Published in final edited form as:
Biol Psychiatry. 2014 January 15; 75(2): 94–95. doi:10.1016/j.biopsych.2013.11.010.

Biased Behaviors: Towards Understanding Vulnerability and Resilience Factors in Addictions

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Keywords

stimulants; cocaine; attention; control; Stroop; fMRI

Despite advances in treatment development, addictions remain prevalent and costly conditions. Understanding the neurobiological factors underlying addictions holds significant promise in developing improved treatments for people with addictions [1]. Similarly important is the investigation of groups demonstrating vulnerability and resilience to the development of addictions as findings from these studies may be used to guide prevention interventions.

The study by Smith and colleagues represents an important contribution in understanding factors that may reflect vulnerability and resilience to stimulant dependence [2]. The investigators use a modified Stroop color-word interference task during functional magnetic resonance imaging (fMRI) to investigate potential biases relating to drug (versus non-drug) words in stimulant-dependent individuals, non-dependent “recreational” stimulant-using individuals, and control comparison non-stimulant-using individuals. Reaction times in the process of color naming in response to drug-word versus non-drug-word stimuli were evaluated to assess degrees of attentional bias to the drug-related stimuli, and neuroimaging during the drug-related Stroop task was used to identify brain regions involved in the process of responding to drug-related and non-drug-related stimuli. As mentioned by the authors, prior studies have found attentional biases to associate with cocaine cravings in cocaine-dependent individuals. However, prior studies had not examined recreational stimulant users, a group that has in prior studies shown fewer or no cognitive deficits as compared to those frequently observed in stimulant-dependent individuals. Significant

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Disclosures: Dr. Potenza has received financial support or compensation for the following: Dr. Potenza has consulted for and advised Boehringer Ingelheim, Lundbeck and Ironwood; has consulted for and has financial interests in Somaxon; has received research support from the National Institutes of Health, Veteran’s Administration, Mohegan Sun Casino, the National Center for Responsible Gaming, and Forest Laboratories, Ortho-McNeil, Oy-Control/Biotie, Glaxo-SmithKline, and Psyadon pharmaceuticals; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse control disorders or other health topics; has consulted for gambling entities, law offices and the federal public defender’s office in issues related to impulse control disorders; provides clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; has performed grant reviews for the National Institutes of Health and other agencies; has guest-edited journal sections; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts.

differences in behavioral and neural responses were observed in the dependent, recreationally using and non-using groups. Specifically, stimulant-dependent individuals showed differences from non-using individuals on task performance whereas recreationally using and non-using individuals did not differ. However, recreationally using individuals showed relatively decreased activation of ventromedial prefrontal cortex (vmPFC, including orbitofrontal cortex and anterior cingulate cortex - ACC), the angular gyrus and posterior cingulate cortex relative to the dependent and non-using individuals. An additional region frequently implicated in impulse control, the inferior frontal gyrus [3], was identified as being differentially activated in response to drug-related as compared to non-drug-related words, and the degree of activation in the inferior frontal gyrus did not differ across groups. As noted by the authors, the findings demonstrate that recreationally using individuals lack the attentional bias for stimulant-related words that is evident in dependent individuals and raise the possibility that recreationally using individuals need not exert the same degree of cognitive control over stimulant-related stimuli, perhaps reflecting less cue-induced craving (although this was not examined directly). Curiously, the dependent and non-using groups did not demonstrate activation differences in the brain regions underlying task performance, a finding reminiscent of those from a study of approach bias and heavy cannabis use ([4]; see below).

The study by Smith and colleagues addresses an important question, provides additional needed information and raises multiple additional questions. In that many people are exposed to potentially addictive substances (or behaviors like gambling) and a minority typically becomes addicted raises questions about what factors underlie these different outcomes. In understanding this phenomenon, a group of individuals displaying recreational use (or engagement in the case of non-substance addictions) becomes an important comparison group. As the authors note, there is no strict definition for this type of drug use, although an absence of interference in major areas of life functioning appears critical and is consistent with proposed core aspects of addictions. Additionally, the authors note important between-group differences (e.g., in education, intelligence, mood, use of other substances, age and sex) that are difficult to match across groups given the co-occurring behaviors and disorders and the sociodemographic features of stimulant-dependent and recreationally using individuals. While analyses may control for these between-group differences, they cannot entirely exclude important contributions from these factors, and future studies are needed to examine the impact of co-occurring disorders (or dimensional contributions from factors like mood and substance use) on biases. Additionally, the authors do not report other domains (e.g., problem-gambling severity) that also likely to co-occur with stimulant dependence. As data indicate strong genetic links between gambling and stimulant-use problems [5], future studies should include and report on such measures.

