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Inhalt

Schweizerische Epilepsie-Liga
Ligue Suisse contre l'Epilepsie
Lega Svizzera contro l'Epilessia
Swiss League Against Epilepsy

Richtlinien für die Autoren

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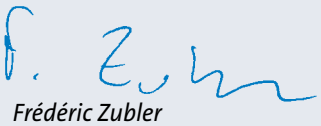
Alle Manuskripte sind inklusive Abbildungen und Tabellen in dreifacher Ausführung einzureichen. Bevorzugt wird eine elektronische Manuskripteinreichung per e-mail (Textverarbeitung: MS Word), alternativ die Zusendung von drei Ausdrucken und einer CD (für Abb. und Tab. ist das verwendete Programm anzugeben).

Dr. med. Dr. sc. nat. Frédéric Zubler

The clinical use of EEG is often associated with epilepsy, whether to diagnose an epileptic syndrome, rule out status epilepticus, or evaluate an individual's ability to drive. However, EEG can also be used in the assessment of other neurological diseases, which is not surprising given that EEG reflects regional neuronal function or activity. With the emergence of newer methodology, especially in neuroradiology, some previous indications for EEG have become obsolete: it is to our great advantage that localization of brain tumors prior to resection no longer depends so heavily on a focal slowing in EEG! More recently, technological advances – for instance in quantitative EEG analysis – have opened the possibility to apply EEG to various other diseases. In this issue we present applications in sleep medicine, neurodegenerative diseases, schizophrenia and patient assessment in the intensive care unit. The list is far from complete, and further applications such as metabolic encephalopathies have been discussed previously in this journal.

In addition, EEG electrodes can be used to detect evoked potentials. Somatosensory, visual and auditory potentials are well-known examples. In the last article, less frequent examinations are presented, namely gustatory, olfactory and trigeminal evoked potentials.

I would like to conclude by thanking all of the authors who contributed to this issue. We hope that it will be as interesting to read as is was to prepare.



Frédéric Zubler

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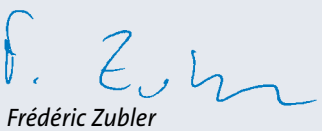
L'EEG est très souvent lié à l'épilepsie, que ce soit pour confirmer un diagnostic en cas de suspicion de crises, pour exclure un état de mal épileptique ou pour juger de l'aptitude à la conduite. Puisqu'il est un reflet de l'activité neuronale, il n'est pas étonnant que l'EEG soit aussi utile dans de nombreuses maladies neurologiques autres que l'épilepsie. Certaines indications plus anciennes sont tombées en désuétude, avantageusement remplacées par l'imagerie: fort heureusement les opérations de tumeurs du cerveau ne sont plus planifiées uniquement en fonction de la localisation d'un foyer lent! Dans le même temps, les progrès techniques et en particulier l'analyse quantitative ont permis d'affiner les techniques d'analyse dans de nombreuses autres maladies. Les exemples que nous vous présentons dans ce numéro vont des troubles du sommeil aux maladies neuro-dégénératives, en passant par la schizophrénie et la prise en charge aux soins intensifs. La liste est loin d'être exhaustive, et certaines autres indications comme les encéphalopathies métaboliques ont été traitées dans de précédents numéros.

Par ailleurs, les électrodes d'EEG sont également utilisées dans l'enregistrement de potentiels évoqués. Si les potentiels évoqués somesthésiques, visuels et auditifs sont les plus courants, le dernier article nous en apprend plus sur d'autres examens encore souvent méconnus, les potentiels évoqués gustatifs, olfactifs et trigéminaux.

Je voudrais terminer par remercier les auteurs qui ont accepté de participer à ce numéro, et vous souhaiter, chère lectrice, cher lecteur, autant de plaisir à le lire que nous en avons eu à le préparer.



Frédéric Zubler

Dr. med. Dr. sc. nat. Frédéric Zubler

Das EEG ist sehr oft mit Epilepsie assoziiert – sei es zur Bestätigung der Diagnose bei Verdacht auf Epilepsiesyndrom, zum Ausschluss eines Status epilepticus, oder zwecks Beurteilung der Fahreignung. Da ein EEG die neuronale Aktivität widerspiegelt, ist nicht erstaunlich, dass es auch zu Beurteilung vieler anderer neurologischer Erkrankungen beitragen kann. Mit der Verbreitung fortschrittlicher Bildtechniken wurden einige ursprüngliche EEG-Indikationen obsolet: Zum Glück erfolgt die Lokalisierung eines Tumors vor dessen Resektion nicht mehr aufgrund des Herdbefunds im EEG! Gleichzeitig erlauben technologische Fortschritte – insbesondere in der quantitativen EEG-Analyse – dessen Anwendung für zahlreiche andere Erkrankungen. So reichen die Ihnen in dieser Ausgabe vorgestellten Beispiele von Schlafstörungen und neurodegenerativen Erkrankungen über die Schizophrenie bis hin zu intensivmedizinischen Problemen. Diese Liste ist bei weitem nicht vollständig, und diverse andere Indikationen wie die metabolischen Enzephalopathien wurden bereits in vorangehenden Ausgaben behandelt.

Darüber hinaus werden EEG-Elektroden auch für die Registrierung von evozierten Potenzialen verwendet. Dabei sind somatosensorische, visuelle und auditive Potenziale am verbreitetsten. Der letzte Artikel allerdings bringt uns Untersuchungen näher, die noch kaum bekannt sind – es sind die gustatorisch, olfaktorisch und trigeminal evozierten Potenziale.

Abschliessend möchte ich den Autoren danken, die sich bereit erklärt haben, an dieser Ausgabe mitzuwirken. Und Ihnen, liebe Leserin, lieber Leser, wünsche ich genau so viel Freude beim Lesen wie wir beim Verfassen hatten.

Frédéric Zubler

The Cyclic Alternating Pattern and the Brain-Body-Coupling During Sleep

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Summary

Sleep measurement is based on conventional rules, which simplify the complex architecture of this mandatory phsyiological activity. The dynamic development of sleep shows a regular cyclic nature, which is reflected also in the microstructural organization of phasic EEG events. In NREM sleep, arousals rarely appear in isolation but are most commonly arranged in sequences recognized as the cyclic alternating pattern (CAP). Composed of EEG features endowed with properties of activation (phase A) and deactivation (phase B), CAP translates a condition of sustained arousal instability. Due to the close temporal relation between CAP, autonomic functions and behavioral activities, CAP operates as a master clock that entrains different rhythms in a common temporal pattern. Crucially participating in the build-up, maintenance and attenuation of slow wave sleep, CAP represents a fundamental pillar of sleep processes together with the homeostatic drive, the ultradian cyclicity and the circadian oscillation. The pivotal role of CAP in the basic sleep mechanisms justifies its involvement in the pathophysiology of most sleep disorders and offers new perspectives in clinical management strategies. The absence of CAP (defined as non-CAP) corresponds to a sustained condition of stability extended to both brain and body. CAP and non-CAP metrics overcome the rigid limitations of conventional stage scoring and provide a more flexible and genuine neurophysiological substrate to shed light upon the brain-body coupling during sleep.

Epileptologie 2016; 33: 150 – 160

Key words: Cyclic alternating pattern, sleep, EEG, arousals

„Cyclic alternating pattern“ und „Brain-Body-Coupling“ im Schlaf

Die Beurteilung des Schlafes erfolgt gemäss konventioneller Kriterien, die die komplexe Architektur dieser essenziellen physiologischen Aktivität vereinfachen sollen. Physiologischer Schlaf folgt in periodischen Zyklen, was sich im EEG in der Mikrostruktur der Schlafphasen widerspiegelt. Im NREM Schlaf kommen isolierte Arousals nur sehr selten vor, meist kommt es zu Sequenzen, die als “cyclic alternating pattern” (CAP) bezeichnet werden. Mit Sequenzen transienter elektrokortikaler Ereignisse von Aktivierung (Phase A) und Deaktivierung (Phase B) repräsentiert CAP eine Schlafinstabilität und ein relativ niedriges Arousal-Niveau. Auf Grund des engen zeitlichen Zusammenhangs zwischen CAP, autonomer Funktionen und Verhalten funktioniert CAP als ein übergeordneter Zeitgeber zu Koordinierung verschiedener Rhythmen in einer gemeinsamen zeitlichen Periodizität. Gemeinsam mit ultradianen Zyklen und zirkadianen Oszillationen wirkt CAP als zentraler Pfeiler des Schlafes im Aufbau, in der Aufrechterhaltung und Vertiefung des Delta-Schlafes mit. CAP spielt in diesen grundlegenden Schlafmechanismen eine zentrale Rolle, daher versteht sich auch die wichtige pathophysiologische Bedeutung von CAP in den meisten Schlafstörungen, wodurch sich neue klinische Perspektiven für Behandlungsstrategien eröffnen. Fehlen von CAP (definiert als non-CAP) ist assoziiert mit einem anhaltenden Zustand von Stabilität, übertragen auf Hirn und Körper. Mittels CAP und Non-CAP gelingt es, starre Limitationen der konventiellen Schlaf-Stadien-Einteilung zu überwinden, was eine flexiblere, authentischere und neurophysiologischere Sicht auf das Brain-Body-Coupling während des Schlafes erlaubt.

Schlüsselwörter: Cyclic alternating pattern, Schlaf, EEG, Arousal

Le tracé alternant cyclique et le couplage du cerveau et du corps durant le sommeil

L’analyse conventionnelle du sommeil repose sur des règles rigides, qui tendent à simplifier l’architecture complexe de cette activité physiologique essentielle. Le sommeil est cyclique par nature, entre autre dans l’organisation des événements EEG phasiques observés sur une courte échelle de temps (microstructure du sommeil). Au cours du sommeil non-REM, ces événements phasiques (“arousals”) apparaissent rarement de manière isolée, mais sont le plus souvent organisés en

séquences appelées tracé alternant cyclique ("cyclic alternating pattern", CAP). Composé d'éléments EEG suggérant l'activation (phase A) et la désactivation (phase B), le CAP est l'expression d'une instabilité prolongée du sommeil. En raison de la concomitance entre CAP, fonction autonome et mouvement, le CAP peut être vu comme le chef d'orchestre qui régule les différents rythmes les uns par rapport aux autres. En participant de manière cruciale dans l'événement, le maintien et l'atténuation du sommeil à ondes lentes, le CAP représente – avec le processus homéostatique, le rythme ultradien et le rythme circadien – l'un des piliers fondamentaux du processus sommeil. Le rôle majeur du CAP dans les mécanismes fondamentaux du sommeil explique son implication dans la pathophysiologie de la plupart des troubles du sommeil, et offre de nouvelles perspectives de traitement en clinique. L'absence de CAP correspond quant à elle à une stabilité prolongée du cerveau, comme du reste du corps. Quantifier les phases de CAP et d'absence de CAP permet de contourner les limitations rigides du scorage des phases de sommeil, et offre un cadre flexible, correspondant plus à la réalité neurophysiologique, pour étudier les relations cerveau-corps pendant le sommeil.

Mots clés : Tracé alternant cyclique, sommeil, EEG, micro-éveils

Introduction

The current method of sleep analysis, according to the AASM system, is centered on sleep macrostructure that identifies rapid-eye movement sleep (REM) and non-REM with its different stages (NREM1, NREM2, NREM3) based on 30-second scoring epochs [1].

Under physiological conditions, sleep macrostructure presents an operational framework based on the following principles and rules:

1. Falling asleep always occurs in non-REM sleep,
2. the brain takes about 25 minutes to reach deep sleep,
3. the first REM sleep episode appears approximately 10 minutes after the end of deep sleep,
4. NREM3 prevails in the first part of the night, while REM sleep dominates in the second half.

This asymmetry reflects the gradual attenuation of the intensity of slow wave sleep during the night, like a spring loaded during the waking hours and progressively discharged across the night. Because it increases after sleep deprivation and drops when the waking period is short, deep sleep is considered an important marker of sleep homeostasis.

The alternation of NREM and REM sleep constitutes the sleep cycle. Each sleep cycle has a duration of approximately 90 minutes. Sleep macrostructure resembles a 5-wagon train, each coach lasting about an hour and a half. The first three wagons, which constitute the core sleep, are controlled predominantly by the acid gamma-aminobutyric acid (GABA), a sedative neurotransmitter. The last two couches compose the so-called optional sleep and are modulated by an activating neurotransmitter, acetylcholine, which prepares the brain to the morning awakening. The turning point between the two types of sleep, in particular between the third and the fourth wagon, coincides with a delicate phase of sleep continuity and is often the time of awakening for many insomniacs.

However, the quality of sleep is not only based on its duration, depth and continuity as arousals are also involved in the restorative properties of sleep. Although scored as single features, arousals rarely appear in isolation, while they are mostly organized in sequences like a swarm of flying birds. The regular organization of arousals, known as CAP (cyclic alternating pattern), defines the microstructure of sleep and measures the amount of unstable sleep.

Accordingly, the quality of sleep is based on 4 pillars:

- Duration (total sleep time)
- Intensity (amount of deep sleep)
- Continuity (nocturnal awakenings)
- Stability (CAP parameters).

The rules of CAP and non-CAP

CAP is the most comprehensive method for the detection and measurement of sleep microstructure. CAP spans across long periods of NREM sleep, it overcomes the boundaries of standard rigid epochs and offers a dynamic contribution to the static framework of conventional scoring. CAP reveals the presence of a complex scaffold, hidden but perfectly integrated beneath the surface of conventional sleep stages [2].

CAP is definied as a periodic EEG activity occurring under conditions of reduced vigilance (sleep, coma). It is characterized by sequences of CAP cycles defined by an A phase (transient electrocortical events that are distinct from background EEG activity) and by the following B phase (return to background EEG activity).

A CAP sequence is composed of at least two consecutive CAP cycles (**Figure 1**).

The absence of CAP for more than 60 s is scored as non-CAP (NCAP) and coincides with a condition of sustained physiological stability [3]. Isolated A phases are classified as NCAP (**Figure 2**).

The last A phase that closes a CAP sequence is not included in the scoring of CAP and is scored as NCAP.

Therefore every CAP sequence begins with an A phase and ends with a B phase. The amplitude of phasic activities initiating a phase A must be 1/3 higher than the background voltage.

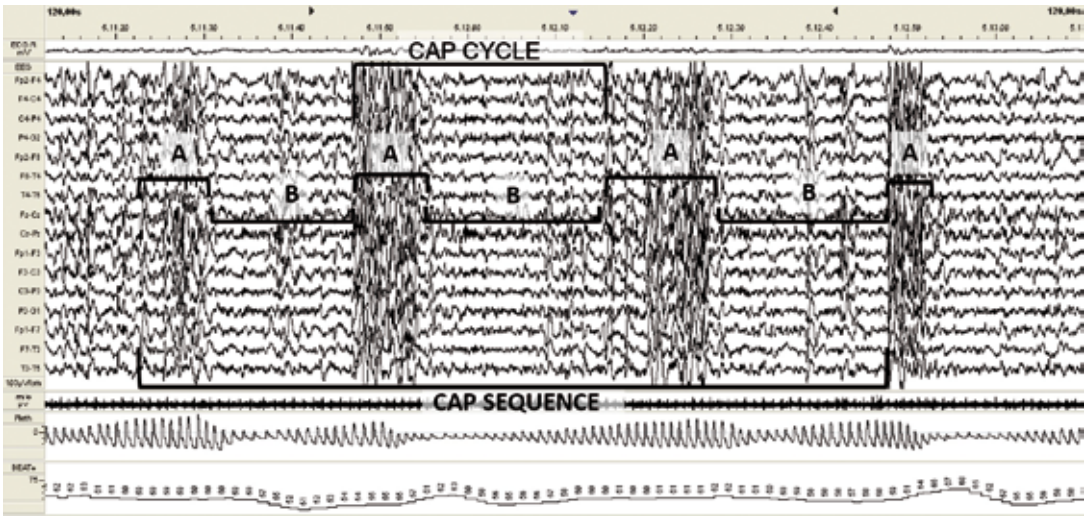

Figure 1: Cyclic alternating pattern (CAP) during NREM sleep. A CAP cycle is defined as a sequence of A phase and B phase. At least two full CAP cycles in succession are needed to define a CAP sequence; thus, the minimum content of a sequence is A–B–A–B–A. Montage, from top to bottom: right electrooculogram (EOG-R); electroencephalogram (EEG; bipolar EEG derivations using international electrode placement FP2–F4, F4–C4, C4–P4, P4–O2, Fp2–F8, F8–T4, T4–T6, Fz–Cz, Cz–Pz, Fp1–F3, F3–C3, C3–P3, P3–O1, Fp1–F7, F7–T3, T3–T5); chin electromyogram (milo); finger photoplethysmogram (Pleth); heart rate (BEAT).

Each CAP phase, both A and B, is 2 - 60 s in duration. This cutoff relies on the consideration that the great majority (about 90%) of A phases occurring during sleep are separated by an interval of less than 60 s [4]. If two consecutive phases A are separated by an interval < 2 s they are counted as a single phase A. CAP sequences are not interrupted by a sleep stage shift if CAP scoring requirements are satisfied. Therefore, a CAP sequence can contain a variety of different phasic activities and extend across adjacent sleep stages.

CAP sequences commonly precede the transition from non-REM to REM sleep and end just before REM sleep onset. REM sleep is characterized by the lack of EEG synchronization; thus phase A features in REM

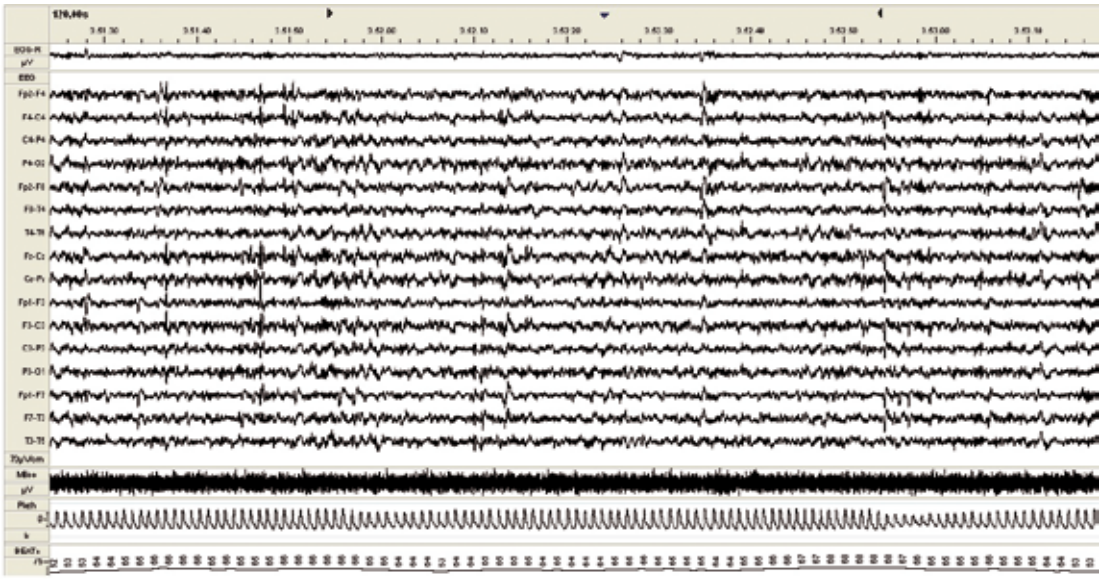

Figure 2: Absence of cyclic alternating pattern (NCAP) during NREM sleep. Montage, from top to bottom: Right electrooculogram (EOG-R); electroencephalogram (EEG; bipolar EEG derivations using international electrode placement Fp2–F4, F4–C4, C4–P4, P4–O2, Fp2–F8, F8–T4, T4–T6, Fz–Cz, Cz–Pz, FP1–F3, F3–C3, C3–P3, P3–O1, Fp1–F7, F7–T3, T3–T5); chin electromyogram (milo); finger photoplethysmogram (Pleth); heart rate (BEAT).

sleep consist mainly of desynchronized patterns (fast low-amplitude rhythms), which are separated by a mean interval of 3 - 4 min [5]. Consequently, under normal circumstances, CAP sequences do not occur in REM sleep.

However, sleep disorders characterized by repetitive A phases recurring at intervals < 60 s (for example, periodic REM-related sleep apnea events), can produce CAP sequences in REM sleep.

Phase A subtypes

Phase A activities can be classified into three subtypes, referring to the reciprocal proportion of EEG synchrony and EEG desynchrony, as follows:

1. Subtype A1. EEG synchrony (high-amplitude slow waves) is the predominant activity. If present, EEG desynchrony (low-amplitude fast waves) occupies < 20% of the entire phase duration.
2. Subtype A2. The EEG activity is a mixture of slow and fast rhythms with 20 - 50% of phase A occupied by EEG desynchrony.
3. Subtype A3. The EEG activity is dominated by rapid low-voltage rhythms with more than 50% of phase A occupied by EEG desynchrony.

Different subtypes of phase A can occur within the same CAP sequence (**Figure 3**).

The majority of EEG arousals occurring in NREM sleep (87%) is included within the CAP sequences and basically coincide with a phase A2 or A3 [6]. In particular, 95% of subtype A3 events and 62% of subtype A2 events meet the AASM criteria for arousals [7].

The significance of CAP

CAP sequences and NCAP periods physiologically appear during the night with a nonstochastic distribution. A detailed investigation showed that the non-triggered EEG fluctuations centered on the 20 - 40 s periodicity of CAP are involved in the subtle mechanisms that control the production and attenuation of sleep slow-wave activities [8]. Comparing spectral assessment [9, 10] and EEG visual scoring of NREM sleep in healthy individuals, the amount of slow rhythmic oscillations (spectral analysis) parallels the number of CAP cycles (visual detection), with a striking agreement between spectral power gatherings and visually scored A phases [11]. Within the sleep cycle, 90% of the A phases detected in the descending branches and 92% of the A phases detected in the troughs are subtype A1. In contrast, 64% of the A phases identified in the ascending branches are subtypes A2 (45%) and A3 (19%). These findings indicate that both slow and rapid EEG activating complexes are involved in sleep architecture [12]. Build-up and maintenance of deep sleep are guaranteed by a process of periodic EEG instability accompanied by mild neurovegetative fluctuations that accompany the downward shift from wakefulness (A1 subtypes). Conversely, the breakdown of slow-wave sleep and the introduction of REM sleep are mostly associated with desynchronized EEG activities and powerful activation of muscle and autonomic functions (A2 and A3 subtypes). Therefore, in addition to their manifold EEG features, the A phases are characterized by a non-random distribution across the night, which assumes a clear-cut periodicity during NREM sleep within the framework of CAP. For this reason, CAP is a “master clock” that determines the pace within which temporal patterns can be generated and implemented [13, 14].

