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Epilepsy, cognition, and neuropsychiatry (Epilepsy, Brain, and Mind, part 2)

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Abstract

Epilepsy is, of course, not one disease but rather a huge number of disorders that can present with seizures. In common, they all reflect brain dysfunction. Moreover, they can affect the mind and, of course, behavior. While animals too may suffer from epilepsy, as far as we know, the electrical discharges are less likely to affect the mind and behavior, which is not surprising. While the epileptic seizures themselves are episodic, the mental and behavioral changes continue, in many cases, interictally. The episodic mental and behavioral manifestations are more dramatic, while the interictal ones are easier to study with anatomical and functional studies. The following extended summaries complement those presented in Part 1.

Keywords

Epilepsy; Behavior; EEG; Mind; Psychiatry; Psychology; Antiepileptic drugs; Cognition; Stress; Imaging; Social issues

1. Introduction

Extended summaries of presentations at the Second International Congress of Epilepsy, Brain, and Mind (Prague, Czech Republic 2012) that focused on epilepsy, cognition, and neuropsychiatry are featured in this paper. The treatment of people with epilepsy (PWE) is complicated not only because of the wide spectrum of epileptic disorders and manifestations but also because of the fact that patients very frequently suffer from comorbidities that need to be addressed. Among the latter, mental manifestations are particularly challenging. The underlying brain lesions, the ensuing electrical activity, the consequent social repercussions, among others, are important considerations when attempting to select drug therapy (or other interventions) for PWE. Some antiepileptic drugs (AEDs) can reduce undesired mental changes, while others can induce cognitive or mental adverse reactions. Furthermore, other drugs affecting the mind, such as antidepressants, can interact with AEDs on a pharmacodynamic level, while others may affect AED concentrations through pharmacokinetic processes. All these factors need to be considered when evaluating an individual patient and trying to optimize therapy. These issues have been reviewed and discussed comprehensively during the Second International Congress of Epilepsy, Brain, and Mind, held in Prague in 2012 and are presented in the following extended summaries.

Another topic that has emerged in the past few years is that of high-frequency electrical activity in the brain. Traditional EEG records could not record this activity, but recently, it

has been realized that this activity is of importance and may be clinically helpful, for example in localizing epileptic foci. The normal and the abnormal physiology of high-frequency oscillations are still being investigated, and several of the new developments are reviewed in this section as well.

People with epilepsy may have difficulties in social integration. Traditionally, this has been ascribed to discrimination. However, recent research has suggested the possibility of an additional contributing factor. Thus, it is possible that patients' behavior may contribute. In that respect, an interesting emerging issue deals with emotion recognition (and expression) by an individual and its possible effects on social cognition and reactions. Data, reviewed here, suggest that PWE may have particular difficulties in that respect.

Neuroimaging of mental states is another attractive and vibrant field of research. The availability of fMRI to examine brain activity during induced or spontaneous "state of mind" is a topic of recent investigations in neurology, psychiatry, and psychology. A relevant question is whether the manifestations observed in PWE are similar or different (qualitatively or quantitatively) from those occurring in others. Another relevant question, discussed here, is to what extent psychic states (such as depression) have the same anatomical correlates in PWE and in people without epilepsy.

2. AEDs and cognition, emotion, and behavior

2.1. AEDs, cognition, and behavior

Marco Mula

Antiepileptic drugs (AEDs) continue to be the mainstay of epilepsy treatment, but benefits of seizure control need to be weighed carefully against possible adverse effects, which can include behavioral problems and psychiatric disorders. In fact, AEDs have a number of mechanisms of action that are likely to be responsible not only for their antiseizure activity but also for their effects on mood and behavior.

A number of studies suggest that treatment with some AEDs may be associated with the occurrence of depressive symptoms, while other AEDs are probably antidepressants. In general terms, the links between depression and barbiturates [1], vigabatrin [2], tiagabine [3], and topiramate [4] seem to be firmly established. In the majority of cases, rapid dose titration in patients with drug-refractory epilepsy [5], a past history of depression [6], and limbic system dysfunction represent major determinants. In fact, it has been pointed out that a subgroup of patients with drug-refractory temporal lobe epilepsy seems to be particularly vulnerable to the psychotropic effects of AEDs independently of their specific mechanisms of action [6].

Psychoses related to AEDs are usually due to AED toxicity or occur in the context of the so-called forced normalization phenomenon. This concept refers to the publications of Heinrich Landolt, who reported a group of patients with florid psychotic episodes associated with "forced normalization" of the EEG [7]. Subsequently, Tellenbach [8] introduced the term "alternative psychosis" for the clinical phenomenon of the reciprocal relationship between

abnormal mental states and seizures, which did not, as Landolt's term did, rely on EEG findings. Since the early observations of Landolt, a sufficient number of patients with alternative psychosis have been reported [9]. The clinical presentation does not necessarily need to be a psychosis, but this is probably the most common. The disturbed behavior may last days or weeks and is often self-limiting with the reappearance of seizures. Landolt originally associated this phenomenon with focal epilepsies, but subsequent studies suggested an association with generalized epilepsies. In any case, what seems to be striking is the association with neurobiological mechanisms underlying seizure control. In fact, forced normalization has been reported not only with AEDs but also with vagus nerve stimulation [10] and may probably be implicated in psychoses following epilepsy surgery.

On the other hand, it is important to acknowledge that AEDs are extensively used in psychiatric practice for a broad spectrum of psychiatric disorders. The primary application is in mood stabilization [11], but interesting data are also emerging regarding anxiety disorders [12] and withdrawal syndromes [13].

As for the old generation of AEDs, both carbamazepine and valproate demonstrated positive psychotropic properties upon their introduction for the treatment of epilepsy [14]. Over time, a number of controlled studies have been carried out in patients with acute mania evaluating the effects of these two AEDs against placebo, lithium, or antipsychotic drugs and demonstrating positive effects, especially in subjects with unstable forms of bipolar disorder such as those who rapidly cycle [15]. As far as new compounds are concerned, some (i.e., tiagabine and gabapentin) have failed to show any efficacy in primary psychiatric disorders, while others (e.g., topiramate) might have adjunctive uses, such as the management of weight gain associated with atypical antipsychotics or in the treatment of eating disorders [16]. Data about oxcarbazepine are definitely less conclusive than those regarding carbamazepine. Oxcarbazepine seems to be as effective as carbamazepine in acute mania but is better tolerated [17]. Cumulative results of the studies on lamotrigine provide evidence that it is effective in the management of the depressed phase of bipolar disorder type II and in the long-term maintenance treatment of patients with rapid cycling bipolar disorders [15].

Some new generation compounds (i.e., gabapentin and pregabalin) have demonstrated some efficacy in anxiety disorders [12]. For both drugs, N-P/Q type channels represent the main molecular target, in particular the α -2-delta subunit, type 1 and type 2. Pregabalin is probably the most interesting molecule in this regard, with a number of controlled studies demonstrating that it is better than placebo in generalized anxiety disorder [18].

Considering the number of AEDs available for the treatment of epilepsy, tailored treatment strategies that take into account comorbidities (i.e., psychiatric and cognitive problems) and the patient's needs are warranted.

2.2. Epilepsy, antiepileptic drugs, and emotions

Andres M. Kanner

One out of every three people with epilepsy (PWE) is likely to experience mood and/or anxiety symptoms over their lifetime that can present as defined disorders, according to

predetermined diagnostic criteria, or as clusters of symptoms [19]. The cause of these “emotional disturbances” is multifactorial, including a family and a personal psychiatric history preceding and/or following the onset of epilepsy, neurochemical and structural changes associated with the seizure disorder, type of epilepsy syndrome, psychosocial obstacles, and iatrogenic effects. Indeed, antiepileptic drugs (AEDs) can play a significant role in the “emotional profile” of PWE through their effects on seizure control and the positive psychotropic properties of some drugs impacting mood and/or anxiety disorders. For example, in the treatment of primary mood disorders, AEDs with mood stabilizing properties that have shown efficacy in double-blind placebo-controlled trials include carbamazepine, valproic acid, and lamotrigine, while mood stabilizing properties have been attributed to oxcarbazepine through extensive use in open trials. Antiepileptic drugs with anxiolytic properties used for the treatment of primary generalized and anxiety disorders and social phobia include gabapentin, pregabalin, tiagabine, and benzodiazepines. On the other hand, AEDs with negative psychotropic properties reported in PWE include barbiturates, ethosuximide, topiramate, zonisamide, and levetiracetam, while some AEDs have mixed positive and negative psychotropic properties such as benzodiazepines and tiagabine.

The negative psychotropic properties of barbiturates and benzodiazepines can result in increased irritability, poor frustration tolerance, aggressive behavior, and full-blown depressive and anxiety disorders. In children, these two AEDs can cause impulsive behavior, poor frustration tolerance, and clinical pictures indistinguishable from attention deficit hyperactivity disorder. Levetiracetam is associated with irritability, which patients are often unaware of, and can also cause depression and anxiety symptoms, while topiramate, zonisamide, and tiagabine can cause overt depressive disorders.

However, the impact (positive or negative) of AEDs on mood and anxiety disorders and/or symptoms is more likely to be evident only in patients who have certain risk factors (e.g., genetic and/or personal predisposition for psychopathology). For example, in a review of the literature, a previous personal psychiatric history and a family psychiatric history in PWE were two variables associated with the development of symptoms of depression attributable to phenobarbital, vigabatrin, levetiracetam, and topiramate [20–22]. Likewise, psychiatric symptoms may result from the discontinuation of AEDs with mood-stabilizing and anxiolytic properties in patients with an underlying mood and anxiety disorder that had remitted with the use of these drugs. Clearly, these data make it imperative to conduct an investigation of the patient’s personal history and family psychiatric history in order to minimize the risk of potential iatrogenic psychiatric symptoms and/or disorders.

On the other hand, given the positive psychotropic properties associated with several of the AEDs cited above, it is reasonable to expect that the use of one of these AEDs may be sufficient to treat the seizure disorder and the comorbid mood or anxiety disorder. Unfortunately, there is no Class I evidence to support this assumption in PWE. The available supportive data are sparse and limited to two open trials of lamotrigine in patients with PWE and suggested an improvement in symptoms of depression [3,23]. As stated above, anxiolytic efficacy of pregabalin and gabapentin has been established in patients with primary anxiety disorders [24,25], and while it is reasonable to assume that this efficacy would occur in PWE, this is yet to be proven.

In January 2008, the Food and Drug Administration (FDA) issued an alert regarding their conclusion that there was an association between suicidality and AED use. The alert was based on their meta-analysis that included data from 199 randomized clinical trials of 11 AEDs encompassing a total of 43,892 patients treated for epilepsy, psychiatric disorders, and other disorders, predominantly pain, with the following AEDs: carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide [26]. The FDA's analysis showed a statistically significant 1.80-fold increased risk of suicidality with exposure to AEDs.

However, the validity of the FDA conclusion has been questioned because of several serious methodological problems [27,28] including the following:

- The assessment of suicidality was based on “spontaneous” reports of patients and not gathered in a systematic, prospective manner.
- The FDA associated the increased risk of suicide with all AEDs despite the fact that statistical significance was found for only 2 AEDs (i.e., topiramate and lamotrigine). Furthermore, inclusion of three additional studies of lamotrigine resulted in the loss of statistical significance for this AED. Two other AEDs, valproic acid, and carbamazepine, actually yielded a “small protective effect.” The FDA's decision to present the risk as involving all AEDs stemmed from a concern that singling out specific AEDs might only change prescribing practices rather than emphasize the suicide risk.
- Most epilepsy trials (92%) include patients taking polytherapy, i.e., combinations of AEDs (compared with 14% of psychiatric trials and 15% of other medical trials). It is unclear whether the higher suicidality rates in the epilepsy trials were due to drug interactions, given the high proportion of epilepsy trials enrolling patients taking polytherapy, or whether they potentially were due to the low suicidality risk associated with carbamazepine and valproate—both drugs are protective for suicidality and are the most common comparison drugs in these trials.
- Suicidal behavior was greater in certain geographic regions. For example, the odds ratio of suicidality was 1.38 (95% CI: 0.9–2.13) in North American studies and 4.53 (95% CI: 1.86–13.18) in studies done elsewhere. Such differences strongly suggest serious methodological errors in data gathering. Of note, five large studies have attempted to reproduce the FDA's data, but results have been contradictory among the different studies.

