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Review

The clinical relevance of neuroplasticity in corticostriatal networks during operant learning

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ABSTRACT

Dopamine and glutamate serve crucial functions in neural plasticity, learning and memory, and addiction. Contemporary theories contend that these two, widely-distributed neurotransmitter systems play an integrative role in motivational and associative information processing. Combined signaling of these systems, particularly through the dopamine (DA) D1 and glutamate (Glu) N-methyl-D-aspartate receptors (NMDAR), triggers critical intracellular signaling cascades that lead to changes in chromatin structure, gene expression, synaptic plasticity, and ultimately behavior. Addictive drugs also induce long-term neuroadaptations at the molecular and genomic levels causing structural changes that alter basic connectivity. Indeed, evidence that drugs of abuse engage D1- and NMDA-mediated neuronal cascades shared with normal reward learning provides one of the most important insights from contemporary studies on the neurobiology of addiction. Such drug-induced neuroadaptations likely contribute to abnormal information processing and behavior, resulting in the poor decision-making, loss of control, and compulsivity that characterize addiction. Such features are also common to many other neuropsychiatric disorders. Behavior problems, construed as difficulties associated with operant learning and behavior, present compelling challenges and unique opportunities for their treatment that require further study. The present review highlights the integrative work of Ann E. Kelley and colleagues, demonstrating a critical role not only for NMDAR, D1 receptors (D1R), and their associated signaling cascades, but also for other Glu receptors and protein synthesis in operant learning throughout a cortico-striatal-limbic network. Recent work has extended the impact of appetitive learning to epigenetic processes. A better understanding of these processes will likely assist in discovering therapeutics to engage neural plasticity-related processes and promote functional behavioral adaptations.

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Operant learning is one of the most elementary forms of behavioral adaptation (Rescorla, 1994). Through interchange with its environment, an animal is able to learn about the consequences of its actions, and thereby modify the current environment through new behaviors to produce more favorable conditions (Skinner, 1953). The resultant change in behavior is dramatic and long-lasting. Some scholars have argued that operant learning is the basis of "knowledge" (Schnaitter, 1987), may underlie "creativity" (Pryor et al., 1969), is the basis of decision-making, and contributes to the intractable nature of drug addiction. As the behavior of an organism is altered by response-outcome contingencies, physiological mechanisms are activated which ensure that these alterations become nearly permanent; they are "stamped in," as Thorndike hypothesized (Thorndike, 1911). Even Skinner intimated that response-outcome contingences change us: "Men act upon the world, and change it, and are *changed* in turn by the consequences of their action." (Skinner, 1957, p. 1).

In light of the ubiquity of operant behavioral relations in our psychological lives, the neurobiology of operant learning (i.e., the initial acquisition of an operant response) has received surprisingly little attention when compared to other basic learning processes such as spatial learning (e.g., Morris Water Maze) or Pavlovian fear conditioning. Yet, operant relations are thought to be at work nearly every moment of our lives and in many prominent neuropsychiatric conditions: drug abuse, autism, and other severe problem behaviors. In this review, we highlight the last two decades of Ann Kelley's research career, when she pursued a greater understanding of the neurobiology of operant learning with the hope that the molecular, cellular, and genomic constituents of operant learning, instantiated in distributed networks, would inform better treatment alternatives.

1. Costly behavioral-health problems and Operant behavior

Drug abuse is one of the most damaging, recalcitrant and costly behavioral-health problems in the U.S., and indeed, the world. Abuse of drugs in this country alone costs an estimated $484 billion annually in health-related problems, accidents, lost work, and insurance premiums (Policy, 2001). It is also estimated that 540,000 people die each year from drug-related illnesses. These estimates do not include the non-monetary or indirect psychosocial costs paid by parents,[1] spouses, siblings, friends, and our community in general. It is quite likely that every citizen in this nation has been adversely affected by drug abuse and addiction in some way (e.g., as the victim of criminal behavior, an automobile accident, or through the actions of a family member). Drug addiction is being increasingly viewed in terms of fundamental changes in cognitions and behaviors, with emphasis on relating the compulsive nature of addiction to pathological changes in decision- and emotion-coding networks (Everitt et al., 2001). Thus, a better understanding of operant learning systems may enhance our understanding of the neural causation of addiction.