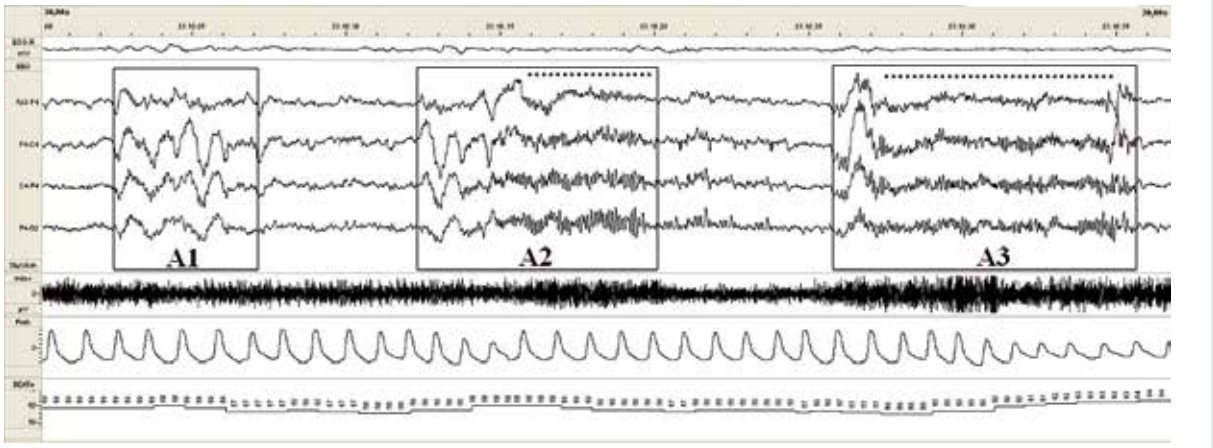

Figure 3: Three CAP A phase subtypes. The phase A subtypes delimitated by the boxes.
The dotted lines indicate the fast low-amplitude portion of the A phase.
Montage, from top to bottom: right electrooculogram (EOG-R); electroencephalogram (EEG; bipolar EEG derivations using international electrode placement Fp2–F4, F4–C4, C4–P4, P4–O2); chin electromyogram (milo); finger photoplethysmogram (Pleth); heart rate (BEAT).

Measuring CAP

EEG features are highly sensitive markers of brain development. Accordingly, during a person's life-span physiological changes can be determined by sleep analysis at different ages. CAP parameters undergo dynamic variations across natural maturation and they can be used to establish the normal ranges of sleep. Studies conducted in childhood sleep disorders, neuro-psychological disabilities, and cognitive retardation have revealed specific alterations of CAP parameters in the different pathological conditions [15, 16].

A phases

A bell-shaped curve describes the normal percentages of A1 subtypes in different age groups, conversely, a linear increase is observable in subtypes A2 and A3 from infancy to advanced age, similar to the arousal patterns during a life span [17] (**Table 1**).

Table 1: The age-related values of cyclic alternating pattern (CAP) rate and percentages of CAP A phases subtypes in healthy subjects.

Age	CAP rate (%)	A1 (%)	A2-A3 (%)
Infant	12.9	69.7	30.3
Preschool-aged children	25.9	63.2	36.8
School-aged children	33.4	84.4	15.6
Peripubertal children	62.1	85.5	14.5
Teenagers	43.4	71.3	28.7
Young adults	31.9	61.4	38.6
Middle aged subjects	37.5	62.0	38.0
Elderly persons	55.3	46.6	53.4

CAP rate

CAP rate is the most widely exploited microstructural parameter for clinical purposes. CAP rate quantifies sleep instability and it is defined by the ratio of total CAP time in NREM sleep to total NREM sleep time. CAP rate increases when sleep is disturbed by internal or external factors, and its variations reflect the perception of sleep quality, with higher values of CAP rate related with poorer sleep quality.

In normal subjects, CAP rate is characterized by a low night-to-night intraindividual variability. Across development CAP rate undergoes complex variations (**Table 1**).

CAP and the autonomic nervous system

CAP represents an integrative tool to enhance knowledge on the interaction between EEG activity and autonomic functions during sleep. CAP translates a state of instability [18] which is not only confined to the cerebral activities but reverberates upon behavioral and autonomic functions in a mutually entrained synchronized oscillation. Indeed, the CAP phenomenon provides a fluctuating web of agreement and order among EEG rhythms, blood pressure, muscle tone and heart rate [19]. On the contrary, during NCAP both arousal and autonomic functions interact in a condition of sustained stability [20]. The relation between sleep microstucture and autonomic functions has been investigated in healthy subjects by means of spectral analysis of heart rate variability during sleep [21]. A significant difference was found between CAP and NCAP conditions in the low frequency (LF) and high frequency (HF) components, which increased and decreased during CAP, respectively. Similar results were described in healthy children and adolescents [22]. By means of the product of the coherence and cross-power of the HRV and the corresponding ECG-derived respiration signal, Thomas et al. [23] showed spontaneous abrupt transitions between high- and low-frequency cardiopulmonary coupling regimes in NREM sleep. The two distinct regimes demonstrated a closer relationship with CAP compared to the standard sleep stages.

EEG arousals commonly produce autonomic nervous system activation, with extensive and rapid parasympathetic withdrawal, consistently with the increased sympathetic modulation of systemic vascular resistance and cardiac contractility [24, 25]. Although with lower intensities, even K-complexes and delta-bursts, which are not scored as conventional EEG arousals, are associated with significant changes in heart rate, consisting of tachycardia followed by bradycardia [26]. These findings indicate a reciprocal interaction between what happens upstairs (brain) and downstairs (body). Endowed with different activation properties the phase A subtypes of CAP (from A1 to A3) allow during sleep a variety of adaptive adjustments to both internal and external inputs. The relation between the different types of A phases and cardiovascular system (heart rate) have been studied in normal and pathological conditions [27, 28].

CAP in sleep disorders

Physiologic, paraphysiologic and pathologic movements during NREM sleep are always organized around a basic, stereotyped, transient activation of the brain regulated by the arousal system [29]. In addition to

being a physiological component of sleep, CAP can be triggered by different external stimuli (tactile, thermal, acoustic, painful, etc.). It has been noticed that applying separately the same arousing stimulus during the phase B of the CAP cycle, this immediately assumes the morphology of the other component; when the stimulus is delivered during phase A the inverse transformation never occurs. This stereotyped reactivity persists throughout the successive CAP phases with lack of habituation. Conversely, the same stimulus presented during NCAP causes an electrocortical response characterized by brief, high-voltage slow waves, with tendency toward progressive habituation [4, 30]. However, a strong or prolongued stimulus delivered during NCAP induces the sudden appearance of repetitive CAP cycles with the same morphology and reactive behaviour of spontaneous CAP sequences that may lead to a lighter stage shift or continue until NCAP is completely recovered.

Coherently, CAP rate increases under noise stimulation [30] or in conditions of sleep disruption such as insomnia [31 - 33], depression [34], eating disorders [35], upper airway resistance syndrome (UARS) [36], obstructive sleep apnea syndrome (OSAS) [37], periodic limb movements [38], sleep related hypermotor epilepsy (former nocturnal frontal lobe epilepsy) [29, 39 - 43], primary generalized [44] and focal lesional epilepsy [45]. In contrast, CAP rate decreases during sleep-promoting conditions such as narcolepsy [46, 47], administration of hypnotic drugs [31, 32, 48 - 50], continuous positive airway pressure (CPAP) treatment in OSAS [15, 16], and night-time recovery sleep after prolonged sleep deprivation [51]. Neurodegenerative disorders, e.g. multiple system atrophy [52], mild cognitive impairment and Alzheimer disease [53], characterized by an interrupted interaction between brain and body, are also associated with low amounts of CAP rate.

CAP is not only influenced by sleep disorders, but in turn it modulates the frequency and distribution of sleep-related events. In particular, phase A triggers bruxism [54, 55], sleepwalking [56, 57], epileptic events [58, 59], periodic limb jerks [38], and rhythmic movements during NREM sleep [60]. Conversely, phase B is associated to the repetitive respiratory events of sleep-disordered breathing, followed by the robust autonomic activation during the following phase A that restores post-apnea breathing [37].

Sleep-disordered breathing

CAP offers a favorable background for phasic and repetitive sleep-related manifestations (**Figure 4**).

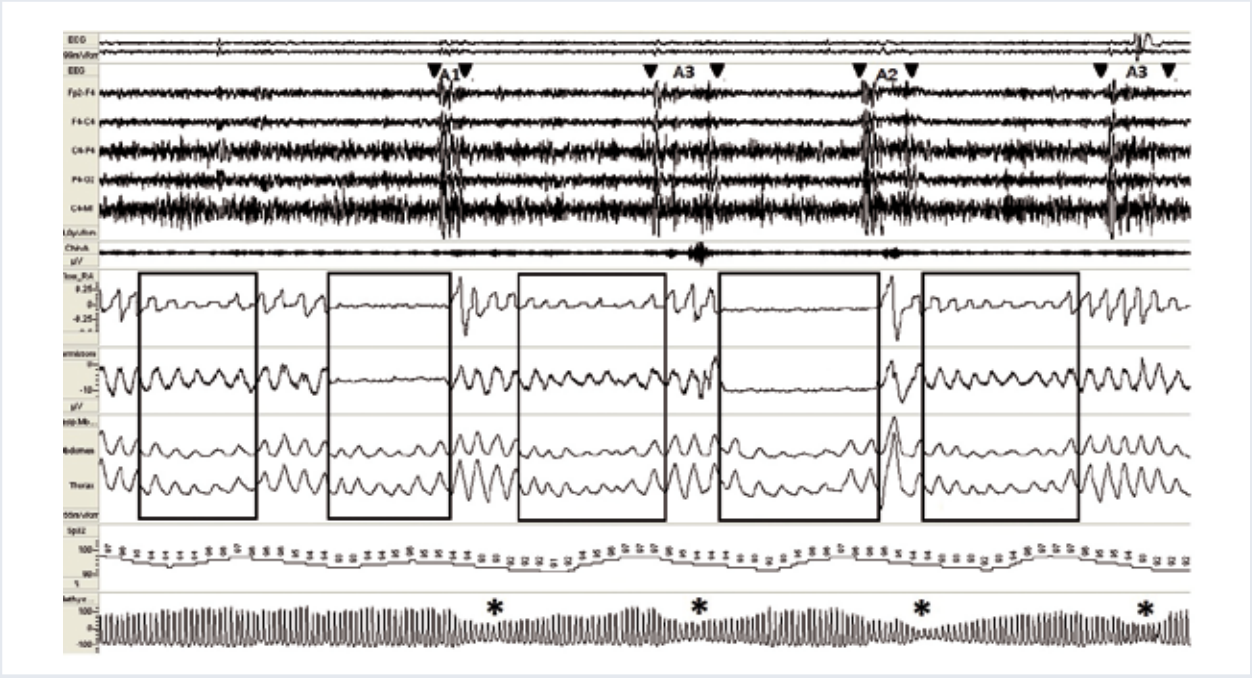

Figure 4. Modulation of EEG response to respiratory events. The figure reports examples of respiratory events (boxes) in which airway re-openings occur with different EEG patterns (delimitated by black triangles). The asterisks show the pulse wave amplitude drops. From the left to the right, a hypopnea without EEG response, an apnea with phasic delta activity (A1 subtype of CAP), a hypopnea with EEG arousal (A3 subtype of CAP), an apnea with a mixture of slow and fast rhythms (A2 subtype of CAP) and a hypopnea with EEG arousal (A3 subtype of CAP). Montage, from top to bottom: electrooculogram (EOG); electroencephalogram (EEG; bipolar EEG derivations using international electrode placement Fp2–F4, F4–C4, C4–P4, P4–O2 and monopolar derivation C4–M1); chin electromyogram (ChinA); nasal pressure airflow (flow-RA), oronasal thermal sensor (termistore), rib cage (thorax) and abdominal (abdomen) movements, and oxymetry (SpO2) finger photoplethysmogram (Pleth).

It is known that increased amounts of arousals are a regular finding in OSAS [37, 61, 62].

However, typical manifestations of secondary cortical events are also the respiratory effort-related arousals (RERAs). More specifically, RERAs are defined by obstructive upper airway flow reductions (which do not meet the criteria of apnea or hypopnea) associated with progressive negative esophageal pressure lasting at least 10 s and culminating in an arousal [63].

In the estimation of cerebral impact of respiratory events in NREM sleep, the CAP metrics offer more extensive information than AASM rules. While the arousal index was statistically similar in mild and moderate-severe OSAS patients, sleep instability, expressed by CAP time, showed a progressive enhancement from normal subjects to mild and moderate-severe OSAS patients. The moderate-severe OSAS showed a significant increase of CAP rate and A3 phases, while a normal CAP rate coexisted with a higher amount of A3 subtypes in the mild group [64].

The sleeping brain can solve respiratory challenges even without involving a cortical arousal. Conventional EEG arousals are elicitated only if thalamo-cortical structures are unsuccessful in modulating breathing or when ascending reticular volleys are necessary to re-establish respiration [65]. EEG activation also enhances the autonomic nervous function as reflected by a greater increase of heart rate during arousals. However, heart rate acceleration can be elicitated also by delta bursts and autonomic activation can occur without a simultaneous EEG arousal [21, 26].

When patients with OSAS are treated effectively with nasal continuous positive airway pressure (CPAP), the ventilatory-induced reduction of CAP rate, which correlates significantly with daytime sleepiness, is associated with a robust curtailment of subtypes A3 and a progressive recovery of the A1 percentages [15, 16].

Insomnia

Patients with chronic insomnia and normal blood pressure values lack physiological nocturnal dipping of both systolic and diastolic values. The missing reduction of blood pressure dipping is linked to brain cortical activation during sleep even without arousal rate variations [66]. These findings suggest a pivotal role of hyperarousal and increased CAP in the missed modulation of autonomic functions during sleep.

The enhancement of CAP time and CAP rate in insomniac patients is a universal feature, independent of cultural or genetic constraints. A study on a large sample of Caucasian patients with primary insomnia showed that CAP parameters consistently correlate with a poor quality of sleep and can be useful to value the effectiveness of hypnotic drugs [49]. Japanese patients affected by psychophysiologic insomnia showed similar results in a randomized crossover comparative study with placebo which demonstrated that hypnotic medication (with zolpidem) increases sleep stability with a reduction of CAP rate and improves subjective sleep perception [67].

Wavelet energy and entropy of CAP parameters allows to quantify objective differences between insomniac patients and normal controls. In particular, insomnia sleep recordings present a longer duration and a higher EEG complexity of B phases between successive A1 subtypes during the build-up phases of slow wave sleep. Moreover, A3 subtypes show an increased duration and a more irregular structure [68].

CAP analysis can be a useful tool also to understand and manage sleep state misperception in insomniac patients. Misperceptors have normal CAP rate in slow wave sleep but considerably higher amounts of CAP rate in stage 1 and 2. Compared with objective polysomnografic findings, misperceptors report lower amounts of subjective awakenings (average: 4 vs 11) separated by longer intervals. Objective awakenings are always separated by periods of superficial sleep (stages 1 and 2) endowed by high amounts of CAP. A shallow and unstable sleep between two separate objective awakenings is perceived as an experience of continuous wakefulness, creating a mismatch between PSG data and subjective interpretation [33].

Nocturnal Frontal Lobe Epilepsy

Nocturnal Frontal Lobe Epilepsy (NFLE) is characterized by a clinical spectrum of paroxysmal motor manifestations ranging from major seizures to paroxysmal arousals and minor motor events. A common feature is the onset of all episodes during NREM sleep, with different distribution with the sleep stages. Major attacks prevail in NREM3 leading abruptly to a wake condition as paroxysmal arousals and minor motor events may recur every night, sometimes several times per night, arising mainly from CAP in stage NREM2 [69]. These nocturnal manifestations cause enhanced sleep fragmentation and higher percentages of wakefulness, as well as increased amounts of CAP time, CAP rate, CAP cycles, and mean duration of CAP sequences [40, 42].

In NFLE patients, the robust enhancement of CAP is associated with a balanced enhancement of all phase A subtypes (especially phases A1), but without relevant changes of respective percentages [42]. This feature differs from other sleep disorders with high values of CAP rates, such as OSAS, where an increase of subtypes A2 and A3 and a significant reduction of phase A1, are observed [15, 16].

Antiepileptic medication reduces the amount of objectively recorded seizures and most conventional sleep measures (i.e. REM latency, wake after sleep onset, sleep efficiency) recover normal values [43]. Nevertheless, NREM sleep instability remains pathologically high (CAP rate +26% compared to controls), and is associated with

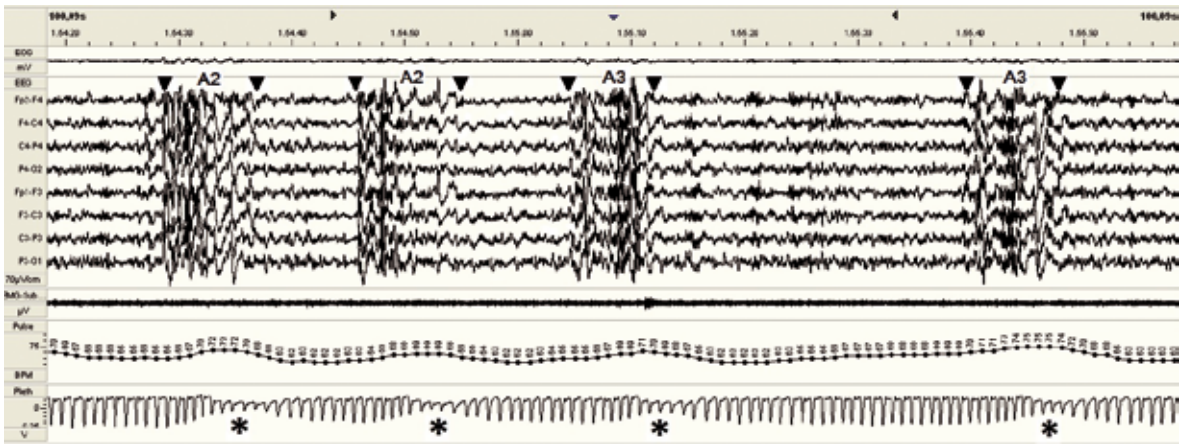

Figure 5: Vegetative instability during inter-ictal EEG abnormalities in NFLE patient.
The phase A subtypes delimitated by the black triangles. The asterisks show the pulse wave amplitude drops (markers of autonomic activation). Montage, from top to bottom: electrooculogram (EOG); electroencephalogram (EEG; bipolar EEG derivations using international electrode placement Fp2–F4, F4–C4, C4–P4, P4–O2, Fp1–F3, F3–C3, C3–P3, P3–O1); chin electromyogram (EMG-Sub); heart rate (pulse); finger photoplethysmogram (Pleth).

persistence of daytime sleepiness. The residual high NREM sleep instability is probably related to the persistence of epileptic discharges that act as internal triggers of subcontinuous arousal fluctuations during NREM sleep [43]. In turn, these arousal swings promote a gait effect on the occurrence of nocturnal motor events, especially in the form of minor motor events that could be the expression of stereotyped innate motor sequences triggered by arousal facilitation and codified by central pattern generators [70, 71].

In patients with NFLE the electrocardiographic RR interval decreases in the post epochs of all A phases suggesting an involvement of sympathetic pathways. Although the decrease in RR interval signal and the in-

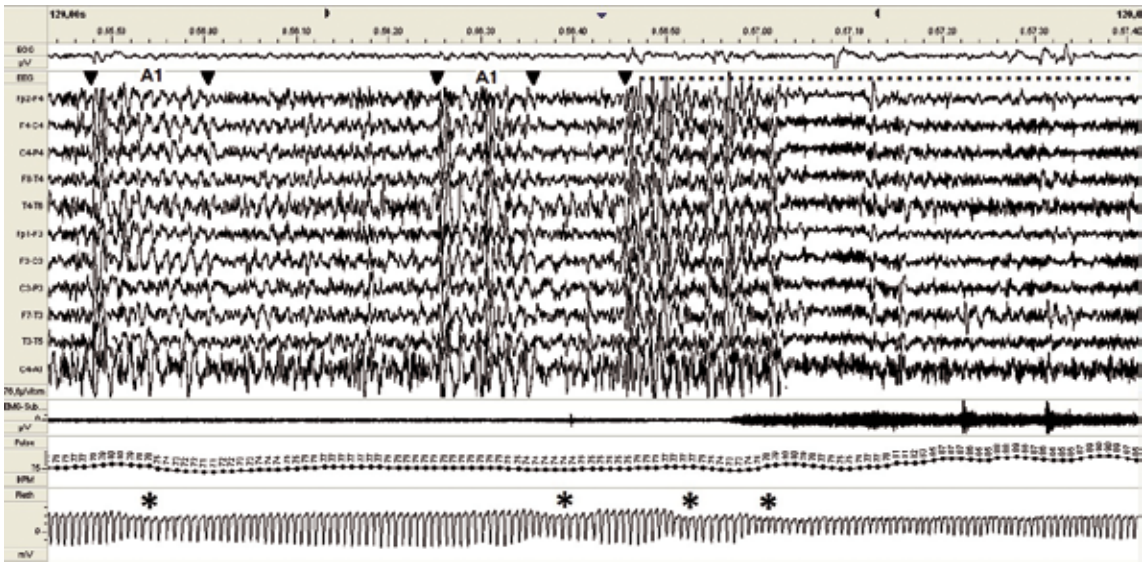

Figure 6: Paroxysmal arousals arising from cyclic alternating pattern (CAP) in stage NREM3.
The phase A subtypes delimitated by the black triangles. The asterisks show the pulse wave amplitude drops (markers of autonomic activation). The dotted lines indicate the paroxysmal arousal event.
Montage, from top to bottom: electrooculogram (EOG); electroencephalogram (EEG; bipolar EEG derivations using international electrode placement Fp2–F4, F4–C4, C4–P4, P4–O2, Fp2–F8, F8–T4, T4–T6, Fp1–F3, F3–C3, C3–P3, P3–O1, Fp1–F7, F7–T3, T3–T5 and monopolar derivation C4–A1); chin electromyogram (EMG-Sub); heart rate (Pulse); finger photoplethysmogram (Pleth).

crease in LF power during post epochs is more evident during A3 subtypes, all the phase A subtypes present a similar latency of 4 seconds in the minimum of the RR series. These findings suggest that the CAP phenomenon exerts an influence on the autonomic response, which is independent from the type of activation and from the time of sleep.

Analyzing the pulse wave amplitude (PWA) drops as a marker of autonomic activation [27], it can be observed that the persistence of inter-ictal EEG abnormalities, determines a sustained condition of vegetative instability characterized by a periodic activation of the sympathetic tone (**Figure 5**).

This means that clinical management of NFLE cannot be considered complete and satisfactory whenever intensive EEG paroxysms fuel high amounts of CAP rate.

A recently published article updates the definition of the disorder and establishes new diagnostic criteria. NFLE is now changed into SHE (Sleep-related Hypermotor Epilepsy), reflecting the evidence that the attacks are associated with sleep, that seizures may arise from extra-frontal sites and that the motor features of the seizures are highly characteristic [72]. The paper confirms that an increase of sleep instability is very common in SHE, particularly when multiple events occur in NREM sleep (**Figure 6**) [40, 42, 69].

Conclusions

Sleep is not an organ and therefore cannot be touched or physically quantified. We cannot taste, smell or take a picture of sleep because sleep is a function. A daily mandatory activity that reflects the need to rest and allows brain and body to carry out specific and non-negotiable performances.

The rules of sleep architecture demand that all parts of the apartment (brain and body) participate in a democratic interaction and reciprocal support in order to warrant survival in a condition of prolonged unconsciousness.

During CAP, sleep microstructure embraces parallel layers of EEG, motor and autonomic functions in coherent columns of activation (phase A of CAP) and deactivation (phase B of CAP) in a cyclic polyphonic image of arousal instability.

During NCAP, the entire apartment reaches a stable multi-voice configuration both upstairs (brain) and downstairs (body).

This approach overcomes the rigid limitations of conventional stage scoring and provides a more flexible neurophysiological substrate to investigate and shed light upon the brain-body coupling during sleep.

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The Sleep EEG in a State Space Model

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Summary

The EEG during sleep shows a recurrent cycling pattern of EEG activity representing alternating phases of NREM sleep and REM sleep. These dynamical changes between sleep behavioral states are only poorly described by visual sleep scoring and conventional spectral analysis of the sleep EEG. This review presents a novel model based approach for sleep EEG analysis (state space model) that allows for a more dynamical description of sleep EEG. Basic principles of mathematical modeling and EEG signal analysis are also reviewed and illustrated.

