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Abstract Background: Delirium (acute brain dysfunction) is a potentially life threatening disturbance in brain function that frequently occurs in critically ill patients. While this area of brain dysfunction in critical care is rapidly advancing, striking limitations in use of terminology related to delirium internationally are hindering cross-talk and collaborative research. In the English literature, synonyms of delirium such as the Intensive Care Unit syndrome, acute brain dysfunction, acute brain failure, psychosis, confusion, and encephalopathy are widely used. This often leads to scientific "confusion" regarding published data and methodology within studies, which is further exacerbated by organizational, cultural and language barriers. Objective: We undertook this multinational effort to identify conflicts in terminology and phenomenology of delirium to facilitate communication across medical disciplines and languages. *Methods:* The evaluation of the terminology

used for acute brain dysfunction was determined conducting communications with 24 authors from academic communities throughout countries/regions that speak the 13 variants of the Romanic languages included into this manuscript. Results: In the 13 languages utilizing Romanic characters, included in this report, we identified the following terms used to define major types of acute brain dysfunction: coma, delirium, delirio, delirium tremens, délire, confusion mentale, delir, delier, Durchgangs-Syndrom, acute verwardheid, intensivpsykose, IVA-psykos, IVA-syndrom, akutt konfusion/ forvirring. Interestingly two terms are very consistent: 100 % of the selected languages use the term coma or koma to describe patients unresponsive to verbal and/or physical stimuli, and 100% use *delirium tremens* to define delirium due to alcohol withdrawal. Conversely, only 54% use the term *delirium* to indicate the disorder as defined by the DSM-IV as an acute change in mental status, inattention, disorganized thinking and altered level of consciousness. Conclusions: Attempts towards standardization in terminology, or at least awareness of differences across languages and specialties, will help cross-talk among clinicians and researchers.

Keywords Delirium · Delirio · Delire · Delier · Delir · Délire · Confusion · Confusione · Coma · Acute brain dysfunction · Psychosis · Delirium tremens · Durchgangs-Syndrom · Acute verwardheid

Introduction

Delirium (i.e., acute change or fluctuation in mental status and inattention, accompanied by either disorganized thinking or an altered level of consciousness) [1] occurs in 20-40% of non-critically ill, hospitalized patients with rates as high as 80% in critically ill surgical and medical ICU patients [2–10], depending on the severity of illness and the instrument used to diagnose delirium [3, 4]. The area of acute brain dysfunction in critically ill patients has rapidly advanced in the last years (Fig. 1) and recent data have shown significantly worse outcomes associated with the development of delirium in different settings. In noncritically ill hospitalized older people, delirium has been linked to increased complications [11-14], poor functional recovery [15], and increased mortality in the hospital [13, 16] up to 2 years after discharge [17]. Patients admitted to post-acute skilled nursing facilities with delirium are also more likely to experience complications, re-hospitalization, and death, than patients without delirium [18]. Moreover patients with pre-existing dementia who subsequently experience delirium during hospitalization have more than a twofold increased

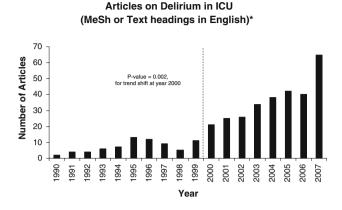


Fig. 1 Histogram showing the number of English articles detected when searching for Delirium and ICU as MeSH or Text Words by year from 1990 through 2007. The figure displays the relative paucity of work performed in this area during the last decade and the comparatively rapid rise in publications since the turn of the century. The average rate of increase in number of publication was 0.83 per year before year 2000 and increased to 5.17 per year after 2000. The difference of 4.34 was statistically significant with P = 0.002. P value was derived using an auto-regressive, interrupted time-series model. * search strategies were performed in the PubMed database as follows: ("Delirium"[MeSH] OR delirium [tw]) AND English [lang] AND ("yyyy"[PDAT]) AND ("Intensive Care Units"[MeSH] OR "critical Care"[MeSH] OR "intensive care"[All Fields] OR "critical care"[All Fields])

risk of mortality in the 12 months following discharge [19]. Research has also shown that the development of delirium in the ICU patients is an independent predictor of longer hospital stay [3, 20, 21], higher hospital costs [22], and, more alarmingly, a threefold increase in death at 6 months [9]. Delirium may be associated with long-term cognitive impairment (LTCI) [23], impaired activities of daily living [3, 14, 24, 25], and decreased quality of life [26, 27] in survivors of critical illness. The relation between delirium and long-term cognitive impairment has yet to be definitely studied, given that there are no data from large longitudinal studies in critically ill patients.

