phase of recovery, PTA is better used to indicate the clinical impairments of anterograde amnesia and disorientation following TBI. As defined by this Workgroup, PTCS encompasses multiple domains, including awareness, cognitive capacity, behavioral regulation and the ability to function safely and independently in daily activities and social interactions. The features of impaired memory and orientation that characterize PTA are subsumed in the PTCS case definition and should be considered a component of PTCS.

Distinctions between PTCS and other types of delirium

The definition of PTCS recognizes that some features of PTCS and the recovery process are particular to TBI and are distinct from existing diagnostic criteria for delirium or acute confusional state. The PTCS definition includes as features disturbances of attention and awareness, fluctuation, and cognitive impairment that are common core features of all forms of delirium as delineated in the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders 5 criteria for delirium. However, the evolving, incremental course of recovery and lower and upper boundaries are specific to PTCS and are not characteristic of other types of delirium. Indeed, the Diagnostic and Statistical Manual - 5 (DSM – 5) criteria exclude “evolving neurocognitive disorder” from the diagnosis of delirium. Anterograde amnesia, with impairment of memory...
encoding, which is a prominent characteristic of PTCS, is not strongly emphasized in DSM – 5 or other diagnostic criteria for delirium. Although PTCS after TBI is usually a transitional condition leading to higher levels of recovery, delirium of other causes may indicate an acute medical problem that may recover, wax and wane, or portend a grave prognosis.\textsuperscript{20, 21}

\textbf{Features of PTCS}

The six-part definition developed by the Confusion Workgroup describes PTCS as a clinical condition that encompasses 4 necessary core features outlined in Table 2: prominent disturbances of attention, orientation, and memory, with marked fluctuation in the cognitive and behavioral manifestations. These core features occur in all those with PTCS but may vary in severity and time course of resolution. There are several other clinical features characteristic of the condition, such as emotional problems, behavioral dysregulation, sleep-wake cycle dysregulation, delusions, perceptual disturbances and confabulation. These may or may not occur in addition to the core features, and they present with varying frequency and severity.

\textbf{Natural History and Lower and Upper Boundaries of PTCS}

Evidence from our review indicates that PTCS is one of several stages of recovery that may be seen in persons who sustain moderate and severe TBI. Those with the most severe injuries commonly show a transition from states in which no consciousness can be detected (coma, VS) to a state (MCS) that is characterized by limited, inconsistent consciousness. After resolution of MCS, patients are more aware of themselves and the world around them, but remain with acute confusion and other deficits. PTCS is the next
period of disturbed consciousness following coma, VS, and MCS as described by the
Aspen Work Group. Consequently, emergence from MCS is seen as the lower limit of
PTCS.

The interval from injury to transition to PTCS varies depending on injury severity, and
different patterns of anatomic lesions and pathophysiology. Some patients present in a
PTCS right after trauma, without unconsciousness or following a relatively a brief period
of loss of consciousness. It is more difficult to specify a lower boundary for these
patients. Others have a period of markedly decreased arousal following the injury, due
to neurologic effects of the injury or sedation, so that the full syndrome of PTCS is not
initially apparent or is difficult to characterize.

As with coma, VS, and MCS, PTCS duration largely varies with severity of TBI and can
range from short periods lasting minutes to hours, to prolonged durations, lasting weeks
or months. For some with very severe injuries, the core features may not fully resolve.
Severity and duration of PTCS are determined by various factors such as the
pathophysiologic profile, secondary complications, age, and cognitive reserve. Greater
duration and severity is generally associated with worse long-term outcome.

In the most comprehensive study of recovery of cognitive function in patients in
confusion to date, Stuss and colleagues demonstrated that patients with mild to severe
TBI showed recovery of orientation before recovery of 3 word recall at a 24 hour delay
and that attention on simple tasks recovered earlier than attention on more demanding
tasks. Similarly, Baird et al. showed that recognition memory generally recovered after
resolution of orientation. Recovery of attention occurred concurrently with recovery of orientation and recognition memory. Components of orientation and episodic memory recovered at different rates. Aspects of personal orientation recovered earliest, while recall of date and episodic recall of the last events before injury and first events after injury were the latest to resolve.\textsuperscript{25, 26} Persistence of certain clinical features is more strongly associated with severity and prognosis, perhaps due to differential underlying pathophysiology. For instance, psychotic features, including delusions and hallucinations, are more prevalent with greater severity of PTCS and indicate less favorable prognosis for return to employment.\textsuperscript{15}

