Schizophrenia Bulletin vol. 43 no. 4 pp. 706–711, 2017
doi:10.1093/schbul/sbx065

COMMENTARY

Preclinical Models to Investigate Mechanisms of Negative Symptoms in Schizophrenia

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Key words: effort/decision making/rats/mice/reward

Introduction

Negative symptom pathology in patients with schizophrenia is an unmet therapeutic need. Beyond schizophrenia, however, amotivation, alogia, and affective flattening are also observed in several other disorders (see Strauss and Cohen, this issue[1]). Given that negative symptoms, together with impaired cognition, predict functional outcome in schizophrenia and depression patients,[2–4] the development of effective treatment strategies is urgently required. Developing targeted treatments requires a greater understanding of the mechanisms underlying such symptoms. This understanding requires objective quantification of negative symptom features that can be applied in animal models. Recent reviews provided insights on techniques and targets to be investigated,[5–8] including a review by Green and colleagues[7] that culminated in a drive toward understanding effort-based decision making. The potential that delineating the mechanisms underlying effort-based decision making could provide novel treatment targets is an important direction for the field. The impact of this research and their resulting assessment of mechanisms underlying negative symptoms of patients with schizophrenia and other psychiatric conditions using preclinical models are discussed below.

This novel direction toward quantifying effort-based decision making is being increasingly reflected in preclinical research, including parsing contributions to such decision making. Early rodent-based investigations of schizophrenia-related negative symptoms focused on depression-relevant tests such as sucrose/saccharin preference tests,[9–12] but evidence suggests patients with schizophrenia exhibit normal sweet solution preference despite their high negative symptom scores.[13] In contrast, people with schizophrenia have consistently exhibited poor reward-associative behaviors (eg, probabilistic learning[14,15]), when rewards are explicitly linked to outcome. Deficits in probabilistic learning are also evident in patients with major depression. In contrast to patients with schizophrenia, however, whose deficits are linked to reductions in reward sensitivity, patients with depression display a greater sensitivity to misleading negative feedback.[16] Similarly, implicit reward-associative learning deficits, which can be measured across species,[5,17] is seen in other psychiatric conditions, such as depression and bipolar disorder,[18,19] but not schizophrenia.[20,21] Such reward-associative learning forms one aspect of effort-based decision making, wherein subjects weigh the benefit of an outcome (ie, reward) against the costs required to obtain it (ie, effort expenditure). Increased physical effort to obtain a reward can be assessed by measuring whether an animal scales a surmountable barrier or presses a lever multiple times to obtain a desirable reward (eg, 4 sucrose pellets), as opposed to opting for the less desirable alternative reward (eg, 2 sucrose pellets) by not expending additional effort.[22,23] Willingness to engage in more cognitively demanding behavior to receive a desirable reward can be assessed by letting the animal choose between trials that present long or short visual stimuli that must be accurately detected.[24] The short visual stimulus is more difficult to detect and is, therefore, the more cognitively demanding choice. An abnormal inflation of perceived effort (cognitive or physical) to obtain a reward, or a reduced perceived value of a reward, would affect a subject's willingness to engage in such effortful behavior. Hence, deficits in the ability to accurately compute effort/cost may translate into motivational impairments evident in schizophrenia patients. Effort-based decision making

is therefore subserved by domains including: physical effortful motivation[25]; cognitive effortful motivation; and reward associative learning (reviewed in[6], see figure 1). Delineating the neural mechanisms subserving these domains, and their commonalities and differences, may result in novel treatment targets that could be individually tailored to the patient.

