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Epilepsy as a Network Disorder (2): What can we learn from other network disorders such as dementia and schizophrenia, and what are the implications for translational research?☆

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ABSTRACT

There is common agreement that many disorders of the central nervous system are 'complex', that is, there are many potential factors that influence the development of the disease, underlying mechanisms, and successful treatment. Most of these disorders, unfortunately, have no cure at the present time, and therapeutic strategies often have debilitating side effects. Interestingly, some of the 'complexities' of one disorder are found in another, and the similarities are often network defects. It seems likely that more discussions of these commonalities could advance our understanding and, therefore, have clinical implications or translational impact. With this in mind, the Fourth International Halifax Epilepsy Conference and Retreat was held as described in the prior paper, and this companion paper focuses on the second half of the meeting. Leaders in various subspecialties of epilepsy research were asked to address aging and dementia or psychosis in people with epilepsy (PWE). Commonalities between autism, depression, aging and dementia, psychosis, and epilepsy were the focus of the presentations and discussion. In the last session, additional experts commented on new conceptualization of translational epilepsy research efforts. Here, the presentations are reviewed, and salient points are highlighted.

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1. Introduction

After decades of focused research into complex disorders such as dementia, schizophrenia, and epilepsy, it has become clear that there are overlapping components. Often, this interrelationship is simplified by stating that seizures are a "comorbidity" of what is considered to be "another" disorder like Alzheimer's disease, or epilepsy is a "risk factor" for Alzheimer's disease. The implication is that "neurology" and "psychiatry" are less divided than one might think, and our approach to research and treatment should be adapted accordingly.

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

The preceding publication by Kanner et al. (in this issue) describes the first presentations of the meeting, which summarized the current understanding of epidemiological data on all the medical conditions listed above in relation to their co-occurrence with epilepsy (Session "A" of the meeting program). The prior paper also discussed the second session of the program ("B"), which provided perspectives on the overlap and/or bidirectional relationship of autism and epilepsy. This was followed by a discussion of depression and epilepsy in the next session ("C"). Below, the second half of the program, sessions D–F, are summarized. First, an overview of session "D" is provided, which focused on the reasons and potential common pathophysiology underlying the comorbidity of aging and dementia. Session D was followed by different viewpoints about psychosis in people with epilepsy ("E"). The last session of the meeting ("F") included presentations of diverse researchers who tried to address a very difficult topic, the current conceptual thinking in translational research with respect to brain networks and abnormalities in neuronal circuitry in epilepsy.

2. Aging, dementia, and epilepsy (part "D" of the meeting program)

A very common complaint in patients with epilepsy is a change in memory and behavior [1,2]. In addition, it has been noted that patients have seizures when the primary diagnosis is dementia [3–6], the prototype being Alzheimer's disease. These clinical observations have led to a great deal of research to clarify the extent of these associations epidemiologically, and led to extensive efforts to develop and use animal models to understand potential mechanisms. In the past decade, the extent of the research has expanded greatly, making it timely to discuss the current state of knowledge. In addition, whether a new direction or set of directions in research should be taken is important to consider.

As pointed out by Nathalie Jette (University of Calgary) in manuscript 1 (Kanner et al., in this issue), epidemiological studies are very heterogeneous in their methods, so it is not clear whether any given comorbidity is common or rare. For example, self-report is not always accurate (and certainly poor in those with dementia), population-based data may include screening tools that are not validated, and underdiagnosis and underascertainment are further limitations. It is also problematic that 'dementia' is increasingly called 'neurocognitive disorder'. The extent of epilepsy (spontaneous recurrent seizures) in dementia is not as clear as the degree that single seizures occur with dementia. Regarding dementia itself, Erkinjuntti et al. [7] report estimates of dementia alone in the range of 3.1–29.1%, depending on diagnostic criteria. 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% (for review, see [8]).

2.1. The neurovascular unit in aging and epilepsy

Alon Friedman

The "neurovascular unit" includes the vasculature and its functional interactions with the adjacent brain neuropil, including pericytes and adjacent extracellular matrix, neurons, and glia. Current animal research demonstrated in several models the role of compromised blood–brain barrier (BBB) in seizures and epileptogenesis, cognitive decline, and neurodegeneration.

Injury to a brain blood vessel not only results in activation of clotting mechanisms but also is followed by a progressive, often long-lasting increase in endothelial permeability [9]. Blood–brain barrier dysfunction following insults to the brain may last months and even years after injury [10,11]. It triggers the activation of astrocytes and neuroinflammation [12,13] that, depending on the brain region involved and age of the animal, will result in epileptogenesis and seizures [14,15]. One reported mechanism is the leak of serum proteins from the blood into the brain neuropil. Albumin, for example, has been shown to leak and activate transforming growth factor tumor growth factor beta (TGFβ) receptors and activate a proinflammatory signaling system. Mediated by phosphorylation of the Smad2/3 pathways, changes in gene expression underlie glial transformation [12] with altered extracellular homeostasis, neuroinflammatory response with rapid increase in IL-6 release as well as other proinflammatory cytokines [13,16], changes in extracellular matrix with reduced Gamma amino-butyric acid (GABAergic) transmission [17], and excitatory synaptogenesis with pathological plasticity [18]. The presence of serum albumin within the hippocampus will lead to further aberrant adult neurogenesis in the dentate gyrus, which has been suggested to alter the threshold for seizures [19–21]. Recent development of imaging methods allow quantitative imaging of BBB dysfunction after injuries to the cerebral cortex and white matter tracts (e.g., in American football players [22]).

Importantly, endothelial dysfunction triggers not only a neuroinflammatory response and epileptogenesis, but also prolonged seizures and status epilepticus — well-known inducers of the epileptogenesis process associated with vascular pathology [23,24] and leaky BBB [25]. In epileptic animals, vascular pathology was also reported to reflect angiogenesis [26] probably because of increased vascular endothelial growth factor (VEGF), which is important because VEGF can have anti-seizure effects [23,24,27]. Changes in BBB integrity are also observed with aging and were recently associated with cognitive decline [28]. The increased occurrence of BBB dysfunction in the aging brain may also explain the well-known increase in the incidence of epilepsy with age. Together with the development of novel imaging methods for the detection of BBB pathology, it has been suggested that a leaky BBB may become a method for the identification of injury- or age-related brain regions with hypersynchronous activity, or undergoing epileptogenesis, thus allowing the prediction of epilepsy [29] and related cognitive dysfunction. Overall, this presentation emphasized the close association of BBB leakages resulting from nonspecific injuries and age-related factors with seizure threshold reduction [22].

