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The Dark Side of Addiction:

The Horsley Gantt to Joseph Brady Connection

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Abstract

W. Horsley Gantt and Joseph V. Brady laid a rich foundation for understanding the concept of emotion, derived from 2 prominent traditions of physiology and psychology: classic conditioning and operant conditioning, respectively. This framework guided my fierce interest in motivation in general and the interaction between reward and stress, which began at John Hopkins with my thesis work under the guidance of Drs. Zoltan Annau, Solomon Synder, and Joseph Brady, among many others. Using the study of the neurobiology of addiction as a framework, I argue that drug addiction not only involves positive reinforcement associated with the rewarding effects of drugs of abuse but also involves another major source of reinforcement, specifically negative reinforcement driven by negative emotional states (termed the “dark side” of addiction). Excessive activation of the brain reward systems leads to antireward or a decrease in the function of normal reward-related neurocircuitry and persistent recruitment of the brain stress systems, both of which may be neurobiologically linked. Understanding the neuroplasticity of the neurocircuitry that comprises the negative reinforcement associated with addiction is a key to understanding negative emotional states in general and their pathophysiology.

Keywords

Addiction; antireward; emotion; neurobiology; stress

Reward and stress are intimately related. Some levels of stress can actually be rewarding, and excess reward can lead to stress. My research career began at John Hopkins University (JHU), where I began my studies that explored this relationship under the tutelage of Dr. Zoltan Annau. He had trained with Dr. James Olds, one of the co-founders (with Dr. Peter Milner) of brain stimulation reward. However, looming in the background of my education at JHU were towering figures in physiology and psychology, W. Horsley Gantt and Joseph V. Brady, who both indirectly and directly influenced my career and future pursuits, respectively. What fundamentals did I learn at JHU that led to what I consider my later seminal discoveries? How is it that these fundamentals looped back to where I began: the study of reward and stress?

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DISCLOSURE

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First, some definitions. *Reward* can be defined as a stimulus that increases the probability of a response and has some positive hedonic connotation. Stress can be defined as anything that causes alterations in psychological homeostatic processes (Burchfield, 1979). I began my career examining how stress influences reward and later moved to trying to understand how reward influences stress. Drs. Gantt and Brady provided the conceptual framework for this transition and imprinted my brain with the information that would later move me to the dark side.

Dr. Horsley Gantt was a student of Ivan Pavlov. As such, he was very well trained in the study of classic conditioning (Pavlov and Gantt, 1941). Pavlov, of course, established, “The fundamental requisite is that any external stimulus that is to become the signal in a conditioned reflex must overlap in point of time with the action of an unconditioned stimulus” (Pavlov, 1927, p. 26). “Further, it is not enough that there should be overlapping between the 2 stimuli; it is also and equally necessary that the conditioned stimulus should begin to operate before the unconditioned stimulus comes into action” (Pavlov, 1927, p. 27). However, Dr. Gantt carried work on conditioned reflexes to the domain of psychopathology by describing the emotional response of an animal when a conflict situation is introduced, generating what he described “experimental neurosis.” He stated:

A strong food excitation is set up in a hungry animal; the giving of food is preceded by a signal over any receptor system so that the signal later acquires the function of producing the food excitation without the food—the conditional food reflex. Next, an inhibitory process is formed on the basis of the food excitation by some such method as giving of a signal similar to the first one but always failing to reinforce it with food, until the animal reacts positively to the signal accompanied by food and negatively to the similar signal unaccompanied by food

(Gantt, 1942, p. 476).

Then a conflict situation was introduced in which they used “2 tones (as signals for the signal for food and nonfood) so close together in pitch that the nervous system is physically incapable of discriminating” (Gantt, 1942, p. 476). This resulted in

the production of a chronic anxiety-like neurosis expressed in his general behavior (restlessness, etc.), by a loss of equilibrium between all the CR’s (changing the relative intensities, e.g., over-reacting to some, underreacting to others) and finally as we have been able to show recently by records of the heart rate and respiration, in emotional changes

(Gantt, 1942, p. 476).