Rodent studies investigating neural mechanisms of physical and cognitive effort have begun given the elevated perceived cost of cognitive effort observed in patients,[26–29] ultimately leading to reduced overall effort.[30,31] Both physical and cognitive effortful motivation were able to predict global cognitive scores (outcome) in schizophrenia patients.[27] Interestingly, in rodents both physical and cognitive effortful discounting were reduced by perturbation of the prefrontal cortex (PFC),[32,33] similar to behavioral deficits and observations of altered PFC functioning in schizophrenia patients. Furthermore, cannabis treatment reduced effortful choices and reduced response-bias development in humans.[34] Similarly, treatment with the psychoactive ingredient of cannabis, tetrahydrocannabinoid (THC), also reduced cognitive effort.[35] Hence, the endocannabinoid system—an on-demand system only activated when required—could be involved in the overall reduced motivation of patients with schizophrenia. It is also important to note, however, that these 2 domains are also dissociable because dopamine receptor antagonists reduce physical but not cognitive effort.[33] The dopamine system is also important for reward learning, whereby adeno-associated viral dopamine D_1 receptor suppression in the striatum impaired probabilistic learning, but not effortful breakpoint in mice.[36] Similarly, infusion of the dopamine D_1 receptor antagonist SCH23390, although not the D_2 antagonist eticlopride, into the anterior cingulate cortex (ACC) disrupted effort-cost decision making.[37] In contrast, systemic dopamine D_2-like receptor antagonism impaired such effort-based decision making that was remediated with a systemic dopamine D_1-like receptor antagonist.[38] These systemic effects may be mediated via the nucleus accumbens because dopamine D_2 receptor over-expression in this region *increased* the willingness to expend effort, confirming the role of ventral striatal dopamine transmission in motivational processing.[39] In contrast, however, D_2 receptor over-expression in the striatum reduced the willingness to expend effort for a preferred reward in mice.[40,41] Given that positive symptoms of schizophrenia patients are treated with dopamine D_2-like receptor antagonists, their effort-cost decision making deficits may be exaggerated, and this dopaminergic interaction remains complicated. Indirect action on dopamine receptors may provide alternative targets for remediation of negative symptoms.[42] For example, α7 nicotinic acetylcholine receptor (nAChR) activation releases dopamine[43] that preferentially acts on dopamine D_1 receptors,[44] perhaps explaining why mice lacking these receptors exhibit some depression-relevant behaviors including immobility in the forced swim test and reduced sucrose preference[45] and impaired probabilistic learning, although they exhibit normal effortful behavior.[46] Interestingly, some clinical trials indicated that α7 nAChR agonist treatments reduced negative symptoms of patients with schizophrenia.[47–49] Thus, its contribution to reward learning may be important for treating negative symptoms, but large-scale follow-up trials are required with negative symptoms as the primary target. Hence, alterations to the endocannabinoid, nicotinic, and/or dopaminergic systems likely contribute to negative motivational states in schizophrenia. More studies are required, however, to test these mechanisms, their locations of effect, and whether they are involved during schizophrenia-relevant manipulations (see below). Moreover, additional studies are required to specifically investigate potential schizophrenia-related pathophysiology in these domains.

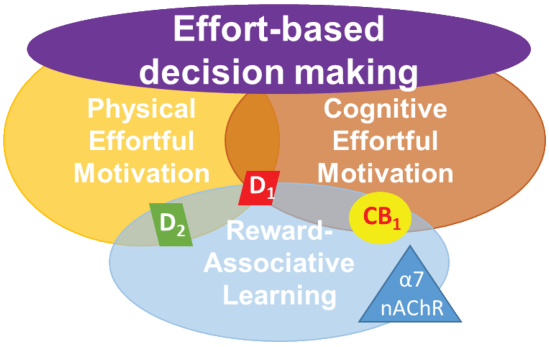

Fig. 1. Subdomains contributing to effort-based decision making. Effort-based decision making is a critical component of negative symptoms in schizophrenia and can be readily assessed in humans and rodents. Further, subdomains are identified whose neural mechanisms can be investigated in rodent studies. Dopamine D_1 receptors have been implicated in each aspect of decision making, while dopamine D_2 receptors contribute toward physical effort and reward-associative learning. Both cannabinoid CB_1 and α7 nicotinic acetylcholine receptors have been implicated in reward associative learning, while CB_1 receptors may also drive cognitive effortful motivation.

The impact of schizophrenia-relevant manipulations on motivational behaviors has also been investigated. For example, the maternal immune activation model (wherein early developmental immune activation) of schizophrenia resulted in an *elevated* breakpoint in a progressive ratio breakpoint task.[50] This finding is in direct contrast with schizophrenia patients who exhibit reduced breakpoints,[25] but the authors maintained that the elevated breakpoint may have been related to an inability to detect changes in reward/behavior contingencies, leading to perseverative-like behaviors.[50] The increased breakpoint is similar, however, to our recent studies demonstrating that repeated phencyclidine treatment (a commonly used manipulation for modeling schizophrenia), also increased breakpoint in rats, even after a 2-week washout period. In contrast, isolation rearing-induced deficits

were observed in the probabilistic reversal learning task, although these deficits were not observed when tested in a single session,[51] as is done in clinical populations.[15] Hence, manipulations commonly used to model cognitive deficits of schizophrenia patients do not always recreate schizophrenia-relevant effort-based decision making.

Some psychiatric disorder-relevant manipulations have resulted in negative symptom-related behaviors, such as reducing Sp4 expression in mice from birth (which negatively impacts numerous systems including NMDA receptor expression[52]), reduced physical effort and lowered reward-associative learning.[53] Environmental manipulations also induce depression-relevant behaviors such as social defeat disrupting implicit reward associative learning in rats.[54] This profile was associated with alterations in stress-related peptide mRNA in the striatum and decreased activity in the ventral tegmental area. Environmental stress also induces negative affective changes in the affective bias task in rats,[55] which may be useful in future studies across multiple psychiatric conditions. Other relevant manipulations arise from the observation that psychiatric disorder diagnoses are higher in births during spring months, leading to the postulation that reduced vitamin D during development may have negative outcomes.[56] Indeed, developmental vitamin D (DVD) deficient rats exhibit some schizophrenia-like behaviors.[57] In contrast, however, DVD rats exhibited normal risk-preference in a rat gambling task,[58] unlike schizophrenia patients whom exhibit deficient Iowa Gambling Task performance that are linked to negative symptoms.[59] To-date, few investigations of negative symptom-related behaviors have been examined using this developmental inducing condition. Given that DVD deficient-induced behaviors have not always been comparable across rats and mice,[60,61] nor within strains of mice,[62] other mechanisms may drive spring birth-induced schizophrenia-like behaviors.