In conclusion, before starting any psychotropic drug for the treatment of comorbid psychiatric symptoms and/or disorders, it is necessary to exclude that the psychiatric symptomatology resulted from the following: (1) administration of AEDs with negative psychotropic properties, (2) recent discontinuation of AEDs with anxiolytic and/or mood stabilizing properties that were keeping an underlying anxiety/depressive disorder in

remission, or (3) introduction of enzyme-inducing AEDs that accelerated the metabolism of concomitant psychotropic drugs that were keeping psychiatric symptoms in remission.

2.3. Epilepsy, AEDs, and suicide

Alla Guekht

Suicide, according to WHO [29], is one of the leading causes of death worldwide. Every year, almost one million people die from suicide, constituting a “global” mortality rate of 16 per 100,000 or one death every 40 s. These figures do not include suicide attempts, which are up to 20 times more frequent than completed suicide. Suicide is an extremely complex problem, involving psychological, social, biological, cultural, and environmental factors. Mental disorders, primarily depression, are a major risk factor for suicide in Europe and North America.

According to a number of studies, the overall risk of committing suicide in people with epilepsy is about 3 times that of the general population [30]. A meta-analysis of 12 studies estimated the standardized mortality ratio for suicide in people with epilepsy as 5.1 (95% CI: 3.9–6.6) [31].

In the general population, about 90% of people who successfully commit suicide have at least one psychiatric disorder at the time. The comorbidity of depression in persons with epilepsy is well established [32,33]. However, this is only a part of the multifactorial association between epilepsy and suicidality. A study using data sources from Denmark investigated over 20,000 people who died from suicide and >400,000 controls (up to 20 for each case) alive on the date of the suicide and matched for age and sex [34]. Of those who committed suicide, almost 500 had epilepsy. Persons with epilepsy were over 3 times more likely to commit suicide than those without epilepsy. More people with epilepsy had psychiatric disease (rate ratio 4.3), but the rate ratio of suicide in people with epilepsy was still 2 compared with those without epilepsy after excluding those with psychiatric disease and adjusting for various factors.

In 2005, the FDA expressed concern whether AEDs might increase the risk of suicidal ideation, suicide attempt, and completed suicide. The FDA sent letters to sponsors of antiepileptic drug trials requesting that they submit data from placebo-controlled trials to the FDA for review of the possible association of suicidality events and AEDs. The review was completed in 2008 [35]. Data from 210 placebo-controlled and low-dose-controlled trials of 11 AEDs were analyzed. In these trials, AEDs were used for epilepsy (73 trials), psychiatric disorders (56 trials), as well as for other indications (81 trials). There were 27,863 patients in drug arms and 16,029 patients in placebo arms. The FDA’s conclusion was that AEDs were associated with increased risk of suicidality relative to placebo and that the effect was consistent among the group of 11 drugs. There were 4 completed suicides among drug patients and none among placebo patients — 1.9 per 1000 (95% CI: 0.6–3.9) more AED-taking patients than placebo-taking patients who experienced suicidal behavior or ideation. In terms of adjusted risk estimates for the treatment groups, 0.43% of the AED-taking patients experienced suicidal behavior or ideation versus 0.24% of placebo-taking patients.

A number of pharmacoepidemiologic studies, focused on the association between AED use and suicidal behavior, have been published recently. According to the study based on the Danish National Prescription Registry, AEDs increased the risk of completed suicide (OR 1.85 (95% CI: 1.4–2.5)), with significant effects for clonazepam, valproic acid, phenobarbital, and lamotrigine [36,37]. Patorno et al. reported that compared with topiramate, several AEDs were associated with a statistically significant increased risk for suicide attempt or completed suicide (gabapentin, lamotrigine, oxcarbazepine, tiagabine, and valproic acid) [37]. VanCott et al., studying data from older patients, revealed that the psychiatric history and use of valproic acid, lamotrigine, or levetiracetam were significant, independent correlates of suicidal behavior [38]. All studies published so far show a lack of concordance and are constrained by various methodological limitations.

The relationship between epilepsy, depression, suicide, and AED use is complex and still not clearly understood. Several factors, especially prior history of suicide attempt and history of psychiatric disorders, should be taken into consideration, together with the type of epilepsy, postictal psychiatric disturbances, and exposure to different AEDs [39,40]. However, AEDs are the mainstay of epilepsy treatment with a 60%–70% efficacy rate; successful control of seizures is associated with improved quality of life, and lack of seizure control is associated with significant morbidity and, in some cases, death. Accordingly, there is a notion that the risk of stopping (or not starting) AEDs in people with epilepsy would be far greater than the proposed small increased risk of suicidal behavior. Further prospective well-designed trials are needed.

2.4. Indications and mechanisms of action of antiepileptic drugs in the treatment of nonepileptic disorders

Cecilie Johannessen Landmark

2.4.1. Antiepileptic drugs—Antiepileptic drugs (AEDs) have a broad spectrum of activity. During the last 20 years, 14 new AEDs have been licensed for clinical use. The newer AEDs in general have improved tolerability as compared with the older drugs, but no major differences in clinical efficacy have yet been found. The pharmacological variability of these drugs is extensive, and various host factors contribute in the individual patient. Antiepileptic drugs have a considerable interindividual pharmacokinetic variability, such as extensive age-related physiological changes in the capacity of drug elimination [41]. Genetic factors also contribute to differences in pharmacodynamic sensitivity, comorbidity, and clinical response, and their contribution to nonepileptic disorders, specifically, is scarcely investigated. Furthermore, AEDs are highly likely to cause adverse effects and drug interactions [42]. Individualization of pharmacological treatment by implementation of therapeutic drug monitoring is, therefore, recommended [41,43].

2.4.2. Mechanisms of action of AEDs in nonepileptic disorders—All AEDs decrease neuronal excitability by affecting the balance between glutamatergic neurotransmission and GABAergic neurotransmission, which may be responsible for the efficacy of these drugs in other disorders besides epilepsy. There is no relationship between chemical structure and targets in the synapse, and most AEDs have several proposed

mechanisms of action. Our knowledge of which mechanisms contribute to the pharmacological effects seen in various disorders has improved, but there is still a knowledge gap in understanding the relationships between molecular mechanisms of action, pathophysiological processes, and clinical efficacy.

There seem to be common pathophysiological pathways in epilepsy and other neurological and psychiatric disorders such as neuropathic pain, migraine, bipolar disorder, and anxiety [17,44]. Antiepileptic drugs affect these processes (Fig. 1). In bipolar disorder, relevant mechanisms involve alterations in intracellular pathways affecting excitability. Thus lamotrigine, valproate, and carbamazepine have shown similar effects as lithium on intracellular signaling pathways, e.g., inositol turnover. In anxiety, GABAergic mechanisms are involved, as well as inhibition of voltage-gated calcium channels, as occurs, for example, with pregabalin [45]. In neuropathic pain, inhibition of voltage-gated calcium channels by pregabalin and gabapentin decreases glutamatergic-mediated excitability in the spinal cord, while similar effects and antagonistic effects on the AMPA receptor by topiramate seem to be important in the prophylactic treatment of migraine [44,46] (Table 1).

2.4.3. Indications and utilization of AEDs—The major indications for AEDs in nonepileptic disorders include treatment of bipolar disorder (lamotrigine, carbamazepine, and valproic acid), generalized anxiety disorder (pregabalin), acute mania (valproic acid), neuropathic pain (pregabalin, gabapentin, and carbamazepine), and migraine (topiramate and valproic acid) (Table 1). Antiepileptic drugs are increasingly utilized in these disorders, and more drugs are being investigated in preclinical and clinical studies.

One way of investigating clinical use and quantitatively measuring the extent of utilization of AEDs in epilepsy and other disorders is with population-based prescription registries. We have observed that during the last years, the utilization of AEDs in disorders other than epilepsy has increased and constitutes 40–50% of the total utilization of AEDs, as demonstrated by studies based on the Norwegian Prescription Database [47]. Lamotrigine is the most commonly utilized AED in psychiatry, while pregabalin and gabapentin are predominantly used in neuropathic pain, while topiramate is predominantly used in migraine, even though it accounts for a minor part of its total use.

Prescription databases are also well suited for investigations of general or specific patient populations to improve our understanding of changes in treatment patterns over time. This is an important aspect of pharmacovigilance, the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems (WHO library cataloging-in-publication data. The importance of pharmacovigilance. Safety monitoring of medicinal products. 2002, ISBN: 9241590157. Accessed April 2012 at: <http://apps.who.int/medicinedocs/en/d/Js4893e/>).

Pharmacoepidemiological studies are now more commonly utilized to assess drug utilization in a clinical population setting [48–50]. Such studies are relevant and important for policy-makers (prescribers, pharmacists, and health authorities) regarding follow-up of changes in prescription patterns and also as an incentive for updating treatment guidelines. Awareness of the increased exposure of AEDs to new groups of patients is a valuable contribution to improved pharmacovigilance.

2.4.4. Clinical implications—Since the introduction of AEDs in other indications, some evidence-based guidelines have focused on the role of AEDs in nonepileptic disorders. Lamotrigine is now regarded as a first-line treatment option in bipolar depression according to evidence-based guidelines [51]. Patients with epilepsy often suffer from comorbid conditions, and lamotrigine is often preferred in these patients, providing an example of rational therapy in cases of epilepsy and bipolar depression [43].

At present, there are no evidence-based treatment guidelines for the use of pregabalin or gabapentin in the treatment of neuropathic pain. A recent study concluded that gabapentin and pregabalin have similar efficacy and tolerability profiles in neuropathic pain, with gabapentin having a slight superiority to pregabalin [52]. Furthermore, gabapentin shows large inter- and intra-patient variability in absorption, which is not desirable [53]. A new prodrug, gabapentin enacarbil XR, may be promising, as studied in restless leg syndrome [54]. Migraine is still a minor indication for AEDs, but the utilization of topiramate as prophylactic treatment has increased every year since 2004 [47].

It is of importance to monitor the increased utilization of AEDs in other indications, as new patient groups are introduced to AEDs and long-term effects in these groups often are otherwise scarcely documented. The extensive pharmacokinetic variability that is seen with all AEDs is regardless of indication, and the implementation of therapeutic drug monitoring (TDM) would be of benefit to a majority of patients [55] and to other groups besides patients with epilepsy. The large increase in utilization of AEDs in nonepileptic disorders may be an indication of the role of AEDs in filling the gap between neurological and psychiatric disorders where established pharmacological treatment alone does not succeed. It has been suggested that drugs targeting GABAergic and glutamatergic mechanisms may be the next wave in CNS therapeutics.

2.4.5. Future perspectives for AEDs—Future directions regarding AEDs include the development of broad-spectrum drugs for several indications and focus on genetic studies to explore common pathophysiological processes. It was recently concluded that a major challenge is to minimize the differences between preclinical and clinical studies [56].

2.5. Pharmacokinetic and pharmacodynamic interactions between antiepileptic drugs and psychoactive agents

Philip N. Patsalos

Concomitant administration of antiepileptic drugs (AEDs) and psychoactive drugs is becoming increasingly common, and consequently, the possibility of pharmacokinetic and pharmacodynamic interactions between these compounds is important. Pharmacodynamic interactions between AEDs and psychoactive drugs are not well documented, but neurotoxic synergism has been reported between both carbamazepine and oxcarbazepine with aripiprazole and also between carbamazepine and lithium. In the latter, patients typically develop a syndrome characterized by somnolence, confusion, disorientation, ataxia, and other cerebellar symptoms [57]. Furthermore, a toxic serotonin syndrome can occur when carbamazepine and fluoxetine are coprescribed. Combining carbamazepine with clozapine is generally contraindicated because of concerns about potential additive adverse

hematological effects. Although pregabalin does not affect the pharmacokinetics of lorazepam, impairment of cognitive and gross motor functions is observed during combination therapy, and these are considered to be the consequence of a pharmacodynamic interaction [58].

In contrast, many pharmacokinetic interactions have been described with most occurring at the metabolic level involving either induction or inhibition in cytochrome P450 (CYP) activity [59]. Enzyme-inducing AEDs (carbamazepine, phenytoin, phenobarbital, and primidone) enhance the metabolism and decrease plasma levels of various antidepressants (e.g., amitriptyline, citalopram, desipramine, doxepin, imipramine, mianserin, mirtazapine, moclobemide, nefazodone, nortriptyline, paroxetine, and sertraline), many antipsychotics (e.g., aripiprazole, bromperidol, clozapine, chlorpromazine, fluphenazine, haloperidol, olanzapine, quetiapine, risperidone, thioridazine, trazodone, and ziprasidone), and some benzodiazepines (e.g., alprazolam, clobazam, and clonazepam). Valproic acid inhibits the metabolism and increases plasma levels of amitriptyline, citalopram, moclobemide, nortriptyline, aripiprazole, and quetiapine. The interaction between valproic acid and clozapine is controversial with plasma clozapine levels reported to increase by 57% in one study, while in another study, plasma clozapine levels were reported to decrease by 15%. Of the new AEDs, lamotrigine, oxcarbazepine, and topiramate have been studied most. While lamotrigine inhibits the metabolism of aripiprazole and olanzapine and increases their plasma levels, it enhances the metabolism of quetiapine and does not affect the metabolism of clozapine, risperidone, and clobazam. Topiramate enhances the metabolism of risperidone and inhibits the metabolism of haloperidol and risperidone but has no effect on the metabolism of venlafaxine, clozapine, olanzapine, and quetiapine. In contrast, oxcarbazepine does not affect the metabolism of citalopram, olanzapine, quetiapine, and risperidone [58].

Pharmacokinetic interactions can also occur, whereby the psychoactive drugs can affect AED plasma levels. Thus, the antidepressants, namely, viloxazine, fluoxetine, and nefazodone can inhibit the metabolism of carbamazepine, via an action on CYP3A4, and increase carbamazepine plasma levels by up to 3-fold. Concomitant increases in the pharmacologically active metabolite, carbamazepine epoxide, complicate these interactions [60]. Similarly, imipramine, fluoxetine, fluvoxamine, nortriptyline, and viloxazine can inhibit the metabolism of phenytoin, via an action on CYP2C9, and increase plasma phenytoin levels [61,62]. Similar interactions have been associated with various antipsychotics; plasma carbamazepine levels are increased by haloperidol and risperidone, while plasma phenytoin levels are increased by risperidone. Plasma lithium levels are increased 3.5-fold and 5-fold by carbamazepine and acetazolamide, respectively, while the effect of clonazepam is relatively modest, with plasma lithium levels increasing by up to 60% [63]. Many of the new AEDs (e.g., levetiracetam, lacosamide, vigabatrin, oxcarbazepine, gabapentin, and pregabalin) have a low potential overall for pharmacokinetic interactions with psychoactive drugs, and these should be preferred whenever possible [64]. Prevention and management of interactions between AEDs and psychoactive drugs consist of avoiding highly interacting drugs, understanding the underlying mechanism of interactions so as to anticipate the therapeutic outcome, and using dosing strategies guided by therapeutic drug monitoring of both AEDs and psychoactive drugs in order to circumvent undesirable consequences [55,65,66].

3. High-frequency oscillations in cognition and epilepsy

3.1. Simultaneous MEG-intracranial EEG: new insights into the ability of MEG to capture oscillatory modulations in the neocortex and the hippocampus

Sarang S. Dalal, Karim Jerbi, Olivier Bertrand, Claude Adam, Antoine Ducorps, Denis Schwartz, Jacques Martinerie, and Jean-Philippe Lachaux

Intracranial electroencephalography (iEEG) is indicated in epilepsy surgery candidates when noninvasive diagnostic techniques prove inconclusive [67]. The objective of these recordings is to localize seizure foci as well as to prevent incidental resection of the “eloquent” cortex that would result in significant cognitive deficits or paralysis [68,69]. These recordings also provide rare but highly valuable data to test basic hypotheses in neurophysiology and cognitive neuroscience.

Using simultaneously acquired intracranial EEG data, it has become possible to validate noninvasive magnetoencephalography (MEG) results. While empirically evaluating the accuracy of various MEG/EEG source localization methods has been historically difficult, improved source localization with the millisecond time resolution that MEG provides can not only elucidate mechanisms of cortical function but also provide further precision for planning of neurosurgical procedures, including functional mapping of tentative resection zones as well as placement of neural stimulators.

The relationship between neural activities recorded at various spatial scales remains poorly understood partly because of an overall dearth of studies utilizing simultaneous measurements. We had the unique opportunity to record MEG simultaneously with intracranial EEG (iEEG) from electrodes implanted in the temporal and occipital lobes of four patients with epilepsy.

3.1.1. Methods—A reading task was given to the patients, as described in Lachaux et al. [70] and Dalal et al. [71], adapted from Nobre et al. [72]. Each block lasted 6 min, and each patient participated in 4 blocks for a total of 24 min of recording time per patient.

Task-related power modulations were detected in iEEG data by convolution with Morlet wavelets, as detailed in Dalal et al. [71]. A time-frequency beamformer was applied to MEG data to localize sources of task-related oscillatory modulations as per Dalal et al. [73]. In both cases, power modulations were calculated relative to a prestimulus baseline period.

Separately, to understand the contribution of various brain structures at different depths to the MEG signal, we also analyzed the cross-correlation of spontaneous hippocampus depth EEG traces with each MEG channel.

3.1.2. Results—Strong alpha/beta suppressions were observed in MEG reconstructions in tandem with iEEG effects. While the MEG counterpart of high gamma-band enhancement was difficult to interpret at the sensor level in two patients, MEG time-frequency source reconstruction revealed additional activation patterns in accordance with iEEG results. In particular, gamma-band activity was observed up to 100 Hz with MEG source reconstructions, validated by gamma-band activity observed from intracranial EEG

recordings in the vicinity of the MEG-derived peaks (Fig. 2). The task additionally modulated both MEG-reconstructed gamma-band activity and intracranial EEG activity as expected, with occipital regions showing similar high gamma power increases with both task conditions, while superior temporal areas (associated with language) showed gamma-band power increases only in response to attended words.

Depth EEG from the hippocampus demonstrated relatively strong correlation at zero lag with patches of MEG sensors, often forming dipolar correlation patterns when visualized as scalp topography (Fig. 3a). The lateralization of the topographies corresponded to the lateralization of the hippocampus implant. Often these correlations were strong enough such that theta oscillations from intracranial hippocampus electrodes could be directly observed in correspondence with similar MEG activity (Fig. 3b). However, the sensor topographies were more complex than the overlapping spheres model often used for MEG forward modeling.

3.1.3. Conclusions—These results suggest that source reconstruction techniques such as beamforming can increase the effective signal-to-noise ratio of MEG data, enhancing detection of gamma-band activity. They also indicate that the hippocampus generates magnetic fields strong enough to be detectable with modern whole-head MEG systems. However, robust MEG localization and reconstruction of such deep sources will likely require MEG forward models based on individual structural MRIs. As realistic head models based on MRI segmentations remain largely unvalidated, the method presented here may also be used to evaluate their performance and provide direction for improvement. More accurate head models will provide immediate benefits to source reconstruction techniques and potentially allow the reliable resolution of historically elusive brain structures.

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3.2. Memory-related oscillations in the hippocampus: an intrace-rebral recording study

Klára Štillová, Pavel Jurák, Jan Chládek, Josef Halánek, Sabina Telecká, and Ivan Rektor

3.2.1. Subjects—The aim of this pilot study was to find an alternative to the WADA memory test (intracarotid sodium amobarbital procedure) for patients with epilepsy with intracerebral electrodes already implanted in the hippocampi bilaterally. We recorded and analyzed high-frequency oscillations in the hippocampus during visual and auditory memory tasks using time-frequency analysis (TFA). We investigated whether the memory testing paradigm might lead to differentiation between the hippocampus ipsilateral and the hippocampus contralateral to the lesion or seizure onset zone (SOZ).

3.2.2. Methods—We studied intracerebral recordings with depth electrodes implanted bilaterally in the hippocampi of 4 epilepsy surgery candidates using the Talairach and

Bancaud methodology [74]. We used 5 to 15 contact platinum semiflexible ALCIS electrodes (Besançon, France), each with a diameter of 0.8 mm, a contact length of 2 mm, and intercontact distances of 1.5 mm. The exact positions of the electrodes were verified using postplacement MRI with electrodes in situ. Table 2 shows the epilepsy type, laterality, and memory performance for each patient.

The episodic memory testing was conducted during the encoding and retrieval phases of visual and auditory modalities based on methods used in studies by Jones-Gotman et al. [75] and Rabin et al. [76]. Patients were tested over 2 consecutive days. During this testing period, the patients performed 4 tasks: 2 visual tasks and 2 auditory tasks. In the first task, the patients were asked to remember 30 neutral pictures presented on a computer monitor. The pictures were shown for 2-second intervals, each followed by a 4-second interval showing a black screen. After the first task (encoding phase), a 15-minute break then followed; during which the patients watched a well-known fairy tale. They were asked not to remember the story, only to relax. In the second task, the patients were asked to recognize the original 30 pictures in a group of 60 pictures (30 of the pictures were new). The pictures appeared on the computer monitor in random order. Recognition was indicated by pushing a button (one button for the familiar and another for the unfamiliar picture). On the second day, we performed an auditory verbal stimuli task based on the same method. During the task, patients looked at a black computer screen and listened to the words through speakers.

Recordings were performed with the TruScan (Deymed Diagnostic, Alien Technic) 128-channel EEG machine. The sampling frequency was 1024 Hz with standard anti-aliasing filters. Recordings from the intracerebral contacts were done in a referential montage (with contacts serving as active poles and with connected earlobes being used as a reference). The signal was filtered from 0.2 to 200 Hz in the time base 2 s before the stimulus and 5 s after.

Data analysis, segmentation, and evaluation were performed with ScopeWin and MATLAB. The data were segmented according to the stimulus onset, and all the segments were visually controlled. Segments with epileptiform activity or technical artifacts were excluded.

For the signal analysis, we used TFA with eliminated phase-lock signals to determine the event-related de/synchronizations (ERD/ERS). The phase-lock signal was eliminated by subtracting the averaged trial from all trials before TFA computation. In the baseline-normalized TFA matrix, ERS is represented by positive values and ERD by negative values.

3.2.3. Results—We recorded high-frequency oscillations from depth electrodes implanted bilaterally in the hippocampus in patients with epilepsy. We detected time-related synchronization (increase in band power) and desynchronization (decrease in band power) in different frequency spectrums bilaterally, on the healthy side as well as on the lesion side (or SOZ), during the recognition task using the time-frequency analysis (TFA). In 2 patients (1 with temporal epilepsy and 1 with extratemporal epilepsy), we detected synchronization on the healthy side in the spectrum of 75–115 Hz after the presentation of the stimulus (picture and word) during the retrieval phase. This synchronization was 10–20 Hz higher than on the lesion side (SOZ). We did not detect any significant differences in the other 2 patients.

3.2.4. Conclusion—We analyzed recordings from contacts placed in the hippocampi bilaterally in patients with epilepsy. The TFA results do not prove any significant difference in the increase or the decrease in band power between the healthy side and the lesion side (or SOZ) in the hippocampus during visual and verbal memory tasks.

A limitation of the study was the absence of significant memory deficit in 3 of the 4 studied patients and a heterogeneity of the patients with regard to different SOZs.

We conclude that the laterality of the SOZ has no constant influence on the hippocampal oscillatory activities in the memory testing paradigm. Further studies are needed to elucidate whether memory impairment would have had an impact on hippocampal oscillation.

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3.3. Decoding cognitive states and motor intentions from intracranial EEG: how promising is high-frequency brain activity for brain-machine interfaces?

Karim Jerbi, Etienne Combrisson, Sarang S. Dalal, Juan R. Vidal, Carlos M. Hamamé, Olivier Bertrand, Alain Berthoz, Philippe Kahane, and Jean-Philippe Lachaux

Whether the future of brain–computer interface (BCI) technology will be predominantly based on noninvasive recordings of brain signals or, on the contrary, on invasive electrophysiological recordings is still a matter of debate. However, it is conceivable that the nature of the optimal recordings that are needed will depend on the application and the context. For example, while intracranial EEG (iEEG) might turn out to be irreplaceable with scalp EEG in the case of certain specific clinical or therapeutic BCI applications (e.g., restoring skilled motor behavior to tetraplegic patients), other applications such as neurofeedback-based cognitive remediation or enhancement strategies will most probably continue to rely on noninvasive brain recordings. In addition, it is a safe bet that the BCI-oriented video gaming industry is unlikely to require in the future that its customers undergo surgery to be able to play their games. We contend, therefore, that research into invasive and noninvasive methods for BCI research will remain complementary and, most importantly, will serve different purposes.

In humans, reports of invasive BCI systems are less numerous than in nonhuman primates, and signal selection for optimal control is still in its early days [77,195]. Furthermore, most reports of invasive BCI studies have relied on electrocorticography (ECoG) subdural grids and strips; however, insights into the putative utility of stereotactic-EEG (SEEG) recordings for BCI applications are scarce [78–80].

We performed a series of studies to evaluate the possible utility of intracerebral recordings obtained via SEEG depth electrodes for the development of novel brain–computer interfaces. In particular, we set out to investigate the efficiency of local broadband high gamma (approximately 50–150 Hz) neuronal activity as a reliable BCI feature. This hypothesis stems from accumulating evidence across both human and animal studies indicating that broadband high gamma activity is a reliable marker of local neuronal processing [81–84].

To test the ability of patients to control various parameters of their intracranial recordings in real time we used the Brain TV setup, a custom-design online signal analysis system that computes and displays the ongoing power variations at various frequencies, including the high gamma band [80]. Combining the findings of task-related power modulations observed with this system with those of classical offline analysis paves the way for the development of novel strategies for BCI and real-time functional mapping. In addition, we used offline analysis of SEEG data acquired during various delayed motor tasks (hand and eye movements) that directly address the question of whether motor intentions can be decoded in the brain not only at execution but also prior to execution during the planning phase.

Our results suggest that BCI performance may be improved by using signals recorded from various neuronal systems such as the oscillatory activity recorded in the motor and oculomotor systems as well as higher cognitive processes including attention and mental calculation networks [79]. We also found that gamma- and alpha-band activities play a key role in motor intention decoding, providing high decoding accuracy even during the delay period preceding movements. Of further interest to invasive BCI applications is our finding that gamma-band power modulations in the prefrontal cortex are differentially modulated by positive feedback and negative feedback on one's performance [85]. Moreover, we recently found using SEEG data that goal-directed behavior is associated with transient suppressions of broadband gamma power in neuronal structures that closely match the so-called default-mode network [86,87].

Beyond advancing our knowledge of the electrophysiological underpinnings of resting state networks observed with fMRI, these recent results suggest that real-time monitoring of gamma power fluctuations in the resting state might be key to assessing a subject's attention state and, possibly, to tracking pathological alteration of fine-grained spatio-temporal network dynamics in patients with epilepsy.

In conclusion, our SEEG findings suggest that local modulations of gamma-band activity can be reliably used to infer the subject's intentions or cognitive states provided that the electrodes are implanted in the involved sites. A small methodological note of caution has to be raised, however, because of the vulnerability of SEEG to eye-movement artifacts. This previously unsuspected phenomenon consists of gamma range contamination of the SEEG signal caused by the activity of extraocular eye muscles during saccade executions. Several techniques (such as bipolar re-referencing) can be applied to minimize or rule out the contribution of such artifacts [88,89].

Taken together, our findings suggest that SEEG depth recordings of high gamma activity provide an extremely promising feature to decode motor intentions and cognitive states and

that noninvasive techniques such as electroencephalography and magnetoencephalography (MEG) might also need to improve their ability to target such high-frequency modulations in order to improve their decoding power. High gamma activity has been reported with MEG (e.g., [71]), but its sensitivity can be improved by adequate task design [90] and, putatively, by improved source modeling approaches (e.g., [73,91]). Finally, while we have focused here on the utility of gamma-band activity for future BCI application, we contend that lower-frequency oscillations (e.g., in the alpha and the beta range) will continue to be very useful features for decoding, both separately and in combination with high-gamma activity.

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3.4. Clinical meaning of high-frequency oscillations in epilepsy

Jerome Engel, Jr.

Pathological high-frequency oscillations (pHFOs) are readily recorded from the hippocampus and parahippocampal structures of patients with mesial temporal lobe epilepsy and in rodent models of this disorder. These oscillations, and similar HFOs recorded from the neocortex in patients, appear to identify brain tissue capable of spontaneous ictogenesis and are believed to reflect neuronal substrates of epileptogenicity, the presence and severity of an epilepsy condition, and epileptogenesis (the development and progression of an epilepsy condition) [92].

In the hippocampus, pHFOs differ from normal HFOs in several ways. Normal HFOs in the frequency range of 80 to 200 Hz, termed “ripples,” reflect summated inhibitory postsynaptic potentials and are important for synchronizing neuronal activity over long distances. They facilitate information transfer. Pathological high-frequency oscillations commonly occur in the frequency range of 250 to 600 Hz, termed “fast ripples,” and appear to reflect summated action potentials, or pop spikes, rather than inhibitory postsynaptic potentials. Normal ripple oscillations are not generated in dentate gyrus, but oscillations in the ripple-frequency range do occur in the epileptic dentate and reflect the same underlying mechanisms as fast ripples. Consequently, the frequency range of pHFOs is actually 80 to 600 Hz, but it is not possible to distinguish pHFOs from physiological oscillations in the lower-frequency range in areas where ripples occur normally. Pathological high-frequency oscillations are generated in small clusters of neurons surrounded by normal tissue. They are widely separated and spatially stable, but changes that decrease inhibitory influences can cause them to increase in size, coalesce, and synchronize, providing a possible mechanism for ictogenesis. The epileptogenic nature of pHFOs is evidenced by the fact that these events uniquely occur in the brain tissue capable of generating spontaneous seizures and that they appear to be involved in ictogenesis.

It is well known that interictal EEG spikes do not reliably identify the epileptogenic region for surgical treatment. Pathological high-frequency oscillations typically occur in association with interictal spikes and may provide a means of distinguishing spikes that have localizing value (so-called red spikes) from those that represent propagation or occur in the tissue that

is not capable of generating spontaneous seizures (green spikes). Interictal pHFOs also occur, however, apart from interictal spikes. The original studies of pHFOs were carried out exclusively with microelectrodes in mesial temporal structures of patients with temporal lobe epilepsy and animal models of this condition; however, numerous presurgical clinical investigations have now confirmed that pHFOs can be recorded with standard depth and subdural grid electrodes not only from the mesial temporal structures but also from the neocortex. These studies have confirmed the unique relationship between pHFO occurrence and the location of the epileptogenic region as determined and confirmed by seizure freedom following resection. The localizing value of these oscillations for resective surgery is not only more reliable than interictal spikes but also more reliable than measurements of ictal onset. Although HFOs in the fast-ripple-frequency range appear to be more localizing than those in the ripple range in these clinical studies, the lower-frequency oscillations also appear to have significant localizing value. It may be that the dipole configuration or other features distinguishing these two electrographic patterns make it easier for the larger standard clinical electrodes to record pathological activity than normal activity.

There is a great need for biomarkers of epileptogenesis and epileptogenicity in epilepsy [93]. In addition to the potential importance of pHFOs as biomarkers to localize the epileptogenic region for surgical treatment, these oscillations are now prime contenders for biomarkers that could be used for other purposes. Biomarkers of epileptogenesis could be used to predict epilepsy in patients with risk factors in order to introduce preventive interventions and would facilitate clinical trials of antiepileptogenic interventions. Biomarkers of epileptogenesis might also diagnose progression in patients with epilepsy in order to determine when to refer a patient for surgical therapy or experimental treatments. Biomarkers of epileptogenicity would improve diagnosis of epilepsy after a single seizure and differentiation of epileptic seizures from nonepileptic events, facilitate clinical trials of antiictogenic interventions, and confirm prevention and cure following antiepileptogenic interventions. Biomarkers of epileptogenicity that could measure severity could be used to determine efficacy of therapeutic interventions in order to tailor individual pharmacotherapy, and biomarkers of pharmacoresistance would aid in identifying surgical candidates and facilitate clinical trials of compounds intended to treat drug-resistant epilepsy. Reliable biomarkers of epileptogenesis and epileptogenicity might also be useful in devising more cost-effective rapid-throughput animal models for drug discovery and preclinical testing.

Except for preclinical testing and presurgical evaluation, the use of pHFOs as biomarkers in epilepsy would only be practical if they could be measured noninvasively. Considerable effort should now be devoted to this effort. High-frequency oscillations have been recorded from scalp EEG, but it is not yet clear whether these events represent the same neuronal mechanisms as pHFOs recorded directly from the brain. As the fundamental neuronal mechanisms underlying interictal EEG spikes with pHFOs are different from those responsible for interictal EEG spikes without pHFOs, their metabolic signatures on fMRI may be different. Consequently, it is possible that future studies will identify ways of distinguishing red spikes from green spikes using simultaneous EEG–fMRI approaches.

4. Emotion recognition and social cognition

4.1. Autism–epilepsy: meeting at the brain

Roberto Tuchman

Autism is a neurodevelopmental disorder affecting primarily social cognition but associated with language impairments, restricted interests, and repetitive behaviors. The term autism spectrum disorders (ASDs) is used interchangeably with autism and includes a broader group of children including those with autistic disorder, pervasive developmental disorders not otherwise specified, and Asperger syndrome. Epilepsy, like ASD, is increasingly being described as a spectrum disorder to account for the multiple etiologies and variable clinical symptoms and outcomes. Epilepsy and autism are not single diseases but in fact symptom complexes, with multiple etiologies and variable clinical symptoms and outcomes. Epilepsy is commonly associated with ASD, and ASD is commonly being recognized in children with epilepsy, particularly those with intractable epilepsies and in children with an epileptic encephalopathy such as infantile spasms [94].

Intellectual disability is not part of the definition of ASD, but intellectual disability is the most significant risk factor determining the association of epilepsy and ASD. The pooled prevalence of epilepsy is 21.4% in individuals with ASD and intellectual disability versus 8% in persons with ASD without intellectual disability [95]. Much less is known regarding the prevalence of autism in epilepsy. In populations of children with epilepsy and an estimated IQ < 80, the prevalence of ASD is approximately 14% as compared with 2.2% in those with normal cognitive abilities [96]. In a series of studies, 14% of infants with onset of epilepsy in the first year of life, 46% of infants with infantile spasms with onset in the first year of life, and 69% of infants whose seizures began in the first year of life and were associated with brain lesions such as hypoxic–ischemic encephalopathy or cortical dysplasia, or specific genetic syndromes such as tuberous sclerosis, developed ASD [97]. Current studies suggest that epilepsy, autism, and intellectual disability commonly coexist; however, pooled analyses of studies are inconsistent regarding the effect of intellectual disability on epilepsy risk in ASD [98]. Nevertheless, individuals with autism and epilepsy have poorer cognitive (lower IQ), adaptive, behavioral, and social outcomes than those with autism without epilepsy [99,100], and epilepsy accounts for increased morbidity and mortality in individuals with autism [101].

Epilepsy and autism are both large-scale neural network disorders, and conceptually, the development of epilepsy, autism, and the common cognitive impairments that travel with both disorders is often secondary to deficits in genes that lead to abnormalities of the physiological balance between excitation and inhibition and disrupted neural network function. Several recent studies in epilepsy and in autism have found recurrent CNVs of interest on chromosomes 15q11.2, 15q13.3, and 16p13.11. These three regions have been tied to multiple neurobehavioral phenotypes besides epilepsy and autism including intellectual disability and schizophrenia. There is also evidence that malformations of cortical development in which focal structural lesions disrupt normal cortical organization and circuitry not only may account for epilepsy but also may be a contributor to autism and may be particularly relevant for individuals with both epilepsy and autism [102].

Further characterization of the common molecular pathways shared by this group of neurodevelopmental disorders will allow for novel therapeutic interventions, which if started early in the process of both disorders and combined with presently available behavioral interventions, will positively impact the outcome of both epilepsy and autism [103].

4.2. Emotion recognition in temporal lobe epilepsy

Stefano Meletti

How many times every single day do we ascribe feelings or emotions to the people we meet? The answer, of course, is that many times each day, consciously or unconsciously, we believe that we understand the emotions and feelings of others. In fact, the recognition of emotional signals, from all sensory modalities, is a critical component of human social interactions because it is through the understanding of the affective states of others that we guide our behavioral responses.

The temporal lobe, as well as the amygdala in particular, plays a crucial role in the processing of the appropriate autonomic and behavioral responses to emotional relevant stimuli. In the past decade, the role and importance of the anteromedial temporal lobe region in decoding the emotions, mental states, and beliefs of others have been demonstrated by a number of lesion and functional imaging studies. In the field of epilepsy, this knowledge has several clinical as well as speculative implications. Temporal lobe epilepsy (TLE), the most common type of focal epilepsy, is frequently characterized by lesions or gliosis/atrophy (hippocampal sclerosis) extending to other structures of the medial temporal lobe, such as the amygdala. Moreover, anteromedial temporal lobe resection is the “standard” treatment for drug-resistant medial TLE. Consequently, the investigation of emotional and social competence in patients with TLE has been the focus of different studies, which have extended the scope of neuropsychological evaluation in TLE beyond the traditional evaluations of memory, language, and executive functions.

The first facial emotion recognition (ER) studies investigated cohorts of patients with TLE after surgery and demonstrated that patients can be impaired in ER skills after anterior temporal lobectomy, especially after nondominant right side resections. More importantly, it was subsequently demonstrated that even before surgery, drug-resistant epilepsy involving the medial temporal region is associated with deficits in facial ER. To address this point, a large cross-sectional study of ER ability in patients with chronic medial TLE confirmed that impaired facial ER is common and widespread across different emotions [104]. Indeed, the analysis of the recognition of specific basic emotions revealed that the recognition of all emotions except happiness was defective in patients compared with controls. This impairment across different negative emotions can be explained when considering that the amygdala and the temporo-medial structures are involved in the processing of multiple emotional dimensions and in the evaluation of stimuli that are particularly salient. Moreover, it must be considered that adult patients with TLE can have atrophy or dysfunctions that extend well beyond the medial temporal lobe to the cortical–subcortical regions that are engaged in processing different emotions, such as anterior insula (i.e., disgust), orbital frontal cortex (i.e., anger and sadness), and somato-sensory cortices.

How many and which types of patients are impaired? The analysis of subject performance across different studies reveals that about half of patients with TLE show facial ER impairments. With regard to whether such deficits are equally frequent in patients with a right-sided or a left-sided seizure focus, a trend for lower accuracy scores in facial ER was present in patients with right TLE. Importantly, all patients with MRI evidence of bilateral amygdala–hippocampal damage appeared to be severely impaired. This result is in accordance with reports, outside the field of epilepsy, of patients with selective bilateral amygdala damage who showed severe deficits in facial ER.

An important question concerning the recognition of facial expression is whether a critical period of life exists for establishing the neural network underlying emotion processing. It has been hypothesized that early insults to the right medial temporal structures could play a crucial role in causing ER impairments. Accordingly, a correlation between age at seizure onset and impaired recognition of emotion from faces has been reported: patients with febrile seizures or seizure onset before five years of age show lower performances on measures of ER compared with patients with seizure onset later in life. Therefore, it is tempting to speculate that interictal/ictal seizure activity involving the right temporal lobe occurring during the critical period of early childhood might affect the development of ER ability. This hypothesis was confirmed by a recent study in children with TLE, which showed that ER deficits were already present during infancy in patients with early-onset seizures [105]. All together, these data support the idea that the ER deficit observed in adults with early-onset TLE (surgical cases or otherwise) is a developmental disorder.

Facial expressions provide most of the emotional cues that are used to recognize ‘basic’ emotions. Emotional signals can also be conveyed through other modalities such as gestures, body posture, and the voice (emotional prosody). In the latter case, we can understand the emotional state of the speaker through the modulation of voice intonation. Does TLE impair selectively the recognition of emotions conveyed by facial expressions? Do we have evidence of impairments in the recognition of emotional signals through modalities other than facial expressions? To address this issue, a few studies have investigated the processing of emotional prosody in patients with TLE [106]. These studies support the hypothesis that impairment in ER extends beyond facial expressions, at least involving emotional prosody. Importantly, a strong correlation emerged between the performances obtained in the two experimental tasks. In other words, patients who showed the lower scores in facial expression recognition were the ones with the lower accuracy scores in prosody recognition. Overall, these results reinforce the idea that patients with drug-resistant TLE have deficits in recognition of emotions that are not specific for facial expressions and do not depend upon the sensory modality of stimulus presentation (e.g., visual versus auditory).

Current evidence supports the concept that ER impairments in patients with chronic, drug-resistant TLE are quite common, with impairments extending from recognition of facial expression to voice prosody. These findings validate the notion that the behavioral impairments and the difficulties in social functioning frequently observed in patients with chronic TLE could be attributed to specific deficits in processing the stimuli that are essential for human social interactions. However, future studies must address the fundamental question of the biological relevance of these laboratory impairments. In this

sense, the first step will be to develop more ecological stimuli with multimodal audio-visual representation of emotional signals.

4.3. Postoperative changes in emotion recognition and social cognition in patients with TLE

Petr Marusic and Jana Amlerova

The cognitive abilities that identify facial expression from another person's face and attribute mental states to others are important aspects influencing everyday activities. Moreover, these processes are tightly connected: any disruption of emotional processing will cause changes in judgment about others' mental states because this ability (called theory of mind) can be affected by emotional states [107].

It has been suggested that the core system for both cognitive domains is located within the temporal lobes [108]. The first empirical study that provided evidence about the importance of temporal regions on emotion recognition and social behavior came from Klüver and Bucy. Their bilateral removal of temporal lobes in monkeys evoked typical changes in social cognition — visual agnosia, decreased fear, tameness, hypersexuality, hyperorality, and social withdrawal [109]. For human studies, the essential step enabling research was the introduction of functional imaging methods that facilitated the investigation of the activity of brain regions during those processes.

Emotion recognition from inspection of a person's face depends mainly on mesial temporal structures, and the importance of the amygdala in this process has been consistently highlighted. For example, normal development of the amygdala has been shown to be essential for adequate fear recognition [110]. This idea was supported by a recent study of children with early-onset temporal lobe epilepsy (TLE), in whom emotion recognition deficit was found to be present since infancy and adolescence [105]. The amygdala also appears to mediate the connection between the perceptual representation of faces expressing emotions and the conceptual knowledge of what these emotions mean [104]. There is controversy about the lateralization of this function: despite the traditional idea of the importance of the nondominant temporal lobe [104,107,110], there is evidence from fMRI studies that cooperation of both temporal lobes is essential [111].

The neuronal network underlying social cognition and judgment is more complex. Imaging studies have shown the involvement of a widespread network of prefrontal and mesolimbic brain structures [112]. Clinical studies reported impairment in theory of mind tasks in patients with bilateral amygdala damage [113], and the amygdala was shown to be essential for the acquisition of theory of mind abilities in childhood [114].

Overall, the nondominant temporal lobe seems to play a pivotal role in social behavior [115]. Review of the literature suggests that right-sided temporal lobe surgery could be considered as a risk factor for impairment for both emotion recognition and social cognition [116,117]. However, these studies focused only on the postoperative performance and did not compare the performance of patients with TLE before and after surgery. Furthermore, the actual

extent of the temporal resections can play an important role. In a study of social cognition, no difference was observed between pre- and postsurgical patients [115].

In our study, we compared the performance of patients with TLE in emotion recognition and social cognition using data before and after epilepsy surgery, both in cross-sectional and longitudinal analysis [196]. We did not find any significant difference in either emotion or faux-pas recognition. Investigating the longitudinal data in more detail, we were able to identify individual patients who became significantly impaired and others who improved after surgery. The change was independent of any monitored variable (age, sex, intelligence level, age at epilepsy onset, duration of disease, and epilepsy lateralization). A degree of individual variability with possible postoperative deterioration should be taken into account for informed decision-making on the management of patients with drug-resistant TLE.

5. Psychiatric comorbidities and epilepsy

5.1. Refractory epilepsy: prequel or sequel?

Martin J. Brodie

“The journey of a thousand miles begins with a single step”.

[Attributed to Lao Tzu, 500 B.C.]

For the past 30 years, I have followed patients with newly-diagnosed epilepsy who were started on their first antiepileptic drug (AED) and attended our service at the Western Infirmary in Glasgow, Scotland. Those presenting in the Accident & Emergency Department with a first seizure or untreated epilepsy were reviewed and arrangements made for their immediate referral to our “first seizure” service [118]. Letters were sent to all general practitioners working in the West of Scotland offering to see untreated patients within a week or two of referral. All patients with a first seizure were given contact details to allow them to telephone the Epilepsy Unit should they have a subsequent event. Those admitted to the Acute Medicine Assessment Unit at the Western Infirmary with a first seizure or with untreated epilepsy were reviewed prior to their discharge from the hospital and followed up by the epilepsy team. Patients starting on treatment were seen in our out-patient clinics and daily as necessary thereafter in the Epilepsy Unit.

Three major sequential sets of analyses have been published from this expanding cohort [119–121]. The first analysis followed outcomes in 470 patients and the second reviewed 780 patients. Both analyses showed that seizures in most patients responded to the first AED or second schedule, with seizures in more than a third of the population remaining uncontrolled. Interestingly, there was no correlation between duration of pretreatment epilepsy and outcome, although the more seizures documented by the patients, the poorer the prognosis. Thus, seizure density within the first 3, 6, and 12 months of starting treatment was the best marker of a suboptimal response to treatment [120]. Predictive factors for “refractoriness” in this population included family history of epilepsy, febrile seizures, traumatic brain injury as a cause of the epilepsy, psychiatric comorbidities (particularly depression), intermittent recreational drug use, and 10 or more seizures before starting treatment [122]. Other groups have reported a poorer prognosis in patients with comorbid

psychiatric problems both in newly-diagnosed epilepsy [123] and in those with refractory epilepsy undergoing anterotemporal lobectomy [124]. These observations support the suggestion of greater brain dysfunction in this population.

The latest analysis explored outcomes in 1098 patients (median age 32 years, range: 9–93) followed up for a median of 7.2 years (range: 2–26). Despite the introduction of many new AEDs possessing different mechanisms of action over the past 20 years, seizure-free rates in the Glasgow population only increased from 64% in 2000 [119] to 68.4% around 10 years later [121]. Overall, however, seizures in 92% of patients reporting a good long-term outcome responded to the first AED or second schedule, supporting the definition of drug-resistant epilepsy recently published by the International League against Epilepsy [125]. Notably, seizures responded in some patients with their 3rd, 4th, 5th, 6th, or even 7th monotherapy or AED combination this time. These findings were similar to those from an analysis performed in a cohort of Israeli patients [126].

The latest paper focused on patterns of drug response [121]. Overall, 59% of the 1098 patients had an excellent prognosis with a prolonged period of seizure remission. More than half of this group became seizure-free from the outset with the remainder taking some time to find the optimal drug or dose. At the other end of the spectrum, 25% of the population never demonstrated a sustained period of seizure freedom, although numbers and severity were often reduced. The final group (16%), interestingly, fluctuated between periods of remission lasting more than a year and relapse. At the time of analysis, 44% of these patients were not seizure-free. Although 69% of the 1098 patients remained in remission for 2 years, the figure for the smaller ($n = 360$) cohort that reached 10 years of follow-up dropped to just 52%. This scenario was similar to that reported in long-term studies for children in Finland [127] and The Netherlands [128]. There was a statistically significantly higher probability of seizure freedom in patients receiving 1 compared with 2 drug regimens and 2 compared with 3 regimens ($p < 0.001$). These differences were greater among patients with symptomatic or cryptogenic epilepsy than with idiopathic epilepsy.

In the Glasgow cohort, 84% of the 1098 patients with newly-diagnosed epilepsy had a consistent course, which could usually be predicted early [121]. Overall, 69% of these patients went into long-term remission either immediately or after a short delay, usually on their first AED (49.5%) or on a second drug or first combination (13.3%). Seizures in only 6.7% of patients responded to subsequent schedules. Around 25% of the population never achieved a full year of seizure freedom. The remaining 16% showed a relapsing/remitting pattern, suggesting in some at least a progressive process.

These observations support the hypothesis that outcomes in the vast majority of patients depend on the underlying presence or absence of pharmacoresistance *de novo* rather than on specific responses to individual AEDs. Thus, the term “prequel” is perhaps more relevant than “sequel” in predicting poor response of seizures for the majority of patients with newly-diagnosed epilepsy. One possible explanation for these observations could be overexpression of drug transporter proteins in the brains of individuals with pharmacoresistant epilepsy [129]. These observations also support the premise that AEDs treat the result, i.e., the seizure but not the causation, i.e., the pathogenesis of the epilepsy. Newer approaches to

modifying the processes underlying the generation and propagation of seizures are required if the current rather disappointing outcome is to be improved.

5.2. NMDA receptors and depression: molecular mechanisms

Pavel Mares

Present-day antidepressant therapy is based on the monoaminergic hypothesis of the pathogenesis of depression. Common antidepressant drugs are focused on serotonergic and noradrenergic systems. This therapy is effective, but a major disadvantage is a slow onset of action. It takes at least a few weeks to achieve the full efficacy of the therapy. A delay may be dangerous for patients with suicidal tendencies; therefore, new drugs with immediate onset of action would be beneficial.

In 2000, Berman et al. [130] described nearly immediate onset of antidepressant action using subanesthetic doses of ketamine, which persisted for at least one week. This pioneering work started a series of papers confirming the efficacy of ketamine, and both fast therapeutic onset and long duration of action were repeatedly demonstrated (for a recent review see [131]).

Experimental studies also demonstrated possible antidepressant action of ketamine, a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptors, more than ten years earlier [132], as recently reviewed [133]. N-methyl-D-aspartate receptors, one type of ionotropic glutamate receptors, are tetramers composed of two NR1 subunits and two (usually) NR2A or 2B subunits. NMDA receptor 2 subunits exist in four types – A, B, C, and D – and their representation leads to different channel properties and different pharmacological sensitivities. Under resting conditions, the cationic channel regulated by NMDA receptors is blocked by magnesium ions inside the channel. Depolarization due to activation of another type of ionotropic glutamate receptor (AMPA) releases Mg^{2+} ions from the channel, thereby setting NMDA receptors in action. Equilibrium between AMPA and NMDA receptors is necessary for normal excitatory neurotransmission. Results of experimental behavioral studies demonstrated antidepressant-like actions of ketamine as well as the more specific NMDA receptor antagonists MK-801 (dizocilpine) and a selective antagonist of NMDA receptors containing the NR2B subunit Ro 25–6981. Antagonists of NMDA receptors shift the equilibrium to the dominance of AMPA receptors, and AMPA receptor antagonists block the antidepressant-like effect of NMDA antagonists.

Actions on NMDA receptors could explain the fast onset of efficacy in patients as well as in animal models of depression but not the long duration of the effect. An important long-lasting change was found in the prefrontal cortex of experimental animals: the number of dendritic spines was higher than in controls, indicating increased synaptogenesis in the prefrontal cortex. Stimulation of the mTOR signaling pathway (mTOR is ubiquitously present large serine/threonine kinase that regulates the initiation of protein translation) appearing within 30 min after ketamine administration results in phosphorylation of different enzymes (mostly kinases) and an increased synthesis of synaptic proteins. Activation of some kinases was demonstrated for 72 h, i.e., for the time necessary to form mature synapses. Rapamycin, a selective mTOR inhibitor, completely blocked dendritic

spine formation by ketamine as well as the antidepressant action of ketamine in animal models of depression. The mTOR signaling pathway may be activated in many other ways, thus indicating an inhibition of this pathway as a new direction in the search for potential antidepressant drugs [134].

5.2.1. Appendix—There are at least four generally accepted animal models of depression:

- Forced swim test, i.e., swimming without a possibility to escape. Time of passive behavior when the animal no longer tries to get out from the water is measured.
- Anhedonia, determined as a loss of preference for sucrose solution.
- Learned helplessness, when an animal cannot escape footshocks; the latency to when the animal stops trying to escape is measured.
- Passive avoidance conditioning; latency to escape 24 and 48 h after two inescapable footshocks is measured.

5.3. What do animal models tell us about depression as a risk factor of epilepsy?

Andres M. Kanner

Several epidemiologic studies have demonstrated an association of a lifetime history of depression with an increased risk of unprovoked epileptic seizures and of epilepsy and a worse response to treatment of the seizure disorder to pharmacotherapy and epilepsy surgery [122–124,135,136].

If depression plays an actual pathogenic role in the development of epilepsy, its own neurobiologic pathogenic mechanisms would be expected to impact the epileptogenic process in some form. Three major categories of pathogenic mechanisms of depression have been identified with potential epileptogenic properties in animal models. These include the following: (i) endocrine disturbances, manifested by a hyperactive hypothalamic–pituitary–adrenal axis (HPAA) resulting in high serum cortisol levels; (ii) neurotransmitter disturbances, including serotonin (5HT), norepinephrine (NE), glutamate, and gammaamino-butyric-acid (GABA); and (iii) inflammatory processes.

5.3.1. Hyperactive hypothalamic–pituitary–adrenal axis—An acceleration of the kindling process has been demonstrated with pre-treatment of rats with corticosterone prior to rapid kindling of the amygdala. For example, in one study, male rats randomized to corticosterone-releasing pellets prior to amygdala kindling displayed accelerated behavioral signs of epilepsy and severe tonic–clonic seizures compared with those randomized to placebo [137]. In a second study, Wistar rats pretreated with a low dose of corticosterone achieved a fully kindled state in the electrical amygdala kindling rat model with fewer stimulations than rats pretreated with saline (32 versus 81), while fewer stimulations were needed to reach the first Class V seizure (14 versus 57) [138]. High cortisol levels can impact cortical hyperexcitability through their effects on neurotransmitter transmission, including glutamate, 5HT, and GABA. For example, a decrease in glial cell density and

function associated with high cortisol levels can result in an excess of synaptic glutamate [139].

5.3.2. Neurotransmitter disturbances

5.3.2.1. Decreased serotonergic neurotransmission and noradrenergic neurotransmission:

Decreased serotonergic neurotransmission and noradrenergic neurotransmission have been viewed as important pathogenic mechanisms of depression. Similar findings have been reported in animal models of epilepsy. For example, in the pilocarpine–lithium animal model of SE, abnormal 5HT secretion was demonstrated in the raphe–hippocampal serotonergic pathway, as well as lower 5HT concentrations and turnover in the hippocampus and decreased 5HT release from the hippocampus following raphe stimulation [140]. Furthermore, lowering of serotonergic transmission and noradrenergic transmission has been found to facilitate the occurrence of seizures in several animal models of epilepsy, including the genetic epilepsy-prone rat model and other nongenetic animal models (such as rats, rabbits, cats, and monkeys). This effect was blocked with the use of serotonergic and noradrenergic agents, such as selective serotonin-reuptake inhibitors (including fluoxetine, sertraline, and citalopram), and tricyclic antidepressants (such as imipramine and desipramine). Of note, high cortisol levels have been associated with a decreased expression of 5HT1A mRNA. Yet, an inverted U-shaped antiepileptic effect of 5HT was demonstrated in an animal model of epilepsy in which seizures were induced in conscious rats with pilocarpine. Hippocampal perfusion of 5HT prevented limbic seizures when its extracellular concentrations ranged between 80 and 350% of baseline levels, while concentrations above 900% of baseline worsened seizures [141]. These findings also mirror the clinical observations that antidepressant-induced seizures (with SSRIs and tricyclic antidepressants) are typically associated with overdoses.

5.3.2.2. Glutamatergic and GABAergic disturbances: Animal models of depression have revealed increased CNS glutamatergic activity, mediated by a decrease in the expression of glutamate-transporter proteins [142]. Furthermore, NMDA antagonists have been found to have an antidepressant effect in animal models of depression [143]. In addition, animal models of depression have revealed decreased GABAergic neurotransmission, resulting in increased cortical hyperexcitability.

5.3.3. Inflammatory processes—An increase in proinflammatory cytokines has been found to be an important pathogenic mechanism of depression. Among these, interleukin 1 beta (IL-1 β) has been found to have proconvulsant properties [144]. For example, seizures triggered in rats with kainic acid and bicuculline are exacerbated with intracerebral injection of IL-1 β , while administration of its naturally occurring antagonist (IL-1RA) leads to anticonvulsant activity. Furthermore, IL-1 β , its receptor type 1 (IL-1R1) and IL-1RA were upregulated in the brains of rats that underwent electrically- and chemically-induced seizures.

In summary, animal models of depression and epilepsy can be very helpful in recognizing potential common pathogenic mechanisms of depression and epilepsy, which may explain the bidirectional relation that exists between these two conditions.

5.4. What do human neuroimaging and neurophysiological studies tell us about depression as a risk factor for epilepsy?

Philippe Ryvlin

Depression has long been recognized as one of the most frequent comorbidities in patients with epilepsy. Its prevalence exceeds that of mood disorders complicating other chronic diseases, suggesting direct neurobiological links between seizures and depression. The latter might be subtended by anatomical connections between the cerebral networks affected by seizures and those regulating mood. In experimental models of epilepsy, depression appears mediated by a seizure-induced biological cascade involving enhanced interleukin-1 β signaling in the hippocampus, dysregulation of the hypothalamus–pituitary–adrenal axis, and altered serotonergic neurotransmission.

The neurobiological link between epilepsy and depression is complicated by the observation that mood disorders represent a risk factor for developing epilepsy [135,145] and resistance to antiepileptic drugs [122]. Depression might also increase the risk of epilepsy surgery failure [124,146], though this finding remains disputed [147]. Such observations have raised the issue of the bidirectional link between epilepsy and depression; the mechanisms of which might be enlightened by the further elucidation of the pathophysiology of major depressive disorder (MDD).

A large number of studies have investigated various aspects of neurotransmission in patients with MDD, including measurements of cortical inhibition and excitability using transcranial magnetic stimulation (TMS), magnetic resonance spectroscopy (MRS) of GABA and glutamate brain concentrations, and positron emission tomography (PET) studies of the serotonergic system. Other investigations have concentrated on the structural and functional changes of cerebral networks using MRI and FDG-PET, respectively.

Studies using TMS have disclosed a variety of findings in MDD; most of which are based on the evaluation of motor evoked potentials (MEP). Decreased cortical excitability was observed during postexercise MEP facilitation [148], as well as with paired-pulse stimulation (PPS), though selectively in the left hemisphere [149]. Studies of PPS have also demonstrated decreased intracortical inhibition [150,151]. Both facilitation and intracortical inhibition were restored by antidepressants [152], with correlations between increased inhibition and response to electroconvulsive therapy [150].

Studies using MRS have demonstrated reduced GABA concentration in the occipital cortex of depressed patients [153] that appeared predominantly in treatment-resistant depression [154]. In the former study, the concentration of glutamate was also found increased in the occipital region, in contrast with the observation by other investigators of decreased glutamate concentration in the anterior cingulate gyrus of patients with depression [155]. These findings echo those reported with TMS, where both GABA-dependent intracortical inhibition and glutamate-mediated facilitation were found to be altered, with less consistency for the latter abnormalities.

The GABAergic system can also be indirectly assessed by looking at the GABAA benzodiazepine allosteric site using [11C]-flumazenil PET. Decreased [11C]-flumazenil binding was observed in patients with depression, primarily affecting the parahippocampal region and the lateral temporal cortex [156].

A large number of PET studies have investigated the serotonergic system in depression. The majority of studies have investigated 5-HT1A receptors using [11C]WAY100635, showing partly conflicting results. Whereas most studies reported a reduction of binding potential (BP) in various limbic and neocortical brain regions, as well as in the raphe nuclei of untreated and treated MDD patients [157,158], a few series found an increased BP over the same regions in patients with MDD never exposed to antidepressants (ADs) or not recently medicated [159]. Using [18F]MPPF, another selective antagonist of 5-HT1A receptors with lower affinity that makes it more sensitive to endogenous concentrations of 5-HT, we recently confirmed the presence of decreased 5-HT1A expression in the anterior cingulate and the orbitofrontal cortex of patients with MDD [160]. These abnormalities partly recovered after six weeks of paroxetine treatment. In contrast, [11C]WAY-100635 PET findings were not modified by SSRI treatment [158,161]. Positron emission tomography studies using alpha-[11C]methyl-L-tryptophan (AMT), a precursor of 5-HT, have reported a reduction of this tracer uptake in the anterior cingulate gyrus and the left mesial temporal cortex in patients with MDD, supporting the possibility of reduced extracellular 5-HT concentration in depression [162]. Finally, PET studies of serotonin transporter (5-HTT), using [11C]DASB or [11C]McN5652, have reported conflicting data in patients with MDD, though most series showed increased 5-HTT binding in the thalamus and limbic regions [163].

The technique of FDG-PET has also been extensively used to look at changes in glucose metabolism in MDD and has revealed a mixed pattern of hypo- and hypermetabolism, suggesting altered functional relations between the various structures involved in the regulation of emotions and mood. Typically, decreased activity is found within the dorso- and ventro-lateral prefrontal cortex, the inferior parietal lobule, and the dorsal anterior and posterior cingulate cortices, while hypermetabolism is usually observed in the subgenual cingulate cortex, the amygdala, the hippocampus, and the insula [164].

Finally, MRI has demonstrated the presence of hippocampal atrophy in patients with depression [165], observed as early as the first depressive episode [166]. In fact, several findings suggest that at least part of this atrophy is genetically driven, such as the observation of hippocampal atrophy in healthy subjects with a familial history of depression [167], and its relation to the BDNF Val66Met polymorphism [168].

All together, neurophysiological and neuroimaging findings in MDD demonstrate the presence of abnormalities that might promote the development of seizures, including altered GABAergic neurotransmission and serotonergic neurotransmission, which have a well-established role in experimental models of epilepsy. The extent of changes in excitatory neurotransmission is less clear, however. The presence of glucose hypometabolism might also represent a proepileptogenic trait in MDD, reminiscent of that observed in epilepsy [169], but this is likely to depend on its underlying mechanisms, which remain to be

elucidated. The same applies to hippocampal atrophy, and the pattern seen in MDD differs from that observed in temporal lobe epilepsy with mesial temporal sclerosis [170].

5.5. Inflammatory processes as common pathogenic mechanisms between depression and neurologic disorders

Hrvoje Hecimovic

Inflammation occurs in tissues in response to noxious stimuli. It presents an important endogenous defense mechanism and produces various inflammatory mediators, such as cytokines. Cytokines are humoral mediators with a role in innate and adaptive immunity, and they activate cytokine receptors within the central nervous system. This increases levels of proinflammatory cytokines such as IL-1 β , IL-6, TNF- α , and IFN- α as the main mediators. Pathologically elevated levels of IL-1 β , IL-6, TNF- α , and IFN- α cause cognitive disturbances and depression-like behavior in animal models. Recent experimental and clinical evidence suggests that inflammatory mediators induce neurovegetative and psychological symptoms of depression. Several mechanisms have been proposed for the depressogenic effects of inflammatory cytokines, including increased expression of the 5-HTT, induction of glucocorticoid resistance, and activation of the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase (IDO). In human subjects with chronic inflammatory disease, it was observed that inflammation may lead to depressive symptoms in 10–35% of the afflicted individuals. However, the relationship between inflammation and depression is not necessarily linear.

Proinflammatory cytokines may have a role in the regulation of synaptic plasticity that is impaired in mood disorders. It is hypothesized that activation of the immune system network may be related to some aspects of the complex neurobiology of depressive disorders and that stress may provide a link between depression and inflammation. Antidepressants like fluoxetine, sertraline, or paroxetine have been shown to inhibit INF- α -induced microglial production of IL-6 and nitric oxide, suggesting that inhibiting brain inflammation may represent a separate mechanism of action of antidepressants. Bipolar disorder and schizophrenia have also been associated with increased inflammatory response and elevated levels of proinflammatory cytokines.

Inflammation can also play an important role in seizure disorders without infectious etiology such as in Rasmussen encephalitis or in immune-mediated etiology (VGKC-complex proteins or NMDA receptors) because of increased levels of inflammatory mediators such as cytokines (IL-1 β , IL-6, and TNF- α) and the IL-1Ra receptor antagonist in serum or in CSF.

What is the current evidence that inflammation contributes to epilepsy? Intrahippocampal injection of IL-1 β enhances seizure duration [171]. Nuclear factor kappa B (NF κ B), which is a transcription factor for different proinflammatory molecules, is upregulated in hippocampal astrocytes and neurons of persons with mTLE due to hippocampal sclerosis [172]. In animal models, epileptic seizures induce rapid expression of cytokine mRNA in glia cells. Systemic immune parameters change in CSF and serum several hours after seizures. Studies indicate increased IL-1 levels in pediatric and increased IL-6 levels in adult

patients with epilepsy. Postictally, some groups found changes of serum levels of the proinflammatory cytokines IL-1 β , IL-6, and TNF α in patients with well-defined TLE [173].

Currently, there are no inflammatory biomarkers detectable in CSF and/or serum that are clinically relevant for persons with chronic refractory focal epilepsy. This remains a major challenge for the future in order to determine whether patients with epilepsy can benefit from antiinflammatory or immunomodulatory therapies.

Recent neuroimaging studies with specific ligands, such as a PET radioligand 11C-PK11195, an antagonist of the peripheral-type benzodiazepine receptors, showed increased expression in activated astrocytes and microglia, thus detecting areas of neuroinflammation that may correlate with an epileptic region. Another study suggested that radiotracer 11C-PBR28-translocator protein (TSPO), also a marker of inflammation, is increased in vitro in surgical samples from patients with TLE. Translocator protein can be measured in the living human brain with PET, and uptake of the novel radioligand 11C-PBR28 was higher ipsilateral to the seizure focus in the hippocampus, parahippocampal gyrus, amygdala, fusiform gyrus, and choroid plexus but not in other brain regions. This asymmetry was more pronounced in patients with hippocampal sclerosis than in those without it, suggesting increased expression of TSPO [174].

Experimental models of TLE support an important role of HMGB1 and TLR-4 signaling in mechanisms underlying hyperexcitability. TLR-2 was detected in cells of the microglia/macrophage lineage, in the balloon cells in focal cortical dysplasia, and in giant cells in tuberous sclerosis complex. HMGB1 is ubiquitously detected in nuclei of glial and neuronal cells. In vitro experiments in human astrocyte cultures showed that translocation of HMGB1 from nucleus to cytoplasm was induced by interleukin-1 β .

Future studies will determine the neural pathways involved in the behavioral effects of cytokines, delineate intercellular interactions between brain macrophages, glia, and neurons within this circuitry, and increase our understanding of the mechanistic interaction between the immune system, synaptic plasticity, and antidepressants. They may lead to the development of novel therapeutics. Cytokine antagonists appear to have antidepressant-like effects, even in the absence of an immune challenge. It is possible that antiinflammatory cytokines, primarily IL-4 and IL-10, may be useful in such therapies.

5.6. Describing seizures: discourse analysis in epilepsy and psychogenic nonepileptic seizures

Markus Reuber

The differential diagnosis of blackouts continues to depend on the doctor's ability to take and interpret the history from patients and witnesses. Previous studies suggest that a modest number of factual items (such as the presence of presyncopal symptoms or rapid reorientation on recovery of consciousness) allow clinicians to accurately identify most patients who have transiently lost consciousness because of syncope. Epileptic and psychogenic nonepileptic seizures (PNESs) are more difficult to differentiate from one another. In fact, several studies have demonstrated that self-reported (or witness-reported)

ictal injuries, incontinence, or seizures arising from sleep cannot be relied upon as diagnostic indicators, at least not in isolation. Some ictal features, such as closed eyes during convulsive seizures or seizure duration of more than 3 min, which would indicate PNEs on a video-EEG (VEEG) recording, are not reliably reported by patients or witnesses [175].

Inspired by these difficulties, we have carried out a number of studies that have focused more on how patients with epilepsy or PNEs speak about their seizure experiences than the specific seizure manifestations they mention. Three of these studies will be described and are based on the same dataset — audio- and video-recordings and verbatim transcripts of first encounters of patients with a neurologist (MR). All patients were undergoing video-EEG (VEEG) because their referring neurologist was uncertain about the nature of their seizure disorder. The interview procedure is shown in Table 3.

Twenty patients were included in the first study, and there was one extra patient in the second and third studies. All patients had seizures involving loss of consciousness, and “gold standard” diagnoses (the observation of a typical attack by VEEG) were made in all cases. The transcripts were analyzed by linguists who were blinded to all additional information (including the results of the VEEG monitoring).

