Chapter 11
The Electroencephalogram and Delirium

Suzanne C. A. Hut, Frans S. Leijten, and Arjen J. C. Slooter

Introduction

Delirium has been recognized since ancient times as an acute brain dysfunction associated with illness. Electroencephalography (EEG) is one of the oldest techniques for studying brain function. Despite this long history, the scientific literature on EEG in delirium is limited. One of the reasons for this lack of progress may be inconsistent terminology across medical disciplines to describe neuropsychiatric changes in acute systemic illness. Whereas most geriatricians, psychiatrists, anesthesiologists, and intensivists appear to prefer the term "delirium," neurologists, neurointensivists, and clinical neurophysiologists would describe the same entity as "encephalopathy." In this chapter, we will use the term "delirium" to refer to a clinical state characterized by a combination of features defined by diagnostic systems such as the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [1] or the tenth revision of the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) [2]. The term "acute encephalopathy" in this chapter will refer to a rapidly developing (over less than 4 weeks, but usually within hours to a few days) pathobiological process in the brain that can lead to a clinical presentation of delirium or, in case of a severely decreased level of consciousness, to coma. In this chapter we will preferentially use the term

S. C. A. Hut (✉) · A. J. C. Slooter
Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

UMC Utrecht Brain Center, Utrecht, The Netherlands
e-mail: s.c.a.hut@umcutrecht.nl

F. S. Leijten
UMC Utrecht Brain Center, Utrecht, The Netherlands

Department of Neurology and Neurosurgery, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

C. G. Hughes et al. (eds.), *Delirium*, https://doi.org/10.1007/978-3-030-25751-4_11

"delirium," and we will review the EEG literature on both delirium and (acute) encephalopathy.

Despite the fact that delirium can be precipitated by a range of pathophysiologically diverse conditions, its clinical presentation is relatively homogeneous leading some to suggest there is a final common pathway. However, the substrate of this presumed common pathway is unclear. Studies on different etiologies of delirium are difficult to perform as it is usually impossible to assign one specific cause for delirium [3]. Studies on encephalopathy are more often focused on one specific etiology (e.g., septic encephalopathy) usually neglecting concomitant pathology (e.g., organ dysfunction or medication use).

EEG in Normal Adults

There may be some misconceptions regarding the interpretation of EEG. We therefore start with a brief introduction on basic concepts of EEG to provide non-neurological clinicians and non-neuroscience researchers an appreciation of its scope and limitations.

EEG signals are voltage potentials mainly generated by neurons in the cerebral cortex (gray matter). However, action potentials of individual neurons are too weak and too brief to be recorded on an EEG. EEG recordings from a single electrode reflect the postsynaptic activity of thousands or even millions of cortical neurons. The EEG signal predominantly originates from neurons that are aligned radially to the recording surface (such that their excitatory and inhibitory postsynaptic potentials can be summated). These compound potentials generate currents flowing in the extracellular space that can be detected at the surface of the brain. Yet electrical activity recorded at the brain's surface does not only reflect the spontaneous activity of large populations of cortical neurons but also depends on important input from subcortical structures, in particular the thalamus and brainstem reticular formation. EEG abnormalities may therefore result from disruption of cortical networks or from modification of subcortical input on cortical neurons. It should be noted that activity generated in the lateral surfaces of the brain is recorded more precisely than is activity arising from interhemispheric, mesial, or basal areas [4]. Further, not all potentials that may be recorded at the cortical surface are detectable at the scalp. Summated potentials from the cerebral cortex are attenuated or distorted by overlying structures, such as the pia mater, the subarachnoid space that is filled with cerebrospinal fluid, the dura mater, and the skull. For these reasons, spatial resolution of regular, low-density EEG is poor, which hampers anatomical inferences. Another limitation of EEG is its low specificity – widely disparate diseases and conditions may produce similar changes in EEG. By contrast, temporal resolution is excellent, so that changes in milliseconds may be visible in EEG. In addition, EEG is rela-

tively cheap and applicable at the bedside in patients with delirium, in contrast with other neuroimaging techniques such as magnetic resonance imaging (MRI) or positron emission tomography (PET).

A basic EEG array usually consists of up to 25 electrodes distributed over the scalp, covering a large part of the underlying cortex. The electrodes are typically placed proportionally to the head size in the so-called International 10–20 system [5], so that in each individual the electrodes carry names that reflect the sub-lobar area that is sampled. Odd numbers indicate left hemisphere locations, and even numbers are on the right (e.g., F3 is over the left lateral frontal cortex).

