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Invited review

Addiction science: Uncovering neurobiological complexity

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ABSTRACT

Until very recently addiction-research was limited by existing tools and strategies that were inadequate for studying the inherent complexity at each of the different phenomenological levels. However, powerful new tools (e.g., optogenetics and designer drug receptors) and high throughput protocols are starting to give researchers the potential to systematically interrogate "all" genes, epigenetic marks, and neuronal circuits. These advances, combined with imaging technologies (both for preclinical and clinical studies) and a paradigm shift toward open access have spurred an unlimited growth of datasets transforming the way we investigate the neurobiology of substance use disorders (SUD) and the factors that modulate risk and resilience.

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1. Introduction

> "Between stimulus and response there is a space.
>
> In that space is our power to choose our response.
>
> In our response lie our growth and our freedom."
>
> Viktor E. Frankl

Frankl's statement distills much of his life-long efforts to wring happiness out of an often agonizing human experience (Frankl, 1959). But the quote is also relevant to addiction for the very "space" Viktor Frankl is talking about, a space whose topology changes naturally throughout life, influences addiction risk and is also changed by addiction. A heuristics model that captures this space starts by defining the relational boundaries between competing cognitive and visceral processes within a triangular space (Fig. 1) (Yang et al., 2012). The cognitive axis has been proposed to fluctuate between the arbitrarily termed system 1 and 2 processes: Because system 1 is largely based on perceptions, intuitions, and emotions, it tends to operate quickly, effortlessly, and automatically. In contrast, system 2 is based more on critical, in depth reasoning, so it is slower, more effortful, and deliberate (Kahneman and Frederick, 2002). The visceral axis, which operates in a range between "cold" and "hot" extremes, exerts powerful effects on cognitive operations (Loewenstein, 1996). Such visceral influences are the driving force behind urges, such as hunger, thirst, pain, and sexual arousal, the immediate satisfaction of which helps explain why people sometimes make unhealthy choices.

At one extreme, integration within this triangular space becomes manifest in "hot" executive function processes that are engaged during situations with stronger affective salience and recruit areas of the brain that control emotions and the brain's reward systems (e.g., orbitofrontal cortex, ventral striatum, and the limbic system). At the other extreme, "cold" executive functions have been associated with more purely cognitive processing and the activation of the dorsolateral parts of the prefrontal cortex (Castellanos et al., 2006). Addiction research is creating a more detailed and multileveled map of addiction trajectories in this triangular space.

Research on addiction trajectories has shown that, while initial experimentation with drugs of abuse is largely a voluntary behavior, continued drug use gradually impairs neural function, eventually impacting the very capacity to exert free will. In persons with genetic vulnerabilities, suffering from chronic stress or comorbid psychiatric conditions, or who have been exposed to drugs, these processes can eventually turn drug use into the automatic and compulsive behaviors that characterize addiction. We now know that addictive drugs can trigger epigenetic mechanisms that modulate (up or down) the expression of genes implicated in neuroplasticity ultimately perturbing the intracellular level of key proteins, and modifying neurotransmitter signaling (both strengthening and blunting) and

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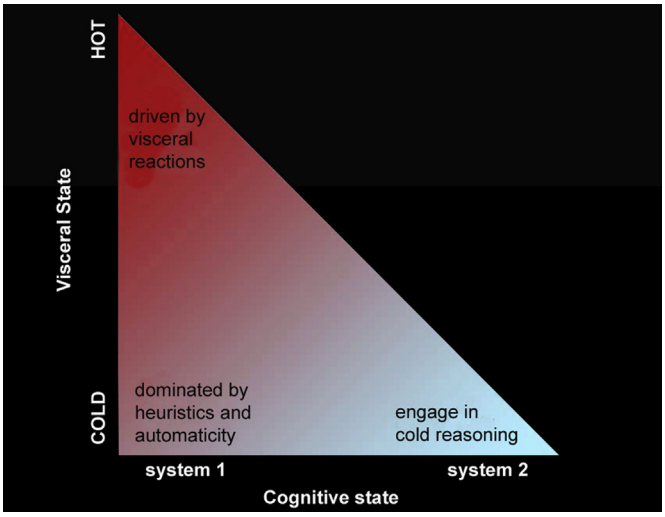

Fig. 1. The triangular space of the framework proposed by (Yang et al., 2012) portrays the relationship between cognitive processes and visceral influences. System 2 processing and the hot visceral state are two extremes of a conceptual continuum. Experiencing hot visceral reactions (e.g., sexual arousal, extreme fear, hunger) inhibit system 2 processing. Conversely, using cold reasoning (careful pondering) through system 2 before visceral reaction kick in can help circumvent the onset or reduce the power of visceral urges, reducing the likelihood that a hot state will take over. Figure reprinted with permission from (Yang et al., 2012).

information processing in various neuronal circuits in the brain (reward/antireward, executive function/control, interoception/awareness, mood/stress reactivity among others). Therefore, the resultant behavioral dysfunctions in addiction reflect the emergent property of complex systems that are disrupted at multiple, interacting levels.

