Mechanistic Classification of Neural Circuit Dysfunctions: Insights from Neuroeconomics Research in Animals

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Many psychiatric conditions present complex behavioral symptoms, and the type and magnitude of underlying neural dysfunction may vary drastically. This review introduces a classification scheme for psychiatric symptoms, describing them in terms of the state of a dysfunctional neural circuit. We provide examples of two kinds of functional deficits: variance-shifted functionality, in which a damaged circuit continues to function albeit suboptimally, and state-shifted functionality, resulting in an absent or qualitatively different functional state. We discuss, from the perspective of neuroeconomics and related areas of behavioral investigation, three broad classes of commonly occurring symptoms in psychopathology based on selected studies of decision making in animals: temporal discounting, social preferences, and decision making under environmental volatility. We conclude that the proposed mechanistic categorization scheme offers promise for understanding neural circuit dysfunctions underlying psychopathology.

Key Words: Animals, decision, electronic circuit, neuroeconomics, psychopathology, reward, state-shifted, suboptimal, variance-shifted

Comprised of constellations of behavioral symptoms, psychiatric disorders frequently frustrate any simple attempt to translate observed phenotype into neurobiological mechanism. Even at the individual symptom level, such translation is challenging and not easily quantifiable. Behavioral symptoms are often compound and thus difficult to interpret. This presents a challenge for understanding their core neurobiological features, creating practical barriers to designing behavioral or diagnostic tests. This difficulty may be amplified when studying the illnesses manifested as a result of dysfunctions in the prefrontal, limbic, and paralimbic regions, which are less well understood, compared with, for example, the occipital cortex. A promising alternative to understanding the neurobiology of psychiatric disorders begins by classifying them according to the ways the underlying mechanisms may fail. In this issue exploring the benefits of a neuroeconomics approach for understanding psychopathology, we outline a mechanistic classification scheme grounded in the principles of neuroeconomic studies of cognition and behavior in animals.

Variance-Shifted Versus State-Shifted Functionality: Insights from Electronics

Dysfunctional neural circuitry can be functionally classified into two different states based on the outputs of disrupted circuits. As an illustration, consider an electronic circuit designed to produce a specific output. A variance-shifted circuit operates with added noise and, therefore, generates a broadened output distribution, resulting in suboptimal performance. However, a suboptimal circuit may continue to process information (1). By contrast, a state-shifted circuit may generate a completely different functional output, either beyond the expectation of a downstream circuit or failing to generate any output at all, producing a qualitatively different or absent output and resulting in behavior drawn from a different distribution altogether (1).

As a simplified analogy, a simple band-pass filter illustrates the different classes of damage-induced functional states. A change in circuit resistance or capacitance will change the effective cutoff frequency, while a short in the system effectively halts filtering (1). Changes in a circuit's resistance will result in a noisier output, analogous to psychiatric conditions in which afflicted individuals show difficulty in evaluating changes in the environment. Such damage to the circuit reveals its critical role for producing adaptive, normal behavior. In contrast, the presence of a short in the system will prevent filtering of relevant information, analogous to situations where afflicted individuals completely lose sensitivity to changes in the environment. In this case, the state-shifted circuit reveals its necessary role in the production of a particular behavior.

The intricate balance between circuit components can result in functional changes that are either large and noticeable or small and subtle. Some neuropsychiatric symptoms only differ from others slightly, whereas others are so specific to a condition that they serve as a diagnostic hallmark. Furthermore, because of the complex and multilayered nature of neural circuits, initial perturbations may result at first in a state-shifted circuit that, due to neural plasticity, resolves back to a variance-shifted, or even fully restored, state. In summary, psychiatric symptoms may result from a relatively preserved neural circuit operating with added noise, producing deviant and suboptimal behavior (variance-shifted functionality). Alternatively, it may arise from a shorted circuit producing completely different or absent behaviors (state-shifted functionality).