Although individual features of PTCS may not fully normalize, with resolution of PTCS, improvements in cognitive and behavioral capacity support improved ability to perform activities of daily living and engage in social interactions. Safety concerns, level of dependence and need for supervision lessen considerably.\textsuperscript{27, 28} Although cognitive function improves significantly with resolution of PTCS, residual cognitive impairments in aspects of attention, memory retrieval and executive functioning are common.\textsuperscript{15} More profound residual impairments may be labeled by the domain(s) affected – e.g. aphasia, amnesia, dysexecutive syndrome. There is no clear consensus on what to label the condition if all 4 core features are still severely affected over the long term, or how to mark the transition from PTCS to a residual multi-domain cognitive dysfunctional condition. Possible labels include, chronic PTCS, post-traumatic dementia, and persisting ‘major neurocognitive disorder’ per DSM - 5 criteria.\textsuperscript{19}
For those in PTCS, impairments of attention, orientation, memory, and consistency of behavior are so severe that the patient’s functional independence is limited (Table 2, Row 3). Resolution of PTCS is associated with improvements in attention, orientation, memory, and consistency of behavior that are sufficient to result in greater functional independence. However, unlike MCS, in which two specific behaviors provide evidence that a person has emerged, there is no generally agreed upon level of functional ability that indicates resolution of confusion. This is because the range of behaviors exhibited by confused patients is substantially greater than for those in MCS and the variety of social contexts in which these behaviors can be manifested is also substantially greater. Additionally, measurement of improvement in the degree of confusion is not precise due to shortcomings of current assessments.

At this point, there are no agreed upon cut-offs for the amount of improvement needed to indicate that a patient is no longer in PTCS. Table 2, Row 6 provides some examples of the degree of improvement that could be taken as evidence that PTCS has resolved. These guidelines are related to the four core features as opposed to behaviors that would occur in naturalistic settings. One could imagine more specific behavioral indices of resolution of confusion such as (1) able to stay at home for periods up to 8 hours with no safety concerns, (2) able to carry on an appropriate conversation with a stranger even if mildly provoked by negative statements made by the stranger, or (3) able to prepare a simple meal with no risk of fire or other safety issue, etc.
Implications for Measurement of PTCS for Clinical and Research Purposes

One key aim in developing a case definition for PTCS was to improve diagnostic accuracy and reliability of assessment of PTCS for clinical and research purposes. Improved measures will contribute to improved understanding of brain injury recovery, care management, and prognostication. The case definition facilitates monitoring the course of recovery, gauging clinical severity, and identifying clinical patterns and profiles. The definition will guide development of measures to better inform prognosis and clinical management.

Comprehensive clinical histories and examinations that account for the four core and five associated features will be necessary for accurate diagnosis of PTCS. As has been recommended for diagnostic assessment of other DoCs, serial, standardized neurobehavioral assessments should be used to promote better diagnostic accuracy and characterize the course of the PTCS. There should be consideration of confounds, such as aphasia that may compromise the accuracy and sensitivity of any assessment.

Measures of core features, such as attention, orientation, and memory may include a variety of established, standardized clinical assessments. However, it would be impractical to rely on separate psychometrics for each characteristic of PTCS and best to use assessments that collectively evaluate multiple features of PTCS. Such a measure should account for all core and associated features of the condition, track severity and provide suggested criteria for the upper and lower boundaries of PTCS. The Confusion Assessment Protocol (CAP), partially based on the Delirium Rating
Scale-Revised 98 (DRS-98)\textsuperscript{32} and other standardized measures, was designed to address the broader range of problems identified in delirium after TBI. However, neither the CAP\textsuperscript{17}, nor the other currently available measures capture all PTCS features. Limitations of existing tools include: 1) failure to cover all aspects of the definition; 2) unknown reliability and validity; 3) subjective ratings that are vulnerable to bias and inaccuracy; and 4) lack of an established comparative diagnostic reference standard (psychometric, behavioral, biologic, or otherwise).