In clinical use, the EEG signal is typically displayed as a tracing of voltage changes over time and can be regarded as composed of oscillatory activity in various frequency ranges, or *bands*. These oscillations may result from the synchronized, rhythmic induction of postsynaptic potentials by populations of neurons that are interconnected with feedback loops. A frequently used measure is *EEG power*, the square of the average of the amplitude of the EEG signal, across the time sampled. EEG power spectrum analysis allows for the calculation of the distribution of signal power across frequency bands in a certain time frame. Distinct frequency bands can often be observed and may all be present in a healthy EEG, depending on the state of the individual or ongoing cognitive processes.

Delta activity (<4 Hz) appears during slow-wave sleep and is not normally present in adults when they are awake. Healthy adults may show some theta activity (4–8 Hz) over the temporal regions during drowsiness. During wakefulness, activity in the 8–13 Hz range is present in occipital regions while the eyes are closed (alpha rhythm) and in pericentral regions while the hands are at rest (mu rhythm), and beta activity (13–30 Hz) is normally present over the frontal areas. Slow activity (in theta bands) slightly increases with aging [6], whereas the use of certain medications such as benzodiazepines or barbiturates may increase the amount of beta activity [7]. In general, the slower the activity, the higher the amplitude, with beta usually below 30 μV, alpha around 70 μV, and delta often over 150 μV. The overall picture of an awake EEG with these frequency characteristics is called the background activity.

Moreover, an EEG in healthy awake individuals shows an *anterior to posterior gradient*, that is, the increase of amplitudes and decrease of predominant frequencies from anterior to posterior sites. In the awake person, the frontal lobe is dominated by beta activity of low amplitude, whereas a prominent alpha rhythm will dominate the posterior regions after eye closure. *EEG reactivity* in healthy individuals refers to the attenuation of the alpha rhythm upon fixation or opening of the eyes and the mu rhythm that disappears with contralateral hand movement. An example is provided in Fig. 11.1a. In summary, EEG rhythms in awake, healthy adults commonly manifest as relatively low in amplitude, while the frequencies of these oscillations may be mixed [8] and the lowest, delta activity, being absent or rare.