An almost identical framework for emotional responsivity derived from the operant behaviorist tradition with a parallel history. Dr. B. F. Skinner, recognized as a prime mover of the behaviorist approach, identified early on that responding for food can be suppressed by a cue that is paired with an aversive stimulus, a phenomenon he termed “conditioned suppression” (Estes and Skinner, 1941). Dr. Joseph Brady, another one of my mentors and chairman of my thesis committee at JHU, began to identify the neuropharmacological bases for conditioned suppression by showing that reserpine could reverse conditioned suppression, and amphetamines could potentiate conditioned suppression (Brady, 1956). My

understanding that conflict and aversive stimuli can result in emotional-like responses and behavioral changes led to my interest in how aversive stimuli can motivate behavior in the form of negative reinforcement and how this process forms the basis for a major part of the pathophysiology of addiction, what I term the “dark side” of addiction. Thus, in a sense, my history could support the argument that new discoveries are facilitated by the prepared mind (“In the fields of observation, chance favors only the prepared mind” [Louis Pasteur lecture, University of Lille, December 7, 1854]).

Together with Dr. Michel Le Moal, I have conceptualized addiction as a 3-stage cycle: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. These stages are thought to feed into each other, become more intense, and ultimately lead to the pathological state known as *addiction* (Koob and Le Moal, 1997). The stages involve positive reinforcement, but as the condition worsens over time, an additional source of motivation is recruited: negative reinforcement. My understanding of the constructs of reinforcement clearly had early influences from training at JHU and the traditions that Gantt and Brady exemplified.

In this context, the development of the aversive emotional state that drives the negative reinforcement of addiction is defined here as the “dark side” of addiction, derived from my early interactions with Dr. Brady. I remember one day after his demonstration of operant conditioning to the medical school psychiatry course where he trained chickens to walk off the end of a large table, I queried him with the following: “Dr. Brady, how hungry were those chickens?” His response: “Koob, damn hungry.” This interaction led to my lifelong interest in motivation and what drives behavior. I have argued that drug addiction progresses from a source of positive reinforcement that activates brain reward systems to sensitization of the brain stress and antireward systems that both mediate the aversive effects of stimuli that generate emotional behavior, as described in the early studies by Gantt and Brady, but in this case set up a powerful negative reinforcement process rather than punishment (Koob and Le Moal, 2008).

My thesis is that a key part of addiction involves long-term, persistent dysregulation of the activity of neural circuits that mediate antireward motivational systems that are derived from 2 sources: a decrease in the function of brain reward systems that normally mediate natural rewards and recruitment of brain stress systems that drive aversive states (Koob and Le Moal, 2008). Such antireward derives from an opponent process concept that is triggered by the excessive activation of brain reward systems that forms a general feature of biological systems (Solomon, 1980).

To place this in the context of the stages of addiction, the *binge/intoxication* stage often involves excessive drug taking and seeking, with strong evidence of roles for dopamine in the acute reinforcing actions of psychostimulants, opioid peptide receptors in the acute reinforcing effects of opioids, and γ -aminobutyric acid and opioid peptides in the acute reinforcing actions of alcohol. Such activation contributes to the enhanced incentive salience of repeated drug taking and habitual-like responding (Everitt and Wolf, 2002). Important anatomical circuits include the mesocorticolimbic dopamine system that originates in the

ventral tegmental area and projects to the nucleus accumbens and opioid peptides in the ventral striatum, extended amygdala, and ventral tegmental area.

In the *withdrawal/negative affect* stage, the key symptoms are of motivational significance and include chronic irritability, physical pain, emotional pain (i.e., hyperkatifeia; Shurman et al., 2010), malaise, dysphoria, alexithymia, and the loss of motivation for natural rewards. Such acute withdrawal is associated with a decrease in function of the mesocorticolimbic dopamine system, reflected by electrophysiology, neurochemistry, and molecular biology (Koob, 2013). Human imaging studies of individuals with addiction during withdrawal or protracted abstinence have generated results that are consistent with such animal studies. There are decreases in dopamine D₂ receptors (hypothesized to reflect hypodopaminergic functioning), hyporesponsiveness to dopa-mine challenge (Volkow et al., 2003), and hypoactivity of the orbitofrontal/limbic cortex system (Volkow et al., 2003).