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Key words: Sleep, EEG, mathematical modeling, state space analysis

L'EEG du sommeil en « state space model »

L'EEG du sommeil présente des motifs distincts récurrents, correspondant aux différentes phases cycliques de l'activité cérébrale au cours du sommeil. Ces changements dynamiques entre les phases de sommeil sont cependant faiblement décrits par l'analyse conventionnelle de l'EEG, qu'elle soit visuelle ou spectrale. Cette revue présente un nouveau modèle mathématique d'analyse de l'EEG du sommeil (« state space model »), qui permet une meilleure description des aspects dynamiques de l'EEG. Les principes de la modélisation mathématique et de l'analyse du signal EEG sont également examinés et illustrés.

Mots clés : EEG du sommeil, modélisation mathématique, state space analysis

Das Schlaf-EEG im « state space model »

Das EEG im Schlaf zeigt wiederkehrende Muster unterschiedlicher EEG-Aktivität, welche den zyklischen Wechsel zwischen verschiedenen Schlafzuständen repräsentieren (NREM-REM-Schlafzyklus). Die konventionelle Schlaf-EEG-Analyse durch visuelles Scoring oder Spektralanalyse kann diesen dynamischen Wechsel zwischen verschiedenen Schlafstadien nur unzureichend beschreiben. Dieser Übersichtsartikel präsentiert eine neue mathematische Methode der Model-basierten EEG-Analyse, welche die dynamischen Aspekte des Schlaf-EEGs besser zur Darstellung bringt und quantifiziert. Die Grundlagen der mathematischen Modellierung und der EEG-Signalanalyse werden im Artikel ebenfalls behandelt.

Schlüsselwörter: Schlaf, EEG, mathematische Modellierung, state space analysis

Mathematical modeling

The scientific approach to a quantifiable problem can be divided in data acquisition (observations) and interpretation of observations based on assumed mechanisms or underlying rules (concepts). Phenomena and observations take place in the external or "real world", where events are observed and then translated to a "conceptual space". In the conceptual space, analysis and interpretation of events can be performed in a model based approach [1]. A model can be thought of as a simplified reflection of reality to interpret and conceptualize observations in the real world. A model in this broad sense can have many forms: e.g. a regression curve, a block diagram or a sketch on the back of an envelope. Modeled data and model-based predictions are then compared to past (real world) observations and can be tested on novel experimental observations in a train-test approach [2]. Mathematical and computational modeling has advantages in analyses with large amount of data and complex interactions within the system that do not allow for direct interpretation of experimental observations.

Usually, the first step after the implementation of a computational model is to reproduce known observations and previously observed effects. An accurate description of known phenomena is a basic condition for a comprehensive and well-designed model. However, the mere replication of known observations reveals little new knowledge and the question arises: what can be learned from mathematical modeling? As discussed in more detail in the next paragraph, a model based approach can have a two-fold impact by (i) predicting future outcome and (ii) improving the understanding of

interactions and causal relationships within a complex system.

For illustration, let's consider the example of weather forecasting. Observing blue sky (in the "real world") today, there is a fair chance that tomorrow the weather will be good, too. Technically speaking, this conclusion derives from a simple model that predicts the weather tomorrow from today's weather based on previous experience. In other words, the brain performs a Markovian analysis on the time series of rainy and sunny days [3]. This model therefore provides a (very simple) prediction of the future weather and can be compared to observations in the real world ("is it really sunny tomorrow?") and it can be verified that this model describes the weather in a short term temporal evolution accurately [4]. However, using this model we still haven't learned much about the underlying mechanisms of weather changes. If we consider a more complex climate model (e.g. modeling long term climate changes from climate data), computational approaches are needed to handle the large amount of multidimensional and interconnected data. Now, if we manage to create an accurate mathematical model of such a system, the possibility arises to tackle a mechanistic question: A model-based approach on slow cyclic climate changes ("el nino years") predicted for example, that solar activity has a predominant effect on the modeled temporal evolution of the climate [5]. Thus, this model delivered a novel hypothesis that could be tested (and verified) by direct observations and correlative analyses in later experiments. Here, the computational approach has revealed an unknown mechanism that was concealed by the overwhelming amount of data.

In summary, the ideal mathematical model describes known observations accurately, predicts future outcome and delivers novel insights in the underlying mechanisms of the observed system. But why do we need a model based approach to sleep EEG?

Sleep architecture and spectral analysis of sleep EEG

Since the introduction of the electroencephalogram (EEG) into clinical practice and neuroscience, different sleep behavioral states have been identified and characterized. From a broad perspective, humans (and most other animals) show two distinct sleep behavioral states: REM sleep and non-REM sleep [5, 6]. The EEG in non-REM sleep is characterized by slowing background activity, sleep spindles, K-complexes and in its most pronounced state by synchronized high amplitude and low frequency oscillatory activity (also referred to as slow wave sleep). REM sleep, on the other hand, shows higher frequency and lower amplitude EEG activity similar as in the waking state. The term "paradoxical sleep" has therefore been introduced by Jouvet and coworkers after the discovery of REM sleep in rodents [8]. Despite the continuous and rather unspectacular absence of consciousness during physiological sleep, the nocturnal EEG reveals a changing sequence of these patterns of cortical activity. Furthermore, physiological sleep shows a cycling pattern with alternating phases of NREM sleep and REM sleep (NREM-REM cycles) that repeat periodically approximately every 90 minutes [9]. The term sleep architecture is used to describe the alternating sequence, global structure and temporal variability of sleep behavioral states and can be summarized graphically in a hypnogram (**Figure 1A**).

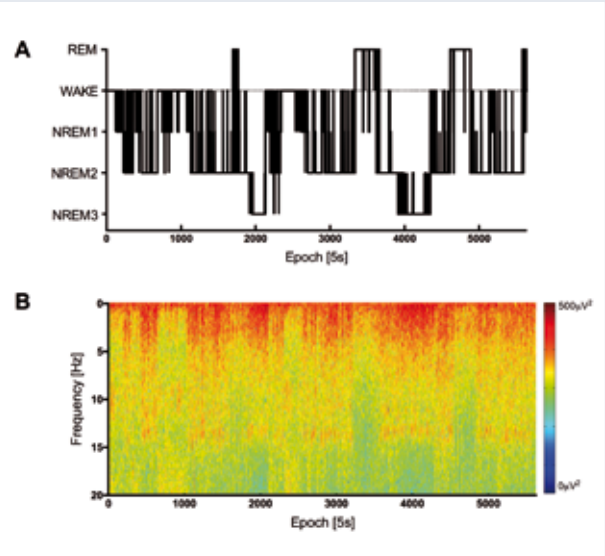

Figure 1. Conventional sleep analysis.
(A) The hypnogram represents sleep stages as a function of time. 5 s epochs are represented for each behavioral state as visually scored. NREM: non-REM sleep; REM: REM-sleep; WAKE: waking state.
(B) The time frequency spectrogram represents power spectral density of consecutive 5 s epochs as calculated by a Fourier transformation algorithm. Epochs are multiplied by a Hann window to address edge discontinuities.

Beyond the behavioral description of sleep, spectral analysis of sleep EEG provides a quantifiable approach to EEG signals. Fourier transformation is the most commonly used method for spectral decomposition of the EEG into a linear superposition of harmonic oscillations. The introduction of spectral EEG analysis dates back to the 1930ies, when Dietsch and Berger introduced quantitative frequency analysis to the human EEG [10]. Digitalization of brain signals and advances in computational methods (e.g. the introduction of fast Fourier transformation) have led to an increased use of quantitative spectral analysis to EEG in general and the sleep EEG in particular [11]. Whereas in recent years, nonlinear methods of data analysis are gaining influence in EEG data analysis in many fields, spectral analysis still has a predominant role in the analysis of sleep EEG for several reasons. Most importantly, sleep EEG – although clearly non-deterministic – can be approximat-

ed as a stationary signal and therefore analyzed by linear methods (such as Fourier transformation) on a short time scale. In other words, by applying Fourier transformation analysis on sleep EEG, we assume that the intrinsic properties of the EEG signal does not change over the time span under consideration. For example, if a 30 s epoch of slow wave sleep is divided into smaller epochs of 5 seconds length, the signal characteristics in these smaller epochs do not change significantly (i.e. this signal is "stationary"). Furthermore, spectral analysis of sleep EEG has revealed fundamental differences between sleep stages and has provided even defining properties of sleep behavioral states. For example, increased slow oscillatory EEG activity is the fundamental property of NREM sleep (**Figure 1B**). A comprehensive review of spectral methods in the analysis of sleep EEG can be found in [12].

These qualitative and quantitative approaches of sleep EEG analysis have been used extensively and describe many aspects of sleep accurately. However, these "conventional" approaches rely on manual scoring of 30 s epochs and therefore dynamical aspects of changes between sleep behavioral states are not, or only poorly described [13]. Therefore, our group recently established a model based approach [13] a model-based approach to sleep EEG emphasizing the dynamical changes between sleep behavioral states.

Introduction of the state space model

Sleep analysis by manual scoring of sleep behavioral states is the gold-standard for clinical sleep assessment. However, conventional scoring in 30 s epochs limits analysis of dynamic properties of sleep EEG. In particular, transitions between sleep behavioral states are poorly described. Conventional scoring of sleep behavioral states in 30 s epochs presents transitions between behavioral states as if they were instantaneous, though the visual appearance and spectral analysis of the EEG suggests the transitions to be gradual with intermediate patterns of EEG activity. For example, in a transition from wake into deep sleep, slow decrease of alpha activity and increase in delta power are observed at the same time indicating a "transitional state" between otherwise well-defined stable sleep stages.

To allow for a more dynamic analysis of sleep EEG a novel method of EEG analysis has been introduced in rodents [14 - 16] and was adapted for analysis of healthy and pathological sleep in humans [13, 17]. In this approach, behavioral changes are described in a 2-dimensional state space that is derived from spectral characteristics of the EEG. Importantly, by automated spectral analysis of subsequent EEG-epochs, this approach allows for a quantitative and un-biased analysis of the temporal dynamics of sleep.

A detailed explanation of the method and an accurate mathematical description can be read elsewhere [13]. Briefly, in state space EEG analysis, the spectral information of each sleep EEG epoch is transformed into a 2-dimensional space by calculating two different frequency ratios of previously determined frequency bands. First, for each 5 second epoch, the power spectral density function is estimated by calculating its fast Fourier transformation [3]. For a discrete signal of length T (defined in the period [-T/2,+T/2], it can be shown that the squared amplitude of the Fourier transform can be taken as an approximation of the power spectral density (PSD) of the original signal. The state space is then constructed by calculating two different frequency ratios from previously determined frequency bands [13]. Thus, each EEG epoch is finally represented by two real valued numbers (ratio1 and ratio2) or as a point in the corresponding 2-dimensional state space. A whole night polysomnography is therefore described as a scatterplot with clusters representing the different sleep behavioral states (**Figure 2A**). However, in contrast to conventional spectral analysis or conventional sleep scoring, transitions between and within sleep states result in trajectories in the state space.

We have adapted this model to human sleep EEG and optimized the parameters (i.e. the frequency bands) in a probabilistic Bayesian approach on sleep EEG of healthy controls. The optimized model has proven to adequately replicate manual sleep scoring by sleep experts and automated sleep state scoring on model naïve data had a mean positive predictive value of 80% to match manual scoring (which is similar to inter-expert variability) [13].

Thus, by reproducing current state-of-the-art concepts (sleep state scoring on a fixed time frame using sleep scoring rules), the state space model fulfills the first condition for a model based approach.

Novel insights using the model based approach

However, what can we learn from the model based approach to sleep EEG beyond the replication of (predefined) human scoring rules? The state space approach to the sleep EEG reveals the possibility to explore sleep in at least two new dimensions: the analysis of topographic and dynamical sleep characteristics [13].

The topography of sleep in the state space refers primarily to cluster arrangement. During consolidated phases of sleep (e.g. stable slow wave sleep), the state space model generates clusters (**Figure 2A**). This finding implicates that in consolidated sleep, the EEG has little spectral variance, because location in state space translates to spectral similarity. In other words, "clustered sleep" refers to stable and consolidated sleep EEG [13]. However, individual cluster distribution differs between individuals and can be altered in pathological sleep. For example, in a mouse model of narcolepsy, clusters of WAKE and NREM sleep were found to be less separated as compared to control animals [15]. In other

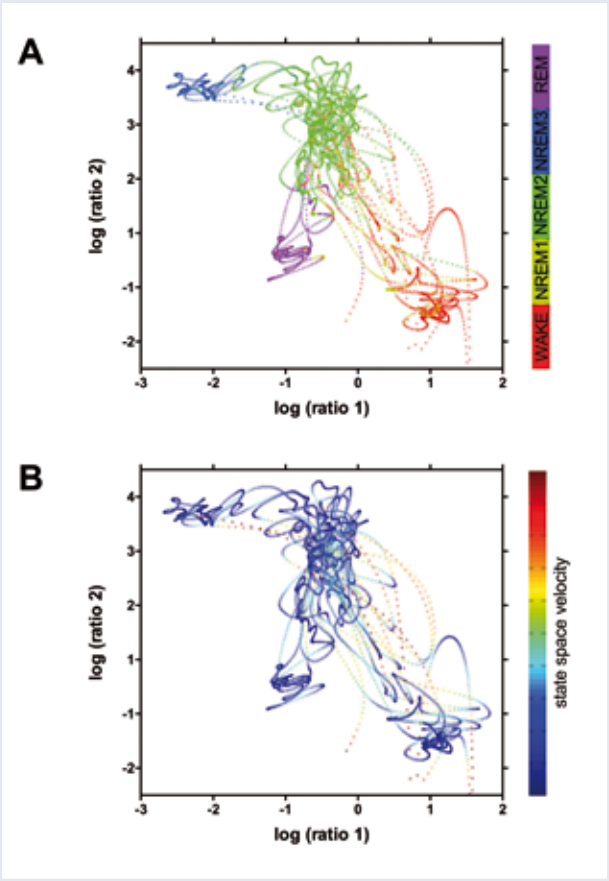

Figure 2. Sleep state clusters and state space velocity.
(A) State space analysis of a whole night polysomnography is shown for one control subject. Each 5 s EEG epoch (raw data) is represented by 2 different frequency ratios plotted on log/log axes. Ratio1=(8.6 to 19.3 Hz)/(1.0 to 10.9 Hz), Ratio2=(11.5 to 20.3 Hz)/(17.9 to 31.5 Hz). Color coding of the clusters is based on expert scoring for WAKE (red), NREM stage 1 (yellow), stage 2 (green), stage 3 (blue), and REM sleep (magenta).
(B) The same EEG trace is analyzed and color coded by state space velocity (right sided color bar, [a.u.]). Stable clusters show low velocity values with points closely spaced (darker colors), whereas transitional states show higher velocities with points widely spaced (lighter colors). Note that low velocity states form clusters in state space, whereas high velocity states correspond to transitional states.

words, the mathematical model revealed that in narcoleptic mice the difference between behavioral states is less distinct. Therefore, this finding can be interpreted as a quantification of state-boundary dysfunction in narcolepsy [9, 18].

Regarding dynamical aspects, the state space model describes transitional states as trajectories between consolidated clusters. Manual scoring of these states is often difficult and ambiguous, because transitional states typically lack a distinct spectral pattern that is required by the scoring rules. Here, the state space model provides a smooth and continuous description of transitional states (**Figure 2**). Transitional states are also characterized and quantified by state space velocity. Velocity in state space (defined as the Euclidean distance between two subsequent states divided by the time interval between these states) is a measure of sleep state stability: High velocity states correspond either to rapid transitions between states or fluctuations within a state, whereas low velocity states form consolidated clusters [13, 17]. Analyzing sleep trajectories, we found that velocities in state space in 5 s intervals increased abruptly during transitions between behavioral states [13].

The state space model in pathological sleep

Using this concept we have applied the state space model to sleep EEG of Parkinson's patients and calculated state space velocity in PD patients and controls as a measure of altered sleep dynamics. We found that Par-

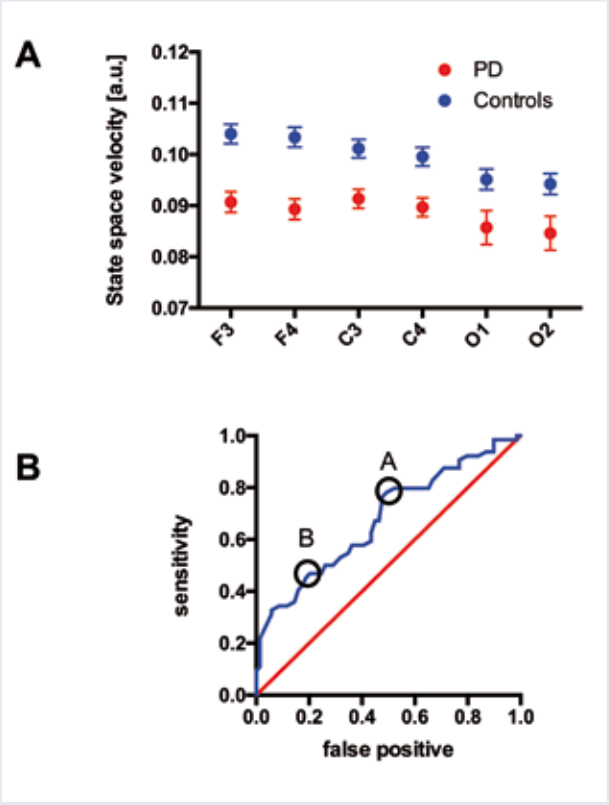

Figure 3. Reduced state space velocity (Bradysomia) in Parkinson's patients and healthy controls.
(A) At all electrodes, PD patients had significantly lower average velocities as compared to healthy controls (adapted from [17]).
(B) Receiver operating characteristic (ROC) analysis for state space velocity as a potential biomarker for PD as compared to healthy controls. Each point on the curve represents the sensitivity (true-positive rate) and false-positive rate (1 - specificity) associated with a particular value for state space velocity (range: 0.05 - 0.14, Point A: high sensitivity/low specificity. Point B: low sensitivity/high specificity.

kinson's patients have a significantly lower state space velocity as compared to controls, i.e. changes in sleep EEG are less dynamic as compared to healthy sleepers [17]. In the terminology of the state space model, Parkinson's patients are therefore "slow sleepers" and in analogy to bradykinesia or bradyphrenia in Parkinson's patients, we introduced the term bradysomnia for this novel observation (**Figure 3A**). Thus, the model-based finding created the hypothesis that sleep in Parkinson's disease is less dynamic and sleep architecture might be less modulated. Indeed, we found, that the observed reduction in state space velocity (corresponding to impaired sleep wake dynamics) correlates significantly with arousability (as measured conventionally by the arousal index) [17]. Furthermore, we found that state space velocity might serve as a diagnostic tool for Parkinson's disease (**Figure 3B**) and a receiver operating characteristic (ROC) analysis showed the feasibility of using this measure as a diagnostic tool [17]. However, this retrospective study obviously does not validate this measure in terms of predictive diagnostic values in a clinical setting. Nevertheless, this example illustrates the link between a model derived finding in the "conceptual world" (bradysomnia) with novel observations in the "real world" (reduced arousability in Parkinson's disease) and its potential use in clinical practice.

Conclusion

The sleep EEG is a complex and highly dynamic electrophysiological signal and is classically analyzed by visual scoring of 30 s epochs. Spectral analysis of sleep EEG provides a quantitative approach to sleep EEG and many aspects of sleep are well represented in this approach. However, dynamical aspects of sleep and spectral variability are only poorly described. Describing sleep EEG in a model based approach allows for an unbiased quantitative description of sleep with emphasis on the dynamical (transitional) sleep phases. The model based approach has proven to be applicable to healthy and pathological sleep in rodents and humans. Controlled studies using this model have revealed novel insights on the regulation of sleep wake dynamics. Furthermore, a model driven analysis may provide novel quantitative measures that are changed in pathological sleep and might even be used as a diagnostic tool. Future studies might include other groups with suspected state boundary dyscontrol (e.g. patients with narcolepsy). Finally, the state space approach is in principle not limited to sleep EEG. For example, dynamic changes of EEG in coma patients are difficult to estimate visually and might be quantifiable using the state space approach.

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Quantitative EEG in the Intensive Care Unit

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Summary

EEG is an important tool in diagnostic and prognostic evaluation of patients in the Intensive Care Unit. Current gold standard in EEG interpretation remains frame-by-frame visual analysis by a qualified encephalographer. This procedure requires highly trained clinicians, is very time-consuming, and often lacks good inter-rater agreement. Computer-based approaches (quantitative EEG; qEEG) allow for faster analysis of long recordings, and for more objective findings. In addition to emulate classical visual analysis, qEEG can provide additional information, which would not be easily apparent to a human observer.

This review presents different qEEG methods that have been proposed in ICU, with a particular focus on the crucial issue of outcome prediction after cardiac arrest. We conclude by discussing possible future development of qEEG in the light of the recent successes of so-called deep-learning.

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Key words: Quantitative EEG analysis, ICU, coma, prognostication

Quantitative EEG-Analyse auf der Intensivstation

Das Elektroenzephalogramm (EEG) spielt bei Patienten auf der Intensivstation sowohl zur Diagnostik als auch zur Prognoseabschätzung eine wichtige Rolle. Der Goldstandard zur Interpretation des EEGs ist zurzeit die visuelle Analyse durch einen erfahrenen Epileptologen. Diese Art der Analyse ist aber einerseits sehr zeitintensiv und setzt hochqualifizierte Kliniker voraus, andererseits bestehen dabei häufig auch deutliche inter-individuelle Unterschiede bzgl. der Interpretation des EEGs. Im Gegensatz dazu erlauben computerbasierte Ansätze (quantitative EEG-Analyse; qEEG) eine schnellere Analyse der EEG-Aufzeichnungen und lassen eine objektivere Analyse zu. Zudem kann die quantitative EEG-Analyse Aspekte hervorbringen, welche dem Menschen bei der visuellen Analyse verborgen bleiben. Die vorliegende Übersichtsarbeit beschreibt die verschiedenen Methoden der quantitativen EEG-Analyse bei Patienten auf der Intensivstation und fokussiert sich insbesondere auch auf das wichtige Thema der Prognoseabschätzung bei komatösen Patienten nach Herzstillstand. Abschliessend wird zudem auf die Entwicklungen der qEEG-Analyse im Hinblick auf die kürzlichen Erfolge von „Deep learning“ eingegangen.

Schlüsselwörter: Quantitative EEG-Analyse, Intensivstation, Koma, Prognoseabschätzung

L‘électroencéphalographie quantitative aux soins intensifs

L’électroencéphalographie reste un outil diagnostique et pronostique indispensable dans la prise en charge des patients aux soins intensifs. Le gold standard de l’interprétation de l’EEG reste l’analyse visuelle page par page par un(e) médecin spécialisé(e) en épileptologie. Ce procédé peut prendre beaucoup de temps et il reste par nature subjectif. L’analyse assistée d’un ordinateur (électroencéphalographie quantitative; EEGQ) permet une interprétation plus rapide et plus objective. En plus de faciliter l’analyse visuelle conventionnelle, l’analyse quantitative permet d’extraire des informations du tracé d’EEG que l’œil humain ne distingue pas forcément.

Cette revue présente différentes techniques d’EEGQ utilisées aux soins intensifs, en particulier pour la question essentielle de la prédiction de l’évolution clinique après arrêt cardiaque. Nous concluons par une discussion sur les possibles futurs développements de l’EEGQ dans le contexte des succès récents de l’apprentissage profond («deep learning»).