According to the Centers for Disease Control (CDC), 1 in 88 children have been identified as having autism (Control, 2012). Autism spectrum disorders (ASDs) affect individuals from all ethnic backgrounds and socioeconomic levels. ASDs can prove profoundly debilitating and likely require life-long care at great expense to the community (>$3,000,000 per individual) (Ganz, 2007). More recently, applied behavior analysis (ABA) and certain derivatives (e.g., Denver Start Model), which emphasize dynamic and flexible academic, social, and communicative behavior, have demonstrated that incredible gains are possible with early, intensive therapy (Sallows and Graupner, 2005, Dawson et al., 2010, Warren et al., 2011). These models have been so successful that many children diagnosed with ASDs are later termed "indistinguishable" from their peers. Some estimate that 40–50% of children diagnosed with autism are fully remediable (McEachin et al., 1993). In addition, the overwhelming success of ABA therapy in the treatment of autism has lead to the general idea that it is synonymous with autism therapy (Dillenburger and Keenan, 2009), much to the displeasure of practitioners, to name a few, of organizational behavior management (OBM), clinical behavior analysis, and animal training; professions that use behavior analysis applied to situations *not* involving autism. Of interest here is the fact that most ABA principles are based on contemporary operant theory and the experimental analysis of behavior: evaluating possible establishing operations, identifying the consequential functions of inappropriate behavior, reinforcing good behavior, punishing unwanted behavior, and assessing these relations in a greater socio-economic context (e.g., behavioral economics). In their seminal piece on ABA, Baer et al. (1968) lay out a clear relationship between operant theory and the "conceptual systems" dimension of ABA, although a full review of that paper is beyond the purview of this current review. Thus, because the etiology of ASDs are largely viewed as neurogenetic, and in light of the prominent role operant behavior plays in learning and therapy vis-à-vis ASDs, a greater understanding of the neurobiology of operant behavior might help our considerations of ASDs.

The term "severe problem behavior" encompasses a wide range of issues from school bullying to extreme self-injury. Severe problem behaviors can be displayed by typically-developing children, but are more prevalent in children with developmental and/or intellectual disabilities. Severe problem behaviors create substantial social and educational obstacles for individuals due to their intensity and seeming unpredictability. Treatment may involve suspensions from school, placement in special environments, engaging the criminal justice system, incarceration or institutionalization. Rather than considering these patterns as "maladaptive" or "inappropriate," psychologists and educators are now viewing many of these problem behaviors as functional. In other words, when considered as operant behavior, the reinforcing contingencies promoting these severe behavior problems can be determined, assessed, and changed. Due to the dangerous nature of these problems and the intrusion of likely neurophysiological issues, however, many individuals spiral into difficult or untenable living conditions or circumstances with a lack of treatment. The possibility that these serious problems emerge through a combination of genetic-environment interactions is only now being seriously considered. A better understanding of the neurobiology of operant behavior would improve treatment alternatives.

2. Mechanisms of neural plasticity in long-lasting behavioral change

It is now well accepted that long-lasting behavioral modifications via operant contingencies are the result of significant changes in the brain: the strengthening of synaptic connections, re-configuring of neural ensembles, synthesis of new proteins, upregulation of gene expression, and epigenetic modifications. Long-term potentiation (LTP) has served as one of the most frequently interrogated plasticity-related systems and data strongly implicate NMDAR activation as a key initiating event. That is, high frequency patterns of synaptic stimulation activate NMDAR resulting in an influx of Ca^{2+}, in turn activating multiple signaling mechanisms, several of which converge on ERK (Extracellular Receptor signaling Kinase). ERK is thought to regulate a variety of

[1] Consider the real, but difficult to estimate, cost of "sleepless nights" or increased stress on the health and well-being of parents of children with drug behavior problems.