2.2. Network abnormalities and interneuron dysfunction in Alzheimer's disease

Jorge Palop

There is increasing evidence of commonalities between epilepsy and Alzheimer's disease in experimental findings in mice that overexpress a mutated form of amyloid precursor protein (APP), so that amyloid Aβ is increased. The original research demonstrated hyperexcitability in several animal models that simulate Alzheimer's disease neuropathology (for review see [30]).

These laboratory findings have been replicated, especially with models using the mice with APP overexpression and mutation [31–35]. Several clinical studies have found sporadic seizures in people with Alzheimer's disease. In one study [36], seizures were found particularly in patients with an onset of Alzheimer's disease that was relatively young (e.g., 50–70). In a recent paper by Zarea et al. [6], 132 patients of dominantly inherited Alzheimer's disease had seizures. However, these studies of familial Alzheimer's disease reflect the minority of patients because the vast majority are sporadic.

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A critical factor in memory encoding is the activation of brain regions by the default mode network (DMN). Here, DMN deactivation is followed by hippocampal activation. In general, low performance on cognitive tasks occurs with high activation of the hippocampus, suggesting that suppressing the activation is critical to cognitive function. Interestingly, the deactivation of the DMN is decreased in Alzheimer's disease. This was found at various stages (e.g., mild cognitive impairment, early onset, and late onset). Buckner et al. [37] showed amyloid deposition in the DMN in Alzheimer's disease which could be a mechanism for the loss of suppressed activation.

Current research addresses the paradox that there is synaptic depression in Alzheimer's disease despite the presence of seizures. There is evidence that gamma oscillations are altered in the mouse models of Alzheimer's disease, which commonly is considered to result from interneuron activity. This led to a closer examination of interneurons. Decreased voltage-gated sodium channels, specifically NaV1.1, were found in interneurons in mice with overexpression and mutation of APP (J20 mice). This finding led to experiments using NaV1.1 overexpression in interneurons, which rescued the deficits in gamma and also stopped seizures. In the J20 mice, 30–50 Hz was most affected. Faster gamma (>50 Hz) is currently considered to be driven by the entorhinal cortex. It has been suggested that normally, there is "competition" and the entorhinal cortical influence usually "wins", but the data from Dr. Palop's laboratory suggest that the entorhinal cortex is not dominant in the J20 mouse model. This could potentially explain the reduced cognitive function in the J20 mice. It is very interesting that J20 mice frequently have sudden unexplained death in epilepsy (SUDEP), a phenomenon found in epilepsy that has prompted intensive research. Preliminary animal data suggest that overexpression of NaV1.1 improves survival, opening a novel approach to understand SUDEP.

One of the barriers to translating these findings is using overexpression of NaV as a therapy in humans. Current ongoing work is focusing on an approach that uses transplantation. Medial ganglionic eminence (MGE) cells were chosen as they develop into interneurons. As a first step, his laboratory has transplanted MGE cells lacking NaV1.1 into J20 mice to determine if this improves the cognitive deficits; Nav1.1 activators are also being used to determine if they are helpful.

2.3. When and how epilepsy is relevant to Alzheimer's disease

Helen E. Scharfman

Findings in animal models of Alzheimer's disease in Dr. Scharfman's laboratory support the view that seizures in Alzheimer's disease are much more common than people often think [38,39]. Literature, both in humans and animals, shows robust evidence for seizures. This is most common in individuals who have familial Alzheimer's disease and mouse models that simulate the familial form of Alzheimer's disease. It is important to recognize that seizures may be underestimated because they are nonconvulsive, a type of seizure that has been documented in mouse models [40].

Electroencephalogram (EEG) abnormalities can be observed as early as the first month of life in mouse models [35]. This was also found in mice as young as 3 months, which simulate Down's syndrome (Ts65Dn mice; [35]), of which almost all develop dementia. The mice that simulate Alzheimer's disease pathology were the mouse lines with mutations in APP that are found in Swedish or London families with Alzheimer's disease (APPSwe or APPLon mice; APPSwe mice are often called Tg2576 mice).

The EEG abnormalities that are found in young mice appear to be interictal spikes (IIS) based on comparisons with recordings from mice with epilepsy (e.g., the pilocarpine model) using the same EEG equipment [35]. However, seizures appear to be rare in the APPSwe or APPLon mice compared with the pilocarpine model, so attention has been focused on understanding the IIS. One clue came from recordings with continuous video-EEG that showed that IIS occurred primarily in rapid eye movement (REM) sleep [35]. Current efforts focus on the novel hypothesis that septohippocampal cholinergic neurons appear to be overly active early in life, leading to IIS in REM sleep. Later in life, there appears to be a deterioration of the septohippocampal pathway, consistent with older views of cholinergic deterioration in Alzheimer's disease. In contrast, the existing view of Dr. Scharfman is that early in life, there is hyperactivity of the cholinergic system and then the cholinergic system degenerates. This has not been found before because the brain has mostly been examined late in life. In support of this hypothesis, several measures of cholinergic neuron activity were shown to be high in young Tg2576 mice, and systemic injection of the muscarinic cholinergic antagonist atropine decreased the IIS in Tg2576 mice [35].

2.4. Features of creatures subjected to seizures

Hans Förstl

> *"There are many sinks (in life) and if you don't fall into one of them you get demented."*

There is a need for novel ways to conceptualize dementia relative to other conditions. These comparisons are problematic, because many diseases can lead to dementia. However, diseases may seem to have a lot in common, but the similarity may only be due to the fact that there are so many contributing factors to each condition.

Complex presentations with both dementia and seizures have a wide range of etiologies from rare fatal familial insomnia [41] to dementia with Lewy bodies [42], a disorder with a delicate neurotransmitter imbalance in the upper brainstem.

