Review

Biological Psychiatry

Excitation-Inhibition Discoordination in Rodent Models of Mental Disorders

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ABSTRACT

Animal models of mental illness provide a foundation for evaluating hypotheses for the mechanistic causes of mental illness. Neurophysiological investigations of neural network activity in rodent models of mental dysfunction are reviewed from the conceptual framework of the discoordination hypothesis, which asserts that failures of neural coordination cause cognitive deficits in the judicious processing and use of information. Abnormal dynamic coordination of excitatory and inhibitory neural discharge in pharmacologic and genetic rodent models supports the discoordination hypothesis. These observations suggest excitation-inhibition discoordination and aberrant neural circuit dynamics as causes of cognitive impairment, as well as therapeutic targets for cognition-promoting treatments.

Keywords: Discoordination, Excitation-inhibition coupling, Neural coordination, Neural ensemble, Neural synchrony, Oscillations

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In *Siddhartha*, Hermann Hesse penned an astute exchange between Kamaswami, the rich merchant, and the hero Siddhartha, who at this stage of his journey is without possessions and appears destitute (1).

> K: "What is it that you've learned, what you're able to do?"
> S: "I can think. I can wait. I can fast."
> K: "That's everything?"
> S: "I believe, that's everything!"

Siddartha explains that he has full control of his mind; he is not distracted by impatience or bodily needs. With his singular ability, Siddhartha becomes rich and powerful.

This is an unusual beginning for an article on rodent models of mental disorders, but this dialog makes the starting point of the present work: cognitive abilities are extremely valuable resources with major economic and social impacts beyond individual well being. The term mental capital expresses this notion that the mental capacities of individuals and the groups that they form are determinants of individual and national wealth and prosperity (2). Research with rodent models of mental disorders aims to improve mental capacities by improving understanding of mental function and dysfunction.

IMPORTANCE OF ANIMAL MODELS

The importance of animal research that translates basic science to understanding mental disorders like schizophrenia has become increasingly apparent: knowledge of basic mechanisms grew enormously while treatment options only expanded slightly (3,4). Understanding such disorders is impeded because animal research traditionally avoids the mental domain where mental illness is prominent. One difficulty in developing more sophisticated approaches to treating psychiatric illness is the gulf between the behavioral/mental spheres in which mental disorders manifest and the biochemical/developmental domains where therapies and interventions are implemented. This is the problem of the missing middle (5). Tools are optimal for the microscopic (genomics and proteomics) and the large ensemble levels (functional magnetic resonance imaging and electroencephalography). The middle level is difficult to access, representing analysis of, for example, temporally organized discharge within neural ensembles or temporally activated synapses called synapsembles (6). Yet this middle level is needed to connect the nuts and bolts of receptors and transmitters with the level of clinical observables (7). A major challenge is to study normal and abnormal mental phenomena at the middle level of neural ensembles. This level of investigation is currently only practical in animal studies and is especially developed for rodents.

Patterns of neural circuit activity in rodent models of mental dysfunction are the focus of this review. I argue that the neurophysiology literature on animal models of mental dysfunction is converging on a specific form of neural discoordination as the basis for impaired cognition: when cognitive deficits manifest, the culprit is likely to be inappropriately coordinated dynamic interactions between excitatory and inhibitory neural discharge within and between neural networks.

THE UTILITY OF ANIMAL MODELS

What is an animal model of a mental disorder and how might it be useful? The phrase implies the animal mimics a patient with

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the disorder being modeled, raising issues of validity (8). However, the notion of a mimic is problematic for mental illness. The mental phenomena that are the foundation of a clinical diagnosis are rarely applicable to animals because it is unclear that animals have corresponding mental capacities, and if they do, they are unlikely to manifest like in people. Consider psychosis, a symptom that involves a distorted sense of objective reality and profound alterations of personality. What would that look like in a nonhuman? Furthermore, many diagnoses of mental dysfunction are open constructs, in that definitive criteria that define the disorder and differentiate it from another are unknown (9). How can one model something that is poorly defined? How can one judge if a model is a valid mimic? Psychosis is a symptom of schizophrenia and schizoaffective and personality disorders, as well as depression and bipolar disorders. If we could agree on what psychosis looks like in a rodent, which disorder would we have modeled? In this regard, the effort to base clinical diagnosis on objective biological criteria, the Research Domain Criteria project (10) may prove invaluable, and the identification of biomarkers for mental disorders, such as genetic variants and mutations, holds substantial promise. Even this can be ethologically problematic because pleiotropy can have species-specific outcomes, so that depending on the species, a gene may confer rather different phenotypes, making it challenging to interpret how a human genetic alteration might be mimicked in a model organism. The penetrance of mental disorder-related genetic variants poses a further complication for animal models because penetrance is typically just a few percent (11), meaning that the probability of a genetic modification leading to an abnormal phenotype can be difficult to detect in laboratory studies (12). There is even substantial overlap in the genetic abnormalities that associate with disorders as diverse as autism spectrum disorder, attention-deficit/hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia (13,14). These issues have been reviewed as they pertain to animal models that are relevant to schizophrenia (15), but the same issues are central to any attempts to model a mental disorder.

