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WHAT'S NEW IN INTENSIVE CARE

Updated nomenclature of delirium and acute encephalopathy: statement of ten Societies

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Segregation of published research

Patients with an acute illness frequently acquire an acute, global disturbance in cognition variably referred to as *delirium*, *encephalopathy*, *acute confusional state*, *acute brain dysfunction*, *acute brain failure*, *and altered mental status* [1]. Although these different terms may have been perceived as distinct clinical entities [2], evidence to support such distinctions is lacking.

Acute disturbances in cognition are particularly prevalent among individuals admitted to the intensive-care unit [3]. These disturbances have been linked to predisposing and triggering factors [4], and have been independently associated with adverse short- and long-term outcomes, including higher mortality and chronic cognitive impairment [5, 6]. While progress has been made in the detection of this problem, research is needed to identify effective interventions for prevention and treatment. A rational approach to nomenclature represents an important basis to enable such advances.

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Societies: American Academy of Neurology (AAN), American Delirium Society (ADS), European Academy of Neurology (EAN), European Delirium Association (EDA), European Geriatric Medicine Society (EuGMS), European Society of Anaesthesiology (ESA), European Society of Intensive Care Medicine (ESICM), Neurocritical Care Society (NCS), Society of Critical Care Medicine (SCCM), and Società Italiana di Anestesia Analgesia Rianimazione e Terapia Intensiva (SIAARTI)

A definition of delirium is provided in the 5th version of the Diagnostic and Statistical Manual (DSM-5) of the American Psychiatric Association [7] and in the 11th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-11) [8]. Encephalopathy is a generic term that has been used to describe a global disturbance in brain function. However, the terms *acute encephalopathy, acute confusional state, acute brain dysfunction, acute brain failure,* and *altered mental status* lack uniform definitions and are not present in formal diagnostic systems. Our analysis focuses on delirium and acute encephalopathy, as these are the most frequently used terms.

We hypothesized that published research on delirium and encephalopathy is highly segregated, and that this segregation would be linked to the clinical discipline of investigators. We conducted a systematic search (see details in the Supplementary Materials) which led to three findings. First, journals on clinical neurology, neurosciences, or general or internal medicine published significantly more articles with 'encephalopathy' in the title, whereas journals associated with geriatrics, gerontology, psychiatry, psychology, intensive-care medicine, or anaesthesiology published significantly more delirium-titled articles ($P<0.001$). Second, articles with 'encephalopathy' in the title rarely (1%, $n=1$ of 100 randomly selected articles) mentioned 'delirium' in the text, and conversely articles with 'delirium' in the title used the word 'encephalopathy' in not more than 2% of publications ($n=2$ out of 100). Third, almost all citations in the delirium and encephalopathy literature (98.77%, $n=36{,}729$) were between papers with matching terms in the titles (i.e., delirium-titled articles citing other delirium-titled articles

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and encephalopathy-titled articles citing other encephalopathy-titled articles). Only a small proportion (0.53%, $n=197$) of citations were from encephalopathy-titled articles citing delirium-titled papers, or from delirium-titled articles referencing papers with the term 'encephalopathy' in the title (0.70%; $n=259$). It should, however, be noted that almost all articles on 'acute encephalopathy' use the term 'encephalopathy' in isolation; therefore, it is possible that segregation of the literature could be driven, in part, by the inclusion of articles on chronic encephalopathy.

These findings confirmed our hypothesis on the existence of segregated literatures, and suggest conceptual or semantic disparities across different medical disciplines. We believe that the lack of a uniform nomenclature represents a significant barrier to scientific progress and has implications for clinical management that might influence patient outcome. For example, use of the term 'delirium' may trigger specific management, whereas 'septic encephalopathy' may overlook mechanisms other than sepsis, such as metabolic alterations or drug side-effects. Additional factors, such as differences in billing and reimbursement between patients diagnosed with encephalopathy (versus delirium), may be a factor driving the selective use of terms in some countries, such as the USA.

Consensus recommendations on nomenclature

To generate expert consensus, we convened an international, interdisciplinary panel of leading experts with expertise in intensive-care medicine, neurology, geriatrics, rehabilitation medicine, pharmacy, anaesthesiology, and psychiatry. Panellists were tasked with generating recommendations on the nomenclature of delirium, acute encephalopathy, and related terms. The definitions were created, refined, and voted on using the modified Delphi method (see Supplementary Materials).

