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Review

Behavioral measures in animal studies: Relevance to patients with epilepsy

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Abstract

The relevance of behavioral endpoints in animal seizure models to clinical epilepsy is outlined and enhanced in the present review by linking specific preclinical dependent measures with a quality-of-life scale that serves as an index of the health and welfare of patients with epilepsy (Quality of Life in Epilepsy inventory). This preclinical-to-clinical translation is possible based on existing literature within at least three behavioral domains: (1) physical and motor actions, (2) affective and emotional responses to environmental challenge, and (3) social, sexual, and parental functions. Face valid commonalities in observable behaviors are emphasized with the goal of engaging basic and applied researchers in collaborative research projects to accelerate the pace of discovery in the behavioral phenotyping of epilepsy field.

Keywords: Motor behavior; Emotionality; Social interaction; Quality of Life in Epilepsy; Well-being; Animal model

> The classical epileptic is apt to be morose, irritable, suspicious, and hypochondriacal. He is quite characteristically unreliable and with it all frequently presents a very aggressive form of sentimental, shallow religiosity.... Many epileptics are feeble minded or more profoundly defective.... He is self-opinionated, egotistical; he is moody with periods of laziness and lethargy alternating with outbursts of nastiness and pugnacity. He craves attention. His ideas of right and wrong are warped. He has violent temper outbursts. His sex behavior may be anti-social.
>
> *Excerpted from [1,2] and quoted in [3]*

1. Introduction

Although the early-20th-century characterizations at left of the "epileptic personality" are undoubtedly in need of modernization, one aspect of the passage with contemporary relevance is the presentation of both cognitive and behavioral characteristics of the prototypical patient description. Behaviors such as lethargy and violent outbursts are of particular and enduring interest to both preclinical and clinical epilepsy researchers because they reflect outwardly observable events that can be monitored without reliance on potentially hidden or inaccessible mentalistic state or trait variables. The important aim of bridging preclinical and clinical bodies of research would clearly be facilitated by the identification of certain behavioral dependent measures that co-vary uniformly with seizure activity in the various species under study. A good deal of research suggests that existing animal models of epilepsy employ locomotor, affective, and social behavior measures that exhibit construct validity for counterpart behaviors exhibited in human epilepsy, and yet additional testing of

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this hypothesis is required. Accordingly, the goal of the present review is to address commonalities in behavioral aspects of animal models of epilepsy and human clinical epilepsy via comparative analysis of well-being and quality-of-life scales.

2. Using the Quality of Life in Epilepsy inventory to select seizure-related behaviors that translate from preclinical to clinical research

One criterion advanced in the literature to ensure successful translation of animal model data to human epilepsy is the requirement that ''behavioral characteristics, including seizure-induced behavioral manifestations as well as short-or long-term behavioral deficits exhibited by the animal, should in some way reflect behavioral manifestations observed in humans'' [4]. This criterion would presumably be fulfilled in the event that identical behavioral manifestations arise in both species; an example could be the frequently reported decline in sexual activity in seizure-prone organisms. The requirement for resemblance of animal and human behaviors would likely also be fulfilled if analogous stereotypies (repetitive but purposeless behaviors), either ictal or interictal, were exhibited in both species; say finger tapping and head nodding in patients with epilepsy together with leaping and back flipping in rodents. One can also reason that such cross-species epilepsy correlates rise to particular prominence when they become significant for the welfare of seizure-prone animals and are recognized as important by persons with epilepsy. The present review attempts to extract from the universe of candidate behaviors those that serve as valid indices of well-being and quality of life in multiple seizure-prone species.

Measures of well-being and quality of life in nonhuman animals are more commonly encountered in veterinary and regulatory domains than in the mainstream scientific literature. Animal well-being can be defined operationally to reflect the biological, physical, and mental status of animals maintained for laboratory research purposes [5]. In practice, investigators and animal care staff are faced with statutory requirements to maintain minimal standards of physical and social environments in the animal colony while minimizing distress in the course of experimental work. In a comprehensive series of articles on animal well-being, Clark and colleagues define specific behavioral indicators of wellness in multiple species [6–9]. The determination of wellness requires the presence of certain species-typical behaviors such as grooming, stretching, and exploration in rodents. Also required is the absence of abnormal behaviors such as non-goal-directed activity and self-mutilation. Although no specific scale exists for scoring animal well-being, the hallmarks of a fitness and health determination when performed by a trained observer include: (1) an assessment of movement and body position, (2) a determination of the ability to cope with environmental challenge as exerted, for example, by the provocation inherent in human handling, and (3) social interactions with other animals in a group setting (Table 1). One can hypothesize that a battery of such motor, affective, and social assessments constitutes a reasonable index of an animal's somatic and psychological equilibrium.

A human analog of the well-being assessment for seizure-prone animals is the Quality of Life in Epilepsy inventory (QOLIE), developed to objectify overall health status and satisfaction with the circumstances of daily living [10]. Subscale QOLIE scores effectively index cognitive, physical, and mental dimensions of health and differentiate among therapeutic treatments in a clinical trial [11]. Moreover, physical, emotional, and social behaviors are among those catalogued to assess well-being, termed *quality of life* in the clinical literature (Table 1). One can hypothesize that behaviors listed in QOLIE were selected because they have an enduring and substantive impact on patients with epilepsy. The core of this questionnaire is the SF-36, a 36-item

Table 1
Behavioral criteria for comparative assessment of motoric, affective, and social well-being and quality of life in preclinical animal models of epilepsy and patients with epilepsy

Behavioral indices of well-being in nonhuman animal models of epilepsy	
Evidence of positive well-being	Evidence of negative well-being
A. Presence of normal behaviors	A. Presence of abnormal behaviors
1. Customary circadian locomotor activity pattern	1. Motor stereotypies
2. Successful coping with environmental stressors	2. Flight and immobility
3. Routine social interaction with conspecifics	3. Social withdrawal/aggression
B. Absence of abnormal behaviors	
Behavioral indices of quality of life in human epilepsy	
High quality-of-life scores reflect	Low quality-of-life scores reflect
A. Presence of normal behaviors	A. Presence of abnormal behaviors
1. Ample and vigorous physical activities	1. Physical activity limitations
2. Routine work activities in absence of emotional problems	2. Emotional problems limit work variety or productivity
3. Customary interactions with friends and family	3. Limited dialog with or visitation of friends or relatives
4. Good cognitive function	4. Medication side effects
B. Absence of abnormal behaviors	

Source. Indices of well-being in animals are adapted from Clark et al. [9]; indices of quality of life in epilepsy (QOLIE) are adapted from Devinsky et al. [10].