Functional Connectivity of Chronic Cocaine Use Reveals Progressive Neuroadaptations in Neocortical, Striatal and Limbic Networks

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Necessary to include baseline measures to determine effects of chronic cocaine use

Human neuroimaging studies have provided evidence for significant changes in neural activity across brain regions in cocaine users. While these studies show that reduced functional connectivity across brain regions is associated with cocaine use, the brain regions involved and the extent of the connectivity changes among them depend on several factors. The specificity of these effects is unclear, however, because of the inherent difficulties in human imaging studies in cocaine users. Preclinical models of cocaine use can therefore be useful as they allow for controlled determination of the conditions in which chronic cocaine impacts the intrinsic functional connectivity of the brain. In the current study, functional magnetic resonance imaging was employed both before and at two time points after intravenous cocaine self-administration in rats to assess how cocaine use alters brain functional connectivity.

Methods

In the present study, adult male Long-Evans rats were trained to self-administer cocaine intravenously for 6-hour daily sessions over 14 consecutive days. Two additional groups serving as controls underwent sucrose self-administration or exposure to the test chambers alone. Functional magnetic resonance imaging was conducted before self-administration and after 1 and 14 days of abstinence (1d and 14d Abs). Images were collected on a 4.7 Tesla/33 cm horizontal magnet (Magnex Scientific) with an 11.5 cm diameter gradient insert (Resonance Research Inc., Billerica, MA) (670 mT/m maximum gradient strength at 300Amps and 120 µs rise time) and controlled by VnmrJ 3.1 software (Agilent, Palo Alto, CA). Functional images were collected using a 2-shot spin-echo echo-planar imaging (EPI) sequence with the following parameters: echo time (TE) = 50 ms, repetition time (TR) = 1 s, 32.5 x 32.5 mm in plane, 12 slices with 1.5 mm thickness per slice, data matrix = 64 x 64. A total of 210 repetitions were collected per EPI scan (7 minutes), with two scans per rat. No stimuli were presented during functional scanning. Anatomical scans for image overlay and reference-to-atlas registration were collected using a fast spin echo sequence (TE = 45 ms; TR = 2 s; RARE factor = 8; number of averages = 10; data matrix = 256 x 256) in the same space as the EPI scan. Images were processed as indicated by our recent work(1-3).

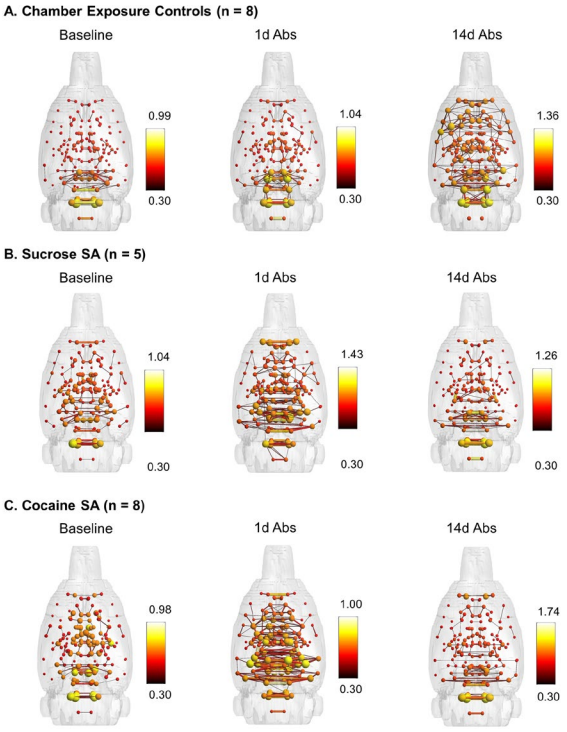

Fig. 1 Three-dimensional functional connectivity maps of the rat brain illustrating significant effects of sucrose or cocaine self-administration and abstinence (Abs). All maps are composites of n = 5-8 rats and are set at a correlation threshold (edge weight) value of 0.3. Spheres represent node strength and line thicknesses represent edge weights.

Results and Discussion

At 1d Abs from cocaine, there was increased clustering coefficient in brain areas involved in reward seeking, learning, memory, and autonomic and affective processing, including amygdala, hypothalamus, striatum, hippocampus and thalamus. Similar changes in clustering coefficient after 1d Abs from sucrose were evident in predominantly thalamic brain regions. Notably, there were no changes in strength of functional connectivity at 1d or 14d after either cocaine or sucrose self-administration. The results suggest that cocaine and sucrose can change the arrangement of functional connectivity of brain regions involved in cognition and emotion, but that these changes dissipate across the early stages of abstinence.

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