Review

Biological Psychiatry

Excitation-Inhibition Discoordination in Rodent Models of Mental Disorders

André A. Fenton

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

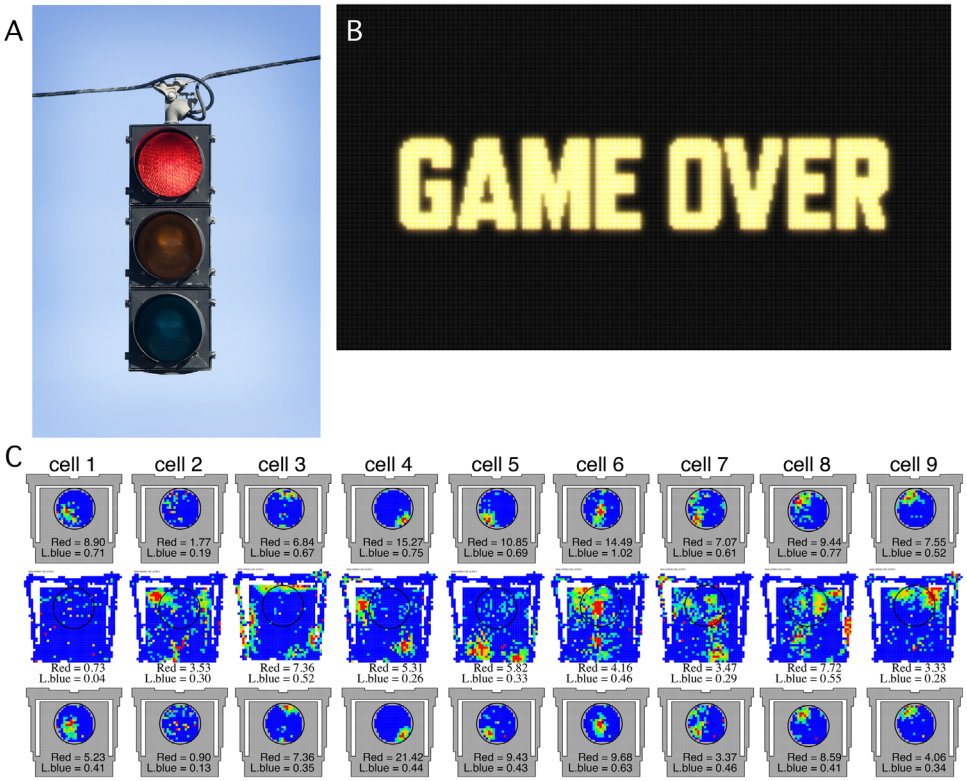

Figure 1. Two classes of neural code. **(A)** Dedicated codes represent information in a form that is analogous to a traffic light. Like the red light signals stop, whenever a neuron discharges, it unambiguously represents the same information. **(B)** Ensemble codes represent information analogous to a jumbotron, which represents information in the pattern of many on and off lights. **(C)** The discharge of hippocampus place cells is localized to single places in a familiar 70-cm cylinder (top and bottom rows) consistent with a dedicated code. However, in a large (1.4 × 1.5 m) environment, the same cells now discharge in multiple locations. The color-coded firing rate maps range from blue = 0 AP/second to red. The red rate is given for each map. [Adapted with permission from Fenton *et al.* (40)].

fire together to represent information by the pattern of active and inactive cells. Place cells recorded from hippocampal subfield cornu ammonis (CA1) that appear to signal single locations in small environments discharge in multiple locations in larger environments (39,40), indicating they are fundamentally an ensemble place code (Figure 1C). Unlike dedicated codes, it is unclear how the brain might read an ensemble code (6).

There are multiple coordinating mechanisms, but this review focuses on the dynamic interactions between populations of excitatory and inhibitory cells, which can be measured directly from ensemble recordings of unitary spike trains as well as recordings of frequency-specific oscillations in the LFP. The oscillatory dynamics provide an electrophysiological infrastructure within which spiking activity is embedded and organized (6,41,42).