Mots clés : Electroencéphalographie quantitative, soins intensifs, coma, prédiction

Introduction

Because it directly reflects the activity of neurons, EEG plays an important role in the diagnostic and prognostic in critically ill patients, in whom the neurological examination is inevitably limited. Indications for EEG in the ICU are multiple: to rule out a non-convulsive status epilepticus in all patients with unexplained alteration in mental status, and to monitor the effect of seizure-suppressant treatment; to assist with prognostication, in particular in patients with post-hypoxic encephalopathy after cardiac arrest (CA); or to detect delayed ischemia in comatose patients with intracerebral hemorrhage in whom neurological examination is unreliable [1]. In addition, EEG can help to identify the cause of coma. Triphasic waves with sagittal (i.e. anterior-posterior or posterior-anterior) phase lag are suggestive of metabolic-toxic encephalopathy, and periodic lateralized discharges might point to limbic encephalitis. These indications have been presented previously in "Epileptologie" (see issues 4/2012 and 2/2014).

In spite of its usefulness, EEG also has several limitations. Despite the attempt to propose standardized interpretations [2], inter-rater agreement remains poor. For instance concerning prognostication after CA, the classification of EEG patterns in prognostic categories varies between studies [3 - 5]. Prognostication is further complicated by the fact that similar patterns can reflect different conditions depending on the timing of the EEG [6]. Moreover, accurate interpretation of EEG requires intensive training and long experience, and can be time-consuming. Most peripheral hospitals will not have an electroencephalographer at disposal during nights or weekends. Even in large centers, long-time recordings cannot always be interpreted in real time, which delays therapeutic interventions.

Quantitative EEG (qEEG) is a tentative approach to circumvent many of these limitations. In short, qEEG is a computer/algorithm-based analysis of EEG. Some authors distinguish the cases where some patterns are automatically recognized in the raw EEG data ("automatic detection") from cases where the EEG signal is transformed prior to automatic analysis. We will refer to both procedures as qEEG.

The aim of this contribution is to give a general overview of the possibilities and limitations of qEEG to an audience not familiar with quantitative methods. We have organized the presentation based on the goals of the different studies, namely to better characterize classical EEG patterns in order to differentiate subtypes; to serve as surrogate electroencephalographers; or, by contrast, to provide the clinicians with additional information that cannot be obtained by a human interpreter. While necessarily arbitrary, this classification has the merit to enforce a fundamental rule of all quantitative approaches: The necessity to first precisely define a question, before hoping to get a meaningful answer from an algorithm.

Quantitative characterization of classical EEG patterns

Generalized periodic discharges (GPD) are a classical EEG pattern recorded in ICU patients, especially after CA, in which case it is usually associated with an unfavorable outcome. In order to increase the diagnostic yield, several studies have tried to identify sub-types of GPD, based on the persistence of a continuous background, on the morphology and the frequency of periodic discharges. In a recent study by Ruijter et al. [7], two qEEG measures were used to assess these aspects more quantitatively in a cohort of patients with post-anoxic encephalopathy. The first qEEG measure was used to quantify the background continuity. It was defined as follows: Continuity = T_{norm}/ (T_{norm} + T_{supp}), where T_{norm} denotes the time during which the EEG amplitude exceeds 10 uV, and T_{supp} the time during which the amplitude is below this threshold. This example represents an ideal qEEG measure: The definition is unambiguous, easily implemented in an algorithm, and extremely fast to compute, so that it can be used even on-line for several days of recordings. In addition, the meaning of this formula is intuitive, because it is easily visualized. There is only one parameter, namely the threshold for defining "suppression". The authors could show that patients with good outcome had a significantly higher continuity index than patients with poor outcome.

Next, the authors wanted to characterize the frequency, periodicity, power, and similarity of discharges. These measures are again straightforward to implement, once the individual discharges have been identified. This implies that the discharges must be marked manually, or automatically with a detection algorithm prior to analysis. To this end a modified version of an algorithm originally developed for the detection of epileptic spike trains in neonatal seizure was invoked, with customized threshold values. In contrast to the continuity measure discussed above, the epileptic spike train detector however is much less intuitive, and relies on several parameters that the user has to set by hand, the effects of which are not immediately obvious. The agreement of the epileptic spike detector with visual inspection by an experienced encephalographer was less than 80%. This example illustrates the dilemma sometimes encountered with qEEG used for pattern recognition: algorithms are more error-prone, but much faster than visual analysis – a crucial point in order to analyze large amount of data. The authors could show that occurrence of status epilepticus prior to improvement to a continuous pattern was highly specific for unfavorable outcome. Other features associated with unfavorable outcome were lower discharge frequency, higher discharge power and periodicity.

In another study, the same group investigated a sub-type of burst suppression patterns, namely "burst-suppression with identical bursts" [8]. In a collective of 970 EEGs, burst-suppression with identical bursts oc-

curred only after CA (and not, for instance, during anesthesia). QEEG was used to define an objective measure: two bursts are identical if their maximum-lagged cross-correlation exceeds 0.75. Interestingly, one EEG initially selected by visual-analysis as having identical bursts was not detected by the algorithm. The reason was the short duration of the bursts compared to the time window used for cross-correlation, which illustrates the critical role of parameters in most qEEG methods.

Reactivity, namely the modification of the EEG pattern following tactile or auditory stimulus, is a classical characteristic of EEG analysis in comatose patients. Preserved reactivity is for instance associated with favorable outcome after CA [9]. In most cases, reactivity is judged solely by visual inspection. A few studies have tried to propose more objective definitions of reactivity based on quantitative measures. Noirhomme et al. [10] compared the power spectrum for one-second time-windows before and after stimulations. The EEG was considered as being reactive if at least 50% of the stimulations induced a significant modification in the peaks of the power spectrum in at least a given number of electrodes. In most cases the interpretation by the qEEG algorithm was in accordance with that of human encephalographers. In one case, present reactivity judged by visual inspection was not detected by the algorithm (and the patient survived). On the other hand in six cases the algorithms detected reactivity against the opinion of the experts: in two of these cases the algorithm was misled by burst suppression, in one case

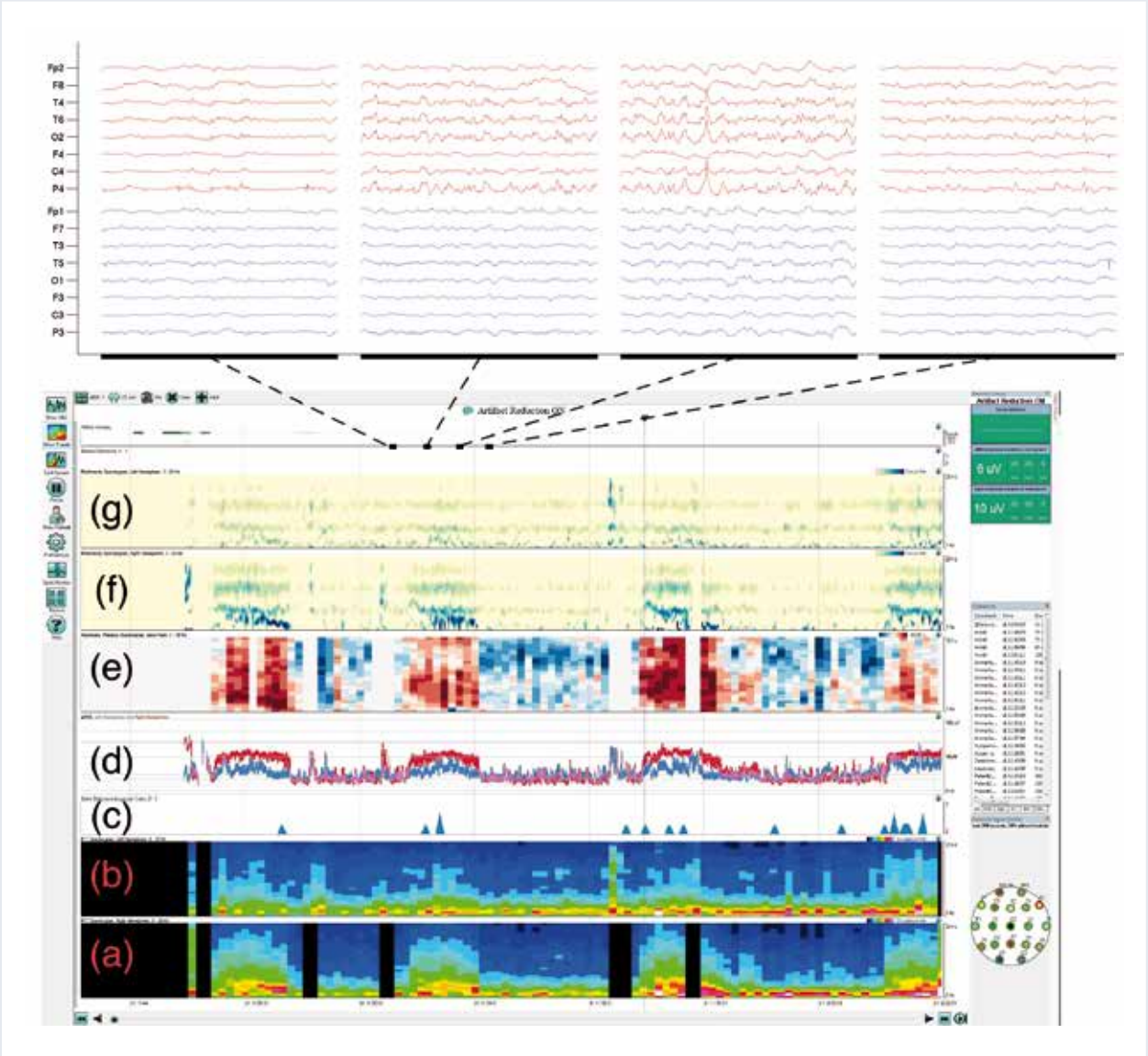

Figure 1: (Top) Focal epileptic seizure in the right hemisphere recorded in the ICU (four 5-second epochs). (Bottom) Analysis by a commercial software («Persyst») of a 30 minutes recording with 4 seizures, from the same patient. (a) Spectrogram of the right hemisphere; (b) Spectrogram of the left hemisphere; (c) Spike detection; (d) Amplitude integrated EEG (blue: left; red: right); (e) Left-right spectrogram asymmetry; (f) Rhythmicity right hemisphere; (g) Rhythmicity left hemisphere. All measures present important changes during the four seizures compared to the interictal baseline.

by epileptiform discharges. In five out of the six "false positive" cases, the patient died.

Hermans et al. [11] compared the frequency content of longer time windows, namely one minute before stimulation, and one minute during which the patient underwent a standardized set of auditive and tactile stimuli. Differences in the power spectrum before and during stimulation were judged with five different quantitative measures. Some of these measures were also tested for specific frequency bands. The results of the algorithm were not compared with clinical outcome, but with a consensus made by 3 EEG-specialists. The qEEG measures considering all frequency bands performed better than the ones restricted to specific frequency bands. Interestingly, the methods using specific frequency bands performed differently according to the channels considered. Specifically, lower frequency bands turned out to be accurate in frontal regions, intermediate frequencies in temporal and parietal regions, and faster frequencies were more reliable in occipital regions. In summary, visual inspection remains the gold standard for assessing global EEG reactivity, however, qEEG methods exist that give results in good accordance and allow for band-specific analysis.

QEEG as surrogate encephalographer

Frame-by-frame visual analysis of EEG is time-consuming, especially for long-term ICU continuous monitoring. Several qEEG measures exist that emulate EEG-interpretation by a human electroencephalographer, some of which are even available in commercial software (**Figure 1**). To this end, algorithms have been implemented to detect features that are both salient for the human visual system, and easily programmed on a computer.

One of the simplest features of an EEG signal is its amplitude. Amplitude integrated EEG (aEEG) is a continuous representation of the average peak-to-peak amplitude on a logarithmic scale. Several hours of recording can be represented on a single screen, which can be quickly scanned by clinicians to identify segments of interest that should be reviewed in detail. aEEG has been initially developed for monitoring neonates with post-hypoxic encephalopathy. It has been since then used to predict outcome after cardiac arrest [12] or to detect seizures in the ICU [13].

Another method often considered for computer-assisted EEG interpretation is frequency analysis. A rough estimation of relative power of the different frequency band is used in visual analysis to characterize the background, describe focal slowings or localized attenuations, and even to recognize seizures, which typically display a monotone decrease in frequency and concomitant increase in amplitude. Computers perform frequency analysis with a much higher precision, using for instance the so-called Fast Fourier Transform (FFT). In cases of non-stationary signals such as the ICU EEG, the recording is decomposed into different time-windows on which the FFT is repeatedly computed. The results are then displayed as an array, referred to as spectrogram, or condensed spectrum array (CSA) with time on the horizontal axis, frequency on the vertical axis, and power color-coded. Similarly to aEEG, several hours of EEG recording can be easily visualized in a single plot for electroencephalographers to identify segments of particular interest. In a study on 118 patients admitted for acute illness and undergoing continuous EEG, CSA-guided analysis was performed 4.75 times faster than classical analysis, identified all patients with seizures (though only 87% of seizures), 100% of periodic discharges, 98% of focal slowing and 100% of generalized slowing [13]. This type of analysis has also been validated for seizure detection in pediatric patients in the ICU [14], or in adults by non-EEG expert [15].

Several numerical values can be derived from the power spectrum, such as the absolute power in different frequency bands, or the ratio of power between different frequency bands. Monitoring these values has proven particularly useful in several cerebro-vascular conditions, because of the progressive decrease in dominant EEG frequency in the minutes following a decrease in cerebral blood flow [16]. This approach has been used for instance to monitor vasospasm-induced delayed ischemia after subarachnoid hemorrhage [17]. Changes in total power, in alpha/(delta + theta) power ratio, in relative alpha (i.e. alpha/all frequencies) and relative delta could detect vasospasms even before clinical or neuroradiological signs.

Sharply-contoured transients are also very salient for visual analysis, and can be detected by algorithms. An epileptic spike train detector was mentioned in the previous section; also isolated spikes can be detected. One elegant method is to use wavelet analysis. Wavelets are short oscillating functions of finite durations that can be used as alternatives to windowed FFT for frequency analysis of non-stationary signals. A few studies used sharply contoured wavelets to detect epileptic spikes: the wavelet is moved along the EEG signals, and at places where the two functions fit best, the EEG is likely to contain an epileptic spike [18]. This method has been used in patients in hypothermia after CA for prognostication, and to monitor status epilepticus [19].

Further criteria classically used by electroencephalographers interpreting the EEG of critically ill patients are continuity, regularity, and synchronization between different channels. The Cerebral Recovery Index (CRI) proposed by Tjepkema-Cloostermans et al. [20] incorporates all these features into a single value, which could assist in prediction in the early phase after CA. Five qEEG measures were used: the standard deviation of the amplitude (SD), the alpha-to-delta ratio (ADR), a measure of continuity for detection of burst-suppression patterns (the regularity, REG), a measure of the irregularity of the signal (entropy, H), and finally the co-

herence in the delta frequency band (COH) as synchronization measure. The five measures were normalized and combined in the following way: CRI = SD*(ADR + REG + H + COH)/4. The rational for multiplying SD with the average of the other four measures was that a non-zero amplitude was required for an EEG to be normal. A low CRI at 24h was associated with an unfavorable outcome, whereas high values were invariably associated with a favorable outcome. As the authors state: "the selection of features was motivated by the EEG characteristics that neurophysiologists evaluate in visual interpretation of the EEG in patients after cardiac arrest".

QEEG as a complement to visual analysis

A 19-channel EEG is a very complex pattern, many properties of which are not easily perceived by humans. Quantitative methods on the other hand can be used to extract parts of this "hidden information", with the hope that it will increase the diagnostic and prognostic yield of EEG.

Non-linear methods are a typical example of measures that humans have little intuition for. Non-linear methods are a set of methods that work well in the study of a particular type of mathematical system (described by a set of non-linear differential equations, hence the name). A detailed presentation of non-linear (vs. linear) methods in EEG analysis can be found in [21]. Here we briefly mention a few: Entropy (which was also already part of the CRI, see above) can be seen as a quantification of the unpredictability for a single event. For instance if a dice has the same number on each face (or: if the EEG voltage is constant at each sampling point), the entropy is low; if a dice has the same probability to give any number from one to six (or: if the amplitude of the EEG can take any value with equal probability), the entropy is maximal. Approximation entropy, or permutation entropy are extensions of the concept of unpredictability to sequences of events (or consecutive sampling point of an EEG channel). These information theoretical measures have been successfully used to differentiate patients in minimal-conscious-state from those in unresponsive-wakefulness-syndrom [22, 23].

Bivariate linear and non-linear measures have been used to compute the synchronization in EEG channels recorded in comatose patients between the left and right parasagittal regions, and between the fronto-central and parietal regions [24]. For each EEG, a total of 8 values were computed (four in the left-right axis, and four in the antero-posterior axis). With these 8 numbers, an EEG could be represented as a single point in an 8-dimensional space. A Bayesian classifier could distinguish regions within this multi-dimensional space containing predominantly EEG from patients who survived, or EEG from patients who deceased during their stay in the ICU. One of the measures also differed according to the etiology of coma.

Classification in a multidimensional space, as performed in the previous example, is called multivariate decoding. This approach can detect information jointly represented by several variables, another property of complex patterns that can be intractable for humans. A series of studies [25, 26] have used multivariate decoding with Bayesian classifiers on multichannel EEGs in a mismatch negativity protocol to predict outcome after CA.

Another type of multivariate information hidden in a multiple channel EEG is the topology of functional networks. Networks can be represented mathematically as graphs. A graph is defined a set of elements (called nodes), and a set of binary connections between pairs of nodes (called links). To construct a graph from a multi-channel EEG, we consider the channels as nodes of the graph, and define links with the help of bivariate measures between the channels. In a study on patients after CA [27], links were defined based on similarity in the power spectrum. The graphs of patients with unfavorable outcome were smaller (less nodes with at least one link), less connected (there were fewer links), and differed in several other graph theoretical properties (such as average shortest path length, cluster coefficient) from graphs derived from patients with normal EEG.

Feature engineering vs. feature learning

In all the methods presented above, the features (frequency, amplitude, entropy, etc.) that are analyzed and then used for interpretation of the EEG have been chosen ahead of time by the programmer, a process called feature engineering. On one hand, this approach makes perfectly sense, since neurophysiologists have acquired a vast knowledge about the meaning of specific EEG features. On the other hand, a potentially extremely useful feature, which no algorithm has been explicitly programmed to detect, might never been used. Feature learning (also called feature extraction, or representation learning) is an approach whereby an algorithm is fed with raw data, and automatically extracts relevant features. Principle component analysis (PCA) and independent component analysis (ICA) are popular feature extraction methods that decompose a signal into decorrelated or independent sub-components, respectively. PCA and ICA can be used on EEG for dimension reduction, artifact eliminations, micro-state definition or source reconstruction. In ICU-EEG analysis, they have been used to measure depths of anesthesia [28] or to identify epochs in coma EEG that should be reviewed by visual analysis [29].

Deep learning methods are a class of methods that have recently been very successful for pattern recognition [30]. In short, deep learning is a set of hierarchical methods, using multiple feature extraction and pro-

cessing units, organized in layers, whereby the output of one layer is used as input for the next layer. The connections between the different units are adapted in a way that was initially inspired by synaptic plasticity in biological neural systems, in order to optimize specific output. A few studies have already applied deep learning methods to EEG. A four-layer network was used for classification of one-second EEG epochs recorded from critically ill patients into five specified categories (epileptic spike, LPD, blink artefact, GPD/triphasic, continuous background) [31]. The deep learning network operating on raw EEG data had performances similar to other classifiers operating onto a set of 11 hand-coded EEG features (frequency band, line length, wavelet energy etc.), while being faster than the other classifiers when operating on the test set. One interesting property of deep learning networks is unsupervised learning, namely the capability of the algorithms to automatically adjust their internal parameters in order to better identify key features of a signal, without knowing what the correct classification is. This capability reduces the size of the training set needed for supervised learning (where the algorithm is informed if its decision/classification was correct or not). Unsupervised and supervised learning have been used to design a patient-specific seizure detector [32].

Conclusion and outlook

Quantitative methods can be used to analyse EEG recordings in the same way a human would, or, alternatively, to extract "hidden information" that can be used to complement visual analysis in order to increase the diagnostic and prognostic yield. With the possible exception of frequency and amplitude monitoring, these techniques have not yet been incorporated in daily clinical routine. Large prospective studies will be mandatory to confirm the benefit of qEEG in the ICU – alone or in conjunction with other modalities.

In most qEEG studies so far, human programmers have selected by-hand the features to be analyzed, and designed algorithms accordingly. While this approach might still dominate qEEG for the next years, in the future EEG analysis might rely more heavily on automatic feature extraction algorithms, in particular deep learning methods. Deep learning has already proven to be an extremely powerful analysis method and has thus been incorporated in large projects of major technology companies: Facebook uses deep learning for face recognition, Apple for voice recognition in iPhones, Google in its artificial intelligence projects, including AlphaGo, the first algorithm capable of beating professional human Go players [33]. The reasons why deep learning methods have not yet been applied more extensively to EEG analysis are multiple: lack of large enough publicly available collections of EEGs, complex classification categories (interpretation of an EEG only in clinical context) etc.

It is to be expected, however, that large companies will begin to massively invest in deep learning for analyzing diagnostic time series such as EEG. At this point, we will be facing not only technological, but also philosophical and even moral challenges. In deep learning nets, it is often no longer possible to determine which feature was most relevant for pattern recognition. As recently mentioned in an editorial in "Nature" about deep learning: "a human can hardly check its working, or verify its decision before they are followed through (...). The machine becomes an oracle; its pronouncements have to be believed" [34]. Will we entrust an algorithm with the decision to withdraw support to a comatose patient, if we cannot follow the arguments of the decision?

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Electroencephalography in the Differential Diagnosis of Dementia

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Summary

In this short clinically oriented review, the value of electroencephalography (EEG) in the diagnostic evaluation of cognitive decline is discussed, based on the recommendations of the European and Dutch guidelines. In general, an EEG with diffuse slowing with or without focal abnormalities argues for the presence of an underlying neurodegenerative illness and against subjective memory complaints or a psychiatric illness such as a depression. The value of an EEG in the differential diagnosis between the most common causes of dementia is dependent on the specific clinical problem. One of the clinical problems in which EEG has the highest yield is the distinction between the two most common dementia types, i.e. Lewy Body Dementia (DLB) and Alzheimer's Disease (AD): severe slowing of the background rhythm with a peak frequency in the theta frequency band (4 - 8 Hz) accompanied by frontal intermittent rhythmic delta activity (FIRDA) gives strong EEG support for DLB, whereas a diagnosis of AD is more likely when the EEG is normal or when only mild diffuse slowing is found. Furthermore, a normal EEG in an early onset dementia gives support for the diagnosis frontotemporal lobar degeneration. In addition, EEG is very useful when a metabolic, toxic or infectious encephalopathy is suspected. An EEG should be performed in subacute disease courses, with auto-immune encephalitis or Creutzfeldt-Jakob disease as possible causes, or when (temporal lobe) epilepsy is suspected. In conclusion, EEG is most valuable in a specific differential diagnosis together with the clinical context and other diagnostic tests. Distinct EEG patterns can then help to make one of the diagnoses a more or less likely cause of the patient's symptoms.

