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Inhalt

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Instructions to Authors

General

"Epileptologie" publishes requested as well as unasked manuscripts on all aspects of epilepsy. In general only previously unpublished articles are accepted. Manuscripts, or the essence of their content, must be previously unpublished, and may not be under simultaneous consideration by another journal. Two reviews are generally obtained. No reprints of the articles will be made, however, the manuscripts will be published on the homepage of the Swiss League against Epilepsy (www.epi.ch) and can be downloaded as pdf-file.

Submission of Manuscripts

Unasked manuscripts (accompanied by a letter to the editor) should be submitted to: Frau M. Becker, Redaktion Epileptologie, Schweizerische Liga gegen Epilepsie, Seefeldstr. 84, Postfach 1084, 8034 Zürich. Phone: 043 488 67 79, Fax 043 488 67 78, e-mail: becker@epi.ch. Manuscript preparation: Manuscripts are only accepted if they meet the following criteria. Manuscripts which do not comply with these standards will be returned to the authors without detailed review.

1. Language: Besides German also English, French and Italian are possible.
2. Spelling (German): Use the German spelling with "z" and "k" (e.g. Karzinom), Latin technical terms keep their spelling (e.g. Arteria carotis).
3. Form:The whole text including references, tables and figure legends have to be typed as follows:

- DIN-A4-Paper, one-sided (1 1/2- or double-space with a max. of 30 lines each page).
- Arrange references in order of citation in the text and cite all references by Arabic numerals in square brackets in the text.
- Tables and figure legends should be numbered consecutively with Arabic numerals.

4. Order: 1. Title page (if necessary incl. acknowledgements, sources of support from others or funding sources). 2. Summary in German, French and English, with key words, 3. Text, 4. References, 5. Tables, 6. Figure Legends and 7. Figures.

- On the title page provide the full title of the article (German and English), list author(s) with full names, highest degree, academic or professional affiliations, complete address of the lead author with phone, fax and e-mail details.
- Summary in German, French and English (including title of the article). Without literature references, acronyms and unusual abbreviations (with a maximum of 250 words).
- 3 to 6 key words in all three languages.
- Text: Full-length papers should be divided into Introduction, Methods (including research material, patients, experimental animals etc., if necessary also reference that the recommendations from the Declaration of Helsinki have been adhered to, incl. a vote from an ethic committee), Results and Discussions. Abbreviations are to be written in full length when appearing for the first time in the text.
- References: All references cited in the text should be listed at the end of the paper in the same order as they appear in the text and cited according to the example given below. Personal communications, unpublished data (which include manuscripts submitted but not in press) must be given in parentheses in the text, not as references. References cited as "in press" refer only to manuscripts which have already been accepted by a journal (please indicate journal – as far as known – edition and year of appearance). The citation of papers such as "in preparation"is not allowed. Congress communications can only be accepted as cited abstracts or as a contribution to a proceeding-edition.
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What should be submitted to the editor?

All manuscripts including figures and tables in three copies, with preference by e-mail (wordprocessing: MS Word), alternatively three hardcopies and a disc by postal mail (for figures and tables please indicate the programme used).

Dr. med. Martinus Hauf

Liebe Leserin, lieber Leser

Das vorliegende Heft der Zeitschrift Epileptologie trägt den Titel „Bewusstseinsstörungen“. Es werden – auf zwei Themenblöcke aufgeteilt – interessante neue Aspekte aus der klinischen Forschung und Übersichtsarbeiten zum Thema von nationalen Experten vorgestellt.

Im ersten Themenblock wird die Frage der diagnostischen und prognostischen Wertigkeit klinischer und nicht-klinischer Parameter zur Beurteilung bewusstseinsgestörter Patienten erörtert.

Andrea Rossetti stellt uns ein ausgezeichneten Update zu den EEG-Kriterien von Bewusstseinsstörungen zur Verfügung. Inhaltlich eng damit verknüpft diskutieren Matthias Haenggi und Kollegen im zweiten Artikel die prognostische Wertigkeit der klinischen und paraklinischen Parameter bei Patienten nach kardiopulmonaler Reanimation. Interessant ist hier insbesondere, dass neue therapeutische Ansätze wie die Hypothermie-Behandlung eine neue Validierung der prognostischen Wertigkeit altbekannte Parameter notwendig macht. Ergänzend werden auch neue bildgebende Methoden vorgestellt, die funktionelle und strukturelle Veränderungen in bewusstseinsrelevanten Hirnarealen detektieren können und potentiell prognostische Aussagen ermöglichen werden.

Im nächsten Artikel beschäftigen sich Elisabeth Springer und Mitarbeiter anhand von illustrierten Fallbeispielen mit den Möglichkeiten, Korrelate zur epileptischen Aktivität und deren Folgen in schnittbildgebenden Verfahren darzustellen. Die diagnostische und potenziell prognostische Wertigkeit wird diskutiert. In diesem Artikel beginnt der zweite Themenblock, der sich mit pathophysiologischen neuen Erkentnissen zu Bewusstseintrübungen auseinandersetzt. Hierbei werden lokalisatorische Befunde zu quantitativen Bewusstseinstörungen wie auch zu qualitativen Bewusstseinsstörungen wie zum Beispiel akustischen Halluzinationen bei Epilepsien diskutiert. Adrian Guggisberg und Mitarbeiter stellen neue physiologische und pathophysiologische Aspekte des Gähnens vor und diskutieren die Rolle des Gähnens in unterschiedlichen Krankheitsbildern. Im abschliessenden Artikel tragen Markus Geschwind und Fabienne Piccard eine ausgesprochen lesenswerte Arbeit zu Glücksgefühlen als seltene Bewusstseinsstörung im Rahmen von epileptischen Anfällen zur Ausgabe bei und diskutieren in diesem Zusammenhang die Funktionen und Rolle des insulären Kortex in der Epilepsie.

Ich möchte meinen Freunden und Kollegen, die zur Realisation dieser Ausgabe mit der Beschreibung klinisch relevanter Aspekte von Bewusstseinsstörungen im Rahmen neurologischen Erkrankungen beigetragen haben, ganz herzlich danken. Nun wünsche ich Ihnen, liebe Kolleginnen und Kollegen, viel Vergnügen und viele neue Erkenntnisse beim Lesen dieser Ausgabe.

Martinus Hauf

Dr. med. Martinus Hauf

Chère lectrice, cher lecteur,

Le présent edition de l' « Epileptologie » est intitulé « altération de la conscience » et il contient des contributions sur le sujet sur des nouvelletés issue de la recherche clinique ainsi que des articles instructives et intéressants de mise à jours par des experts nationaux.

Il contient deux blocs thématiques. Le premier est consacré à la question de la valeur diagnostique et pronostique des paramètres cliniques et paracliniques pour évaluer les patients avec un état mental altéré. Andrea Rossetti nous offre une excellente mise à jour sur les critères de l'EEG dans les troubles de la conscience. Étroitement liée Matthias Haenggi et collaborateurs discutent dans le deuxième article la valeur pronostique des paramètres cliniques et paracliniques chez les patients après une réanimation cardio-pulmonaire. Il est intéressant en particulier que de nouvelles approches thérapeutiques comme le traitement de l'hypothermie rend une nouvelle validation des paramètres pronostic nécessaires. Nouvelles méthodes d'imagerie sont complémentaires présentées, qui peut détecter des changements fonctionnels et structurels dans les régions du cerveau impliquées dans la régulation de la vigilance et de « awareness ».

L'article par Elisabeth Springer et al. se focalise sur les corrélats cérébraux de l'activité épileptique et ses séquelles visualisés par des techniques de l'imagerie biomédical. La valeur diagnostic et pronostic des résultats est discutée. Dans cet article, le second sujet de l'édition est initié et des nouvelles observations sur la physiopathologie d'un état mental altéré et des troubles de la conscience sont présentés. Adrian Guggisberg et al., introduit de nouveaux aspects physiologiques et physiopathologiques du bâillement et discute le rôle du bâillement dans différentes maladies. Markus Geschwind et Fabienne Piccard contribuent un article particulièrement intéressant sur des crises extatiques comme rares troubles de la conscience d'origine épileptique et résument le rôle et fonctionnement du cortex insulaire.

Je tiens à remercier de tout cœur mes amis et collègues qui ont contribué à la réalisation de cette édition et je vous souhaite, chers collègues, une très bonne lecture.

Martinus Hauf

Dr. med. Martinus Hauf

Dear Readers,

The present issue of the journal Epileptologie is entitled “alteration of consciousness” and it contains contributions on new aspects resulting from clinical research activities as well as interesting review articles on the subject presented of national experts.

The issue is dived in two thematic blocks. The first is dedicated to the question of diagnostic and prognostic value of clinical and non- clinical parameters to assess patients with altered mental state. Andrea Rossetti provides us with an excellent update on the EEG criteria in consciousness disorders. Closely related, Matthias Haenggi and colleagues discuss in the second article the prognostic value of clinical and paraclinical parameters in patients after cardiopulmonary resuscitation. Interesting is in particular that new therapeutic approaches such as hypothermia treatment makes a new validation of the prognostic value of well-known parameters necessary. New imaging methods are complementary presented, which can detect functional and structural changes in brain areas involved in regulation of vigilance and awareness. These new approaches will potentially disentangle prognostic information in the clinical context.

The article by Elisabeth Springer and al. focuses on imaging correlates of epileptic activity and its sequellae visualised by cross-sectional imaging techniques. The diagnostic and prognostic value is discussed. In this article, the second topic of pathophysiological new findings in altered mental state and disorder of awareness is initiated by reporting localisation correlates to quantitative and qualitative impairment of consciousness in epilepsy. Adrian Guggisberg and al. introduces new physiological and pathophysiological aspects of yawning and discusses the role of the yawning in different diseases. Finally, Markus Geschwind and Fabienne Piccard contribute with a very worth reading work on ecstatic seizures as rare disturbance of awareness and discuss the role of the insular cortex in epilepsies.

I would like to whole-heartedly thank my friends and colleagues who have contributed to the realization of this issue with the description of clinically relevant aspects of impaired consciousness in the context of neurological disorders and I wish you, dear colleagues, a pleasant reading.

Martinus Hauf

The Role of EEG for the Prognostication of Patients in the Intensive Care Unit

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Summary

The role of EEG in the context of prognostication in patients with acute disorders of consciousness in the intensive care unit has expanded over the last decades, in parallel with technical developments and refinements. This article will review the most common EEG patterns, and outline their prognostic implications. Then, several diagnostic categories will be analyzed regarding the prognostic role of the EEG. Finally, a brief overview will be offered on the most recent approaches, such as intracranial EEG or automated EEG interpretations. While the EEG is clearly and robustly established in the process of prognostication, its role is still that of a marker, rather than truly representing a tool generating therapeutic implications.

Epileptologie 2014; 31: 58 – 67

Key words: reactivity, burst-suppression, triphasic waves, PLEDs, alpha coma, spindle coma, FIRDA, rhythmic delta activity, SIRPIDs, sleep, seizures, status epilepticus

Die Rolle des EEGs bei der Prognose von Patienten auf der Intensivpflegestation

Die Rolle des EEGs für die Prognose von Patienten mit Bewusstseinsstörungen auf der IPS hat in den letzten Jahrzehnten ein zunehmendes Interesse erfahren, das mit bedeutenden technischen Entwicklungen und Verbesserungen einhergegangen ist. Dieser Artikel wird die gängigen EEG-Charakteristika und ihre prognostischen Bedeutungen in diesem Zusammenhang erwähnen. In einem zweiten Schritt werden verschiedene klinische Diagnosen in Zusammenhang mit EEG-Aspekten diskutiert. Eine Übersicht über die neuesten Entwicklungen, inklusive intrakranielles EEG oder automatische Analysen, wird das Ganze abschliessen. Das EEG ist weit und breit für seine prognostische Bedeutung bei komatösen und stuporösen Patienten anerkannt, jedoch bleibt seine Rolle bisher eher diejenige eines prognostischen Markers als eines Werkzeugs, welches unmittelbare therapeutische Schlussfolgerungen generiert.

Schlüsselwörter: Reaktivität, burst-suppression, triphasische Wellen, PLEDs, alpha-Koma, Spindelkoma, FIRDA, Status epilepticus

Le rôle de l'EEG dans le pronostic des malades aux soins intensifs

Le rôle de l'EEG dans le pronostic auprès de patients ayant des troubles de la vigilance dans des soins intensifs a vécu une expansion remarquable au cours des dernières décennies, en même temps que les améliorations techniques. Cette contribution discutera des patrons EEG les plus importants dans ce contexte clinique, avant d'aborder des situations cliniques particulières à la lumière de la littérature EEG concernée. Finalement, un aperçu des développements les plus récents, tels que l'interprétation automatisée ou les enregistrements intracrâniens, sera donné. Le rôle de l'EEG est certainement solidement implanté dans les algorithmes de pronostication du patient avec atteinte de la vigilance; cependant, à ce stade, son rôle reste celui d'un marqueur de pronostic, plutôt que d'un outil générant des implications thérapeutiques.

Mots clés : Réactivité, burst-suppression, ondes triphasiques, PLEDs, alpha coma, spindle coma, FIRDA, état de mal

Background: some history

In parallel to the increasing use of the EEG for clinical purposes since the 1930s, electroencephalographers started unraveling changes occurring in physiological sleep and pathological consciousness impairment. After almost a century, this field still experiences a dynamic evolution. A brief overview of the most important classification systems will illustrate some approaches and the related terminology.

We owe Hockaday and her colleagues one of the first thorough descriptions of the alterations found in patients with acute cerebral anoxia [1]. The classification system relies on five grades, with background frequency and amplitude representing the dominant

variables (**Table 1**); while all patients with grade I and none with grade V survived, the other grades represented a progressive impairment of normal cerebral function. The relevance of background reactivity was added twenty years later. Based on his personal experience, in 1988 Synek refined the prognostic classification for comatose patients after trauma or cerebral anoxia; he also made the observation that the prognostic significance of EEG should be assessed not within a few hours after the beginning of coma [2]. The breakdown into several categories renders the classification very accurate on the one side, but also somewhat unpractical (**Table 2**); the Hockaday grades are scattered among different prognoses, as is background reactivity. Ten years later, Young proposed an updated system based on their observation of comatose patients (**Table 3**), and compared it to the Synek classification, finding a higher interobserver agreement [3]. Furthermore, they pointed out that *burst-suppression* implies flattening for at least 1 second/20seconds, while Synek did not specify the denominator.

This illustrates the need for more uniformity, in order to allow a general understanding of what is described. Very recently, a common effort of several North American experts has produced a detailed description of the EEG terminology in an intensive care setting [4] (**Table 4**). While unequivocal electrographic seizures should show generalized spike-wave discharges >3 Hz, or clearly evolving discharges of any type reaching a >4 Hz frequency, other recurrent patterns (which would not be necessarily labeled as seizures) represent the subject of this classification; the term "epileptiform" was avoided. The first main term is related to the spatial distribution, the second to describe the type of discharges; to qualify, the discharges should recur at least 6 times. Then, modifiers appear, such as prevalence

Table 1: The Hockaday prognostic classification of EEG changes in postanoxic patients (modified after [1]).

Comment	Grade	Appearence
Normal	I	Predominant α with rare θ
Mildly abnormal	II	Predominant θ with rare δ
Moderately abnormal	III	Predominant δ
Severely abnormal	IV	Predominant δ with brief isoelectric intervals
Extremely abnormal	V	Nearly flat or flat record

Table 2: The Synek prognostic classification of EEG changes in postanoxic and brain trauma patients (modified after [2]).

Comment	Grade	Appearence
Optimal	I	Predominant α with rare θ
Benign	II	Predominant θ, reactive
	III	Spindle pattern
	III	Frontal rhythmic δ
Uncertain	II	Predominant θ, not reactive
	III	Diffuse δ (regardless of reactivity)
	III	Diffuse δ with epileptiform discharges
	IV	α pattern coma, reactive
Malignant	III	Low amplitude δ
	IV	Burst-suppression
	IV	Burst-suppression with epileptiform discharges
	IV	α pattern coma, not reactive
	IV	θ pattern coma
Fatal	IV	Low output EEG (<20 μV δ activity)
	V	Isoelectric EEG

Table 3: The Young prognostic classification of EEG changes in postanoxic and brain trauma patients (modified after [3]).

Category	Subcategory
I : θ/δ >50% of the record	Reactive
	Not reactive
II : triphasic waves	
III : Burst-suppression	With epileptiform activity
	Without epileptiform activity
IV : α/θ/spindle coma (unreactive)	
V : Epileptiform activity (not in burst-suppression)	Generalized
	Focal
VI : Suppression	Between 10-20 µV
	≤ 10 µV

Table 4: Older EEG terms and the newer terms after the standardized critical care EEG terminology proposed by the American Clinical Neurophysiology Society (modified after [4]).

Older Terms	Newer terms
PLEDs (periodic lateralized epileptiform discharges)	LPDs (lateralized periodic discharges)
PLEDs+	LPDs+
BIPLEDs (bilateral independent periodic lateralized epileptiform discharges)	BIPDs (bilateral independent periodic discharges)
GPEDs (generalized periodic epileptiform discharges)	GPDs (generalized periodic discharges)
Triphasic waves, most of the record	GPDs with triphasic morphology
FIRDA (frontal intermittent rhythmic delta activity)	GRDA (generalized rhythmic delta activity with frontal predominance)
SIRPIDs (stimulus-induced rhythmic, periodic, or ictal discharges)	SI- GPDs or RDA or SW (spike waves)
Lateralized seizure, δ frequency	Evolving RDA

over the recording, duration, frequency, sharpness, amplitude, and stimulus-induction. The EEG background is described according to symmetry, predominant posterior frequency, reactivity, voltage, sleep transients, and continuity (i.e.: suppression implies the whole recording being <10 µV, *burst-suppression* that 50 - 99% of the recording is attenuated, and a discontinuous trace is attenuated over 10 - 50%).

Particular patterns in patients with disturbed consciousness

Background slowing and reactivity

In cats, lesions confined to the cerebral cortex lead to attenuation of the alpha background, while subcortical lesions induce polymorphic delta [5]; unsurprisingly, this seems to apply also to humans in the emergency ward or in the intensive care unit (ICU) [6]. The etiologies are extremely broad. The previous paragraphs and **Tables 1 - 3** illustrate well the prognostic correlation of an increasing background slowing; it is however important to always perform activation procedures to test the reactivity, including sounds, eye opening, and painful stimulations. It seems reasonable to apply the stimuli on the face or the trunk; furthermore, stimulations should be performed at least 20 - 30 sec. apart. Even on a very slow EEG, a clear reactivity (regardless of either acceleration with amplitude attenuation, or high-voltage slowing) heralds a better prognosis [2, 3, 7 - 9]. Furthermore, with video-EEG recordings, correlation of stimulations with the EEG signal is very easy to assess.

Triphasic waves

These EEG transients owe their appearance in the literature to their observation in patients with hepatic impairment [10]; they are described as sharp deflections with two or three phases, where the second one has the highest amplitude and is surface positive; a phase lag may be observed. These transients, which often can be attenuated along with variation in consciousness, are by no means specific to liver disturbance [11]. They should be considered possibly epileptiform if occurring strictly unilaterally [12]; in this case

they usually do not show any clear reactivity. Of relevance, triphasic waves may be attenuated or abolished by benzodiazepines, their disappearance in this context does therefore not imply any epileptiform nature [13].

Rhythmic delta activity

The eponym is RDA, but these features are also commonly labeled as *frontal intermittent, rhythmic delta activity* (FIRDA, see **Table 4**) because of the frequently observed anterior predominance. This EEG pattern is common, and usually reactive. Symmetric rhythmic delta is not related to epilepsy, and represents an unspecific finding seen in patients with various etiologies [18, 19]. A marked asymmetric appearance may be associated

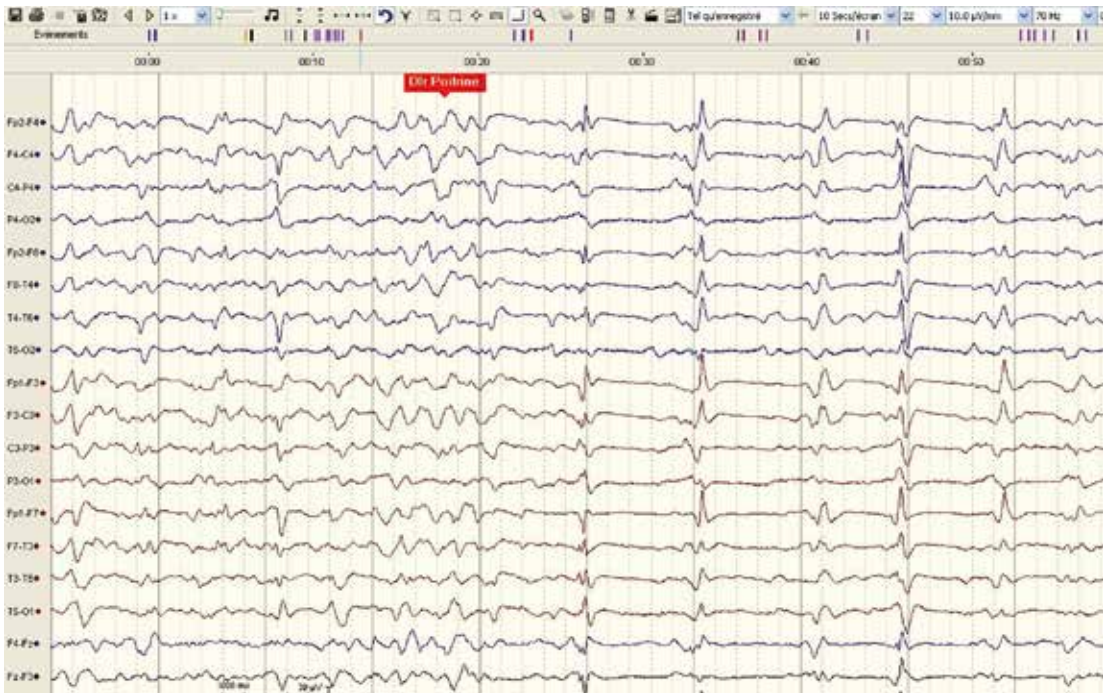

Figure 1: Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs), in this case stimulus-induced generalized periodic discharges (SI-GPD), in a man, during normothermia 36 hours after a cardiac arrest. The painful stimulation is marked in red (longitudinal bipolar montage, 30 mm/sec, 10 µV/mm).