The single most important cause of dementia is Alzheimer's disease. The most prevalent type of dementia is the so-called "mixed dementia", because the elderly usually do not have only one clinical condition, and age-related changes to vascular factors certainly play a significant role in most of these scenarios. The current operational definition of dementia is a loss of cognitive function affecting several domains that is so severe that the usual activities of daily living are significantly impaired. Historically, Alzheimer's disease as a disease concept started when Alois Alzheimer studied the brain of a 52 year-old with symptoms of what is now considered Alzheimer's dementia. He saw plaques, which had already been described by others, and identified a new staining method for neurofibrillary tangles. These observations led him to call the condition presenile dementia, but his superior suggested he call the condition Alzheimer's disease. During that period, Solomon Carter Fuller (1872–1953), a guest in Alzheimer's laboratory, had invested even more time into the investigation of senile dementia and saw similar neurodegenerative changes. Oskar Fischer (1876–1942) had also described a "sphaerotrichia multiplex cerebri" (=amyloid plaques) in the brains of patients with senile dementia. Heiko Braak clearly described the systematic development of neurofibrillary tangle pathology over a lifetime. The clinicopathological Medical Research Council Cognitive Function and Ageing Study (MRC-CFAS) demonstrated that there was no categorical, but only a gradual difference regarding plaque, tangle, and vascular pathology between epidemiologically representative groups of demented and not (yet)-demented individuals [43]. McKhann et al. [44] published the recent National Institutes of Aging criteria clearly distinguishing between Alzheimer's disease (biology, etiology, brain change) and Alzheimer's dementia (the clinical syndrome of significant cognitive impairment due to Alzheimer's disease). There is evidence from neuropathological studies showing that first tangles occur already in childhood. The current goal is to identify Alzheimer's disease at an early stage.

A limited number of interventions are currently available for the symptomatic pharmacological treatment of Alzheimer's dementia. Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist with modest effects. Cholinesterase inhibitors are helpful if there are no serious contraindications or side effects. A promising treatment is

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immunization [45], but some drugs that have reached clinical trials had to be discontinued because of encephalitis. Later, passive immunization was developed as an alternative approach, but that appears to be problematic also, possibly because treatment may be too late. Monoclonal antibodies for amyloid are being tested [46]. One of the reasons why treatments based on antibodies may not work well is based on research from Busche and Konnerth [47]. What may be better is a gamma secretase inhibitor, but these drugs also have side effects.

There is a need for novel ways to conceptualize dementia relative to other conditions. These comparisons are problematic, as almost any severe disease can lead to dementia. Diseases may seem to have a lot in common, but the similarity may only be due to the fact that there are so many contributing factors to each condition.

Complex presentations with both dementia and seizures have a wide range of etiologies. They are found in rare fatal familial insomnia [41] or in more common types of dementia with Lewy bodies [42] — a disorder with defects in brainstem, substantia nigra, as well as in the basal forebrain cholinergic neurons.

3. Schizophrenia (part "E" of the meeting program)

For decades, it has been noted that seizures and schizophrenia may coexist and share relevant pathophysiological mechanisms. The following contributions will provide diverse perspectives on the two disorders from both clinical and experimental views.

3.1. The face of postictal psychosis: the meeting of epilepsy and schizophrenia

Candice E. Crocker

Brain diseases with neurological functional deficits in general tend to increase susceptibility to psychiatric diseases. For example, psychiatric comorbidities in epilepsy such as anxiety and depression are well recognized. There has been also striking evidence for a long time that individuals with epilepsy are at greater risk of experiencing psychotic episodes than the general population, and conversely, people with schizophrenia may develop epilepsy [48]. It is estimated that 10–30% of patients with epilepsy may have psychotic symptoms [49,50]. When these symptoms evolve into clear psychotic episodes, they are referred to as the psychoses of epilepsy.

The classification of the psychoses of epilepsy is traditionally based on the timing of the psychotic symptoms relative to seizure occurrence (i.e., ictal, postictal, and interictal [48]). "Alternative psychosis" is well known to occur in relation to successful seizure control as a result of antiepileptic drug (AED) treatment or after epilepsy surgery [51]. Interictal psychosis of epilepsy is likely the most common and best characterized psychotic disorder in patients with epilepsy. In postictal psychosis (PIP), psychotic symptoms occur after a seizure or series of seizures followed by a lucid interval, and within 7 days of the seizures, delusions and hallucinations occur (often associated with postictal confusion), but there is preserved orientation and alertness; the presentation can have a strong affective component [52]. The psychotic event can be prolonged, lasting for days or sometimes weeks, and it terminates on its own. The prevalence of postictal psychosis has been estimated to occur in as many as 10% of people with pharmacoresistant temporal lobe epilepsy (TLE), but a meta-analysis suggests that the overall rate is closer to 2% of people with epilepsy [50,52].

How close the psychoses of epilepsy are to primary psychotic disorders such as schizophrenia is debated. Psychotic disorders are characterized by abnormal thinking and perception and a loss of touch with reality. Schizophrenia has both positive and negative symptoms (emotional flatness, apathy, lack of speech) and cognitive impairments as well as challenges with social functioning. Schizophrenia is characterized by periods of psychosis that vary in duration. By comparison, PIP lacks negative symptoms. It is also usually of comparatively short duration. However, there are points of convergence as well. There is some evidence of overlap in genetic abnormalities that can be seen in both schizophrenia and epilepsy, but the possible associations have not been well-studied [53]. Schizophrenia can develop following postictal psychosis, and patients with chronic psychoses of epilepsy can have enlarged ventricles similar to those seen in patients with schizophrenia [54]. These comparisons raise the possibility of overlap in brain structure and neuronal networks between the two conditions. A pressing question is why negative symptoms are absent in postictal psychosis, and why this condition is generally time-limited. The answers might be very important to understand in which way psychosis in epilepsy and schizophrenia share certain networks and circuits.

With regard to magnetic resonance imaging (MRI)-documented structural changes, defects in white matter networks may play a role in which patients with epilepsy develop PIP. A diffusion tensor study suggested that duration of epilepsy and fractional anisotropy value of the right arcuate fasciculus were independent risk factors of psychoticism in patients with epilepsy [55]. Another study showed significant decreases in white matter volume (corpus callosum and cingulum bundle) in people with TLE and psychosis compared with that in patients with TLE alone [56]. This MRI evidence suggests that there is a structural abnormality leading to psychosis in epilepsy, but further investigation is needed.

3.2. Temporal lobe epilepsy and schizophrenia psychosis have common substrate in hippocampal dysregulation of the dopamine system

Anthony A. Grace

Clinical practice and human studies show that many individuals with TLE have hallucinations and delusions similar to schizophrenia [57], except that the person with TLE often has insight into the abnormal nature of the psychic phenomenon. In this context, it is relevant that animal models of schizophrenia often reveal hyperactivity in the hippocampus [58,59]. It is believed that this phenomenon is driven by parvalbumin interneuron loss [60,61] and hyperresponsivity of the mesolimbic dopamine (DA) system [62].