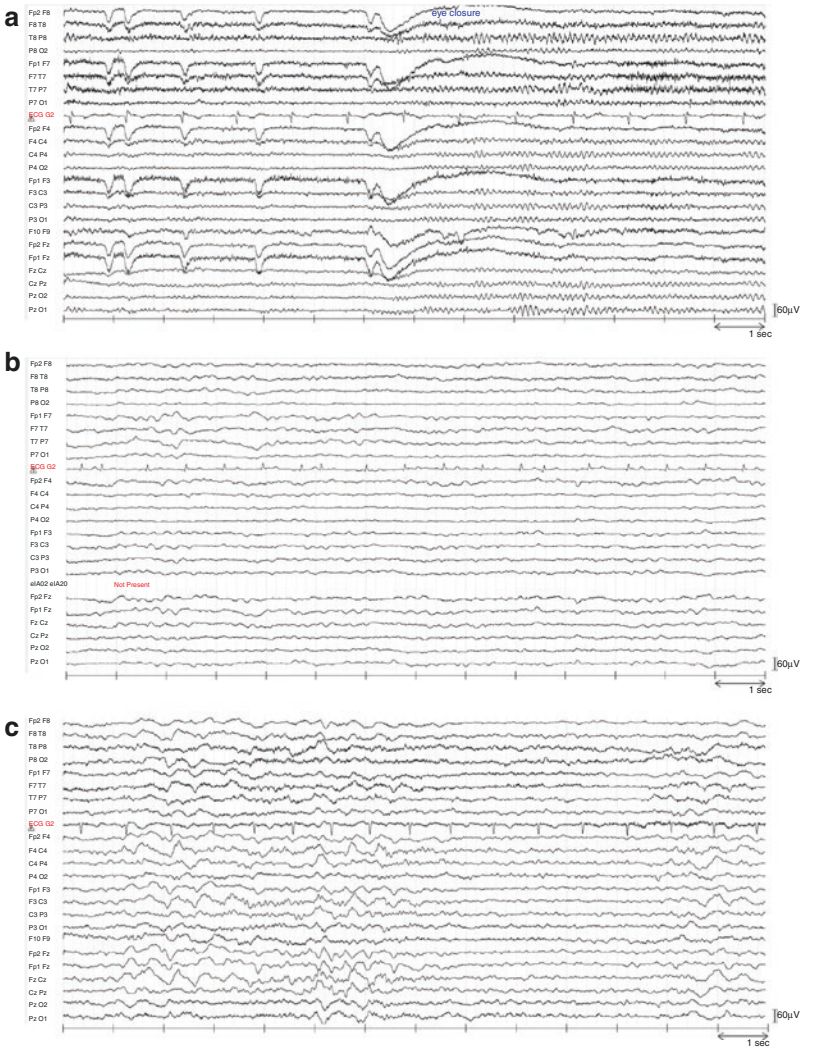

Fig. 11.1 Examples of 14 s of EEG recordings. EEGs are represented in a bipolar montage. The first four lines represent the most lateral part of the right hemisphere, the next four the corresponding part on the left. Under the ECG, lines represent the lateral part more cranially, halfway over the side of the skull, again the first four over the right and then four over the left. The last six channels are over the cranial midline. Filter settings 0.16–70 Hz. (**a**) 45-year-old male, 3 days after cardiac surgery, without complications. He is awake and oriented. The EEG shows eyeblink artifacts in the frontopolar leads and muscle artifacts (dense blackening of the curve, especially in the second four lines at the end). After eye closure, halfway the page, an alpha rhythm arises over the posterior leads. Conclusion: normal EEG. (**b**) 80-year-old female, heart and kidney failure. She is slightly obtunded and confused. The EEG shows no anterior to posterior gradient and is dominated by polymorphous slow (delta) rhythms. There is no background differentiation; the eyes are closed. Conclusion: delirium. (**c**) 60-year-old male with cerebral aspergillosis after stem cell transplant for multiple myeloma. Clinical delirium. The EEG shows periods of high-amplitude polymorphous delta activity, interspersed with periods of attenuation. There are no features of stage 2–3 sleep such as spindles or K-complexes. Conclusion: delirium

EEG Characteristics of Delirium

In delirium, the EEG is characterized by a diffuse increase of theta and delta oscillations. This pathological slowing is typically more prominent over frontal regions where low-amplitude beta normally reigns. Increased power in the delta band may consist of polymorphous (i.e., irregularly shaped) delta activity, frontal intermittent rhythmic delta activity (FIRDA), and triphasic waves (TWs) [9].

The presence of diffuse polymorphous delta activity during the awake state is typical in the delirium EEG. Polymorphous delta activity when restricted to lateralized or focal regions is also seen with focal brain pathology such as stroke or brain tumors [10–12]. Thus, it is important that the delta activity is bilateral and diffuse to indicate delirium. However, diffuse polymorphous delta activity is also a characteristic of stage 2–3 non-rapid eye movement (NREM) sleep [9]. This delta activity will be more continuous during sleep and not intermittent such as in most cases of delirium. Normal stage 2–3 NREM sleep can further be distinguished because of special features (sleep spindles, vertex waves, K-complexes) that are absent in the EEG of an awake delirious patient. Still, an EEG suggestion of delirium is best taken from an awake EEG. In a way, one might speculate that delirium is the intrusion of bouts of NREM sleep in the awake state. Indeed, extreme sleep deprivation may cause delirium as well as produce such EEG sleep intrusion in the healthy adult [13].

Polymorphous delta activity in delirium may be continuous (Fig. 11.1b) but is usually intermittent (Fig. 11.1c). Intermittent delta activity may appear in a rhythmical (i.e., monomorphic and repetitive) fashion as short, moderate- to high-amplitude runs that last between 2 and 6 s over the frontal areas, alternated by episodes of faster frequencies or even a normal background pattern. Frontal intermittent rhythmical delta activity (FIRDA), also referred to as generalized rhythmic delta activity (GRDA) with frontal predominance, is associated with various pathological processes such as increased intracranial pressure, intoxication, posterior fossa pathology, and certain diseases such as Lewy body dementia, as well as with hyperventilation in normal individuals [14]. Due to its non-specificity, it may not be surprising that FIRDA may also manifest with delirium of various etiologies, such as sepsis [15], hyperglycemia, and uremia [16].

Triphasic waves may also occur in the delta frequency band and can be recognized by their large, frontally predominant positive peak (>70 μV), flanked by two negative deflections (i.e., plotted upward, in accordance with the EEG polarity convention for surface negative waveforms). They typically occur in prolonged runs approximately once per second and attenuate during sleep. In the American Clinical Neurophysiology Society standardized ICU EEG nomenclature, these are referred to as generalized periodic discharges (GPDs) with triphasic morphology. TWs are associated with delirium due to a variety of causes and with increased risk of unfavorable outcomes such as mortality [17, 18]. Akin to FIRDA, TWs may be a reflection of a number of conditions but have historically been described in hepatic failure [19], which frequently results in delirium [20]. An example of TWs is provided in Fig. 11.2a.

