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Review

Can we and should we use animal models to study neurobehavioral comorbidities of epilepsy?

Andrey Mazarati *

Department of Pediatrics, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA

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ABSTRACT

Animal systems have been widely used to examine mechanisms of neurobehavioral comorbidities of epilepsy and to help in developing their effective therapies. Despite the progress made in the field, animal studies have their limitations stemming both from issues with modeling neuropsychiatric disorders in the laboratory and from drawbacks of animal models of epilepsy themselves. This review discusses advantages and weaknesses of experimental paradigms and approaches used to model and to analyze neurobehavioral comorbidities of epilepsy, from the perspectives of their needs, interpretation, ways of improvement, and clinical relevance. Developmental studies are required to adequately address age-specific aspects of the comorbidities. The deployment of preclinical Common Data Elements (pCDEs) for epilepsy research should facilitate the standardization and the harmonization of studies in question, while the application of Research Domain Criteria (RDoC) to characterize neurobehavioral disorders in animals with epilepsy should help in closing the bench-to-bedside gap.
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1. Introduction

With the rise of the awareness about neuropsychiatric comorbidities of epilepsy, the number of experimental studies of epilepsy-associated neurobehavioral impairments has been growing over the years, in good parallel with clinical reports (Fig. 1). The amenability of animal systems to reproducing a variety of behavioral perturbations comorbid with epilepsy has been shown by many groups. On the one hand, epilepsy induced in laboratory rats and mice leads to changes in cognition [1–3], "mood" and motivation [4,5], sociability [6,7], levels of anxiety [8–10], and attention and impulsivity [11,12] — that is, perturbations that are commonly observed in people with epilepsy. On the other hand, several rodent models of primary neuropsychiatric disorders are characterized by the increased susceptibility to epileptogenic events [5,9,13–16] and, thus, reproduce the known bidirectional connection between epilepsy and several of its comorbidities [17].

While phenomenological aspects of neurobehavioral impairments in laboratory animals (predominantly rodents) with epilepsy have been clearly established, questions persist on how informative such findings are vis-à-vis comorbidities in people with epilepsy. Face, construct, and predictive validities of animal models of neuropsychiatric disorders in general remain subjects of vivid debates [18–21]. When applied to animal models of epilepsy, the issue is further complicated, as it requires separating true comorbidities from nonspecific changes in the animal's behavior stemming from broad effects of epileptogenic insults and of recurring seizures in terms of histopathology, neuronal plasticity, and the involvement of irrelevant neuronal circuits. This overview, which has been invited as a contribution to the issue commemorating the 20th anniversary of *Epilepsy & Behavior*, is an attempt to reflect on the state of experimental studies of epilepsy comorbidities in terms of their need, interpretation, ways of improvement, and clinical relevance.

2. Do we need animal models of epilepsy comorbidities?

Clinical research of epilepsy comorbidities has been making remarkable progress. In vivo imaging of neuroanatomical, neurophysiological, and neurochemical substrates of neuropsychiatric disorders has been yielding meaningful insight into their mechanisms. Nevertheless, there remain areas, which are best served by nonhuman systems.

2.1. Neurobiological vs. social and psychological aspects

While the neurobiological basis of comorbidities has been accepted, social and psychological aspects of neuropsychiatric disorders are equally important in people with epilepsy [22]. For example, the burden

Abbreviations: 5-CSRT, 5-Choice Serial Reaction Time Task; ADHD, attention-deficit/hyperactivity disorder; DSM, Diagnostic and Statistical Manual of the American Psychiatric Association; FST, forced swimming test; HPA-A, hypothalamo-pituitary-adrenocortical axis; LRTT, Lateralized Reaction Time Task; pCDE, preclinical Common Data Element; PND, postnatal day; RDoC, Research Domain Criteria; STFP, social transmission of food preference tests; MWM, Morris Water Maze.

* Department of Pediatrics, Neurology Division, David Geffen School of Medicine at UCLA, Box 951752, 22-474 MDCC, Los Angeles, CA 90095-1752, USA.
E-mail address: mazarati@ucla.edu.