Figure 2 describes a winner-take-all configured competitive neural network architecture in which the interactions between excitatory and inhibitory neurons is explicit and illustrative of how optimal and aberrant excitation-inhibition interactions underlie neural coordination (Figure 2A–C) and discoordination (Figure 2D–F), respectively. Such networks are proposed to explain phenomena like cognitive control and attention (43), as well as the tuning of spatially selective neurons like place cells, head-direction cells, and grid cells (44–46). The architecture is such that for any excitation, a subset of similarly tuned excitatory neurons will become active and suppress the remaining neurons. This is because of mutual excitation among subsets of the similarly tuned excitatory cells and because the excitatory activity activates interneurons that produce widespread inhibition, phenomena that can be assessed by measures like excitatory postsynaptic potential-spike (E-S) coupling. From the ensemble coding perspective, this network describes how subsets of cells are recruited to represent distinct classes of information by their coactivity. Disturbing the excitation-inhibition interactions can dramatically alter the network's ability to represent multiple classes of information, resulting in the superposition catastrophe (Figure 2D–F).

LFPs arise from the synchronous occurrence of postsynaptic potentials at many neighboring cells, resulting in rhythmic activity (47). These oscillations are typically temporally correlated with discharge of a small proportion of neurons due to strong feedback and feedforward inhibition, and modulation of E-S coupling (39,40). The correlation does not mean the oscillations are due to the spiking; quite the contrary, the synaptic activity underlying the oscillations forms a neural infrastructure that organizes temporal opportunities for spiking due to the coupling of excitation and inhibition (48,49).

Gamma (30–100 Hz) is probably the best understood oscillation. Gamma tends not to synchronize across distant sites, as these oscillations arise from the coincident local release of gamma-aminobutyric acid (GABA) because GABA type A receptor-mediated inhibition has a ~25 millisecond time constant (50–52). Tonic excitation of inhibitory neurons generates gamma oscillations by synchronous release of GABA that limits the possibility of excitation to the next gamma cycle. This organizes principal cell spiking in cortical networks (53,54). Greater excitation drives faster oscillations because GABA inhibition can be overcome sooner (53). This interaction between excitation and inhibition illustrates how excitation and inhibition are dynamically coupled. As reviewed below, the exact timing between excitatory and inhibitory