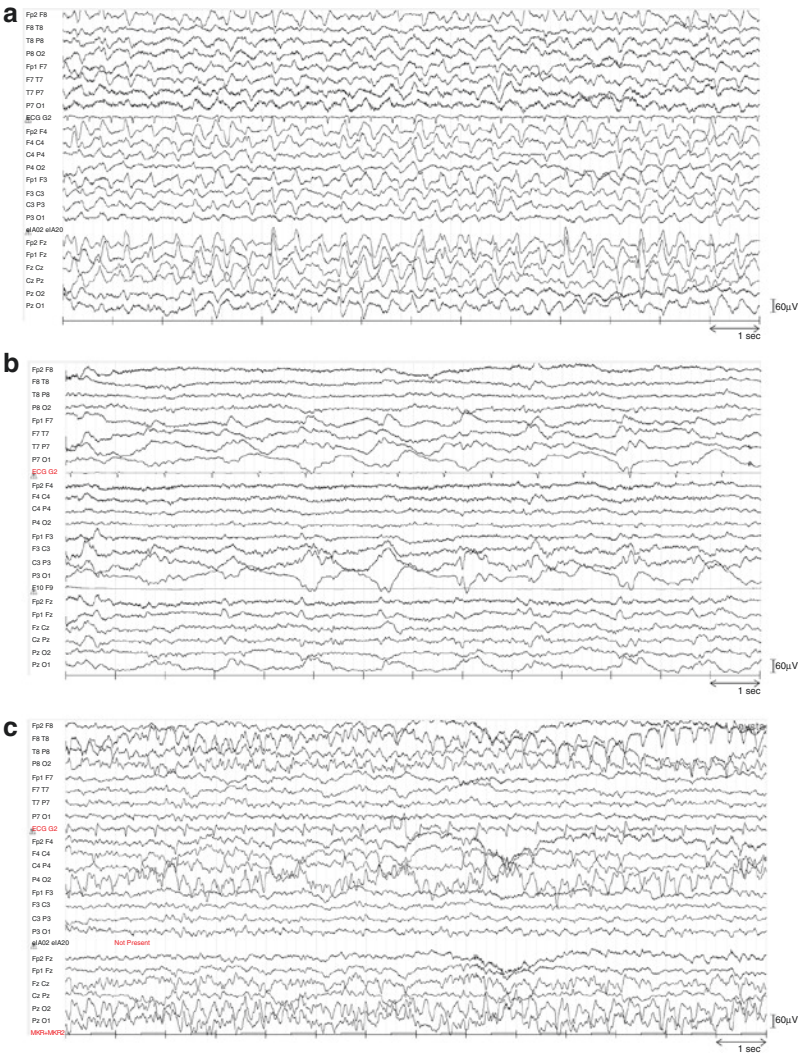

Fig. 11.2 Some specific examples of 14 s EEG recordings. Filter settings 0.16–70 Hz. (**a**) 43-year-old female, hepatic failure with high ammonia serum levels due to valproic acid intoxication. Clinical delirium with periodic unrest; also asterixis and confusion. The shown episode is during a short period of relaxation. The EEG shows high-amplitude delta with prominent frontal-predominant sharp waves at leads, so-called triphasic waves in delirium associated with hepatic failure. (**b**) 58-year-old male, glioblastoma in the left hemisphere, after he suffered a generalized tonic-clonic seizure. He has dysphasia, but is responsive, no unrest. The EEG shows relatively normal background activity over the right hemisphere, but a highly abnormal pattern over the left hemisphere with so-called periodic lateralized discharges, which in this case reflects a postictal and tumor-related focal phenomenon. (**c**) 66-year-old male, glioblastoma in the right hemisphere with focal seizures with jerking of the left arm. He was found at home and brought to the ICU with respiratory problems and unresponsiveness, but no jerking. The EEG shows an evolving rhythmical pattern over the right hemisphere that waxes and wanes and polymorphous delta activity over the left hemisphere. Conclusion: non-convulsive status epilepticus

The occurrence of various features of the EEG thus sometimes allows for the detection of underlying causes of delirium. Nevertheless, quantitative spectral patterns may vary between individuals, and more research is needed to associate certain spectral features with clinical phenotypes, e.g., hypoactive or hyperactive delirium [21]. For now, general slowing and disorganization of the background EEG appear to be shared features of the delirium EEG.