The two damaged states can be described in terms of neural network models as well. In a trained neural network, the organizational principles involve individual computational units, or nodes, whose functionalities may be obscure and may encode information idiosyncratically (2,3). A variance-shifted functional state may result from damage to peripheral nodes, whereas a state-shifted state may be induced by damage to a central node in the network. The two functionalities can also be described based on the output statistics of an implicated circuit. A variance-shifted dysfunction in a neural circuit may produce circuit (or behavioral) outputs characterized by a broadened and/or attenuated distribution compared with optimal functionality (thus less specific or more noisy). In contrast, a state-shifted dysfunction in a circuit may produce an output

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drawn from a completely different distribution (thus qualitatively different) or may result in a complete failure to produce any output. It is worthwhile to note that a state shift could occur in the direction of extreme enhancement, resulting in exaggerated behavior such as positive symptoms in schizophrenia.

Our classification scheme, though neither exceptionless nor exhaustive, provides insight into the possible mechanisms underlying psychiatric symptoms. The two deficit types may occur simultaneously or sequentially (and the distinction sometimes can be ambiguous until a given circuit is fully understood) but may provide novel mechanistic insights into psychopathology and inform the relationship of pathology to health. This approach differs fundamentally from the *Diagnostic and Statistical Manual of Mental Disorders*, the *International Classification of Diseases*, and the like, which are designed to describe a disorder using a list of behavioral symptoms for diagnostic purposes. The present scheme is useful for directly comparing the functionality of neural mechanisms and their corresponding behaviors across normal and dysfunctional states of the brain. A successful distinction between variance- and state-shifted dysfunction is constrained by our understanding of a given circuit. For example, a variance-shifted dysfunction under one functional criterion could be seen as a state-shifted condition under a different framework. Such ambiguity, which is present in any classification scheme, can only be resolved through more comprehensive understanding of a circuit.

Examples from Oculomotor System

Examples from oculomotor system help illustrate the two distinct dysfunctional states described above. The superior colliculus and frontal eye fields belong to a distributed oculomotor circuit spanning cortical and subcortical structures (4,5). Frontal eye field lesions increase variability in saccade trajectories and severely disrupt selection of targets in the contralesional hemifield (6). Frontal eye field lesioned animals, however, can still saccade (6). By contrast, superior colliculus lesions temporarily abolish contralesional saccades altogether (7). They also permanently increase saccade latencies and eliminate the animal's ability to make express saccades (saccades with reaction times less than 100 msec in monkeys) in a gap task (7), designed to bypass the time required to disengage from visual fixation by inserting a gap between the offset of a fixation stimulus and target onset (8). Therefore, for saccades, frontal eye field disruption results in noisy (i.e., variable) performance but preserves overall functionality, a variance-shifted dysfunction. Superior colliculus damage alone, by contrast, is sufficient to temporarily abolish saccades, which is consistent with a state-shifted dysfunction. These examples demonstrate that distinct mechanistic deficits can impair or abolish normal function.

Neuroeconomics of Decision Making in Animals

Neuroeconomics, a discipline that marries the mathematical formalisms of classical economics, the psychophysical methods of behavioral economics, and contemporary neurosciences (9–11), provides an illuminating test of the functionality-based classification scheme for defining mechanistic pathologies in decision making (for a review regarding the benefits of animal models in neuroeconomics, see [12]). The approach applies mathematically tractable economic formalizations to the nervous system and focuses on basic economic concepts such as utility (9,13–15), risk (16,17), and temporal discounting (18,19), providing quantitative frameworks for examining the neural mechanisms underlying cognitive processes (12).

The neuroeconomic framework in animal models is advantageous for studying complex forms of decision making by tapping into their innate reward-seeking behaviors while maintaining ethological validity. Unlike in humans, animal models offer access to studying complex behaviors at the resolution of single neurons. Further, insights into different types of mechanistic deficits in neuropsychiatric symptoms can be obtained by studying decisions animals make following perturbation of neural circuits. Thus, animal models of decision making provide valuable insights into characterizing the biological mechanisms of behavior, detailing the formal operations the brain performs in realizing different cognitive capacities.