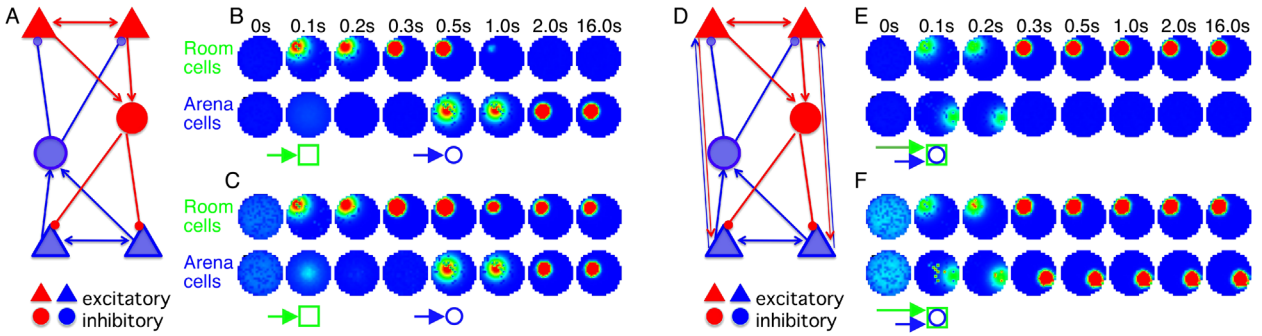

Figure 2. Winner-take-all competitive networks illustrate how excitation-inhibition interactions can organize neural network activity into coordinated network patterns. **(A)** The network is configured such that there is relatively strong mutual excitation among subgroups of pyramidal cells and these subgroups drive feedforward inhibitory neurons. Because of this configuration, the subgroup that receives more excitation will out compete the other subgroup, causing it to suppress. **(B,C)** Network simulations illustrate the network behavior. Each blue to red color-coded circle represents the collective activity of a 632 place cell network divided into two subnets, one for room locations (upper row) the other for arena (lower row) locations. The cells representing nearby locations were mutually exciting and cells representing far apart locations were less mutually exciting. Each cell generates global inhibition proportional to its current activity. The initial activity of all cells is low (blue) until a stimulus corresponding to a location in the room or arena occurs during the time of the second plot. Network activity persists after the stimulus is removed. **(B)** The network first represents a room location then switches to an arena location in correspondence with the stimulation (square and circle). **(C)** The network is simultaneously presented with separate room and arena stimulus locations, with the room input slightly stronger. Both the room and arena subnets initially activate but the room subnet predominates and the other is suppressed. **(D)** The same network is corrupted by randomly increasing connections 0% to 25%. The most significant impact is to increase the connections between the weakly connected cells. After the network corruption **(E)**, responses to the initial stimulus location are normal, but the network fails to switch to represent an arena location. The corrupted response is to represent both the room and arena locations, amounting to a nonsense representation and an example of the superposition catastrophe. **(F)** Similarly, the corrupted network fails to represent either of the room or arena locations when the two inputs are simultaneous. [Adapted with permission from Olypher *et al.* (26)].

discharge within identified subsets of excitatory and inhibitory neurons provides a rich palette of excitation-inhibition coordination phenomena. Additional mechanisms provide for neural coordination and these include long-term potentiation (LTP), long-term depression (LTD) and adjustments of E-S coupling, which has an inhibitory component (55), as well as intrinsic rhythmic and bursting properties such as what are discussed next for theta oscillations (56,57).

Theta oscillations synchronize neural activity on a ~140 millisecond time scale such that the sequence of theta phases is associated with the alternation between reduced and enhanced discharge probability (58,59). In the hippocampus, this is largely due to rhythmic inhibition that waxes and wanes with corresponding membrane potential fluctuations. This temporal organization is also spatially organized; theta oscillations propagate as a travelling wave along the septotemporal (dorsoventral) hippocampal axis (60,61). Unlike gamma oscillations, which are generated locally and do not synchronize across long ranges, theta oscillations can synchronize between distant sites, such as the hippocampus and prefrontal cortices (62–64), and are more synchronous between prefrontal cortex and ventral than dorsal hippocampus, consistent with the direct and indirect anatomical connectivity, respectively (65–67). Spike-field coherence can be observed across distant sites; LFPs and single neuron spiking in hippocampus and neocortex can be synchronized at a variety of oscillatory frequencies during both waking and sleep behaviors (68–71).

NEURAL DISCOORDINATION IN PHARMACOLOGIC MODELS OF MENTAL DYSFUNCTION

Under urethane anesthesia, exemplary aberrant neural coordination caused by excitation-inhibition discoordination is observed in one hippocampus after inactivating the other hippocampus by tetrodotoxin (26). Inactivation disinhibits the uninjected hippocampus (56,72), transiently increasing excitatory cell discharge for ~15 minutes (Figure 3A) and uncoupling excitatory and inhibitory cells (Figure 3B), despite the inactivation lasting ~10 hours. This resulted in a persistent discoordination among principal cells an hour after tetrodotoxin, when baseline rates had restored. Excitatory cell pairs that had previously been weakly coactive were now strongly coactive; initially strongly coactive pairs were unchanged, demonstrating aberrant circuit function (Figure 3C). This discoordination of cell pair spike timing was selectively associated with impaired cognitive control in the Room+Arena- variant of the place avoidance task but not control task variants requiring limited cognitive control (73), as predicted by the discoordination hypothesis (Figure 3D).