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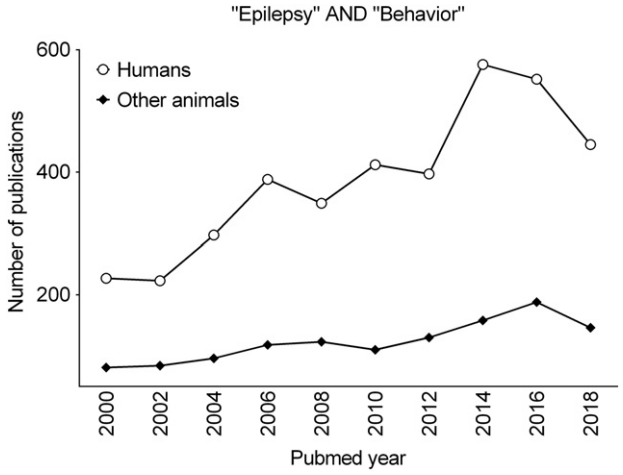

Fig. 1. Nonscientific presentation of number of publications found in Pubmed, using search terms "Epilepsy" and "Behavior", and filters "Humans" and "Other animals". (Source: National Center for Biotechnology Information/Pubmed).

of seizures on the quality of life, including stigma, dependence on antiepileptic drugs, fear of impending seizure, employment, driving, and learning, all may exacerbate, if not precipitate depression and anxiety. Social and psychological aspects of comorbidities certainly deserve special studies, which are feasible only in people with epilepsy. At the same time, the coexistence between social/psychological and neurobiological contributors to comorbidities complicates the examination of the latter, as the two domains are not easily disentangled. In animal systems, the occurrence of neurobehavioral perturbations (almost) in the absence of psychological and social factors allows isolating neurobiological features of neurobehavioral disorders for both mechanistic insights and for the development of therapeutic interventions.

2.2. Unimpeded progression of the disease

Some antiepileptic drugs may themselves affect behavior (via modifying the underlying substrates) in both positive [23] and negative [24] manners. That is, anticonvulsant therapy may either precipitate behavioral deficits or improve them, which, in both cases, would confound proper design of clinical studies and interpretation of the obtained results. Furthermore, those behavioral deficits that have stronger dependence on recurring ictal events may be mitigated by the virtue of anticonvulsant therapies. Conversely, in the laboratory setting, epilepsy does not need to be treated, which affords studying natural evolution of comorbidities of interest, with no interference from medications.

2.3. Technical feasibility

Despite the aforementioned progress in clinical research, there are techniques, which remain mostly, if not exclusively, reserved for animal systems. Examples include viral transfection [25] and optogenetic tools [26], use of inbred and transgenic lines of animals [13,27,28], and direct interrogation of monoaminergic pathways in mood disorder studies using in vivo brain dialysates and fast scan cyclic voltammetry [29]. These and other such studies yield information on the substrates of comorbidities, which are all but unattainable in people.

2.4. Primary vs. secondary condition

Bidirectional connections between epilepsy and neuropsychiatric comorbidities are frequently cited [17,30], but in clinics, it is not always easy to discern chronologically which of the disorders is primary and which is secondary. This is not the case in animal systems where, with the exception of breeding and genetic manipulations, the primary condition (whether it is an epileptogenic insult or a behavior-altering procedure) is most commonly unambiguous.

2.5. Epidemiological issues

Other advantages of animal experimentation compared with clinical research include control over the population in terms of sex, age, sample size, genetic background, type of epilepsy, etc., thus facilitating standardization of research conditions and attaining an adequate statistical power.

3. Are there good assays and models for studying epilepsy comorbidities?

This question cannot be answered unequivocally. Aside from such obvious defining factors as study goals, experimental design, and data interpretation, the answer also depends on what is recognized as an acceptable degree of face, construct, and (when applicable) predictive validities of existing behavioral paradigms.