The increase of power in the theta and delta band is inseparably paired with a reduction of power in the alpha and beta frequency band. While EEG reactivity with appearance of a posterior alpha rhythm upon eye closure is observed in healthy adults, during delirium the EEG often shows an abnormal lack of posterior alpha rhythm. The relative alpha power is thus reduced in delirium, while relative power in the theta and delta band typically increases. Consequently, the ratio of fast-to-slow band power is reduced in delirium. Interestingly, upon recovery, a shift from predominant delta power back into theta, alpha, and higher frequency bands may be observed [21]. EEG manifestations of delirium are thus reversible, following the clinical symptoms.

In clinical practice, EEG may be helpful in detecting delirium in certain populations [21], and the amount of relative delta power in spectral analysis might provide a tool for quantification and follow-up [22].

Delirium Due to Non-convulsive Seizures

Non-convulsive seizures can be thought of as abnormal excessive or synchronous neuronal activity without obvious motor activity [23, 24]. In case of persistence or recurrence without interictal return to baseline, the term non-convulsive status epilepticus is used. Criteria for non-convulsive seizures include the presence of epileptic activity as detected with EEG (e.g., Figure 11.2b, c) and clinical or EEG improvement after the administration of a rapidly acting anti-epileptic drug [25, 26]. Non-convulsive seizures can present with a variety of symptoms and signs that may be nonspecific, including a decreased level of consciousness, confusion, psychosis, eye deviation, nystagmus, subtle convulsions, rigidity, automatisms, chewing, tachycardia, sweating, or an increase in intracranial pressure [27].

Some symptoms and signs of non-convulsive seizures therefore show overlap with features of delirium, and their persistence could point to non-convulsive status epilepticus. Causes of non-convulsive status epilepticus overlap with causes of delirium. These include metabolic alterations (such as hepatic and renal failure, electrolyte abnormalities), drug intoxications, and acute withdrawal of certain drugs [28]. Not only can delirium manifest during seizures (in the ictal period), delirium can also persist after or between electrographic seizures (postictal confusion) [29]. The issue whether non-convulsive status epilepticus leads to delirium is relevant, as status epilepticus should be treated with anti-epileptic drugs, which might be withheld in case of a mistaken diagnosis of delirious state due to other causes. Sometimes, non-convulsive status epilepticus may consist of intermittent seizures that can be

missed with a conventional 30-min EEG recording. To definitely rule out non-convulsive status epilepticus, prolonged or continuous EEG recording is advised [30], which may be logistically challenging.

It may not come as a surprise that the literature on delirium due to non-convulsive status epilepticus is limited. In three studies on non-neurological intensive care unit (ICU) patients who underwent continuous EEG monitoring for evaluation of altered consciousness, non-convulsive status epilepticus was detected in 0% ($n = 62$ patients with sepsis), 6% ($n = 154$ surgical ICU patients), and 10% ($n = 201$ medical ICU patients) [15, 31, 32]. Another study in patients presenting with delirium found a much higher proportion of patients with non-convulsive status epilepticus using continuous EEG (28%) or conventional 20-min EEG (6%) [33]. However, the selection of study participants was unclear, as well as the required quantity of certain EEG features to classify as epileptic. Furthermore, the majority of patients classified with non-convulsive status epilepticus showed an EEG feature of generalized periodic discharges, which most experts do not consider typically epileptic.

Non-convulsive status epilepticus is an important but relatively rare underlying cause of delirium, especially in the patient without primary (focal) brain disease and without a history of seizures. Clues to non-convulsive status epilepticus may include subtle motor movements, such as gaze deviation, nystagmus, subtle limb twitches, rigidity, and oral and manual automatisms, particularly in cases with a (hyper)acute onset of delirium and a prior history of seizures. The single most helpful test to detect non-convulsive status epilepticus is EEG [28].

During a 30-min EEG recording, brief episodes of non-convulsive seizures may be missed. However, if electrographic seizure activity does not occur during apparent behavioral phenomena, this argues against an epileptic origin of these features. Diagnosis of non-convulsive status epilepticus is supported when the administration of a rapidly acting anti-epileptic drug results in both clinical and EEG recovery.

Applications of EEG in Delirium Research and Management

The EEG has the potential to contribute to various areas of delirium research and management.