Evaluation of the DA system in the well-validated methyl axozymethanol acetate (MAM) prenatal disruption model provided interesting new insights. Pregnant rats are given MAM at gestational day 17 and, as adults, recapitulate many of the behavioral, anatomical, pharmacological, and molecular characteristics observed in patients with schizophrenia [63,64]. This includes a behavioral hyperresponsivity to amphetamine in both humans and rats, consistent with a hyperresponsive DA system. There was also a selective loss of parvalbumin interneurons in the hippocampus [65,66] and an increase in DA neuron population activity. Dopamine neuron activity in vivo can be defined in three ways: the proportion of DA neurons that are spontaneously active (population activity), their firing pattern (burst firing), and their firing rate [64]. Burst firing represents the rapid, behaviorally relevant phasic response of the DA neurons to salient environmental stimuli. However, for a DA neuron to be driven to fire in bursts, it must be firing spontaneously. The ventral pallidum regulates this baseline spontaneous activity via potent GABAergic afferents. By regulating the number that is active, the pallidum can regulate the responsivity of the system. This pathway is in turn controlled by the hippocampus via the hippocampal–ventral striatal–ventral pallidal pathway ([67]; Fig. 1). This system is modulated in a context dependent manner. In a benign environment when significant threats or reward opportunities are unlikely, the hippocampus keeps the DA system in a low activity state, so that stimuli can produce a simple orienting response via burst activation of the small population of active DA neurons. However, in a highly threatening environment or one associated with potential significant reward (e.g., an animal hunting for food) in which environmental stimuli are likely to be highly salient, the hippocampus causes the DA system to be in a highly responsive state, so that a large population of active DA neurons will burst fire and ready the organism for

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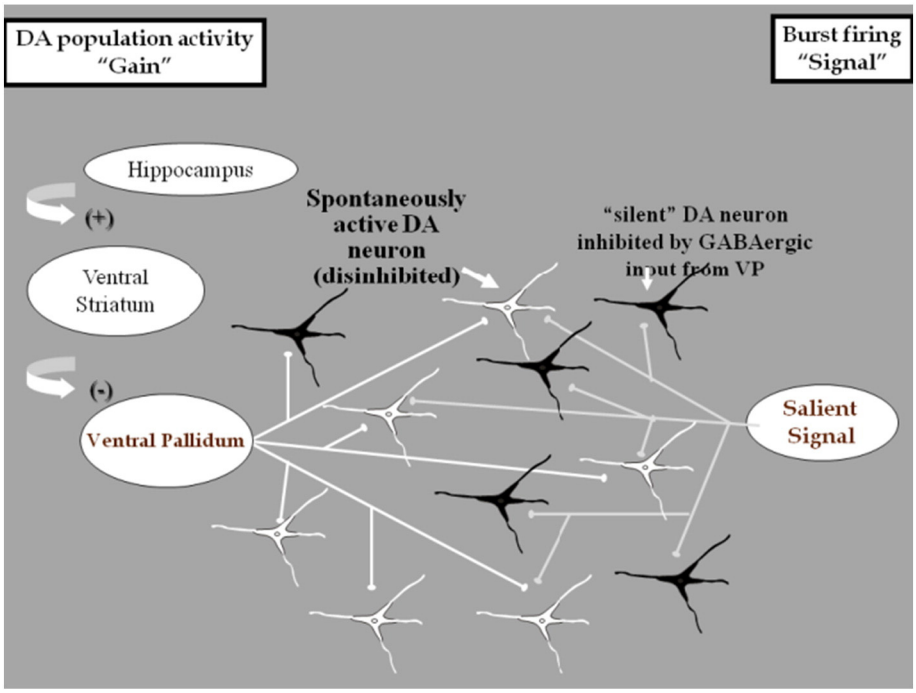

Fig. 1. DA neuron activity states are regulated by distinct afferent circuits. In the baseline condition, approximately half of the DA neurons are firing spontaneously; the rest are held in a hyperpolarized, inactive state by strong inhibitory input from the ventral pallidum. The ventral pallidum in turn is controlled by a circuit originating in the ventral hippocampus. In contrast, the burst firing pattern is controlled by a glutamatergic input activated by salient stimuli. Therefore, when an animal is exposed to a behaviorally salient event, DA neurons are driven to fire in a rapid, phasic burst firing state. However, to burst fire, a DA neuron must be spontaneously active. Whether it is active or not is controlled by the hippocampus–ventral striatum–ventral pallidum circuit. Therefore, in environmental contexts where rapid responses are required, the hippocampus drives the DA system into a highly responsive state via activation of silent neurons. However, if the hippocampus is pathologically hyperactive, the DA system is rendered hyperresponsive to stimuli, leading to overactivation by stimuli and overinterpretation of events, which is proposed to be the basis for psychosis.

an immediate response. However, in the MAM rat and presumably in schizophrenia, the constant hippocampal hyperactivity driven by the developmental loss of parvalbumin interneurons causes the DA system to remain in a state in which the system is hyperresponsive to all stimuli whether they are salient or not. The resultant hyperresponsive DA system would constantly alert the individual to the threatening nature of all stimuli, flooding them with input that overwhelms their ability to selectively ignore irrelevant events and overinterpret benign events [64]. This is proposed to underlie the psychotic features of schizophrenia [64].

The state of the DA system in TLE was examined in the pilocarpine model of this disorder [68]. After intrahippocampal administration of pilocarpine, the rats were found to also show a significant increase in DA neuron population activity. However, only the rats that had substantial seizure activity showed a near doubling in the number of active DA neurons in the ventral tegmentum [69], which was similar to that observed in MAM rats [59]. Furthermore, as in MAM rats, the pilocarpine-responsive rats that showed increased DA population activity were also hyperresponsive to amphetamine administration [69]. This is interesting given that in TLE and MAM animals, there is hyperactivity in the hippocampus presumably driven by a loss of parvalbumin interneurons. However, there is one significant difference in the MAM rats: the parvalbumin loss appears to occur early in adolescence and is accompanied by a loss of parvalbumin-containing GABA interneurons in the adult [65]. In contrast, in the pilocarpine model, there is a loss of parvalbumin protein without GABA neuron loss, likely indicative of a loss of parvalbumin interneuron drive [70]. Given the resistance of TLE psychosis to antipsychotic drug therapy, this suggests that in TLE, a drug that may selectively restore parvalbumin interneuron drive could potentially be highly therapeutic in restoring balance to the disrupted system.