3.1. Case in point: forced swimming test (FST)

A good example of questioning face, construct, and predictive validity of behavioral assay is forced swimming test (FST), often used in several variations when studying major depressive disorder. Originally designed as a quick method to evaluate the effectiveness of antidepressant drugs [31,32], the test, largely due to its simplicity, was widely adopted in behavioral studies beyond the drug screening purposes, but as a means to both induce and to evaluate depressive state, and later, made its way into epilepsy research [4,33–36]. However, its face validity has been questioned for almost as long as this test has existed. Thus, it has been pointed out that the test gauges the animal's ability to cope with stress, but not strictly the state of despair/hopelessness as a symptom of depression [37] (although the ability to cope with stress is not irrelevant, as it may serve as a marker of predisposition to depression, particularly from the endophenotype perspective, and when applied in epilepsy studies [5]). Questions have been also raised about predictive validity of the paradigm, whereby not only antidepressants, but also psychostimulants exerted "antidepressant" effects [38,39]; this, in turn, raised concerns about its construct validity, since what is construed (or misconstrued) as despair-like behavior may instead involve mechanistically irrelevant determinants.

Still, with all the criticism accepted, FST may be valuable, particularly in the context of epilepsy–depression comorbidity. Thus, in animals with epilepsy, despair-like behavior in the FST correlates well with the preceding depressogenic event [5]; with the hyperactivity of the hypothalamo-pituitary-adrenocortical axis (HPA-A) [40]; is present concurrently with other putative symptoms of depression (e.g., anhedonia-like state [4,41], and diminished sex drive [42]); and is driven by specific perturbations in depression-relevant neuroanatomical pathways [29,43]. The lesson here is that FST alone may say very little about the "mood" of the animal; however, when taken in context, and in conjunction with other depression-relevant alterations, it may serve as a reasonable indicator that the animal has indeed developed a depression-like disorder.

3.2. Conducting behavioral tests in animals with epilepsy

Within the epilepsy framework, one important thing to remember is that in the laboratory setting, largely due to specifics of behavioral tests and of epilepsy models (as discussed below), both epileptogenic insult and recurrent seizures are likely to affect multiple systems — substrates of behavior, and separating them is often complicated, if at all possible. This involvement of multiple behavioral substrates may show on different levels.

The most basic level concerns the integrity of motor and sensory systems required for the adequate performance in behavioral tasks. For example, preserved motor function is critical for many tests, such as FST and Morris Water Maze (MWM, which is used to examine spatial memory [44]); olfaction is critical for such assays as taste preference test (which is used to examine anhedonia-like state [45]) and social transmission of food preference test (STFP, used to gauge lack of sociability as a symptom of autism [46]), etc. [47]. Widespread neuronal injury after epileptogenic events may lead to motor and sensory impairments, which in turn may affect performance in respective tests, but are mechanistically unrelated to the comorbidities in question. Thus, the inability to maintain balance may result in the increased struggling behavior in the FST [33], which may be misinterpreted as an "antidepressant" effect of seizures. Anosmia may result in the loss of taste preference (i.e., pseudo-"anhedonia") and of STFP (i.e., pseudo-"autism").

It is, therefore, important that respective control experiments are conducted in conjunction with main assays, in order to confirm that the observed behavioral deficits are true comorbidities of epilepsy, rather than its mere artifacts — results of sensory and/or motor dysfunction. For example, such simple tests as Rotarod and quinine aversion may respectively attest to the animals' ability to maintain proper balance and to discriminate odors.

The situation becomes even more complicated on a deeper level — within the realm of comorbidities, because of two factors. Firstly, many behavioral tests are multipurposed (e.g., fear conditioning is used to gauge both memory and anxiety), with the interpretation of outcomes often left to the investigator; this bears a certain degree of bias, and the latter is often under the influence of the experiment's goals. Secondly, animals (much like people) may truly have several concurrent neurobehavioral disorders (e.g., there is known comorbidity between depression and attention-deficit/hyperactivity disorder [ADHD] [48], also shown in the laboratory, specifically in conjunction with epilepsy [49]). As a result, it may be difficult to determine whether the animal with epilepsy presents with several comorbidities, or only with one, manifesting itself in different ways in different tests.