The panel recommends the term *acute encephalopathy* to describe a rapidly developing (in less than 4 weeks) pathobiological brain process which is expressed clinically as either subsyndromal delirium, delirium or coma and may have additional features, such as seizures or extrapyramidal signs (Box). The term acute encephalopathy is not recommended as a descriptor of clinical features that can be observed at the bedside. Instead, the panel recommends the term *subsyndromal delirium* for acute cognitive changes that are compatible with delirium, but do not fulfil all DSM-5 delirium criteria, *delirium* for a clinical state defined according to the criteria of the DSM-5 [6], and *coma* for a state of severely depressed responsiveness defined using diagnostic systems such as the Glasgow Coma Score (GCS) or the Full Outline of UnResponsiveness (FOUR) score (Box) [9, 10]. The panel further recommends against use of the terms *acute confusional state, acute brain dysfunction, acute brain failure*, or *altered mental status* in clinical practice or research (Box). Although these terms might have relevance for educational purposes, the panel felt that they lacked face or construct validity.

The recommendations in this manuscript have been endorsed by ten key professional societies (see Supplementary Materials), and this terminology is congruent with the recent recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery [11]. Delayed neurocognitive recovery after anaesthesia and surgery can be regarded as consequence of prolonged postoperative acute encephalopathy.

In conclusion, current literature on delirium and acute encephalopathy is highly segregated, presenting an obstacle for clinical care and research. We recommend a consensus-based, pragmatic nomenclature which we expect will establish a foundation for advances in the field. Following dissemination of these recommendations, future research should evaluate the impact of this revised nomenclature on clinical practice and research.

Box: Recommendations for the nomenclature of delirium, acute encephalopathy, and related terms

1. The term *acute encephalopathy* refers to a rapidly developing (over less than 4 weeks, but usually within hours to a few days) pathobiological process in the brain. **This is a preferred term**
2. *Acute encephalopathy* can lead to a clinical presentation of subsyndromal delirium, delirium, or in case of a severely decreased level of consciousness, coma; all representing a change from baseline cognitive status
3. The term *delirium* refers to a clinical state characterized by a combination of features defined by diagnostic systems such as the DSM-5. Delirium according to the DSM-5 is defined if criterium A-E are fulfilled: A. Disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment). B. The disturbance develops over a short period of time (usually hours to a few days) represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of the day. C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception). D. The disturbances in criteria A and C are not explained by another pre-existing, established, or evolving neurocognitive disorder, and do not occur in the context of a severely reduced level of arousal, such as coma. E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal (i.e. because of a drug of abuse medication), or exposure to a toxin, or is because of multiple etiologies. **This is a preferred term**
4. The term *coma* refers to a clinical state of severely depressed responsiveness defined by diagnostic systems such as the GCS or FOUR score. **This is a preferred term**
5. The term *acute confusional state* **should not be used** in addition to the terms delirium and acute encephalopathy
6. The term *acute brain dysfunction* **should not be used** in addition to the terms delirium and acute encephalopathy
7. The term *acute brain failure* **should not be used** in addition to the terms delirium and acute encephalopathy
8. The term *altered mental status* is not synonymous with *delirium* and **should not be used**

DSM-5 means the Diagnostic and Statistical Manual (DSM-5) of the American Psychiatric Association. GCS refers to Glasgow Coma Score; the FOUR score means the Full Outline of UnResponsiveness score.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05907-4) contains supplementary material, which is available to authorized users.