The discoordination hypothesis emerged from animal studies that used pharmacologic agents that produce altered mental states in people, in addition to the theoretical considerations of how neurons code information. Cannabinoids like delta(9)-tetrahydrocannabinol cause acute, reversible memory impairments. Cannabinoids slightly decrease the overall firing of hippocampal principal cells but not interneurons. Nor do cannabinoids disrupt the spatial discharge of hippocampus place cells, demonstrating maintained single cell discharge properties (74).

In contrast, cannabinoids discoordinate the discharge of place cells in relation to each other and in relation to LFPs at multiple timescales (75). At theta timescales and faster, cannabinoids reduce cell pair coactivity, possibly disrupting the gathering of principal cells into coactivity-defined cell assemblies (24) that carry place information (30,76). Cannabinoids disrupt the relationship between the theta phase

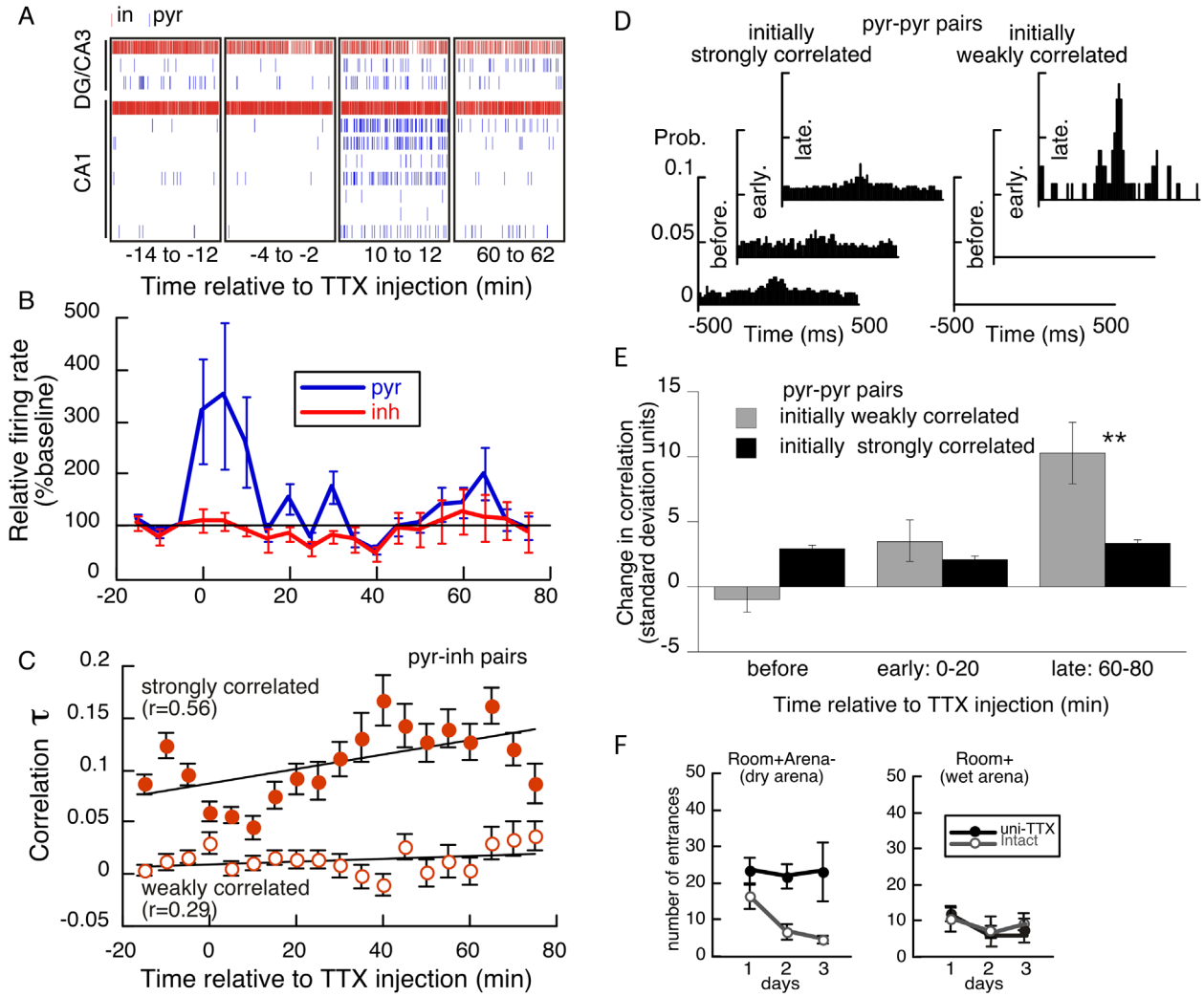

Figure 3. Neural discoordination following disinhibition of one hippocampus by unilateral injection of tetrodotoxin (TTX) into the other hippocampus. **(A)** Rasters of an ensemble recording and **(B)** average firing rate changes before and after TTX injection into the contralateral hippocampus. The injection transiently increased pyramidal (pyr) cell discharge without changing inhibitory interneuron (inh) discharge, consistent with disinhibition. **(C)** Excitation-inhibition coupling was transiently reduced by the TTX injection when pyramidal cell rates increased. Coactivity of pyramidal cell–interneuron pairs was selectively reduced if the pairs were strongly correlated before the contralateral TTX injection. **(D)** Cross-correlograms of individual cell pairs illustrating that 1 hour after TTX injection, the coactivity of pyramidal cell pairs (left) that had previously discharged together did not change (right), whereas coactivity increased if the pair had previously only rarely discharged together. **(E)** Summary of how initially weakly and strongly correlated cell pairs changed before and after TTX. **(F)** One hour after TTX injection (left), Room+Arena- place avoidance with high cognitive control demand was impaired but not (right) Room + place avoidance with low cognitive control demand. In both task variants, the arena rotates at 1 rpm and the shock zone is defined in stationary room coordinates. The dry area has salient but irrelevant rotating olfactory cues to actively ignore in the Room+Arena- task variant, whereas the irrelevant cues are attenuated by shallow water in the Room+ task variant. [Adapted from Olypher *et al.