Periodic discharges

These represent one of the most common findings in the ICU setting, and are labeled as *generalized periodic [epileptiform] discharges* (GPEDs or GPDs), and, if lateralized, PLEDs or LPDs (**Table 4**); since their presence does not necessarily represent an ongoing seizure, as they lay somewhere on the so called *ictal-interictal* continuum, the term "epileptiform" should indeed better be avoided [4, 14]. Many etiologies may be responsible, and the impact on prognosis is not uniform: some authors recognize an independent association with poor outcome [15], while others don't [16, 17].

with an underlying ipsilateral lesion [18]. As compared to triphasic waves and severe, diffuse EEG slowing, FIRDA seems to be related to a better outcome [19]. Recently, occurrence of lateralized rhythmic delta activity has been described, with a prevalence of associated seizures similar to that observed with periodic discharges [20].

Stimulus-induced patterns

The first systematic description of stimulus-induced rhythmic, periodic or ictal discharges (SIRPIDs, see **Table 4** for the last proposed terminology) is recent [21]. These patterns had a prevalence of 22% in the original description of a neuro-ICU cohort, encompassing a broad etiological spectrum (**Figure 1**); as the authors

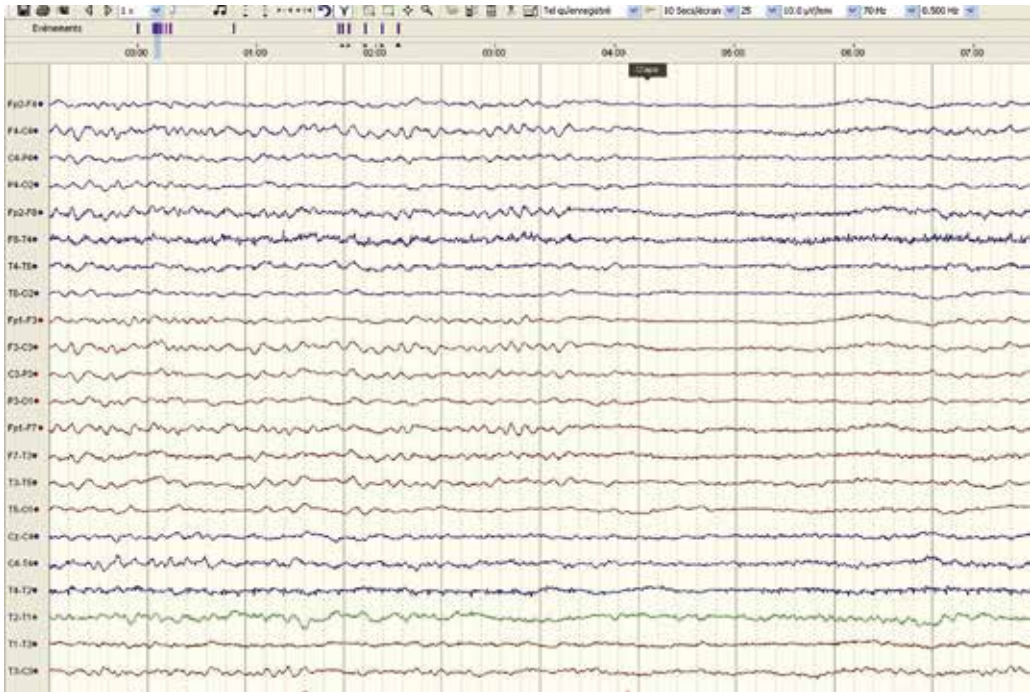

Figure 2: Auditory stimuli (clapping of hands marked in black) induce a diffuse attenuation of the recording in a woman under mild therapeutic hypothermia, 21 hours after a cardiac arrest (bipolar longitudinal montage, 30 mm/sec, 10 µV/mm).

pointed out, a video-correlation to recognize the stimuli is mandatory. SIRPIDs may represent a heterogeneous EEG reaction that should not be regarded as a normal reactivity. Interestingly, SIRPIDs have received relatively little attention regarding their prognostic significance, but recently, their occurrence in postanoxic patients undergoing hypothermia has been related to poor outcome [22].

Electrographic seizures

Seizures and status epilepticus represent a common challenge for caregivers in the ICU. It is difficult to identify a common pattern summarizing their impact independently from the etiology and the extent of active comorbidities. Earlier observations that myoclonic status following cardiac arrest, often along with periodic EEG discharges, is linked to poor outcome [23] has been corroborated recently, particularly if seizures appear during cooling and despite pharmacological sedation [8], while prognosis is not invariably catastrophic for patients experiencing seizures after rewarming [24]. In patients with brain trauma, seizures have also been independently associated with mortality [25], and it has been suggested that they aggravate cerebral damage [26]; similar findings also apply for subarachnoid hemorrhage [27], while in subjects with intracranial hemorrhage they do not seem to independently predict prognosis [28 - 30]. Acute seizures or status epilepticus in patients with ischemic stroke have been reported to be independently related to worse clinical outcome in hospital-based [31], but not in population-based studies [32]; globally their occurrence is limited to about 2% of the patients [33]. Patients with sepsis in the medical ICU are also subject to (mostly nonconvulsive) seizures, which correlate with bad prognosis [15].

Alpha, theta and spindle coma

These EEG patterns are relatively infrequent; mostly observed in comatose patients experiencing a cardiac arrest, they can also be found in subjects with other etiologies [34, 35]. They are mainly defined by the dominant frequency, and by higher amplitude in the frontal regions. Lack of reactivity to stimulations is regarded as characteristic [3, 36], but not by all authors. Alpha and theta coma probably represent a single phenomenon, and are usually seen at the low alpha band (7-8Hz) [37, 38], and a progressive slowing leading to a diffuse EEG attenuation may be observed over some days in patients with poor prognosis. The presence of a reproducible variation of the background modulates the earlier assumption that alpha and theta coma invariably herald a poor outcome: the majority of patients showing a “reactive”

alpha coma have been described to awaken, as opposed to those with no reactivity [34, 36]. Spindle coma may reflect the preservation of thalamo-cortical loops following lesions located in the lower diencephalon or brainstem, and therefore a lesser degree of brain dysfunction [35].

Sleep spindles

The occurrence of physiologic sleep patterns in patients with disorders of consciousness has recently been outlined as an important prognostic factor. This is illustrated in patients with consciousness impairment following deep cerebral vein thrombosis involving the thalami and acutely lacking spindles; these return upon resolution of the vasogenic edema [39]. In subjects with severe traumatic brain injury [40, 41] and anoxic-ischemic encephalopathy [41], occurrence of K complexes and sleep spindles correlates with a lesser degree of consciousness impairment. Of note, these studies have been conducted in a rehabilitation setting, up to 150 days after the initial insult [40]; therefore, one should not be automatically infer that the lack of physiologic sleep in the acute setting portends the same dismal prognosis.

Particular clinical situations

In recent years, moderate therapeutic hypothermia has experienced an increasing popularity, mainly in the context of anoxic-ischemic brain injury in neonates and adults. Of interest, it's not until below 30°C that periodic complexes appear on the EEG, the temperature has to lower below 24°C in order to observe diffuse intermittent suppression, and below 18°C for electrocerebral silence [42].

Hypoxic-ischemic encephalopathy: adults

The timing of assessment is critical, as electrophysiological evaluations within 12 hours after the insult may lead to overestimation of the brain damage [36, 43, 44]. In normothermia, patterns of monotonous, diffuse low voltage, or repetitive electric seizures or status epilepticus, as well as periodic discharges without any identifiable background, are considered to herald a poor prognosis [9, 45 - 48]; lack of background reactivity is also a reliable prognosticator [9, 46]. The EEG during therapeutic hypothermia has been recently described to provide valuable prognostic information, not only regarding the continuity of the tracing (an isoelectric recording during hypothermia, 24 hours after the cardiac arrest, is tightly related to non-awakening [49]),

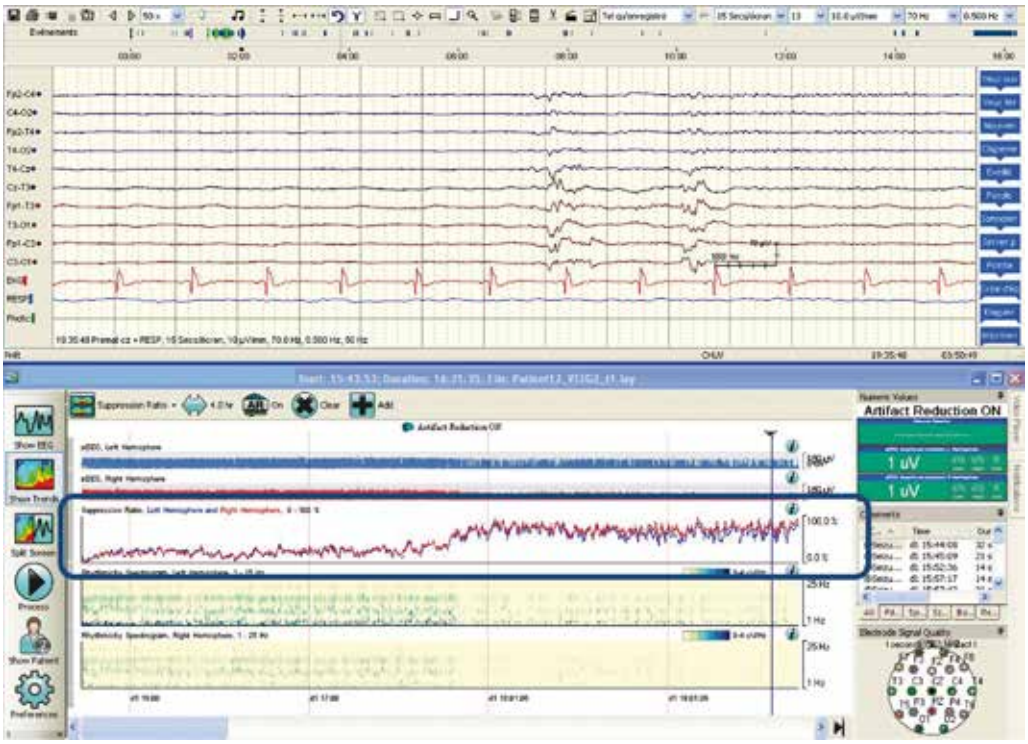

Figure 3: Upper panel: raw EEG of a man under general anesthetic for refractory status epilepticus; the screen represents 15 seconds (bipolar longitudinal montage, 20 mm/sec, 10 µV/mm). Lower panel: quantitative EEG over 4 hours; the blue box highlights the suppression ratio, which may be easily followed in order to adapt the sedation.

but also lack of reactivity: this feature, despite the use of moderate doses of sedation, has been related to a reliable forecast of poor outcome (**Figure 2**) [8]. In automated, amplitude integrated EEG softwares to the favorable prognostic role of a continuous signal, without electrographic status epilepticus has been outlined [50]; this approach is however not widely applied.

Since the false prediction of death or non-awakening is still possible using EEG (numbers oscillate between 0% and 10%), a complete evaluation in normothermia and off-sedation, and the integration with other prognosticators is mandatory [51, 52]. This is underscored by the description of patients awakening despite postanoxic status epilepticus [24]: these subjects had a particular clinical profile, namely preserved brainstem reflexes, reactivity of the EEG background, and early cortical somatosensory evoked potentials.

Hypoxic-ischemic encephalopathy: neonates and children

EEG alterations described in adults are also found in children under therapeutic hypothermia after cardiac arrest [53], and in general, bear the same prognostic value. Burst-suppression or a diffuse, extremely low-voltage pattern herald a poor prognosis [54]; background reactivity seems conversely to forecast a good outcome [55]. Considerable attention has been directed towards the prognostic significance of amplitude-integrated EEG: persisting burst-suppression or very low-voltage recordings with lack of a normal sleep-wake cycling are related to poor outcome [56, 57]. Also for newborns, timing of the assessment is critical, especially for those undergoing hypothermia: evaluation during the first 24 hours are less reliable [54, 56, 57].

Traumatic and hemorrhagic etiologies

EEG may be helpful in terms of correlations with vasospasm in patients with subarachnoid hemorrhage, not only to unravel subclinical seizures: recordings displaying focal slowing correlate with vasospasm [58]. These observations were confirmed using continuous EEG with quantitative analyses: decreasing alpha variability might precede by 2 - 3 days the insurgence of a vasospasm [59]. Nevertheless, to date, it has not been demonstrated that EEG influences clinical prognosis in this context. An analogous approach has also proven useful in patients with moderate to severe traumatic brain injury [60]. However, as in other etiologies, it remains still unclear whether the prescription of antiepileptic treatment may have a prognostic impact [61].

Other conditions

The clinical situations listed above are by far not exhaustive. For example, toxic-metabolic conditions are frequently encountered in this context [6]. General anesthetics are often prescribed in the ICU, and a multitude of compounds, such as inhalation anesthetics, barbiturates, propofol, and midazolam, may induce diffuse slowing, a discontinuous EEG, burst-suppression, or even complete suppression. Since most drugs act principally by modulating the $GABA_A$ receptor, these may enhance fast rhythms or spindle-like figures at low doses [62]. Intoxications may considerably affect the EEG [6]. Opioids generally slow the background, while neuroleptics and antidepressants may induce in addition generalized or focal epileptiform abnormalities, as well as triphasic waves [63, 64]; similar changes may be observed with lithium [65]. Hypnotic compounds, which modulate $GABA_A$ receptors in a different way as compared to barbiturates and benzodiazepines, can also enhance beta activity [66]. Antibiotics with beta-lactam rings act as GABA antagonists, but under therapeutic dosages it is rare to observe intoxications or seizure-induction, apart from cefepime [67]. Metabolic disturbances are reflected on the EEG by progressive background slowing up to complete EEG suppression in dramatic cases and the appearance of rhythmic delta (FIRDA) or triphasic waves [19].

Outlook

The ongoing technological improvements, which not only have allowed considerable performances in EEG-video-recordings at the patient's bed, but also simplify data storage, are experiencing a new momentum in recent years, with the development of devices for automated EEG analysis [68 - 70]. These are already popular in several North American centers, and are making their way also in Europe; they are based on several mathematical approaches using amplitude-integrated EEG signals of a standard 10-20 EEG montage, which allow not only seizure and spike detections, but also artifact rejections, and quantification of several indices (e.g., suppression ratio, alpha/delta ratio) that are important for a multimodal monitoring in brain injured patients. Furthermore, the possibility of a live display of the analyses during the recording renders EEG information more accessible to non-trained caregivers (**Figure 3**). While the performances are steadily improving, all methods still lack independent validations and therefore require, as a gold standard, inspection of the raw EEG trace. Intracerebral electrodes are also receiving increasing attention, although, for the moment, rather for scientific purposes than clinical implications. For example, in patients with subarachnoid hemorrhages, seizures are seen more often intracortically (38%) than on scalp (8%), and prognosis seems to be better

for patients without any seizures (no risk of severe disability), than for those with scalp seizures (25% risk), or with intracortical seizures only (50% risk) [71]. In another study, spreading depolarizations were observed in half of the studied patients with severe traumatic injury, and were associated with poor outcome [72]. Spreading depolarization may correlate with delayed ischemia in patients with subarachnoidal hemorrhage [73]. While these observations open exciting new avenues for the understanding of brain patho-physiology in these particular clinical conditions, there is still no answer regarding the prognostic impact of seizure treatment, and an important limitation should be remembered: sampled tissues are limited and often are not comparable among the studied patients in terms of concomitant pathological involvement.

Over the last decade, continuous EEG monitoring in the ICU has been markedly developed. It has been shown that this patient population should be monitored for at least 48 hours in order to detect 93% of (mostly nonconvulsive) seizures [74]. More recently, however, in an analysis on 242 patients (not restricted to ICU, and as the former one including heterogenous underlying diagnoses), the lack of epileptiform activity during the first 30 EEG minutes rendered extremely unlikely a subsequent seizure on continuous EEG (3%, versus 22% in those with epileptiform discharges). This suggests that a first routine EEG may help identifying those subjects that would deserve EEG monitoring [75]. Similarly, in patients with postanoxic coma, it has been demonstrated that repeated routine EEG recordings may prove as informative as continuous EEG monitorings [44, 76].

In conclusion, EEG represents a very useful tool for prognostic assessment of patients with acute cerebral dysfunction; as every other prognosticator, however, it has to be integrated with other variables for a multimodal approach that proves more robust for the clinical forecast, but also minimizes false positive poor predictions. Somewhat disappointingly, EEG in the ICU still represents rather a prognostic marker than a diagnostic tool with therapeutic implications. It is to hope that the future will outline the best approaches in terms of effectiveness and define potential therapeutic consequences.

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Prognostic Markers for Coma and Disorders of Consciousness

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Summary

Etiologies of coma are various and prognosis is tightly linked to the underlying pathology. In this inhomogeneous patient group no simple prognostic parameter has an universal value. The largest subgroup of comatose patients consists of patients after outpatient circulatory arrest. For this group of patients, there is some empirical data, which can predict an unfavorable outcome. However, these data were validated before the therapy concept of therapeutic hypothermia and now new therapeutic temperature management were introduced. In this article, the current state of prognosis estimation using clinical and electrophysiological parameters is resumed for this group of patients. The significance of modern imaging techniques in this condition is discussed.

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Key words: Out of hospital cardiac arrest, prognosis, coma

Prognostische Parameter für Koma und Bewusstseinsstörungen

Die zugrunde liegenden Ursachen eines Komas sind mannigfaltig, die Prognose bezüglich Verlauf und Erwachen aus dem Koma ist sehr mit der ursächlichen Pathologie verknüpft. Aus diesem Grunde gibt es keine einfachen prognostischen Parameter, welche allgemein gültig sind. Die grösste Untergruppe der komatösen Patienten sind Erkrankte nach einem ausserhalb des Spitales erlittenen Herz-Kreislauf-Stillstand. Für diese Patientengruppe gibt es einige empirische Daten, welche ein ungünstiges Outcome vorhersagen können. Problematisch ist jedoch, dass diese Daten validiert wurden, bevor das Therapiekonzept der therapeutischen Hypothermie und nun neu des therapeutischen Temperaturmanagements eingeführt wurden. In diesem Artikel wird der aktuelle Stand des Abschätzens des Verlaufs für klinische und elektrophysiologische Parameter in dieser Patientengruppe dargestellt und weiterhin der Stellenwert moderner bildgebender Verfahren beschrieben.

Schlüsselwörter: Herz-Kreislauf-Stillstand ausserklinisch, Prognose, Koma

Les signes pronostiques du coma et des troubles de la conscience

Les étiologies de coma sont diverses et le pronostic est étroitement lié à la pathologie sous-jacente. Dans ce groupe de patients non homogène, aucun paramètre pronostique simple n'a une valeur universelle. La plus importante sous-groupe de patients dans le coma se compose des patients après un arrêt circulatoire en ambulatoire. Pour ce groupe de patients, il y a certaines données empiriques, qui peuvent prédire une évaluation clinique défavorable. Cependant, ces données ont été validées avant l'introduction du concept de traitement de l'hypothermie thérapeutique et, plus récente, de la gestion de la température thérapeutique. Dans cet article, l'état actuel de l'estimation de pronostic à l'aide des paramètres cliniques et électrophysiologiques est repris pour ce groupe de patients. L'importance des techniques d'imagerie modernes dans cette condition est discutée.

Mots clés : Arrêt cardiocirculatoire extrahospitalière, pronostic, coma

Introduction

Coma is a state of unarousable unconsciousness and is characterized by a failure of the arousal and alerting system of the brain (the ascending reticular activating system ARAS) [1]. Disorders interfering with

the ARAS may produce at least transient coma. Causative disorders can be grouped into i) structural brain lesions (other than traumatic brain injury), ii) metabolic and nutritional disorders, iii) exogenous toxins, iv) central nervous system infections and septic illness, v) seizures and status epileticus, vi) hypo- and hyperthermia and vii) head trauma. Whereas coma per se puts the patient's life at risk independent of the underlying disease, chance of recovery from a comatose state is determined largely on cause of coma and on age of the patient. Because of these numerous variations, this manuscript further aims to focus on comatose adult patients suffering from hypoxic ischemic encephalopathy after cardiac arrest.