Both past and recent English medical literature unfortunately uses many different synonyms when referring to delirium, such as acute confusional state, ICU psychosis, acute brain dysfunction, and encephalopathy. Additionally, it is not uncommon for health care providers to link delirium to its etiology, resulting appropriately (when applicable) in terms such as septic encephalopathy and hepatic encephalopathy to describe delirium in the setting of sepsis or hepatic failure, respectively [28].

In other languages besides English, which use the Romanic characters (Italian, Portuguese, Portuguese– Brazil, Spanish–Spain, Spanish–Latin America, French, French–Swiss, Dutch, Norwegian, Danish, Swedish and German) the word delirium is used in different contexts. This paper has been designed to bring to the attention of clinicians and researchers all over the world the diagnostic criteria for delirium as described in the Diagnostic

Statistical Manual-Fourth Edition-Revised (DSM-IV-TR) [1], with the hope of standardizing and clarifying the use of the word "delirium" as a unifying term across the languages and medical disciplines, when referring to a syndrome of brain dysfunction as defined below. In this manuscript we will focus our attention on the following:

- 1. Definition, differences in phenomenology, subtypes of delirium and overlap with neuropsychiatric disorders.
- 2. Differences in terminology across the languages.

Methods

This report is a clinical commentary generated via experts in the areas of intensive care, geriatrics, anesthesiology, and psychiatry. In order to conduct the assessment of the international scope of terminology currently used for acute brain dysfunction, we first determined 24 authors from academic communities throughout countries/regions that spoke the 13 variants of Romanic languages incorporated into this manuscript. To conduct these communications, we used in-person, email, and telephone contacts over a period of 8 months from September 2007 through April 2008. Over this period, we had 280 email exchanges, numerous phone conversations, and several in-person communications through which we navigated the initially confusing and then progressively clear interactions regarding the substance and goals of this manuscript. We used a medical librarian from Vanderbilt University who conducted the literature search initially on 15 June 2007 and then again on 4 April 2008 via the following search strategy: ("Delirium"[MeSH] OR delirium [tw]) AND English [lang] AND ("yyyy" [P-DAT]) AND ("Intensive Care Units" [MeSH] OR "Critical Care" [MeSH] OR "intensive care" [All Fields] OR "critical care" [All Fields]). P value for Fig. 1 was derived using an auto-regressive, interrupted time-series model.

Definitions and categories of delirium

Delirium is an acute change or fluctuation in mental status plus inattention, accompanied by either disorganized thinking or an altered level of consciousness [1] and can be diagnosed in the ICU settings by non-psychiatrists, even in mechanically ventilated, non-verbal patients, using validated instruments such as the Confusion Assessment Method for the ICU (CAM-ICU) (Fig. 2), and the Intensive Care Delirium Screening Checklist (ICDSC) (Table 1) [3, 4]. A complete description of the CAM-ICU and ICDSC as well as training materials can

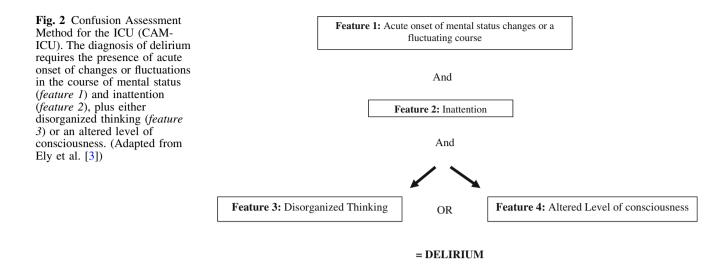


 Table 1 Intensive Care Delirium Screening Checklist (ICDSC)

Patient evaluation	
Altered level of	A: No response, score: none
consciousness (A–E)	B: Response to intense and repeated stimulation (loud voice and pain), score: none C: Response to mild or moderate stimulation, score 1
	D: Normal wakefulness, score: 0
	E: Hypervigilance, rated as abnormal level of conciousness, score: 1
Inattention	Difficulty in following a conversation or instructions. Easily distracted by external stimuli. Difficulty in
	shifting focuses. Any of these scores 1 point
Disorientation	Any obvious mistake in time, place or person scores 1 point
Hallucinations-delusion- psychosis	The unequivocal clinical manifestation of hallucination or of behavior probably due to hallucination or delusion. Gross impairment in reality testing. Any of these scores 1 point
Psychomotor agitation or retardation	Hyperactivity requiring the use of additional sedative drugs or restraints in order to control potential danger to oneself or others. Hypoactivity or clinically noticeable psychomotor slowing. Any of these scores 1 point
Inappropriate speech or mood	Inappropriate, disorganized or incoherent speech. Inappropriate display of emotion related to events or situation. Any of these scores 1 point
Sleep/wake cycle disturbance	Sleeping less than 4 h or waking frequently at night (do not consider wakefulness initiated by medical staff or loud environment). Sleeping during most of the day. Any of these scores 1 point
Symptom fluctuation Total score (0–8)	Fluctuation of the manifestation of any item or symptom over 24 h scores 1 point