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Key words: Electroencephalography, dementia, memory clinic, diagnostic tool

Der Stellenwert der Elektroenzephalographie in der Differenzialdiagnose demenzieller Erkrankungen

Basierend auf den Empfehlungen der Europäischen und Niederländischen Guidelines gibt dieser kurze, klinisch orientierte Review einen Überblick über den diagnostischen Stellenwert der Elektroenzephalographie (EEG) in der Untersuchung demenzieller Erkrankungen bzw. kognitiven Abbaus. Grundsätzlich spricht eine diffuse Verlangsamung im EEG, mit oder ohne fokale Auffälligkeiten, eher für eine zugrundeliegende neurodegenerative Erkrankung als für subjektive Gedächtnisstörungen oder Psychiatrische Erkrankungen wie Depression. Die Aussagekraft des EEGs in der Unterscheidung häufiger Demenzen ist abhängig von der jeweiligen klinischen Fragestellung. Eine hohe Treffsicherheit hat das EEG in der Differenzialdiagnose einer Lewy-Body-Demenz (DLB) gegenüber einer Alzheimer Demenz (AD), zwei der häufigsten vorkommenden Demenztypen: eine schwere Verlangsamung der Grundaktivität mit einem maximalen Frequenzspektrum im Theta-Band (4 - 8 Hz), begleitet von frontalen intermittierenden rhythmischen Delta-Wellen (FIRDA) ist ein direkter Hinweis auf das Vorliegen einer DLB, wohingegen bei einer AD ein Normalbefund im EEG bzw. nur eine leichte, eher diffus verteilte Verlangsamung der Grundaktivität zu erwarten ist. Ebenso findet sich im Frühstadium einer frontotemporalen Lobärdegeneration häufig ein normales EEG. Des Weiteren bringt das EEG nützliche Zusatzinformation in vermuteten metabolischen, toxischen oder infektiösen Enzephalopathien. Die Durchführung eines EEGs ist auch hilfreich bei subakuten Krankheitsverläufen, zum Beispiel bei einer möglichen Autoimmun-Enzephalitis oder Creutzfeldt-Jakob-Erkrankung, aber auch bei Verdacht auf Temporallappen-Epilepsie. Zusammenfassend, bringt

This text is based upon a workshop during the 2016 annual meeting of the Dutch Clinical Neurophysiology Society.

das EEG gemeinsam mit den klinischen und diagnostischen Befunden wertvolle Zusatzinformationen zur Unterscheidung demenzieller Entitäten. Charakteristische EEG-Befunde können die Diagnosefindung erheblich erleichtern.

Schlüsselwörter: Elektroenzephalographie, Demenz, Memory-Klinik, diagnostische Massnahmen

L'électroencéphalographie dans le diagnostic différentiel des démences

Dans cette revue, nous discutons du rôle de l'électroencéphalographie (EEG) dans le diagnostic et l'évaluation clinique du déclin cognitif, en nous référant aux recommandations néerlandaises et européennes. D'une manière générale, un ralentissement diffus à l'EEG, avec ou sans anomalie locale, suggère la présence d'une maladie neurodégénérative sous-jacente, et parle contre un trouble subjectif de la mémoire, ou une maladie psychiatrique telle qu'une dépression. Le rôle de l'EEG dans le diagnostic différentiel des causes les plus courantes de démence dépend du contexte clinique. L'un des problèmes dans lesquels l'EEG est le plus à même de se révéler utile est la distinction parmi deux des causes les plus fréquentes de démence, c'est-à-dire la démence à corps de Lewy (DCL) et la maladie d'Alzheimer (MA): un ralentissement diffus marqué avec pic de fréquence dans la bande thêta (4 - 8 Hz), accompagné d'une activité delta rythmique intermittente au niveau frontal (FIRDA) suggère fortement une DCL, tandis que la présence d'une MA est plus probable en présence d'un EEG normal ou avec ralentissement diffus modéré. Par ailleurs, un EEG normal au cours d'une démence d'apparition précoce suggère une dégénérescence lobaire fronto-temporale. L'EEG est également très utile si une encéphalopathie métabolique, toxique ou infectieuse est suspectée. Un EEG est recommandé en cas de progression lente si une encéphalite auto-immune, une maladie de Creutzfeldt-Jakob ou une épilepsie (du lobe temporal) sont une cause possible. En résumé, l'EEG peut s'avérer très utile dans certains diagnostics différentiels, en fonction du contexte clinique et en relation avec d'autres tests. Certains tracés EEG peuvent appuyer, ou contredire certains diagnostics suspectés.

Mots clés : Electroencéphalographie, démence, clinique de la mémoire, outils diagnostiques

Background

The diagnostic evaluation of patients with cognitive complaints, both in the Netherlands and in other (European) countries, is increasingly performed in specialized memory clinics and is often organized in the form of a one-day screening. The diagnostic decision making takes place at two different levels: the establishment of the presence or absence of the syndrome diagnosis "dementia" [1]; and the diagnosis of the underlying cause of the dementia, the "nosologic diagnosis". The Dutch guideline "diagnosis and treatment of dementia" advises to perform additional assessments in the case of an established diagnosis of dementia, but with an uncertain nosologic diagnosis [2]. These may include MRI (or CT) imaging, but also electroencephalography (EEG), a lumbar puncture or positron emission tomography (PET)/single-photon emission computed tomography (SPECT) scanning.

Several memory clinics offer EEG as an additional investigation, both as a standard examination during a day screening or as an additional test after the first assessment of the medical specialist [3]. The latest Dutch guideline on dementia which was published in 2014 gives recommendations when to perform an EEG during the diagnostic evaluation of cognitive complaints (**Table 1**). Important to note is that these recommendations are in line with the European guidelines on dementia and Alzheimer's disease [4, 5]. Furthermore, it needs to be emphasized that these guidelines are aimed to give guidance to a broad range of professionals in dementia care, including primary care providers (e.g. general practitioner, specialized nurses), medical specialists (e.g. neurologists, nursing home physician specialists, geriatricians) and academic expertise centers. The first recommendation of the guideline, stating "not to perform an EEG on a routine basis during dementia diagnostic screening", therefore needs to be interpreted in this context. A large proportion of the patients with dementia are elderly subjects with memory complaints, and there will be little doubt on the underlying disease, i.e. Alzheimer's disease. This large patient group will be diagnosed and treated by the primary care physicians. The patient group that is referred to a memory clinic will therefore be a selected group, usually young, with more patients presenting with a diagnostic dilemma. In these patients, the second and third recommendation of the guidelines will more often be applicable. These recommendations state to perform an EEG when there is a suspicion for Creutzfeldt-Jakob disease or temporal epilepsy. It can also be considered when in doubt of Lewy Body Dementia and when the differential diagnosis includes a metabolic, toxic or infectious encephalopathy. In addition, an EEG can provide support for or against a diagnosis when there is doubt on the existence of the underlying cause of dementia, depending on the differential diagnostic considerations. However, to be able to assess in which differential diagnostic considerations an EEG may be useful and to be able to actually differentiate between two diagnoses, knowledge on the different EEG patterns in the specific diagnoses is highly important.

Table 1: Recommendations of Dutch guideline "diagnosis and management of dementia" (2014): electroencephalography (EEG) [2]

1. **Do not perform an EEG on a routine basis during dementia diagnostic screening**
2. **Consider to perform an EEG when in doubt of the diagnsis Lewy Body Dementia and when a metabolic/toxic/infectious encephalopathy is suspected. When the diagnosis Alzheimer's Disease is suspected, an EEG can be performed dependent on the differential diagnosis.**
3. **Perform an EEG when there is a suspicion for Creutzfeldt-Jakob disease of (temporal) epilepsy**

This overview will therefore address the following question: "what are the EEG patterns observed in the most prevalent dementia diagnoses and what is the value of EEG in several of the most common diagnostic problems in a memory clinic?". The recommendations of the guidelines will be further explained based on (recent) literature and complemented with expert opinion and illustrative cases. This text will mainly focus on straightforward visual assessment and spectral analyses of the EEG signals. Recently gained knowledge on more advanced techniques, such as functional connectivity analyses, machine learning algorithms or magneto-encephalography, will not be the focus of this review as they have no additional value in clinical practice at the moment. However, we will highlight some of these techniques as they are promising tools for clinical diagnostic use in the (near) future.

EEG patterns in dementia

Alzheimer's disease

Alzheimer's disease (AD) is the most prevalent dementia diagnosis. The a priori chance of this diagnosis in a specialized memory clinic is 30% [3]. In the typical form of AD there are disturbances in several cognitive domains, but the presence of slowly progressive episodic memory decline is most outspoken [1]. Atypical phenotypes of AD are posterior cortical atrophy, which is characterized by higher order visual disturbances, the variant of AD with logopenic aphasia as the main characteristic, and the frontal variant of AD, where the typical behavioural changes and executive dysfunction may resemble fronto-temporal lobe dementia [6, 7].

EEG findings in AD have often been described and consist of global slowing of the posterior dominant rhythm [8 - 11]. In early stages of the disease, relative theta power increases together with a decrease in relative beta power and slowing of the peak frequency (**Figure 1**). In later stages, further slowing occurs reflected by additional decreases in relative alpha power and increases in relative delta power [8]. However, in early stages of dementia the EEG can also be normal, especially in patients whose symptoms start at a later age (late onset dementia; defined as > 65 years) [12]. A normal EEG in an elderly patient with clinically evident dementia is in fact very likely due to AD. On the other hand, a normal EEG is less likely in patients with a symptom debut at a younger age (early onset; defined as < 65 years). Moreover, these younger patients have more severe diffuse and focal abnormalities than those with late onset AD. In this study, the positive predictive value of an abnormal EEG is 75 - 80% for the distinction between the total group of AD patients and cognitive normal individuals [12]. Furthermore, the severity of the EEG abnormalities is correlated with the severity of clinical symptoms and with the speed of future cognitive decline [8, 13].

In short, diffuse slowing of the EEG supports the diagnosis of AD, but a normal EEG does not exclude AD as a diagnosis. When the patient has an early onset of the cognitive symptoms, a normal EEG is less likely than when the onset is at an older age.

It is important to note however, that the value of EEG is higher in the clinical context and within a specific clinical differential diagnosis. For example, if a 70-year old man with evident cognitive disturbances including memory complaints has a normal EEG, it is more likely that the patient has AD as underlying diagnosis than dementia with Lewy Bodies, vascular dementia or Creutzfeldt-Jakob disease. Or: when a 60-year old patient with cognitive complaints and behavioural changes has a severely diffusely abnormal EEG, this argues for a diagnosis of AD with frontal characteristics and against the behavioural variant of fronto-temporal dementia. The EEG patterns in other causes of dementia are described below.

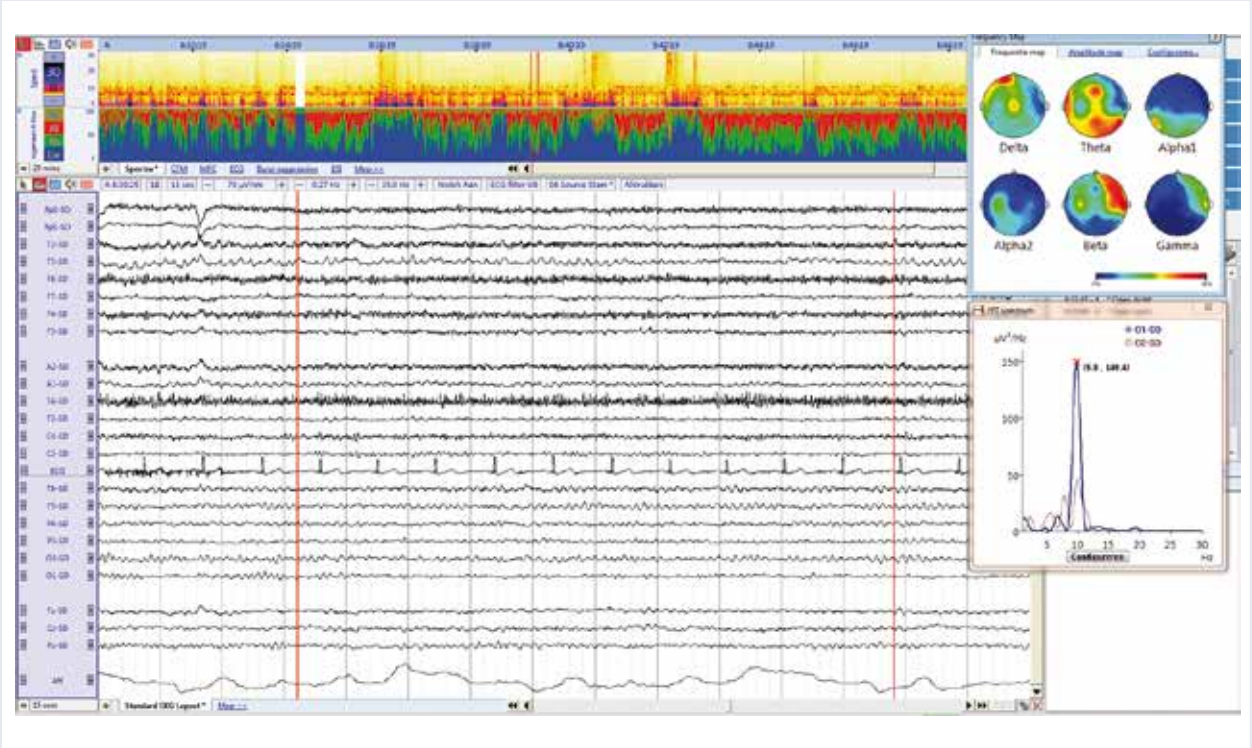

Figure 1.
A 72-year old female patient presented with behavioural changes and memory complaints. A 23-channel resting state eyes closed EEG of this patient is shown at a source derivation, accompanied with several quantitative tools (time-frequency plot, time-relative power plot, head plots with distribution of relative power in separate frequency bands, and a powerspectrum). The EEG shows a diffuse slowing of the background rhythm (peak frequency of 9.8 Hz with admixture of theta activity) and almost continuous theta-delta activity in the left more than right temporal lobes. This EEG pattern makes the diagnosis of AD more likely than FTLD.

Dementia with Lewy Bodies

Dementia with Lewy Bodies (DLB) is, behind AD, the most prevalent cause of dementia. The core symptoms of DLB are fluctuations in cognition, attention and alertness, repetitive visual hallucinations, and parkinsonism [14]. As especially in the early stages of the disease not all core symptoms may be evident, and its clinical picture often overlaps with that of AD, the distinction between the two diseases is sometimes difficult. As DLB lacks specific neuroimaging features that can support the diagnosis, EEG is the test of choice in this clinical dilemma. EEG abnormalities consisting of "prominent slow wave activity with temporal lobe transient sharp waves" are included in the diagnostic criteria of DLB as a suggestive feature [14].

Several studies have compared EEG patterns of patients with DLB and AD. In DLB, the slowing in the background rhythm is mostly more severe and more variable than in AD. Its peak frequency often falls in the theta range (13 of 18 pathology-confirmed DLB patients) and there is more admixture of delta activity in addition to theta activity than in AD [15, 16]. Besides the outspoken diffuse slowing of oscillatory activity, reactivity to eyes opening and closing is more severely affected and focal temporal abnormalities are more common. Finally, frontal intermittent rhythmic delta activity (FIRDA) has been described to be distinctive between the diagnoses as it is present in 17.2 - 33.3% of DLB patients compared to only 1.8 - 2.3% of AD patients [17, 18] (**Figure 2**). Two studies have described that the "Grand total EEG score" is a useful tool for the distinction between both diseases with a sensitivity of 72 - 79% and a specificity of 76 - 85% [17, 18]. This semi-quantitative visual scale (range 1 - 31) scores the background activity (peak frequency, diffuse slow wave activity, reactivity), focal abnormalities and paroxysmal and sharp wave activity, and is easy to apply in the clinical practice. In a large cohort of memory clinic patients, only 3% of the (not pathologically confirmed) DLB patients had a normal EEG [19].

A normal EEG or an EEG with only mild abnormalities therefore argues strongly against the diagnosis of DLB. Moderately severe diffuse slowing with focal abnormalities and the presence of FIRDA argues for the diagnosis of DLB and against AD.

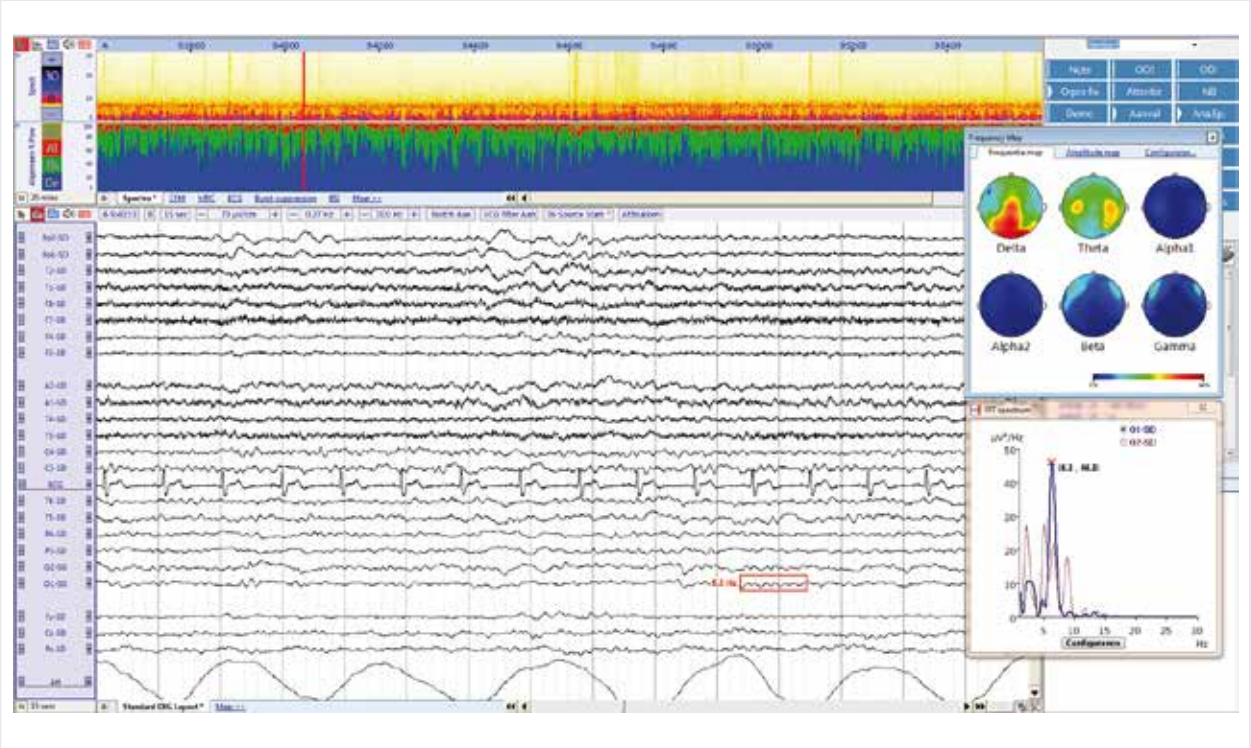

Figure 2.
A 68-year old male patient with fluctuating memory complaints and mild extrapyramidal signs that started a couple of years ago. Clinically, a DLB or AD was suspected as cause of his symptoms. His EEG (23 channels; source derivation) was moderately severely abnormal with an evident slowing of the background rhythm (peak frequency 6.3 Hz, only theta-delta activity at the posterior EEG channels) and FIRDA. This EEG pattern argues in favour of a diagnosis of DLB.

Fronto-temporal lobar degeneration

The most common form of fronto-temporal lobar degeneration (FTLD), the behavioural variant frontotemporal dementia, is characterized by dementia and in particular disturbances in behavior and executive functions [20]. It is associated with atrophy and/or hypometabolism (MRI and PET/SPECT, respectively) in the frontal/anterior temporal lobe. The other variants of FTLD, i.e. non-fluent progressive aphasia and semantic dementia, have language problems as debuting symptoms [21]. In the clinical setting, the distinction of FTLD with psychiatric illnesses or AD may be challenging.

Generally, normal or only mildly abnormal EEG patterns with preserved posterior dominant rhythm are found in patients with FTLD, even in the case of clinically evident dementia [22, 23]. In the last but one set of diagnostic criteria, a normal EEG was described as one of the supportive features of FTLD [24], but in the latest criteria EEG as a supportive test is not included anymore [20]. In a memory clinic population of a university hospital, a large majority (77%) of the FTLD patients had a normal EEG or an EEG with only mild focal abnormalities [19]. In a small group of pathology confirmed FTLD patients (n = 24), EEGs were described based on the appearance of the posterior dominant rhythm as normal, mildly abnormal (slowing of posterior dominant rhythm), or severely abnormal (sparse or absent posterior dominant rhythm, predominantly theta/delta activity). In 42% patients, a normal EEG was found, whereas only a minority (n = 2) had severe EEG abnormalities [23]. Both of the patients with severe EEG abnormalities had the temporal variant of FTLD. Furthermore, this study also found that the severity of the EEG abnormalities was associated with the severity of the dementia.

Vascular dementia

The clinical criteria for vascular dementia (VaD) comprise the diagnosis of dementia, the presence of large vessel or small vessel cerebrovascular disease demonstrated on brain imaging and a (time) relation between those features. The course of the disease may be associated with an abrupt start or with a stepwise deterioration [25].

In a study of 53 VaD patients, only a small proportion had a normal EEG (11%) and almost half of the patients with an abnormal EEG had both diffuse slowing and focal abnormalities [19]. Focal abnormalities are especially associated with large-vessel infarcts, while patients with subcortical ischaemic VaD, based on the presence of vascular white matter hyperintensities and lacunar infarcts, have an evidently diffusely slowed background pattern. In the distinction with cognitively

normal subjects, a sensitivity of 0.82 and a specificity of 1.0 was found for lower relative beta power (< 0.14) and a sensitivity of 0.94 and a specificity of 0.88 for higher relative theta power (> 0.20) [26]. However, in practice, the clinical problem is often the distinction with AD, instead of with cognitively normal subjects. As EEG patterns of VaD and AD may largely overlap and as neuro-imaging is key in the distinction between those two diagnoses, EEG does not have a central role in this specific differential diagnosis.

Creutzfeldt-Jakob disease

Sporadic Creutzfeldt-Jakob disease (CJD) is a fast progressive dementia with at least two of the following symptoms: myoclonus, visual or cerebellar symptoms, (extra-)pyramidal signs and/or akinetic mutism. For the diagnosis probable CJD at least one of the following typical abnormalities with regard to additional examination should be present: a typical EEG pattern, the presence of 14-3-3 protein in cerebrospinal fluid, or typical MRI abnormalities [27].

The typical EEG pattern in CJD consists of periodic sharp wave complexes (PSWC). These are strictly defined as generalized and/or lateralized periodic complexes with a duration of 100 - 600 ms and an inter-complex interval between 500 - 2000 ms. The inter-complex intervals of at least five consecutive complexes should differ less than 500 ms [28]. In two studies in which 214 respectively 150 pathologically confirmed CJD patients were compared to 77 respectively 56 controls (clinical suspicion of CJD but no evidence for CJD at autopsy), a relatively low sensitivity of 44 - 64% and a high specificity of 91 - 92% was found for EEG [28, 29]. The low sensitivity can be explained by the fact that in the early phases of the disease the EEG only shows non-specific diffuse slowing with occasional FIRDA. The typical PSWC is thus a relatively late sign in the disease course and becomes visible around twelve weeks after the onset of the first symptoms (see **Figure 3**). Moreover, the EEG has been shown to be positive in only a subset of CJD patients (usually molecular subtypes MM1 or MV1). In the last stages of the disease the EEG pattern changes into a low-voltage pattern and finally an iso-electric pattern. False positive findings sporadically occur in fast progressive AD, DLB, or limbic encephalitis [29, 30].

In short, an EEG with PSWC in a patient with fast progressive dementia points strongly towards CJD. When PSWC are not seen, one can consider to repeat the EEG after a couple of weeks.