Fluctuation, a core feature of the PTCS, is challenging to measure; repeated observation or measurement is required.\textsuperscript{33} Individuals who are inconsistent in their neurobehavioral presentation may manifest variability within short intervals or over more prolonged periods. Severe fluctuation can be observed during bedside examination with inconsistencies in presentation noted to occur over the course of minutes. In mild fluctuation, patients manifest variability over longer periods of time. Variability can be observed in level of arousal and/or responsiveness, behavioral disturbance, emotional lability, and cognitive performance (e.g., following instructions, orientation). Significant fluctuation that is consistent with PTCS results in the need for greater supervision as the patient poses a safety risk. Clinician ratings are commonly used to assess fluctuation. Sources of information may include direct observation (e.g., during mental status examination), informant report, and medical record review. Improved standardized measures are needed to assess fluctuation and other associated features PTCS (e.g., emotional and/or behavioral disturbances, sleep-wake cycle disturbance, delusions, perceptual disturbances and confabulation).
One of the key challenges for a standardized measure is defining the upper boundary and resolution of PTCS, recognizing that impairments in some of the core and associated features may still be evident. At present, the best description of the upper boundary of PTCS is the point at which deficits in attention, orientation, memory, and behavioral consistency have improved sufficiently to no longer have major impact on the patient’s functional independence for basic self-care and safety awareness.

More research is needed to create and validate both psychometric and behavioral referents of emergence from PTCS. As is the strategy in defining resolution of PTCS for the Confusion Assessment Protocol, improvement in combinations of clinical features, some weighted more than others, may better indicate resolution of PTCS rather than specific cutoffs for each domain. Measures of overall function and social competence may also help define PTCS resolution.

In summary, no current measure assesses the full range of core and additional neurobehavioral deficits seen in PTCS (Table 3). The two measures that are closest to achieving this goal are the CAP and the DRS-98. The CAP includes a mixture of clinical rated items and objective cognitive tests. Assessment of cognition is limited due to failure to assess verbal declarative memory. Among clinician rated scales, agitation is assessed using the Agitated Behavior Scale. Authors of the CAP provide criteria for determining whether or not a patient is confused. The DRS-98 consists entirely of clinician rated items and thus the assessment may be less reliable. Further, there are no clear criteria to determining whether a patient is in PTCS. Though flawed, at this point, it appears that the CAP is best measure to assess PTCS.
Implications for Treatment

Improved characterization of the features of PTCS may result in application of interventions for the various clinical features and promote improved monitoring of the responses to interventions. For persons in PTCS, treatment goals include maintaining safety, preventing secondary complications and restoring functional independence in self-care and mobility. Patients with emotional and/or behavioral disturbances benefit from environmental and behavioral interventions. Persons in PTCS with severe amnesia have the potential to acquire skills and improve performance using preserved procedural memory capacity, despite profound deficits in attention and declarative learning. A recent randomized controlled trial demonstrated significantly greater improvement in functional performance in activities of daily living on the FIM in persons in PTA after severe TBI in the treatment group using retraining strategies based on errorless and procedural learning principles compared to a usual treatment group. Persons who have emerged from PTCS are particularly strong candidates for active participation in rehabilitation interventions.

Limitations and Directions for Future Research

The case definition was derived based on the existing literature and extensive clinical experience. Prior studies have largely focused on memory and orientation impairments associated with PTA and few studies simultaneously examine all of the features of PTCS in this case definition. There was also limited evidence to fully inform the natural history and upper boundary of this condition. The natural history of PTCS has not been fully characterized, as measures used in PTCS research do not capture the full array of
core and additional neurobehavioral features. No studies meeting inclusion criteria for this review addressed confabulation and the decision to retain it in the definition was based solely on the consensus of the Workgroup.

A primary goal for future research is the development of a new instrument for assessing degree and pattern of confusion, with sufficient precision that natural history studies are more feasible and accurate. Accordingly, new measurement tools that assess all features of the PTCS should be validated, including cut-offs for the lower and upper boundaries. The lack of a reference standard or biomarker for PTCS will make it challenging to validate new tools. Research on functional abilities that distinguish confused and non-confused patients may provide additional guidance for assessment.

