# The effects of transcranial alternating current stimulation on cocaine seeking following prolonged abstinence in rats

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***Background***

In individuals with substance use disorders (SUDs), the duration of abstinence from drug plays a critical role in the propensity to relapse. In animal models, prolonged cocaine abstinence alters neural activity in brain reward circuitry, which is accompanied by heightened cue-induced drug-seeking. We previously reported that one-month abstinence from cocaine robustly increased the proportion of neurons in the nucleus accumbens (NAc) core and prelimbic cortex (PrL) that were phasic (i.e. displayed significant changes in firing rate) to cocaine-associated cues, and increased drug seeking [1-2]. However, neuroimaging studies in rats also show reduced resting state functional connectivity between the NAc and the medial prefrontal cortex (which includes the PrL) following one-month abstinence from cocaine [3], paralleling studies showing 'hypofrontality' following prolonged abstinence (e.g. 3-4 months) in people with SUDs [4]. Collectively, dampened resting state activity in conjunction with enhanced responsiveness of PrL and NAc core neurons to drug-associated cues may contribute to impaired control over drug-directed behavior in SUDs. Here, preliminary studies examined the effects of prolonged cocaine abstinence on PrL-NAc core connectivity and whether cocaine-seeking and underlying alterations in PrL-NAc core activity following one-month abstinence could be ameliorated with transcranial alternating current stimulation (tACS).

***Methods***

Adult male rats (n=13) were surgically implanted with intrajugular catheters and multielectrode arrays (8 channels/region) into the PrL and ipsilateral NAc. Rats were trained to self-administer cocaine (~1 mg/kg/inf) or saline/water (2 h/day, 14 days), paired with an audiovisual cue (20 s), then underwent 1 month of abstinence with tACS (16 Hz, 18 uA, 10 s on/off, 40 stims/day) or sham administered on the last five days of abstinence. Next, animals were given a test session consisting of 10 non-contingent presentations of the audiovisual cue (15 min), extinction (lever press resulted in cue but no drug; 2 h) and resumption of self-administration (2 h). Single unit activity and local field potentials were simultaneously recorded from PrL and NAc core to examine synchronized oscillatory dynamics to assess functional connectivity between these regions. Spontaneous neural activity was recorded on day 1 of abstinence, prior to each tACS/sham session following 1 month of abstinence, and prior to the test.

***Results***

Preliminary data show that 1-month cocaine abstinence reduced PrL-NAc coherence in the beta (12-20 Hz) and high gamma (>70 Hz) ranges compared with controls (n=5 for cocaine, 3 for saline/water). These reductions were not observed on day 1 of abstinence. Following five days of 16 Hz tACS (n=5), coherence was increased relative to sham-treated animals such that coherence was restored to the level of controls. Further, the change in peak beta coherence from the first to last tACS session was significantly and negatively correlated with cocaine seeking.

***Conclusions***

Our preliminary data suggest that one-month cocaine abstinence decreased beta and high gamma coherence in the PrL-NAc circuit, and tACS may restore this activity and reduce drug-seeking. Ongoing investigations will more fully characterize the relationship between PrL-NAc connectivity and cocaine seeking, as well as examine the effects of 80 Hz tACS on cocaine seeking and PrL-NAc connectivity to determine whether tACS effects are frequency specific.

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