Firstly, it may provide insight in the pathophysiology of delirium. In the last two decades, there appears to be a renaissance of interest in EEG among neuroscientists fueled by rapid developments in network science. Network science has introduced new opportunities for understanding the brain as a complex system of interacting units [34]. Networks consist of nodes (vertices) that are connected to edges. When a neural network is constructed from EEG, the EEG electrodes can be considered the nodes of the network and the strength of the phase coupling between the EEG channels as edges. Using this network construct, EEG is usually analyzed within the commonly accepted EEG frequency bands (i.e., delta, theta, alpha, and beta). A variety of network characteristics can thus be computed, including the average con-

nectivity strength and measures of network topology. It appears that network alterations during delirium are characterized by loss of functional connectivity in the alpha band and changes toward a more random and less integrated network [35, 36]. With these analyses, hypoactive delirium could be distinguished from a similar state which occurs during recovery from anesthesia [36].

Network analyses can also be used to study whether delirium due to different causes results in similar alterations in connectivity and topology, strengthening the argument for a final common pathophysiologic pathway. This could be investigated by comparing delirium due to a different etiology (e.g., postoperative, infectious, metabolic) with regard to various EEG characteristics. It is however difficult to classify delirium into etiological subgroups because of its multifactorial nature.

Another interesting approach is to build computational models that represent populations of interconnected inhibitory and excitatory neurons, resulting in an artificial EEG signal. By modifying the components of these so-called neural mass models, such as ion channel thresholds, this EEG signal acquires or loses certain characteristics and features, which can be compared with an EEG signal during delirium. Neural mass *in silico* models can thus fundamentally increase our understanding of EEG disturbances in delirium [37].

Secondly, EEG may be applied in routine diagnosis and monitoring of delirium. Delirium is often not recognized in daily clinical practice by non-delirium experts, such as ICU physicians [38]. To improve recognition, delirium screening tools have been developed. While clinical tests suffice in a research setting with a limited number of research assistants administering the test [39, 40], they appear insensitive in daily routine practice with numerous nurses in day-to-day care [41, 42]. There is therefore a need for an objective delirium detection tool which is easy to use. A conventional 30-min 25-channel EEG recording is not practical for large-scale, routine monitoring. Fortunately, quantitative analysis of 1-min, two-channel EEG could reliably distinguish patients with "definite delirium" from those with "definite no delirium" after cardiac surgery [43]. These results were validated in an independent cohort of postoperative patients (n = 159, area under the receiver operating characteristic curve 0.75 based on the relative delta power, and 0.78 based on explorative analysis of relative power from 1 to 6 Hz) [44]. Another recent study also showed high specificity and sensitivity when a bispectral EEG device was used, even with the inclusion of patients with dementia [45]. Before brief EEG recordings can be introduced in daily clinical practice, usability needs to be optimized.

Thirdly, EEG could be used to assess prognosis of delirium. Quantification of slowing of EEG background activity over time might provide a more accurate measure of monitoring the resolution of delirium than clinical monitoring with scores such as the Glasgow Coma Scale. However, although associations have been described between different grades of slowing of EEG background activity and outcome, prognosis seems to be predominantly determined by etiology [46]. EEG reactivity, e.g., modulation of background activity in response to stimulation, is related with a more favorable prognosis. Further more, presence of physiological EEG elements during NREM sleep appears to have prognostic value. These include vertex waves, sleep spindles, and K-complexes. Particularly the presence of K-complexes

was found to be associated with favorable outcomes [47]. In summary, EEG is a sensitive tool, and various EEG features seem to have prognostic value in delirium. It is still unclear which EEG characteristics are optimal in predicting delirium outcome [48].

Conclusions

The EEG in delirium is characterized by slowing of background activity, resulting in increased power in the theta and especially delta frequency range. Several other features may also be present in the EEG of delirious patients, such as FIRDA and TWs. The use of EEG in detection and monitoring of delirium seems promising, and the sensitivity of EEG for delirium is high. Certain EEG elements may also have prognostic value, which could be of clinical relevance. Moreover, network analyses and *in silico* models offer opportunities to study the presence of common pathways due to different causes. Lastly, EEG is a useful tool in further investigation of non-convulsive seizures and their link to delirium. EEG, even when a limited number of electrodes is used, is thus a valid method that could aid prediction, detection, and monitoring of delirium.

