Dr. Stephen Kohut: Identifying Neural Mechanisms of Abused Drugs in Nonhuman Primates

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Drug abuse is a multimodal disorder which can be characterized by behavioral, neurological, and pharmacological dysfunction. Multiple lines of preclinical science have explored these facets of addiction while/by utilizing various techniques influenced by various fields of research. However, multidisciplinary approaches to addiction research have begun to develop a more complete and broader understanding of how these various aspects of drug-taking and drug-seeking behavior interact to maintain abuse-related pathologies. Preclinical models of drug-taking behavior (i.e., intravenous self-administration in animals) have been an invaluable tool in evaluating the reinforcing effects of drugs and examining candidate medications for the treatment of substance use disorders. Yet little is known about the neurobiological mechanisms involved not only with drug consumption, but stimuli associated with drug-taking and drug-seeking behavior.

In an effort to elucidate the complex interaction between behavior and drug-consumption, Dr. Stephen Kohut, an Assistant Professor of Psychiatry at McLean Hospital/Harvard Medical School, has been developing neuroimaging procedures to examine the effects of drugs in nonhuman primates. These studies can be broadly divided into two main categories: 1) changes in resting state neural connectivity in anesthetized monkeys following repeated drug exposure, and 2) changes in neural connectivity in awake monkeys self-administering drugs. To conduct these experiments, Dr. Kohut designed custom chambers so that monkeys can rest comfortably within the bore of an fMRI. For experiments in awake monkeys, Dr. Kohut constructed topographical maps of each individual monkey's head to make custom-fitted masks that constrain movement and allow for clean imaging data. Furthermore, Dr. Kohut established a novel fixed ratio operant procedure in which pressing a lever for an established period of time resulted in drug injections. This hold-down fixed ratio procedure limits movement that traditional operant self-administration tasks create.

Studies conducted in anesthetized monkeys aimed to elucidate the impact of adolescent exposure to cannabinoids on resting state neural activity. In these experiments, 4 female adolescent rhesus macaques were repeatedly exposed to the CB1 full agonist AM2389. Resting state connectivity data was collected in a 3.0T fMRI before, during, and after 30 days following discontinuation of chronic drug treatment. This study used a multimodal imaging approach that generated structural, neurochemical, and functional data. In these studies, Dr. Kohut found regionally selective changes in the posterior singulate cortex during chronic AM2389 treatment, and magnetic resonance spectroscopy showed decreased n-acetylaspartate (NAA) levels in the medial orbital frontal cortex (mOFC) during acute and chronic treatment with AM2389 that recovered 30 days following discontinuation of chronic treatment. These changes in NAA levels were accompanied by functional changes between the mOFC and other brain regions. For instance, during acute treatments, there was decreased connectivity between the mOFC and the anterior cingulate; however, during chronic AM2389 treatment, there was increased connectivity between the mOFC and temporal brain regions (e.g., hippocampus) but decreased connectivity in regions associated with motoric behavior.

Currently, these resting state studies are being extended to rhesus macaques self-administering various abused drugs within an fMRI. While this research is currently ongoing, early results have demonstrated that during cocaine self-administration, there is decreased activity in the putamen, premotor regions, and nucleus accumbens. These results are consistent with cocaine's known pharmacological actions. Dr. Kohut plans to extend this research to elucidate neural activation patterns during self-administration of other abused drugs (e.g., nicotine, heroin). These developing studies and procedures are important as they can be used to evaluate neurobiological mechanisms of abused drugs and candidate medications.

Overall, the research conducted and developed by Dr. Kohut provides an exciting new frontier in the fields of behavioral pharmacology and neuroscience. Results from these studies will provide key information on how drug exposure and drug-taking behavior interact and can be used to identify specific neural signatures associated to particular drugs of abuse. In turn, these unique neural signatures may be useful in identifying targets for the development of novel treatments to curtail addictive behaviors. Furthermore, studies conducted in awake, behaving monkeys will also deepen our understanding on drug-paired stimuli (e.g., lights that indicate responses will be reinforced with a drug infusion) impact drug-taking behavior, and may identify neurological indices of conditioned behavior (e.g., self-administration).

Dr. Kohut has been attending CPDD annual meetings since 2006 and has been an associate member since 2011. Dr. Moura has been an associate member of CPDD since 2017 and currently serves on the Animals in Research Committee.