We discuss a selection of experiments, categorizing the observed deficits as the variance-shifted and state-shifted model of neural circuit dysfunctions. We organize this discussion around three examples of circuit dysfunction in light of neuroeconomics and other related disciplines: disorders of temporal discounting in addiction, social and other-regarding preferences (ORP), and decision making under environmental volatility. Our intention is not to establish necessary and sufficient conditions for connecting a specific dysfunction and a specific neural circuit. Doing so would not be practically possible. Instead, in this exercise, we attempt to label experimentally induced behavioral deficits observed in animals as dysfunctions arising from either a variance- or state-shifted functional state in the implicated circuit. Although this classification scheme can be just as easily applied to any perturbation results (e.g., microstimulation or drug infusion), we focus on lesion studies for their blunt effectiveness in perturbing circuit function.

Addiction as a Disorder of Temporal Discounting

Single-unit recordings in animals, as well as neuroimaging in humans, have found that striatal dopaminergic signaling is critical for reward-related processing, including motivation and learning (20–22), and that dysfunctional dopaminergic signaling disrupts reward anticipation in drug addiction (for a review, see [23–25]). Firing rates of midbrain dopamine neurons compute economic decision parameters, such as reward probability, reward delay, and reward uncertainty (26–28). Dopaminergic signaling is also involved in evaluating the economic costs and benefits of upcoming rewards. For example, neurons in rodent nucleus accumbens (NAc) encode anticipated reward benefits, without encoding response costs to achieve the reward (28). Such economic computations by the mesolimbic dopamine system may contribute to addiction and other motivation-related disorders.

Temporal discounting describes a time-dependent devaluation of economic value (18). It is a phenomenon observed across multiple species including rodents, monkeys, and humans (18,29,30). When provided an option to choose an immediate but smaller reward over a larger reward with a longer delay, animals reliably prefer the immediate option (31). Addicted individuals discount more than nonaddicted individuals (24,32), as evidenced by behaviors manifested in addiction to cocaine, alcohol, opioid, nicotine, and gambling (for a review, see [32]). Therefore, a disruption in temporal discounting may be a common mechanistic deficit shared by many classes of addiction.

Single-unit recordings in monkeys demonstrate that neurons in the striatum mediate computations underlying temporal discounting (33). Rats with NAc lesions display severe difficulty in choosing a delayed reward option in an intertemporal choice task, suggesting a critical role of NAc in computing economic values of rewards in time (34). Further, NAc lesions do not abolish reward sensitivity altogether but impair the implementation of an optimal (reward-

maximizing) strategy (35), as if these animals cannot accurately compute temporally discounted utility to guide decisions. Similarly, addicted individuals rarely lose the ability to seek addicted substances. Rather, they display impaired impulsive control in pursuing immediate rewards, consistent with atypical temporal discounting. Thus, addiction-related deficits resemble a variance-shifted functionality, resulting in disrupted decisions in time, though retaining some sensitivity to reward (i.e., performance does not become random and the discounting function does not become flat). Deficits resulting from perturbations to dopamine circuits performing economic calculations seem to cause noisy mappings, or variance shifts in the representations, among reward, action, and time.

Neural correlates of temporal discounting are also found in the prefrontal cortex (for a review, see [36]). Neurons in dorsolateral prefrontal cortex (dlPFC) encode the temporally discounted value of upcoming rewards (19). A cocaine self-administration study in monkeys found that activity in the anterior cingulate cortex (ACC) is enhanced upon cocaine intake (37), consistent with human neuroimaging studies showing that drug seeking in addiction is linked to the prefrontal cortex (38,39). ACC involvement in reward-guided decision making is not limited to processing directly experienced outcomes but also includes fictive outcomes (40), similar to the human ventral striatum (41). Correctly utilizing such fictive signals may be critical in addiction. Individuals with chronic nicotine addiction fail to utilize these signals to adjust their choices in an investment task (42). Furthermore, gambling addiction seems to require rewards that are delivered according to a partial or a variable schedule (43), coupled with near-miss fictive reward signals.