Declaration of Interests Authors AJCS and FSL are advisors for Prolira, a start-up company that is working on the development of an EEG-based delirium monitor. Any (future) profits from EEG-based delirium monitoring will be used for future scientific research only.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th Edition (DSM-5). Diagnostic Stat Man Ment Disord 4th Ed TR. 2013.
2. World Health Organisation. ICD-10 version: 2010. World Health Organisation. 2010.
3. Ely E, Gautam S, Margolin R, Francis J, May L, Speroff T, et al. The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med. 2001;27(12):1892–900.
4. Hahn CD, Emerson RG. Electroencephalography and evoked potentials. In: Daroff RB, Jankovic J, Mazziotta JC, Pomeroy SL, editors. Bradley's neurology in clinical practice. 7th ed. Philadelphia: Elsevier Saunders; 2016.. chap 34.
5. Seeck M, Koessler L, Bast T, Leijten F, Michel C, Baumgartner C, et al. The standardized EEG electrode array of the IFCN. Clin Neurophysiol. 2017;128(10):2070–7.
6. Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res Rev. 1999;29(2–3):169–95.
7. Van Lier H, Drinkenburg WHI, Van Eeten YJ, Coenen AM. Effects of diazepam and zolpidem on EEG beta frequencies are behavior-specific in rats. Neuropharmacology. 2004;47(2):163–74.
8. Britton JW, Hopp JL, Korb P, Lievens WE, Pestana-Knight EM, Frey LC. The normal EEG. In: Louis EK, Frey LC, editors. Electroencephalography (EEG): an introductory text and atlas of normal and abnormal findings in adults, children, and infants. Chicago: American Epilepsy Society; 2016.

9. Niedermeyer E, Lopes da Silva FH, editors. Electroencephalography: basic principles, clinical applications, and related fields. London: Lippincott Williams and Wilkins; 2005. p. 441.
10. Fernandez-Bouzas A, Harmony T, Fernandez T, Silva-Pereyra J, Valdes P, Bosch J, et al. Sources of abnormal EEG activity in brain infarctions. Clin Electroencephalogr. 2000;31(4):165–9.
11. Hess R. Localized abnormalities. In: Rémond A, editor. Handbook of electroencephalography and clinical neurophysiology, vol. 11. Amsterdam: Elsevier; 1976. p. 11B88–11B1116.
12. Goldensohn ES. In: Klass DW, Daly DD, editors. Use of the EEG for evaluation of focal intracranial lesions. New York: Raven Press; 1979. p. 307–41.
13. Watson PL, Ceriana P, Fanfulla F. Delirium: is sleep important? Best Pract Res Clin Anaesthesiol. 2012;26(3):355–66.
14. Accolla EA, Kaplan PW, Maeder-Ingvar M, Jukopila S, Rossetti AO. Clinical correlates of frontal intermittent rhythmic delta activity (FIRDA). Clin Neurophysiol. 2011;122(1):27–31.
15. Young GB, Bolton CF, Archibald YM, Austin TW, Wells GA. The electroencephalogram in sepsis-associated encephalopathy. J Clin Neurophysiol. 1992;9(1):145–52.
16. Watemberg N, Alehan F, Dabby R, Lerman-Sagie T, Pavot P, Towne A. Clinical and radiologic correlates of frontal intermittent rhythmic delta activity. J Clin Neurophysiol. 2002;19(6):535–9.
17. Sutter R, Kaplan PW. Clinical and electroencephalographic correlates of acute encephalopathy. J Clin Neurophysiol. 2013;30(5):443–53.
18. Kaplan PW, Sutter R. Affair with triphasic waves – their striking presence, mysterious significance, and cryptic origins: what are they? J Clin Neurophysiol. 2015;32(5):401–5.
19. Amodio P, Montagnese S. Clinical neurophysiology of hepatic encephalopathy. J Clin Exp Hepatol. 2015;5:S60–8.
20. Coggins CC, Curtiss CP. Assessment and management of delirium: a focus on hepatic encephalopathy. Palliat Support Care. 11.4. 2013;11.4:341–52.
21. Palanca BJA, Wildes TS, Ju YS, Ching S, Avidan MS. Electroencephalography and delirium in the postoperative period. Br J Anaesth. 2017;119(2):294–307.
22. Fleischmann R, Tränkner S, Bathe-Peters R, Rönnefarth M, Schmidt S, Schreiber SJ, et al. Diagnostic performance and utility of quantitative EEG analyses in delirium: confirmatory results from a large retrospective case-control study. Clin EEG Neurosci. 2018;50(2):111–20.
23. Fisher RS, Van Emde Boas W, Elger C, Genton P, Lee P, Engel J Jr. Epileptic seizures and epilepsy: definitions proposed by the international league against epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005;46(4):470–2.
24. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the international league against epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):522–30.
25. Sutter R, Semmlack S, Kaplan PW. Nonconvulsive status epilepticus in adults — insights into the invisible. Nat Rev Neurol. 2016;12(5):281–93.
26. Kaplan PW. EEG criteria for nonconvulsive status epilepticus. Epilepsia. 2007;48:39–41.
27. Kaplan PW. Behavioral manifestations of nonconvulsive status epilepticus. Epilepsy Behav. 2002;3(2):122–39.
28. Kaplan PW. Delirium and epilepsy. Dialogues Clin Neurosci. 2003;5(2):187.
29. Shorvon S, Trinka E. Nonconvulsive status epilepticus and the postictal state. Epilepsy Behav. 2010;19(2):172–5.
30. Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology. 2004;62(10):1743–8.
31. Kurtz P, Gaspard N, Wahl AS, Bauer RM, Hirsch LJ, Wunsch H, et al. Continuous electroencephalography in a surgical intensive care unit. Intensive Care Med. 2014;40(2):228–34.
32. Oddo M, Carrera E, Claassen J, Mayer SA, Hirsch LJ. Continuous electroencephalography in the medical intensive care unit. Crit Care Med. 2009;37(6):2051–6.