Given the nature of this commentary, not covered here is a comprehensive overview of other important topics. Full descriptions of the tasks described have not been provided but if interested, the reader is directed toward the appropriate references. One point that should be made clear irrespective of task though is that researchers control for any potential indirect effects of treatments or manipulations, eg, slowed motoric capability, perseverative behavior, cognitive impairments etc. that may contribute to disruptions in task performance. Exhaustively

Table 1. Summary of Studies on Mechanisms and Models Underlying Effort-Based Decision Making Related Negative Symptoms (PFC, Prefrontal Cortex; ACC, Anterior Cingulate Cortex; THC, Tetrahydrocannabinoid; GlyT, Glycine 1 Transporter)

Study Type	Domain	Manipulation	Brain Region	Effect on Behavior	Ref.
Mechanistic	Cost/benefit decision making	GABAa antagonist	PFC	Impaired decision making	32
	Physical/ cognitive effort	Dopamine D_1- or D_2-family receptor antagonists	Systemic	Decreased physical effort, little effect on cognitive effort	33
	Cognitive effort	THC/CB_1 receptor agonist	Systemic	Decreased cognitive effort	35
	Reward learning	Suppression of dopamine D_1 receptor expression	Striatum	Impaired probabilistic learning; effort unaffected	36
	Physical effort	Dopamine D_1-family receptor antagonist	ACC	Impaired physical effort	37
	Physical effort	Dopamine D_2-family receptor antagonist	Systemic	Impaired physical effort	38
	Physical effort	Dopamine D_2 receptor overexpression	Nucleus accumbens	Increased physical effort expenditure	39
	Physical effort	Dopamine D_2 receptor overexpression	striatum	Impaired physical effort	40,41
	Physical effort	GlyT1 inhibition	N/A	No effect	52
Animal Models of Negative Symptoms	Reward learning	Knockout of α7 nicotinic acetylcholine receptors	N/A	Impaired probabilistic learning	43
	Physical effort	Maternal immune activation	N/A	Increased breakpoints	50
	Physical effort	Repeated phencyclidine	N/A	Increased breakpoint	
	Reward learning	Social Isolation Rearing	N/A	Impaired probabilistic reversal learning	51
	Physical effort	Reduced Sp4 expression	N/A	Reduced physical effort	53
	Reward learning	Reduced Sp4 expression	N/A	Impaired reward associative learning	53
	Reward learning	Social defeat	Striatum, VTA	Blunted response bias	54

discussing these necessary controls is beyond the scope of this short commentary, but these are important considerations and are often performed within the same task (eg, blocking both arms in the T-maze with barriers or measuring response/reward latencies in operant tasks) or by conducting complementary, multivariate assessment of behavior (eg, locomotor activity/open-field or a battery of cognitive testing) to aid the interpretation of a specific change in effortful decision making. Other areas not covered are the use/utility of social-based tasks to assess negative symptom-related behavioral profiles in animal models. Although there is increasing use of such tasks,[63,64] their links to negative symptoms remain unclear, as do their specificity to negative vs cognitive deficits of psychiatric patients. Similarly, studies have begun using rodent ultrasonic vocalizations.[65–67] Such discussions are beyond the scope of this short commentary, but were reviewed in part by Wilson and Koenig.[68] Another avenue of future investigations is the observation that cognitive remediation can attenuate negative symptom scores in schizophrenia patients.[69] Delineating the neural mechanisms of its effect could be useful for developing more targeted therapeutics, and/or for validating animal models of schizophrenia.

The recent work outlined above (summarized in table 1) provides quantifiable targets of disordered behavior in schizophrenia patients linked to their negative symptoms. The advent of modern techniques in neuroscience that allows unparalleled visualization and/or manipulation of neural activity during the assessment of reward-related behaviors is advancing our fundamental understanding of how the brain processes reward-related stimuli.[70,72] Combining these modern techniques with behavioral procedures that assess reward with high translational validity, and inducing conditions that impair effort-based decision making in a manner consistent with those observed in disorders characterized by negative symptoms, may lead to a better mechanistic understanding of this cluster of symptoms and the development of future treatments for individuals with negative symptoms behavioral profiles.

Funding

This work was funded in part by National Institute of Mental Health grant funding (R01MH104344 and R01MH108653); a NARSAD Young Investigator Award; as well as the Veteran's Administration VISN 22 Mental Illness Research, Education, and Clinical Center.

Acknowledgments

The authors would like to highlight the importance of Dr. Athina Markou on the development of each of our careers, a giant in the field, sorely missed. The authors report no conflict of interest.

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