Other neurological disorders

Temporal epilepsy

Temporal lobe epilepsy is an important diagnosis to consider in the differential diagnosis of dementia, as it theoretically is a treatable cause of the cognitive complaints. The Dutch and European guidelines for dementia advise to perform an EEG when (temporal lobe) epilepsy is suspected. As the clinical signs during temporal lobe seizures are often very subtle and could exist of only episodic amnesia without any other symptoms, this diagnosis can easily be missed [31, 32]. On the other hand, it is often not clear whether the epileptiform EEG discharges are the actual cause of the cognitive complaints and whether the use of anti-epileptic drugs will diminish the symptoms.

A case series described four patients with temporal lobe epilepsy as the cause of subacute cognitive complaints, mostly memory problems [31]. The EEG showed left temporal spikes in three patients and left central spikes in the fourth patient. None of them had clinically evident epileptic seizures, but in all of them the cognitive complaints disappeared or improved after treatment with carbamazepine. In a prevalence study of 1674 memory clinic patients who all underwent a 20-minute routine EEG during a diagnostic day screening, epileptiform EEG discharges were found in 42 patients (3%) [33]. These abnormalities were all focal and mainly localized in the temporal lobes. Some of these patients were already diagnosed with epilepsy, but 31 patients did not have a previous diagnosis of epilepsy. In six of these patients, a new diagnosis of epilepsy was made based on the combination of clinical symptomatology and the EEG abnormalities. Of the remaining 25 patients, a different correlate for the epileptiform discharges could be determined in 13 patients, such as the use of atypical antipsychotic drugs, migraine, a history of cerebrovascular accident, head trauma, or anoxic injury. Five patients were treated with an empirical treatment of anti-epileptic drugs based on clinical decision making, but in this retrospective study none had a more favourable course of the cognitive symptoms than untreated patients.

In addition to epilepsy as a rare cause of cognitive decline, patients with dementia have a 5 - 10 times increased risk of epilepsy compared to the general population in comparable age categories. In a large retrospective study with 1738 memory clinic patients, 63 patients (3.6%) were found to have epileptic seizures (mostly complex partial seizures) [34]. The underlying neurodegenerative diagnoses of these patients were mainly mild cognitive impairment, AD, VaD, DLB. When treated with anti-epileptic drugs, 79% of the patients had a good response on the seizures with seizure freeness or less than three seizures a year [34].

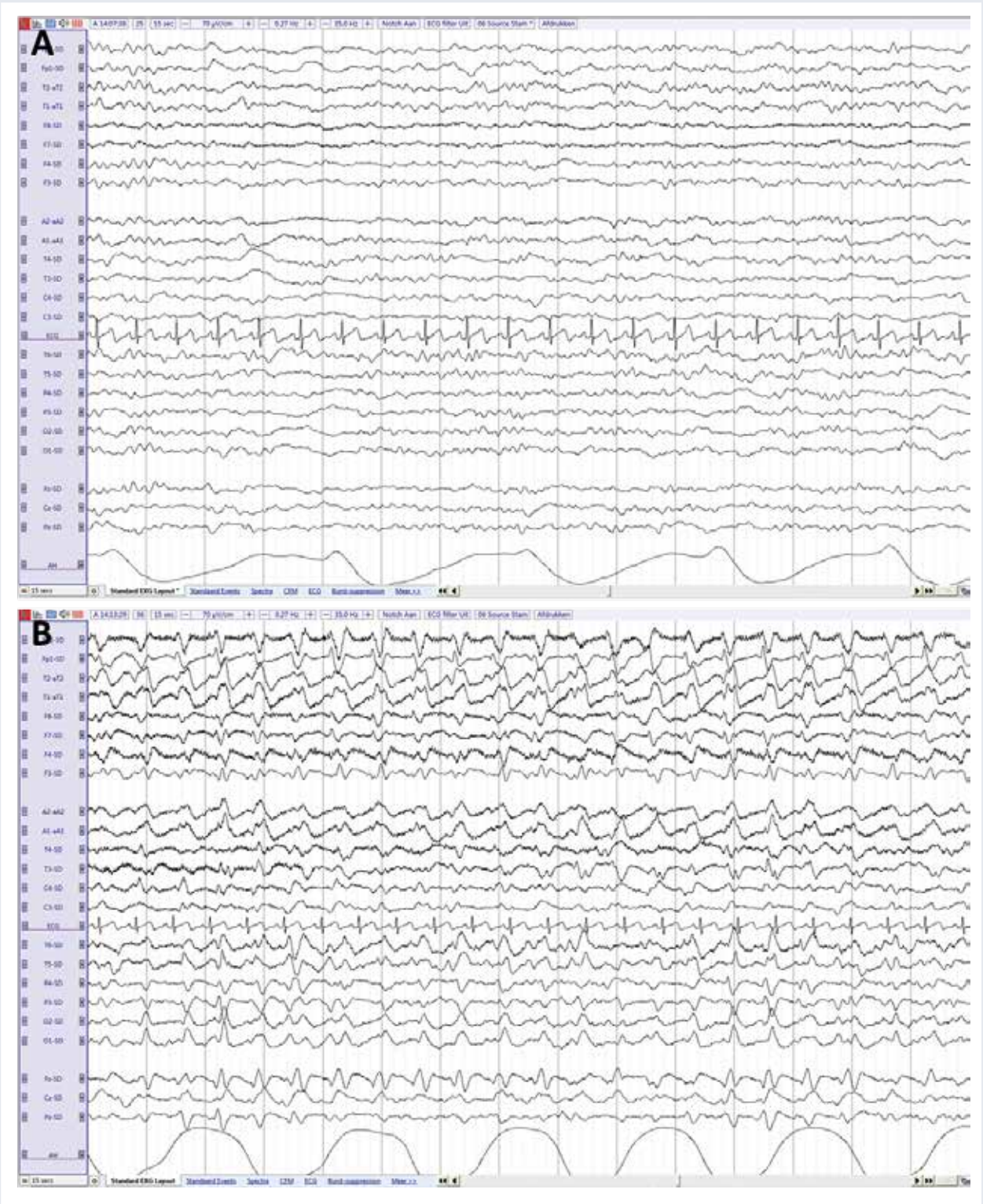

Figure 3.
A 62-year old female patient with left sided hemi-ataxia, gait problems and dysarthria that developed within 2 months. After a couple of weeks, progressive confusion and speech and swallowing problems started. The differential diagnosis consisted of auto-immune encephalitis or Creutzfeldt-Jakob disease. Her first EEG (23-channels; source derivation) shows remarkable but nonspecific diffuse slowing. A repeated EEG after one week, showed typical generalized periodic sharp wave complexes providing strong support for the diagnosis of CJD.

Taken together, temporal epilepsy is a very rare cause of cognitive disturbances, but the possible favorable reaction to anti-epileptic medication indicates that this diagnosis should be considered when there is an atypical course or when there are episodic cognitive complaints.

Auto-immune encephalitis/encephalopathy

When a patient has fast progressive cognitive disturbances that develop within days or weeks, limbic encephalitis should be included in the differential diagnosis. In a large proportion of these patients, the cognitive problems are associated with psychiatric symptoms, epileptic seizures or neurological impairment. In recent years, several antibodies have been discovered that can cause a fast progressive dementia: NMDAR, AMPAR, Caspr2, DPPX, GABAbR, LI1, Hu, GlyR [35, 36]. The findings in EEG have only been described in case reports. Although EEG findings are rather non-specific, they are mostly quite outspoken: prominent diffuse slowing (theta and delta waves) and temporal/frontal sharp waves or spikes or with lateralized periodic discharges (see **Figure 4**) [37]. In NMDA-encephalitis however, "extreme delta brushes" are a typical/pathognomonic EEG phenomenon [36, 38].

Future techniques

For clinical purposes, only visual analysis of the EEG has been used up to now, sometimes aided by quantitative spectral analyses techniques. For more than a decade however, it has been known that EEG contains more information than can be seen with "the naked eye" and new techniques have been developed to improve distinction between dementia types. A few of these new developments will be highlighted here, as they have potential to become a valuable clinical tool in memory clinic patients in the (near) future.

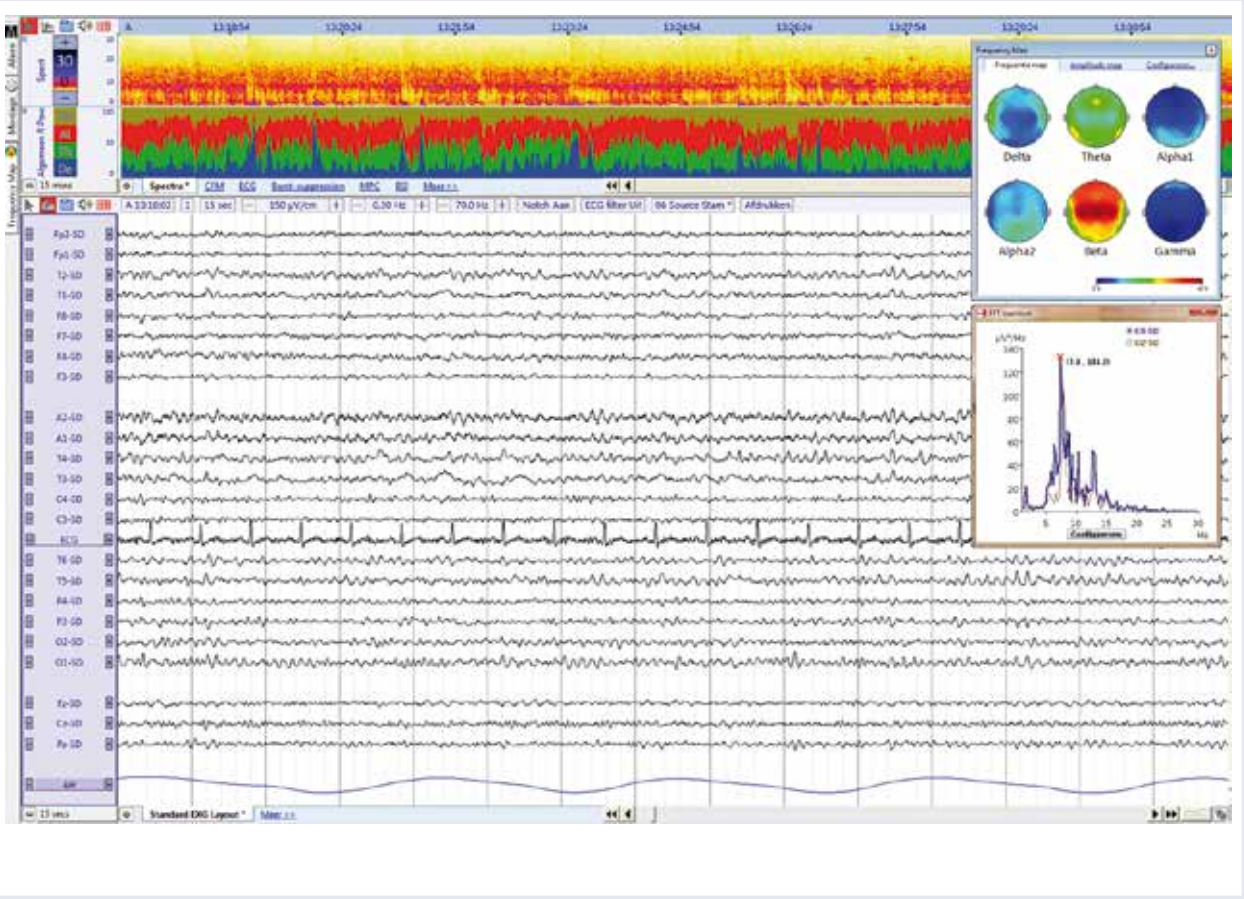

Figure 4.
A 67-year old female patient with a history of recurrent major depressive episodes, presented with fast progressive memory complaints, depressed mood, weight loss, and episodes of malaise. There was doubt on whether her symptoms were of organic or psychiatric nature. Her EEG (23-channels, source derivation) showed both diffuse slowing of the background rhythm (peak frequency 7.3 Hz) and focal abnormalities consisting of delta waves in the left more than right temporal lobes. This EEG argues strongly for an organic substrate of her complaints and further evaluation for subacute cognitive decline was performed. A diagnosis of anti-AMPA encephalitis was eventually made and the patient was treated with corticosteroids and intravenous immunoglobulins.

First, the concept that the brain is a complex network, in which cognitive processes rely on the integrity and optimal organization of dynamic communication between brain areas, has been widely accepted in recent years. A large amount of literature involving functional connectivity and network analyses has provided evidence for disruption of the underlying functional network in many distinct brain disorders including dementia [39, 40]. Moreover, several studies have compared dementia types with respect to brain connectivity and network changes and described that network disruption in the specific dementia types, e.g. AD, DLB and FTLD, can manifest itself in distinct ways [41 - 43]. Second, these network features may also be combined with simple spectral or visual EEG analyses to increase classification accuracies between patient groups. When modern algorithms referred to as machine learning techniques are used, the features that perform best at distinguishing groups are extracted in an automatic way, and these methods have yielded accuracies around 80% - 90% for the distinction between AD and healthy controls [44]. It may also be worthwhile to combine EEG with features of other modalities such as MRI or cerebrospinal fluid, to reach optimal discriminatory values [45]. Finally, magneto-encephalography (MEG) is a technique that measures the magnetic fields of the electric neuronal activity and may provide more information than standard EEG, as it has a superior spatial resolution and is able to measure oscillatory activity of deeper (subcortical) regions that are inaccessible with EEG [46, 47]. For example, signature brain regions in specific dementia types, such as the deeper lying hippocampus in AD, which cannot be measured by EEG, can be targeted specifically in MEG. This study found that the peak frequency of the hippocampal activity correlated better with cognitive test scores in AD patients than cortical activity [48]. Although MEG is not as widely available as EEG, it may give a wealth of information about the underlying pathophysiological mechanisms of the disease and is therefore a promising future diagnostic tool.

Conclusion and discussion

The studies described in this review have investigated EEG mostly as an isolated diagnostic tool in the diagnosis of underlying causes of dementia. In clinical practice however, EEG has the highest value when it is used in clinical context and in combination with other diagnostic tests [49]. EEG can then be of help in a specific differential diagnosis to make one of the diagnoses a more or less likely cause of the patient's symptoms.

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Quantitative EEG in Schizophrenia: Current State and Future Direction

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Summary

The research paradigm of biological psychiatry assumes that mental disorders can be explained by structural and functional changes in the brain. Indeed, schizophrenia patients show many biological abnormalities, including consistent EEG alterations. However, these findings are still insufficient for a clinical impact. One explanation for this gap is the heterogeneity of the disorder and the biological measurements, because, a) on the psychopathological level, widely different symptoms are summarized under the same diagnosis, and b) on a neurophysiological level, the EEG represents a mixture of brain processes that cannot easily be separated. The different EEG analysis strategies that have been used so far prove some sensitivity in finding biological abnormalities for schizophrenia. However, the models we use to decompose the mixture in the EEG have to be further elaborated, and need to be related to biologically informative definitions of the psychopathological state of patients.

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Key words: Inverse problems, modelling, psychopathological dimensions, heterogeneity

Quantitatives EEG bei Schizophrenie: Heutiger Stand und zukünftige Ausrichtung

Das Forschungsparadigma „biologische Psychiatrie“ geht davon aus, dass psychiatrische Erkrankungen durch Veränderungen in der strukturellen und funktionellen Hirnorganisation erklärt werden können. Schizophreniepatienten zeigen in der Tat eine Reihe biologischer Veränderungen, insbesondere auch EEG-Anomalitäten. Trotzdem sind diese Befunde in der Klinik wenig relevant. Eine mögliche Erklärung dafür stellt die Heterogenität der schizophrenen Erkrankung und der biologischen Daten dar, weil a) aus psychopathologischer Sichtweise dieselbe Diagnose sehr unterschiedliche Symptome beinhalten kann, und weil b) aus neurophysiologischer Perspektive das EEG aus vielen, gleichzeitig aktiven Hirnprozessen hervorgeht, welche schwierig voneinander zu trennen sind. Die verschiedenen bisher genutzten EEG-Analysemethoden können zwar biologische Veränderungen der Schizophrenie nachweisen, aber die Modelle zur Beschreibung des EEG als raumzeitliche Hirnprozesse müssen weiter verbessert und in Bezug gesetzt werden zu biologisch informativen Definitionen des psychopathologischen Status der Patienten.

Schlüsselwörter: Inverses Problem, Modellierung, psychopathologische Dimensionen, Heterogenität

EEG quantitatif dans la schizophrénie: état actuel et futures directions

Le paradigme de recherche de la psychiatrie biologique part du principe qu’un trouble mental peut être expliqué par des changements structuraux ou fonctionnels du cerveau. Les patients souffrant de schizophrénie présentent en effet de nombreuses anomalies biologiques, parmi lesquelles des modifications du tracé EEG. Cependant, ces modifications sont peu utilisées de routine en clinique. L’une des explications possibles est l’hétérogénéité des troubles cliniques ainsi que des données biologiques, puisque a) sur le plan psychopathologique, des troubles différents sont regroupés sous le même diagnostic, et b) sur le plan neurophysiologique, l’EEG résulte de nombreux processus cérébraux qu’il n’est pas aisé de séparer. Les différentes approches utilisées dans l’analyse de l’EEG ont démontré une certaine sensibilité dans la détection d’anomalies biologiques spécifiques pour la schizophrénie. Cependant, les modèles utilisés dans l’interprétation de l’EEG doivent encore être améliorés, et doivent être confrontés aux définitions biologiquement informatives sur l’état psychopathologique des patients.

Mots clés : Problème inverse, modélisation, dimensions de psychopathologie, hétérogénéité

Introduction

Biological psychiatry is a research paradigm that assumes that the causes of mental disorders can ultimately be explained by alterations in the structure and function of the brain. While there seems to be a broad consensus that there are no reasonable alternatives to this view, the promise of the paradigm, namely that the diagnosis and treatment of mental disorders receives its justification in fully biological terms, and that such a biological understanding of these disorders overcomes the current shortcomings of psychiatric diagnoses and treatments, seems yet to be unfulfilled.

An obvious explanation for this state of affairs can be given by referring to the immense complexity of the human brain in conjunction with the strong limitations of the historically and currently available methodology to assess human brain structure and function. But how far have we gotten, how useful are the existing findings today, and what may be the most reasonable next steps in this endeavor? The aim of the current article is to shed some light on these questions from the perspective of one of the oldest methods available to study an intact human brain "at work", namely the EEG, in one of the most severe mental disorders, namely schizophrenia. We will further limit the focus of this article on baseline EEG, because a) the plethora of tasks and the associated event-related potential (ERP) components that have been studied in schizophrenia cannot reasonably be accommodated within a single article, and because b) the brain's responses to any task demand do not occur in a void, but interact with the current baseline state of the brain. Alterations of baseline state are thus important candidates to causally explain alterations in task response because they precede in time, and thus potentially can modify task response.

Early visual characterization of EEG in psychiatry and pathological EEG findings

It is notable that the feasibility of EEG recordings in humans was the achievement of a psychiatrist. Hans Berger was driven by his hope for obtaining "a mirror into the brain" of his patients. Nevertheless, the primary impact of the availability of EEG measurements was in neurology, where particular, visually recognizable EEG patterns became pathognomonic for particular forms of neurological diseases, most importantly epilepsy. While there are still no pathognomonic EEG patterns of schizophrenia, there are nevertheless some important points to retain here:

- There seems to be an unspecific increase of abnormalities in the EEG of schizophrenia patients. In an overview that was assembled before quantitative EEG became the mainstream approach to EEG in schizophrenia, Itil [1] concluded that the rate of EEG abnormalities was higher in patients with schizophrenia compared to controls, and that these abnormalities were predominantly spikes and atypical sharp waves.
- Epileptic seizures may be followed by psychosis. In a recent review, Trimble and Kanner [2] concluded that up the 18% of patients that have intractable focal epilepsy may develop a postictal psychosis, but that the link between the seizures and the psychosis is often overseen because there is a characteristic delay between the seizures and the onset of the psychotic symptoms.
- Similarly, epilepsy seems to be a risk factor for psychosis. A recent systematic meta-analysis found that compared to controls, patients with epilepsy had an almost 8 times increased risk of also having a psychotic illness [3].

Quantitative spectral EEG (QEEG) for diagnosis and treatment prediction in schizophrenia

With the advent of the computational facilities to digitally record and process EEG data on a large scale, systematic efforts were made to find biomarkers of schizophrenia in quantitative spectral EEG [e.g. 1]. Already the first findings reported an increase of slow (theta and delta) power, other studies [e.g. 4] reported also a reduction of alpha-band power and increased high frequency (beta & gamma) activity. From early on, it has been argued that these effects were unlikely to be explained by medication, because they were stronger in unmedicated patients [5]. Meanwhile, the finding of increased slow wave activity has been confirmed in a meta-analysis [5], but the authors also noted that the effect sizes were moderate. Furthermore, the same group of authors concluded that there is a notable lack of effort towards using quantitative EEG as a clinical test for schizophrenia [6].

The attempts to use QEEG as a diagnostic tool for schizophrenia were complemented by efforts to characterize the EEG spectral signatures of psychoactive substances and thus obtain QEEG profiles of particular neurotransmitter systems [7]. On one side, the QEEG correlates of experimentally induced transient states of psychosis were investigated [e.g. 8 (Amphetamine), 9 (Ketamine), 10 (Ayahuasca)]. On the other side, substances known to have a therapeutic effect upon existing psychotic symptoms were systematically studied [e.g. 4, 11] with the idea to identify a "key-lock" principle. This principle assumes that a drug with a QEEG profile opposite to the abnormalities observed in a patient would also counteract the symptoms observed in the patient. This view was in part motivated by the report that the abnormalities of QEEG of schizophrenic patients would aggregate in several clusters, but that these clusters would not systematically relate to the observed psychopathology [12]. Thus, it was concluded that there may be a series of biologically rather than

clinically defined subtypes of schizophrenia that may also have different treatment needs. However, the initial hope to predict treatment response based on the combination of QEEG profiles of individual patients and particular drugs has not been fulfilled [13].

Dealing with heterogeneity

The obvious explanation for the gap between the conviction that schizophrenia has a specific biological origin, and our capacity to explain schizophrenia in biological terms is that there is heterogeneity. Something like a mean EEG spectrum, which results from a large variety of processes, in a group of subjects commonly diagnosed with schizophrenia, but showing different symptoms, may not be sufficiently informative. Importantly, heterogeneity may blur the biological image both on the psychopathological and the neurobiological level:

- On the psychopathological level, two patients may have received the same diagnosis of schizophrenia, but have little to no overlap in the individual symptoms that lead to the diagnosis. It may therefore be quite unjustified to expect finding common markers of an underlying individual biological pathophysiology [14]. In addition, complex behavior is typically explained by the activity of large scale, and distributed cognitive networks. Thus, a symptom, as it appears on the behavioral level, may result from the interaction of several, potentially differentially altered functional entities, and/or from a disintegration of the networks themselves. This entails a non-trivial, and non-unique problem of defining the "right" psychopathological system. The problem has been increasingly recognized, and met by the development of various diagnostic systems that assess psychopathology in terms that may reasonably be related to putative brain functional and structural entities [15, 16].
- On the neurophysiological level, it is equally well known that the EEG signal, at the level of any single electrode, is produced by a mixture of brain processes that are separated in space, time, spectral distribution, and thus function. This implies that also EEG data needs to be "properly" unmixed to obtain biological indices that are specific for particular functions [17]. Scalp mapping of spectral power as function of frequency band may only be a first, but insufficient step to separate different indices of brain function. Similar problems arise for other neurobiological measurements.

To link psychopathology and EEG, both the psychopathological and the biological levels of the problem thus require a separation into the "right" entities. Unfortunately, these types of "unmixing" problems cannot be solved without a priori choices from the investigators. This entails that the choices that the investigators have to make are not easily justifiable post-hoc by the data; this would lead into circular arguments. The endeavor to understand "schizophrenia" in biological terms thus seems to be bound to a time-consuming, and iterative adaptation [18] of psychopathological and neurobiological models that take into account both phenomenological and theoretical considerations.