Thus, on the one hand, many behavioral tests used to gauge attention and impulsivity, (e.g., Lateralized Reaction Time Task [LRTT] [12] and 5-Choice Serial Reaction Time Task [5-CSRT] [11]), fear (as in fear-conditioning tests [50]), and sociability (as in three-chamber test and STFP [45,46]) rely on intact episodic and working memory, and impairments recorded in these tests may be due to learning and memory dysfunction, rather than to other presumed behavioral disorders (i.e., ADHD, anxiety/fear, autism, etc.). On the other hand, increased thigmotaxis in MWM will increase the time needed to locate the platform and, thus, may give a false positive result for the impaired spatial memory [51,52] while in fact, being a manifestation of anxiety [53]. "Decreased" level of anxiety observed in the elevated plus maze as reported in rats with epilepsy [54] may instead be a nonspecific manifestation of hyperimpulsivity, as confirmed in an ADHD-specific task [12].

These examples show how problematic it may be to properly interpret behavioral impairments, which develop in conjunction with experimental epilepsy. This problem may be difficult, if not impossible to overcome. Judging an animal's behavior in context, and conducting multiple assays, which gauge the same deficit through different methodologies, may help proper interpretation. For example, impairments in both STFP and the three-chamber test may make a stronger case for autism-like deficit in sociability than a single test; impairments in both Barnes and MWM make stronger case for deficit in spatial memory; impairments in 5-CSRT and attentional set-shifting task [55] make stronger case for attention-deficit, and so on.

In the same vein, a "syndrome" approach in studying comorbidities may be more instructive than a "symptom" approach. For example, the diagnosis of depression requires the presence of at least five defined symptoms; diagnosis of autism — three [56]. Because plainly transferring the human nosology of neuropsychiatric disorders to animals is not possible, the animal can hardly be classified as "depressed" or "autistic" in the first place. But the "diagnosis" becomes even more questionable if it relies on a single test (e.g., FST for depression to characterize despair-like behavior but with no examination of anhedonia or sleep structure etc.; or the three-chamber test to show diminished sociability but with no examination of restrictive behavior or impaired vocal interaction).

Whenever possible, supporting behavioral observations with meaningful mechanistic studies, to address construct validity, may be useful. For example, are deficits in MWM accompanied by the impaired functioning of hippocampal place cells [57]? Do impairments in the FST correlate with the dysfunction of serotonergic transmission in raphe–forebrain pathways, and impairments in the taste preference test — with the dysfunction in reward pathways [29]? Does increased impulsivity correlate with the deficiency in locus coeruleus-forebrain noradrenergic neurotransmission [12]? Does impaired social interaction correlate with dysfunction in brain connectivity [58,59]? Addressing such questions is important not only for establishing the validity of animal models of comorbidities, but also for understanding their (comorbidities') underlying mechanisms with translational application in mind (of course, we should be mindful with not falling a victim of circular logic, when the same experiment is conducted to examine mechanisms of the disorder and to validate the model). Outside of mechanistic studies, verification of behavioral tests by objective surrogate markers may be helpful (e.g., showing the dysregulation HPA-A [14,40] or of serotonergic transmission [60] when studying major depressive disorder).

Choice of a meaningful epilepsy model is important. Aside from the obvious proper choice of the model based on the epilepsy type and etiology (although these features are not infrequently ignored), the multiplicity of behavioral changes reported in some epilepsy paradigms questions the relevance of these models for studying the comorbidities in the first place. Often times, such a large collection of neurobehavioral deficits is observed in a single animal with experimental epilepsy that is rarely, if ever, seen in people with epilepsy (and some impairments are never observed in people) [61–63]. Such reports may in effect invalidate the selected epilepsy paradigm as a good system for studying the comorbidity, and even though the reporting may be useful (even for the purpose of emphasizing the weaknesses of the model), the applicability of the findings for preclinical research may range from limited to nonexistent.