Future studies may consider using this case definition to identify subtypes of PTCS and patterns of recovery. The pathophysiologic mechanism of TBI recovery and PTCS remain poorly understood. Identification of biomarkers with relationship to PTCS subtypes, patterns, and prognosis would have substantial clinical and research utility. Use of this case definition should help inform future guidelines for clinical management of PTCS, including maintaining safety, promoting injury prevention, identifying supervision needs, optimizing sleep, and mitigating behavioral dysregulation and perceptual disturbances. This case definition is a new starting point to facilitate more consistent and reliable diagnosis of PTCS for research and clinical purposes. As new evidence emerges and the case definition is tested, revisions to the case definition may be required.
Figure Legend

Figure 1: Number of articles addressing each domain of the PTCS case definition
References

1. Symonds CP. Mental Disorder Following Head Injury: (Section of Psychiatry). Proc R Soc Med 1937;30(9):1081-94.


Table 1. Comparison of Clinical Signs of Disorders of Consciousness

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Consciousness</th>
<th>Sleep/wake Cycles</th>
<th>Command Following</th>
<th>Communication</th>
<th>Cognition</th>
<th>Neurobehavioral Signs</th>
<th>Signs of Transition to Higher Level of Consciousness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coma</td>
<td>None</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>None detected</td>
<td>None exhibited</td>
<td>Eye opening</td>
</tr>
<tr>
<td>Vegetative State</td>
<td>None</td>
<td>Present, but sleep disturbance and fluctuating arousal common</td>
<td>Absent</td>
<td>Absent</td>
<td>None detected</td>
<td>None exhibited</td>
<td>Visual fixation, localization to noxious stimulation, intelligible verbalizations, yes/no responses even if inaccurate, reproducible movement to command</td>
</tr>
<tr>
<td>Minimally Conscious State</td>
<td>Partial</td>
<td>Present, but sleep disturbance and fluctuating arousal common</td>
<td>Inconsistent, if present.</td>
<td>Inaccurate or inconsistent yes/no responses, if present</td>
<td>Some cognitive function can be discerned from command following, communication, etc. but fluctuation makes this difficult to assess</td>
<td>Contingent emotional response to family or familiar stimuli</td>
<td>Functional communication – yes and no responses are accurate and reliable, appropriate functional object use of at least 2 common objects</td>
</tr>
<tr>
<td>Post-traumatic Confusional State</td>
<td>Intact for internal states and external events but often does not lead to functional behavior due to disorganization, misinterpretation, etc.</td>
<td>Present, but sleep disturbance and fluctuating arousal common</td>
<td>Usually consistent, but may fluctuate</td>
<td>Ability to communicate generally intact, but social appropriateness and accuracy vary.</td>
<td>Impaired attention and memory, disorientation</td>
<td>Fluctuation in presentation, emotional and/or behavioral disturbance, confabulation, delusions, perceptual disturbances</td>
<td>Ability to attend to and process simple information, general orientation, recall of some recent events, lack of marked cognitive or behavioral fluctuations</td>
</tr>
</tbody>
</table>

1 While eye opening is commonly accepted as indicating transition from coma to VS, there is no consistent evidence that this transition is associated with an improved level of consciousness
### Table 2: PTCS Case Definition

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Clinical Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The post-traumatic confusional state is a disorder of consciousness characterized by all of the following core neurobehavioral features:</td>
<td>Phenomenology</td>
</tr>
<tr>
<td>A. <strong>Disturbances of Attention</strong>: reduced ability to focus or sustain attention.</td>
<td>Assessment</td>
</tr>
<tr>
<td>B. <strong>Disorientation</strong>: impaired orientation to place, time and situation.</td>
<td></td>
</tr>
<tr>
<td>C. <strong>Disturbances of Memory</strong>: impaired ability to encode and recall new information.</td>
<td></td>
</tr>
<tr>
<td>D. <strong>Fluctuation</strong>: The character and severity of the disturbance waxes and wanes during the course of the day.</td>
<td></td>
</tr>
</tbody>
</table>

Identifying the core clinical features of PTCS requires systematic serial assessment, recognizing that these features vary in severity and improve at different rates as the condition evolves.