Disorders of Social and Other-Regarding Preferences

Precisely how social information is integrated into economic decisions in neural circuits remains obscure. Understanding whether social disorders are manifested by a deficit in a decision circuit or a circuit purely involved in evaluating social information from the environment remains a challenge. ORPs describe a consideration for the economic well-being of others. ORP computations may reflect a stage where decision making and social information processing are partially integrated. Consider autism spectrum disorder (ASD), which handicaps social and communicative abilities of ~1 per 110 children in the United States (44). Autism spectrum disorder individuals show little interest in others (45). This lack of interest is associated with other complex social deficits, including reduced empathy and joint attention, further disrupting the capacity for normal social interactions (46,47). Differences between ASD and typically developing individuals are illustrated by performance in economic bargaining games designed to elicit ORP. While healthy individuals readily engage in reciprocal cooperation in these games, ASD individuals adopt simple rules that are both less flexible and more laboriously employed (48). It remains unclear whether circuit dysfunctions in ASD more closely resemble variance-shifted or state-shifted states. Comparison with other disorders marked by social deficits, such as schizophrenia, psychopathy, and eating disorders, may help to illuminate the underlying pathology in ASD.

ACC is critical for social processing. ACC gyrus lesions in monkeys abolish the animal's ability to evaluate social information, as measured by response latencies to retrieve food in the presence of socially arousing images, such as staring monkeys (49). Although the changes in response latencies in ACC-lesioned animals can differ substantially depending on the types of social stimuli and often on the individuals, sensitivity to social stimuli can be eliminated by the lesion (49). This social evaluation deficit therefore resembles a state-shifted functionality, in which social evaluation processing is no longer intact. In contrast, ACC sulcus and orbitofrontal cortex (OFC) lesions produce deviant behaviors but fail to abolish the sensitivity to social stimuli (49), resembling a noisy suboptimal state and a variance-shifted functionality.

Closely related to ORP, empathy-related processing by ACC has been investigated in the context of perceiving painful events of others. The brain areas involved in pain perception in humans, namely ACC and frontal insula, are more metabolically active when perceiving a painful stimulus delivered to fair compared with unfair players in an economic game (50). In rodents, ACC, along with other medial pain systems, mediates observational fear conditioning while watching a conspecific receive a shock (51). Both lidocaine-induced inactivation and targeted deletion of a voltage-gated calcium channel in ACC can substantially reduce observational fear conditioning but not eliminate it (51). A dysfunction in empathy-related processing in ACC might be driven by variance-shifted dysfunctional states, resulting in degraded sensitivities to process or simulate the painful events of others.

A link between ORP and emotional processing remains elusive. Amygdala is one of the primary structures linked to emotional processing and is reciprocally connected to ACC and OFC (52,53). Amygdala dysfunction is related to a number of psychiatric symptoms, including major depression and bipolar disorder and affective psychosis in schizophrenia (54). Typically, amygdala contribution to emotional processing has been investigated using fear-inducing or social stimuli. Monkeys with bilateral amygdala lesions show abolished fear responses, as measured by response latencies to retrieve food in the presence of a fearful stimulus (52,55). Consistent with these observations, amygdala-lesioned rats completely lose the ability to acquire conditioned fear, even when the lesion occurs a month after the initial Pavlovian training, suggesting a necessary role in emotional memory (56,57) (i.e., state-shifted due to an absent distribution). Notably, in many psychiatric conditions involving emotion, the gain on emotional processing in amygdala might be set too high, possibly due to impaired communication with other structures, such as prefrontal cortex, that modulate amygdala activity (58). Such unregulated emotional processing might lead to exaggerated behavior, presumably due to a state shift. For example, this state shift might result in a more responsive and less regulated state. The reciprocal information transmission among the amygdala, ACC, and OFC (52,53) suggests that the emotional component of ORP may originate from the amygdala.

Disorders of Decision Making Under Environmental Volatility

Several neurological and psychiatric disorders compromise the adaptive abilities of cognitive systems, whether updating the expected values of targets according to task demands or appropriately reorienting to reflect changes in the environment. Notably, some cognitive deficits such as an inflexibility to adapt to environmental changes are shared across multiple neurological and psychiatric conditions. For example, degeneration of mechanisms that contribute to adaptive decision making, including task set switching, task set maintenance, and inhibitory control, characterizes cognitive and executive deficits in schizophrenia (59,60). From a neuroeconomic perspective, these may emerge from failures in updating reward valuation, risk, and volatility. In the Wisconsin Card Sorting Task (WCST), typically used to probe the ability to adjust to changing environments without explicit cues, participants sort a deck of cards according to unpredictably changing rules (61). During the task, schizophrenic patients perseverate more on choosing

incorrect responses, persisting longer with a previous rule despite negative feedback (62). These individuals also show increased response times and make more errors in the Stroop task (63–67).