In the following section, we will briefly review a series of particular EEG models that have been applied to data from patients with schizophrenia. We will however not further develop the part about psychopathological models of schizophrenia, since this is a) not the scope of this journal, and b) not our expertise.

Models of EEG

Inverse models

One obvious strategy to further decompose EEG signals is through modeling the data in three-dimensional brain space, because different brain regions obviously implement different, and well-known brain functions. For resting state EEG, such so-called inverse models typically try to account for a potentially broadly distributed pattern of activity, and introduce a priori assumptions about this distribution. The probably most widely used type of assumptions is that there is a certain amount of spatial smoothness in brain electric activity, i.e. neighboring regions can be expected to show similar amounts of activation [19]. The so called LORETA (low resolution electromagnetic tomography) inverse solutions have repeatedly been applied to frequency transformed EEG data of patients with schizophrenia (**Figure 1**), and localized the previously reported slow wave abnormalities primarily to the frontal cortex [20 - 23] and temporal regions that have long been suspected to be abnormal in schizophrenia [24].

Microstate models

Schizophrenia has often been claimed to resemble a disconnection syndrome [25]. At the same time, in EEG data, it has often been noted that there is a remarkable amount of organization in patterns and dynamics of the recorded scalp electric fields. In particular, it has been observed that spontaneous EEG scalp electric fields display quasi-stable configurations for periods of approximately 80 msec on average, before rapidly changing into a new configuration that again persists for a certain period of time (**Figure 2**). These quasi-stable periods have been called microstates [26]. Conceptually, it can be argued that microstates must have been generated by a network of brain regions that operate in a synchronous, non-lagged mode [27], which dovetails with theoretical considerations about puta-

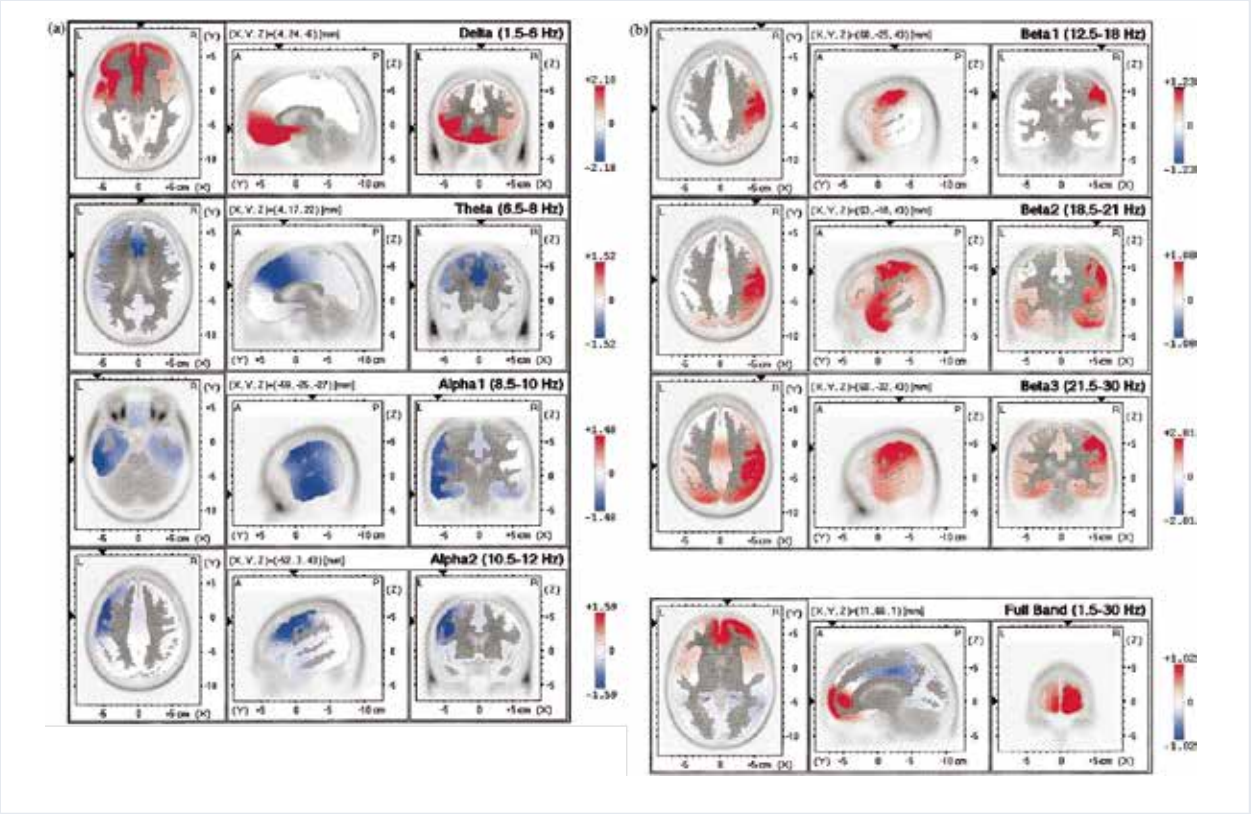

Figure 1: Images of voxel-by-voxel t-statistics of brain regional electrical activity using LORETA, for the 7 frequency bands and the "full band", and comparing 9 acute, medication-naive schizophrenic patients vs. 36 control subjects; hyperactivity (excess) in patients is indicated by red, hypoactivity (deficit) by blue. From Pascual-Marqui, Lehmann [22], with permission.

tive non-causal binding mechanisms in brain networks [28]. Furthermore, the spatial configurations of these microstates cluster well into a small set of prototypical configurations [26, 29, 30]; an observation that anticipated similar conclusions coming from fMRI data [31], however, without directly giving information about the involved regions. Later studies combining EEG and fMRI have shown that there is indeed a systematic relationship between EEG microstates and fMRI resting state networks [32].

Schizophrenia patients have been shown to have systematic abnormalities in microstate parameters. A recent meta-analysis by Rieger, Diaz Hernandez [33] concluded that a particular class of microstates related to a fronto-parietal executive control network was impaired in patients, whereas a microstate class related to saliency processing was over-active. The effect sizes were higher than those found in classical spectral analyses [5], but lower than in evoked potential studies. Furthermore, some of these microstate parameters were found to be related to the presence of auditory verbal hallucinations, and to treatment response. Diaz Hernandez and Rieger [34] have recently also been able to show that such microstate features can be systematically modified using a neurofeedback training protocol, which may offer new treatment options in the future.

Future directions

The fact that there are consistent, but not sufficiently well defined EEG abnormalities in what is called schizophrenia, and the fact that several, conceptually very different analysis strategies such as spectral analysis and microstates prove to be sensitive for schizophrenia indicates that the models we employ to decompose the EEG before it can be related to the psychopathological state of a patient are only partially suited, and need to be elaborated further. In particular, it seems to be necessary to apply methods that simultaneously do justice to the frequency domain information, to the network features of the signal and to the transient dynamics of the signal. The complex patterns of correlation of fMRI networks with EEG spectra [35] and the role of EEG phase information for these networks [36, 37] suggests that such networks are maintained through precisely timed functional interactions at various frequencies. Such a conception of brain functional networks is not yet sufficiently accommodated in the available analysis models. Another aspect that may be relevant for the understanding of the relation of baseline brain activity and the behavior and experiences of an individual is what determines the transition of one network state to the other, how these transitions are affected by external demands, and how they modify the content of our experiences and actions. Initial steps

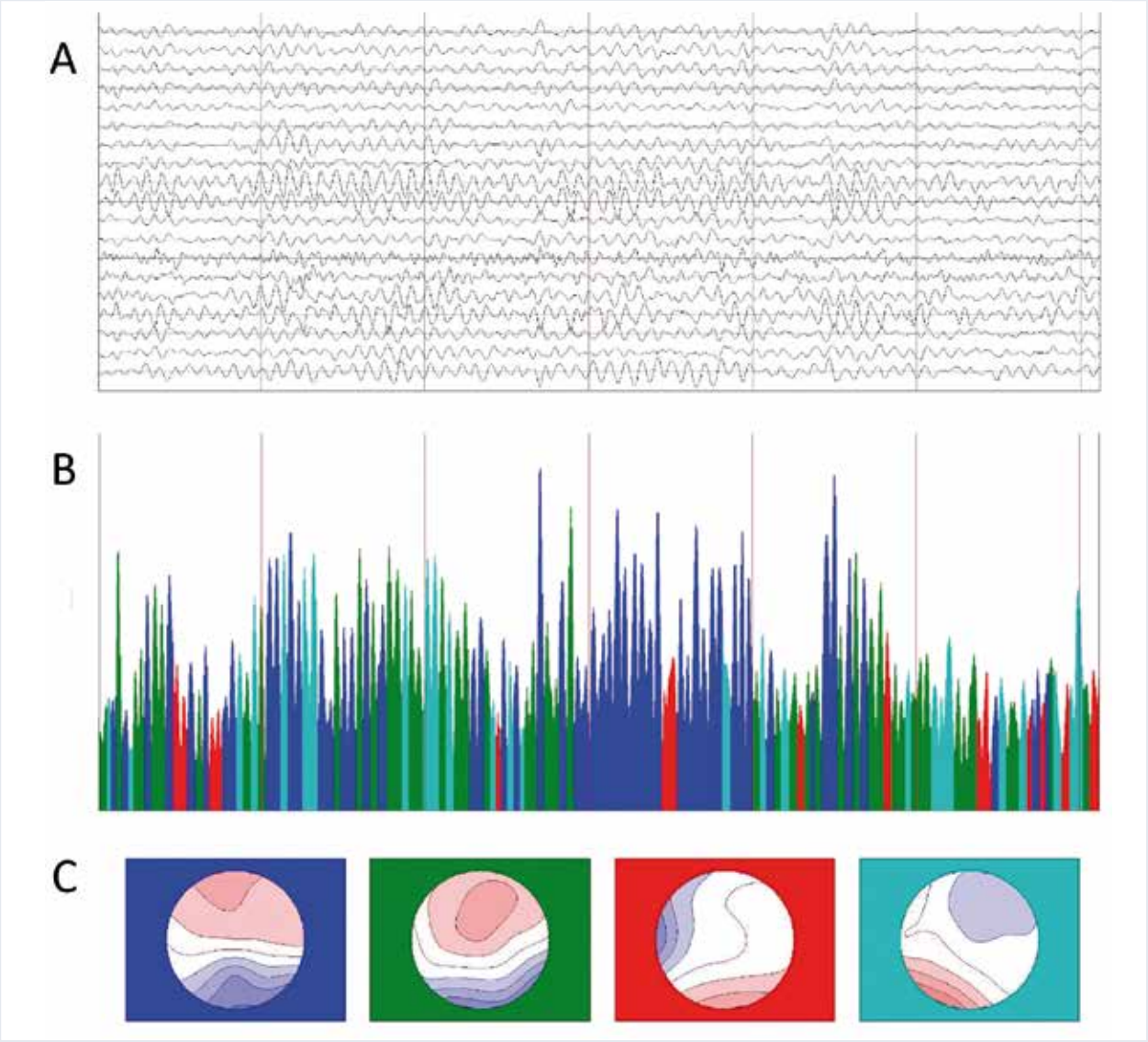

Figure 2: An example of a microstate analysis of spontaneous EEG. A: the EEG traces. B: The momentary Global Field Power (GFP), with colors indicating the assignment to one of the microstate prototype maps shown in C.

in such a direction have been done, e.g. in a recent study by Razavi and Jann [38], who showed in a simultaneous EEG-fMRI study that the EEG correlates of fMRI resting state networks were shifted to lower frequencies in their patients, indicating that the functionality of brain functional networks depends not only on the integrity of the involved nodes, but also on the proper modes of interactions among these nodes. The importance of the rules of state transitions at rest and following task demand has also been demonstrated, making a tentative causal link between at-rest abnormalities of default-mode network activity in schizophrenia patients and an insufficient recruitment of task relevant processing resources [39].

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Chemosensory Event Related Potentials

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Summary

Chemical senses comprise olfactory, gustatory and trigeminal (somatosensory) function. The chemosensory functions are still not fully understood. Consequently, the workup and understanding of chemosensory disorders is limited. With the present article we try to update the knowledge on human chemosensory disorders with a special focus on measurement of these functions.

Epileptologie 2016; 33: 189 – 196

Key words: Taste, olfaction, trigeminal

Chemosensorisch evozierte Potenziale

Die chemischen Sinne umfassen neben dem Riechen und Schmecken auch den intranasalen und intraoralen Tastsinn. Die chemischen Sinne sind in ihrer Funktionsweise noch nicht ganz verstanden. Dementsprechend fehlt es derzeit noch an profundem Wissen über Ursachen, Abklärungen und Therapie chemosensorischer Störungen. Mit der vorliegenden Arbeit möchten wir eine kurze und aktuelle Übersicht zu den menschlichen chemischen Sinnen geben, wobei ein Fokus auf die Abklärung und Messung chemosensorischer Störungen gelegt wird.

Schlüsselwörter: Riechen, Schmecken, Trigeminus

Potentiels évoqués chémosensoriels

L'odorat, la gustation et le sens trigéminal intraoral et intranasal sont considérés comme étant des sens chimiques qui nous permettent la perception de signaux moléculaires. Le fonctionnement des sens chimiques n'est pas compris en détail, et par conséquent nos connaissances de prise en charge et traitement des troubles chémosensoriels sont en encore peu établies. La revue suivante essaie de faire un résumé des connaissances cliniques, en focalisant sur la prise en charge et les mesures des fonctions chémosensoriels.

Mots clés : Goût, odorat, trigéminale

Introduction

Before focusing on chemosensory event related potentials it is necessary to explain the chemical senses which are not familiar as such in the current language. Chemical senses are defined as human senses that allow us the decoding of molecular information surrounding us in our daily life. Most of these molecular stimuli are volatile such as odors or irritants perceived through the nose but might also be non volatile such as spices or tastants perceived orally. Having said this it becomes clear that the main organs for chemosensory perception are the nose or nasal cavity and the mouth or oral cavity. A closer look shows that three sensory systems are located within these two cavities giving rise to the chemical perception of inhaled and ingested air and substances respectively. Olfaction or smell, gustation or taste and somatosensation or trigeminal perception, are the three afferent systems commonly called chemical senses. Olfactory innervation is only present in a circumscribed area within the nasal cavity, the olfactory epithelium (**Figure 1**) that comprises the olfactory neurons that project to the olfactory bulb, the very distal enlarged part of the olfactory nerve (cranial nerve I). Taste innervation is only located within the oral cavity with the most dense innervations on the tongue and soft palate. Three cranial nerves convey gustatory fibers, the intermediate, glossopharnygeal and vagal nerve (cranial nerves VIIbis, IX and X), whereas none of them is an exclusive taste nerve. All the taste fibers coming from these three nerves converge to the nucleus tractus solitarius (NTS) located within

the brain stem. In contrast, somatosensory innervation is present in the nasal and oral cavity. Irritants or spices are consecutively perceived in the oral as in the nasal cavity. The overwhelming majority of smells cannot be perceived by the oral cavity as most basic tastes such as salt or sugar cannot be perceived by the nasal cavity. This is pointed out to familiarize the reader with the fact that the oral and nasal cavities are double sensory organs that perceive smells and irritants or both (nasal cavity) and tastes and spices (oral cavity) simultaneously. As most of the stimulations encountered in daily life such as during eating and drinking are composed of multiple chemical stimuli this makes it clear that it is not always easy to separate the stimulated chemical sense and to know which of the mentioned sense have been stimulated and to which extent. The possible co-stimulation and contamination by a second chemical sensory afference is probably one of the reasons why proper chemosensory testing has been an issue for many years and still is not yet part of clinical routine testing.

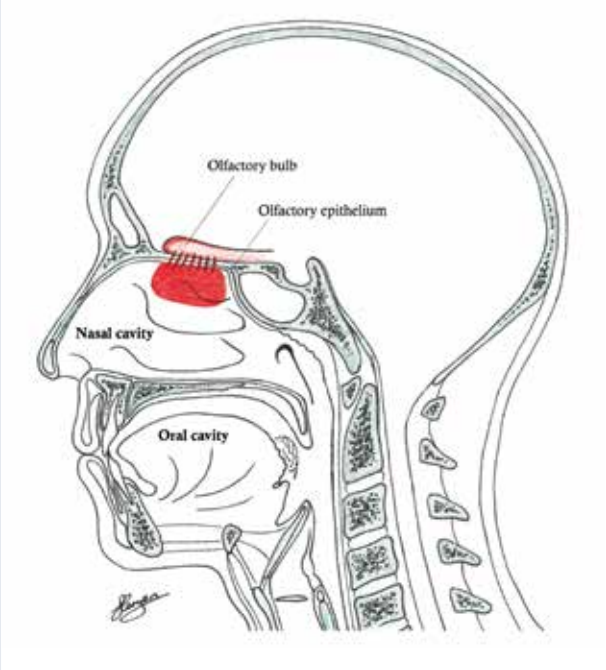

Figure 1: Sagital section showing the nasal cavity and the olfactory epithelium

Chemical Senses

The chemical senses have been explained in the introduction. What stimuli are these senses able to decode? An overview is given in **Table 1** showing that the olfactory system is the sense with the broadest range of perceivable stimuli [1]. The chemosensory trigeminal nerve is stimulated via TRP-channels that are activated by many molecular substances but also temperatures or touch. The overwhelming majority of molecules that we call odors are indeed substances that activate ORs as well as TRPs [2]. Only a handful of odors do selectively activate only ORs without doing so for TRPs [2 - 3]. Reaching a certain, high enough concentration even these "pure olfactory" substances become trigeminal meaning that they co-activate TRP channels [4]. The other way around only few substances selectively stimulate only TRPs and are consequently used for trigeminal testing. Taken together, the temperature, the molecular concentration and the kind of molecular substance are factors that influence chemosensory co-activation. It becomes thus clear, that it is crucial to stimulate the chemical sense we want to investigate in a very selective way by choosing not only the stimulus substance but also its concentration and temperature in order to avoid mixed chemosensory stimulation.

Central connections

As mentioned the three chemical senses show distinct differences in terms of receptors they express on their sensory nerve endings and the selectivity of the respective information is thus given. However, many substances are able to stimulate simultaneously receptors of the different modalities taste, smell and somatosensation. There is also considerable overlap in peripheral innervation of the oral and nasal mucosa [5 - 6] that makes it furthermore difficult to be selective in stimulation in an isolated way a given chemical sense. The three chemosensory afferencies are conducted to the central nervous system by very distinct cranial nerves. As shown in an adapted figure from Rolls [7] the sensory information of olfaction, taste and trigeminal origin converges within the central nervous system after only two or three synaptic changes. Although every sensory system has its own nerve fibers the chemosensory information of smell, taste and somatosensation becomes again, like at the peripheral level, intermingled at a cortical level [7 - 8]. This intimate relation at a central nervous level with bi- and trimodal neurons for smell, taste and touch at the level of the orbito-frontal cortex has [8] led to the assumption that the three chemical senses are differently related and influenced by each other than the other sensory modalities such as audition and vision. In contrast to compensatory mechanisms, often observed with the other non chemical senses in case of sensory loss (e.g. improvement of mechanical touch in blind) no similar mechanisms have so far been observed within the chemical senses. The current opinion is that sensory loss of one chemosensory modality often entails subclinical weakening of the other chemical senses. Numerous observations in healthy [9] and diseases [10] states seem to confirm this still controversially discussed [11] assumption.

Table 1: Overview of the chemical senses, their localization, types of receptors and the stimuli they can perceive.

	Olfaction / Smell	Somatosensation / Trigeminal Nerve	Gustation / Taste
Innervated organ	Nasal cavity	Nasal and oral cavity	Oral cavity
Receptors	Olfactory receptors (OR)	Transient Receptor Protein (TRP)-Channels	Taste Receptors (TR)
Recognition of	Unlimited number of odors	Numerous substances	Five basic tastes
	Substances stimulating only OR - Vanilla - H_2S (hydrogensulfide) - Phenylethylalcohol (rose odor)	Substances/stimuli stimulating only TRP - Acetone - Capsaicin (red pepper extract) - CO_2 (carbon dioxide) - Temperature (heat/cold) - Touch	- Sweet - Sour - Bitter - Salty - Monosodiumglutamate - MSG (Umami)
	Many substances stimulating two or all three sensory systems simultaneously (e.g menthol)		

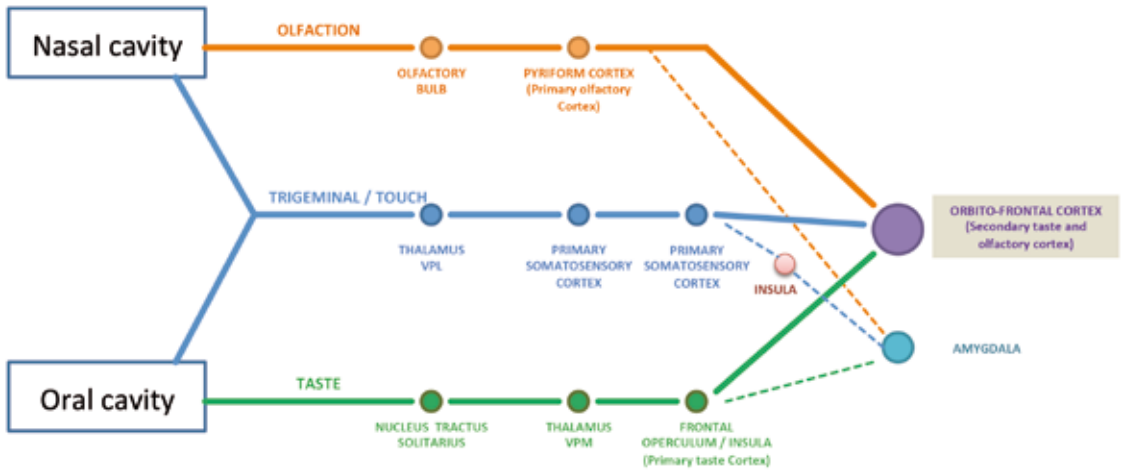

Figure 2: Overview of the pathway from periphery to central connections of the three chemical senses.

Chemosensory disorders

Compared to hearing or vision loss, the impairment or loss of any of the chemical senses has less obvious and visible consequences for social functioning. However, any of the chemical senses' dysfunctions has clear and sometimes very handicapping consequences [12] and they should no longer be considered minor or neglected senses [13]. Besides decreased pleasure for food, the lacking of meaningful odors such as that of beloved persons or situations may lead to major mood changes [14]. Besides these painful experiences of missing the olfactory world, invariably all patients concerned of olfactory loss experience hazardous events such as eating spoiled food or non detection of smoke or gas leaks [15 - 16]. This shows at which point chemical senses serve as alarm system since even persons who could adapt to the lack of one of these systems such as congenital anosmics do not really overcome the increased risk of hazardous events [17]. The three chemical senses are not equally often concerned by dysfunction. While olfactory impairment is very prevalent within the general population [18 - 19] as well as in specialized outpatient clinics [20], taste disorders are far less frequently encountered [21 - 22] and intranasal and intraoral trigeminal disorders are not well investigated and no reliable data concerning its prevalence in the general population or in specialized outpatient clinics are yet available. The most frequent types and reasons for smell, taste or trigeminal loss or impairment are summarized in **Table 2**.

Assessment of chemosensory function

Similarly to other sensory systems it has first of all to be decided if there is a qualitative or quantitative

Table 2: Overview of the most frequent causes for olfactory, gustatory or trigeminal impairment.