Here, we highlight some of the most significant and recent findings in addiction research and assess their impact on our understanding of substance use disorders (SUD) and their implications for prevention, treatment and public health policy. A common target that emerges for prevention and treatment is the need to balance the critical space that exists "*between stimulus and response*" and that becomes increasingly disrupted as the severity of a SUD deepens.

2. Genetics

It has been known for a long time that addiction has a prominent hereditary component. Yet, the goal of finding genes with definite contributions to this disorder has been elusive. Indeed, genome wide association studies (GWAS) have yielded several polymorphic variations with very modest contributions to the overall addiction vulnerability (Bierut et al., 2006; Rutter, 2006). However, this is a recurring theme when investigating other complex phenotypes, such as depression (Hamet and Tremblay, 2005) and schizophrenia (Doherty et al., 2012), which can, incidentally, also modulate risk for SUD. This is consistent with the notion that addiction (like other psychiatric disorders) is a polygenic disease that hinges on a vast number of genes with an ability to impact the risk of abuse and addiction (Drgon et al., 2010; Tyndale and Sellers, 2002; Uhl et al., 2008). Such genes are likely to operate through their influence, either direct or indirect, on brain development, relevant neurotransmitter systems, drug metabolic pathways, neural circuitry, cellular physiology, behavioral patterns, and the responses to environmental stimuli (i.e., stress, social support, social deprivation) and an individual's personality traits (e.g., novelty seeking, impulsivity, stress reactivity).

Thus, teasing apart the causal relationships, timing, strength and contingent nature of any genetic contribution to SUD is a challenging endeavor. Yet, for the past decade or so, the steady characterization of hundreds of genes that interact among themselves and with the environment has begun to coalesce into an increasingly coherent, albeit highly nuanced narrative on the role of genes in SUD.

A genetic foundation of personality. Several genes, whose proteins have a central role in brain function have been independently identified as influencing an individual's susceptibility to different psychiatric conditions, including depression, anxiety, antisocial behavior, and SUD (Caspi et al., 2002, 2003; Lau et al., 2009; Nilsson et al., 2006, 2008) as opposed to being specific to a given disorder. For example, variations in the genes that encode monoamine oxidases (MAOs), which play a central role in monoaminergic balance in the brain, have been linked to personality styles that are influenced by their environmental exposures. Specifically, adult carriers of the "low-activity" *MAOA* alleles *(MAOA-L*), who were exposed to moderate maltreatment as children, have been shown to be more likely to develop conduct disorder, antisocial personality symptoms, and violent behaviors relative to either controls or maltreated carriers of the "high-activity" *MAOA* alleles (*MAOA-H)*(Caspi et al., 2002; Weder et al., 2009). Further insight into the effects of early MAO action on the brain's architecture comes from the association between the *MAO-L* allele and reduced volume and function of the anterior cingulate cortex (ACC) (Meyer-Lindenberg et al., 2006), a region belonging to one of the main control networks in the brain whose function is disrupted in SUDs. On the other hand, carriers of the *MAOA-H* allele (in combination with the s/s version of the serotonin transporter (5HTT)) display more efficient executive control of working memory-related performance (Enge et al., 2011). Similarly, variations in other gene classes could affect their expression at critical stages in brain development, compromising the function of neural circuits regulating emotion, negative affect, and stress later in life (Meyer-Lindenberg et al., 2006). Similar mechanisms may underlie the hereditary abnormalities in frontostriatal connectivity that compromise inhibitory control as observed in both stimulant-dependent individuals and their drug naïve siblings (Ersche et al., 2012). However, attempts at mapping the genetic contributions to addiction must take into account the obvious lack of univocal relationships between genetic inputs and behavioral outputs, which hinders the more straightforward interpretation of genetic data. For example, *5-HTT* gene promoter polymorphisms have been associated not only with anxiety and dysphoria, but also with altered stress responsiveness (Oroszi and Goldman, 2004). Another good example is the *BDNF* gene, whose product controls maturation of neurons during childhood and adolescence, and that has also been implicated in various neuropsychiatric disorders. In fact, a low level of BDNF impedes the normal development of serotonin neurons, and could help explain the serotonin dysfunction that has been associated with some suicidal behaviors (Sher, 2011). Interestingly, preliminary results suggest that the BDNF Val(66) Met genotype, which has been associated with neurobehavioral deficits, may promote drug-seeking phenotypes in heroin-dependent individuals (Greenwald et al., 2012).

Polymorphisms in the nicotinic acetylcholine receptor (nAChR) system have also emerged as modulators of nicotine dependence and other SUDs, likely in part partly due to their influence on the maturation of brain circuits implicated in attention and sensory processing (Heath and Picciotto, 2009). Brain nicotinic receptors appear early and reach high levels during human gestation (Hellstrom-Lindahl and Court, 2000) modulating the expression of many downstream genes, neuronal differentiation, synapse formation, and neuronal path finding. Together with the fact that