It is composed of eight items. Each of the eight items is scored as absent or present (0 or 1), respectively and summed. A score ≥ 4 indicates delirium (Adapted from Bergeron et al. [4])

be found at http://www.icudelirium.org. The DSM-IV-TR classifies the various components that make up the essential features of delirium in the criteria outlined in Table 2 and in Fig. 3, in which we further highlight the distinction between coma and delirium and identify the cardinal symptoms of delirium. Some researchers believe that delirium is a part of a spectrum of "brain failure" with a common neuro-pathological pathway, as long as the patient meets the DSM-IV-TR criteria irrespective of whether it is secondary to medications or acute illness (e.g., septic encephalopathy, metabolic encephalopathy or hepatic encephalopathy) [29, 30].

However, others disagree, and a recent Canadian study [28] suggests that some intensivists use the term delirium

to describe the symptomatology of fluctuating mental status, inattention, perceptual changes and disorganized thinking only when the etiology is not known and use etiology specific diagnosis, e.g., drug or alcohol withdrawal if "delirium symptoms" occurs in the context of a history of drug or alcohol abuse. This is similar to the use of terms such as septic, metabolic and hepatic encephalopathy, which are used to describe patients with delirium in the context of sepsis, metabolic disturbances and hepatic failure, respectively. To overcome some of these terminology differences, there has been a recent call to abandon terms such as "septic encephalopathy" and substitute it with sepsis-associated delirium [31], to have a unifying term "delirium" with its etiology if known. Table 2 DSM-IV-TR diagnostic criteria for delirium

Criteria DSM- IV-TR [1]	Delirium
Criteria A	Disturbance of consciousness, with reduced ability to focus, sustain or shift attention
Criteria B	Altered cognition (memory, orientation, language disturbance) or the development of a perceptual disturbance (delusion or hallucination or illusion) that is not better accounted for by preexisting dementia
Criteria C	Disturbance develops over hours or day and tends
	to fluctuate during the course of the day
Criteria D	There is evidence of an etiological cause

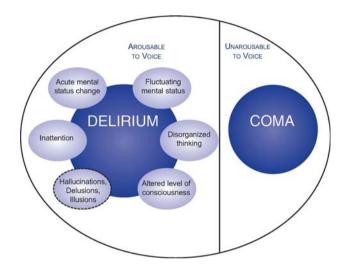


Fig. 3 Delineation between delirium and coma, *highlighting* the cardinal symptoms of delirium. The *dashed line indicates* optional symptoms of delirium (i.e., those sometimes present but not mandatory for the diagnosis of delirium as defined by the DSM-IV-TR) [1]

Subtypes of delirium

Delirium is classified according to motoric (psychomotor) subtypes as hyperactive delirium, hypoactive delirium and mixed delirium [6, 7, 32, 33]. Hyperactive delirium is characterized by increased psycho-motor activity with agitated behavior. Hypoactive or "quiet" delirium is characterized by reduced psycho-motor behavior and lethargy. Mixed delirium alternates unpredictably between a hyperactive and a hypoactive manifestation throughout a day or over the course of several days. Both manifestations have been shown to be common in the critical care setting [7, 34].

Sub-syndromal delirium

Sub-syndromal delirium (SSD) has been described [32, 35–39] as a condition in which patients have one or more

symptoms of delirium (e.g., inattention, disorganized thinking, anxiety and irritability) that never progresses to a full diagnosis of delirium as described by the DSM-IV-TR criteria [1]. A recent study by Ouimet et al.[35], has shown that ICU patients with sub-syndromal delirium have worse outcomes than those who have no delirium at all, confirming a previous report [36, 37] of graded severity of brain dysfunction from normal to sub-syndromal delirium to delirium.

A number of neuropsychiatric disorders also share symptoms in common with delirium, and the combination of these discrete symptoms determines the specific diagnosis (Table 3).

