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Found in Translation: Understanding Impulsivity and Related Constructs Through Integrative Preclinical and Clinical Research

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Addictions are amongst the most costly disorders, estimated at over \$500 billion annually. The multi-dimensional construct of impulsivity has received increased attention recently as a potential endophenotype for addictions. As questions relating to how best to define and categorize addictions are being discussed in anticipation of DSM-V, a growing role for empirical, neurobiological understandings of addictions exists. Given that this process involves gathering, analyzing and synthesizing data from multiple lines of investigation, the importance of translational, interdisciplinary research has never been greater. Here, we highlight how the manuscripts in this issue inform a translational neurobiological understanding of impulsivity in addiction and identify existing challenges that await future investigation.

Impulsivity and Its Core Components

Impulsivity has been defined as “a predisposition toward rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions to the impulsive individual or others” (1). From this and other definitions of impulsivity, it is apparent that impulsivity represents a multi-dimensional construct and decomposing impulsivity into its component psychological processes (and their related neurobiological underpinnings) will help elucidate its relationship to addictions and other psychiatric disorders. For example, some aspects of impulsive temperament relate to aspects of poor working memory, potentially through impaired ability to maintain and update representations of distant goals and/or strategies to obtain them. A more complete understanding of the cognitive bases of dimensions of impulsivity should facilitate a systems-level explanation of individual variation in impulse control.

A recent focus has been to use translational research to fractionate impulsivity in terms of its neurobehavioral and neurochemical basis. Two dissociable domains repeatedly identified correspond to impulsive choice and impulsive response (2), and measures in one domain often do not correlate (or may correlate inversely) with one another and may reflect preferential involvement of ventral as compared to dorsal cortico-striatal circuits. Other theoretically related constructs (e.g., sensation-seeking, risk-taking) have at times been clustered with impulsivity and dissection of their potential influences is important in better understanding how impulsivity relates to clinical phenomena. How best to conceptualize impulsivity (i.e., as a “state” or “trait” phenomenon) is also an active area of investigation as recent findings suggest

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that self-reported “personality” measures of impulsivity change during the course of effective treatment. Additionally, how best to measure impulsivity warrants clarification. Self-report as compared to behavioral measures of impulsive choice operationalized as temporal discounting have been found not to uniformly correlate with one another and to have different relationships with clinically relevant variables including treatment outcome in addiction. As the field of impulsivity research matures, consensus views in these areas will help guide and direct future investigations.

Impulsivity as a vulnerability factor for compulsive behavior

Animal models can provide a valuable mechanism for disentangling influences of pre-existing vulnerability, drug effects and other individual difference measures that may contribute to the development of addictions. While inter-related drug-induced dysfunctions in cortico-limbic-striatal circuits are central to hypotheses of addiction (3–6), these alterations may also be predisposing vulnerability factor(s) that increase susceptibility. Impulsivity may represent a primary “trait” that mediates addiction vulnerability and is associated with enhanced sensitivity to dopaminergic drugs. Animal studies suggest distinct behavioral and physiological traits that reflect individual differences in aspects of addiction. Impulsivity measured by pre-potent responses and sensitivity to reward delay predict increased drug-taking behavior and is associated with low striatal (accumbens) D2/D3 receptor availability (7). This report provides a framework for studies of interactions between vulnerability factors and cocaine exposure in rats. Indeed, in this model, pre-existing impulsivity predicted a switch from controlled to “compulsive”, addictive cocaine use (8).

Together, these studies provide an important avenue for understanding better the precise factors involved in the progression from pre-existing vulnerabilities to addiction and a theoretical framework for how impulsivity can lead to compulsive drug-seeking behavior. However, as evidenced by several articles in the present issue, individual differences related to age/adolescence, genetic composition (9–11) or environmental factors such as in utero drug exposure (12,13) may influence drug use or the development of addiction. As evidenced particularly by the Thapar et al investigation, disentangling the influences of in utero drug exposure *per se* from predisposing factors related to maternal drug use may be particularly complex in humans. As such, animal studies can be particularly important and informative as they can systematically investigate drug-induced and pre-existing cognitive deficits. It also is important to conduct and extend such studies to non-human primates because monkeys display close homology to humans in multiple domains and offer an opportunity to validate the translational value of this line of research. There exists compelling evidence for drug-induced deficits in cognitive inhibition and flexibility in monkey. Stimulant drugs down-regulate D2/D3 receptor function in monkeys and humans, and disruptions in D2/D3-mediated neurotransmission can impair inhibitory control. Collectively, these data provide convergent evidence in support of an important role for D2/D3 receptor function in aspects of impulsivity in drug addiction. Additionally, studies in non-human primates indicate progressive influences of cocaine on prefrontal cortex (moving from more ventral to dorsal involvement), which would be expected to progressively influence neurocognitive functions in a corresponding progressive manner. It is likely that drug exposure also interacts with vulnerability factor(s) and these processes have yet to be directly investigated in non-human primates.