Chemical Senses – Disorders and Causes

	Olfaction / Smell	Somatosensation / Trigeminal Nerve	Gustation / Taste
Type of disorder	Quantitative Disorder Anosmia = total loss Hyposmia = deceased perception Qualitative Disorder Parosmia = triggered distortion Phantosmia = not triggered deceased	Quantitative Disorder Anaesthesia = total loss Hypaesthesia = deceased perception Qualitative Disorder Paraesthesia= prickling, tingling Dysaesthesia = distorted sensory perception	Quantitative Disorder Ageusia = total loss Hypogeusia = deceased perception Qualitative Disorder Parageusia= triggered taste distortion Phantogeusia = not triggered distortion
Most frequent causes of disorder	Sino-nasal disorder Posttraumatic Post-infectious (upper respiratory tract infection) Neurodegenerative diseases Toxic exposure Congenital Absence Idiopathic	Postoperative - Trauma Toxic exposure Medication side effects Neuropathies /Neurological Metabolic diseases Idiopathic / Burning mouth syndrome	Postoperative / Nerve lesions Post-infectious Medication side effects Metabolic / Systemic diseases / Deficiencies Posttraumatic Idiopathic / Burning mouth syndrome
Recovery / Treatment	Depending of the cause. Poor recovery for posttraumatic. Excellent recovery in postinfectious or sinunasal causes Treatments: - Smell training - Spontaneous recovery - Nasal steroids / Surgery	Poor knowledge on recovery of trigeminal disorders. Similar to that of peripheral nerve lesions. Relatively good spontaneous recovery depending on the extent of the nerve lesion. Treatments: - Spontaneous recovery	Depending of the cause. Overall good recovery for most causes. Treatments: - Spontaneous recovery - Treating underlying cause - Substitution of deficiencies - Medication discontinuation -Zinc

dysfunction or both are present (**Table 2**). To take audition as example, this would mean to distinguish between a tinnitus (qualitative disorder) or hearing loss (quantitative disorder). Exactly as for other sensory modalities (e.g. audition), quantitative chemosensory disorders are measurable whereas qualitative disorders are not measurable [23]. As for every sensory modality there is an objective and psychophysical way to assess chemosensory function. The psychophysical tests for olfaction, taste and trigeminal function have been developed to a very different extent and are quickly overviewed. The big advantage is the easy handling and the relative little time consumption which makes psychophysical attractive for clinical use. However, these tests often lack absolute precision and are prone to diverse biases reaching from the patient's collaboration and motivation to verbal confusion and patient's comprehension as well as the tester's experience [24]. It is therefore especially important to have objective tests such as chemosensory event related potentials to assess chemosensory function with more precision and less biases.

Psychophysical tests

Why is testing of chemical senses important at all? Different reports show that neither for olfaction nor for taste self rating of the respective sensory function by the patient is reliable [25 - 26]. It is thus mandatory to test chemosensory functions by means of tests rather than to simply ask about how people consider their chemical senses.

Olfactory tests

Olfaction has probably been the most explored of the three chemical senses with first testing procedure proposed for over a century ago [27]. It is only a little more than 30 years that a breakthrough in clinical and psychophysical olfactory evaluation has been achieved with the establishment of the forced choice identification procedure [28] and the development of easy to handle and re-usable tests which could be reproduced everywhere [29]. The last twenty years have been marked by an amazing amount of literature and increase of clinical knowledge regarding olfactory function in humans. This has been largely possible due to psychophysical tests that could be used in different populations simultaneously with multicenter studies and large sample sizes. One of these very widespread tests is the European Sniffin'Sticks test battery [30]. There are worldwide many test devices that have more or less been well validated, whereas only few tests offer available normative data based on large observations [20, 31].

Gustatory tests

Although taste as modality seems much easier since it comprises only five basic tastes the testing devices and their standardization have been a problem for many years. First efforts to have a uniform and reproducible taste testing were done by two different means. Some authors concentrated on electrical taste testing [32], which consists of application of electrical current to the tongue, eliciting a tingling and sour prickling sensation. Although there is a debate about how much of this sensation is trigeminal and how much gustatory it is meanwhile accepted that this electrogustometry reflects to some extent gustatory function [33]. The second way of testing was by means of chemical stimuli (e.g. sugar, salt) which is probably a more taste specific stimulation but a little more time consuming since all tastes need to be tested. One of the first methods was the three drop method [34] which has been replaced by the Taste Strips [35], a filter based test device that fulfils the criteria of easy to handle and reproducible gustatory testing with meanwhile normative data available [36]. However, there are still improvements possible for psychophysical taste testing since the current methods still lack the possibility to test for routine taste thresholds or umami, the fifth taste.

Somatosensory/Trigeminal tests

Measuring intranasal and intraoral trigeminal somatosensation is still difficult and only practiced in specialized Smell and Taste Clinics. It is the least well investigated chemical sense in terms of available psychophysical test devices. This is partly due to the fact that olfaction and taste seemed more interesting for the chemosensory community and avoiding trigeminal contamination was more important than trigeminal examination itself [2]. Further, for probably many years it was not clear what importance trigeminal testing might have in a clinical setting. Meanwhile things change and testing trigeminal function (intranasal and intraoral) has become very interesting especially for clinicians since it is speculated that trigeminal function largely contributes to airflow perception and feeling of nasal patency and thus well being during breathing [37]. Thus, altered trigeminal function might have direct clinical consequences with patients complaining of nasal blockage. Recent studies suggest that patients with low intranasal trigeminal function may be more prone to get nasal surgery than those with better trigeminal function [38]. To investigate such findings it is necessary to have adequate tools. It is only very recently that reliable psychophysical test devices have been developed. These tests use either pure trigeminal active substances such as CO_2 [39 - 40] or the principle of lateralization [41]. Lateralization uses the fact that molecular stimuli that trigger exclusively olfactory receptors without trigeminal co-stimulation (e.g. vanilla) cannot be localized reliably to the side of application if they are given to either the left or right nostril. The more the used substance is also stimulating trigeminal receptors (e.g menthol) this localization becomes reliable [4]. Due to this relatively new test devices and their availability, it is likely that more knowledge on intranasal trigeminal function will be coming up in the years to come.

Objective tests

Psychophysical tests for chemosensory functions have many limitations. Testing children is difficult especially below a certain age where collaboration is limited. The same is the case for malingerer's simulating a smell, taste or trigeminal loss as well as unconscious and dement patients. Further, psychophysical measures lack a certain precision to measure very subtle modifications that might be measurable with more objective tests. The need for objective test devices for chemical senses is thus obvious. Functional imaging techniques based on either functional magnetic resonance imaging (fMRI) or positron emission tomography (PET), have been used to assess objectively olfactory function [42 - 43]. Both techniques show a varying degree of spatial resolution but a rather poor temporal resolution. This is mainly due to the fact that they measure metabolic changes in the active brain regions, rather than measuring direct electric brain activity. Thus, the signal to noise ratio is very high and both techniques are not yet meaningful in the clinical workup of individual patients and both techniques are mainly used in research.

Chemosensory event related potentials

Olfaction and Trigeminal ERP

Event-related potentials are EEG-derived poly-phasic signals. They are caused by the activation of cortical neurons which generate electro-magnetic fields. As the EEG is a noisy signal which contains activity from many cortical neurons, ERP need to be extracted from this background activity. The classical approach to this problem involves averaging of individual responses to olfactory stimuli such that random activity would cancel itself out while all non-random activation would remain. Olfactory ERP (1) are direct correlates of neuronal activation, unlike the signals that are seen, for example, in functional MR imaging, (2) have an extremely high temporal resolution in the range of micro-seconds, (3) allow the investigation of the sequential processing of olfactory information, and (4) can be obtained independently of the subject's response bias.

Olfactory and trigeminal event related potentials were developed more or less at the same moment.

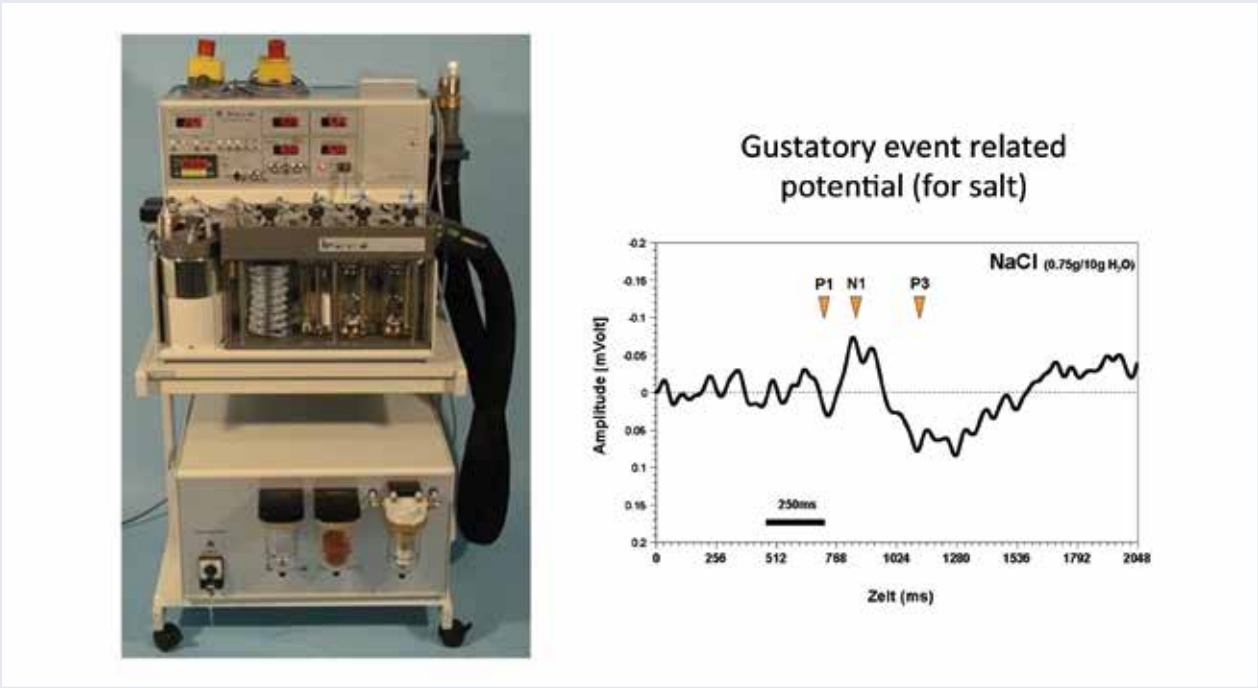

Figure 3: Olfactometer and typical curve of normal event related potential to a gustatory stimulus.

Compared to auditory and visual ERPs, which were recorded much earlier, olfaction and trigeminal ERPs have reliably been recorded only in the beginning of the 1980ies [44]. The major problem to overcome was to produce a stable stimulus that did not contain possible contamination by the other chemical sense of the nasal cavity. Since the nasal cavity perceives odors and somatosensation, a simple odor puff applied into the nose would stimulate olfactory nerves but the sudden airflow change (puff) would also produce a trigeminal/touch response which would then add some somatosensory response. The solution was brought up by Kobal who developed an olfactometer that made it possible to produce an olfactory or trigeminal stimulus that is embedded in a constant airflow of constant humidity and temperature [44]. Based on a valve system built into the nosepiece of the olfactometer, it is possible to change from a trigeminal to an odor stimulus within less than 50 ms. The stimulus for each modality is specific with trigeminal event related potentials being generated with CO2 as stimulus and olfactory ERPs generated with H2S, vanilla or rose odor (Phenylethylalcohol). The olfactometer is unfortunately and still nowadays not a small and easy to transport box but resembles middle size lab equipment (**Figure 3**) and measurements are relatively time consuming. However, in contrast to fMRI and PET CT, the trigeminal and olfactory event related potentials have found their way into clinical workup. Olfactometers are still quite expensive and their use is currently not as user-friendly as this is known from other electronic products. As consequence olfactory and trigeminal potentials are mainly used in specialized Smell and Taste Clinics and for special mostly assurance and expertise questions. Regardless of the restricted routine use in clinics, olfactory and trigeminal event related potentials have helped to understand many aspects of these two chemical senses [45]. Particularly the exact interaction and mutual interaction between olfaction and trigeminal stimuli as well as the precise measuring of olfactory function in small children has been possible with olfactory and trigeminal event related potentials [46]. The same is the case for precise assessment of olfactory deficits in mild cognitive impairment [47]. Recently, it has been shown, that olfactory ERPs also predict recovery after olfactory impairment [48].

Recent developments in electric source localization made it even possible to identify deep brain generators, which were so far only identified by fMRI [49].

Gustatory ERP

In contrast to olfaction where objective measurement methods have been developed two decades ago and are currently integrated into clinical workup, objective taste measurement remained for very long an experimental tool. Similarly to olfaction, taste function can be assessed by means of functional imaging such as fMRI and PET. The literature and the number of studies on functional gustatory imaging is however relatively little compared to that on olfaction [50 - 54]. These techniques are yet still restricted to research and are not used in clinical workup of patients. The same is true for magnetic encephalography (MEG), which has been a very elegant tool to unravel and confirm the gustatory central nervous cortices [55 - 58] but is not yet a clinically used instrument.

Gustatory evoked potentials (GEPs) have been successfully recorded the first time in 1985 by Kobal [59]. However, mainly for technical reasons GEPs have not been continued and it is only 20 years later that we tried again to reactivate this technique, showing its clinical feasibility [60]. Some technical difficulties could be overcome but considerable problems and shortcomings persist in the way Kobal proposed the recording of potentials. A recent approach with a gustometer based on water-diluted stimuli (in contrast to air-diluted stimuli) showed the feasibility of this technique and first published articles are promising [61 - 63]. Future work will have to focus on the clinical use of gustatory event related patients with taste disorders.

Future outlook

Within the field of chemical senses we are now at the point where we have a considerable but still insufficient knowledge on causes, recovery rates and psychophysical assessments of smell, taste and to a certain extent also trigeminal function. However, many aspects of the chemical senses are poorly understood. Especially measurement techniques and particularly objective measurements are now possible but not used in a widespread way manly because of cost and time reasons. It will be a clear future issue to improve the available techniques or bring up new possibilities of objective measuring. One of these new techniques is the frequency analysis of cortical response to chemical senses which opens potentially the door to very easy objective assessment of olfactory, taste and trigeminal function. First steps have shown its feasibility [64 - 65] and it will be interesting to see if this new method can be improved and simplified sufficiently to find its way into clinical routine use.

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- 2013 Youth on the move Germany Selbsthilfeverein Kirstin Nahrmann, Einreichung: Dokumentarfilm, Titel: Es gibt nur ein Ich und im Ich verweilt meine Seele... , Flyer, generelle Information über Epilepsie „emPower talents with epilepsy“
- 2015 Das Theaterstück „Steile Welle“ von Marion Witt und Hans König

Das Preisgeld stammt aus den Erträgen einer Zustiftung an die Stiftung Michael, zu der die Firmen Aventis Pharma, Bayer AG, Boehringer-Ingelheim Intern, B.V. Prohema, Desitin Arzneimittel, GlaxoSmithKline, Janssen-Cilag, Sanofi-Synthelabo und der Blackwell Wissenschafts-Verlag, die Familie Ried, Frau Anna Ruths, Frau Frauke von Thümen, die Adolf Messer Stiftung und andere beigetragen haben. Die Stiftung Michael trägt im Bedarfsfall auch mit eigenen Mitteln bei.

Zur Bewerbung um den Preis können sämtliche Formen von Publikationen, dokumentierte Aktivitäten und Methoden eingereicht werden, deren Ziel eine Verbesserung der Betreuung von Menschen mit Epilepsie und ihrer Lebensbedingungen ist. Eine Beschränkung auf bestimmte Berufsgruppen erfolgt nicht, und es gibt auch keine Altersbeschränkung.

Die Mitglieder des Preisrichter-Kollegiums sind:
- Dr. med. Günter Krämer, Past-Präsident der Schweizerischen Epilepsie-Liga;
- Ingrid Coban, Leiterin des sozialtherapeutischen Diensts im Epilepsie-Zentrum in Bethel;
- Dr. Gerd Heinen, psychologischer Psychotherapeut in Berlin; und
- Dr. med. Matthias Ried, Bruder von Sibylle Ried (Frankfurt am Main).

Datum zum Einreicheschluss: **31.12.2016**

Geschäftsstelle der Stiftung Michael
Alsstr. 12
D-53227 Bonn
Deutschland

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 2016

Les demandes sont à adresser par voie électronique à strassmann@epi.ch.

Voir instructions : www.epi.ch/soutien_recherche

Ligue Suisse contre l'Epilepsie
Seefeldstrasse 84
8008 Zurich
Tél. 043 488 67 77
Fax 043 488 67 78
info@epi.ch

Mise au concours – Prix de la meilleure thèse

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, 8008 Zurich) jusqu'au

31.12.2018

et comporter les pièces suivantes :

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

Alfred-Hauptmann-Preis für Epilepsieforschung
Ausschreibung 2017

Dieser Preis ist nach dem deutschen Neurologen und Psychiater Alfred Hauptmann (1881–1948) benannt. Hauptmann hatte 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, seit 2009 ist er ein gemeinsamer Preis der Deutschen und Österreichischen Gesellschaften für Epileptologie und der Schweizerischen Epilepsie-Liga 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. Es können mehrere Einzelpersonen oder Arbeitsgruppen ausgezeichnet werden. Stammt eine Arbeit von mehreren Autoren, so wird der ihnen zuerkannte Preis in gleichen Beträgen aufgeteilt, sofern diese nicht bei Einreichung der Arbeit einen anderen Verteilungsschlüssel festgelegt haben.

Die Arbeiten sind entweder elektronisch per E-Mail an **strassmann@epi.ch** oder in vierfacher Ausführung per Post bis zum

31.12.2016

an folgende Adresse zu senden:

Schweizerische Epilepsie-Liga
«Alfred-Hauptmann-Preis»
Seefeldstrasse 84
8008 Zürich
Schweiz

Unvollständige Unterlagen werden nicht bearbeitet. Es können sowohl bereits publizierte als auch zum Druck angenommene Arbeiten eingereicht werden. Bei der Einreichung ist mitzuteilen, ob und wo die Arbeit veröffentlicht bzw. zum Druck angenommen wurde.

Die Arbeiten können in deutscher oder englischer Sprache verfasst sein. Dem Kollegium können auch Arbeiten zur Preisvergabe vorgeschlagen werden.

Zusätzlich zu den Arbeiten sind folgende weitere Unterlagen einzureichen:

- ein 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. Unter den für den Preis vorgeschlagenen Autoren einer Arbeit muss der korrespondierende Autor der Arbeit sein. Falls dies nicht so ist, ist dies zu begründen.

Über die Preisvergabe entscheidet in geheimer Wahl das Preisrichterkollegium aus Vertretern der Deutschen und der Österreichischen Gesellschaft für Epileptologie sowie der Schweizerischen Epilepsie-Liga: Dr. med. Günter Krämer (Zürich; Vorsitz), Prof. Dr. med. Rudolf Korinthenberg (Freiburg), Prof. Dr. med. vet. Wolfgang Löscher (Hannover), Prof. Dr. med. Günther Sperk (Innsbruck).

Das Kollegium ist in seinen Entscheidungen frei und unabhängig. Seine Entscheidungen sind nicht anfechtbar. Der Rechtsweg ist ausgeschlossen. Die Preisverleihung nimmt der Vorsitzende des Kollegiums auf der Dreiländertagung in Wien (3.-6. Mai 2017) vor.

Mit freundlicher Unterstützung von UCB Pharma GmbH.

2016

28.-30.9.2016 | Basel
3rd SFCNS Congress – Swiss Federation of Clinical Neuro-Societies: Swiss Neurological Society (SNS), Swiss Society of Neurosurgery (SSN), Swiss Society of Clinical Neurophysiology (SSNC), Swiss Society of Neuropediatrics (SSNP), Swiss Society of Neuroradiology (SSNR), Swiss Society of Neuropathology (SSNPath) and further Societies
Information: www:kongress.imk.ch/sfcns2016preview/Intro

4.10. 2016 | Basel, 19.30 Uhr
Lesung „Panthertage: Mein Leben mit Epilepsie" mit der Autorin Sarah Elise Bischof
Information: Stephan.Rueegg@usb.ch

5.10.2016 | Zürich, Karl der Grosse, 19.30 Uhr
Tag der Epilepsie
Information: Epilepsie-Liga,
Seefeldstrasse 84, 8008 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch,
www.epi.ch

20.-22.10. 2016 | Prien, Deutschland
Annual Meeting of the German-Swiss-Austrian Epilepsy Working Group DACH-AK
Information: margitta.seeck@hcuge.ch

26.10.2016 | St. Gallen, 17 Uhr
Fachveranstaltung der Epilepsie-Liga
Information: Epilepsie-Liga,
Seefeldstrasse 84, 8008 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch,
www.epi.ch

26.10.2016 | St. Gallen, 19.30 Uhr
Publikumsveranstaltung der Epilepsie-Liga
Information: Epilepsie-Liga,
Seefeldstrasse 84, 8008 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch,
www.epi.ch

5.11.2016 | Zürich, Klinik Lengg, Gründerhaus
Patiententag
Information: Epilepsie-Liga,
Seefeldstrasse 84, 8008 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch,
www.epi.ch

2.-6.12.2016 | Houston, Texas, USA
70th 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

2017

16.-18.2.2017 | Luxor, Ägypten
4th East Mediterranean Epilepsy Congress
Information: ILAE/IBE Congress Secretariat,
7 Priory Office Park, Stillorgan Road,
Blackrock, Co. Dublin A94 FN26, Ireland,
Tel. 00353 / 1 / 2056720,
Fax 00353 / 1 / 2056156,
e-mail: luxor@epilepsycongress.org

23.-26.3.2017 | Athen, Griechenland
11th World Congress on Controversies in Neurology (CONy)
Information: comtecMED, Medical Congresses, 53 Rothschild Boulevard, PO Box 68, Tel Aviv, 6100001, Israel,
Tel. 00972 / 3 / 5666166,
Fax 00972 / 3 / 5666177,
e-mail: Info@comtecmed.com,
www.comtecmed.com/Cony

6.-8.4.2017 | Salzburg, Österreich
6th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures
Information: pco tyrol congress, Ina Kaehler,
Rennweg 3, A 6020 Innsbruck,
Tel. 0043 / 512 / 575600,
Fax 0043 / 512 / 575607,
e-mail: se2015@cmi.at, www.statusepilepticus.eu

3.-6.5.2017 | Wien, Österreich
10. Dreiländertagung der Österreichischen und Deutschen Gesellschaften für Epileptologie und der Schweizerischen Epilepsie-Liga
Information: Epilepsie-Liga,
Seefeldstrasse 84, 8008 Zürich,
Tel. 0041 / 43 / 4886777,
Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch,
www.epi.ch

5.-7.5. 2017 | Dakar, Senegal
3rd African Epilepsy Congress
Information: ILAE/IBE Congress Secretariat,
7 Priory Office Park, Stillorgan Road,
Blackrock, Co. Dublin A94 FN26, Ireland,
Tel. 00353 / 1 / 2056720,
Fax 00353 / 1 / 2056156

24.-27.6.2017 | Amsterdam, Holland
3rd Congress of the European Academy of Neurology (EAN)
Information: ean Head Office, Breite Gasse 4/7,
A 1070 Wien, Österreich,
e-mail: amsterdam2017@eaneurology.org,
www.eaneurology.org/amsterdam2017

2.-6.9.2017 | Barcelona, Spanien
32th International Epilepsy Congress
Information: ILAE/IBE Congress Secretariat,
7 Priory Office Park, Stillorgan Road,
Blackrock, Co. Dublin A94 FN26, Ireland,
Tel. 00353 / 1 / 2056720,
Fax 00353 / 1 / 2056156,
e-mail: barcelona@epilepsycongress.org

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