Sub-syndromal delirium and the overlap between features of delirium and other neuropsychiatric disorders described in Table 3 may lead to the misdiagnosis of delirium, because in these instances only certain components of brain organ dysfunction occur that cannot be classified as full delirium per the DSM-IV-TR.

Differences in terminology for acute brain dysfunction across languages

This manuscript will focus on 13 languages that use Roman characters (English, Italian, Portuguese, Portuguese–Brazil, Spanish, Spanish–Latin America, French, French Swiss, Dutch, German, and Scandinavian Languages (Danish, Norwegian and Swedish). Though important, we have not included languages that use other character systems such as Chinese, Japanese, Arabic, and Cyrillic because this was beyond the scope of this project.

The word *delirium* is derived from the Latin verb *delirare*, which means "to be crazy, deranged, or silly." Literally "de" means to be away or down and "lira" means furrow or truck fields. With its root being from the agricultural term "lira" (to plow in a straight line), delirare conjures up images of a madman plowing a field with no discernible plan. Patients with symptoms consistent with delirium have been described throughout ancient medical writings. Hippocrates described patients with "phrenitis," a syndrome marked by confusion and restlessness that fluctuated unpredictably and was associated with physical illness, often a febrile illness [40]. Celsus and other Roman writers used "delirium" interchangeably with "phrenitis" to designate a temporary change in mental status associated with a physical illness characterized by restlessness and excitement and with "lethargus" to describe illness-associated confusion characterized by sleepiness and inertia [32].

In the *English language delirium* (as defined by the DSM-IV-TR [1]) is still underused by physicians who do not specialize in neuropsychiatric disciplines. Synonyms such as acute mental status change, confusional status,

Table 3 Delirium symptoms compared to different mental illness

	Delirium	Dementia	Delirium tremens	Schizophrenic psychosis	Depression
Onset	Sudden	Slow	Onset usually 48–96 hafter cessation of drinking	Variable	Variable
Duration	Day to weeks	Years	Up to 2 weeks	Variable	Variable
Reversibility	Fluctuating	Persistently progressive	Variable	Variable	Variable during the day
Variation at night	Almost always worse	Worse	Can be worse at night	Generally none	Generally none
Level of consciousness and orientation	Fluctuates, disoriented	Impaired, worsening in the last stages	Impaired and fluctuating	Awareness of time, date, place, identity	Generally normal
Attention and memory	Inattention and poor short term memory	Attention retained, but loss of short term memory	Reduced attention and global amnesia	Attention retained, memory intact	Intact memory, may have poor attention
Cognition	Focal to global cognitive deficits	Global cognitive failure	Acute change	Intact	Impaired in severe stage
Psychotic symptoms	May have hallucinations (mostly visual), delusions and illusions	Less frequent	May have hallucinations (usually tactile, visual) and delusions (persecutory)	Frequent psychotic symptoms and often paranoid	Rare: psychotic ideation is complex and related to the mood of the patient
Speech	Often incoherent words	Difficulty finding words	Slurred	Normal	Normal
Other disorders or physical symptoms	Comorbidities often present	Comorbidities often present	Comorbidities generally present. Tremor, hypertension, tachycardia, fever, severe agitation.	Generally none	Comorbidities often present
EEG	Generalized diffuse slowing	Variable	Variable	None	None

confusion, acute brain dysfunction, brain failure, encephalopathy, postoperative psychosis, acute organic syndrome, hallucinations and delusions have been used to describe brain organ dysfunction in the hospitalized patient [41]. However, to avoid the pitfalls of having different terms to describe the same syndrome, the medical community should strive to standardize terminology and perhaps adopt the unified term of *delirium*, when a patient meets all the criteria described in the DSM-IV-TR (Table 2). As it stands now, for example, neurologists often use the word encephalopathy to refer to hypoactive subtype and restrict the use of delirium to the hyperactive subtype. Psychiatrists and geriatricians, and increasingly ICU personnel, use delirium to refer to both motoric subtypes since patients tend to fluctuate between them and clinical management is not distinct. If acute mental status changes or hallucinations occur in isolation, without the other diagnostic features of delirium, the patient should not be classified outright as delirious, but rather considered to be in a sub-syndromal delirious state [32, 35–39]. On the other hand most patients currently categorized as encephalopathic or in ICU psychosis are very likely to be in hypoactive or hyperactive delirium, respectively, since most have the diagnostic criteria of delirium such as fluctuating levels of consciousness, inattention, and disorganized thinking.