Influences of other substances (e.g., alcohol) have similarly been studied to examine their potential neurotoxic and neurocognitive effects. Findings from animal studies into alcohol's influences on brain structure and function can inform human cross-sectional studies that investigate neurocognitive deficits related to alcohol use by simultaneously studying alcohol dependent subjects as compared to those with pathological gambling (posited as an “addiction without the drug”). Findings from such studies indicate similarities and differences between

the substance and non-substance addictions, with similarities observed in neurocognitive measures related to ventromedial prefrontal cortical and ventral striatal circuitry, consistent with brain imaging findings in pathological gambling and reflecting aspects of reward processing and choice impulsivity (14). In particular, relatively diminished activation of ventromedial prefrontal cortex and/or ventral striatum has been observed during reward processing in individuals with alcoholism, cocaine dependence, and pathological gambling, and these findings may reflect differences in dopamine D2/D3 function. The report from Beck et al (15) further suggests that self-reported impulsivity may be reflected in the relatively diminished activation of this circuitry during reward processing in alcoholism. In that such findings extend to groups with familial histories of alcoholism, the findings raise the possibility that ventral striatal activation during reward processing, possibly as linked to impulsivity, may reflect an endophenotype for alcoholism and possibly other addictions. However, the extent to which other factors (e.g., syndromal or subsyndromal substance use) may influence these findings, particularly within a developmental exposure framework, warrants additional investigation. Brain volumetric measures are also important to consider (10), and further investigations extending the Salvatore et al findings to individuals with addictions in a reward-processing context represents a relevant future direction for study.

The use of complex neurocognitive tasks across species can provide important information. For example, the widely used Iowa Gambling Task assesses risk-reward decision-making in a manner that incorporates executive functioning elements related to strategy deciphering and learning and memory. Individuals with addictions often perform disadvantageously on the task and task performance has been found to correlate with clinically relevant and real-life measures such as the ability to maintain abstinence and retain employment. The availability of animal versions of the task should facilitate a neurobiological understanding of risk-reward decision-making through the use of approaches (e.g., molecular, cellular, neurochemical, genetic and proteomic) that are feasible in controlled animal studies (16,17).

Future Directions

Tremendous strides have been made over the past decade in terms of understanding multidimensional aspects of impulsivity and their relationship to neuropsychiatric conditions, including addictions. Nonetheless, given the increased amount of research in this area using multiple measures and investigations into theoretically related constructs like sensation-seeking, risk-taking and emotional regulation, considerations regarding how best to define and assess impulsivity and related constructs deserve additional discussion and clarification. As addiction has been proposed to involve the progression from “impulsive” to “compulsive” behavioral engagement, a working definition of compulsivity (considering aspects of habit, harm avoidance, ego-dystonia, perfectionism, etc) is warranted. Such a framework would help guide investigations that could dissect components of compulsivity and investigate their relationships to neuropsychiatric disorders as has been done over the past decade for impulsivity. Performing concurrent impulsivity and compulsivity research seems particularly attractive as these constructs do not seem diametrically opposed, but rather overlap in a complex manner. Similarly, the application of translational and interdisciplinary research approaches to impulsivity and compulsivity investigations in neuropsychiatric disorders, as well as the application of advanced analytical techniques that incorporate a broad range of influencing measures, are critically important if we are to make significant advances in terms of understanding the neurobiological processes underlying complex disorders like addiction and translate such understanding into improved prevention and treatment strategies. The consideration of important individual difference measures (e.g., related to sex, genes, proteins, environment, age, and developmental exposure) will be critical in this endeavor.

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