Schizophrenia is accompanied by both negative symptoms, such as lack of emotion, and positive symptoms, such as hallucinations and delusions (68). In addition, schizophrenia is associated with deficits in executive and cognitive functions (68). Such deficits include inflexible adjustments in behavioral strategies, or policies, that require computing expected value of reinforcers on the basis of the accumulation of evidence over time, assessment of value on the basis of reinforcer identity, and projecting these evaluations into the future (69). Schizophrenic patients also show decreased abilities to stay on task (70,71). Deficits related to executive control are suggested to be caused by noisy dopaminergic gating of prefrontal neurons (70). Symptoms in the domain of executive control may thus reflect variance-shifted processing. Positive and negative symptoms, on the other hand, are associated with exaggerated (e.g., hallucinations) and abolished (e.g., lack of emotion) processing, respectively, and thus are more consistent with a state-shifted condition.

In schizophrenia, the posterior cingulate cortex (PCC) is associated with increased default network connectivity, with the degree of enhanced connectivity positively correlating with the severity of psychopathology, and these patients show increased cannabinoid receptor expression (mediating inhibitory neurotransmitters like gamma-aminobutyric acid) (72,73). A case study of lesions in the human PCC found an inability to adapt to new environments (74). Consistent with this, neuronal activity in monkey PCC tracks the level of risk in changing environments (17) and is correlated with setting a behavioral strategy to explore or exploit different options (75,76). Thus, disruptions to PCC seem to compromise an ability to detect and incorporate discontinuities in environmental statistics such as changes in expected value and risk. It remains unclear whether volatility-related deficits in PCC lesions reflect variance- or state-shifted functionalities.

An explicit task-switching paradigm, in which a correct response on a given trial or group of successive trials is explicitly cued, is often used to investigate executive control. In such a task, neurons in ACC increase responses following task switches (77), suggesting sensitivity to changes in reward information used in executive control. Lesions to ACC gyrus increase the frequency of consecutive errors, whereas more comprehensive lesions in ACC (gyrus and sulcus) result in slowed response times, errors in switching, and greater overall consecutive errors (78). Critically, although ACC lesions increase switch-related errors, monkeys are still able to switch tasks above the chance level, suggesting the mechanisms responsible for cognitive flexibility are not completely abolished (78). These results implicate a variance-shifted deficit inducing suboptimality in the ability to adapt to changing environments by explicit changes in the expected values of the targets.

Perseveration of maladaptive behavior is one of the most striking features of prefrontal lesions. Such deficits are apparent in environments without explicit rule-changing cues. In WCST, patients with dlPFC lesions fail to switch to a correct response and instead perseverate on an incorrect response (79). Indeed, schizophrenia is associated with inefficient dlPFC function, particularly with respect to working memory (80). Activity of dlPFC neurons in monkeys is correlated with the level of conflict in WCST (81) and different strategies employed within the task (82,83). In a WCST analog, lesions to monkey OFC, ACC, or dlPFC in and around the principal sulcus (but not superior and medial to the sulcus) all result in fewer uncued rule-guided behavioral shifts, though the animals still execute switches, indicating variance-shifted, as opposed to fully state-shifted, dysfunction (84). In contrast, dlPFC-lesioned animals no longer show a stereotypical increase in response times as a function of conflict, an abolition of conflict-induced changes in motor responses (81), consistent with the full destruction of conflict-detection mechanisms in dlPFC (state-shifted). Conflict detection and resolution in these tasks may map onto running calculations of instantaneous utility and uncertainty, though this remains a topic of ongoing debate. By perturbing circuits that detect conflict or encode strategy, dlPFC damage leads to a computational deficiency in value updating for flexible environmental adaptation.