In non-English languages such as Italian, Portuguese, Portuguese-Brazil, Spanish, Spanish-Latin America, French, Dutch, German, and Scandinavian Languages (Norwegian, Danish, and Swedish) various words have been identified: delirium, delir, delirio, délire, delier, confusion, confusion mentale, acute verwardheid, intensiv-psykose, IVA-psykos, IVA-syndrom, akutt konfusion/ forvirring, and Durchgangs-Syndrom. Our international panel of authors has done its best to outline the salient differences in languages for this form of organ dysfunction (Table 4), though sometimes we have detected differences of opinion even within languages. Interestingly, two terms are very consistent: 100% (13/13) of the selected languages use the term *coma* or *koma* to describe a state of unresponsiveness in which the patient lies with the eves closed, cannot be aroused, and has no awareness of self and surroundings [42]; 100% (13/13) use delirium tremens to define delirium due to alcohol withdrawal. On the other hand, only 54% (7/13) use the term *delirium* to indicate the disorder as defined by an acute change in mental status, inattention, disorganized thinking and altered level of consciousness.

The word *delirium* is currently used to describe all the components of delirium as defined by the DMS-IV-TR criteria in the following three languages: (1) *Italian* (modificazione acuta dello stato di coscienza o decorso

Table 4	Differences	in	international	terminology	for	five	types of	f acute	brain	dysfunction

	Coma ^a	Delirium ^b	Confusion ^c	Delusion ^d	Delirium tremens ^e
Dutch	Coma	Delirium or delier or Durchgangs-Syndrom	Acute verwardheid	Waan	Delirium tremens
English	Coma	Delirium	Confusion	Delusion	Delirium tremens
French	Coma	Confusion mentale	Désorientation temporo-spatiale	Délire	Delirium tremens
French-Swiss	Coma	État confusionnel	Désorientation temporo-spatiale	Délire	Delirium tremens
German	Koma	Delir	Verwirrtheit or Konfusion	Halluzination	Delirium tremens
Italian	Coma	Delirium	Confusione	Delirio	Delirium tremens
Portuguese	Coma	Delirium	Confusão mental	Delírio	Delirium tremens
Portuguese-Brazil	Coma	Delirium	Confusão mental	Delírio	Delirium tremens
Scandinavian (Norwegian, Swedish, Danish)	Koma	Delirium or IVA-syndrom ^f or Intensiv psykose	Forvirring or Konfusion	Illusion	Delirium tremens
Spanish-Spain	Coma	Delirio	Confusión	Delirio	Delirium tremens
Spanish-Latin America	Coma	Delirium	Confusión	Delirio	Delirium tremens

^a Coma: absence of arousal and thus also of consciousness: a state of unresponsiveness in which the patient lies with the eyes closed, cannot be aroused, and has no awareness of self and surroundings [42] ^b Delirium: acute change or fluctuation in mental status, inatten-

tion, and disorganized thinking or an altered level of consciousness [1]

Confusion: impaired orientation with respect to time, place, or person

fluttuante, disattenzione, e pensiero disorganizzato o alterato livello di coscienza), (2) Portuguese and Portuguese-Brazil (alteração aguda no estado mental ou curso flutuante, falta de atenção, e pensamento desorganizado ou nível de consciência alterado), and (3) Spanish-Latin America (sindrome neuropsiquiátrico de inicio agudo, evolución oscilante, con compromiso en el nivel de conciencia, alteraciones cognitivas y especialmente de la atención, asociada a cambios psicomotores, perceptivos, del ciclo sueño-vigilia y de origen multifactorial). Though delirium is the term used most frequently in Italian, Portuguese, and Spanish-Latin America, some variability still exists, with the use of the word *delirio* for delirium in these languages by some healthcare professionals and non-medical persons. In French and Spanish-Spain the word delirium is mainly synonymous with delirium tremens (alcohol withdrawal), while confusion mentale (French) and *delirio* (Spanish-Spain) are the terms used to refer to delirium as described in the DSM-IV-TR.