33. Naeije G, Depondt C, Meeus C, Korpak K, Pepersack T, Legros B. EEG patterns compatible with nonconvulsive status epilepticus are common in elderly patients with delirium: a prospective study with continuous EEG monitoring. Epilepsy Behav. 2014;36:18–21.
34. Stam CJ. Modern network science of neurological disorders. Nat Rev Neurosci. 2014;15(10):683.
35. Van Dellen E, Van Der Kooi AW, Numan T, Koek HL, Klijn FAM, Buijsrogge MP, et al. Decreased functional connectivity and disturbed directionality of information flow in the electroencephalography of intensive care unit patients with delirium after cardiac surgery. Anesthesiology. 2014;121(2):328–35.
36. Numan T, Slooter AJC, van der Kooi AW, Hoekman AML, Suyker WJL, Stam CJ, et al. Functional connectivity and network analysis during hypoactive delirium and recovery from anesthesia. Clin Neurophysiol. 2017;128(6):914–92.
37. Ponten SC, Tewarie P, Slooter AJC, Stam CJ, van Dellen E. Neural network modeling of EEG patterns in encephalopathy. J Clin Neurophysiol. 2013;30(5):545–52.
38. Van Eijk MMJ, Van Marum RJ, Klijn IAM, De Wit N, Kesecioglu J, Slooter AJC. Comparison of delirium assessment tools in a mixed intensive care unit. Crit Care Med. 2009;37(6):1881–5.
39. Inouye SK, Van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method: a new method for detection of delirium. Ann Intern Med. 1990;113(12):941–8.
40. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001;286(21):2703–10.
41. Van Eijk MM, Van Den Boogaard M, Van Marum RJ, Benner P, Eikelenboom P, Honing ML, et al. Routine use of the confusion assessment method for the intensive care unit: a multicenter study. Am J Respir Crit Care Med. 2011;184(3):340–4.
42. Rice KL, Bennett MJ, Gomez M, Theall KP, Knight M, Foreman MD. Nurses' recognition of delirium in the hospitalized older adult. Clin Nurse Spec. 2011;25(6):299–311.
43. Van Der Kooi AW, Zaal IJ, Klijn FA, Koek HL, Meijer RC, Leijten FS, et al. Delirium detection using EEG: what and how to measure. Chest. 2015;147(1):94–101.
44. Numan T, Van den Boogaard M, Kamper AM, Rood PJT, Peelen LM, Slooter, AJC on behalf of the Dutch Delirium Detection Study Group, et al. Br J Anaesth. 2019;122.1:60–8.
45. Shinozaki G, Chan A, Sparr N, Zarei K, Gaul L, Heinzman J, et al. Delirium detection by a novel bispectral EEG device in general hospital. Psychiatry Clin Neurosci. 2018;72(12):856–63.
46. Sutter R, Kaplan PW, Valença M, De Marchis GM. EEG for diagnosis and prognosis of acute nonhypoxic encephalopathy: history and current evidence. J Clin Neurophysiol. 2015;32(6):456–64.
47. Sutter R, Barnes B, Leyva A, Kaplan PW, Geocadin RG, Basel H. Electroencephalographic sleep elements and outcome in acute encephalopathic patients: a 4-year cohort study. Eur J Neurol. 2014;21(10):1268–75.
48. Claassen J, Taccone FS, Horn P, Holtkamp M, Stocchetti N, Oddo M. Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM. Intensive Care Med. 2013;39(8):1337–51.