* (26), Wesierska *et al.* (73)]. CA, cornu ammonis; DG, dentate gyrus; Prob., probability; $^{**}p < .01$.

difference at which a pair of CA1 place cells fires and the distance between their place fields, a representation of place sequences (77,78). At timescales of a few seconds, cannabinoids increase coactivity, potentially causing excessive formation of cell assemblies that signal distinctive contexts or tasks (35,36). These forms of discoordination are accompanied by reduced theta, gamma, and sharp wave associated ripple (100–200 Hz) oscillations in the hippocampus LFP, and the theta reduction indexes impairment in a task that requires segregation of memories of more and less recent places (75). This pattern of preserved discharge in individual cells with disorganized intercell activity resembles the effects of unilateral tetrodotoxin and is predicted by the discoordination hypothesis.

Cannabinoids also discoordinate activity between brain areas. While hippocampal theta is reduced by cannabinoids, theta is preserved in prefrontal areas during stillness and rest, whereas gamma is decreased (79). Cannabinoids disinhibit by activating cannabinoid receptor type 1 receptors on cholecystokinin-positive interneurons to decrease GABA release. Cannabinoid receptor type 1 receptors are also on excitatory terminals so that instead of increasing firing rates, the disinhibition primarily disturbs spike timing (80–83).

Cannabinoids reduce correlated <10-millisecond burst spiking in the hippocampus, whereas the effect is to reduce prefrontal coactivity over a wider range of time scales (10–100 msec), again with minimal effects on overall firing rates. Although the cannabinoid effects coincide with impaired spatial choices in normal animals (79), the reductions in coordinated activity have beneficial potential when baseline activity is hypersynchronized, as in pathological conditions. Resting gamma hypersynchrony is observed in schizophrenia as well as some experimental conditions that selectively cause cognitive coordination deficits (26,84,85).