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All authors contributed to the conception and design. Material preparation, data collection and analysis were performed by Arjen J. C. Slooter, Wim M. Otte, John W Devlin, Matthew S. Duprey, and Robert D Stevens. The first draft of the manuscript was written by Arjen J. C. Slooter and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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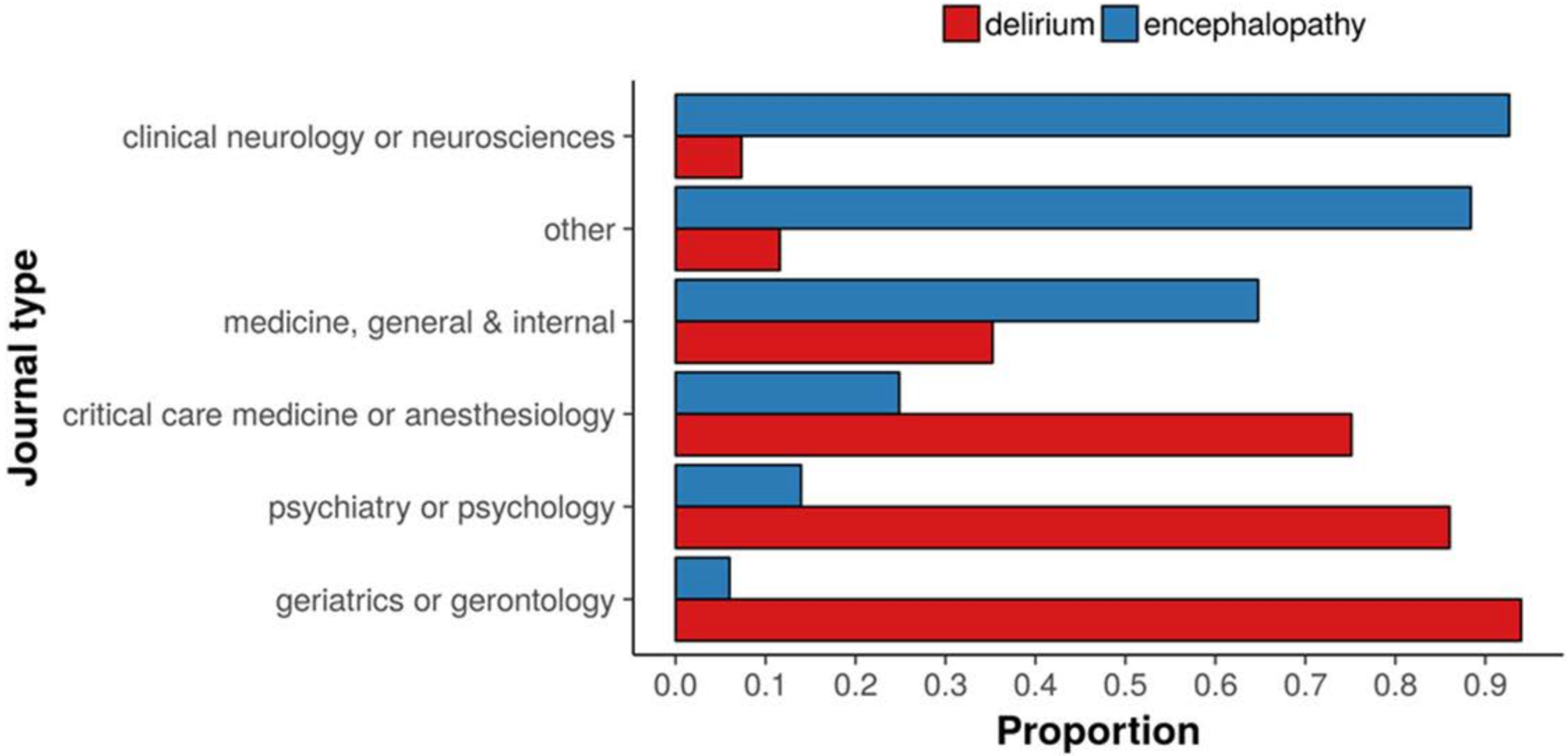
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encephalopathy
clinical neurology or neurosciences
other
medicine, general & internal
critical care medicine or anesthesiology
psychiatry or psychology
geriatrics or gerontology
Journal type
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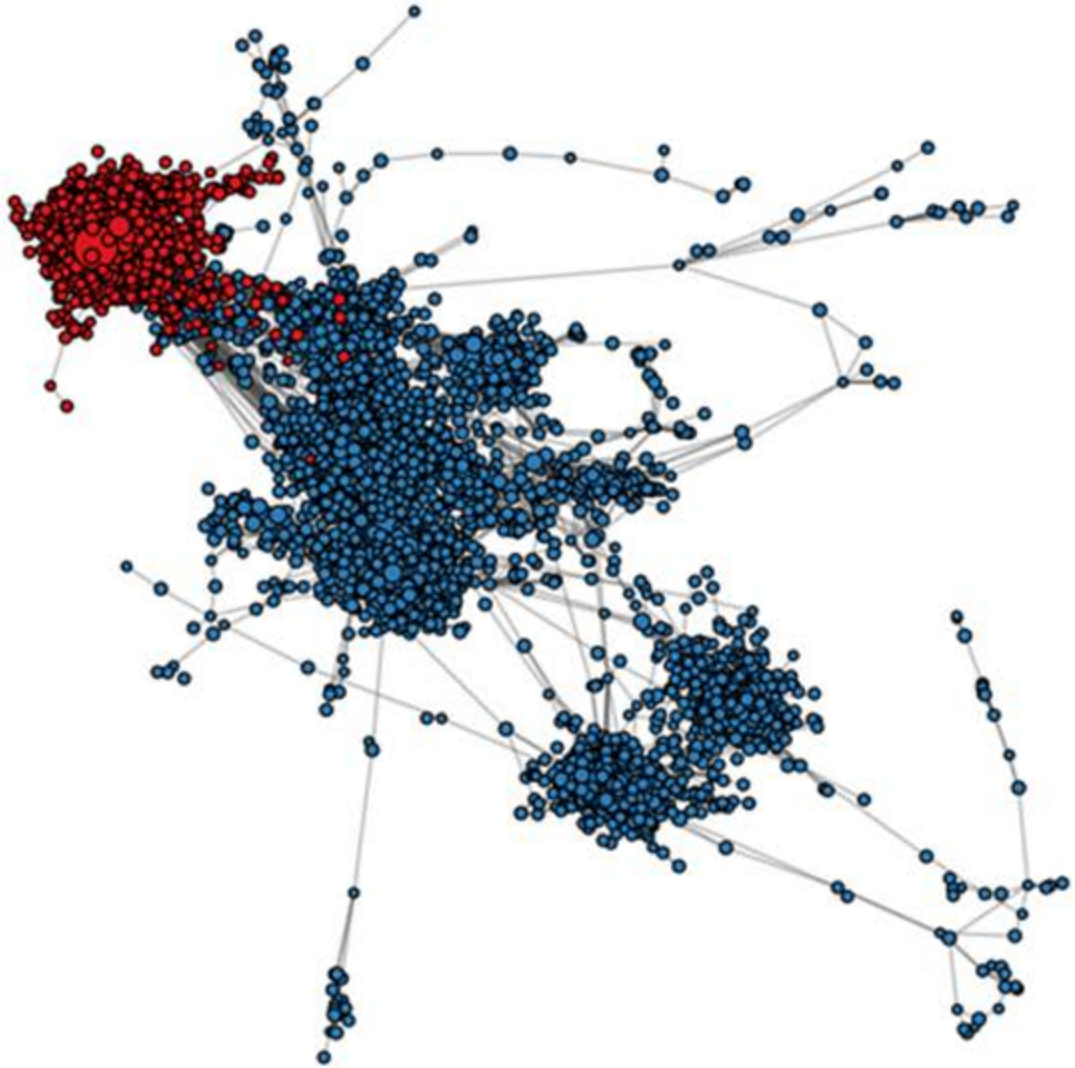