Patients suffering from sudden unexpected out-of-hospital cardiac arrest (OHCA) have a dismal prognosis if no efforts to restore circulation are immediately undertaken. The London Ambulance Service (LAS) is the largest single provider of emergency medical service of the world and serves Greater London's population of about 8.2 million people. In the Cardiac Arrest Annual Report 2012/13, which covers the period from 1st April 2012 to 31st March 2013, LAS attended a total of 10,111 patients who presumably had suffered an OHCA [2]. In 55.8% (n=5645) of these cases no attempts to resuscitate the patient were made. Of those patients in whom resuscitation was attempted, the great majority had a presumed cardiac origin of the cardiac arrest (n= 3848). Although 63.7% of these patients were transported to hospital, only 9.3% (n=355) were discharged alive. The proportion of surviving patients suffering from cardiac arrest from trauma was 5.1% (n=12), and survival of cardiac arrest from "other" causes (mainly respiratory, terminal illness and overdose) was 6.1% (n=23). No data of outcome other than dead or alive were reported, so quality of life after discharge of hospital remains obscure. These data undermine that most patients suffering an OHCA do not survive until hospital admission, thus introducing a large bias in literature reporting predictors of good outcome, which range up to 50% [3]. Another problem in the literature of prognostication of outcome in critically ill patients (not limited to comatose survivors of OHCA) arises because of the phenomena of "self-fulfilling prophecy". This term was coined by Merton, who characterized the self-fulfilling prophecy as, in the beginning, a false definition of the situation evoking a new behavior, which makes the original false conception come 'true'. This specious validity of the self-fulfilling prophecy perpetuates a reign of error [4]. Translated into clinical practice this means that the initial belief in bad outcome will later lead to withdrawal of support, mostly ventilation and circulatory support, and the patient inevitably dies. The clinician, who has to put a decision on further treatment – and to provide his best advice to the family – in order to continue or to withdraw life-sustaining treatment is stuck in the dilemma on which side to weight his information: in case of a "low" probability of good outcome, the probability is not zero, and some patients will survive with a good outcome. Unfortunately, most patients in this particular situation will receive treatment for an unwanted outcome, either death or with a substantial risk survival with disabling neuropsychological deficits [5]. This "risk/benefit ratio" has to be explained to the next of kin, and individual decisions have to be made. The base of this decision have to be made first on clinical grounds, supported by electrophysiological methods and, in selected cases, by neuroimaging or laboratory testing, the latter being reviewed later in this issue.

Clinical and paraclinical prognostic factors

Determination of possible outcomes relying on clinical examination and medical history is dependent on timing: in an ideal world, patients with terminal illness or elderly patients have already discussed with their family and family physician what can be expected in quality of life in case of an unexpected event and therefore have put an advanced medical directive with or without a DNR (do not resuscitate) order in place. In case of an OHCA, survival is dependent on whether or not the arrest is witnessed, the initial cardiac rhythm (asystolic arrest and pulseless electrical activity versus ventricular fibrillation and ventricular tachycardia without pulse, the latter is also considered as shockable rhythm), bystander cardio-pulmonary resuscitation (CPR), and time to defibrillation in case of an initial shockable rhythm [6]. Rules for termination of resuscitation efforts have been developed, but validation is difficult to achieve. In the Japanese population (in which a larger proportion of patients with OHCA suffer from central nervous bleeding), the combination of no prehospital return of spontaneous circulation, an unshockable initial rhythm, and unwitnessed onset by bystanders was shown to predict a very poor outcome in > 99% of the patients [7]. Another easily available parameter to predict outcome during resuscitation is the end-tidal CO2 value, which is a parameter of circulation under cardiopulmonary resuscitation (CPR). After 20 minutes of CPR, an end-tidal CO2 < 1.9 kPa (14.3 mmHg) predict unfavorable outcome with accuracy [8].

There exists no proven clinical prognostic factor for poor outcome immediately after return of spontaneous circulation, and after hospital admission. Absence of pupillary reflexes are seen frequently, but have no association with outcome. Even absence of all brainstem reflexes is not sufficient for formal brain death testing within the first hours after OHCA. Only, ancillary tests such as computed tomographic angiography, cerebral angiography transcranial doppler or duplexsonography demonstrating absence of cerebral blood flow are valuable at this time interval.

In the era preceeding therapeutic hypothermia (TH), a large body of evidence existed to predict unfavorable outcome in patients after cardiac arrest [9]. The indi-

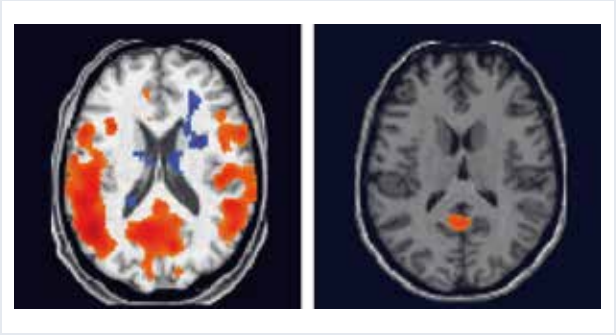

Figure 1: Resting state fMRI: Seed-based functional connectivity map of the Default mode network in a) a healthy wake subject and b) a patient with OHCA. Note the disrupted connectivity between the precuneus and the fronal/parietal association cortices following loss of consciousness.

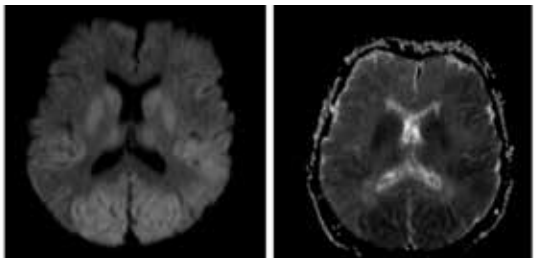

Figure 2: Diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) of a patient with OHCA. Note the widespread DWI restrictions in the precuneus, basal ganglia and thalamus (ADC < 480 mm/s2) indicating a poor prognosis.

cators of poor outcome after CPR are absent pupillary light response or corneal reflexes at least 24 hours after arrest, and extensor or no motor response to pain after 3 days of observation, and myoclonus status epilepticus after day 1. Bilateral absent cortical responses on somatosensory evoked potential studies recorded 3 days after CPR also predicted poor outcome, the same is true for serum neuron-specific enolase (NSE) higher than 33 microg/L. Burst suppression or generalized epileptiform discharges on EEG predicted poor outcomes but with insufficient prognostic accuracy [9].

Therapeutic hypothermia – changing prognostic factors

In 2002, 2 studies demonstrated a superior outcome in patients after OHCA treated with therapeutic hypothermia [10, 11], and meantime induced hypothermia replaced standard therapy in these patients in many centers. With this treatment, prediction had become more difficult, because the "old" guidelines had no validity anymore. It has been shown that hypothermia delays recovery of motor responses and renders clinical examination unreliable [12]. The reason for the delayed recovery is because induced hypothermia regularly requires deep sedation for 12 - 24 hours (depending on the protocol used), and the pharmacokinetic and -dynamic change with body temperature. So weaning off the sedative medication can be delayed, and timing of prognostication becomes more difficult.

Meanwhile solid data for prognostication of outcome of OHCA patients treated with therapeutic hypothermia have been published [12, 13]. The most recent publication by Rossetti and Oddo describes the performance of the so called early multimodal outcome prediction approach, derived from a cohort of 134 patients treated with TH [14]. Clinical examination comprised of brainstem reflexes (pupillary, oculocephalic and corneal reflex, either all present versus at least one absent after rewarming, but before 72 hours after CA) and occurrence of myoclonus (appearing within 24 h after sedation stop). EEG was categorized as "presence of background reactivity", "spontaneous discontinuous pattern" and "epileptic activity" during TH and at normothermia. NSE was collected at different time points within the first 72 hours, and a cut-off higher than 33 microg/L was used. SSEP were performed at early normothermia. The combination of clinical examination, EEG (background reactivity) and high NSE-levels had a 1.00 (CI 0.89 – 1.00) positive predictive value (PPV) for predicting mortality at 3 months, and a 1.00 (CI 0.90 – 1.00) PPV for prediction of a poor outcome (defined as death or dependency on daily activities) at 3 months. Addition of SSEP did not improve the performance of the prediction model, and, albeit not reported in detail, the addition of NSE into the model seemed to have added only little value. Unfortunately, the accuracy of predicting good outcome of this model was poor. By now, this is the largest cohort of patients, and although it comes from a single center, these results seem to be generalizable.

Criticism about TH arose because albeit both big studies in 2002 claimed to compare therapeutic hypothermia versus normothermia, in reality therapeutic hypothermia was compared to standard care. Because cardiac arrest evokes a global ischemia-reperfusion syndrome, the consequence is reperfusion injury with associated cytokine release and fever. In the European HACA-trial, the temperature of one quarter of the patients in the normothermia group exceeded 38.0°C [10]. So discussion arose weather TH improves outcome because of hypothermia, or simply because of the absence of fever. In 2013, a multicenter trial was published in which 939 patients suffering from OHCA were randomized into either a TH group (33°C) or a targeted temperature of 36°C [3]. The primary outcome was all-cause mortality through the end of the trial. Secondary outcomes included a composite of poor neurologic function or death at 180 days, as evaluated with the Cerebral Performance Category (CPC) scale and the modified Rankin scale. The study did not demonstrate any difference between both groups, patients survived

in > 50%. One of the greatest innovations in this trial was the adoption of a protocol for withdrawal of life-sustaining treatment to avoid the above discussed problems. The earliest time point for prognostication was 108 hours after study inclusion, until then, therapy could be withdrawn only either in case of brain death due to cerebral herniation, or myoclonus status (defined as generalized myoclonic convulsions in face and extremities and continuous for a minimum of 30 min) within the first 24 hours after admission and a bilateral absence of N20-peak on median nerve somatosensory evoked potentials (SSEP), or for ethical reasons (for instance: previously unknown information about disseminated end-stage cancer or refractory shock with end-stage multiorgan failure). The neurological evaluation was based on clinical neurological examination (including Glasgow Coma Scale (GCS), pupillary and corneal reflexes), SSEP and EEG. Biomarkers for brain damage were not used for operational prognostication. Findings allowing for discontinuation of active intensive care after 108 hours were brain death due to cerebral herniation, severe myoclonus status within the first 24 hours after admission and a bilateral absence of N20-peak on median nerve SSEP (if not already therapy withdrawn), persisting coma with a Glasgow Motor Score 1-2 and bilateral absence of N20-peak on median nerve SSEP, or persisting coma with a Glasgow Motor Score 1-2 and a treatment refractory status epilepticus (defined by EEG as sequences (>10 sec) of repetitive epileptiform discharges with an amplitude >50µV and a medium frequency ≥1Hz, constituting >50% of a 30 minute period in a patient with or without clinical manifestations; treatment refractory defined as unresponsive to treatment with propofol, midazolam or pentothal to a slow suppression burst pattern for 24 hours in combination with at least one intravenous antiepileptic substance (including valproate and/or fos-Phenytoin) in adequate dose for at least 24 hours; free use of further antiepileptic substances and combinations at the discretion of the attending physician). This protocol of withdrawal of therapy was based on consensus. The analysis of the data of this trial is ongoing, and in the future results of accuracy of this withdrawal protocol to predict outcome will arise. We believe that the retrospective analysis of these data will allow accurate prediction of poor outcome only, and that we will still lack good and reliable prognostic markers of a good outcome.

Neuroimaging in coma

The ongoing search for novel biomarkers has led to a novel field of promise for prognostication – the use of advanced neuroimaging, since it is less prone to biases due to sedation and metabolic distress, the unravelling of structural abnormalities underlying coma and the information about regional and/or global hypoxic damage in brain areas crucial for maintenance of consciousness. MRI is hampered by the requirement of trained personnel, MR-compatible material and larger examination slots to carry out MR studies in ventilated and sedated patients. The principal advantage of MRI is the application of diffusion-weighted imaging, a MRI technique used to image the movement of molecules. Molecular diffusion is limited by boundaries such as membranes and interaction between molecules in the extracellular space and can be used as a measure of hypoxic damage in case of restricted extracellular movement of water protons. The apparent diffusion quotient (ADC) can be calculated from two or more DWI images with different b-values and is displayed as an ADC map. A low diffusion value appears dark on the ADC and indicates restricted diffusion in that area. In the largest study used to investigate comatose cardiac arrest survivors (n=80) ADC values lower than 665×10^{-6} mm^2/s correlated with poor outcome *regardless* of the time to MRI with a specificity of 100%, but low sensitivity of 21% [15]. Diffusion-tensor imaging has been used as a prognostic tool in traumatic brain injury, where damage of specific brain areas (the internal capsule, corpus callosum, cerebral peduncle and white matter tracts) correlated with unfavorable outcome [16, 17]. MR-Spectroscopy of the brain stem has been successfully applied to disentangle patients who did not recover from those who regained consciousness [18]. Very recently, resting-state fMRI examinations have been applied to investigate disruptions of coherent fluctuations among functionally defined neuroanatomical networks encompassing the precuneus, posterior parietal lobe and medial prefrontal cortex. Fluorodeoxyglucose positron emission tomorgraphy studies confirmed these findings of widespread thalamocortical network disruptions (encompassing the thalamus, precuneus and mesiofrontal, prefrontal, and posteroparietal cortex) and showed impaired metabolism in unresponsive wakefulness syndrome patients [19]. Functional connectivity in the thalamocortical network correlated with the level of consciousness up to complete disruption in brain-dead patients [20]. However, up to now, no prospective studies for any of these modalities are available to validate the use of neuroimaging for coma and disorders of consciousness. In daily practice, intensive care physicians will continue to talk to families who are filled with fear and hope. The certainty of poor outcome is helpful for discontinuation of futile care, but as long as a good outcome cannot be predicted, the decision to continue or to withdraw life-sustaining therapy must be practiced with the art of medicine: a shared decision between the family and the physician, based on honest discussion, presumed wishes of the patient and best evidence, if available.

Conclusion

Clinical markers that indicate favorable outcome are lacking, especially due to the heterogeneity of underlying pathologies. Clinical criteria that aid to identify OHCA patients with poor prognosis encompass the absence of pupillary or corneal reflexes, whereas motor responses are not considered as reliable indicators, especially in patients treated with hypothermia. Exact definitions of time frames to estimate the outcome by clinical and neurophysiological examinations are still lacking. Novel imaging biomarkers, especially DWI, PET and recently, BOLD-fMRI appear to be promising but are difficult to perform in ICU patients and have an uncertain predictive value. Further research is needed to better define the prognostically meaningful patterns of brain damage and their sensitivity with respect to fair vs. poor outcome.

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Summary

Considering the high prevalence of non-convulsive Status epilepticus (NCSE) in emergency admissions of patients with altered mental state and the high proportion of cross-sectional imaging performed in this patient cohort, imaging marker suggesting an epileptic origin of the clinical symptoms and – even more critical – indicating ongoing seizure activity would potentially modify therapeutic decisions and patients outcome. In this article we review the cross-sectional imaging techniques to identify pathophysiological processes related to epileptic activity. We discuss the diagnostic potential of brain perfusion imaging to detect hemodynamic correlates of epileptic activity and structural imaging to identify the sequelae of prolonged epileptic activity e.g. cytotoxic/vasogenic edema, gliosis and brain atrophy.

In the atlas part, we aim to include a number of cases of NCSE with representative imaging findings and discuss the correlation of the findings with the clinical semiology and epilepsy syndrome.

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Key words: cerebral perfusion, MRI, CT, epilepsy

Atlas der zerebralen Bildgebung im nicht-konvulsiven Status epilepticus

Status epilepticus non-convulsivus (NCSE) ist eine häufige und schwierige Diagnose bei Patienten mit Bewusstseinsstörungen auf der Notfallaufnahme. In dieser Patientengruppe wird häufig eine zerebrale Schnittbildgebung durchgeführt. Bildgebende Befunde, die eine epileptische Genese der klinischen Symptome oder sogar Hinweise auf fortbestehende epileptische Aktivität liefern könnten, würden potenziell die therapeutischen Entscheide und die Prognose der Patienten ändern. In diesem Artikel diskutieren wir das Potenzial der Hirnperfusionsmessungen, hämodynamische Korrelate epileptischer Aktivität zu detektieren sowie die Resultate der strukturellen Bildgebung, um die Folgen der prolongierten epileptischen Aktivität (zytotoxisches, vasogenes Ödem sowie Gliose und Atrophie) darzustellen.

Schlüsselwörter: Zerebrale Perfusion, MRT, CT, Epilepsie

Atlas de l'imagerie cérébrale du status épileptique non-convulsive

Le status épileptique non-convulsive (NCSE) est une entité fréquente et cliniquement difficile à détecter chez les patients amenés aux urgences avec des troubles de la conscience. En vue de la fréquence élevée avec laquelle une imagerie cérébrale est effectuée chez ces patients, des signes radiologiques suggérant une origine épileptique des symptômes cliniques et – encore plus précieux – des signes indiqueront une activité épileptique persistante, pourront potentiellement modifier la démarche thérapeutique et le pronostic des patients. Dans cet article nous discuterons le potentiel des mesures de perfusion cérébrale d'identifier des corrélats hémodynamiques d'activité épileptique et les marqueurs de l'imagerie structurelle qui sont la conséquence d'activité épileptique prolongée (œdème cytotoxique/vasogenic ainsi que gliose et atrophie).

Mots clés : Perfusion cérébrale, IRM, CT, épilepsie

Introduction

NCSE is defined as a change in behavior and/or mental processes from baseline associated with continuous epileptiform discharges in the electroencephalographic recordings (EEG) in absence of convulsive symptoms [1]. This pragmatic definition encompasses

various subtypes of NCSE with different clinical symptoms, notably regarding the degree of impaired consciousness, different ictal EEG patterns and different etiologies. The current diagnostic criteria of NCSE – additional to the clinical evaluation – are based on visual EEG analysis and response to anti-convulsant medication. It reflects clinical limitations to attribute a rapid and specific diagnostic and prognostic evaluation of the epileptic activity. Currently, major efforts are underway in adapting the classification algorithms of NCSE to identify patients requiring immediate and sustained therapeutical interventions [2].

NCSE has an estimated incidence of 3.5 complex partial Status epilepticus (SE) and 15 other NCSE per year and population of 100,000 and therefore accounts for one quarter of all SE. It occurs in up to 9.3% of patients with altered mental state at emergency admission [3] as well as in about 8% of comatose patients without any clinical sign of ongoing epileptic activity. In unselected cases an associated mortality was reported in up to 18% [4]. Mortality is reported to be mainly dependent on the underlying etiology and age. However, NCSE has been shown to be an independent predictor of high mortality, high morbidity and for the occurrence of refractory SE [5].

Age and the underlying etiology have been repeatedly identified as prevalent prognostic factors in NCSE [6]. According to the Nice guidelines (www.nice.org.uk/CG020NICEguideline) emergency cross-sectional neuroimaging is indicated if the clinical symptoms in the context of an epileptic seizure may be caused by an acute neurologic condition. The etiologies of NCSE most frequently identified by neuroimaging are stroke, intracranial tumor, sinus thrombosis and traumatic contusions [7]. Computed tomography (CT) is widely used in this condition mainly motivated by the broader availability, shorter acquisition time and the ease of patient surveillance. Magnetic Resonance Imaging (MRI) has to be considered as alternative in function of the clinical state of the patient as it is superior to CT in the detection of parenchymal lesions and its methodological superiority to CT to differentiate ongoing pathophysiological processes as vasogenic and cytotoxic edema.

Considering the high prevalence of NCSE in emergency admission in patients with altered mental state [3] and the high proportion of cross-sectional imaging performed in this patient cohort, an imaging marker suggesting an epileptic origin of the clinical symptoms and – even more critical – indicating ongoing seizure activity would potentially modify therapeutic decisions and patients' outcome. In this article we review the potential of cross-sectional imaging techniques to identify pathophysiological processes related to epileptic activity. We discuss the 1) diagnostic potential of brain perfusion imaging to detect hemodynamic correlates of epileptic activity and 2) the structural imaging findings of the sequelae of prolonged epileptic activity e.g. cytotoxic/vasogenic edema, gliosis and brain atrophy.

In the atlas part, we aim to include a number of cases of NCSE with representative imaging findings and discuss the correlation of the findings with the clinical semiology and epilepsy syndrome.

Hemodynamic correlates

Hemodynamic correlates of epileptic seizures in the brain were first described by W. Penfield in the 1930ths. In the following decades this initial observation has been confirmed in many instances, showing that excessive or hypersynchronous epileptic neuronal activity is accompanied by focal brain hyperperfusion (**Figures 1,4,5**). Important observations have been reported based on ictal and postictal SPECT data, showing that the observed hyperperfusion is temporally confined to seizure activity and tends to normalization or hypoperfusion in the postictal state within 90 seconds [8] **(Figure 2)**. A second important observation was the correlation of hemodynamic correlates of seizures to the seizure onset zone, including a spatial distribution of hemodynamic changes within the brain that was concordant with the symptomatic zone of seizure semiology [9]. In mesiotemporal lobe epilepsy (MTLE) the spatial distribution of hemodynamic changes reflects physiological neuronal networks involved in seizure propagation [10]. In addition cortical abnormalities in MTLE were observed in a similar distribution (**Figure 8**) [11]. Two recent studies of our group showed the feasibility and diagnostic value of perfusion computed tomography measurements in the emergency setting to differentiate NCSE from post-ictal state [12, 13]. However, the current retrospective studies allow only limited conclusions about the diagnostic value with respect to an unselected cohort of patients and in the differentiation of alternative etiologies of altered mental state (**Figure 4**). Differential diagnosis of altered mental state is broad and includes various conditions such as trauma, tumor, vascular disease, infection, metabolic and toxic encephalophathies. In a subset of patients these conditions may coincide with epileptic activity fulfilling the diagnostic criteria of NCSE (**Figure 3**). In this case, in addition to the evaluation of the structural brain damage, the rapid assessment of how strongly the ongoing epileptic activity contributes to the altered mental state is of crucial importance for prognosis and therapy. The larger the contribution of epileptic activity to the clinical symptoms, the more successful and necessary is a vigorous treatment with seizure suppressive drugs [14]. Here, brain perfusion measurements have the potential of providing important contribution in the diagnostic workup in patients with suspicion of NCSE.

In recent research activity brain perfusion measurements have been used to characterize different epilepsy syndromes and to report the localization of various clinical seizure semiology [15 - 17] (**Figures 3-5**). The atlas part of this article aims at documenting illustrative

cases discussing hemodynamic correlates of ongoing epileptic activity in patients with altered mental state compared to simple focal NCSE as well as showing typical distribution of perfusion changes in patients with different epilepsy syndromes (**Figures 1,5,6**).