Epilepsy models that are characterized by infrequent seizures (so that the latter do not directly and nonspecifically affect behaviors) [1,64,65], or by no spontaneous seizures at all (such as kindling, which affords studying consequences of chronic epileptic state but in the absence of spontaneous seizures [66]), may be advantageous [9,14,41,67,68] and so are protocols that produce specific, clinically relevant pattern of neuronal injury [1,69]. Among available models of epilepsy, the pilocarpine model is conceivably most often employed because of its technical simplicity and high throughput but may be least useful because of very high seizure frequency, excessive seizure clustering, widespread neuronal injury (beyond of what is typical of temporal lobe epilepsy) [70], and a wide, not always coherent array of behavioral perturbations [3,4,12,61,62]. At the same time, the paradigms that model posttraumatic epilepsy [69], poststroke epilepsy [71], and genetic absence epilepsy [27] may exemplify more refined protocols both in terms of etiology, seizure type, incidence, frequency, severity, and neuroanatomical substrates, potentially making them more amenable for studying neurobehavioral comorbidities.

4. Can we improve experimental studies of epilepsy comorbidities?

There are obvious ways to advance the comorbidities research, such as deployment of new techniques to interrogate mechanisms [72]; introduction of novel behavioral assays with the increasing degree of clinical relevance [73] as a means of model validation; use of species which are more sentient and socially organized than rodents (such as nonhuman primates) [74]; publication of null data as a path to the model

refinement and the avoidance of duplicative research [65,75]; closer interaction with clinicians when posing study objectives, to consider type of epilepsy, age, clinical importance of the observed or expected behavioral changes, etc. At the same time, it is also evident that in order to address core weaknesses of the state of comorbidities research, certain changes may be required as to how the studies are designed, conducted, and reported. Three examples are discussed next.

4.1. Research Domain Criteria (RDoC) vs. Diagnostic and Statistical Manual of the American Psychiatric Association (DSM)

The application of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM)-like approach for sorting out neurobehavioral disorders in animal systems, including epilepsy models [76], has been proposed. While the idea is commendable as a means to connect laboratory observations to clinical practice, it may be hardly achievable [21]. The main issue with transplanting DSM classification into the laboratory appears to be anthropomorphism. When it comes to interpreting an animal's behavior from the perspectives of both normal human behavior and abnormal behaviors, which are characteristic of mental disorders, anthropomorphism is unavoidable and is not necessarily unacceptable. However, there is a thin line between reasonable interpretation of changes in standard animal's behavior and wishful thinking of the investigator. Even with all the earlier discussed precautions, describing a rat or a mouse as "autistic" or "depressed" is hardly accurate. Furthermore, DSM has inherent weaknesses, the main being that (a) different diseases are characterized by the same symptoms, which complicates the "diagnosis" in experimental animals and (b) DSM criteria have no mechanistic grounding [77]. The latter weakness of DSM is especially critical when it comes to the construct validity of animal models. The deficiencies of DSM have led to the emergence of an alternative framework to classify mental disorders — Research Domain Criteria (RDoC), which has been promoted by the National Institutes of Mental Health to complement or possibly even replace DSM, (https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/index.shtml), and which appears to be well applicable to animal research [77–79]. With regard to experimental studies, RDoC, which "provide a dimensional framework of psychiatric classification focused on multilevel analyses which includes genes, molecules, cells, circuits, physiology, and behavior irrespective of DSM categories [79]", better suits for analyzing neurobehavioral comorbidities of epilepsy. Thus, under RDoC, depression falls into two domains: the Loss construct within the Negative Valence Systems and Reward construct within the Positive Valence Systems, and is further characterized through the integration of respective genes (e.g., those encoding serotonin and dopamine transporters and receptors, glucocorticoid receptors), molecules (e.g., monoamine neurotransmitters, glucocorticoid, and sex hormones), circuits (e.g., ascending raphe pathways, mesolimbic pathway), physiological parameters (e.g., the state of HPA-A, electrophysiological hallmarks of arousal and of sleep structure), and behaviors (e.g., motivation, sleep, sustained attention) [78]. Anxiety is categorized as a Potential Threat Construct within the Negative Valence systems, with the involvement of (as examples) transient receptor potential channels 4/5 on the gene and molecular levels, amygdala on the circuit level, HPA-A on the physiology level, and avoidance of the environment, which is deemed threatening (e.g., avoiding open brightly illuminated spaces) on the behavioral level [80].