Different forms of neural discoordination are caused by psychotomimetic uncompetitive antagonists of *N*-methyl-D-aspartate receptors (NMDARs) like phencyclidine (PCP), MK801, and the noncompetitive antagonist ketamine (86,87). In addition to impairing LTP, LTD and learning, psychotomimetics produce psychotic symptoms in healthy people (88) and exacerbate symptoms in schizophrenia patients (89), making them once the most widely used animal models in antipsychotic drug development (90). Use of PCP models is dwindling, perhaps due to an overemphasis on the PCP-induced sensorimotor deficits as a model for positive symptoms (90), as well as the recognition that cognitive impairments are a core deficit of schizophrenia (91,92) (see the MATRICS: http://www.matrics.ucla.edu/ and CNTRICS: http://cntrics.ucdavis.edu/ initiatives of the National Institute of Mental Health). Because cognitive symptoms are found in nearly all patients (93,94) and are among the strongest predictors of clinical outcome (91,95), emphasis has shifted to develop cognition-promoting antipsychotic treatments (91,92). Although it has not been sufficiently emphasized, psychotomimetics discoordinate neural activity and impair cognition (18), consistent with the discoordination hypothesis.

Psychotomimetics activate prefrontal (96,97) and cingulate cortical areas (98,99) in human neuroimaging studies, which seems paradoxical since the drugs reduce excitatory currents through NMDARs. In rat prefrontal areas, MK801 decreases interneuron firing. The drug increases principal cell firing rates in ~40% of these cells but decreases burst discharge (100,101) and firing rates in a small fraction (102). This suggests MK801 disinhibits cortical networks, potentially resolving the paradox. Consistent with the reduced inhibitory control of principal cell spiking, psychotomimetics enhance action potential associated high-frequency oscillations (103–105) in motor cortex concurrent with hyperlocomotion (106). MK801 also disrupts the coupling of spiking to gamma oscillations in the LFP (102).

Ketamine also discoordinates hippocampus discharge by interfering with the coupling of inhibitory and excitatory cells, producing abnormal coordination in a variety of ways. Ketamine weakly decreases pyramidal cell firing and increases and decreases firing rates in distinct inhibitory neuron subclasses, producing no net change (107). CA1 cells usually discharge asynchronously but synchronize under ketamine (107). Ketamine causes both (excitatory) pyramidal cells and (inhibitory) parvalbumin-positive basket cells to increase near-synchronous discharge, such that they are inhibited from firing together for a few hundred milliseconds before and after coactive discharge. Ketamine changes the phase of theta at which putative basket cells discharge (107). Whereas pyramidal cells preferentially discharge at the trough of local theta oscillations, basket cells preferentially discharge just earlier, on the descending theta phase. Another class of interneuron (possibly bi-stratified cells) prefers to fire at the theta trough, when pyramidal cells discharge, but a third class, possibly chandelier cells, prefers to fire at the peak of theta (108–110). Ketamine also changes the theta-related firing probabilities of these cell classes, which is how network discharge can discoordinate without changing overall activity. These observations demonstrate that oversimple notions, like more or less neural activity in an inhibitory or excitatory population, are poor descriptors and predictors of discoordination. Because distinct interneuron classes target distinct input-specific perisomatic and dendritic compartments of hippocampus and neocortex (111–113), these findings emphasize the importance of measuring and manipulating the subcellular and circuit-specific features of neural networks rather than standard analyses that are prone to overaveraging across heterogeneous subpopulations of signals and cell types.

NEURAL DISCOORDINATION IN GENETIC MODELS OF MENTAL DISORDERS

Human genomic investigations identify genetic alterations that are associated with mental disorders, and animal models are valuable for identifying the functional consequences. The 22q11.2 microdeletion increases risk of schizophrenia and autism (114–117) but it is not obvious why. Abnormal neural synchrony between the dorsal hippocampus and prefrontal cortex was identified in a mouse model that mimics the deletion and expresses working memory deficits. During working memory tasks, rodents increase the synchrony of hippocampal–prefrontal theta and phase locking of prefrontal discharge to theta (63,118). This coordination is reduced in the mutant and the reduction predicts the working memory deficit magnitude (118).