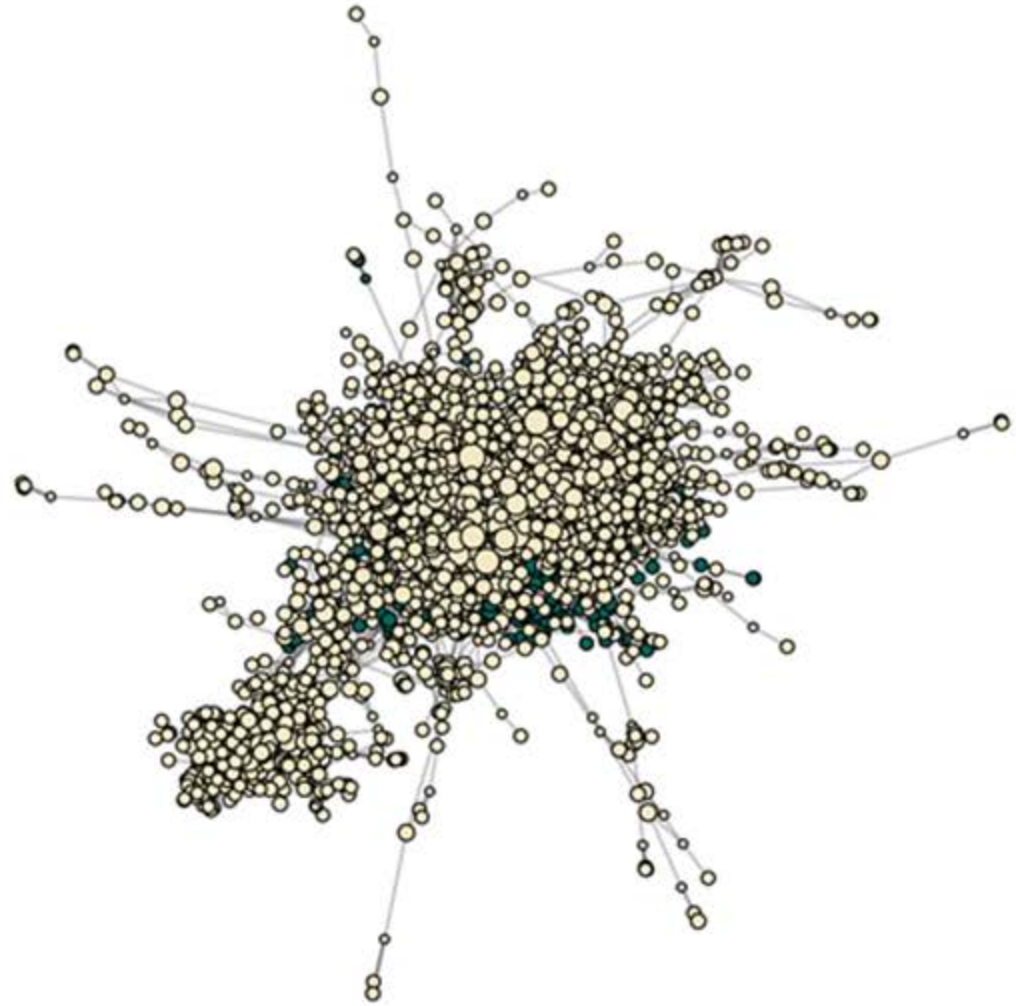

Supplementary Material

To assess the extent of segregation of the literature on delirium and encephalopathy, we performed the following systematic search in the PubMed database [1]. The titles of all publications, including reviews and editorials, between January 1, 1990 and June 1, 2018 were searched for the terms *delirium, encephalopathy, acute confusional state, acute brain dysfunction, acute brain failure*, and *altered mental status*. We elected to start the search in 1990 as this was the year when a widely used tool for delirium screening was published [2]. Publications on chronic encephalopathy were excluded. Unique PubMed IDs, assigned to every publication, were automatically collected using Entrez Programming Utilities [3].

The queries for searches in the PubMed database were as follows: [delirium[ti] AND ("1990/01/01"[PDAT] : "2500/12/31"[PDAT])] for delirium publications, [(encephalopathy[ti] AND ("1990/01/01"[PDAT] : "2500/12/31"[PDAT])) NOT "chronic traumatic encephalopathy"[tiab]] NOT "chronic encephalopathy"[tiab]] for articles on encephalopathy, ["acute confusional state "[ti] AND ("1990/01/01"[PDAT] : "2500/12/31"[PDAT])] for publications on acute confusional state, ["acute brain dysfunction"[ti] AND ("1990/01/01"[PDAT] : "2500/12/31"[PDAT])] for papers on acute brain dysfunction, and ["acute brain failure"[ti] AND ("1990/01/01"[PDAT] : "2500/12/31"[PDAT])] for articles on acute brain failure, and ["altered mental status "[ti] AND ("1990/01/01"[PDAT]: "2500/12/31"[PDAT])] for publications on altered mental status.

The PubMed search yielded 18,865 unique publications, of which 5,709 were delirium-titled articles, and 13,156 were encephalopathy-titled articles; 13 publications had both terms in the title. A limited number of publications had acute confusional state (n=69), acute brain dysfunction (n=10), acute brain failure (n=6), or altered mental status (n=315) in the title.