The working group on epilepsy comorbidities of the Translational Task Force of the International League Against Epilepsy (ILAE) has proposed a matrix to facilitate the transition from the DSM-like to the RDoC classification when characterizing most common neurobehavioral impairments reported for animal models of epilepsy (Fig. 2) [47].

4.2. Common data elements for preclinical research

One common problem with the laboratory research of epilepsy comorbidities (which merely reflects a larger issue beyond the scope of this review) is high degree of disparity when approaching the subject matter. Different groups examine the same behavioral deficit using not just different paradigms to induce epilepsy, species, and strains, but also their own modifications to the protocols, time points for behavioral assays, outcome measures, and criteria. Along with that, some experimental conditions are often deemed to be insignificant and as such, not worthy to be documented and reported, although it is widely accepted that animals' behavior is highly sensitive to a variety of factors. Among the consequences of such disparities are the inconclusiveness of the findings and difficulty in consistently reproducing results reported in one study by other research groups.

The introduction of preclinical Common Data elements (pCDEs) for epilepsy research, as proposed by the Translational Task force of the ILAE and by the National Institutes of Neurological Disorders and Stroke [81], has become the first coordinated attempt to address this problem. It should be noted that pCDEs are not intended to impose on the investigator certain protocols, assays, or paradigms. Instead, in the core of pCDEs is comprehensive, transparent, accessible reporting of all conditions surrounding the experiment, even those that are often considered insignificant and remain either overlooked or unreported.

The first issue of pCDEs covers several areas of epilepsy research, including electroencephalography [82], physiology [83], pharmacological studies [84], and behavior/comorbidities, the latter classified by loosely following DSM [47]. Within behavior, pCDEs are grouped in individual case reports according to the tests (e.g., FST under "depression", MWM under cognitive dysfunctions, STFP under autism, and elevated plus maze under anxiety) and are designed to document even minute conditions of the experiment, as well as how and which data are collected and analyzed [47]. Access to such information should allow detailed comparison of study designs, experimental conditions, and data acquisition, which are often omitted in research publications and which may provide insight into the disparities in the outcomes of experiments, as observed by different groups. In addition, pCDEs should help the investigators who only begin their research in the field with proper experimental setup, design, data collection, and analysis. As the pCDEs are novel, we do not know whether their implementation will be able to solve the problem entirely; however, their usefulness is apparent, especially for current common multigroup collaborative projects, where standardization and harmonization are critical, and in light of research rigor and transparency as required by the National Institutes of Health [85].

4.3. Developmental studies

Neuropsychiatric comorbidities are common in children; some are more prevalent in children than in adults and/or bear particularly negative impact on the childrens' Quality of Life [86,87]. It is also recognized that "children are not small adults" when it comes to disease treatment [88] and disease modeling [89,90]; this recognition prompts special investigation of neurobehavioral comorbidities of epilepsy during early stages of development. Such studies, however, still occupy relatively small place in epilepsy research. It is also not uncommon for behavioral studies to be performed in adult subjects but discussed from the perspective of pediatric epilepsies, including comorbidities and therapies [6,91–94] (not to diminish the importance of the findings!).

