Structural trajectory induced by chronic alcohol model: Prediction of high alcohol intake using two latent classes.

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Introduction

Alcohol use disorder (AUD) is a complex neuropsychiatric disorder that combines behavioral, neurobiological, and psychosocial alterations. The development of AUD has been characterized as a three-stage cycle: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. Although these stages have been studied in humans and animals, there is still missing knowledge of the neuroadaptative changes happening across the brain during each stage. Knowledge of these changes would possibly help us understand how AUD is established.

Aim

Understanding the neuroadaptive brain changes in AUD, caused by high and low consumption.

Method

In this study we used the Intermittent-Access Ethanol 2-Bottle-Choice Drinking Paradigm in n = 48 (24 female), Wistar rats, starting at a weight of 160 g (~7 weeks old−45 days post-natal corresponding to adolescence). Animals had ad-libitum access to standard laboratory chow and water. After the baseline MRI scans, 24 rats were assigned to the EtOH group and 24 to the Control group. EtOH group underwent a modified version of the Wise pre-clinical AUD model where, briefly, rats received continuous access to 20% ethanol on a 12-hour reversed light/dark cycle (lights off at 7 am) for 45 days. Animals were anesthetized during MRI sessions with a single bolus of 0.012 mg/kg of dexmedetomidine and combination Isoflurane with oxygen (50/50). Brain images were acquired using a Bruker 7T MRI scanner with a 2x2 surface array rat coil. T1-weighted images were acquired using a FLASH 3D sequence, TR/TE = 30.76/5 ms, isometric voxel = 160 μm with two repetitions.
All images were converted from Bruker format to nifti using brkraw tool, and then preprocessed using an in-house pipeline based on MINC-toolkit-v2, ANTs and MRtrix V3 which performed the following steps: center image, denoising and N4 Bias Field Correction. We used deformation-based morphometry to create Jacobian maps per subject and time point

using a Two Level DBM based on ANTsX/ANTs tools v2.3.1 5 using a SIGMA rat atlas template and parcellation.

Analysis

We implemented a latent class mixed model (lcmm), in order to classify high and low consumption after 20 sessions of alcohol consumption. The independent variable to classification was main alcohol intake g/Kg/24h per rat and per session, for this we used the "Icmm" R package. Structural changes were performed using a Linear Mixed-Effects Model using a RMINC .We compared the within-subjects effect of baseline (T1-session) after 20 sessions of intermittent alcohol (T3-session). The model consisted of an interaction effect Group X Age and with a random effect such as subject. All changes were corrected by multiple comparisons FDR correction. In order to know whether the local brain deformations predict high alcohol consumption, it employed a Bayesian inference analysis, using the probabilistic language STANv2.26 , this method was employed with the "*brms*" R package . As above was mentioned, previously it employed a high and low consumption segregation. Then, we got the distribution peaks for each brain region Finally, we propose a Bayesian logistic regression.

$$Yi \sim Bernoulli\ (\pi i),\ i = 1\ ...,\ n\ logit\ (\pi i) = \beta 0 + \beta 1 * ROIi + ... \beta 2 * ROIi ... n + \varepsilon i$$

Results

The latent class model separated two groups (high consumption and low consumption). Finally, we found significant differences in brain volume comparing these two classes. We found local structural changes after 20 sessions of high alcohol consumption in several brain regions. Between groups contrast showed reduced volume of thalamus , dorsal hippocampal commissure and Caudadoputamen.

Conclusions

A deformation-based morphometry approach identified significant brain volumes modulated by EtOH exposure. this results indicating that some local neuroadaptive structural changes related to high and low voluntary alcohol consume in Wistar rats

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