The coupling of theta between the prefrontal cortex and ventral hippocampus increases during anxiety-related behavior, as does the theta-phase synchrony of discharge that distinguishes between parts of an environment with different anxiogenic potential (119). The theta synchrony increase is exaggerated in serotonin 1A receptor knockout mice, a model of increased anxiety-related behavior (67).

There is substantial evidence of impaired NMDAR function of cortical interneurons in schizophrenia (120,121), the functional consequences of which were investigated by knocking out the NR1 receptor subunit in mouse interneurons either early or after adolescence (122). In addition to a variety of schizophrenia-relevant behavioral and histological abnormalities, the discharge of S1 neurons in the early knockouts was faster but poorly correlated. Although baseline oscillatory power in the auditory cortical LFP was greater in the mutant, evoked 20-Hz and 40-Hz oscillatory activity was reduced and short lived in response to steady-state click stimulus trains (123). The abnormalities were not observed if the gene was deleted after adolescence, indicating a neurodevelopmental consequence of NMDAR loss of function in interneurons (122).

Schizophrenia risk is associated with abnormality at a gene locus that codes for the phosphatase calcineurin (124). Calcineurin knockout mice revealed that loss of the phosphatase severely impairs LTD, slightly increases LTP, and causes

schizophrenia-related behavioral abnormalities (125,126). Hippocampal LFPs were normal, except ripples were more frequent in the knockout, indicating a specific form of increased excitability (127–129) that is sensitive to long-term synaptic plasticity changes (127). During exploration, individual hippocampal place cells appeared normal in the knockout, but discharge timing was abnormal during ripple-associated replay of the discharge sequences that were observed during exploration. This discoordination is specific to quiet rest when neural activity during recent experience is re-expressed, presumably to organize and store memory (129–134).

SUMMARY: THE DISCOORDINATION HYPOTHESIS AND BEYOND

Processing information and generating knowledge are valuable, making mental illness devastating and costly. Mental disorders are being reconceptualized and analyzed as genetically and environmentally driven developmental alterations in specific neural circuit operations (135). Typically, these circuits are robust and adaptive, partly because of multiple synaptic, structural, and functional plasticity mechanisms for maintaining function. Unfortunate and inconveniently timed genetic and environmental influences can alter neural circuits in myriad ways with consequences that depend on the exact genetic, environmental, and developmental interactions. Accordingly, a good bet to promote understanding and effective treatment outcomes is to look (and hope) for disruption in a limited set of common pathways that mediate cognition and behavior (15). This is the inspiration for the discoordination hypothesis, which focuses on neural network function in hopes of affecting outcomes rather than correcting the root causes.

The discoordination hypothesis does not eschew genetic or other etiological accounts for mental disorders, it just does not focus on or aim to correct them. The hypothesis embraces data suggesting that diverse etiology converges to change neural circuit function, often by altering synaptic structure and function (136). The hypothesis supposes that dysfunction emanates from distributed disturbances and secondary adaptations within synaptic networks, suggesting that pathology is difficult to localize in space and time. The patterns of neural activation and inactivation captured by the patterns and interactions of neural oscillations reviewed here can only be fully understood in the context of their use and time evolution. These dynamics may at once be the precious information that the brain processes and generates, as well as the substrate for processing that information (56). The relationship between the information and the functional infrastructure for it is analogous to the relationship between water and the river that it at once forms and is guided by. Tools and concepts are developing to identify and precisely measure these dynamics. We even see that appropriately curated experience can itself repair and improve outcomes (137–139). The neural patterns themselves are the therapeutic target (92,95,140,141).

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ARTICLE INFORMATION

From the Neurobiology of Cognition Laboratory, Center for Neural Science, New York University, New York, New York.

Address correspondence to André A. Fenton, Ph.D., New York University, Neurobiology of Cognition laboratory, Center for Neural Science, 4 Washington Place, New York, NY 10003; E-mail: afenton@nyu.edu.

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