3.3. Excitation–inhibition coordination and discoordination in the judicious and pathological use of information

André Fenton

Information processing in the brain operates at spatial scales from the molecular to the social, and time scales from milliseconds to decades. Accordingly, traditional univariate approaches to understanding brain networks and brain disorders have likely been over simplistic. Fresh conceptual frameworks such as *Neural Coding, Neural Dynamics, and Neural States*, many derived from the physics of dynamical physical systems, offer new opportunities to understand how brain networks function and hopefully also offer new treatment strategies.

Regarding neural coding, the conventional view is that the action potential is the primary unit of information, and the rate of discharge is how a neuron encodes information [71]. While useful, modern techniques that record the simultaneous activity of many individual neurons suggest that a distributed "ensemble coding" concept may be more accurate. Ensemble coding is analogous to a stadium jumbotron's display, in which distributed patterns of on-and-off lights encode information but the activity of an individual light is not meaningful [72,73].

Regarding neural dynamics, a major advantage of ensemble codes is that they can generate huge numbers of patterns, which offers a potentially feasible way to encode all of an individual's experiences. Practically, ensemble coding requires that the patterns change in time, and the ways in which the patterns change is called the "dynamics". If neural dynamics are crucial to information processing, it is important to understand the dynamics that organize the ensemble activity patterns and how the patterns constitute items of information ('words') and sequences of items of information ('sentences') within a neural syntax. One salient shortcoming is that it is essentially unknown how information is read out from a neural ensemble code [74,75].

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Nonetheless, these notions illustrate the need for neural coordination. This is shown schematically in Fig. 2, where the message "EXPERIENCE" is distributed across four display cubes, each able to participate in encoding "EXPERIENCE" as well as potentially three other words. While the cubes all revolve on an axis, the turning of the cubes must be properly coordinated and remain sufficiently synchronized for the set of four blocks to collectively convey the message. Discoordination causes catastrophic loss of the ability to encode the message, even though the signals carried by the four individual elements are unchanged.

Regarding *Neural States,* this can be explained by again considering the individual cubes of Fig. 2, which are analogous to individual neurons. Each cube is fundamentally independent, but by design, each turns at a particular frequency. If the turning frequency is the same across the cubes, it would lead to a functional state of the system, where "EXPERIENCE" is readily decoded as the message. If the individual cubes turned at different frequencies, this would define a distinct state, perhaps one signifying dysfunction because decoding EXPERIENCE would become problematic.

While these considerations of neural coding, dynamics, and states are theoretical, adopting these concepts has important practical consequences for understanding diseases like schizophrenia. Rather than emphasizing the information carrying processes, these concepts emphasize the network coordination processes and the properties that emerge from these network interactions [73].

To illustrate these concepts in experimental work with relevance to schizophrenia, consider the use of phencyclidine (PCP), a drug that induces psychosis in humans. Using hippocampal area CA1 place cells as a model system, we find that systemic administration of PCP impairs cognitive control in spatial behaviors, but does not change the spatial tuning of the neurons — under PCP, place cells maintain the same firing rates and place fields as before PCP [76,77]. Yet PCP significantly discoordinates how the cells discharge together in time, increasing errors and uncertainty when the rat's location is decoded against the pre-PCP ensemble discharge in the place cell population. Under PCP, the place cell population discharges in an abnormal pattern, indicating that the maintained place cells adopt an abnormal neural activity state. Phencyclidine also disturbs when individual cells fire action potentials relative to ~8-Hz theta oscillations in the ongoing local field potential (LFP) — LFP oscillations reflect time-synchronized synaptic input. Phencyclidine discoordinates how ~70-Hz gamma oscillation amplitudes are coupled to the phases of theta oscillations, indicating that synaptic activity is abnormally timed under PCP. Such diverse forms of neural discoordination within the hippocampus and other brain circuits may account for the failures of cognitive control and other disorders of thought under PCP, with possible relevance for conceptualizing the network dysfunction in schizophrenia.

3.4. Schizophrenia as a network disorder: the clinical perspective

Jason Morrison

On a clinical level, schizophrenia is a challenging but treatable illness, with several effective treatments available. Despite this, the pathophysiology remains unknown. Network models have grown increasingly influential as a rubric for conceptualizing this complex illness from a biological perspective. A strength of these models is that they provide an account of how, with time, dysfunction in one brain region can spread to other linked regions causing deficits in several domains. This temporal dimension of network models is important as it can explain the progressive accumulation of deficits seen clinically in untreated schizophrenia.

To date, network accounts of schizophrenia have yet to lead to insights that can be used clinically. Animal network models have grown increasingly sophisticated and shed light on how the brain regions and neurotransmitter systems implicated in psychosis from human research may be linked in a pathophysiological sequence [64]. A weakness of animal models is that they cannot incorporate the phenomenological aspects of schizophrenia that define the illness. For example, it is not possible to say whether a mouse is hallucinating or having a delusion, and indeed, it is unclear what an analogous experience might be for a rodent. Human network model research primarily uses functional neuroimaging as a tool and has moved from brief cross-sectional recordings (e.g., what brain areas are active when someone is hearing voices) to modeling how different brain regions interconnect and affect each other over time. This is achieved by applying graph theory mathematics to recorded brain activations over time to map putative brain networks involved in a brain function of interest, such as cognitive impairment or voice hearing, or to describe general characteristics of a network [78].

While individual papers from human research have linked network changes to specific symptoms in schizophrenia, findings are not consistent [79]. This is not surprising given the challenges of achieving consistent, generalizable results with this approach. Most papers group subjects according only to DSM diagnosis of schizophrenia vs. control with the assumption that (i) the clinical group shares a common underlying biological disturbance and (ii) this disturbance will not be present in the control population. It is unclear if this is a solid assumption. The clinical concept of schizophrenia is highly heterogeneous, and symptoms and deficits can vary widely both between individuals and within individuals depending on the stage of illness. The underlying biology likely shows a similar individual and temporal variability. If the underlying pathophysiology is not common, then the heterogeneity within comparison groups would prevent finding consistent or significant results. A modern neuroimaging protocol trying to model massive amounts of data points sequenced over time may amplify heterogeneity-related noise even further.