More importantly for the present thesis, as dependence and withdrawal develop, brain stress systems, such as corticotropin-releasing factor (CRF) and dynorphin (to focus on 2 prominent examples), are recruited in the extended amygdala. The extended amygdala is composed of the central nucleus of the amygdala, bed nucleus of the stria terminalis, a transition area in the medial (shell) part of the nucleus accumbens, and a massive projection to the lateral hypothalamus. For example, extracellular CRF in the extended amygdala increases during acute withdrawal from all drugs of abuse. Critically, CRF receptor antagonists that are injected into the extended amygdala block the anxiety-like effect of withdrawal from all drugs of abuse and blunt excessive drug taking during escalated drug taking with extended access to all drugs of abuse (Zorrilla et al., 2014). Similarly, blockade of the κ opioid system can also block the aversive stimulus effects of drug withdrawal and stress (Chartoff et al., 2012). Even more compelling is that excessive drug self-administration can be blocked by κ opioid receptor antagonists and may be mediated by the shell of the nucleus accumbens (George et al., 2014).

Perhaps most compelling is that both the CRF and dynorphin systems may respond to overactivation of the brain reward system. Originally hypothesized by Carlezon et al. (1998), the activation of cyclic adenosine monophosphate response element binding protein by excessive dopamine and opioid peptide receptor activation in the nucleus accumbens triggers the induction of dynorphin to feedback to suppress dopamine release. More recently, we identified dopamine cells in the ventral tegmental area that express CRF during nicotine withdrawal and decrease dopamine function (Grieder et al., 2014). Thus, we hypothesize that the brain stress neurotransmitters CRF and dynorphin, known to be activated during the development of excessive drug taking, contribute to opponent processes, and this activation is manifest when the drug is removed, producing anxiety, hyperkatifeia, and irritability symptoms associated with acute and protracted abstinence.

In the *preoccupation/anticipation* stage of the addiction cycle, converging lines of evidence suggest that impairment of medial prefrontal cortex cognitive function and overactivation of the basal ganglia and central nucleus of the amygdala may be linked. Thus, hypofunctioning of the prefrontal cortex may set up and perpetuate dysregulations that comprise the “dark side” of drug addiction and persist during protracted abstinence to set the tone for

vulnerability to craving by activating drug-, cue-, and stress-induced reinstatement through neurocircuitry that is now driven by a reorganized and possibly hypofunctioning prefrontal system (George and Koob, 2010). One may speculate that prefrontal cortex dysfunction may be a trigger for impulsivity, contribute to the loss of control associated with compulsive drug use, and facilitate the progression to drug addiction.

In summary, the combination of decreases in reward neurotransmitter function and the recruitment of anti-reward systems, both facilitated by neurocircuitry changes in the *binge/intoxication* and *preoccupation/anticipation* stages of the addiction cycle, provides a powerful source of negative reinforcement that defines compulsive drug-seeking behavior and addiction and contributes to relapse. The development of the aversive emotional state that drives the negative reinforcement of addiction is the “dark side” of addiction.

So how did I get to the “dark side” from my graduate studies at JHU with Dr. Zoltan Annau? We identified a role for catecholamines in how mild to moderate stress can facilitate brain reward systems. Dr. Solomon Snyder introduced me to how drugs of abuse can profoundly activate the brain reward systems. Perhaps as part of the rich tradition of the study of reinforcement, from both classic and operant conditioning perspectives, Drs. Horsley Gantt and Joseph Brady laid the conceptual groundwork for motivation and emotion that resonated in my brain and prepared me to recognize that the converse could also be true: excess reward can engage homeostatic mechanisms to regulate motivation. However, when Michel Le Moal and I embraced Dr. Richard Solomon’s opponent process theory with an overlay of allostasis, the neuro-circuitry of the emotional states described by Gantt and Brady was unveiled. Thus, after spending the first half of my career understanding how we feel good, I have spent the remainder of my career trying to understand how we feel bad.

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