It is often assumed that the armamentarium of available behavioral assays is more limited in immature animals than in adults. While this is may be generally correct (especially considering that rodents progress through developmental stages fast, while many behavioral tasks require days or even weeks to complete, and thus lag behind the ontogenetic development of the research subject), many neurobehavioral disorders can be indeed examined in immature animals with epilepsy using either conventional or age-specific tests. For example, rats and/or mice are amenable to cognitive tests such as MWM as early as at postnatal

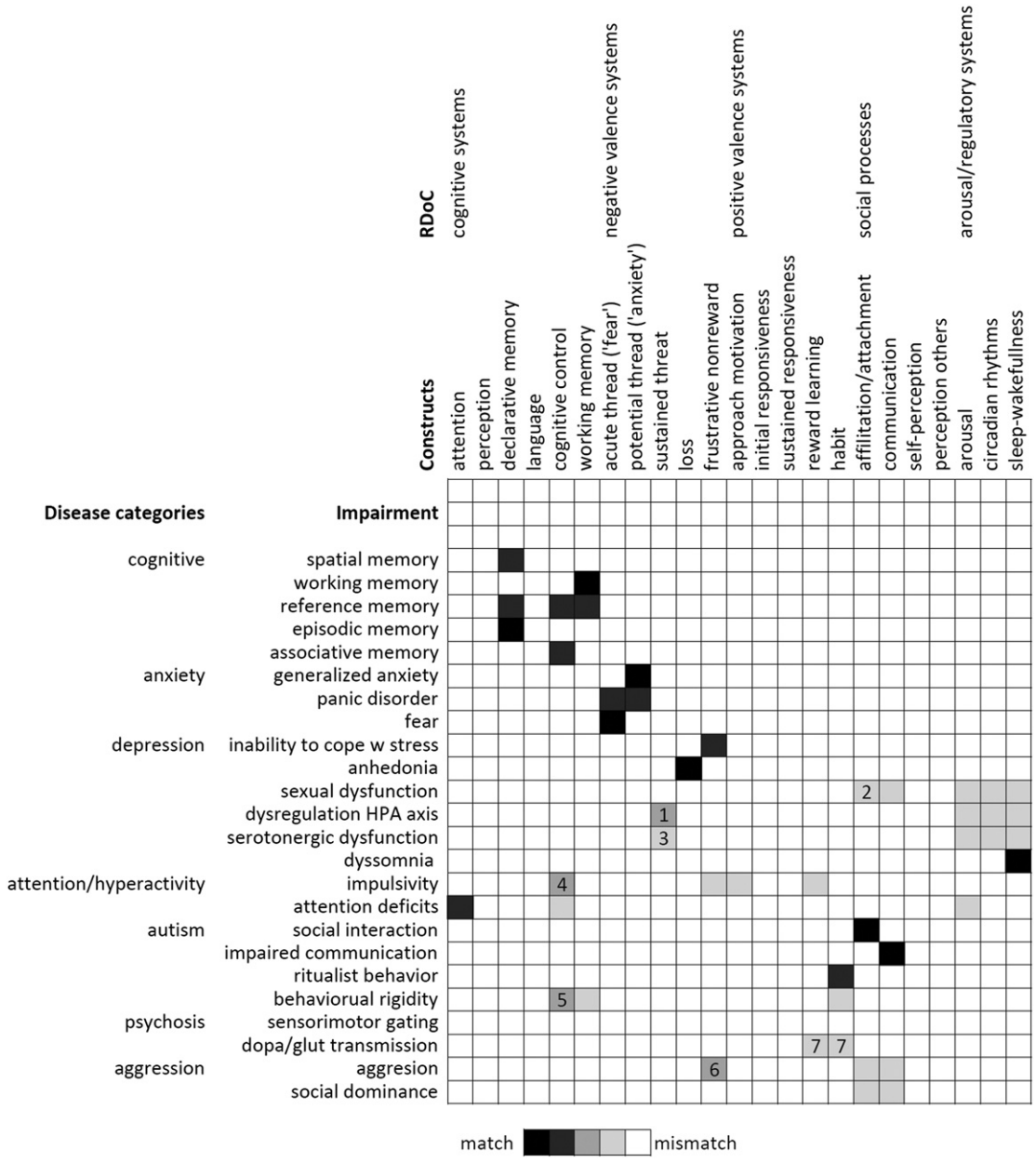

Fig. 2. Correspondence between disorders and RDoC constructs, as applied to animal models of epilepsy comorbidities. The matrix shows comparison between comorbid perturbations organized by disease categories, and further subcategorized by impairments (vertical alignment) and RDoC constructs (horizontal alignment), as assessed by the degree of matching between the descriptors. The transition from black to white through the shades of gray reflects the progression from perfect match (black) to partial and diminishing match (dark to light gray) to nonoverlapping descriptors (white). 1, dysregulated HPA axis enters as element of Physiology in this construct; 2, sexual dysfunction enters as communication and affiliation in Social Processes and as sex generically in Regulatory Systems; 3, serotonergic dysfunction enters as element of Molecule; 4, impulsive behaviors are included in the subconstruct Response Selection; Inhibition/Suppression; 5, behavioral rigidity enters as the subconstruct Flexible Updating; 6, Physical and Relational Aggression is included in this construct; 7, Dopaminergic/glutamatergic enters as elements of the unit Molecule in Reward Learning and Habits. (Composed by L.M. de la Prida as a part of [47]).
The figure and the legend are reused from [47] under Creative Commons Attribution Non-Commercial No Derivatives License (CC BY-NC-ND).

day (PND) 16 and match-to-sample/nonmatch-to-sample — at PND18 (i.e., during the preadolescent age); depression tests such as sleep structure/dyssomnia — at PND 8 (i.e., neonatal), and tail suspension test (an analog of FST) — at PND 21; tests for anxiety such as elevated plus maze and open-field test at PND 14 and PND 12, respectively (i.e., during the postneonatal stage); tests for autism such as ultrasonic vocalizations to examine vocal interaction at PND 1, and self-grooming to examine repetitive behavior — at PND 15, etc. (see [47] for further details and citations). When performed in conjunction with relevant models of epilepsy, behavioral tests conducted in immature animals can, without doubt, contribute to understanding aspects of comorbidities specific for pediatric populations [57,89,90,95–97].