We manually labelled all journal titles into six clinical domains using the Web of Science classifications as follows: a) psychiatry or psychology, b) geriatrics or gerontology, c) critical care medicine or anaesthesiology, d) clinical neurology or neurosciences, e) internal or general medicine, and f) other disciplines, such as surgery. We then determined the distribution of the delirium- and encephalopathy-titled articles according to the six journal domains (Supplementary Figure 1).

PubMed IDs were linked to one another based on cross-citations with other publications in the database, and citation links were converted into citation networks. Citation networks can be quantified using social network methods by identifying the proportion of citations within and between clusters of related publications [4]. All network links point backwards in time given that articles can only cite prior publications; longer

temporal periods give rise to denser networks. All nodes from the citation network covering the 1990-2018 timespan were represented in two-dimensional space with a force-directed drawing algorithm, where each node corresponds to a publication and the edges are cross-citation [5]. To limit bias due to citation identification based solely on the title, we repeated our analysis using the full text of all article abstracts. We used a force-directed algorithm as this does not require specific prior network knowledge. The positioning was established with a combination of attractive forces on adjacent nodes, and a general repulsive force on all nodes. The nodes were moved iteratively within the two-dimensional space to minimize the total energy. Consequently, network nodes with many connecting links cluster together, whereas nodes with no or few links move apart. Publications not connected to other publications (that is, not a single matching citation) were not visualized and excluded from the analyses.

The citation network of papers published between 1990 and 2018 on delirium and encephalopathy is shown in Figure 2 (left). On visual inspection, the network was highly segregated, with a single cluster of delirium articles and several clusters of encephalopathy articles.

To confirm the validity of this approach, a reference citation network was constructed for another disorder having terminological uncertainty, seizures and epilepsy, with restriction to the common subtype temporal lobe epilepsy. A reference citation network over the same time period of 10,175 papers with the term temporal lobe seizures in the title and 3,480 with epilepsy in the title is shown in Figure 2 (right). This network had a significantly higher proportion of between-group citations compared to the delirium-encephalopathy literature (13.04% versus 1.18%, $P<0.0001$).

To assess cross-citation of the delirium and encephalopathy literature, we randomly sampled original, English-language, research articles evaluating ≥20 patients with delirium or encephalopathy in the title. Two hundred articles (100 delirium-titled and 100 encephalopathy-titled) were randomly selected from 5-year epochs starting in 1990 by dividing the total number of articles in each epoch by 40. For example, if 120 articles existed in an epoch, the text of every third article was reviewed.

To generate recommendations on the uniform use of the terms acute encephalopathy, coma, and delirium, and related terms, an international, interdisciplinary panel of leading experts was assigned. Participants were selected based on their field of expertise, relevant publications, and leadership in relevant professional societies. These included the following authors: AJCS, RCA, JWD, TPB, JC, EWE, PWK, NL, AM, KJN, TS, AMJM, RDS. The Delphi process and all panel deliberations were coordinated by a steering committee (AJCS, RCA, AMJM, RDS).

Consensus was established using the Delphi approach [6,7] and included the following features: a) recruitment of a panel of experts; b) iterative rounds of voting on key statements using web-based surveys; c) anonymity of the voting procedure; and d) provision of a summary of voting results after each round to enable participants to compare their responses to others before voting in the subsequent round. Recommendations were forged through discussion via e-mail and teleconferences. Based on preliminary discussions involving the entire panel, the steering committee drafted statements that were rated by all panel members on a five-point Likert scale (ranging from strongly disagree to strongly agree) using a web-based tool. Consensus was defined a priori as an 80% agreement between responding panel members with regard to a given statement. After each Delphi round, panellists received voting results as anonymized, summary group scores. Based on responses and comments from the entire panel during conference calls and follow up e-mails, statements were modified or eliminated prior to the next Delphi round.

Consensus on the nomenclature of delirium, acute encephalopathy, and related terms was developed in seven Delphi rounds (each with a 100% response, except for the sixth round with a 92% response). The consensus threshold of >80% agreement was reached for the statements indicated in bold below, indicating a strong agreement among responding panel members.