Sequelae of epileptic activity

Cytotoxic edema

Cytotoxic edema is due to a disruption of the cellular metabolism that impairs functioning of the Na+/K+- ATPase in the glial cell membrane, leading to intracellular retention of sodium and water. In consequence astrocytes and neuronal cells increase intracellular volume and extracellular space is reduced. This elicits a hyperintensity on diffusion weighted images (DWI) and lower apparent diffusion coefficient (ADC) values (**Figures 4,5,7**). These image properties are believed to reflect a reduction in the diffusibility of extracellular protons [18]. In epilepsy cytotoxic edema is reported in cases of prolonged epileptic brain acitity. The observed changes are in large parts reversible (**Figure 1**) but may as well result in consequent brain volume loss (**Figure 9**). In acute cerebrovascular disease ADC values below 6x10-6 mm2/s are considered irreversible, indicating infarction core [19]. The use of ADC values in the acute state of an epileptic condition as a predictive factor of consecutive brain damage is not established. Our observation (unpublished data) suggest that the ADC values in cytotoxic edema of epileptic origin tend to be higher (less severe cytotoxic edema) than in patients during the acute phase of ischemic stroke.

Vasogenic edema

Vasogenic edema occurs when intravascular proteins and fluids penetrate into the parenchymal extracellular space predominantly in subcortical areas. The vasogenic edema typically results from the breakdown of the blood-brain barrier in inflammation, trauma, tumors or subacute stages of cerebral ischemia. In epilepsy, an increase of fluids in the extracellular space may as well result indirectly from hypersynchronous or excessive neuronal/glial activity [20, 21]. In MRI vasogenic edema is characterized by a hyperintense signal on T2 weighted images, hypointense signal on T1 weighted images and, in a quantified manner, by an increase of ADC values. On diffusion weighted images (DWI) vasogenic edema may also be visualized as increased signal intensity related to the "T2 shine-through effect" from the B0 images [22] (**Figures 1,2,5**).

Brain atrophy

Epileptic seizures are not considered to induce neuronal damage in general. Recently analysis of structural brain imaging has identified progressive cortical changes as a function of disease duration, interictal spike and seizure frequency [23 - 25]. The distribution of these changes are concordant to the seizure semiology/epilepsy syndrome to some extent [11]. In status epilepticus non-reversible clinical deficits as well as brain atrophy may occur [26, 27]. Lacking substantiated evidence on the prognostic and diagnostic value it is not established to which extent vasogenic/cytotoxic edema as discussed above may be predictive for consequent focal brain atrophy or gliosis (**Figures 8,9**).

Conclusion

Currently major efforts are underway to refine definition and classification of NCSE. The lack of consensus on this topic arises because the EEG expression of NCSE does not exist in isolation, but reflects status epilepticus under the variety of pathologic conditions that occur with age, cerebral development, encephalopathy, and epilepsy syndrome [28, 29] (**Figure 7**). Well established is the benefit of structural brain imaging documenting etiology and severity of the underlying brain process causing the NCSE. Clinically important may be the consideration, "that the larger the contribution of epileptic activity to the clinical symptoms, the more successful and necessary is a vigorous treatment with seizure suppressive drugs" [14]. In this perspective imaging correlates of epileptic activity and its sequelae, as presented above, may contribute to enhance patients' diagnostic workup and consequently therapeutic decisions and prognostic outcome. The present review aims to give a comprehensive selection on typical pathological imaging findings correlated to the epileptic activity. These imaging findings develop on top of the underlying pathology causing NCSE and represent pathophysiological changes as typically cortical hyperperfusion in ongoing epileptic activity or sequelae of prolonged epileptic activity as cytotoxic/vasogenic edema. Gliosis and brain atrophy represent the end stage of most likely irreversible brain damage of NCSE. The case series of the atlas part point out to following consideration:

a) Cortical hyperperfusion, particularly if it exceeds vascular territories (thalamic involvement?) may represent ongoing epileptic activity and, in our opinion, should prompt to an explicit diagnostic workup of NCSE.
b) Diffusionrestriction and/or T2 hyperintensities – particularly if they a) exceed vascular territories, b) are subtle, c) are restricted to gray matter and d) have a spatial distribution that corresponds to the patients (past) symptoms suggest an epileptic eti-

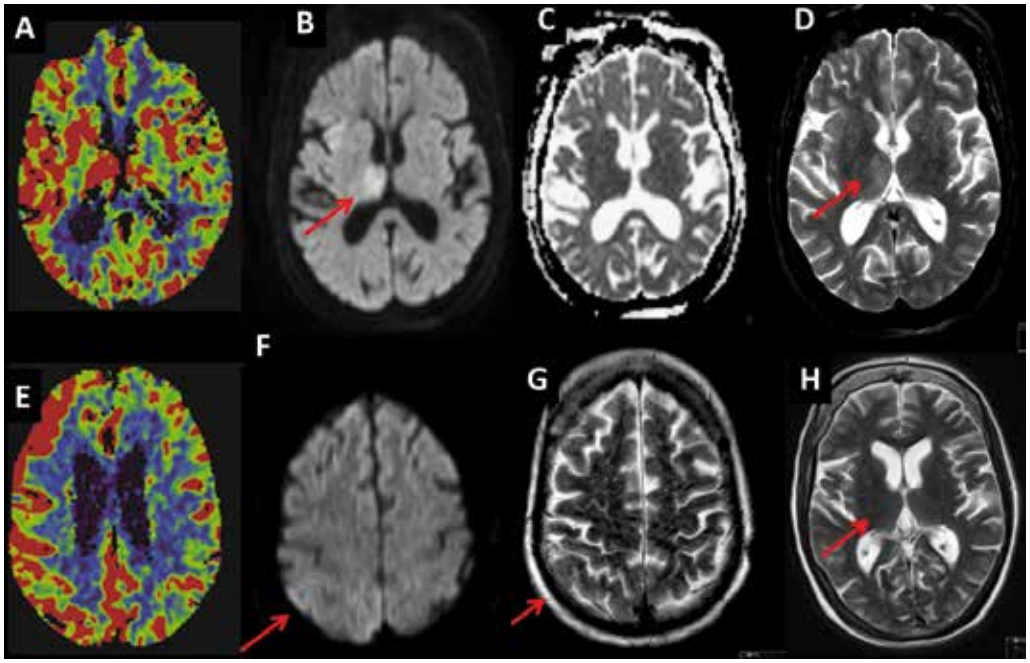

Figure 1: 59 year old female with structural epilepsy, during drug withdrawal occurrence of a complex focal SE with clonic movements of left face, shoulder and proximal arm and psychomotor slowing. A-G MRI at 4 days of ongoing focal SE under multiple antiepileptic drugs, A- Hyperperfusion of the right hemisphere including right basal ganglia and right thalamus, B/C- DWI hyperintensity right thalamus; ADC isointens to the contralateral hemispheres representing a mixed cytotoxic and vasogenic edema, D- T2w hyperintensity of the right thalamus (vasogenic edema), E- Hyperperfusion of the right hemisphere fronto-parieto-occipital, F- DWI hyperintensity of the right parieto-occipital cortex, ADC isointensity representing a mixed cytotoxic and vasogenic edema, G- T2w hyperintensity of the right parieto-occipital cortex (vasogenic edema), H- 2 weeks after successful treatment of focal SE – T2w isointensity of thalamic tissue representing (at least in part) reversible structural changes.

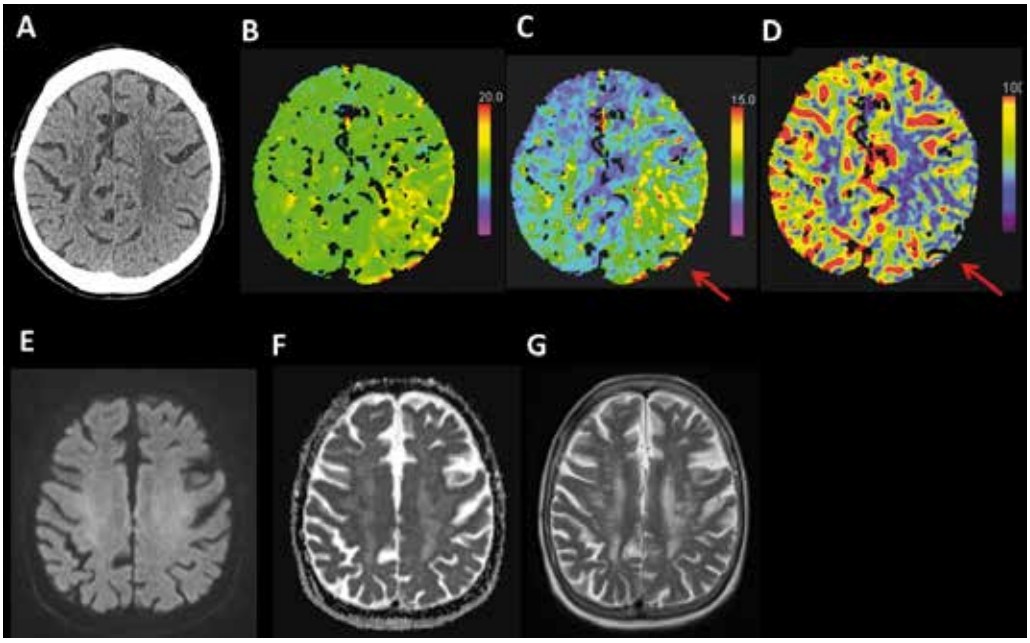

Figure 2: 91 year old female in postictal state after prolonged generalized tonic-clonic seizure with acute hemiparesis on the right for 3h, GCS 7. EEG showed slowing on the left hemisphere. A- CT nativ without abnormality, B-D hypoperfusion of the left parietal hemisphere with B- prolonged TTP (time to peak), C- prolonged TTD (time to drain), and D- decreased CBF (cerebral blood flow). E-G follow-up MRI one day later: no diffusion restriction, leukencephalopathic changes within the white matter. Postictal hypoperfusion is observed particularly in patients with postictal focal deficits (Todd's paresis or aphasia). Perfusion changes are most easily seen on maps of contrast transition times (TTD, mean transit time (MTT) or TTP). We note a diffuse cortico-subcortical pattern and a spatial distribution not corresponding to vascular territories.

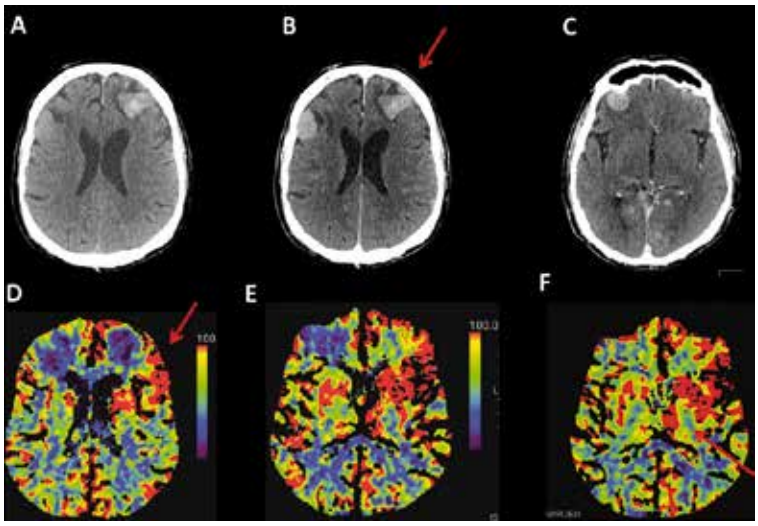

Figure 3: 67 year old male, malignant melanoma, cerebral metastasis, no reaction to speech since 2 hours, spasticity on the right, anisokoria of pupils, clinical diagnosis of NCSE. A- CT unenhanced B/C and after contrast showing multiple metastasis and hemorrhage in one metastasis left frontal, D-F hyperperfusion of the left Insula and left frontal lobe, left thalamus and basal ganglia. Complex situation, in spite of multiple intracranial metastasis with acute hemorrhage frontal left, perfusion imaging detects hyperperfusion in a cortical distribution involving basal ganglia associated to ongoing epileptic activity. The hyperperfusion is distinct from tumor related hyperperfusion by its distribution and intensity in this case.

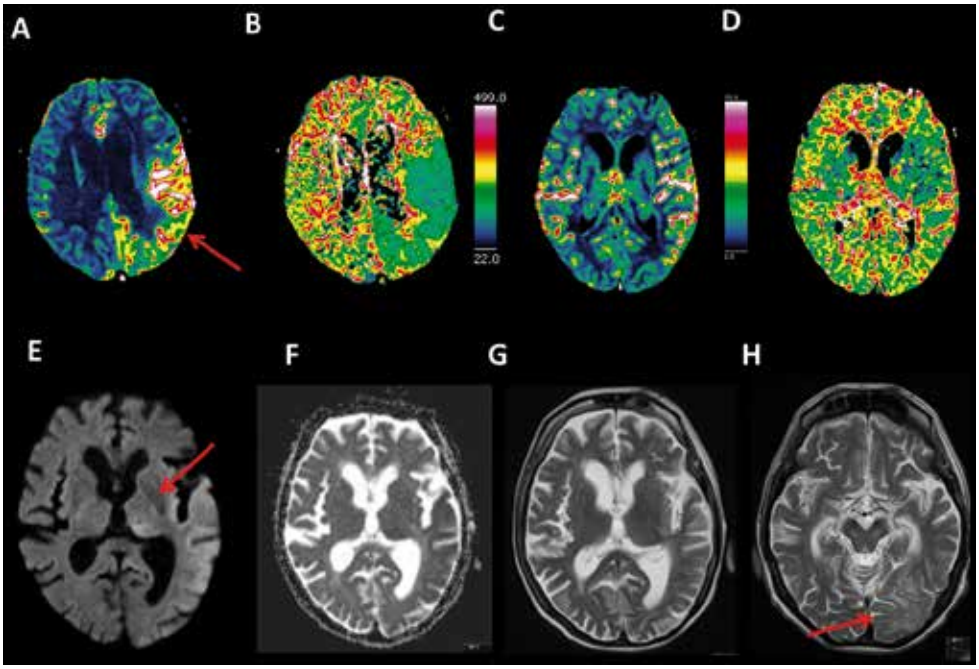

Figure 4: 67 year old male with acute sensomotoric aphasia and hemiparesis on the right since 2 hours, EEG documents left seizure activity with temporal dominance leading to an electroclinical diagnosis of NCSE. A-D increased CBF of the left hemisphere temporo-parieto-occipital (A,C) and MTT shortening (B,D), E-G cytotoxic edema temporo-parieto-occipital and pulvinar thalami, H- follow-up MRI: vasogenic edema left occipital. Patient with inaugural NCSE without documented preceding generalized tonic-clonic seizure. Here, hyperperfusion without territorial distribution initiated the EEG-based diagnosis of NCSE.

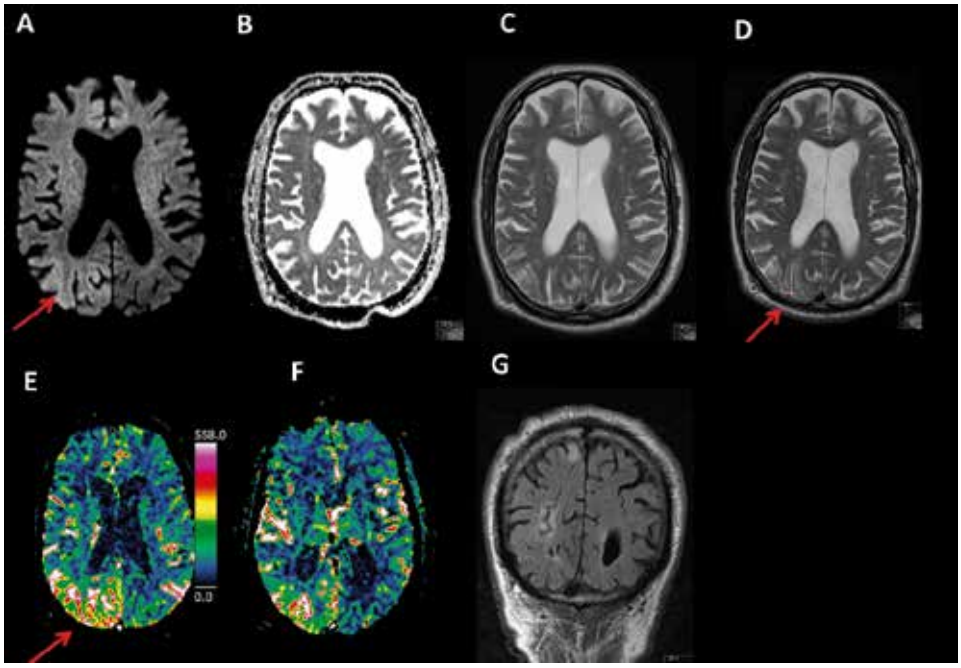

Figure 5: 74 year old male with hemianopsia to the right and ataxia, and intermittent cloni of the left foot correlating to rhythmic discharges on EEG. No altered mental state. A-D cytotoxic edema in the occipital lobe on the right, E-F hyperperfusion in the right occipital and temporal lobe, no thalamic involvement evident G- one week later T2w hyperintensity (vasogenic edema/gliosis) in the cortex of the right occipital lobe.
In patient without impaired consciousness (vigilance) no thalamic cytotoxic edema or perfusion changes were visible

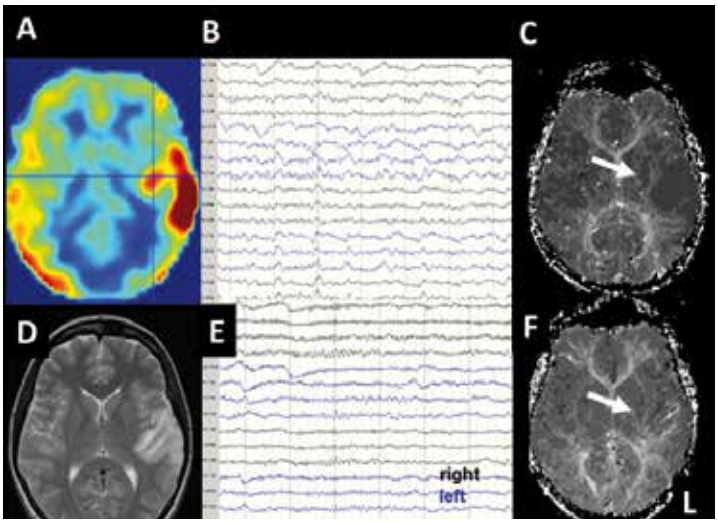

Figure 6: 31 year old female with MELAS syndrome. For 24 hours rushing on the right side. A-D MRI at admission A- hyperperfusion latero-temporal left (measured by arterial spin labeling), B- EEG showing left hemispheric periodic sharp transients, C- TTP map confirms hyperperfusion, D- T2-weighted images with acute lesion temporal left, E-F EEG and MRI 7 days later, NCSE successfully treated, E- EEG without evidence of ongoing epileptic activity F- TTP map showing normalization of brain perfusion. In Case 6 acoustic hallucination as ictal semiology has been confined to the contralateral temporal lobe including the primary auditory cortex and illustrates the potential of perfusion imaging to provide pathophysiological insights into clinical symptoms independent to their underlying etiology.

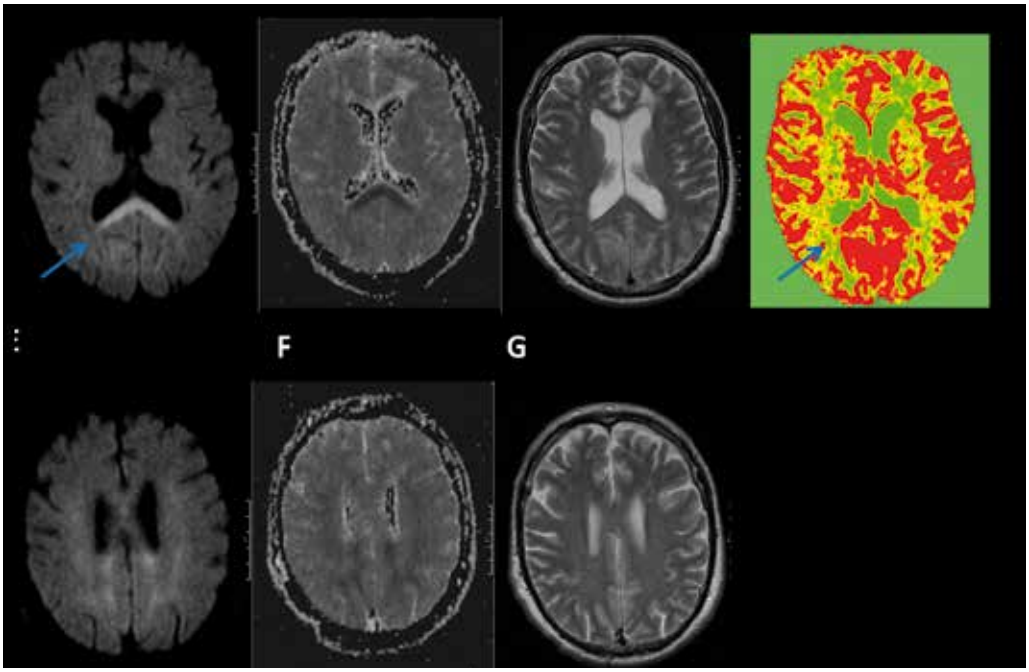

Figure 7: 59 year old male with status post myocardial infarct and resuscitation 6 days before MRI with postanoxic (myoclonic) SE, A-C cytotoxic edema in splenium corporis callosi (arrow), D- hyperperfusion bilateral in the cuneus, temporal on the left, and in the corpus callosum (arrow) , E-G cytotoxic edema bilateral mainly in the periventricular white matter, (C/G) Example of a pattern of cytotoxic edema predominant in the white matter tracts correlating to the underlying pathology of cerebral hypoxia due to cardial arrest. Cross-sectional imaging discloses a diffuse pattern of hyperperfusion including corpus callosum unusual to all other cases reported here. Postanoxic SE is harboring a poor prognosis in a relevant portion of patients. Cross-sectional imaging play a role together with clinical and electrophysiological parameters to estimate prognosis of the underlying pathology (see article from Rossetti and Hänggi et al. in this issue). The experience with perfusion imaging as isolated parameter of epileptic activity is yet limited and to the authors conviction no comment or suggestion can be made at this stage.