Conclusions

We are just beginning to understand what constitutes a psychiatric disease. Neuroeconomic studies in animals provide new insights into the affected neural circuits (85). Our proposed classification scheme establishes a new framework for thinking about psychiatric disorders formulated in the language of neural circuits. It remains to be seen how the circuit-based classification could augment the existing typological schemes to help assess and treat psychiatric disorders. As a first step, we have focused on deficits tied to specific breakdowns in selected neural circuits. Some deficits are shared and thus might appear in multiple classically defined illnesses. Our interpretation is intended to point out that what superficially might appear to be very different syndromes may, in fact, share common disruptions in the underlying neural circuitry.

Psychopathological symptoms can be approached based on the precise type of deficits induced in neural circuits. A neural circuit will show different outputs depending on the affected circuit components. A noisy state broadens the width of the output distribution, leading to suboptimal performance, but may not alter the basic functionality of a given circuit. In contrast, a circuit could break down or be extensively modified, introducing a new state into the system with abnormal or absent functionalities that are qualitatively different from the norm.

Most psychiatric disorders present compound symptoms. It is not surprising then that a single psychiatric illness arises from a combination of variance-shifted and state-shifted circuit dysfunctions, involving multiple brain areas. For example, under a connectionist neural network framework, variance-shifted dysfunctions may result from damages to peripheral processing nodes. When the most critical region of the distributed network is disrupted, however, we may observe a fully compromised, state-shifted dysfunction instead (though the deficits may eventually be restored by other areas in the network on a longer time scale). Note that there are clear cases of state-shifted psychopathology when the deficits are not due to targeted traumatic brain injury. For example, in visual or auditory hallucinations, commonly found with severe schizophrenia, individuals experience percepts in the absence of actual sensory signals. The circuits that mediate these experiences are clearly behaving very differently and seem likely to be induced by a state-shifted process.

Our circuit-based scheme may be relevant for the ongoing debate in psychiatry over the need for incorporating dimensional diagnosis to traditional categorical diagnosis (86–90). The variance- and state-shifted models effectively redescribe such dimensional criteria at the level of neural circuits. For example, the severity or idiosyncrasy of a given symptom for a given individual could be linked to either the degree of variance shift (e.g., the magnitude of change in the variance of the distribution) or the degree of state shifts (e.g., the magnitude of mean shifts in the distribution) in behavioral or cognitive output according to the proposed scheme. Translating psychiatric symptoms into dimensional outcomes of

neural circuit dysfunction may open up new avenues for improved therapeutic intervention.

The circuit-based classification does not describe a relationship between implicated circuits and psychiatric disorder types. Our classification scheme, which critically depends on our understanding of the functionality of a given circuit, is not intended to replace existing typologies of psychopathology. Rather, it describes a mechanistic relationship between implicated circuits and behavioral deficits caused by failures of those circuits. In our view, the current scheme can provide easily quantifiable grounds for hypothesis testing for linking a circuit-level dysfunction and an afflicted behavior (e.g., Supplement 1) and thus may provide novel insights into the mechanistic dysfunctions underlying psychiatric conditions.

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Supplemental Information

An Example of Hypothesis Testing Under the Variance- and State-Shifted Framework

Lesions to the dorsolateral prefrontal cortex (dlPFC) in monkeys impair executive control (1). The posterior cingulate cortex (PCC) has been implicated in tracking volatility in the environment (2). Both dlPFC and PCC are implicated in schizophrenia (see Main Text). However, it remains unknown how the two areas interact to exert flexible cognitive control. Recording neuronal activity from PCC after a dlPFC lesion could provide a unique opportunity to test how the executive control impairments due to a dlPFC lesion affect volatility-tracking signals in PCC. More precisely, comparing the response profiles of PCC neurons before and after the dlPFC lesion could reveal whether the prefrontal lesion induces either variance-shifted or state-shifted dysfunctions in PCC neurons. Similarly, a neuroimaging experiment could test, in individuals with schizophrenia who show abnormal dlPFC and PCC metabolic activity, whether and how (e.g., variance- or state-shifted) the activations in dlPFC and PCC are functionally linked. Results from studies like these can help reveal novel insights into how certain circuits malfunction during specific behaviors being tested. Unlike traditional classification schemes of psychiatric symptoms, the current circuit-based scheme can provide straightforward testable grounds for understanding how a given circuit dysfunction might be related to behavioral deficits observed in psychiatric conditions.

Supplemental References

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