Brain Morphology And Connectivity After Focal Repetitive Stimulation As A Therapeutic Intervention On Preclinical Alcohol Model: A Prospective Study

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Introduction

About 3 millions of people died worldwide in 2016 due to Alcohol Use Disorder (AUD) which is defined as: excessive alcohol use that affects physical and mental health. Although treatments for the AUD are mostly pharmacological and psychotherapeutic approaches, only about 40% to 60% of discharge patients are continuously abstinent. Neuromodulation interventions, such as Deep Brain Stimulation (DBS) and repeated transcranial magnetic stimulation (rTMS), are proposed possible new therapies to treat AUD. Studies in humans have shown that rTMS reduces frequency of use and alcohol craving. It is hypothesized that neuromodulation may induce neural plasticity in the reward and frontostriatal systems via electrical field induction, possibly reducing symptoms. However, information about mechanism of action, optimal brain targets and types of stimulation protocols remain insufficient.

Preclinical self-administration rodent models of AUD may help us gain knowledge on the effect of neuromodulation therapies on pathology, as well as the neural mechanisms behind the positive effects. Brain imaging, based morphometry provides evidence for macro-structural plasticity of the brain which is a valuable tool for longitudinal assessment.

Method

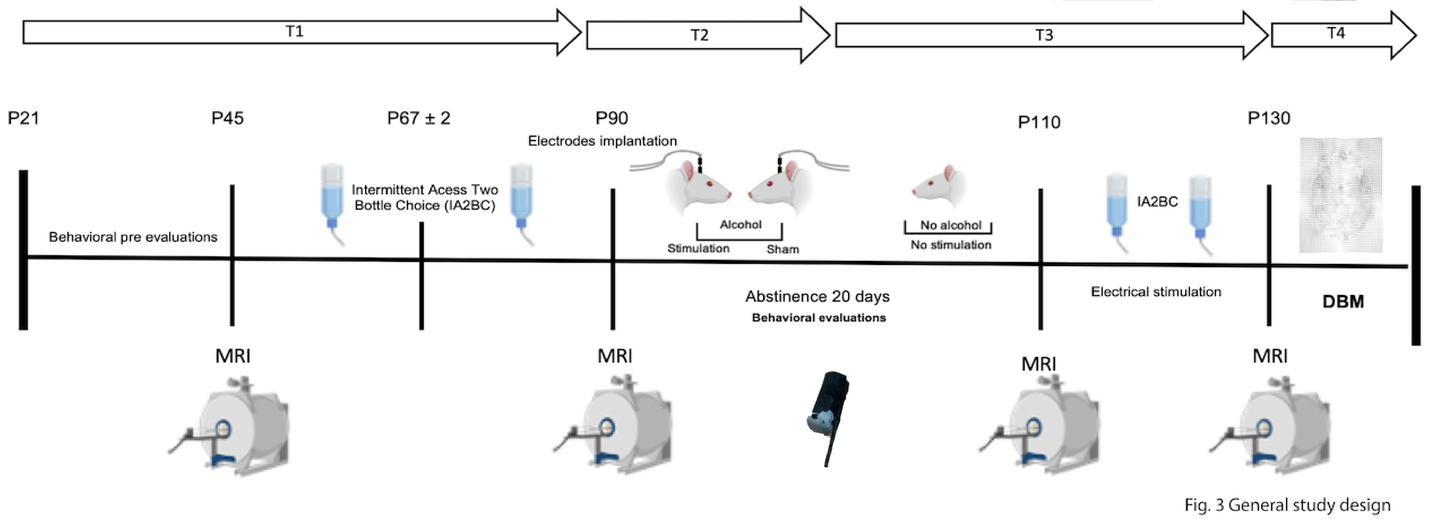

Fig. 3 General study design

In this study, we will use the intermittent access two bottle choice (IA2BC) preclinical model of AUD on young adult wistar rats (P45) through 20 sessions and divide them into high drinkers (>4.5 g/kg/day) and low drinkers (<4.5 g/kg/day). Then we will implant MRI compatible carbon electrodes in the prelimbic cortex (PL: mPFC on humans) as an essential area of the reward circuit (Fig. 1). Afterward we will conduct a high frequency stimulation protocol (20 Hz) for 10 consecutives days at 100 pulses (duration= 0.2µs intensity= 400µA) on twelve randomly assigned subjects (Fig. 2), who will be separated into: 1) a stimulated group, 2) a sham stimulation group, 3) a control group (no surgery, stimulation nor alcohol). To study plasticity mechanisms, we will use in vivo structural and functional MRI scanning T1w 3D Flash (TE: 5 ms, TR:30.76 ms FOV 25.6 ms X 19.098 ms X 25.6 ms) at baseline (T1), IA2BC conclusion (T2), pre-stimulation (T3) and post-stimulation (T4). We will analyze changes in volume using deformation-based-morphometry (DBM) and changes in resting state functional connectivity (Fig. 3).

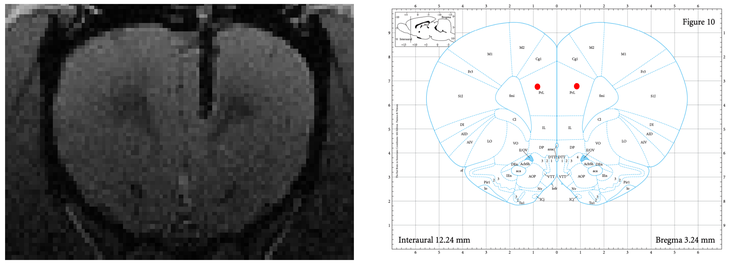

Fig. 1 Implantation of MRI compatible carbon electrodes in the PL

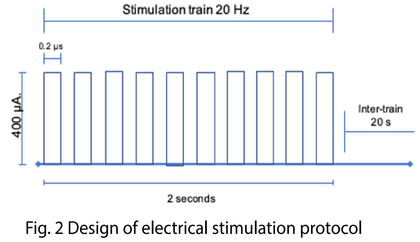

Fig. 2 Design of electrical stimulation protocol

Prospects

We expect the following results:

1) Repeated electrical stimulation to PL will reduce alcohol intake in AUD rats.
2) Changes in consumption will relate to changes in brain morpho logy and connectivity.

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Investigation ethics committee of Institute of Neurobiology, UNAM. Proyect No. 119. A