One way to address heterogeneity is to try and tighten the phenotype studied to people with schizophrenia and a certain symptom (e.g., voice hearer or blunted affect) or an endophenotype (e.g., P50 suppression or prepulse inhibition deficits). Alternatively, research designs that use individuals as their own control such as a within-subjects statistical analysis or even single case design may lead to new insights that between-subjects designs cannot. While single case designs may lack generalizability, they can be useful for the exploratory research phase that psychiatry is still in (although pretends not to be). Remember that modern neurological phenotypes were discovered in this manner during the 19th century by careful clinicians like Charcot and Gowers. The fuzziness of current clinical phenotypes in psychiatry is

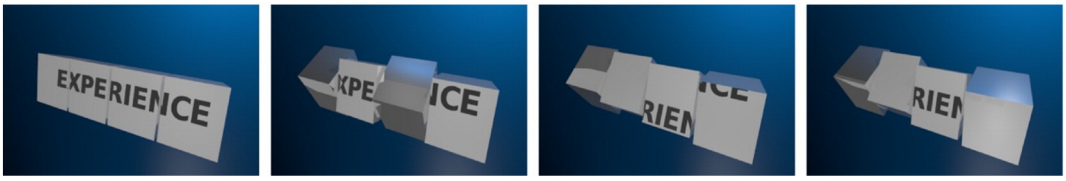

Fig. 2. Neural coordination. Example illustrating the need for coordination in a system where information is distributed across multiple (here only 4), potentially independent elements. Although each cube only reports a particular subset of information, the message "EXPERIENCE" is only encoded when the synchronous display of all four cube faces is accomplished. Here, analogous to neural coordination, coordinating mechanisms are crucial for keeping the four cubes synchronous in space and time.

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reminiscent of neurological phenotypes during the mid-19th century. More resources may need to be spent on complementary techniques with an exploratory purpose for our understanding of the neurobiology of schizophrenia to move forward.

3.5. Temporal lobe epilepsy and schizophrenia — is there a link? A basic science perspective

Astrid Nehlig

There is general agreement that there are common etiologies, pathophysiology, and genetics between schizophrenia and TLE. In both conditions, one often finds a pre- or postnatal insult that precedes the diagnosis, which is considered to be the cause of the disorder. There are also data suggesting disconnection/misconnection within brain circuits and interactions between the genetic background and environment that play an important role. The burning question is whether we currently have suitable animal models to address this complex issue and identify similarities between the two disorders. It is intriguing to compare a TLE model induced in the immature brain by lithium and then pilocarpine administration versus a schizophrenia model that is produced by ibotenic acid injection. In the model of schizophrenia, or a schizophrenia-like condition, ibotenic acid is injected bilaterally at postnatal day (PD) 7 in rats, and it produces ventral hippocampal damage. It is often called the neonatal ventral hippocampal lesion (NVHL) model [80].In the NVHL model, lesioned rats develop a sensorimotor gating deficit during adulthood. They also show abnormal EEG activity reflected by thalamocortical oscillations called spike–wave discharges (SWDs) [81]. There are changes in cortical excitability reflected by the higher susceptibility to SWDs and decreased susceptibility to clonic seizures induced by the convulsant pentylenetetrazol [82]. Data on neuronal damage outside the hippocampus in this model are missing. After the insult, active brain reorganization occurs, mainly around the 3rd week of age, but this reorganization translates only into subtle activity changes in adult rats [82].

In the NVHL model, which is also a TLE-like condition, spontaneous nonconvulsive seizures occur in 25% of adult rats after an initial period of severe seizures early in life. The severe seizures are status epilepticus (SE), and they are induced at PD12 by the convulsant pilocarpine. Prior to pilocarpine, the drug lithium is administered, and this increases the effects of pilocarpine. There is an important developmental window in the effects of lithium–pilocarpine [83]. The only link with schizophrenia that we have in the latter model is that the efficacy of sensorimotor gating is not affected when SE is induced in adult rats [84] while data from rats at PD12 are not available.

A very important issue is how to compare ages in rats and humans. This is important when discussing developmental disorders because it has implications for predictions about humans based on the animal data. The problem is that a rodent appears to be born at a time equivalent developmentally to the 6th month of gestation in humans. It is suggested that a PD7 rat brain is considered equivalent to the end of gestation in humans. Two weeks of age might be similar to 2–3 years in humans. However, little is known about the respective developmental ages that would render the brain specifically vulnerable either to schizophrenia or epilepsy after an early insult to the hippocampus.

In this respect, we are still missing some directly comparable data. For example, to what extent would the bilateral injection of pilocarpine into the hippocampus at PD7 differ from the changes induced by ibotenate? How late in development can the NVHL lead to behaviors like schizophrenia? A combination of the models of schizophrenia and TLE is likely the next step. For example, one could use a different model of schizophrenia from the NVHL model, one where injection of an NMDA receptor antagonist early in life leads to discrete lesions that are closer to schizophrenia in humans in this respect, and combine it with a model of TLE where SE is induced at young ages. A comparison of how pathologies develop in this context would be fruitful.

4. Translation and epilepsy (part "F" of the meeting program)

4.1. Shared focal cortical dysplasia pathology in autism and epilepsy

Ingmar Blümcke

An obvious commonality between autism and epilepsy is that both diseases are mainly cortical. Another commonality is that both diseases share partial and generalized manifestations. Presurgical evaluation in patients with drug-resistant focal epilepsy often identified focal lesions on MRI, which were postsurgically confirmed by histopathological examination. It is also common to see focal lesions in autism. It is surprising that MRI is not applied more often in autism to document these changes and potentially allow new insights into this disorder.

Currently, the best neuropathological information regarding co-occurrence of autism spectrum disorder and focal epilepsy originates from the European Epilepsy Brain Bank consortium, which has collected almost 10,000 patients from 36 centers [137]. Unpublished observations from the Vogtareuth Epilepsy Center in Southern Bavaria, Germany, identified 33 (out of 312) children with drug-resistant epilepsy also having pervasive developmental disorders (10 female, 23 male; Anja Karlmeier, personal communication). Most were 1 year of age (26/33) at seizure onset. Focal cortical dysplasia (International League Against Epilepsy (ILAE) Type I–III; [85–87]) were most common in these patients.

In autism spectrum disorder, there is also a high risk of malformations of cortical development, such as polymicrogyria and tuberous sclerosis complex. Forme fruste of polymicrogyria (without epilepsy) was reported in autism [88].

