Striatal circuits underlying the persistence of cocaine addiction

Funding country: Netherlands
Project starting year: 2010
Project ending year: 2011
Area(s) of research: Mechanism of drug use and effects

Objectives:
Scientific discipline(s) involved: Neurosciences, Pharmacology

Objectives (native):

This project serves two purposes: 1. To elucidate the striatal circuits involved in different aspects of cocaine addiction. 2. To further explore the usefulness of DBS for the treatment of cocaine addiction, which could lead to a novel treatment for this devastating disorder.

Initial identified needs:

Drug addiction is an enormous medical problem, not least because of the ensuing unhealthy lifestyle and the co-morbidity with other neuropsychiatric disorders. Moreover, because of its socio-economic and legal impact on society, it affects many more people than the addicts themselves. Cocaine addiction is a major concern in both the Netherlands and the USA. However, effective treatments for cocaine addiction remain elusive. Understanding the neural underpinnings of cocaine addiction is essential for the development of novel treatments for this disorder. The present project aims to further elucidate the neural basis of cocaine addiction, and to explore the possibilities for novel treatment strategies. During the last decades, research on the reinforcing and addictive properties of cocaine has for the most part focused on the dopaminergic innervation of the ventral striatum, including the nucleus accumbens. However, there is general agreement that this neurobiological view on cocaine addiction is too narrow, both from a neurochemical and a neuroanatomical perspective. Alongside its dopaminergic innervation, glutamatergic input into the nucleus accumbens plays a critical role in relapse to cocaine seeking after detoxification. Moreover, there is increasing evidence that the circuitry involved in cocaine addiction also includes dorsal regions of the striatum. Thus, during initial stages of cocaine use, dopamine in the ventral striatum mediates goal-directed, motivational aspects of cocaine use. However, over many episodes of drug taking, drug-associated cues gain increasing control over behavior, which is mediated by dorsal regions of the striatum. Indeed, research in primates has shown that with prolonged cocaine self-administration experience, neural adaptations spread more dorsally into the striatum. This ventral-to-dorsal intrastralial progression of regions engaged by cocaine use may be subserved by striato-nigro-striatal pathways, whereby ventral striatal regions influence not only their own dopaminergic innervation, but also that of progressively more dorsal areas through spiraling projections via dopamine neurons in the ventral tegmental area and substantia nigra. Studies into the role of striatal subregions in cocaine addiction support the notion that the development and expression of cue-controlled cocaine seeking is subserved by these spiraling striato-nigro-striatal pathways. Remarkably however, our own recent work suggests that dorsal striatal dopamine also mediates the reinforcing properties of cocaine itself during early stages of the addiction process, perhaps in concert with dopamine in the ventral striatum. These findings call for a deeper investigation of the striatal subregions mediating distinct aspects of the cocaine addiction process. The present research proposal aims to further delineate the respective roles of dorsal and ventral striatal subregions in different aspects of cocaine addiction. Specifically, we will investigate which striatal subregions mediate cocaine taking, motivation to self-administer cocaine and relapse to cocaine seeking after detoxification. To that aim, we will employ pharmacological means (dopamine receptor antagonists, glutamate receptor antagonists) as well as reversible inactivation of striatal regions using deep brain stimulation (DBS). Using asymmetrical disconnection procedures, we will be able to reveal whether distinct striatal subregions mediate different aspects of cocaine addiction, and whether these regions function in series (i.e. through the ventral-to-dorsal striatal spirals) or in parallel. In addition, the use of DBS will allow for a further exploration of the usefulness of this technique for the treatment of cocaine addiction. DBS has attracted a great deal of attention as a potential treatment for various neurological and psychiatric disorders, including d

Performed by: LJM Vanderschuren, UMC Utrecht
Funded by: RC Pierce, Perelman School of Medicine, Philadelphia PA, USA

Summary references: