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Epilepsy as a Network Disorder (1): What can we learn from other network disorders such as autistic spectrum disorder and mood disorders?

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Abstract

Epilepsy is a neurologic condition which often occurs with other neurologic and psychiatric disorders. The relation between epilepsy and these conditions is complex. Some population-based

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studies have identified a bidirectional relation, whereby not only patients with epilepsy are at increased risk of suffering from some of these neurologic and psychiatric disorders (migraine, stroke, dementia, autism, depression, anxiety disorders, Attention deficit hyperactivity disorder (ADHD), and psychosis), but also patients with these conditions are at increased risk of suffering from epilepsy. The existence of common pathogenic mechanisms has been postulated as a potential explanation of this phenomenon.

To reassess the relationships between neurological and psychiatric conditions in general, and specifically autism, depression, Alzheimer's disease, schizophrenia, and epilepsy, a recent meeting brought together basic researchers and clinician scientists entitled “Epilepsy as a Network Disorder.” This was the fourth in a series of conferences, the “Fourth International Halifax Conference and Retreat”.

This manuscript summarizes the proceedings on potential relations between Epilepsy on the one hand and autism and depression on the other. A companion manuscript provides a summary of the proceedings about the relation between epilepsy and Alzheimer's disease and schizophrenia, closed by the role of translational research in clarifying these relationships. The review of the topics in these two manuscripts will provide a better understanding of the mechanisms operant in some of the common neurologic and psychiatric comorbidities of epilepsy.

Keywords

Autistic spectrum disorder; Major depression; Stress; Cortisol; Glutamate

1. Introduction

The evaluation of patients with epilepsy (PWE) is not limited to the characterization of the epileptic seizures and syndrome; it demands an early identification and management of common comorbid neurologic and psychiatric disorders that, in fact, tend to occur with a higher frequency in these patients than in the general population. These include stroke, migraine, dementia, and autistic spectrum disorder (ASD) [1] among the neurologic comorbidities, and mood, anxiety, attention-deficit hyperactivity, and psychotic disorders among the psychiatric comorbidities [2]. The need to include these comorbidities in the management of PWE stems from their negative impact at multiple levels, which may be worse than that of the actual seizures, and which can impact the actual course and response to treatment of the seizure disorder [3].

The relation between epilepsy and these comorbidities can be complex and often bidirectional. That is, not only PWE are at greater risk of developing these comorbidities but also patients with these primary psychiatric and neurologic disorders are at greater risk of developing epilepsy [4]. This phenomenon does not imply necessarily causation, but could be explained by the existence of common pathogenic mechanisms operant in epilepsy and these comorbidities.

The Fourth International Halifax Epilepsy Conference and Retreat in September 2016 in Nova Scotia, Canada was devoted to the recognition of potential common pathogenic mechanisms operant in epilepsy, ASD, dementia, depression, and schizophrenia. The goal

was to use these data as a way of understanding reasons behind the relatively high comorbid occurrence of these neurologic and psychiatric comorbidities in PWE and to develop new hypotheses on the pathophysiology of these comorbid conditions.

The first day of the meeting was devoted to the review of ASD and depression, and the highlights of these presentations are summarized in this initial manuscript. The second day focused on dementia, schizophrenia, and translational research, and these are summarized in the companion document.

2. The epidemiology of comorbidity in epilepsy: advantages and limitations (Nathalie Jette)

The meeting was introduced with a review of epidemiologic aspects of these psychiatric and neurologic comorbidities and the limitations of the available data. It is important to understand the epidemiology of epilepsy comorbidity, as these comorbid disorders can contribute to poorer outcomes. For example, depression in epilepsy is associated with poorer response to antiepileptic drugs (AEDs) [5-7], worse seizure outcome after epilepsy surgery [8], poor tolerance of AEDs [9], higher risk of premature mortality [10], and higher health resource utilization [11].

However, there are important methodological issues that must be considered when evaluating epidemiological studies of epilepsy comorbidity. First, the control group (if applicable) should be matched for age and sex and, ideally, also for psychosocial factors as these can influence the prevalence and/or incidence of comorbidity. Second, selection bias must be minimized. Comorbidity, for example, may be more prevalent in a tertiary care clinic where more severe and complex PWE are followed or may be more prevalent in uninsured individuals. The source of ascertainment and the validity of the case definitions used to ascertain epilepsy and its comorbidity must also be carefully considered. Self-report could be associated with under- or overascertainment and recall bias, while administrative data may underascertain psychiatric comorbidities. Most contemporary studies tend to consider many of the above issues, but these caveats must still be considered when interpreting the findings of a study examining the comorbidity of epilepsy.

2.1. Epilepsy and autism

The prevalence of epilepsy in ASD and vice versa can range from about 1% (similar to the general population) to more than 40% depending on the source population. This variation can be explained by a multitude of factors such as methodological variables (e.g., different ascertainment methods), misdiagnosis in those with intellectual disabilities, and more recently, changes in diagnostic criteria. Autism spectrum disorder according to DSM-5 now includes not only autism, but also pervasive developmental disorders not otherwise specified and Asperger's syndrome [12]. A recent systematic review confirmed that the prevalence of epilepsy in females with autism is consistently higher than that noted in males (e.g., 34.5% vs. 18.5% respectively) [13]. In addition, the prevalence of epilepsy in autism tends to be higher in those with lower intelligence quotient (IQ). Finally, in general, the prevalence of epilepsy in children with autism tends to increase with age [14].

2.2. Epilepsy and depression

Depression in epilepsy is common, affecting 24% of those with epilepsy in the general population according to a systematic review. Indeed, those with epilepsy have close to three times the odds of having active depression compared with those without epilepsy in population-based studies [15]. There is excellent evidence to support the bidirectional association between epilepsy and depression [16] (see also below).

2.3. Epilepsy and psychosis

The association between epilepsy and psychosis has been extensively studied relative to other psychiatric comorbidities. A recent systematic review with high level of heterogeneity reported a pooled estimate prevalence of psychosis in epilepsy of 5.6%, psychosis in temporal lobe epilepsy of 7%, interictal psychosis of 5.2%, and postictal psychosis of 2% [17]. Overall, those with epilepsy had an almost 8-fold increase risk of psychosis compared with those without epilepsy. There is also evidence to support the bidirectional association between epilepsy and psychosis [17].

2.4. Epilepsy and dementia

Although epilepsy and dementia are considered common neurological conditions, studies examining their association are scant. In addition, many diagnostic criteria have been proposed for dementia over the years, with one study showing that estimates of dementia ranged from 3.1% to 29.1% depending on the diagnostic criteria applied to the same population [18]. Keeping this in mind and the limited studies on the topic, the pooled period prevalence of epilepsy in dementia is around 5%, while the period prevalence of dementia in epilepsy ranges from 8.1 to 17.5% [18]. Recent studies, however, suggest that the prevalence might be higher especially when considering, for example, focal hippocampal nonconvulsive seizures [19].

3. Autistic spectrum disorder

The session on ASD and epilepsy was introduced with a review of ASD in adult patients with newly diagnosed epilepsy; it was followed by a discussion of clinical and therapeutic aspects of ASD in children with epilepsy. The potential pathogenic mechanisms reviewed included (i) the genetic aspects of ASD, (ii) the theory of an imbalance between excitation and inhibition in children with ASD, such that neural circuits exhibit abnormally high excitation to inhibition ratios, and (iii) the theory of an abnormal connectivity in the brain of these patients, highlighted in the last presentation.

3.1. Autism as comorbidity in new-onset epilepsy: the perspective from an adult first seizure clinic (Bernd Pohlmann-Eden and Karen Legg)

Autism spectrum disorder and epilepsies are both considered brain network disorders (BND) which may cooccur as mutual comorbidities in complex brain diseases. Childhood data suggest that every 20th child with epilepsy develops ASD, and up to 2 out of 5 children with ASD develop epilepsy [13,20], while data from controlled studies in adults are lacking. It is uncertain, which distinct shared causal mechanisms play a role and how to disentangle contributing factors. The topic is further complicated by the fact that there are currently no

biological or specific golds standard diagnostic tests for ASD, while seizures and epilepsy become increasingly well defined as functional and/or structural entities with variable roles of genetic determinants. As indicated by Dr. Jette above, low IQ is a well-established risk factor for ASD in children with epilepsy [13] and vice versa, but there is no consensus on how to conceptualize ASD (without epilepsy) with and without intellectual disability (ID).

Whether epileptiform activity in patients with ASD is a risk factor for the development of clinical seizures remains a source of speculation among investigators. Shared neuropathological findings in ASD and epilepsy include altered excitatory-to-inhibitory balance (mainly dysfunctional gamma-aminobutyric acid (GABA)) neurotransmission and structural abnormalities in the columnar organization of the cortex [21].

Four biological genetically determined pathways of neuronal development and brain function have been implicated in ASD and epilepsy pathogenesis [22]. These pathways include [genes in brackets] 1) transcriptional regulation [FOXG1, MECP2, and MEF2C], 2) cellular growth [PTEN, TSC1, and TSC2], 3) synaptic channels [SCN2A], and 4) synaptic structure [CASK, CDKL5, FMR1, and SHANK3].

The detailed study of adult patients with new-onset seizures who suffered from a preexisting long-term ASD may provide a new perspective to the relation between the two conditions that will potentially help to better understand the concert of mechanisms in BND, and more specifically, about the overlap between ASD and epilepsy. In one retrospective study, 150 individuals diagnosed with autism in childhood were followed to the age of 21 + years old [23]. Epilepsy developed in 22%, and >20% of these patients had developed seizures at or after the age of 20 years. However, there are currently no high quality data derived from prospective longitudinal cohorts.

Unpublished preliminary data from the prospective Halifax First Seizure Clinic (HFSC) cohort identified 6 out of 386 consented adults (as of the data entry starting in 4/2015) with preexisting ASD or 1.6%, who presented with either a first seizure, new-onset epilepsy, or newly diagnosed epilepsy [Pohlmann-Eden et al. 2013, unpublished data]. This percentage most likely represents a significant underestimate of the comorbidity of ASD in our PWE, as the HFSC data bank at this time was set up to identify psychiatric and cognitive comorbidities only (depression, anxiety, and cognitive impairment), and not ASD. In this cohort, the six patients who displayed a high heterogeneity for both ASD and epilepsy syndromes were males with ages ranging from 22 to 29 years; two had mild, two moderate, and two severe ASD. All index seizures leading to clinical attention were generalized tonic–clonic seizures (GTCS). A single GTCS and up to three sporadic GTCS occurred in three patients; all three had an excellent outcome with no further seizures (two were taking an AED) within the following 12 months. Two of these patients had minor structural changes on magnetic resonance imaging (MRI), including a left cavernoma, a Chiari malformation, and a mega cysterna magna. The other three patients developed drug-resistant epilepsy, which failed to be controlled after two to five AEDs, with ongoing GTCS and in one patient, additional focal seizures with loss of consciousness. The patient with the most severe epilepsy had a focal cortical dysplasia in the right frontocentral region, the second had a left temporal heterotopia, while the third had a normal brain CT with MRI still pending. Among

these six patients, electroencephalograms (EEGs) were normal in four, while in the other two patients, focal epileptiform activity was identified in the left temporal region (one in the good and one in the bad outcome group). Though the data are very limited, our findings display a high prevalence of structural epileptogenic lesions, which may be associated with several operating mechanisms in people with ASD who develop seizures.

3.2. The childhood perspective on autism–epilepsy spectrum disorder (Carol S. Camfield & Peter R. Camfield)

3.2.1. Potential causes of ASD—A popular magazine noted: “It is believed that autistic individuals have a surplus of synapses in the brain, due to a slowdown in normal brain pruning” [24]. The association between epilepsy, ID, and ASD is complicated and a common causal factor(s) is possible. For example, it is suggested that “Autism is in part a heritable developmental disorder involving macroscopic early brain overgrowth and dysfunction that affects several cortical and subcortical regions mediating autistic symptoms, including prefrontal and temporal cortices” [25,26]. A specific CLCN4 sex-linked mutation that leads to decreased pruning is associated with autism and epilepsy [27]. However, the causes of ASD appear to be multiple and the biological underpinnings of the associated cognitive impairment and behavioral disorders may be quite distinct from the pathophysiological processes that cause seizures.

Approximately 5–7% of childhood with epilepsy have ASD [28]. Conversely, 29–40% of those with ASD have epilepsy [29]. As already indicated above, the prevalence of epilepsy increases with the severity of the ASD-related ID and age. A Japanese study from a tertiary clinic followed 1014 autistic children and reported that by age ~20 years, the prevalence of epilepsy was 40% with a mean age of onset of 6 years [30]. Interestingly, spike discharges on EEG were identified in 85.8% (870/1014) of patients, although most of the patients with EEG spikes did not develop seizures.

3.2.2. Which children with epilepsy are more likely to have ASD?

1. *Early age of onset of epilepsy:* As noted previously, in a population-based study of 102 Icelandic children with epilepsy onset in first year of life (*excluding West Syndrome*), 7% (6/102) had ASD (all with ID) [13]. Most had generalized epilepsies of structural origin. The Connecticut study which included 613 children with new-onset epilepsy found that 5% (56/613) also had ASD (compared with 0.8% general population) [20]. Ten percent (6/56) of children with ASD had the onset of seizures at <2 years of age.
2. *Intellectual disability (ID) with IQ <70*: A meta-analysis of 10 papers describing the association of ASD and epilepsy found that 627/2112 (30%) had an IQ ≤70 [13]. The prevalence of epilepsy was 8% in autistic subjects without ID. However, epilepsy was present in 21% when ASD occurred with ID. Interestingly, 46% of those with an IQ <40 developed epilepsy. In the Connecticut study, while 5% (56/613) of all children with epilepsy also had ASD, the percentage increased to 14% with IQ <80 [20].

3. *Specific epilepsy syndromes*: The following syndromes are commonly associated with ASD: Dravet syndrome, Landau–Kleffner syndrome, Lennox–Gastaut syndrome, Rett syndrome, CSWS (continuous spike–wave in slow sleep), and any epilepsy caused by tuberous sclerosis.

3.2.3. Treatment of EEG spike discharge associated with ASD—There is controversy concerning treatment for patients with ASD, spike discharges on EEG but no clinical seizures. The frequency of interictal spikes in healthy children is 8%, but it is ~60% in ASD when EEG is recorded during sleep [30]. When a child has epileptiform discharges but no clinical seizures, there is no compelling evidence for or against treatment with AEDs for ASD symptomatology, characteristics, or associated social/behavioral problems. For those with epileptiform discharges and clinical seizures, improvement in ASD symptoms has often been noted with AEDs such as valproate (VPA), levetiracetam (LEV), and clobazam (CLB). However, blinded controlled studies are lacking and a positive outcome may be confounded by concomitant psychosocial interventions. We did not find reports that related the likelihood of improvement with the ease of seizure control or the frequency/severity of generalized or focal seizures. Finally, there are a group of patients with epileptiform discharges, no clinical seizures and cognitive deterioration with ASD. Anecdotal reports suggest cognitive improvement in some with AED treatment, but comprehensive studies are lacking.

For the conundrum of treatment decisions when epileptiform discharges are found, a "nonevidence-based practical approach" was suggested by Sanchez-Fernandez et al. [31]. They made three recommendations, which could also be applied in those with ASD: 1) Epileptiform discharges on EEG in asymptomatic individuals should not be treated – the risks of treatment "*probably outweigh its dubious benefit*". 2) A *treatment trial may be warranted* in patients with epileptiform discharges on EEG plus cognitive dysfunction, regression, or neurologic symptoms that are unexplained by the underlying etiology, comorbid conditions, or seizure severity. 3) Treatment *may be warranted* in patients with cognitive or neurologic dysfunction with epilepsy or epileptiform discharges to control the underlying epileptic syndrome.

In clinical practice, we have found double-blind, "N of 1 trials" to be useful when a caretaker insists on AED treatment for their child with ASD without clinical seizures. Treatment with an AED (usually VPA) or identical placebo is prepared by a pharmacy. Then "treatments" are randomly alternated in 4–8 week blocks with 4–6 separate trials. The blinded parent, school, and other caretakers document weekly cognitive and behavioral function. At the end of the trial, it is usually clear if AED treatment is of any benefit.

In summary, ASD is common in early onset epilepsy, and severe medical and social handicaps need continued attention. Effective early behavioral intervention and intensive teaching can improve the outcome of ASD. In a few children with ASD, treatment with an AED may control seizures and possibly improve cognition and behavior.

3.3. Bridging autism and epilepsy by examining trial-by-trial neural variability (Ilan Dinstein)

Autism, like epilepsy, is often described as a disorder where there is an imbalance between excitation and inhibition, such that neural circuits exhibit abnormally high excitation to inhibition ratios [32]. Evidence for this hypothesis comes from genetic studies that have reported mutations in GABAergic genes [33,34] and postmortem studies that have reported downregulation of GABA-A receptors [35,36] in individuals with autism. Additional studies have also reported reduced inhibition in several animal models of autism [37,38] and the existence of psychophysical phenomena in individuals with autism that are consistent with overexcitation [39-41].

Accurately measuring excitation and inhibition levels in neural circuits requires intracellular recordings, which are not possible in humans. Recent studies, however, have demonstrated that it is possible to measure a potentially related measure of trial-by-trial variability [42]. The mammalian cortex exhibits remarkable trial-by-trial neural variability such that even sensory neural responses to an identical stimulus are variable [43,44]. It has been suggested that the magnitude of trial-by-trial variability of a neural circuit is dependent on the excitation–inhibition balance of neurons in the circuit with larger excitation leading to larger trial-by-trial variability [45]. In autism, it has been specifically hypothesized that overexcitation would lead to excessive trial-by-trial variability [46] and loss of information processing capacity [47].

When considering measures of trial-by-trial neural variability, it is important to distinguish between stimulus-evoked neural variability, which is apparent across trials where an identical stimulus has been presented, and ongoing neural variability, which is apparent across trials without stimuli. A large number of studies have demonstrated that trial-by-trial variability is smaller (“quenched”) after the presentation of a stimulus [48,49]. When measuring trial-by-trial variability in clinical populations and considering potential inferences regarding excitation–inhibition imbalances, it is, therefore, critical to compare corresponding neural measures across similar experiments.

Previous research has demonstrated that individuals with autism indeed exhibit excessive trial-by-trial neural variability in stimulus evoked responses when examined with either functional magnetic resonance imaging (fMRI) [50,51] or EEG [52,53]. These empirical findings suggest that at least some individuals with ASD exhibit less reliable sensory processing. Whether these findings are indicative of abnormal excitation–inhibition balance will require analogous work in animal models of autism, which is currently under way.

Given the strong comorbidity of ASD and epilepsy and their potential shared mechanisms, we believe that these promising results from the autism literature yield strong motivation for examining the same trial-by-trial variability measures in individuals with different types of epilepsy to identify potential similarities and differences across groups and with respect to controls.

3.4. Atypical connectivity in ASD (Evdokia Anasnogstu)

Autism spectrum disorder is a collection of neurodevelopmental disorders characterized by social deficits and repetitive patterns of cognition and behavior. Children and youth with ASD, however, also present with a variety of other signs and symptoms including irritability, hyperactivity, high levels of anxiety, as well as epilepsy, sensory motor issues, and gastrointestinal and immune differences, at rates much higher than predicted by chance.

The etiology of ASD remains largely unknown with rare genetic mutations accounting for 20% of cases [54]. More than 400 genes have been implicated as risk genes, however there is little specificity to ASD. Genes seen in ASD also are seen in ADHD [55], OCD [56], epilepsy [57,58], and ID [59], among others. As such, we started challenging the notion that these disorders represent district biological entities. A recent Canadian research network, the Province of Ontario Neurodevelopmental Disorders Network (POND), is based on this premise and is attempting to use genomic, imaging, cognitive and behavioral phenotypes to stratify patients into subgroups that may respond more uniformly to treatment rather than groupings based on existing diagnostic categories that may or may not be biologically based (pond-network.ca).

Epilepsy and ASD are of interest in this context. As stated in previous presentations, a high prevalence of interictal spikes on EEG has been reported in up to 60% of children with ASD [30], and estimates of prevalence of epilepsy in ASD vary, with as many as 21% of children with ASD and ID having seizures, based on a large meta-analysis from 1963 to 2006 [13].

As stated above, ASD is much more prevalent in children and youth with epilepsy than those without, with a large population-based study estimating the odds ratio of having ASD if having epilepsy to be 22.2 [60]. A large number of studies would support common genetic susceptibility to ASD and epilepsy in a variety of syndromes including tuberous sclerosis, Fragile X syndrome, Angelman syndrome, and Phelan–McDermid syndrome [61-63], among others. As discussed in the next presentation, abnormalities in the excitation/inhibition balance have long been implicated in both conditions. Furthermore, early life seizures in the rodent lead to persistent excitation and decreased GABA currents, as well as short-term plasticity in the prefrontal cortex, which are associated with decreased hippocampal prefrontal cortex synchrony and impaired sociability as well as rigidity [64,65].

Accumulating evidence from independent routes of study suggests that ASD, like epilepsy, is a network disorder. We and others have shown age-related changes in long range structural connectivity in children with ASD compared with sex-matched controls [66-68] as well as aberrant functional connectivity during resting state in fMRI [69], and alterations in linear and nonlinear age-related changes in resting oscillatory power and network synchrony [70]. Such changes correlate with severity of core symptom domains or adaptive skills, suggesting that they are describing at least part of the pathophysiology of ASD.

In this context, both ASD and epilepsy can be conceptualized as disorders of aberrant connectivity, with one shared mechanism being a distorted excitation/inhibition balance. Overlapping genomic structure as well as environmental influences as demonstrated by early life seizure rodent models likely account for this overlap. Understanding that which

is shared and that which is distinct between the two disorders is likely to illuminate both the neurobiology of these disorders but also provide new molecular and circuitry targets for intervention that may benefit shared phenotypes and potentially change the developmental trajectory of those affected.

4. Depression and epilepsy

The second session of this meeting was devoted to the discussion of potential common pathogenic mechanisms operant in depressive disorders and epilepsy with the aim of trying to understand the relatively high comorbidity of the two conditions and a suspected negative impact of mood disorders on the course of the epilepsy. The first presentation reviewed a variety of pathogenic mechanisms that have been identified in both mood disorders and epilepsy which could explain these observations. In a second presentation, an animal model of stress is used to suggest an explanation of the high comorbidity. Finally, the use of deep brain stimulation for the treatment of treatment-resistant depression and treatment-resistant epilepsy serves as an example of abnormal networks operant in both conditions.

4.1. Do neurobiologic pathogenic mechanisms in epilepsy facilitate the development of treatment-resistant epilepsy? (Andres M. Kanner)

As stated above, depression is the most frequent psychiatric comorbidity in PWE, often occurring together with anxiety disorders, with lifetime prevalence of up to 35% in population-based studies [11]. Several population-based studies have demonstrated a bidirectional relation between epilepsy and depression, in which people with primary depressive disorders have a two to fivefold higher risk of developing epilepsy [7,71-73]. Furthermore, one population based-study [7] and two other studies with newly diagnosed epilepsy [5,6] have suggested that patients with a depressive disorder preceding the onset of epilepsy have a twofold higher risk of developing treatment-resistant epilepsy, particularly among patients with depression with more severe mood disorder [7]. Can pathogenic mechanisms operant in mood disorders help mediate the higher risk of developing epilepsy and/or the worse course of the seizure disorder?

4.1.1. Pathogenic mechanisms of depression that could facilitate the epileptogenic process—Three potential types of pathogenic mechanisms operant in mood disorders could potentially have an impact on cortical hyperexcitability and the epileptogenic process; they include the following: 1) neurotransmitter disturbances involving serotonin, norepinephrine, glutamate, and GABA; 2); endocrine disturbances manifested by a hyperactive hypothalamic–pituitary–adrenal axis (HPAA), which can result in structural and neuropathologic abnormalities of cortical and subcortical structures, and 3) immunologic disturbances.

4.1.2. Neurotransmitters' disturbances—Decreased serotonergic and noradrenergic activity are pivotal pathogenic mechanisms of mood disorders and have been found to be present in several animal models of epilepsy as well as in functional neuroimaging studies of humans with temporal lobe epilepsy (TLE) [74].

Glutamate and GABA are two neurotransmitters with pivotal pathogenic roles in epilepsy with opposite effects: glutamate is a neurotransmitter with excitatory properties “par excellence”, while GABA has widespread inhibitory effects. Yet, high glutamate activity has also been identified in animal models of depression [75], and high glutamate concentrations have been identified in CSF and plasma of patients with major depression, while high cortical glutamate has been reported in neuroimaging studies with magnetic resonance spectroscopy (1-MRS) in these patients [76].

Similarly, low cortical GABA concentrations have been reported in 1-MRS studies of patients with primary depression, as well as in neuropathologic studies of suicide victims [77]. Finally, a low GABA tone has been documented with neurophysiologic studies of transcranial magnetic stimulation (TMS) of patients with major depression [78]. Transcranial magnetic stimulation is based on the activation of cortical neurons with pulsatile magnetic fields and relies on GABAergic inhibition measured with two variables: short-interval cortical inhibition and the cortical silent period, both of which were abnormal in these patients. Thus, the same neurotransmitter abnormalities that are present in epilepsy can be identified in experimental and clinical studies of mood disorders.

4.1.2.1. Endocrine disturbances.: A hyperactive HPAA yielding high cortisol blood levels was among the first neurobiologic disturbances identified in up to 50% patients with primary major depression [79]. Likewise, in experimental animal models of epilepsy with rats, corticosterone has been found to facilitate the kindling process, one of the principal models of epileptogenesis [80,81]. High cortisol levels can impact cortical hyperexcitability through their effects on neurotransmitters' transmission, including glutamate, 5HT, and GABA. For example, a decrease in glial cells' density and function associated with high cortisol levels can result in an excess of synaptic glutamate.

High cortisol serum concentrations have been associated with structural and neuropathologic changes in temporal and frontal lobe structures. In animal models of depression, a reduction in the total number of CA3 neuronal cells and interference with neurogenesis of granule cells in the adult hippocampal dentate gyrus have been reported [82], two changes that are typically seen in animal models of chronic TLE and which have been associated with persistence of spontaneous seizures. Furthermore, in patients with primary major depression, a 10 to 20% bilateral decrement in the hippocampal volume has been reported by several investigators [83], the magnitude of which has been correlated with the duration of the depressed state.

Likewise, high cortisol plasma levels have been associated with decreased cortical thickness in the frontal lobe of patients with primary major depression, which has been attributed to a decrease in glial and/or neuronal cell density and size identified in the cingulate gyrus, in several layers of the rostral orbitofrontal cortex, and of the caudal orbitofrontal cortex, and the dorsolateral prefrontal cortex [84,85]. The impact of these changes in PWE is illustrated in one study, which used voxel-based morphometric analyses in brain MRI studies of 48 adults with treatment-resistant TLE, 24 with and 24 without MDE, and 96 healthy controls [86]. Patients with TLE and depression had a greater number of areas with gray matter

volume loss than those without depression in temporal and frontal lobe regions bilaterally and in the left thalamus.

4.1.2.2. Immunologic disturbances.: Proinflammatory cytokines, in particular interleukin-1β (IL-1β), IL-2 IL-6, interferon-γ (IFN-γ), and tumor necrosis factor-α have been identified as pathogenic mechanisms in animal models of depression and in clinical studies in patients with mood disorders [87,88]. Among these, IL-1β has been found to have proconvulsant properties in animal models of epilepsy with rats using kainic acid and bicuculline, in which seizures were exacerbated with its intracerebral injection [89,90], while administration of its naturally occurring antagonist (IL-1RA) was found to show anticonvulsant activity [91]. Furthermore, IL-1β, its receptor type 1 (IL-1R1) and IL-IRA were found to be overexpressed in human brains of patients with TLE, cortical dysplasias, and tuberous sclerosis [92-94].

Yet, most patients with mood disorders do not develop epilepsy and/or in those that do, not all develop treatment-resistant epilepsy. One possible explanation is suggested in the next presentation by Christoph Bernard.

4.2. Comorbidities in brain disorders: is the answer to be found in a history of stress? (Christophe Bernard)

Most, if not all, neurological disorders, including epilepsies, Alzheimer's disease, and Parkinson's disease, are associated with comorbidities such as depression and cognitive deficits. But why do only some patients suffer from comorbidities? One possibility is that the complex reorganizations of brain circuits that accompany these disorders are patient-specific, and that these pathology-specific reorganizations directly enable the expression of comorbidities. Another, non-exclusive and complementary, hypothesis involves reorganizations of brain circuits occurring *before* the onset of the disorders. In the latter case, the pathological processes associated with the brain disorder would act as a trigger for the expression of comorbidities in an already vulnerable environment.

One of the most common events experienced by all living organisms is stress. Stressful occasions induce numerous circuit alterations in the brain (e.g., dendritic retraction and spine loss). Such alterations can be transient with a return to prestress conditions. But if they accumulate as one goes through multiple stressful situations during one's life, the threshold for the expression of comorbidities may be crossed. This is known as the diathesis–stress model, which was introduced to explain why stress triggers psychiatric disorders, including depression, in some individuals and not others [95].

The diathesis is the intrinsic vulnerability of an individual, which depends upon genetic and environmental factors. The diathesis sets the threshold. The model posits that when unresolved stress crosses the threshold, depression is expressed. We have validated the diathesis–stress model experimentally [96]. When exposed to an intense stress (social defeat), rats display numerous anatomical alterations, including dendritic retraction, spine loss, and accumulation of reactive oxygen species. These alterations are transient in 50% of the animals, while they are maintained in the other half. Hence, the intense stress left a stable alteration of brain circuits in some animals. When exposed to a mild stress one month

after social defeat, a depression-like phenotype is found solely in animals with maintained alterations. This study shows that social defeat produced a state of vulnerability in half of the animals, in effect bringing close to the threshold to express depression [96]. The mild stress made them cross the threshold. The nonvulnerable population remained far from the threshold. I extended the diathesis–stress model to the diathesis–disease model, in which a pathology would act as a force to push a vulnerable population over the threshold of comorbidities [97]. We validated this model using epilepsy as the trigger in animals exposed to social defeat [98]. We found that only vulnerable animals display cognitive deficits and a depression-like phenotype after epilepsy onset [98]. In addition, epilepsy was more severe in vulnerable animals as compared with nonvulnerable animals, demonstrating that the sustained circuit alterations induced by an intense stress have a direct impact in the development of phenotypic traits.

Importantly, we found that low serum Brain derived neurotrophic factor (BDNF) levels is a predictive biomarker of the vulnerable population [96], together with altered EEG patterns [99]. We have identified the mechanism of vulnerability, which involves a BDNF-dependent downregulation of the transcription factor Nrf2, which controls antioxidant defense mechanisms [100]. Treating animals with a BDNF mimetic, an activator of Nrf2, or antioxidants abolishes the state of vulnerability, hence, the occurrence of comorbidities [96,98,99].

This validation of the diathesis-disease model supports the hypothesis that a history of unresolved stress may be responsible for the expression of comorbidities in some patients. Animal studies suggest the existence of predictive biomarkers of vulnerability and ways to reverse it before the occurrence of the pathology. This information needs to be translated to the clinic.

4.3. Deep brain stimulation and depression: a model for a network approach (Peter Giacobbe)

Depression, much like epilepsy, is a heterogeneous condition both clinically and etiologically. Rather than being conceptualized as a simply “deficit state”, evidence from neuroimaging suggests that depression may reflect abnormalities in distinct neurocircuit subserving functions such as cognitive control, affect regulation and cognition. Converging factors have contributed to an interest in the reconceptualization of depression as a “circuitopathy”. There is growing recognition among psychiatric clinicians that the brain is an electrochemical organ, and both medication and brain stimulation can have synergistic effects [101,102]. Furthermore, advances in brain stimulation technologies have provided multiple means of modulating activity in discrete structures in the brain [103]. One such brain stimulation approach to treatment-resistant forms of depression is Deep Brain Stimulation (DBS), an invasive surgical approach most often employed for the treatment of movement disorders [104].

The results of DBS studies for drug-resistant depression suggest that it appears to alter homeostatic activity in emotional circuits in the brain leading to delayed but sustained improvements in depressive symptoms and quality of life [105], as well as electrophysiological changes [106] that may accrue over months of stimulation. In a similar

fashion, chronic electrical stimulation of the brain for epilepsy leads to acute and sustained long-term antiseizure effects [107]. Exploration of the shared and distinct short- and long-term adaptations that occur with chronic DBS and chronic electrical stimulation for epilepsy may help to elucidate the mechanisms of action whereby electrical brain stimulation leads to remodeling of pathological circuit and network activity, leading to improved patient outcomes for patients with difficult-to-treat neuropsychiatric illnesses.

5. Summary and conclusions

A review of the concepts discussed in the previous sections clearly demonstrates a complex relation between psychiatric and neurologic disorders. Available preclinical and clinical data appear to support the existence of common pathogenic mechanisms and/or disruptions of common neurocircuits in the brain that may start providing explanations for the higher prevalence of neuropsychiatric (e.g., depression and ASD) and neurologic (e.g., epilepsy) disorders.

The Fourth Halifax International Epilepsy Conference & Retreat (HIECR) was an innovative attempt to bring experts from very different fields together to focus on the concept of BND. It was meant to be a think tank and allow fresh discussions across disciplines which usually would not take place, as increasing specialization unfortunately has led to mainly “in-group conferences”. In other words, epileptologists, for example, usually gather in several meetings over the years, repeatedly share their experiences among colleagues, and try to grasp the underlying mechanisms of seizures and epilepsy, while often unconsciously sitting and acting in silos. The same is true for psychiatrists, internists with focus on geriatric topics, etc. A need for new formats of sharing scientific information in medicine is obvious. We have to challenge our own methodology and view of phenomena by aiming for a bigger picture and inviting approaches from other fields in brain research.

The 4th HIECR certainly revealed a treasure of data and new insights and sometimes surprising overlap.

The various contributions from highly diverse perspectives seem to have as common agreement that we are just at the beginning in understanding the complexity of brain circuits and in which way symptoms in an individual patient manifest dependent on many factors including genes, acquired hits, aging factors, and predisposing functional or morphological parameters.

The increasingly recognized bidirectional relationship between epilepsy and depression is an excellent example for the concert of biochemical and structural components in brain circuits challenging the concept of disease entities and opening a discussion around terms such as comorbidity and spectrum disorders. The frequent overlap between autism and seizure threshold reduction as demonstrated in several contributions is another highly fascinating perspective into shared common mechanism.

It is obvious, that we have to take more advantage of new techniques available, e.g., applying more rigorously modern MRI modalities in autisms. This appears to be a real opportunity.

An extension of the outlined new themes around brain circuits will be found in part 2 of the 4th HIECR proceedings with focus on dementia, schizophrenia, and translational research in light of seizures and epilepsy.

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Conflict of interest

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