| Phenomenology |

2. In addition to these four core neurobehavioral features, PTCS can include any of the following:

| Emotional and/or Behavioral Disturbances: including but not limited to agitation/restlessness and/or hypoactivity; irritability, impulsivity, disinhibition, aggression and/or decreased responsiveness; affective lability and/or flattening. | |
| Sleep-wake Cycle Disturbance: excessive sleep, insufficient sleep, alteration of normal sleep pattern, or decreased level of arousal. | |
| Delusions: fixed false beliefs | |
| Perceptual Disturbance: illusions, hallucinations | |
| Confabulation: false memory | |

3. Impairments in the core and associated areas are of sufficient severity to limit functional independence and interfere with the individual’s ability to cooperate with needed medical care, maintain personal safety, and/or interact effectively with others and the environment.

4. The core and associated features are not better explained by another preexisting, established, or evolving neurocognitive disorder, psychiatric disorder, medical condition, substance intoxication or withdrawal, or exposure to a toxin or medication.

5. PTCS can occur immediately after trauma or as a transition from a lower or higher level of consciousness. For those individuals who transition from a lower level of consciousness, such as coma, VS/UWS or MCS, the lower boundary of the PTCS is characterized by recovery of at least basic functional communication and/or simple, meaningful environmental interactions. The period of transition can be indistinct or fluctuating in some patients.

6. Emergence from PTCS is defined by clinically important improvement in the four core and associated neurobehavioral features as demonstrated by:

| Ability to attend to and process simple information so that the individual is able to cooperate with caregivers by following instructions and attending when performing basic familiar tasks | |
| General orientation to time, place, and personal circumstances, | |
| Ability to recall some recent events or learn at least limited new information that can be recalled later, and | |
| Lack of marked cognitive or behavioral fluctuations so that the patient can participate in simple social interactions. | |

A portion of individuals will have more severe persisting problems in one or more cognitive domains that inform the diagnosis of the residual clinical condition (e.g. aphasia, amnesia).
Table 3: Composite measures that assess at least two features of PTCS

<table>
<thead>
<tr>
<th>Domains</th>
<th>CAP</th>
<th>DRS- R98</th>
<th>CAM</th>
<th>CTD</th>
<th>TOTART</th>
<th>NBRS</th>
<th>GOAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>P</td>
<td>O</td>
<td>O</td>
<td>P</td>
<td>P</td>
<td>O</td>
<td>NA</td>
</tr>
<tr>
<td>Memory</td>
<td>P</td>
<td>O</td>
<td>O</td>
<td>P</td>
<td>P</td>
<td>NA</td>
<td>P</td>
</tr>
<tr>
<td>Disorientation</td>
<td>P</td>
<td>O</td>
<td>O</td>
<td>P</td>
<td>P</td>
<td>O</td>
<td>P</td>
</tr>
<tr>
<td>Symptom fluctuation</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Behavioral disturbance</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>NA</td>
<td>NA</td>
<td>O</td>
<td>NA</td>
</tr>
<tr>
<td>Sleep-wake cycle disturbance</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>NA</td>
<td>NA</td>
<td>O</td>
<td>NA</td>
</tr>
<tr>
<td>Confabulation</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Delusions</td>
<td>O</td>
<td>O</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>O</td>
<td>NA</td>
</tr>
<tr>
<td>Perceptual disturbance</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>NA</td>
<td>NA</td>
<td>O</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations:

P: performance-based, O: observational, NA: not assessed

CAP: Confusion Assessment Protocol\textsuperscript{41}, DRS-R98: Delirium Rating Scale-Revised 98\textsuperscript{44},
CAM: Confusion Assessment Measure\textsuperscript{46}, CTD: Cognitive Test for Delirium\textsuperscript{47}, TOTART: Toronto Test of Acute Recovery After TBI\textsuperscript{6}, NBRS: Neurobehavioral Rating Scale\textsuperscript{48},
GOAT: Galveston Orientation and Amnesia Test\textsuperscript{15}
Figure 1

PTCS Definition Component

![Bar chart showing the number of articles meeting inclusion criteria for different components of the PTCS definition: Phenomenology, Time Course, Pattern of Recovery, Implications for Function, Upper Boundary, Lower Boundary, and Pathophysiology. The chart indicates a higher number of articles meeting the criteria for Phenomenology compared to other components.]