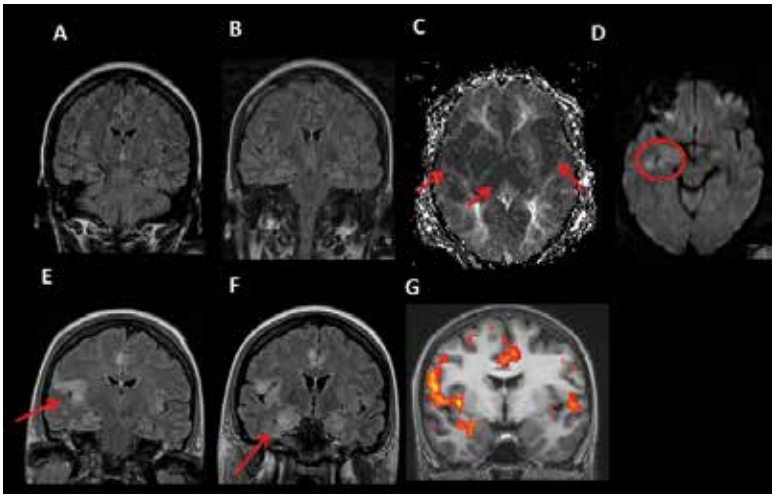

Figure 8: 43 year old female, recurrent secondary generalized seizures for 2 days of unknown etiology, previously influenza symptomatology, at admission convulsive drug resistant status epilepticus, waxing and waning evolution with right hemispheric dominance of epileptic activity on EEG. A-D MRI at admission, unspecific white matter lesions, right dominant diffuse hyperperfusion (TTP), DWI restriction right hippocampus, E-F follow-up MRI: increasing gliosis/vasogenic edema bilateral in the hippocampus, the insula, fronto-basal and cingulum on FLAIR images, G- interictal hemodynamic correlates of MTLE (data from [11]). The distribution of the gliotic changes in drug resistant SE (no etiology of epilepsy disclosed on autopsy) and the interictal hemodynamic changes in MTLE are closely related, endorsing the notion that interictal epileptic activity involves identical neuronal networks as seizure activity.

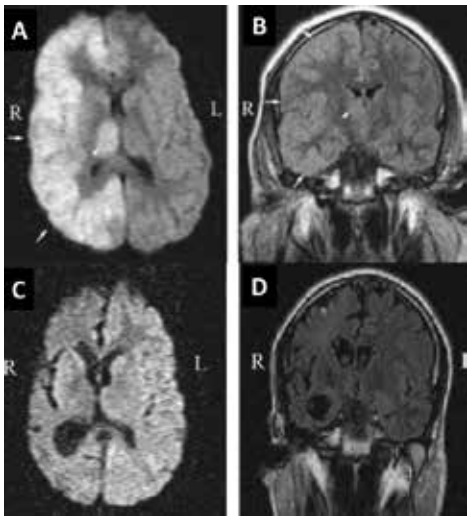

Figure 9: MRI 5 days after the onset of SE illustrates acute brain injury. A- Restricted diffusion in the entire right hemisphere (arrows) and the right thalamus (arrowhead), sparing the deep white matter and basal ganglia, B- Coronal FLAIR shows increased signals in the gray matter of the right cerebral cortex (arrows) and the right thalamus (arrowhead), C-D MRI 6 months later following prolonged complex focal SE reveals advanced brain atrophy limited to the right hemisphere, C- Diffusion weighted image, D- Coronal FLAIR image.

Prolonged epileptic activity may result in irreversible brain damage documented on cross-sectional imaging by gliosis (case 8) evolving to brain atrophy in case 9.

Fig. 9. Reprinted adopted from Epilepsy & Behavior, Vol 11/ Edition 2, L. Korngut et al. Irreversible brain injury following status epilepticus, 235-240. Copyright (2007), with permission from Elsevier

ology of at least part of the clinical symptoms. The cytotoxic and vasogenic edema of epileptic origin are frequently found to be reversible.

c) Gliosis and brain atrophy with cortical predominance can represent final stages of NCSE. Prognostic factors predicting irreversible brain damage due to epileptic activity need to be further studied. Focal atrophy due to NCSE may be considered in the diagnostic workup of cortical dementia.

d) Cross-sectional imaging results presented here suggest an absence or less prominent involvement of thalamic structures in epileptic activity in patients with NCSE without altered mental state (**Figures 5,6**). These results are compatible with the current concepts of generalization and network inhibition of epileptic activity [28].

e) Further prospective studies are warranted to elucidate the diagnostic value of cross-sectional imaging. The current observations are promising in respect of a potential role in diagnostic workup and in the understanding of the pathophysiological processes of NCSE.

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Clinical Significance of Yawning in Disorders of Consciousness and Vigilance

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Summary

Yawning is a stereotyped normal behaviour with unknown physiological role. It can occur in excess due to a large variety of medical conditions. Acute bouts of yawning are an early but unspecific warning sign for upcoming disorders of consciousness or clinical worsening, which should prompt the clinician to be prepared for supportive measures. Chronic excessive yawning may lead to medical consultations. In this case, medication side effects and excessive daytime sleepiness are the most frequent aetiologies. Epileptic seizures are occasionally followed by post-ictal yawning which lateralizes the seizure origin to the right hemisphere.

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Key words: Yawn, sleepiness, consciousness, epileptic seizure

Gähnen als klinisches Zeichen bei Bewusstseins- und Vigilanzstörungen

Gähnen ist ein stereotypes normales Verhalten mit unbekannter physiologischer Rolle. Es kann aufgrund einer grossen Vielzahl von Erkrankungen vermehrt auftreten. Akute Attacken von Gähnen sind ein frühes, aber unspezifisches Warnzeichen für bevorstehende Bewusstseinsstörungen oder klinische Verschlechterungen. Sie sollten den Arzt darauf hinweisen, unterstützende Massnahmen vorzubereiten. Chronisches übermässiges Gähnen kann zu medizinischen Konsultationen führen. Medikamenten-Nebenwirkungen und übermässige Tagesschläfrigkeit sind hier die häufigste Ätiologie. Epileptische Anfälle werden gelegentlich von postiktalem Gähnen begleitet, was den Anfallsursprung auf die rechte Hemisphäre lateralisiert.

Schlüsselwörter: Gähnen, Schläfrigkeit, Bewusstsein, epileptischer Anfall

La signification clinique du bâillement dans les troubles de la conscience et de la vigilance

Bâillement est un comportement normal stéréotypé avec un rôle physiologique inconnu. Il peut se produire en excès en raison d'une grande variété de conditions médicales. Les épisodes aigus de bâillements sont un signe d'alerte précoce mais non spécifique pour des troubles de la conscience ou lune aggravation clinique, ce qui devrait inciter le clinicien à préparer des mesures de soutien. Les bâillements excessifs chroniques peuvent conduire à des consultations médicales. Dans ce cas, les étiologies les plus fréquentes sont les effets secondaires des médicaments et la somnolence diurne excessive. Les crises d'épilepsie sont parfois suivies par des bâillements post-critiques ce qui latéralise l'origine de la crise dans l'hémisphère droit.

Mots clés : Bâillement, somnolence, conscience, crise épileptique

Introduction

Yawning is a frequent behaviour occurring in most vertebrate species [1, 2] from foetal stages [3] to old age [4]. In mammals, it consists of an involuntary sequence of about 5 to 10 seconds duration with wide mouth opening, deep inspiration, brief apnoea, and slow expiration. Similar jaw movement sequences have also been observed in reptiles, birds, amphibians, and fish species, but it is controversial to which degree such yawn-like behaviour is homologous to human yawning [5, 6].

The role of normal yawning remains currently unknown, although numerous hypotheses have been put forward throughout the centuries [7]. It is also not known whether the early morning yawns associated with stretching of limb and neck muscles (stretch yawns) are a separate entity or rather a stronger variant of isolated yawns. From an evolutionary perspective, one would expect that such a ubiquitous and frequent behaviour provides an advantage for survival. Yet, no

consistent physiological effects of yawning could be demonstrated so far. In particular, the wide-spread notion that yawning might oxygenate the blood or increase vigilance could not be confirmed experimentally [8, 9]. The only specific effect of yawning that could be demonstrated so far was its contagiousness in humans and some – but not all – animal species [10 - 13]. Yawning by contagion is associated with activations in neural networks responsible for empathy and social skills [14 - 17]. Hence, there seems to be a link between yawning and social functions [18].

Although yawns are usually accompanied by a pleasant feeling of satisfaction, they can occur excessively in which case they can lead to discomfort and medical consultations [19]. Furthermore, acute bursts of excessive yawning, also labelled "chasm", should be recognized as early but unspecific warning sign for imminent disorders of consciousness and clinical worsening.

It is unclear whether there exists a centre for yawn execution. However, given the implication of oropharnyngeal muscles, it is assumed to be located in ponto-bulbar parts of the brain stem. This centre seems to receive afferents from several deep brain structures, in particular from the paraventricular nucleus of the hypothalamus. Numerous neurotransmitters, neuropeptides, and hormones have been found to modulate yawning. Neuroendocrine substances as diverse as, among others, dopamine, acetylcholine, glutamate, serotonin, nitric oxide, adrenocorticotropic hormone (ACTH) related peptides, oxytocin, and steroid hormones facilitate yawning wheras opioid peptides exert an inhibitory effect. Some of these mediators (e.g., dopamine, glutamate, oxytocin) interact in the paraventricular nucleus of the hypothalamus and induce yawning via oxytoninergic projections to the hippocampus, the pons, and the medulla oblongata. Other pathways seem to be effective for serotonin, acetylcholine, and ACTH related peptides [20].

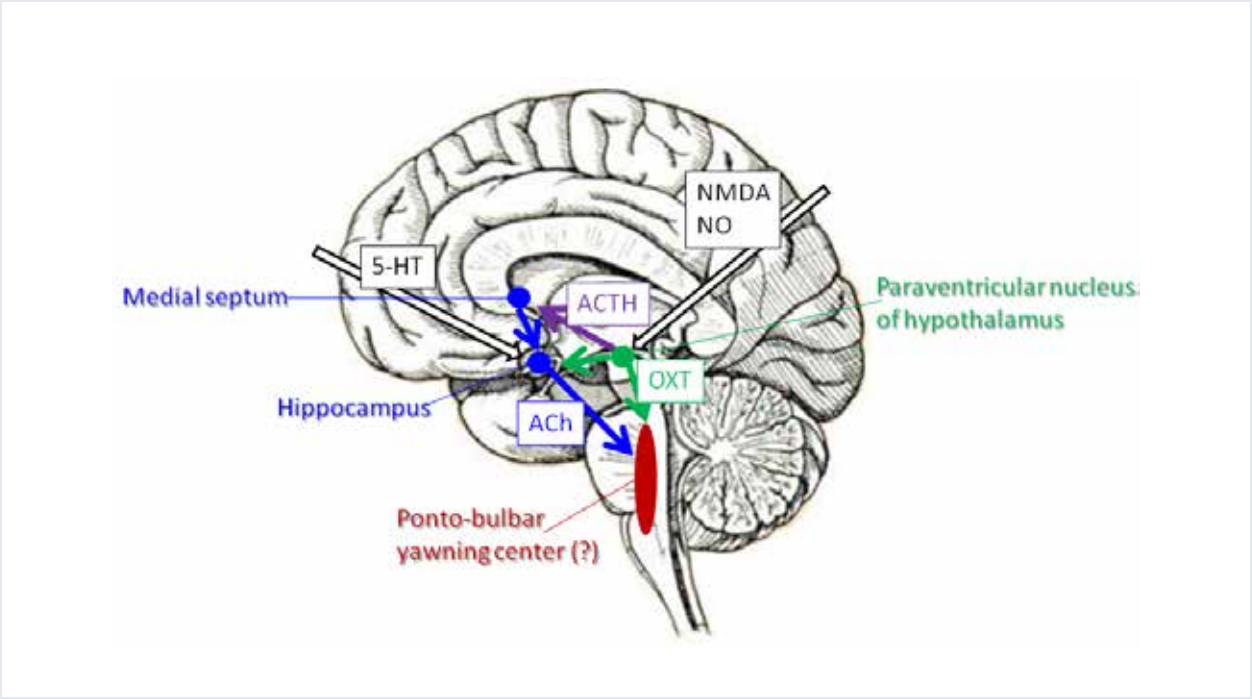

Figure 1: Pathways of yawn control. The location of the centre for yawn execution is not known, but based on the implicated muscles, it is assumed to lie in ponto-bulbar parts of the brain stem. Additional cortical centres are probable, but insufficiently understood. Abbreviations: Ach, acetylcholine; ACTH, adrenocorticotropic hormone; NO, nitric oxide; OXT, oxytocin.

Anatomy

A good understanding of the anatomical basis of yawning would be necessary to fully appreciate the pathomechanisms of excessive yawning. Unfortunately, research has been essentially limited to investigations of pharmacological triggers of yawns, and lesion studies are scarce. **Figure 1** gives an overview of the main currently known pathways.

Behavioural observations of contagious yawns and recent lesion analyses further suggest that cortical structures also contribute to yawn control, in particular the insula [21], but the corresponding pathways are unclear.

Chronic excessive yawning and sleepiness

There is convergent evidence from different areas of research that sleepiness triggers yawning. Behavioural studies consistently reported that yawns occur most frequently before and after sleep, i.e., during periods with lower levels of alertness [22, 23]. The circadian distribution of yawns follows the individual sleep-wake rhythm [24, 25, 4], and the individual subjective feeling of drowsiness correlates with increased yawning rates [4]. Furthermore, yawns are accompanied by electroencephalographic (EEG) signs of drowsiness. In particular, power density of delta waves over the vertex, which is considered to be a marker of sleep pressure [26], is greater before yawns than before control movements without yawning [9].

Accordingly, excessive daytime sleepiness is the most frequent cause of excessive yawning [19]. In this case, excessive yawning is usually present chronically over weeks to months. It can be due to lack of sleep or secondary to other sleep pathologies such as sleep apnoea syndrome. Frequent yawning can therefore be one of the symptoms of excessive daytime sleepiness but is often overlooked. Similarly, patients can be instructed to recognize yawns as sign of sleepiness, in particular when driving.

Acute bouts of yawning and disorders of consciousness

Excessive yawning can also appear acutely, often in form of bouts or salvoes. In particular, it can be frequently observed in patients presenting current or imminent disorders of consciousness and then opens a large differential diagnosis.

Syncopes and malaises with a sudden overstimulation of the parasympathetic system can be preceded by bouts of yawning [27], sometimes even before the appearance of nausea and pallor. The occurrence of yawning during medical interventions may therefore not be due to sleepiness or boredom of the patient, but should prompt the medical attendant to put the patient in a supine position.

Similarly, excessive yawning can be one of the first manifestations of hypoglycaemia in diabetic patients [19]. Yawning is associated with hunger in healthy animals [6], and may therefore be a physiological manifestation of hypoglycaemia.

The frequency of yawning tends to increase in patients with brain lesions, in particular stroke. Lesions in the internal capsule [28], the brain stem [29], as well as in the insula and the caudate nucleus [21] seem to be particularly associated with increased yawning. The mechanisms of this increase are unknown. One reason may be that patients with severe hemiparesis after stroke can experience automatic, involuntary movements of their paralysed arm during yawns. Since this is usually the only occasion when they see their affected arm moving, they are particularly keen to yawn. The movement consists of involuntary rising of the arm and has been named “parakinesia brachialis oscitans” [28]. It is associated with severe motor deficits and disappears in case of clinical improvement. The mechanisms are incompletely understood. Walusinski et al. [28] suggested that it may be mediated by spino-cerebellar pathways which become autonomous due to damage of corticospinal, cortico-nuclear and and cortico-cerebellar tracts.

Although the overall yawning frequency can be increased in patients with brain lesions, the appearance of acute, repetitive bouts of yawning is suspicious of additional intracranial hypertension. Although rare, its occurrence in patients with recent trauma or stroke should lead to the consideration of brain imaging. In patients with reduced levels of consciousness, the sudden appearance of yawning may be a sign of herniation.

Of particular interest to epileptologists is yawning associated with seizures. Post-ictal yawns are relatively common and were described in 4% of patients with temporal lobe epilepsy in a systematic retrospective analysis. Interestingly, it occurred only in patients with right temporal seizure origin [30]. Post-ictal yawning therefore seems to have a lateralizing value to the non-dominant hemisphere. In contrast, yawning during actual seizures is very rare and only a few cases have been described [31]. These patients had partial seizures of temporal origin, but yawning during 3/sec spike-wave episodes was also described in young patients with probable idiopathic generalized epilepsy [32]. An epileptic trigger of yawning is particularly probable if it occurs in a stereotyped way during seizures.

Yawning is one of the most common and consistent prodromal symptoms before migraine attacks and seems to occur more frequently before attacks with aura [33 - 35]. It can also occur after the headache period together with tiredness, depressed mood, and concentration difficulties [36]. Rarely, yawning can be painful by itself in patients who do not suffer from headaches. In this case, pain seems to be due to affections of craniopharyngeal muscles or nerves [37].

The mechanisms by which these diverse conditions increase yawning have not been investigated. However, pathological yawns seem to be triggered either by local compression or irritation of the putative yawning centers (in particular the hypothalamus), or by one of the many neuroendocrine substances which have been shown to facilitate yawns in animal models.

Table 1: Differential diagnosis of excessive yawning

– Medication: Antidepressants (especially SSRI, and tricyclics), dopaminergic substances, withdrawal of opiates or coffeine
– Insufficient sleep or sleep pathology with excessive daytime sleepiness
– Functional and somatoform disorders, hyperventilation, dyspepsia
– Intracranial hypertension, herniation
– Vaso-vagal syncopes
– Migraine
– Compression of hypothalamus or the pituitary gland
– Stroke lesions
– Epileptic seizures
– Progressive supranuclear palsy
– Amyotrophic lateral sclerosis

Other causes for excessive yawning

Excessive yawning is not always accompanied by disorders of consciousness or excessive sleepiness. For instance, compression of the hypothalamus or the pituitary gland are rare causes of yawn salvoes. They can lead to particularly frequent and disabling yawns [38, 19].

Another important cause for excessive yawning is the intake of neurological and psychiatric medication. Serotoninergic and tricyclic antidepressants are most frequently involved [39 - 42, 19]. In this case, it is important to recognize it as iatrogenic side effect and not to misinterpret it as signs of sleepiness or asthenia of the patients.

Other rare conditions which have been associated with excessive yawning include progressive supranuclear palsy [43] and amyotrophic lateral sclerosis [44]. The mechanisms of this association are unknown.

Conclusions

Frequent yawning can be a normal manifestation of, among others, sleepiness, boredom, hunger, and social interactions [7], as well as associated with a large variety of medical conditions. It is therefore unspecific. Yet, in acute pathological conditions, it usually appears early before the appearance of disorders of consciousness or clinical worsening. Its recognition can give the clinician a head start for preparing therapeutic and supportive measures.

The management of excessive yawning consists in finding and treating the underlying cause. **Table 1** gives an overview of the large differential diagnosis. Medication associated with yawning and excessive caffeine consumption should be adapted first. Hereby, it is important to avoid abrupt stopping of opiates or caffeine, as this can lead to excessive yawning. Insufficient sleep or sleep pathologies should be actively searched. Finally, a careful history taking and clinical examination may reveal further abnormalities which guide the treatment, e.g., if they reveal functional disorders, headaches, or neurological deficits. Finally, specialized exams may be considered in selective cases to look for epileptic activity, pituitary pathologies, or brain lesions. Treatment consists in the elimination of the cause. There is no established pharmacological therapy to reduce yawning frequency, but based on a case report, propranolol can be tried [45].

Finally, it is noteworthy that yawning can also be reduced or suppressed by medical conditions, in particular Parkinson's disease [46] and neuroleptic drugs [47].

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Ecstatic Epileptic Seizures – the Role of the Insula in Altered Self-Awareness

Markus Gschwind and Fabienne Picard

Summary

Ecstatic auras are a rare but compelling epileptic entity. During the first seconds of the seizure, ecstatic auras provoke feelings of well-being, intense serenity, bliss, and enhanced self-awareness. They can be associated with the impression of dilated time, and are sometimes described as a mystic experience by some patients. The functional neuroanatomy of ecstatic seizures is still debated. During recent years several patients presenting with ecstatic auras have been reported by us and others; one of them even in the setting of pre-surgical electrical brain stimulation. According to the results of nuclear brain imaging and electrical stimulation, the common seizure localization in those patients appeared to be the anterior-dorsal insular cortex, where we thus propose to locate this rare ictal phenomenon. Here we summarize the role of the multiple cognitive, affective, sensory and autonomic functions of the insular cortex, which may be integrated into the creation of self-awareness, and how this system may become dysfunctional on several levels during ecstatic auras.