Although the possibility of resilience and vulnerability factors are raised by the findings, longitudinal studies are needed to examine the processes by which attentional biases relating to drugs develop. Recent data suggest that similar brain regions as identified in the current study as underlying attentional biases to stimulant-related cues and showing differences between recreationally using versus dependent individuals may relate to cocaine exposure. In adolescents, diminished gray-matter volume in regions including the orbitofrontal cortex and ACC has been linked to prenatal cocaine exposure [6]. Future studies should examine

the extent to which specific alterations in the structure and function of these regions relate to the developmental timing and extent of cocaine exposure, particularly as preclinical data indicate a dose-dependent effect of cocaine on PFC structure and function, with early drug-related effects seen in the vmPFC [7]. As the vmPFC and adjacent ACC have been implicated in multiple processes including mood regulation, substance use, craving and decision-making to name a few, future studies should seek to understand how specific drug-related perturbations may lead to the development of multiple clinical concerns. Of particular importance, the study of young individuals prior to substance-use exposure studied in a longitudinal fashion may help disentangle the effects of pre-existing vulnerability factors from those related to drug exposure.

An additional posterior region (including the posterior cingulate) was identified as distinguishing the recreationally using group from the dependent group in the drug-related Stroop task. This pattern of findings is similar to that seen in a recent study pf approach bias development involving groups characterized by the presence or absence of heavy cannabis use [4]. In this study, the heavy-cannabis-using group did not show differences from the comparison group on these brain activations, and perhaps the inclusion of a recreationally using group may have helped to identify meaningful between-group differences relating to resiliency. Nonetheless, in the heavy-using group, relatively enhanced regional activation within the vmPFC was related to cannabis-use severity and relatively diminished activation of the dorsolateral PFC and dorsal ACC were related to more severe cannabis use over time. As such, these two studies of stimulant and cannabis use both support a role for biases (attentional, approach) in substance addictions, and suggest overlapping neural circuits underlying these constructs across addictive processes.

The findings have multiple clinical implications for prevention and treatment efforts. First, the identification of biological differences that relate to recreational as compared to addictive use represents an additional step towards improving prevention efforts, although more research is needed prior to having such efforts exert a significant clinical impact. Second, the findings suggest possible neural targets for behavioral or pharmacological therapies. Recent research efforts have been investigating how brain structure and function might relate to treatment outcomes in addictions ([1]; see also June, 2013 issue of *Psychology of Addictive Behaviors* at http://psycnet.apa.org/journals/adb/27/2/). As specific behavioral treatments like cognitive-behavioral therapy in part help people with drug addictions manage exposure to drug-related stimuli, the current findings complement an emerging literature that examines how treatments work and how they might be improved or tailored through a better understanding of their mechanisms of action. Third, the findings raise questions as to whether additional constructs might differentiate recreationally using from dependent individuals and link onto the neural mechanisms identified as contributing to drug-related biases. For example, constructs like impulsivity and compulsivity may importantly distinguish these groups, and understanding the neural contributions to these constructs remains an important undertaking [3]. Fourth, as the neuroimaging field matures, additional analytic approaches (e.g., connectivity-based) are gaining increasing acceptance and are being more widely used in the study of addictions (see November, 2013 issue of *American Journal of Drug and Alcohol Abuse* at http://informahealthcare.com/loi/ada). Such

approaches (e.g., independent component analysis) have the potential to identify brain activity that traditional general-linear-model-based analyses might miss [8]. Connectivity-based approaches can provide insight into how brain circuits operate and how they might relate to clinically relevant phenomena like treatment outcomes, as has been reported recently for cocaine dependence during Stroop performance [9, 10]. The application of such approaches to the currently reported data could provide additional insight into the neural correlates of recreational versus addictive stimulant use. As such findings are generated and communicated, the scientific and clinical communities may use this information to advance public-health strategies aimed at reducing the currently devastating impact of addictions.

Acknowledgments

This research was funded in part by NIH grants from NIDA (R01 DA018647, P20 DA027844, R01 DA035058, P50 DA09241) and NIAAA (RL1 AA017539), the Connecticut State Department of Mental Health and Addictions Services, the Connecticut Mental Health Center, an unrestricted research gift from the Mohegan Sun casino, and the Yale Gambling Center of Research Excellence Award grant from the National Center for Responsible Gaming. The funding agencies did not provide input or comment on the content of the manuscript, and the content of the manuscript reflects the contributions and thoughts of the authors and not necessarily reflect the views of the funding agencies.

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