Delphi round 1 (November 2016)

1. Diagnostic criteria for acute encephalopathy are needed so that clinicians and researchers can agree on the meaning of this term and use it in a consistent fashion.
2. The diagnostic criteria for delirium as articulated in the DSM-5 accurately describe this syndrome.
3. The terms delirium and acute encephalopathy have the same meaning and are interchangeable.
4. The term acute confusional state means the same as the term delirium.
5. **Acute encephalopathy refers to a spectrum of brain disorders whose expression may include delirium and coma.**
6. The spectrum of acute encephalopathy encompasses additional clinical features such as stupor, obtundation, and lethargy.
7. There may be overlap between the clinical features of delirium and stupor, obtundation, or lethargy.
8. A patient with stupor cannot have delirium, because the level of arousal is too low. In other words, making a diagnosis of delirium requires a minimum level of arousal which is above the level of stupor.
9. While they may have the same aetiology, delirium and coma are separate and mutually exclusive clinical

phenotypes. In other words a patient with delirium cannot be comatose, and a patient with coma cannot be delirious.

10. An acute encephalopathy should be defined in relation to one or several causal factors. Stated otherwise, acute encephalopathy is best used in association with a known or presumed etiologic process, for example septic encephalopathy, hypoxic-ischemic encephalopathy, posterior reversible encephalopathy syndrome.
11. The term acute encephalopathy may be used even when the causal factor is not known.
12. While the DSM criteria state that there must be evidence of a causal mechanism, the term delirium may be used in the absence of a known aetiology.
13. The term acute encephalopathy is so broad that it may not be meaningful in the clinical or research setting.
14. Acute encephalopathy encompasses alterations in mental status induced by pharmacologic agents.
15. Delirium associated with use of prolonged sedation can be of short duration and has a better prognosis than delirium caused by other conditions, but is still appropriately labelled as delirium.
16. Delirium can be diagnosed in acute neurological patients with ischemic stroke, subarachnoid haemorrhage or traumatic brain injury, but further changes in attention, awareness and cognition should be evaluated taking into account the new basal status after brain injury.

Delphi round 2 (August 2017)

1. The term delirium refers to a clinical state due to a combination of symptoms as defined by DSM criteria.
2. **The term encephalopathy refers to a pathobiological process of functional and/or structural brain abnormalities.**
3. **Acute encephalopathy can present as delirium, or in case of a severely decreased level of consciousness, as coma.**
4. Chronic encephalopathy presents mainly as chronic cognitive dysfunction.
5. The term encephalopathy is imprecise without further specification and should therefore not be used in isolation.
6. The term encephalopathy should only be used in conjunction with a known or presumed single etiopathogenic factor (for example epileptic encephalopathy or Hashimoto encephalopathy).
7. In case of multiple potential causative factors (for example sepsis with multiple organ system failure and drug side-effects), or if the cause is unknown, the use of the term encephalopathy is discouraged. The descriptive non-interpretive terms delirium or coma.

Delphi round 3 (November 2017)

1. **The term delirium refers to a clinical state characterized by a combination of features defined by diagnostic systems such as the DSM-5.**
2. The term acute confusional state is synonymous with delirium.
3. The term altered mental status is synonymous with delirium.
4. The term acute brain dysfunction is synonymous with delirium.
5. The term acute brain failure is synonymous with delirium.
6. The term delirium should be preferred over acute confusional state, altered mental status, acute brain dysfunction and acute brain failure to facilitate scientific and clinical communication.
7. **The term coma refers to a clinical state of severely depressed consciousness defined by diagnostic systems such as the GCS, FOUR score, or CRS-R.**
8. The term acute encephalopathy refers to a rapidly developing (over less than 4 weeks, but usually hours to a few days) pathobiological process in the brain, which is associated with a predisposition, one or several triggering mechanisms, and functional and/or structural changes in the brain.
9. **Acute encephalopathy can lead to a clinical presentation of delirium, or in case of a severely decreased level of consciousness, as coma.**
10. The term acute brain dysfunction is synonymous with acute encephalopathy.
11. The term acute brain failure is synonymous with acute encephalopathy.
12. The term acute encephalopathy should be preferred over acute brain dysfunction or acute brain failure to facilitate scientific and clinical communication.