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Key words: Ecstatic seizure, epilepsy, well-being, bliss, self-awareness, time dilatation, insula, MRI, PET, SPECT, electrical brain stimulation

Crises extatiques – le rôle de l'insula dans la modification de la conscience de soi

Les crises extatiques constituent une entité épileptique rare mais fascinante. Pendant les premières secondes de la crise, les auras extatiques provoquent une sensation de bien-être, de bonheur et de sérénité intense, et une conscience de soi augmentée. Ces auras sont souvent associées à une impression de temps dilaté, et peuvent être décrites comme une expérience mystique par certains patients. La neuroanatomie fonctionnelle des crises extatiques est encore débattue. Au cours des dernières années, plusieurs patients avec des auras extatiques ont été rapportés par nous-mêmes et par d'autres équipes, incluant une patiente dans le cadre d'une évaluation pré-chirurgicale de l'épilepsie avec électrodes intracérébrales. La localisation commune des crises (ou «zone symptomatique») pour quelques patients semble être le cortex insulaire antérieur-dorsal selon des résultats d'imagerie nucléaire et de stimulation cérébrale, et nous postulons donc que cette région est impliquée de façon majeure pour ce phénomène ictal rare. Nous résumerons dans cet article les rôles multiples du cortex insulaire au niveau cognitif, affectif, sensoriel (stimuli externes et internes, intéroceptifs) et végétatif (autonome), avec un phénomène d'intégration qui pourrait jouer un rôle majeur dans la conscience de soi, et nous proposerons des hypothèses sur la dysfonction de ce système à différents niveaux pendant les auras extatiques.

Mots clés : crises extatiques, épilepsie, bien-être, bonheur, conscience de soi, perception du temps, insula, IRM, PET, SPECT, stimulation électrique cérébrale

Ekstatische epileptische Anfälle und die Rolle des insulären Kortex bei einem veränderten Ich-Bewusstsein

Ekstatische Anfälle sind seltene, jedoch faszinierende epileptische Phänomene. In den ersten Sekunden eines Anfalls provozieren ekstatische Auren ein Gefühl des Wohlbefindens, der intensiven Zufriedenheit, von Glück und erweitertem Selbstbewusstsein, sie können mit dem Eindruck von gestörtem Zeitempfinden verbunden sein, und einige Patienten beschrieben sie als mystische Erfahrung. Die funktionelle Neuroanatomie von ekstatischen Anfällen ist weiterhin nicht vollständig verstanden. In den letzten Jahren wurden mehrere Patienten mit ekstatischen Auren von uns und anderen dokumentiert; eine Patientin sogar unter direkter zerebraler Elektrostimulation, im Rahmen einer prächirurgischen Epilepsie-Abklärung. Aufgrund dieser Resultate und der nuklearmedizinischen Bildgebung scheint sich das Anfallskorrelat im anterior-dorsalen Kortex der Insula zu befinden, wo wir demzufolge dieses seltene iktale Phänomen lokalisieren würden. Im Folgenden fassen wir die Rolle der vielfältigen kognitiven, affektiven, sensorischen und autonomen Funktionen des insulären Kortex zusammen und diskutieren ihre Rolle im Aufbau des Ich-Bewusstseins (self-awareness) und, wie dieses System im Rahmen von ekstatischen Anfällen gestört sein kann.

Schlüsselwörter: ekstatische Anfälle, Epilepsie, Wohlbefinden, Glück, Selbstbewusstsein, Zeitwahrnehmung, Insula, MRT, PET, SPECT, kortikale Elektrostimulation

Introduction

– "He fell to thinking, among other things, about his epileptic condition, that there was a stage in it just before the fit itself (if the fit occurred while he was awake), when suddenly, amidst the sadness, the darkness of soul, the pressure, his brain would momentarily catch fire, as it were, and all his life's forces would be strained at once, in an extraordinary impulse. The sense of life, of self-awareness, increased nearly tenfold in these moments, which flashed by like lightning. His mind, his heart were lit up with an extraordinary light; all his agitation, all his doubts, all his worries were as if placated at once, resolved in a sort of sublime tranquility, filled with serene, harmonious joy, and hope, filled with reason and ultimate cause. But these moments, these glimpses were still only a presentiment of that ultimate second (never more than a second) from which the fit itself began. That second was, of course, unbearable. Reflecting on that moment afterwards, in a healthy state, he had often said to himself that all those flashes and glimpses of a higher self-sense and self-awareness, and therefore of the "highest being", were nothing but an illness, a violation of the normal state and if so, then this was not the highest being at all but, on the contrary, should be counted as the very lowest. And yet he finally arrived at an extremely paradoxical conclusion: "So what if it is an illness?" he finally decided. "Who cares that it's an abnormal strain, if the result itself, if the moment of the sensation, remembered and examined in a healthy state, turns out to be the highest degree of harmony, beauty, gives a hitherto unheard-of and unknown feeling of fullness, measure, reconciliation, and ecstatic, prayerful merging with the highest synthesis of life?"[1] p. 225f

In these words Prince Myshkin reflects the moments of his epileptic condition in Dostoevsky's "The Idiot". For a long time those sentences were regarded as a product of the novelist's artistic talent. Since recently only, we might suppose that they, in fact, realistically describe the great novelist's own personal experience with ecstatic auras [1, 2], and Dostoevsky's testimony can be considered the first appearance of ecstatic auras in literature [3]. However, the existence of ecstatic seizures was initially even denied by some leading epileptologists [4, 5], for review see also [6, 7] and its further documentation was only scarce, probably also because the "hallucination of emotion" [8] seems abnormal to such an extent that patients often are reluctant to divulge such personal feelings; the experience seems "beyond what can be described in words" [9]. The frequency of such cases is therefore probably underestimated [6, 7, 9 - 18]. In order to find those rare cases, the epileptologist needs to address the possibility of ecstatic auras directly with the patient. And in turn, he also needs to recognize typical ecstatic elements in a patient's report. Patient descriptions of ictal episodes with emotional disturbances strongly depend on vocabulary, intelligence, and power of introspection [8]. Some patients have troubles finding appropriate words, or give very simplified descriptions (e.g. feeling of warmth rising in the body, "rising in the head, like bubbles in the head", see below). The fearful apprehension of the imminent complex focal or secondary generalized tonic-clonic seizure can also obscure the ecstatic aura.

Semiology of ecstatic seizures and patients' testimony

While a total of about 30 patients describing ecstatic auras are reported in literature [8 - 10, 12 - 18], we had the chance to meet and document eight additional patients during the last six years [3, 19 - 21]. These patients were between 17 and 64 years old, and engaged in all kinds of professions, e.g. female teacher, male electronics assembler, male office worker, female architect, male apprentice farmer, male philosopher etc., and from different nations as Switzerland, France, Spain, United States. Their descriptions of their own ictal events, although varying in detail and complexity, condensate a semiology of ecstatic auras comprising several typical features [3, 20].

Below we report some of the key sentences of their testimony according to different semiological elements, which are feelings of heightened well-being, enhanced self-awareness, dilated time perception, bliss/intense serenity [3, 19, 20]. Sometimes feelings of overload, of mystic experience or even of intricate anxiety are described.

Heightened well-being. One of the first mentioned features, in all patients, was the "very pleasant filling of the whole body with a wave of warmth or well-being."

– "It was something that I have never felt before. It felt as though my body was filling up with a sensation which was quite surreal. The feeling was almost out of this world." – "[...] a halo, something pleasant which fills my inner body, wrapping me, with a rapid crescendo. It is a well-being inside, a sensation of velvet, as if I were sheltered from anything negative. I feel light inside, but far from being empty. I feel really present. Something has taken possession of my body, to feel really good..." – "rising in the head, like bubbles in the head." – "the sensation was a feeling of pleasure. I felt intensely well in my body." – "My inner body rises from an unalterable bliss [...] it is an unconditional, privileged moment of inhaled sensations. My body and my head may interact differently to what every human knows. It is a sensation that is not common, something to discover."

Enhanced self-awareness. All patients reported an "augmentation" of consciousness to a vividness of perception and a clearness that was not known before.

– "During the seizure it is as if I were very, very conscious, more aware, and the sensations, everything,

seems bigger, overwhelming me." – "every sensation is stronger; for instance I see more colors than before, and I have more detailed perceptions, particularly when listening to music." – "I feel rooted to the spot with a more developed consciousness. I feel a stronger consciousness of the body and the mind, but I do not forget what is around me". – "My head fills with feelings and emotion ... I feel more conscious of myself, more concentrated on myself ... I feel more present from a psychological point of view, with more sensations. It is something very intimate. It is as if I rose a little into the air." – "It affects both the cerebral thought, which is very intense and concentrated on itself, and the physique." – "Being very conscious of myself, I feel discharged from anything else, although I do not lose consciousness." – "I feel very, very, very present at that time; the consciousness of myself is very increased, rather on a psychic point of view. I am one hundred percent concentrated on myself." – "When these boundaries are erased, a second phenomenon begins – all the ordinary facts about the environment seem suddenly to become infused with certainty and a sense of inevitability [...] One often has (what is sometimes called) an "aha!" moment when we can suddenly explain several puzzling facts simultaneously with the same answer. The sense that I had when I was experiencing some of these seizures was not unlike a continuous series of profound "aha!" moments.

Feeling of dilated time. This high clearness of consciousness can also affect time perception. Time seems to hold on at the moment.

– "I escape into the time space of my body. It is a moment of fullness in the loophole of time, a return to myself." – "Entirely wrapped up in the bliss, I am in a radiant sphere without any notion of time or space. My relatives tell me that it lasts two to three minutes, but for me these moments are without beginning and without end."

Intense serenity and bliss. There is a feeling of great serenity and peace.

– "This led to a feeling of complete serenity, total peace, no worries; it felt beautiful, everything was great." – "The immense joy that fills me is above physical sensations." – "It is a feeling of total presence, an absolute integration of myself, a feeling of unbelievable harmony of my whole body and myself with life, with the world, with the 'All'."

Feeling of overload. Some patients reported that this feeling was evolving to a very strong intensity, causing a feeling of overload.

– "It is a physical state, an overload. The feeling is intense, with a sensation of fullness." – "The sensation is certainly more intense than could be achieved with any drug." – "The pleasure goes crescendo until it reaches a peak." – "This feeling became stronger and stronger, until it became so strong that it was unbearable and led to a loss of consciousness."

Mystic/religious experience. Some patients reported strong religious or religious-like feelings:

– "Maybe the closest sensation that I know would be an orgasm, but what I felt was not at all sexual. I have no religious feeling, but it was almost religious." – "a wellbeing of almost spiritual consonance" – "These experiences brought me confidence. They confirm that there is something that surpasses us." – "It is a big happening in your life to have these seizures. Thanks to these experiences, I do not fear death anymore. I see the world differently."

Anxiety. In some cases the experience of a generalized seizure after the ecstatic aura or of a loss of consciousness (secondary "complex" focal seizure) led to increased anxiety in expectation of a new seizure.

– "... soon after the very first seizures, an anxiety intermingled very rapidly with the bliss sensation" – "...because of the anticipated fear of how he would appear to other people during his complex focal seizures. However, as the bliss increased, it overcame the associated anxiety." – "His first seizure was the most pleasant because the following ones included a feeling of fear and anxiety as he knew they would end in a generalized tonic-clonic seizure."

Seizure trigger. Some patients described that their ecstatic seizure could be triggered by a positive emotion:

– "A joy or a sense of relief can trigger seizures." – "a tractor with the harvest, nice photos, a nice color, a flower, a nice landscape, a bird singing, grazing animals, branches that move with the wind, a beautiful woman." – "or on the occasion of a kiss, a caress, a nice thought about someone, a hope."

Etiological considerations

There is no doubt that ecstatic auras emerge of focal epilepsy. In the first reports of patients with ecstatic seizures, usually a temporal lobe origin was suspected [6, 7, 9-18], yet without demonstration of any precise localization [3]. Indeed, some cases of ecstatic seizures displayed findings suggestive of anterior temporal lobe involvement, e.g. an anterior-temporal tumor [13], or left anterior temporal interictal discharges in the EEG [15, 18]. However, there were some inconsistencies in the reported cases as to the semiologic-anatomical correlation, e.g. in one case showing calcifications of the hippocampus, the ecstatic seizures occurred much later than the other ictal symptoms [11], or in another case, the ecstatic seizures disappeared after the neurosurgical treatment of an occipital arterio-venous malformation, although the gliotic ipsilateral hippocampus was not removed [13]. In another case, the ecstatic symp-

toms appeared not before but after removal of the sclerotic part of the mesiotemporal lobe [15]. Finally, already during Dostoevsky's auras laryngeal spasms were reported [22], a symptom that is quite specific for insular seizures [23].

Half of the eight patients we met suffered from epileptogenic brain lesions like meningiomas (n=2), xanthoastrocytoma (n=1) and a dysembryoplastic neuroepithelial tumour (DNET; n=1), with an age of onset of their epilepsy between 15 and 43 years. The four other patients had normal MRI and an age of onset of their epilepsy between 12 and 18 years. The tumoral lesions (all of low grade or benign tumoral nature) were located in the temporal pole (n=3), and in the parahippocampal region (n=1) (**Figure 1A, B, C**). Accordingly, the FDG-(fluorodeoxyglucose)-PET showed right temporal and insular hypometabolism in the patient with the DNET, right temporal hypometabolism in the patient with the parahippocampal xanthoastrocytoma, and in a third patient with normal MRI but clear temporal lobe seizure semiology, there was a hypometabolism in the anterior part of the right temporal lobe [19]. Two of the patients with a temporal pole lesion showed also an anterior insular involvement on the ictal SPECT (tracer injected during the ectstatic aura; **Figure 1D, E**) [3, 20]. To note, other authors also reported a hyperactivation of the left anterior insula during the ictal SPECT in another patient [24].

Based on the analysis of these patients with ecstatic auras, we have recently proposed that ecstatic symptoms originate in the anterior insula [3], even when the epilepsy is related to a temporopolar lesion. This interpretation appears consistent with a large body of recent findings on the functions of this brain region [25, 26],

Since the late 1940s, the possibility of seizures originating from the insular cortex has come into view of epileptologists [27, 28], however for a very long time it was nearly impossible to disentangle insular seizures from MTL seizures due to the very similarity of the symptoms, because seizures of MTL origin seem to often also invade the insular cortex [29]. It was only with the recent advent of sophisticated stereo-guided insertion of depth electrodes, allowing to place them precisely deep in the insular cortex, together with video-EEG evaluation, that specific features of insular seizures could systematically be investigated. The typical insular onset occurred in full consciousness, beginning with laryngeal constriction, dyspnea, unpleasant perioral or somatic paresthesias, and dysarthric speech, followed by a complex partial seizure [23]. Therefore if on video-EEG recordings this clinical sequence is observed at the onset of a complex partial seizure in TLE patients, it strongly suggests actual seizure-onset in the insular cortex, not in the mesiotemporal region [23]. In their study of electrical stimulation on the implanted insular electrodes of 50 TLE patients, Isnard et al. [23] reported only 5 patients having seizures originating within the insula, one of whom reported symptoms of mirth and clairvoyance, suggesting a hypothetical possibility of ecstatic auras.

Ecstatic seizures caused by electrical stimulation

The proof of concept for the anterior-dorsal insular localization of ecstatic seizures was given when we met another patient, a 23 year-old right-handed woman, in pre-surgical evaluation for her refractory right temporal lobe seizures. Since the age of 12 she had reported intense feeling of bliss and well-being, consisting of "sensations of airflow" from her stomach, associated with a feeling of "floating". In the moments before seizure she reported enhanced sensory perception, especially of intense colors, and a feeling of dilated time. Her seizures evolved then into loss of consciousness together with gestural and oro-alimentary automatisms [19].

After her brain MRI was unremarkable, she was implanted with intracerebral electrodes covering the right temporal lobe and the insular cortex (**Figure 2**) for presurgical evaluation (phase II). Her seizures were recorded, and were found to originate always from the right mesiotemporal region, rapidly propagating (<1sec) to the anterior-dorsal insula. During systematic testing of implanted electrodes with electrical stimulation (50Hz, 0.5 – 2 mA, 1ms pulse width; the patient was blinded), none of the stimulated electrodes triggered a seizure. Stimulation of the right amygdala elicited strong unpleasant sensations like anxiety and epigastric pressure, however the stimulation of the anterior-dorsal insular electrode (OF1 – 2) suddenly provoked a "very pleasant funny sensation of floating and a sweet shiver" in her arms, identical to her usual ecstatic auras. Stimulations between 1mA and 1.6mA provoked this sensation, but not below 1mA. None of the stimulation on other electrodes had a similar effect [19].

To date this is the only published case describing induction of ecstatic symptoms by intracerebral electrical stimulation. While induction of unpleasant emotions have been reported during stimulation of amygdala and hippocampus already long ago [30, 31], moderately pleasant feelings have been induced in left amygdala in a more recent study [32]. Electrical stimulations of the insula have elicited a variety of symptoms in different systems, depending on the stimulated insular subregion, such as interoception, somatosensation, emotion, cognition, gustation, olfaction (also pleasant) [28, 33], but no ecstasy-like feelings, except possibly in one study, where a "weird feeling of flying away" was reported in one patient [34]. As reported above, one study recorded a spontaneous seizure starting with a feeling of clairvoyance and mirth, which was correlated with epileptic discharges in the insula, which did not spread to other cortical regions in the intracranial EEG recording [23].

The case of our patient demonstrates several highly

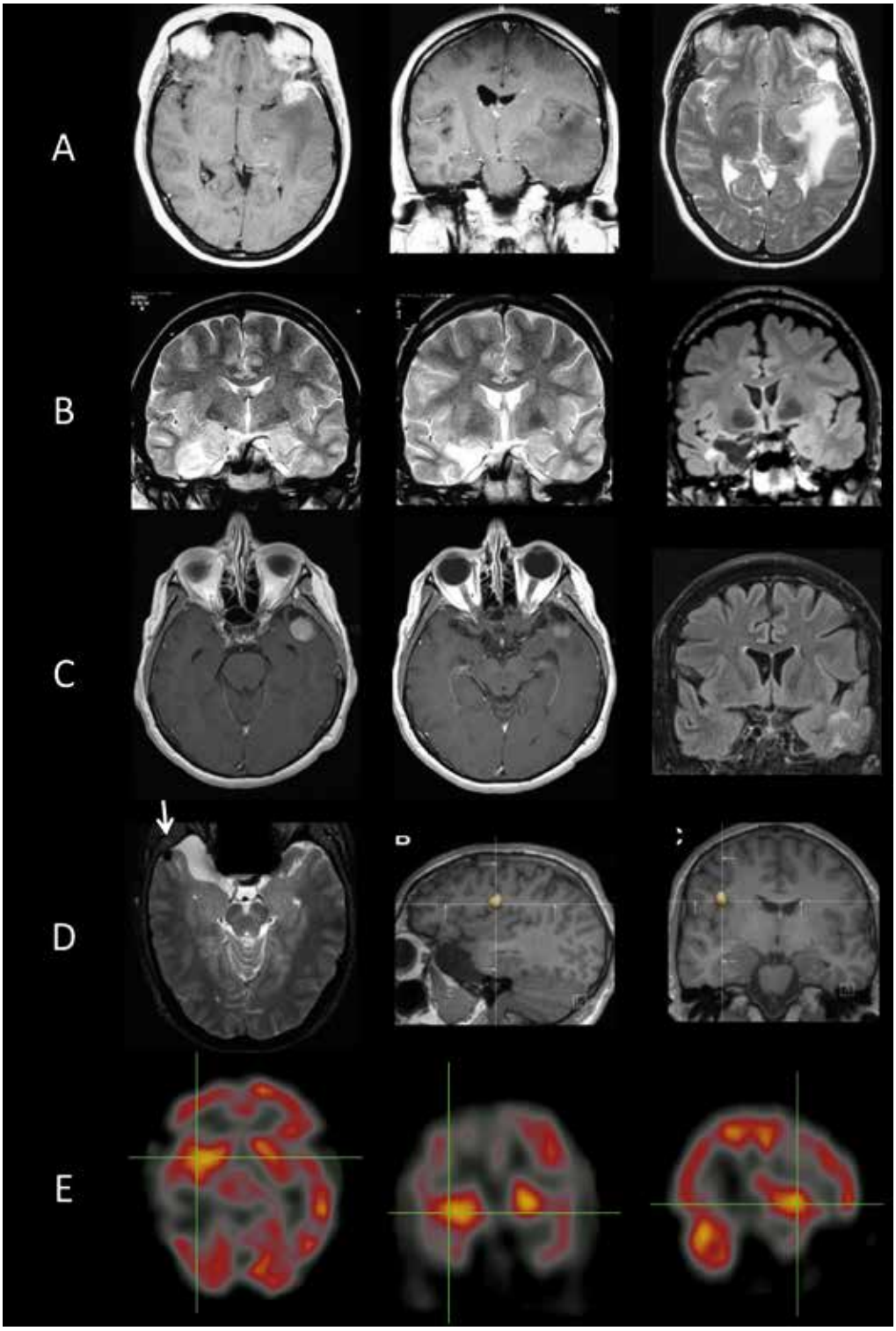

Figure 1: Brain imaging of patients with brain lesions causing ecstatic auras[1].
A. MRI of a 53-year-old woman showing a left sphenoidal meningioma causing extensive edema involving the whole temporal lobe and extending up to the anterior insula (from left to right: post-contrast T1-weighted axial and coronal image, T2-weighted axial image).
B. MRI of a 37-year old man with a xanthoastrocytoma. Left: Presurgical T2-weighted coronal image (1996) showing a right temporal lobe tumor in the parahippocampal gyrus. The border of the tumor is close to the inferior part of the anterior insula. Middle: Post-operative T2-weighted coronal images (1997), showing that the gliosis reaches the anterior insula. Right: FLAIR coronal image, 12 years after the resection (2008).