Inconsistencies in terminology "within languages" do occasionally occur. For example, Delirio has been used occasionally in the medical literature in Italy. Portugal and South-America to define delirium, leading to misunderstanding, given that the real definition of *delirio* is psychotic delusions in these languages. Delirio or delusion is therefore a false belief based on incorrect inference about external reality that is firmly sustained by the patient despite what almost everyone else believes. Delusions, like hallucinations can be perceptual disturbances that are seen in delirium, but are not by themselves diagnostic features of delirium. Currently in Italian,

Delusion: a false belief based on incorrect inference about external reality firmly sustained despite what almost everyone else believes [1]

Delirium tremens: delirium due to alcohol withdrawal

IVA-syndrom: intensivvårdsavdelnings-syndrom

America, delirio is consistently used to define delusions. The Italian definition of *delirio* is literally "convinzione errata che non cede alle critiche e all'evidenza dei fatti"; the Portuguese definition is "Alteração do conteúdo do pensamento, com crenças falsas, que resultam de uma apreciação errada da realidade, que não cedem à lógica nem à evidência do real"; the Spanish-Latin America definition is "afirmación y conducta de realidad, basadas en evidencias mutadas, insólitas y productivas." Interestingly in Spanish-Spain, delirio is used by the intensivists to define delirium as described by the DSM-IV-TR (Cambio agudo en el estado mental, inatenctión, v pensamiento desorganizado, o nivel de conciencia alterado) and to define delusion.

In France, but not in Ouebec, the terminology differs from the Romanic languages in that they do not use the words delirium or delirio, but rather use delire and confusion mentale.

In French, délire (convictions non fondées sur les données du réel et non partagées par le groupe auquel la patient appartient; la patient n'a pas conscience qu'il se trompe et adhère totalement à sa conviction) is the word used to define the term delusion; and *confusion mentale* is used to represent the DSM-IV-TR definition of delirium. This contrasts with the use of the word *confusion* as currently used in the English language, to define an impaired orientation with respect to time, place and person, and not accompanied with the hallmark features of delirium as described by the DSM-IV-TR. A similar word exists also in Italian, Portuguese, Spanish-Latin American: in Italian (confusione: incapacita' di pensare con la Portuguese, Portuguese–Brazilian and Spanish–Latin consueta chiarezza e coerenza), Portuguese (confusão

mental: falta de ordem ou método, incapacidade de reconhecer diferenças ou distinções, perda de orientação), Spanish–Latin America and Spanish–Spain (*confusión*: pérdida de capacidad para tener un pensamiento claro y coherente) refer to confusion as the English word. French instead uses the term désorientation temporo-spatiale referring to define confusion.

German intensivists use the term *delir* in the medical literature referring to delirium as described in the DSM-IV-TR, and in the German every day common language, *delirium* is nearly always automatically interpreted by nurses as delirium tremens related to alcohol abuse. *Durchgangs-Syndrom* (transient syndrome), is a term coined by german psychiatrist H. H. Wieck [43] to denote an acute organic psychic disorder following surgery or traumatic brain injury. This diagnosis described a mild, reversible disorder without disturbance of consciousness and is thus not appropriate to describe delirium, nor is it part of german DSM-IV-TR or ICD-10-GM coding systems.

Finally, in the Netherlands the term *delier* and *delirium* refer to delirium as described in the DSM-IV-TR; healthcare professionals (both physicians and nurses) use the term (*acute*) *verwardheid* to refer to the English word confusion (acute confusional state). In the Scandinavian languages (Norwegian, Danish, and Swedish) delirium is used by trained specialists as described in the DSM-IV-TR and in some areas, delir as a short form/synonym. Unfortunately, many health professionals interpret delirium as alcohol withdrawal, and use different synonyms when referring to delirium, such as *ICU psychosis* (intensiv-psykose, IVA-psykos), *ICU-syndrome* (IVA-syndrom), *acute confusion* (akutt konfusion/forvirring) [44, 45].

Conclusions

There are striking differences in standard terminology internationally related to acute brain dysfunction in critical care (delirium), limiting cross-talk and collaborative research efforts. Aligning our terminology, therefore, will speed progress in this rapidly advancing area. The work that went into this paper was conducted with the aim of clarifying terminology for researchers and health care providers, as well as to strive for the adoption of the term delirium regardless of the native language to describe patients experiencing acute changes or fluctuation in mental status and inattention, when accompanied with either disorganized thinking or an altered level of consciousness. Further investigations are needed to address if the cause subtending the development of delirium (e.g., liver failure, sepsis, respiratory failure) plays a role in explaining the different phenomenology as well as predicts markedly different prognoses. The semantic and terminology differences listed in this paper should also be useful to promote cross talking between different medical subspecialties (intensive care, geriatrics, neurology, psychiatry) for the management of a syndrome that is widely present across a huge array of clinical settings and patient types.

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Conflict of interest statement None of the authors have any potential conflicts of interest as related to the content of this manuscript.

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