In conclusion, it is anticipated that David Taylor's original description of Focal cortical dysplasia (FCD)[89] will likely include acquired autism spectrum disorders. Sporadic observation that autism improved after early epilepsy surgery in young children will need further confirmation and was controversially discussed during the meeting.

4.2. Brain networks in epilepsies: what we have learned by recent neuroimaging studies?

Fernando Cendes

> *"It takes the world to understand the brain."*
>
> [90]

Multimodal imaging techniques are crucial in the definition of the epilepsy etiology, including those that combine metabolic and functional investigation, such as fluorodeoxyglucose positron emission tomography (FDG-PET), single-photon emission computed tomography (SPECT), diffusion MRI, and magnetic resonance spectroscopy (MRS). Familiarity with the different protocols of imaging studies is required for the optimized investigation of seizure etiology [91]. The application of neuroimaging in epilepsy has advanced our understanding of mechanisms underlying the epilepsies and helped guide decisions for treatment on an individual basis [92]. Structural neuroimaging may be able to identify patients more likely to respond to AED treatment and patients who are better candidates for earlier surgical treatment. In the last decades, quantitative analyses have also improved our knowledge about epileptogenic lesions and networks as well as prognosis on seizure control, cognitive outcome, and comorbidities.

Functional magnetic resonance imaging (fMRI) has helped to improve our understanding about deficits affecting memory and language in patients with epilepsy. For example, memory encoding fMRI paradigms that activate language areas in both hemispheres have been used for predicting memory decline after surgery for mesial temporal epilepsy with hippocampal sclerosis (MTLE-HS) with mixed results [93–97]. However, new methods of data analyses are improving this approach. For example, the presence of a positive fMRI lateralization index within the mesial temporal and frontal lobes is associated with

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postoperative verbal memory decline, with a sensitivity of 87.5% and specificity of 80% [98]; this suggests a stronger engagement of extratemporal neocortex during memory tasks in patients with bilateral hippocampal dysfunction. This is important because it explains why these subjects cannot maintain their memory scores after temporal lobe resections, especially in the language-dominant hemisphere. This concept is consistent with the concept that MTLE-HS is a network disorder with widespread microstructural brain damage and dysfunction [99–101].

Another example of the power of fMRI is a study showing that a complex network including parietal and frontal cortices are involved in verbal memory encoding and retrieval tasks in normal controls and patients with MTLE-HS [100]. However, these activations are more intense and widespread, particularly in the frontal lobes, in patients with left MTLE-HS, suggesting a functional reorganization of verbal memory processing due to the failure of left hippocampal network system, or perhaps a bilateral limbic dysfunction [100].

There is also structural MRI evidence that atrophy of gray matter in the cingulate and orbitofrontal cortices are independently associated with verbal memory performance, suggesting that atrophy and dysfunction of limbic and frontal structures contribute to memory impairment in MTLE-HS [102].

Studies of quantification of gray matter in MTLE-HS have demonstrated a network of subtle gray matter atrophy beyond the mesial or neocortical temporal structures, including predominantly other limbic areas as bilateral thalamus, but also extralimbic structures as the frontal lobes [103–105]. Although this gray matter damage is more evident in pharmacoresistant MTLE-HS and it has been correlated with seizure frequency [106], there is also evidence of diffuse atrophy in patients with MTLE-HS with well-controlled seizures [107,108]. In addition, this atrophy may progress even in patients who are seizure-free on medication [109]. Studies analyzing functional and structural networks have shown diffuse and distinct abnormalities when comparing patients with left and right MTLE-HS, which involves the default mode networks [110] as well as an aberrant topological organization of the whole brain volumetric network, with disruption of patterns of cortical/subcortical morphology that is different between left and right MTLE-HS, indicating that these are indeed different diseases in several biological aspects [111].

New advanced neuroimaging techniques (such as diffusion tensor imaging and fMRI) and the development of biomarkers that reflect inflammation or genetic mutations will add further knowledge about epilepsy, as well as normal brain network function.

4.3. Network disorders: genetic, biochemical, and molecular connections

Asuri Prasad

Epilepsy can be a primary or a comorbid feature, and there is a biological continuum of expression of genetic and inherited biochemical defects in children. Affected individuals exhibit phenotypes that include overlapping features of epileptic seizures; autistic traits; and cognitive, mood, and behavioral impairments. Evidence suggests that shared molecular, biochemical, and signaling pathways particularly at the synapse and subcellular levels are involved in the genesis of the epilepsy and comorbid features of different unrelated conditions.

Case studies from the pediatric epilepsy clinic in South-Western Ontario nicely illustrate how changes at synaptic and postsynaptic subcellular level influence network behavior: early onset epilepsy with evolution to a developmental disability in a child with a microdeletion involving the neurexin *NRXN1* gene; a 22q133 microdeletion syndrome involving the *SHANK3* gene (Phelan–Mcdiarmid syndrome); tuberous sclerosis with mutation in the *TSC1* gene; Rett syndrome with *MECP2* gene mutation; infantile spasms evolving to intractable epilepsy; and severe developmental disability due to methylene tetrahydrofolate reductase (MTHFR) deficiency.

These case examples show altered protein–protein interactions at the synapse and postsynaptic signaling pathways. The mutations and their pathogenic effects demonstrate the critical role of anchoring proteins at the synapse (neurexin *NRXN1*), through interactions in signal transduction or transcriptional pathways (*SHANK3*, TSC1 in the mammalian target of rapamycin (mTOR) pathway); epigenetic changes involving methylation (*MECP2* in Rett syndrome and in MTHFR deficiency) that lead to dysregulation of transcription; and resultant changes in network behavior [112–116]. Cellular metabolism and epigenetic cross talk add another layer of complexity [117,118]. Fortuitously, these pathways can be modulated by a variety of pharmacological and other interventions. The ketogenic diet, for instance, appears to have a favorable effect by elevating BDNF levels and the mTOR pathway.

Studying the "molecular interactome" will open up fresh insights into network function, epileptogenesis, and comorbid conditions as well as help identify novel drug targets for treatment.