C. MRI of a 64-year-old woman showing the recurrence of a meningioma in the left temporal pole. Left and middle: Postcontrast T1-weighted axial images, FLAIR coronal image showing that the edema and/or gliosis reaches the temporal operculum, impinging on the anterior insula.
D. MRI and ictal SPECT images superimposed (SISCOM[2]) of a 17-year-old man. Left: The gradient echo T2* axial image shows a small round (hypointense) tumor in the right temporal pole and a neighboring arachnoid cyst. Middle and right image: sagittal and coronal view, showing a maximally increased blood flow at the junction of the right dorsal mid-insula and the central operculum.
E) Ictal SPECT images of a 37-year-old patient (the same as in B.) using technetium-99m-ethylcysteinatedimer (99mTc-ECD), in axial, coronal and sagittal view, showing increased blood flow maximal in the right anterior insula. The ictal SPECT was performed postsurgically (2005) during a seizure with an ecstatic aura. The analysis program BRASS (Brain Registration and Analysis Software Suite) was used for automatic fitting of brain perfusion scans and quantification and localization of abnormal perfusion regions.
[1] Images used from [3, 20]
[2] SISCOM = Subtracted ictal SPECT corregistered with MRI [99]: Ictal/interictal technetium-99m HMPAO (99mTc-HMPAO) SPECT subtraction using BRASS analysis program. The software allows automatic fitting of brain perfusion scans and subtraction.

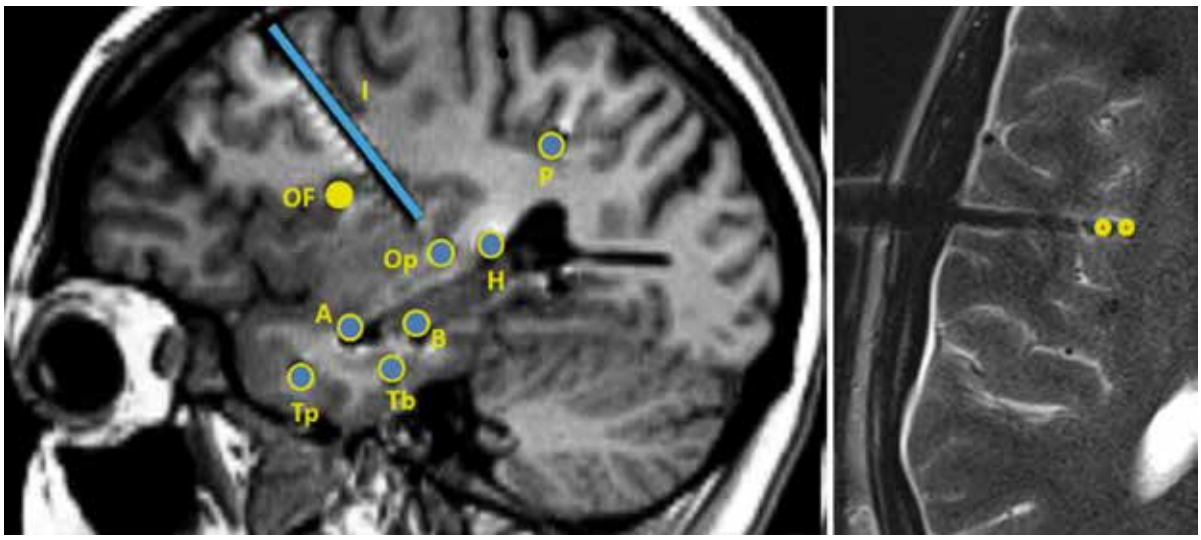

Figure 2: Sagittal view of the patient's MRI with localization of intracerebral electrodes. Nine electrodes were implanted with each of them containing 10-15 contacts. Electrodes A, B and Tb explore the right medial temporal lobe. Electrodes I (insula) and OF (frontal operculum) reach the right insular cortex. Right part: axial view, with detail of the electrode OF reaching the anterior-dorsal part of the insula. The two first contacts (1 and 2) are highlighted in yellow. Bliss sensation was elicited by bipolar stimulation (1-1.6 mA, 4 sec-train duration) of these contacts.
Tp, temporal pole; Tb, temporobasal cortex (lateral contacts) and entorhinal cortex (medial contacts); A, middle temporal gyrus (lateral contacts) and amygdala (medial contacts); B, middle temporal gyrus (lateral contacts) and anterior hippocampus (medial contacts); H, superior temporal gyrus; P, inferior parietal lobule (lateral contacts) and posterior cingulate cortex (medial contacts); OF, frontal operculum and anterior insula (medial contacts); I, middle insula; Op, parietal operculum. Reprinted from [19].

interesting facts which complete our understanding of the function of the insula and of brain mechanisms leading to ecstatic seizures: First, the intense feelings of bliss with interoceptive and emotional components can be induced by the stimulation of a relatively small area within the right anterior-dorsal insula. Second, the stimulation was low in intensity, and there was no after-discharge effect, which further confirms the very localized region for this blissful feeling. Moreover and very importantly, this region did not correspond to the initial seizure generator zone, but was the symptomatic zone of seizure propagation, meaning that functional or plastic tissue alteration is not necessarily to be expected in this region. And finally, the fact that the patient reported such ecstatic symptoms since the very beginning of her epilepsy suggests that this anterior-dorsal insular region likely fulfilled a similar function originally, before any seizure related brain tissue destruction occurred in this place.

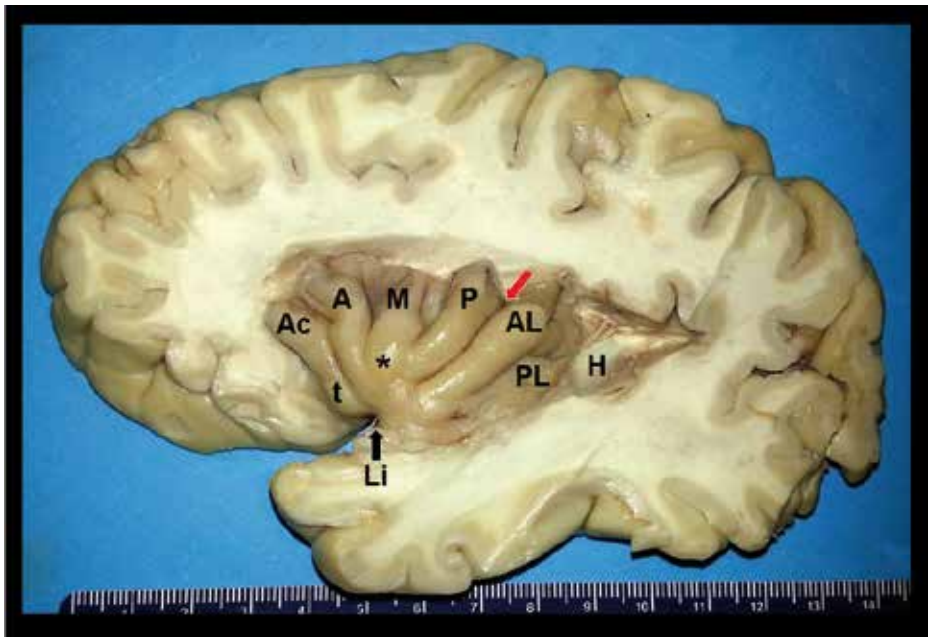

Figure 3: Anatomy of the insula and its relationship with the sulci of the inferior frontal lobe, as disclosed in the depth of the lateral fissure. The central sulcus (red arrow) divides the lateral surface of the insula into a large anterior insular lobule composed of the anterior short (A), middle short (M) and posterior short (P) insular gyri that converge to the apex of the insula (*) and a small posterior insular lobule is composed of the anterior long (AL) and posterior long (PL) insular gyri that converge to the limen insulae (Li, black arrow). The anterior face of the insula displays a constant transverse insular gyrus (t) that connects with the orbital surface of the frontal lobe and a variably present accessory insular gyrus (Ac) further superiorly. H = the posterior medial stub of the transverse temporal gyrus of Heschl (primary auditory cortex) that was resected to uncover the posterior long insular gyrus. Figure courtesy of Drs. Thomas P. Naidich and Mary E. Fowkes, the Icahn School of Medicine at Mt. Sinai, New York.

Neuroanatomy of the insula and its functions

The insula lies hidden deep under the temporal lobe, the frontal and parietal opercula, within the Sylvian fissure, as well as under arterial and venous vessels, making its access particularly difficult. It spans Brodmann Areas BA13 to BA16 [35], and it is cytoarchitectonically subdivided in a rostroventral agranular zone and a dorsocaudal granular zone [36 - 38] (**Figure 3**). The rostroventral agranular zone and its immediate surroundings are connected with the limbic structures such as amygdala and posterior orbitofrontal and anterior cingulate cortices [39]. The borders and connections of the dorsocaudal granular zone are much less clear and still under debate [38], as it is largely connected to many other brain regions as, e.g. parietal and mesio-prefrontal cortex as well as anterior cingulate and temporal cortex [38, 40, 41]. Inbetween the agranular and the granular zones, a dysgranular part has been described, which covers the anterior-dorsal and central insula [35, 42]. The insula is a relatively old structure [42], and especially the anterior part has passed through an impressive differentiation during hominoid evolution, but there is still ongoing debate about the existence of a homologue structure in primates and other animals [38, 41].

Coinciding with its wide connections, the insula is implicated in a large variety of brain functions. Auditory function, vestibular function, somatosensation, pain and temperature perception, viscerosensation, gustation, olfaction, visceromotor control, somatomotor control, motor plasticity, speech production, language, attention, cognitive control, bodily awareness, self-recognition, individual emotions, empathy [25, 38, 43], which can be grouped into four functional domains, defined as an olfacto-gustatory, a sensorimotor, a cognitive, a social-emotional domain [43]. Another meta-analysis also supports a tripartite subdivision of the insula with dorso-anterior, ventro-anterior and posterior regions, corresponding to cognitive, affective/chemosensory and sensorimotor processing, respectively [44]. The analysis over all categories except somatosensation and motion revealed an overlap on the anterior-dorsal insula, located at the dorsal end of the sulcus between the middle and anterior short gyrus [43], exactly the region where the electrodes of our patient had been placed [19].

According to the authors, the overlap in the mapping of the categories in the anterior-dorsal insula, could be due to a basic functional role that all categories have in common, which might be a general role in

task processing, like starting, updating, and maintaining of a task. Given the dense interconnection between the different subparts of the insula, information flows rapidly to the anterior-dorsal insula [35, 38], and this region was recently proposed to represent the final stage of the hierarchical processing from the other subparts of the insula, i.e. starting with pure sensory information in the posterior insula, integrating emotional and cognitive valuation, and ending in the anterior-dorsal insular region with a full representation of a "sentient self", the sine qua non of self-awareness [25, 26, 43].

It is from here that goal-directed acting will occur, and one of the most influential concepts in nowadays neurobiological comprehension of decision making and choice behavior is the feedback loop of error prediction [45]: In a perpetual process the present state is extrapolated, and a prediction is generated which is then compared to the actual state. Based on the comparison the neuronal system aims to minimize the resulting error. In this evaluation loop the anterior-dorsal insula, as the center of interoception (self-sensation) and self-awareness, has been suggested to play the role of the comparator of the predicted to the present outcome [46 - 48], and the role in task-control initiation, maintenance and adjustment, in the context of switching between different mind states [49 - 51]. This model also applies to estimation and processing of risk [52, 53]. During risky decisions in gambling tasks, the anterior insula encodes the risk prediction while waiting for the outcome. Once the outcome is known, it reflects the prediction error, by acting as a comparator between predicted risk and realized risk [46, 54]. Various imaging studies have shown that the anterior insula is an important controller of switching between different tasks and states [44, 50, 55], and it is specifically sensitive to salient environmental events, with one of its core functions being to mark such events in space and time for additional processing [56 - 59]. The temporal judgement of the "nowness" has been shown to be tightly linked to the function of interoception and to emotional processing [25, 60, 61]. It is modulated by arousal, attention and the sentient processing [62]. Several imaging studies have confirmed insular implication in time judgments [63 - 68]. Craig proposed that there is a dorsal to anterior insular integration of interoceptive, sensorial and emotional information at each moment to a "global emotional moment" [25, 60], the succession of which would produce a cinematoscopic "image" of the sentient self serving as a basis for time perception with an approximate frame rate of 7 - 8 Hz (i.e. each "global emotional moment" lasting 125 - 150 ms) [3, 64].

Hypothesis of mechanisms on consciousness

Ecstatic seizures are of focal nature. The ictal discharge implicates at a certain moment the anterior-dorsal insula, the region located at the highest level of insular information processing, which has been suggested to be the neuronal correlate of self-awareness, where the "sentient self" is formed [3, 25, 60]. The already mentioned dense fiber connection of the insula with the cingulate, parietal, temporal and frontal cortex [39, 40, 42], as well as interconnection within the subparts of the insula [35 - 37, 41, 43], enable rapid seizure propagation from adjacent areas like the mesiotemporal region. This propagation likely causes the individual manifestation of ecstatic seizures with very different attendant symptoms like auditory, gustatory of olfactory sensations (depending on the exact focus of the ictal discharge) [3, 20]. Especially the mesiotemporo-insular connections serve as a direct seizure propagator to the insular region [23, 29], explaining the strongly "insular" semiology of many mesiotemporal lobe seizures. However seizures originating in the lateral temporal neocortex can propagate to the anterior insula without going through the mesiotemporal region [29]. Moreover, recordings of synchronous spikes at the temporal pole and in the insula shows an instantaneous spreading of ictal activity also from the temporal pole toward the insula [29].

On the other hand, a pure neocortical temporal symptomatology seems unlikely in patients with ecstatic auras, because the classic clinical features of lateral temporal seizures as auditory and visual illusions and hallucinations, vertiginous auras and early contralateral dystonic posturing [69], were absent in our patients. For temporal pole seizures, no specific symptoms have been described except for an earlier occurrence of loss of consciousness compared to mesiotemporal seizures [70]. Orbitofrontal propagation finally also seems unlikely to explain ecstatic semiology. Such seizures are described as sometimes complex automatisms (bizarre gesticulations and often violent movements mimicking fearful behavior with autonomic signs), as well as a sudden loss of contact [71].

There are two other areas of current research, in which very similar subjective experiences to those during ecstatic seizures are described: brain mechanisms implicated in meditation and those implicated in illicit drug addiction. We will shortly discuss them here, in order to better understand the semiologic-neurobiologic relationship of ecstatic seizures.

Brain mechanisms in addiction. Reports of experiences with use of stimulant drugs such as heroine, cocaine, amphetamine or ecstasy (3,4-methylene-dioxy-methamphetamine) usually mention strong feelings of bliss, enhanced instrospective awareness, inner peace, and the breakdown of the barrier between the subject and the surroundings, creating a heightened

union with the world. Numerous recent neuroimaging studies have shown implication of the anterior insula in drug addiction [72 - 74], and the key role of this structure in the neurobiology of addictive behavior is now well established. The insula acts as integrator of interoceptive (i.e. bodily) states and conscious emotions into decision-making processes involving uncertain risk and reward [75]. For example, a positive correlation between the dose of administered cocaine and the insular activity (as well as the cingulate cortex and nucleus accumbens activity) was found in rats [76]. In nonhuman primates, cocaine administration was shown to induce immediate early gene expression in the insular and ventromedial prefrontal cortex [77]. In humans, a longer duration of cocaine dependence was shown to correlate with a reduction of gray matter volume in the insular, cingulate, and orbitofrontal cortices [78, 79]. The comparison of patients with left insular lesions and normal controls showed that the emotional effects of nicotine (a stimulant at small doses), were lost in patients with lesion and that they failed to find more pleasure in puffs with nicotine compared to puffs without nicotine [74]. The consumption of Ayahuasca tea, a central element of Amazonian shamanism which produces enhanced introspective attention and euphoria, was shown to activate bilateral anterior insula [80].

It is thus likely that the implication of the anterior insula in both illicit drug use and ecstatic seizures explain the similarity of subjective symptoms [3].

Brain mechanisms implicated in meditation. With some variation, depending on the type of meditation practiced, one of the general aims of meditation techniques is to bring the conscious mind into a state of enhanced awareness of the present moment, and to minimize mind wandering. With these techniques often a cognitive reappraisal of emotionally salient sensory events is attempted, a process for which again the anterior insula has been shown to be involved [81 - 84]. For example, functional brain imaging studies have reported that modulation of state anxiety by mindfulness meditation engaged a network of brain regions including the anterior insula [81]. Activation in the dorso-anterior insula during meditation correlated with the self-reported intensity of meditation [83], and was higher in advanced meditators (>10'000 hours of practice) compared to beginners [55]. Conversely, structural imaging studies have demonstrated a thicker cortex [85], with more gray matter concentration [86], and a stronger gyrification in the anterior insula in meditators compared to controls, which in turn also correlated with the number of meditation years [82] and with increased pain tolerance [87].

Taken together, the insula's multiple functions, especially those of the anterior-dorsal subpart interestingly could integrate the symptoms of ecstatic seizures. When we go back to the semiologic elements taken from the patients' descriptions, we can try to hypothesize what might explain them in the light of our neurobiologic knowledge about the insula.

Enhanced self-awareness and heightened well-being. The anterior insula is the anatomical substrate for the capacity of self-awareness, represented in the "global emotional moments", integrated from multisensory input and the processing of interoception [25]. An ictal storm in this region will alter this integrative cycle and mostly provoke unpleasant feelings [23] but it is also possible that it elicits very pleasant ones [8, 16]. The ictal activation of the saliency detection system will then add a feeling of importance, of heightened consciousness of any stimulus [3, 20, 21, 25]. The anterior-dorsal insula essentially participates in the self-reflective network, maintaining a coherent first-person perspective, on the bases of its connections towards inferior parietal lobe (temporo-parietal junction) [25, 35, 40, 50, 88, 89].

Feeling of dilated time. As above-mentioned, time perception has been related to self-referential processing [63], given the insular integration of interoceptive, sensorial and emotional information to a "global emotional moment" [3, 25, 60] in a perpetual cycle. The sampling rate of this integration is not fixed, but is modulated by the salience of the input, i.e. salient moments increase the sampling rate, leading thus to a subjective dilation of time. In an ecstatic aura, when each moment is perceived as salient, we propose that the extremely high number of consecutive salient moments would increase the sampling rate to a maximum, leaving the patient subjectively timeless in a sustained state of "present-moment awareness" [21]. Other insular functions like the task monitoring and task switching, or the prediction error [20] equally display cyclic properties and might equally contribute to the altered feeling of time.

Intense serenity versus anxiety. The human brain is a prolific generator of beliefs, and personhood is the result of the capacity to evaluate new propositional truth in the light of all the others that are already accepted [90]. Decision-making in uncertainty has been shown to be altered in patients with anxiety disorders, where there is a particular intolerance of uncertainty and ambiguous situations [91, 92]. These patients, when confronted with a mismatch between predicted state and actual state, interpreted neutral stimuli even as threatening, evoking anxiety and avoidance behavior, which correlated with enhanced anterior insula activity [92]. Also in obsessive-compulsive disorder, specifically characterized by a high subjective experience of doubt, patients had a greater activation in anterior insula and frontal operculum in an error-eliciting interference task [93], and were shown to have a larger gray matter volume in the anterior insular cortex [94, 95]. During ecstatic seizures these mechanisms of compari-

son between predicted states and actual states seem to be blocked leading to the intense serenity and absence of any anxiety. The sustained state of conscious awareness of the present moment, which takes away the worries about the past and the future, seems to express itself in a feeling of inner peace [19 - 21].

Religious interpretation by some patients. When the comparator between the predicted and the actual state no longer functions during ecstatic seizures, there is no mismatch. This could lead to a feeling of clarity and certainty, because the predicted states are preserved. A long-lasting state without any mismatch during several seconds is like a strong contemplation and can be blissfull and serene, as experiences in meditation [96], or as "state of union with God" [97].

Outlook and open questions

While we can now explain a great deal of the initially mysterious Dostoevsky's syndrome, and while the neurobiological background starts to be clarified, we still face many unanswered questions. Is the presentation of ecstatic seizures sufficiently explained with insular discharges or is there necessity of additional involvement of any other structures, or of so far unknown conditions? Why did the systematic electrical insular stimulation of so many other patients across several studies never provoke ecstatic seizures? Could it be explained by the researchers' focus of interest? What role does lateralization play and is there a preferential side? Lastly, the Geschwind's syndrome [98], an interictal syndrome reported in some patients with temporal lobe epilepsy consisting of the association of hyperreligiosity, hypergraphia and hyposexuality, could have some overlapping features with ecstatic seizures, yet among our patients we have not found a patient with Geschwind's syndrome.

Most probably many of those questions could be answered with the observation of a higher number of cases, and we are still looking for further patients presenting ecstatic ictal experience. Therefore, if you, after having read this article, encounter such patients, please feel free to get in contact!