It may be ill advised to consider animal models of mental disorders as mimics of the target disorder (16). Rather, animal models are among our most powerful tools to test hypotheses about the disorder (15). We do not consider any of the rodent models reviewed here models of disease per se; rather, they are tools, a reagent that when used effectively can evaluate key hypotheses to drive understanding of relevant mental disorders.

NEURAL COORDINATION: NETWORK PATTERNS OF ELECTRICAL ACTIVITY AND NEURAL CODES

Much of the research on neural network patterns in rodent models is conducted within the hypothesis that discoordinated patterns of electrical neural activity are a core deficit in a variety of mental disorders (17–22). According to the hypothesis, cognitive deficits arise because of inappropriately coordinated neural electrical activity within and between neural networks (23). This causes neural information processing failures that preferentially manifest when there are competing sources of information. These coordinating processes are best studied as the temporal discharge relationship between two or more neurons (24) and/or their relationship to the local field potential (LFP) that arises from the spatiotemporal patterns of synaptic currents (6).

The coordinating processes are thought to be distinct from the more unitary processes that determine spiking characteristics, such as the firing rate and the tuning curves of individual neurons (25) and the frequency of oscillations in the LFP. Coordinating activity can also impact these unitary properties and can manifest as failures to sufficiently amplify neural representations of relevant information and sufficiently suppress the representations of irrelevant information without explicit discoordination of temporal discharge (26). It may be that such abnormalities in unitary processes are secondary to failures of coordination between excitation and inhibition (26). Nonetheless, the discoordination hypothesis predicts that basic properties and neural network functions, such as responses to stimuli and memory, can maintain under simple conditions. In contrast, functional and discoordination abnormalities will manifest under complex conditions that require using relevant information and ignoring irrelevant information to meet competing demands as in tasks like the Stroop test for people (27) and tasks that require contextual modulation of responses like the two-frame place avoidance task, set-shifting tasks, and other tests of cognitive flexibility for rodents (28–30), especially those that require the subject to selectively use the information that is inherently not preferred, which may be the case for the Room+Arena- variant of the place avoidance task (29).

The discoordination hypothesis emerges from a concept of how neurons represent information, which remains unknown. At the core of the dedicated-coding hypothesis is the notion of cardinal cells. Analogous to how the red light in a traffic signal unambiguously means stop (Figure 1A), these are neurons dedicated to signaling high-order stimuli and concepts like face or grandmother. Examples include single cell firing tuned to faces (31), celebrities, which was recorded from people (32) and hippocampus place cells (Figure 1C). A place cell tends to discharge at a single location in standard experimental environments (33). Although the capacity of a dedicated code is limited, how brains read the information in the firing of such cardinal cells seems straightforward and isomorphic with perception (34).

The discoordination hypothesis is founded in the ensemble-coding hypothesis. Information is represented by patterns of activity across many cells in an ensemble code, analogous to a jumbotron display that uses many lights to signal a message (Figure 1B). No particular bulb is essential for a message, many more messages can be encoded than there are bulbs, and the same bulbs can only represent one message at a time. Such properties require temporal coordination among neurons to represent and transmit information, perhaps at multiple time scales (35,36). Ensemble codes must avoid simultaneously representing multiple items with the same cells (37). Just as a jumbotron cannot simultaneously display two messages using many of the same lights, cell assemblies with many cells in common cannot coactivate if they share cells because the cells will merge into a unique, coactivity-defined cell assembly. Without effective neural coordination, multiple assemblies will coactivate, merging into one assembly with catastrophic information loss (37). Hebb's cell assembly postulate is an ensemble-coding scheme (38) in which a subset of linked cells