4.4. Inflammation and neural circuit behavior in brain disorders

Karen S. Wilcox

A common underlying factor in brain network diseases is likely inflammation. A new animal model of epilepsy has been established in Utah where an initial infection using Theiler's Murine Encephalomyelitis Virus (TMEV) is the stimulus to cause chronic seizures. This concept is further supported by the fact that common viral infections have been associated with acute seizures and the subsequent development of temporal lobe epilepsy include human immunodeficiency virus (HIV), Japanese Encephalitis Virus, West Nile virus, Herpes Simplex Virus-1 (HSV1), and Human Herpes Simplex Virus-6 (HHV6; [119,120]). Theiler's Murine Encephalitis Virus in C57BL6 mice led to 3–7 days of seizures immediately after virus exposure [121]. On day 8, the seizures stopped, and much later, the animals developed epilepsy, with both convulsive and nonconvulsive seizures [122,123]. These mice developed significant neuronal loss and persistent astro- and microgliosis in the hippocampus, cortex, and limbic system [124], as well as behavioral comorbidities [125].

Current research focuses on TNFα and its regulation of seizures in the TMEV model. Interestingly, TNFα knockout mice have a reduced seizure burden. Usually, TNFα binds to two membrane receptors tumor necrosis factor receptor (TNFR1 or 2) with TNFR1 having "good effects" and TNFR2 having "bad effects". Seizures in response to the TMEV virus increased seizures in the TNFR2 knockout, but if both receptors are deleted, seizures are reduced [126]. The TMEV model is the only viral model of epilepsy at the present time and shows promise for future drug development. Along those lines, the National Institutes of Neurologic Diseases and Stroke (NINDS) Epilepsy Therapy Screening Program (ETSP) recently implemented the TMEV model into its compound screening efforts, and it has been demonstrated that this model is an etiologically relevant platform for therapy discovery [127]. New drug targets for disease modification of temporal lobe epilepsy have been identified. For example, novel antiinflammatory agents that target diverse molecular targets such as the prostaglandin E2 receptor [128], TGF-α signaling [15], and Il-Iβ [129] are potential disease modifying inflammatory targets that might provide protection against the development of seizures or associated comorbidities following brain insults if they are blocked. Recent work in the TMEV model suggests that interleukin 6 (IL-6) and TNFα may also be important inflammatory signaling systems that could be exploited for disease modifying therapies following CNS insults that lead to epilepsy [126,130,131].

Future work will focus on strategies to blocking signaling through inflammatory pathways to prevent the epileptogenesis in the TMEV model.

4.5. Endophenotypes of traumatic brain injury: designing the next generation of clinical trials for post traumatic epilepsy

Ramon Diaz-Arrastia

Traumatic brain injury (TBI) is very important to address because of its devastating consequences to cognition and behavior. Traumatic

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brain injury is a major risk factor for Alzheimer's disease. It is also a common finding in epilepsy. From the Rochester study of 888 patients, 4% of individuals had head trauma in their history [132]. However, this statistic underestimates the importance of trauma in epilepsy. For example, in the 15–24 year-old age range, approximately 40% of individuals with symptomatic epilepsy had head trauma [132]. If one studies the cumulative probability of posttraumatic seizures, up to 15% percent of individuals with severe injury developed seizures [132]. More recent data from the Veterans Administration support the importance of TBI in epilepsy [133].

Trauma results in both focal and diffuse injuries, and both can result in epileptogenesis. Thus, posttraumatic epilepsy (PTE) is heterogeneous. Between 25 and 30% of cases of intractable epilepsy after TBI are associated with mesial temporal sclerosis, and therefore, TLE is a major concern. Surgery is a viable option in selected cases. Animal models that reproduce some of the features of human PTE have been developed, and they are helpful [134–136].

What do we need to know for the next generation of clinical trials? Endophenotyping can potentially help. An endophenotype (also called an endotype, or a subphenotype) is an internal or intermediate phenotype that is closer to the underlying pathophysiology of disease (whether genetic or environmental). It is a continuous quantitative variable, in contrast to a phenotype that is usually a categorical variable. An endophenotype can be measured quantitatively using physiologic, biochemical, or imaging techniques. Endophenotypes should be developed iteratively between clinical and preclinical studies. The studies in humans can provide the natural history of endophenotypes and possibly subtypes that will most likely benefit from therapy. Preclinical studies can confirm the benefits of therapy, advance a more mechanistic understanding, and establish pharmacodynamics.

5. Summary, conclusions, and future directions

A number of disorders, particularly those of developmental origin, often show comorbidity as well as tendency to occur in families. Furthermore, there is increasing evidence that metabolic disturbances, particularly those related to oxidative stress and neuroinflammation, have recently been linked to the etiology of many of these disorders. Epilepsy itself is known to put a high metabolic load on systems, which could exacerbate the damage caused by susceptibility to oxidative stress. Particularly sensitive to metabolic load and oxidative stress are the interneuron populations. Given that this neuronal class is the last to develop, emerging as a mechanism to stabilize excitatory networks, it is likely that this class of neurons is more vulnerable to insults [64]. Therefore, destabilization of excitatory/inhibitory balance, combined with the metabolic overdrive associated with ictal activity, could be a driving force in the pathophysiology underlying many of these disorders and their link to epilepsy.

The type of format chosen by the 4th Halifax International Epilepsy Conference (HIECR) appeared to be successful in many ways. The postmeeting evaluation was outstanding. The conference bridged specialties in neuroscience, neurology, and psychiatry, engaging individuals who would usually not meet in such a small group setting with focused and often intense dialog. The nature of the meeting allowed informal discussions throughout, induced an inspiring out-of the-box-thinking, and created a superb opportunity for educating one another about the most current activity in each specialty. It also clarified where some of the most controversial and difficult issues lie and the challenge to address those in the future. We all believe that interdisciplinary "think tanks" such as the HIECR will significantly enrich our understanding of complex diseases. Stepping out of our usual day-to-day activity and general mindsets opens unexpected opportunities to develop innovative perspectives and helps rewire our own way of thinking and approaching these issues.

Conflict of interest

Anthony Grace has worked with and received honoraria related to that work from Lundbeck, Pfizer, Otsuka, Lilly, Roche, Asubio, Abbott, Autofony, Janssen, Alkermes, Newron. Andre Fenton is a founder and director of Bio-Signal group Corp. Helen Scharfman received research funding from Pyramid Biosciences in 2017 and is on the Scientific Advisory Board. Asuri Prasad has received honoraria from Eisai Inc. for lectures about epilepsy. Karen Wilcox is on the Scientific Advisory Board of Blackfynn Inc. The other authors declare no conflicts of interest.

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