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1 Crepeau AZ et al. Levetiracetam: a comprehensive review, Expert Rev Neurother. 2010 Feb. 10(2). 159–171

Levetiracetam-Mepha Teva® **Z:** Filmtablette zu 250 mg *(blau)*. Color.: E 132, E 133, 500 mg *(gelb)*. Color.: E 102, E 132 oder 1000 mg *(weiss)* Levetiracetam. **I:** Monotherapie von partiellen Anfällen mit oder ohne sekundäre Generalisierung bei Patienten ab 16 Jahren mit Epilepsie oder als Zusatzbehandlung bei Erwachsenen und Kinder ab 4 Jahren. Zusatzbehandlung von myoklonischen und von primären generalisierten tonisch-klonischen Anfällen bei Erwachsenen und Jugendlichen ab 12 Jahren mit juveniler myoklonischer oder idiopathischer generalisierter Epilepsie. **D:** Tagesdosis in 2 Gaben unzerkaut mit Flüssigkeit einnehmen. Monotherapie > 16 J: initial 2 × 250 mg/Tag nach 2 Wochen 2 × 500 mg/Tag bis max. 2 × 1500 mg/Tag. Zusatzbehandlung (≥ 18 Jahre) und Jugendliche (12–17 Jahre) ab 40 kg: initial 1000 mg/Tag bis max. 3000 mg/Tag. Kinder und Jugendliche unter 40 kg: initiale therapeutische Dosierung 10 mg/kg Körpergewicht zweimal pro Tag. Spezielle Dosierungsanweisungen vgl. Arzneimittelinformation. **KI:** Überempfindlichkeit gegenüber Levetiracetam bzw. verwandten Substanzen oder einem der Hilfsstoffe. Schwangerschaft/Stillzeit. **V:** Psychiatrische Erkrankungen, Suizidversuche und Gedanken. **UW:** Infektionen, Nasopharyngitis, Thrombozytopenie, Anorexie, Gewichtszunahme, Agitation, Depression, emotionale Labilität/Stimmungsschwankungen, Feindseligkeit, Aggression, Schlaflosigkeit, Nervosität, Reizbarkeit, Persönlichkeitsveränderungen, abnormales Denken, Somnolenz, Amnesie, Ataxie, Konvulsion, Benommenheit, Kopfschmerzen, Hyperkinesie, Tremor, Gleichgewichtsstörungen, Aufmerksamkeitsstörungen, Beeinträchtigung des Gedächtnisses, Diplopie, verschwommenes Sehen, Schwindel, Husten, Abdominalschmerzen, Diarrhoe, Dyspepsie, Nausea, Erbrechen, Hautausschlag, Ekzem, Juckreiz, Myalgie, Asthenie, Müdigkeit, Verletzungen, Ruhelosigkeit. **IA:** Enzym-induzierende Substanzen. **Liste:** B. [3413] Weiterführende Informationen siehe Arzneimittelinformation www.swissmedicinfo.ch

Mepha Pharma AG, 4010 Basel, Telefon 061 705 43 43, Fax 061 705 43 85, www.mepha.ch

0414

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Bioäquivalenz-Daten und Präparateprofile finden Sie online unter: www.mepha.ch, Fachpersonen, Qualidoc oder via QR-Code.*

Die mit dem Regenbogen

mepha

Epilepsie-Liga

forscht – hilft – informiert

Die Vagusnervstimulation ist eine Möglichkeit zur Behandlung von Epilepsien, die auf Medikamente alleine nicht ausreichend ansprechen. Dazu wird ein batteriebetriebenes Stimulationsgerät in Art eines Herzschrittmachers unterhalb des Schlüsselbeins unter die Haut implantiert und mit dem Nervus vagus am Hals verbunden.

Ketogene Diäten sind extrem fettreiche, kohlenhydratarme, Eiweiss- und Kalorien-bilanzierte Diäten, die den Stoffwechselzustand des Fastens nachahmen. Diese Diäten kommen prinzipiell für alle Menschen mit einer Epilepsie in Frage, bei denen eine übliche medikamentöse Behandlung allein nicht erfolgreich ist, unabhängig vom Lebensalter.

Eine erfolgreiche Zusammenarbeit von Patienten und Ärzten (Patientinnen und Ärztinnen sind selbstverständlich mit gemeint), setzt gegenseitiges Vertrauen und Respekt voraus. Zum Gelingen einer Therapie braucht es beide Partner. Das gilt in besonderem Masse für die Epilepsiebehandlung.

Erhältlich sind die Informationsflyer bei der Epilepsie-Liga, Tel. 043 488 67 77 oder info@epi.ch.

Bestellgutschein

Bild: Pinnwand / photocase.com

D	F	I	**Senden Sie mir bitte:**
■	■		Flyer „Epilepsie im Alter“
■	■	■	Flyer „Mann und Epilepsie“
■	■	■	Flyer „Was ist Epilepsie“
■	■	■	Flyer „Ursachen von Epilepsien“
■	■	■	Flyer „Merkmale von Anfällen“
■	■	■	Flyer „Häufige Anfallsformen bei Kindern“
■	■	■	Flyer „Medikamentöse Behandlung“
■	■	■	Flyer „Erste Hilfe bei Epilepsie“
■	■	■	Flyer „Frau und Epilepsie“
■	■	■	Flyer „Kinderwunsch und Epilepsie“
■	■	■	Flyer „Reisen und Epilepsie“
■	■		Programmheft Veranstaltungen der Epilepsie-Liga
■	■	■	Flyer „Autofahren und Epilepsie“
■	■		Flyer „Sport und Epilepsie”
■	■		Flyer „Arbeit und Epilepsie”
■	■		Fachzeitschrift „Epileptologie“
■	■		Flyer „Ketogene Diäten“
■	■	■	Einzahlungsschein(e) zur Unterstützung der Epilepsie-Liga
■	■	■	Ratgeber für Legate
■	■	■	Ratgeber „Epilepsie und Versicherungen”
■	■	■	Flyer „Vagusnervstimulation“
■	■	■	Flyer „Compliance“

DVDs und übrige Publikationen siehe www.epi.ch

Ich (wir) möchte(n):

■ Einzelmitglied der Epilepsie-Liga werden und bezahle mindestens 50 Franken jährlich.

■ Kollektivmitglied der Epilepsie-Liga werden und bezahlen mindestens 100 Franken jährlich.

Epilepsie-Liga DVD

"Im Schatten des Wolfes"

Mit der freundlichen Erlaubnis der finnischen Regisseurin und des Produzenten realisierte die Epilepsie-Liga eine DVD des Spielfilms „Im Schatten des Wolfes" und fügte den englischen und französischen Untertiteln noch deutsche hinzu, um den sehr berührenden und ästhetischen Film einem möglichst grossen Publikum zugänglich zu machen.

Erhältlich bei der Epilepsie-Liga, info@epi.ch, Tel. 043 488 67 77

Sari ist eine begabte Literaturstudentin, die äusserlich beherrscht und selbstbewusst wirkt. Ihr Leben ist jedoch durch eine gewisse Zurückgezogenheit geprägt. Die Kolleginnen beneiden sie um ihre Intelligenz und Schönheit, die männlichen Komilitonen bewundern sie aus der Ferne aus denselben Gründen. Aber in Saris Innerem lauert eine Bestie, die sie vom Rest der Welt isoliert: die junge Frau hat Epilepsie, eine gefürchtete und geheimnisvolle Krankheit, und die Angst vor Anfällen macht sie vorsichtig. Sie achtet auf eine gewisse Distanz zu anderen Menschen. Als Sari dem älteren Literaturdozenten Mikko Groman begegnet, erkennt sie in ihm ein ähnliches Element von Reserviertheit. Mikko, der sich in seiner ganz eigenen, komplizierten Gedankenwelt bewegt, fühlt sich nur in der Dichtkunst des 19. Jahrhunderts so richtig zuhause. In der leistungsorientierten modernen Welt der Computer und Iphones ist er ein Sonderling. In Mikko findet Sari einen Seelenverwandten, doch in den Augen der anderen scheinen die beiden überhaupt nicht zueinander zu passen.

Absender/in

Name | Vorname

Strasse | Nr.

PLZ | Ort

Telefon

eMail

Bitte frankieren

Schweizerische Liga gegen Epilepsie

Seefeldstrasse 84
Postfach 1084
CH 8034 Zürich

Epilepsie-Liga-Mitteilungen

Ausschreibung – Forschungsförderung

Förderung der wissenschaftlichen Forschung im Bereich der Epilepsie (vorwiegend Starthilfen) durch die Schweizerische Liga gegen Epilepsie (Epilepsie-Liga)

Die Epilepsie-Liga unterstützt wissenschaftliche Projekte im Bereich der Epileptologie im Gesamtbetrag von

CHF 25'000.—

pro Jahr. Insbesondere soll die Erforschung von Ursachen und Behandlungen der Epilepsie gefördert werden.

Stipendien für Aus- oder Weiterbildung oder Auslandaufenthalte werden nicht ausgerichtet. Hingegen können Reise- und Aufenthaltskosten (ohne Salär) für Kurzaufenthalte (maximal einige Wochen) finanziert werden, sofern sie dem Erlernen von Methoden dienen, welche im Rahmen eines unterstützten Projektes in der Schweiz eingesetzt werden.

Falls der Antragsteller/die Antragstellerin bereits anderswo Anträge für Unterstützung gestellt hat, ist offen zu legen, bei wem und mit welchem Ergebnis.

Termin für die Einreichung von Gesuchen: 31. Dezember 2014

Formulare und Wegleitung für Gesuchstellende können angefordert werden bei:

Schweizerische Liga gegen Epilepsie
Seefeldstrasse 84 | Postfach 1084
8034 Zürich
Tel. 043 488 67 77 | Fax 043 488 67 78
info@epi.ch

Vorschau Epileptologie 3 | 2014

Kulturelle Aspekte der Epilepsie

Zur Kulturgeschichte der Epilepsie
Prof. Dr. med. Peter Wolf | Dianalund, Dänemark

Epilepsy care in resource-poor settings
Prof. Dr. med. Ley Sander and Dr. med. Mark Keezer | London, Montréal

Epilepsiebehandlung im Hôtel Dieu von Mome Katihoé, einem ländlichen Gesundheitszentrum in Togo
Dr. med. Bernhard Oehl | Zürich

Aufbau eines Epilepsiezentrums in Westafrika
Dr. med. Aribert Bauerfeind | Zürich

Erste Schritte zu einer Epilepsieambulanz im ländlichen Kamerun
Dr. med. Matthias Bacher | Kehl-Kork, Deutschland

Ausschreibung – Promotionspreis

Die Schweizerische Liga gegen Epilepsie (Epilepsie-Liga) vergibt alle 3 Jahre einen Preis in Höhe von

CHF 1'000.—

für die beste Dissertation auf dem Gebiet der Epileptologie.

Bewerbungen sind aus allen Fachbereichen und Berufsgruppen möglich und erwünscht, sowohl aus Grundlagen- als auch klinischen Fächern. Eine Altersbeschränkung erfolgt nicht.

Das Preisrichterkollegium setzt sich aus drei Vorstandsmitgliedern der Epilepsie-Liga zusammen, das bei Bedarf zusätzlich externe Gutachter hinzuziehen kann. Es trifft seine Entscheidung in geheimer Wahl.

Falls der Antragsteller/die Antragstellerin bereits anderswo Anträge für Unterstützung gestellt hat, ist offen zu legen, bei wem und mit welchem Ergebnis.

Die Preisverleihung erfolgt jeweils im darauf folgenden Jahr anlässlich der Jahrestagung oder Mitgliederversammlung der Epilepsie-Liga.

Bewerbungen sind **bis zum 31.12.2015** an die **Geschäftsstelle der Epilepsie-Liga** (Seefeldstrasse 84, Postfach 1084, 8034 Zürich) einzureichen und müssen beinhalten: vier Exemplare der abgeschlossenen und beim Dekanat eingereichten Dissertation, vier Exemplare einer Stellungnahme des Doktorvaters (dabei kann es sich auch um das entsprechende Gutachten für die Dissertation handeln).

Mise au concours – Soutien de la recherche

Promotion de la recherche scientifique dans le domaine de l'épilepsie (surtout sous forme d'aide initiale) par la Ligue Suisse contre l'Epilepsie (Ligue contre l'Epilepsie)

La Ligue contre l'Epilepsie soutient les projets scientifiques dans le domaine de l'épileptologie par un montant total de

CHF 25'000.—

par an, la priorité étant accordée aux projets cherchant à élucider les causes et à mettre au point des traitements de l'épilepsie.

Aucune bourse ne sera octroyée pour la formation de base ou continue ou pour des séjours à l'étranger. En revanche, la prise en charge de frais de voyage et de séjour (sans salaire) est possible pour les séjours de courte durée (quelques semaines au maximum) lorsque ces séjours servent à apprendre des méthodes appliquées dans le cadre d'un projet bénéficiant de soutien en Suisse.

Si le requérant a déjà fait une demande de soutien ailleurs, il faut nous en informer en spécifiant où et avec quel résultat.

Délai de remise des demandes :

31 décembre 2014

Les formulaires, ainsi que le guide pour les candidats peuvent être demandés à l'adresse suivante :

Ligue Suisse contre l'Epilepsie
Seefeldstrasse 84
Case postale 1084
8034 Zurich
Tél. 043 488 67 77
Fax 043 488 67 78
info@epi.ch

Mise au concours – Prix de promotion

La Ligue Suisse contre l'Epilepsie (Ligue contre l'Epilepsie) décerne tous les 3 ans un prix d'un montant de

CHF 1'000.—

pour la meilleure dissertation dans le domaine de l'épileptologie.

Tous les domaines spécialisés et tous les groupes professionnels couvrant les disciplines fondamentales ou cliniques sont invités à soumettre leur candidature. Aucune limite d'âge n'a été fixée.

Le jury décernant le prix se compose de trois membres du comité directeur de la Ligue contre l'Epilepsie. Il peut être complété au besoin par des experts externes. La décision est prise par vote secret.

Si le requérant a déjà fait une demande de soutien ailleurs, il faut nous en informer en spécifiant où et avec quel résultat.

Le prix est toujours décerné l'année suivante dans le cadre de l'assemblée annuelle ou générale de la Ligue contre l'Epilepsie.

Les dossiers de candidature doivent parvenir au Secrétariat de la Ligue contre l'Epilepsie (Seefeldstrasse 84, case postale 1084, 8034 Zurich) jusqu'au

31.12.2015

et comporter les pièces suivantes :

- quatre exemplaires de la dissertation achevée et remise au décanat,
- quatre exemplaires d'une prise de position du directeur de thèse (il peut par exemple s'agir de l'expertise concernant la dissertation).

Ausschreibung Alfred Hauptmann-Preis

Dieser Preis ist nach dem deutschen Neurologen und Psychiater Alfred Hauptmann (1881 - 1948) benannt. Dieser hatte u.a. schon 1912 - noch als Assistenzarzt - erstmals auf die antiepileptische Wirkung von Phenobarbital aufmerksam gemacht. 1935 wurde er aufgrund seiner jüdischen Abstammung von den Nationalsozialisten aus dem Dienst als Direktor der Psychiatrischen und Nervenklinik der Universität Halle/Saale entfernt und musste in die USA emigrieren.

Der Preis wurde von 1980 bis 2008 in der Regel alle zwei Jahre durch das Epilepsie-Kuratorium e.V. vergeben, ab 2009 ist es ein gemeinsamer Preis der Deutschen Gesellschaft für Epileptologie, der Österreichischen Sektion der Internationalen Liga gegen Epilepsie und der Schweizerischen Liga gegen Epilepsie mit Vergabe auf den alle zwei Jahre stattfindenden gemeinsamen Tagungen.

Ausgezeichnet wird die beste wissenschaftliche Arbeit aus dem deutschsprachigen Raum auf dem Gebiet der experimentellen und klinischen Epileptologie aus den beiden letzten, der Verleihung vorangegangenen Jahren.

Arbeiten werden besonders aus den Fachgebieten Neurologie, Pädiatrie, Psychiatrie, klinische Pharmakologie, Neurophysiologie und Neurobiologie erwartet.

Die ausgezeichneten Personen erhalten eine Urkunde. Darüber hinaus ist der Preis mit

10‘000 Euro

dotiert. Das Preisgeld wird seit 2009 von der Firma UCB GmbH (Deutschland), Monheim, zur Verfügung gestellt. Es können mehrere Einzelpersonen oder Arbeitsgruppen ausgezeichnet werden.

Einzureichende Unterlagen:

Die Arbeiten sollen in englischer Sprache verfasst sein. Zusätzlich zu den Arbeiten sind folgende weitere Unterlagen einzureichen:

- Lebenslauf,
- eine Stellungnahme des Klinik-/Institutsvorstandes zur Bewerbung,
- für den Fall von Mehrautorenarbeiten, bei denen nicht alle Autoren am Preis beteiligt werden sollen, eine Aussage über den Anteil der einzelnen Autoren an der publizierten Arbeit.

Die Arbeiten sind in vierfacher Ausführung bis zum

31.12.2014

An den Vorsitzenden des Kollegiums zu senden:

Herrn Dr. med. Günter Krämer
Präsident der Schweiz. Liga gegen Epilepsie
Seefeldstrasse 84
Postfach 1084 CH
8034 Zürich

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2014

29.6.-3.7.2014 | Stockholm Schweden
11th European Congress on Epileptology
Information: ILAE/IBE-Congress Secretariat,
7 Priory Hall, Stillorgan Road, Blackrock,
Co. Dublin, Ireland,
Tel. 00353 / 1 / 2056720,
Fax 00353 / 1 / 2056156,
e-mail: Stockholm@epilepsycongress.org
www.epilepsystockholm2014.org

3.-8.8.2014 | Trakai, Litauen
8th Baltic Sea Summer School on Epilepsy
Information: petra.novotny@wolfstiftung.org,
www.epilepsie-stiftung-wolf.de

7.-10.8.2014 | Singapur
7th Asian & Oceanian Epilepsy Congress
Information: ILAE/IBE-Congress Secretariat,
7 Priory Hall, Stillorgan Road, Blackrock,
Co. Dublin, Ireland,
Tel. 00353 / 1 / 2056720,
Fax 00353 / 1 / 2056156,
e-mail: singapore@epilepsycongress.org,
www.epilepsysingapore2014.org

4.-7.9.2014 | Basel
The World Congress on NeuroTherapeutics: Dilemmas, Debates & Discussions (DDDN)
Information: NeuroTherapeutics Secretariat, Congress-Med, 20 Lincoln St., Floor 13, Tel Aviv 67134, Israel,
Tel. 00972 / 73 / 7066950,
e-mail: dddn@congressmed.com,
www.congressmed.com/neurology/

15.-19.09.2014 | München, Deutschland
Neurowoche 2014
87. Kongress der Deutschen Gesellschaft für Neurologie
40. Jahrestagung der Gesellschaft für Neuropädiatrie
Information: www.neurowoche2014.org

17.-20.9.2014 | Buenos Aires, Argentinien
8th Latin American Congress on Epilepsy
Information: www.epilepsycongress.org

18.-20.9.2014 | Oldenburg, Deutschland
29. Jahrestagung der Gesellschaft für Neuropsychologie
Information: Valerie Stähler, Kongress- und MesseBüro Lentzsch GmbH Büro:
Gartenstr. 29, D 61352 Bad Homburg, Deutschland,
Tel. 0049 / 6172 / 67960,
Fax 0049 / 6172 / 679626,
e-mail: valerie.staehler@kmb-lentzsch.de
www.kmb-lentzsch.de

21.-24.9.2014 | Gargnano, Italien
26. Praxisseminar über Epilepsie und EEG
Information: Stiftung Michael
Alsstrasse 12, D 53227 Bonn, Deutschland,
unterstützt von Desitin,
Tel. 0049 / 228 / 94554540,
Fax 0049 / 228 / 94554542,
e-mail: post@stiftung-michael.de,
www.stiftungmichael.de

25.9.2014 | Lugano, 14 Uhr
Fachveranstaltung der Epilepsie-Liga
Information: Epilepsie-Liga,
Seefeldstrasse 84, Postfach 1084, 8034 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch
www.epi.ch

3.10.2014 | Lugano

Publikumsveranstaltung der Epilepsie-Liga
Information: Epilepsie-Liga,
Seefeldstrasse 84, Postfach 1084, 8034 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch
www.epi.ch

29.10.-31.10.2014 | Interlaken
SNG-Tagung – Gemeinsame Jahrestagung mit der Schweizerischen Gesellschaft für Intensivmedizin (SGI), Schweizerischen Gesellschaft für Neurologie (SNG), Schweizerischen Gesellschaft für Neuroradiologie (SGNR), Schweizerischen Hirnschlaggesellschaft (SHG), Schweizerischen Gesellschaft für Notfall- und Rettungsmedizin (SGNOR), Gäste: Schweizerische Gesellschaft für Verhaltensneurologie (SGVN), Schweizerische Liga gegen Epilepsie SLgE
Information: http://www.imk.ch/sgi2014

17.-18.11.2014 | Zürich
Aufbaukurs Epilepsie
Information: Jörg Wehr, Bildung und Öffentlichkeitsarbeit, Schweiz. Epilepsie-Stiftung, EPI WohnWerk, Bleulerstr. 60, 8008 Zürich,
Tel. 0041 / 44 / 3876480,
Fax 0041 / 44 / 3876138
e-mail: joerg.wehr@swissepi.ch
http://www.epi.ch/_admin/02_cms/www.epi-wohnwerk.ch

5.-9.12.2014 | Seattle, Washington, USA
68th Annual Meeting of the American Epilepsy Society
Information: American Epilepsy Society,
342 North Main Street, West Hartford,
CT 06117-2507 USA,
Tel. 001 / 860 / 5867505,
Fax 001 / 860 / 5867550,
e-mail: info@aesnet.org,
www.aesnet.org

2015

22. - 25.4.2015 | Dresden, Deutschland
9. Gemeinsame Jahrestagung der drei deutschsprachigen Sektionen der Internationalen Liga gegen Epilepsie (Dreiländertagung)
Information: www.epilepsie2015.de
http://www.epilepsie2015.de/fileadmin/media/2015/dgfe/DGfE2015_Ankuendigung.pdf

6.-10.9.2015 | Istanbul, Türkei
31th International Epilepsy Congress
Information: Congress Secretariat,
7 Priory Hall Stillorgan Road, Dublin, Irland,
Tel. 00353 / 1 / 2056720,
e-mail: istanbul@epilepsycongress.org

4.-8.12.2015 | Philadelphia, Pennsylvania, USA
69th Annual Meeting of the American Epilepsy Society
Information: American Epilepsy Society,
342 North Main Street, West Hartford,
CT 06117-2507 USA,
Tel. 001 / 860 / 5867505,
Fax 001 / 860 / 5867550,
e-mail: info@aesnet.org, www.aesnet.org

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