Delphi round 4 (April 2018)

1. The term acute confusional state is not synonymous with delirium and should not be used.
2. **The term altered mental status is not synonymous with delirium and should not be used.**
3. The term acute brain dysfunction is not synonymous with delirium and should not be used.
4. **The term acute brain failure is not synonymous with delirium and should not be used.**
5. **The term coma refers to a clinical state of severely depressed responsiveness defined by diagnostic systems such as the GCS, FOUR score, or CRS-R.**

6. **The term acute encephalopathy refers to a rapidly developing (over less than 4 weeks, but usually hours to a few days) pathobiological process in the brain.**
7. The term acute brain dysfunction is not synonymous with acute encephalopathy and should not be used.
8. The term acute brain failure is not synonymous with acute encephalopathy and should not be used.

Delphi round 5 (May 2018)

1. The term acute confusional state is not synonymous with delirium.
2. The term acute confusional state should not be used.
3. **The term acute brain dysfunction is not synonymous with delirium.**
4. The term acute brain dysfunction should not be used.
5. The term acute brain dysfunction is not synonymous with acute encephalopathy.
6. The term acute brain dysfunction should not be used.
7. The term acute brain failure is not synonymous with acute encephalopathy.
8. **The term acute brain failure should not be used.**

Delphi round 6 (June 2018)

1. **should the term acute brain dysfunction be used in addition to the terms delirium and acute encephalopathy?**
2. if yes: what is in your view the definition of acute brain dysfunction?
3. **should the term acute confusional state be used in addition to the terms delirium and acute encephalopathy?**
4. if yes: what is in your view the definition of acute confusional state?

Delphi round 7 (December 2019)

1. **Acute encephalopathy can lead to a clinical presentation of subsyndromal delirium, delirium, or in case of a severely decreased level of consciousness, coma.**
2. **The clinical presentation of acute encephalopathy (i.e. subsyndromal delirium, delirium, or coma) represents a change from baseline cognitive status.**

This work has several strengths. The evaluation of the literature on delirium and encephalopathy was comprehensive and based on state-of-the-art network analysis. The Delphi approach used to reach consensus was carried out rigorously in accordance with current recommendations, and it effectively leveraged collective input from a highly interdisciplinary international panel of experts in the field. On the other hand, several limitations need to be acknowledged. First, the literature search was conducted exclusively using the PubMed database to facilitate a network analysis on citations of the delirium and encephalopathy literature and it is possible that we may have missed relevant citations not captured by PubMed. The robustness of our observations, however, makes it unlikely that extending the search to other databases would have changed our findings. Second, the main search was restricted to titles alone. A number of articles dealing with delirium, acute encephalopathy or related terms, but lacking any of these terms in the title, may therefore have been excluded. Third, for technical reasons, we had to exclude publications with both delirium and encephalopathy in the title, and this could have biased our results. It should be noted, however, that the number of excluded articles (13/18,865; 0.07%) was very small relative to the total number of delirium- or encephalopathy-titled articles, and the impact of this exclusion is therefore negligible. Fourth, ~~we focused on acute encephalopathy. Almost all articles on 'acute encephalopathy' use the term 'encephalopathy' in isolation, therefore it is possible that segregation of the literature could be driven, in part, by the inclusion of articles on chronic encephalopathy. Fifth,~~ although we worked to establish a truly interdisciplinary panel with representation from key specialties, some disciplines, such as nursing and psychology, were not included. Alternative compositions of the expert panel, such as inclusion of members from low and middle income countries, might have yielded different results.

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Supplementary Fig 1 The distribution of delirium (red) and encephalopathy (blue) articles according to journal focus areas

Supplementary Fig 2 Citation network of delirium and encephalopathy and reference network of epilepsy and seizures

Left: citation network of published literature on delirium (red) and encephalopathy (blue). Each dot (node) represents an individual paper. Lines (edges) represent the citations between papers. The size of nodes is scaled according to their number of citations. Node positioning is based on an iterative force-directed layout algorithm which causes highly connected sets of nodes to cluster together. Right: reference network, with similar scaling and layout parameters, of papers on epilepsy (green) and seizures (yellow). This figure shows that the literature on delirium and encephalopathy is highly segregated.