5.6.1. Study 1: conversation analysis—In the first study, two linguists used interactional and linguistic profiles typical of epilepsy or PNEs to predict the eventual medical diagnosis. For our study, we initially produced a linguistic scoring form based on an operationalization of 17 previously-described features of potential discriminating value (see Table 4 for the most prominent differential diagnostic features).

Next, two linguists, blinded to the VEEG results, were asked independently to rate each interview on each feature, produce a total score, and generate a diagnostic hypothesis. Both linguists correctly predicted the VEEG-based diagnosis in 17/20 patients. This is quite an achievement considering that two-thirds of the patients carried an incorrect clinical diagnosis prior to their admission [176].

5.6.2. Study 2: metaphor analysis—In the second study, we focused on all metaphors patients used for their attacks in the encounters described above. One linguist, blinded to the medical diagnosis, identified all seizure metaphors. He then categorized the metaphors into different conceptualizations. Of 382 metaphors identified, 80.8% belonged to one of three categories (see Table 5). Most patients used metaphors from all categories, but patients with epileptic seizures strongly preferred metaphors depicting the seizure as an agent/force or event/situation. By contrast, patients with PNEs more often used metaphors of space/place. Logistic regression analyses correctly predicted the diagnosis of PNEs or epileptic seizures in 81.0% of cases [177].

5.6.3. Study 3: textual analysis of references to third parties—In our third study, one linguist, blinded to the medical diagnoses, identified all references to persons not present during the interaction between doctor and patient (third parties). A total of 510 references were identified. Third-party references were used as commonly by patients with epilepsy (mean 23.1/encounter) as by patients with PNEs (mean 26.8/encounter, difference;

n.s.). However, patients with epilepsy were more likely to use a normalizing reference (playing down the significance of their seizures) and patients with PNEs more likely to use catastrophizing references (magnifying symptoms or communicating their own helplessness; $p < 0.01$). Catastrophizing references were 72 times more likely to be used in encounters with PNEs patients (95% CI: 3.8–1361), normalizing references were 33 times more likely to be used in encounters with patients with epilepsy (95% CI: 2.5–444) [178].

5.6.3.1. Psychodynamic significance: Close linguistic analysis can help with the differential diagnosis of seizures, and it can also help us learn more about the nature of PNEs, a condition that remains poorly understood. Detailing block, focusing resistance, and the other discriminating interactional observations communicate aspects of the psychopathology that underpins PNEs. Although further research is needed in this area, the memory gaps, sudden topic shifts, and interactive avoidance of the first-person ictal perspective or of detailed symptom descriptions are likely to be related to ego-structural deficits, dissociative tendencies, attachment difficulties, and unhelpful coping preferences, which put patients at risk of developing PNEs in the first place or that maintain the occurrence of PNEs. Our study of seizure metaphors showed that epileptic seizures are described (and probably experienced) as a more external, self-directed entity that does something to the patient or is witnessed by the patient. Patients with PNEs, on the other hand, are more likely to experience their seizure as a state or place they go into. Patients may feel better understood by physicians who pay attention to their preferred seizure metaphors and who conceptualize the seizures like they do. Our analysis of third-party references reveals that patients with epilepsy use these references to represent themselves as having strong coping skills. Patients with PNEs, on the other hand, use third-party reference to communicate the severity of their condition. The fact that they mention other people when they catastrophize their condition hints at the interactional function of catastrophization — as a potent method to recruit support and protection from others.

5.7. Treatment of psychiatric comorbidities in people with epilepsy

Marco Mula

Data on treatment strategies for psychiatric disorders in epilepsy are still limited. For mood disorders, the evidence for treatment strategies relies heavily on clinical experience. An expert U.S. panel comprising members from the Epilepsy Foundation's Mood Disorders Initiative [179] and an international expert panel of the Commission on Neuropsychiatric aspects of the International League Against Epilepsy [180] composed a consensus statement. In general terms, guidance for treatment of primary psychiatric disorders outside epilepsy is valuable [181,182], taking into account a number of recommendations concerning the underlying neurological condition. In this regard, it is important to point out that whether patients with epilepsy respond equally to psychotropic medications or have different remission rates is still unclear. In fact, it has to be stated that full remission is the final goal of the treatment of a major depressive episode.

The SSRIs (e.g., citalopram 20 mg/day) can be reasonably considered the treatment of first choice, bearing in mind that drug doses need to be adjusted according to clinical response,

especially if AEDs with enzyme-inducing properties are coprescribed [183,184]. Fluvoxamine and nefazodone are the only difficult-to-use compounds. In fact, they are enzyme inhibitors and may potentially increase plasma levels of a number of AEDs (especially carbamazepine and phenytoin) [184]. Adverse effects of SSRIs include hyponatremia, sexual dysfunction, bleeding, and extrapyramidal symptoms [185]. In case of malaise or confusion, electrolytes need to be tested and particular attention is required when SSRIs are prescribed in combination with oxcarbazepine or carbamazepine, both of which are associated with hyponatremia. Sexual dysfunction has been reported in up to 70% of patients taking SSRIs [186]. Therefore, in young males, the use of SSRIs should be carefully considered and other compounds such as bupropion or duloxetine can be considered. Bleeding may represent a concern, especially in elderly patients.

With regard to thought disorders, the treatment of periictal and paraictal psychoses is connected with the treatment of the epilepsy. Neuroleptics can be used for a short period of time as symptomatic therapy to reduce morbidity and mortality. Interictal psychoses may require long-lasting antipsychotic drug treatment. In such cases, patients need to be followed in a psychiatric setting. Neurologists need to be aware that the dose of neuroleptics should always be tailored to the patient's response because in almost all cases, enzyme inducers reduce the plasma levels of these drugs [187]. In particular, the use of clozapine has to be carefully monitored because its metabolism has high interindividual and intraindividual variability and, especially in combination with VPA, interactions are difficult to predict [188]. Weight gain and sedation are among possible adverse effects of antipsychotic drugs and can be accentuated by combination with some AEDs (e.g., valproate and barbiturate). The combination of clozapine with AEDs associated with bone marrow suppression (e.g., carbamazepine and oxcarbazepine) is highly contraindicated.

Finally, the issue of seizure worsening with psychotropic medication represents a special concern for clinicians. However, it has to be acknowledged that for the majority of compounds prescribed at dosages within the therapeutic range, the incidence of seizures is less than 0.5% when other risk factors are excluded [189]. In fact, the proconvulsive effect is likely to be dose-dependent. Among antidepressant drugs, SSRIs can be considered reasonably safe while clomipramine and maprotiline may represent a concern [190]. Among neuroleptics, chlorpromazine and clozapine are generally considered proconvulsant, the former only at high doses (1000 mg/daily) and the latter at medium and high doses (>600 mg/daily) [191]. Clozapine may cause epileptiform EEG changes and seizures even at therapeutic doses. Such effects seem to be dose-dependent and titration-dependent [192]. Electroencephalography abnormalities have been reported in 1%, 2.7%, and 4.4% of patients for doses <300 mg, 300–600 mg, or 600–900 mg/daily, respectively [193]. However, the prevalence of seizures in subjects without a previous history of epilepsy seems to be much lower and in the region of 0.9%, 0.8%, and 1.5% for the same range of doses of the previous study [194]. Seizures are often myoclonic but also generalized tonic-clonic or partial depending on the individual patient. New antipsychotic drugs are usually well tolerated and can be considered reasonably safe as compared with clozapine and chlorpromazine. In particular, olanzapine and quetiapine showed a seizure rate of 0.9% and risperidone an even lower risk of seizures (about 0.3%) [189].

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Fig. 1.
Proposed mechanisms of action in nonepileptic disorders.

Fig. 2.

Spectral modulations derived from MEG source reconstruction compared favorably with those derived from intracranial EEG data. At left, the MEG reconstruction for a visual cortex source and the time-frequency map from the nearest intracranial EEG electrode, with power modulations up to 100 Hz detected with both techniques in both conditions. At right, the activity from left superior temporal gyrus (STG), showing task modulation of high gamma activity with both MEG source reconstruction and intracranial EEG. For each location, the activation maps superimposed on the structural MRI slices correspond to the MEG power modulation over the time-frequency window indicated by the red box on the MEG spectrogram.

Fig. 3.

- a. Zero-lag correlation of a right hippocampus electrode with the MEG sensor array is shown as MEG scalp topography. Sensors with peak correlations at nonzero lag are masked to eliminate spurious correlations due to neural connectivity rather than volume conduction.
- b. In this trace, spontaneous theta oscillations are visible with zero-lag synchrony in the hippocampus depth electrode recording and the most correlated MEG sensor.

Table 1

Antiepileptic drugs in nonepileptic disorders.

Nonepileptic disorder	Antiepileptic drug	Involved mechanism of action
Bipolar disorder	Lamotrigine Valproic acid Carbamazepine	Effects on intracellular signaling pathways, e.g., inositol turnover and metabolism
Acute mania Generalized anxiety Disorder	Valproic acid Pregabalin	GABAergic mechanisms and inhibition of voltage-gated calcium channels
Neuropathic pain	Pregabalin Gabapentin Carbamazepine	Inhibition of voltage-gated calcium channels decreases glutamatergic excitability from the spinal cord
Migraine	Topiramate Valproic acid	Similar effects as for neuropathic pain and antagonistic effects on the AMPA receptor

Table 2

Epilepsy type, laterality, and memory performance for each patient.

Patients	Localization	Lesional/non lesional epilepsy	Memory performance	Hand dominance
Patient 1	Temporal lobe Epilepsy	DNET ^a in the right amygdala	In average	Right
Patient 2	Temporal lobe Epilepsy	Nonlesional	In average	Right
Patient 3	Multifocal extratemporal epilepsy	Nonlesional	In average	Right
Patient 4	Multifocal extratemporal epilepsy	Nonlesional	Lower memory output	Left

^aDNET — dysembryoplastic neuroepithelial tumor.

Table 3

Interview procedure.

Interview phase	Inquiries	Approximate duration
'Open' phase	What were your expectations when you came to the hospital?	10 min
Elicited seizure episode accounts	Can you tell me about the first seizure you can remember? Can you tell me about the last seizure you can remember? Can you tell me about the worst seizure You can remember?	10 min
'Challenge' phase	Inquiry or inquiries challenging the patient's description	5 min
Topic shift	Can you tell me about things which You enjoy doing?	5 min
Doctor's instructions		

Avoid introducing new topics

Tolerate silence

Use continuers (mmm, right etc.) to indicate continued attention

Repeat what the patient has said to encourage elaboration

Table 4

Most important interactional, topical, and linguistic differential diagnostic features.

Feature	Epilepsy	PNESs
Subjective seizure symptoms	Volunteered, detailed	Avoided, no detail ("detailing block")
Formulation work	Extensive	Practically absent
Focus on seizure symptoms	Volunteered, easily maintained	Resisted ("focussing resistance")
Gaps in consciousness	Exact description	Little description

Table 5

Metaphoric conceptualization of seizures.

Category	Seizure as an agent/force	Seizure as an event/situation	Seizure as a space/place	Other
Grammatical subject	Seizure	Seizure	Patient	Variable
Semantic agency	With the seizure	Variable	With the patient	Variable
Examples	Seizures come, go, come in, come on, come up, creep up on you, get you, try to do things, set off, are sent in, are straight there, are fought, counteracted, contained, are let pass, wear off	Seizures happen, occur, take place, are due, start, finish, go on, carry on, develop, are experienced, witnessed, handled, controlled, stopped, avoided/put off, are brought on, run their course	Drifting off, being off somewhere else, going, going off, being gone, coming back, coming round, coming to, going down, being down, not being there, being out into seizures, in seizures, out of seizures, within seizures, through seizures	Seizures are started up, are fixed, like an electrical charge, like the lights are on but nobody's at home, like something going off, like shutting a computer off, like cold or hot water on the top of your head, are as if your head carries on without you