5. Can we and should we use animal models to study neurobehavioral comorbidities of epilepsy?

Experimental studies of epilepsy comorbidities are complicated. Some of the difficulties reflect larger issues with animal models and assays of neuropsychiatric disorders, including their face, construct, and predictive validities [21], as well as ambiguity of the observed changes in behavior. The usefulness of these models may be further questioned based on the fact that no major successful neuropsychiatric drugs were discovered using animal models, and "the molecular targets of current major classes of psychotherapeutic drugs were all reverse engineered from drugs discovered before 1960 by clinical observation"

[21]. Other difficulties are specific to modeling epilepsy to include immediate effects of seizures, neuronal injury, and multiplicity of behavioral impairments that are not always congruent with clinical observations. Furthermore, if properly designed, conducted, and analyzed, experimental comorbidity studies are low-throughput, highly time-consuming and expensive; the end product will most likely remain open to interpretation and subject to criticism. Nonetheless, this overview should not be construed as one advocating agnosticism and discouraging endeavors in preclinical comorbidities research. On the contrary, seizing on advantages offered by animal systems (while always having patients in mind), coupled with thoughtful approach, clever design, and attempts to account for confounding factors, with careful interpretation, animal studies can certainly produce results welcomed by clinicians [98–100].

Most importantly, comorbidity studies should be regarded as an essential part of epilepsy research in general. Because neuropsychiatric comorbidities represent an inherent component of epilepsy in humans [101,102], proper validation of epilepsy models should always include not only characterization of seizures and their underlying pathophysiology, histopathology, etc., but also of concurrent neurobehavioral disorders and whenever possible, of their substrates. Only a model that strives to reproduce a spectrum of perturbations characteristic epilepsy (or, more specifically, of the type of epilepsy in question), can be deemed ultimately suitable for preclinical research. This in no way diminishes the usefulness of narrower approaches, including ex vivo and specialized in vivo studies; however, it should be admitted that the latter reproduce only selected features of epileptic system and as such cannot be regarded as true models of the disease. In conclusion, to answer the question posed in the title of this article, animal models can and should be used to study neurobehavioral comorbidities of epilepsy for as long as animal models are used to study epilepsy.

Declaration of competing interest

The author reports no conflicts of interest.

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