Binge drinking differentially impairs decision making and dopamine transmission in the core of the nucleus accumbens depending on sex

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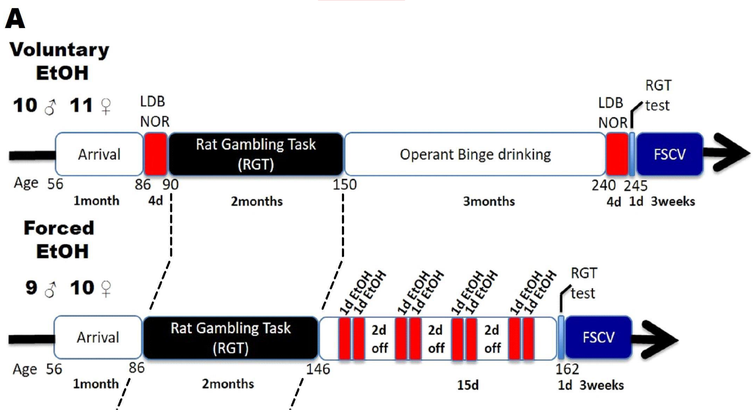
Introduction: Binge drinking (BD) is a harmful behavior for health and is a predictive factor for the development of alcohol addiction (AUD). Weak decision-making (DM) capacities could play a role in vulnerability to BD which in turn would lead to DM impairments and thus perpetuate BD. Differences in BD vulnerability have been reported according to sex. Few longitudinal studies have attempted to understand the mechanisms underlying the interaction between decision-making and BD. We used two procedures to mimic binge-like alcohol intake in male and female rats, one passive exposure and one voluntary ingestion, and assessed DM capacity before binge exposure onset and after the end of the BD period. Dopaminergic transmission is well known to underly both the DM mechanisms and the rewarding effects of alcohol. Dopamine (DA) release in the core of the nucleus accumbens (NAc) is a mechanism involved in both DM and rewarding effect of alcohol; and is regulated by dopamine D2/3 autoreceptors. *Ex vivo* DA transmission was assessed short term after the end of the binge exposure in the core of the NAc using the fast-scan cyclic voltammetry (FSCV) technique.

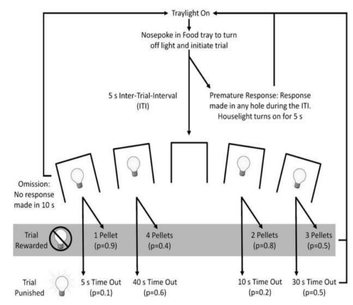
Material and Methods

Timeline



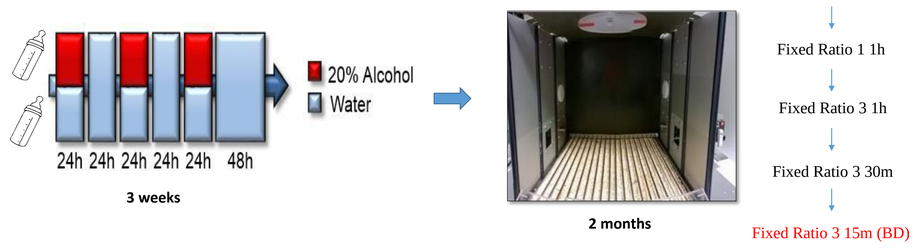
We assessed DM abilities of male and female rats before and after an exposure to ethanol mimicking BD, either a voluntary or forced procedure, using the Rat Gambling Task (RGT). Anxiety and learning abilities were also assessed using the Light-Dark Box (LDB) and Novel Object Recognition (NOR) procedures. We studied modifications of the dopaminergic phasic transmission in the Nac core at the end of the experiment, using the Fast-Scan Cyclic Voltammetry (FSCV) procedure in brain slices.

Decision-making: Rat gambling task

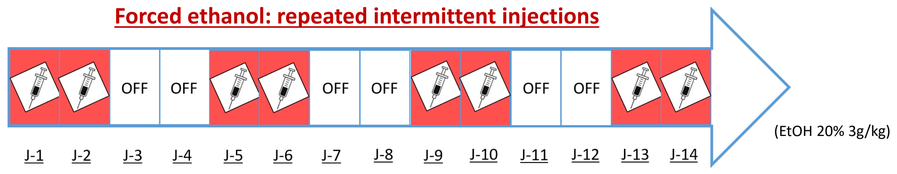


Rats were trained daily to nose poke in response holes to earn sugar pellets. Each hole was associated with a fixed probability of reward (sugar pellets) and punishment (time-out period), allowing to discern between advantageous options (P1 and P2, with P2 being most profitable) and disadvantageous ones (P3 and P4, with P4 being least profitable).

Voluntary ethanol: operant binge drinking



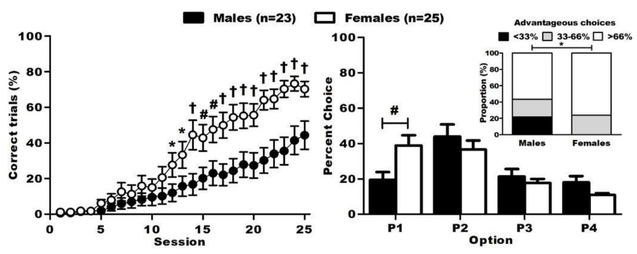
Forced ethanol: repeated intermittent injections



Rats in the voluntary procedure had access to two bottles in their stabulation cage, one with tap water and one with 20% EtOH, every other day for 3 weeks, to developp EtOH preference. They were then trained to self-administer EtOH in operant cages, during sessions with progressively decreased duration and increased workload. Rats in the forced procedure were injected reapeatedly and intermittently for a total of 8 injections in 14 days.

Results: behavior

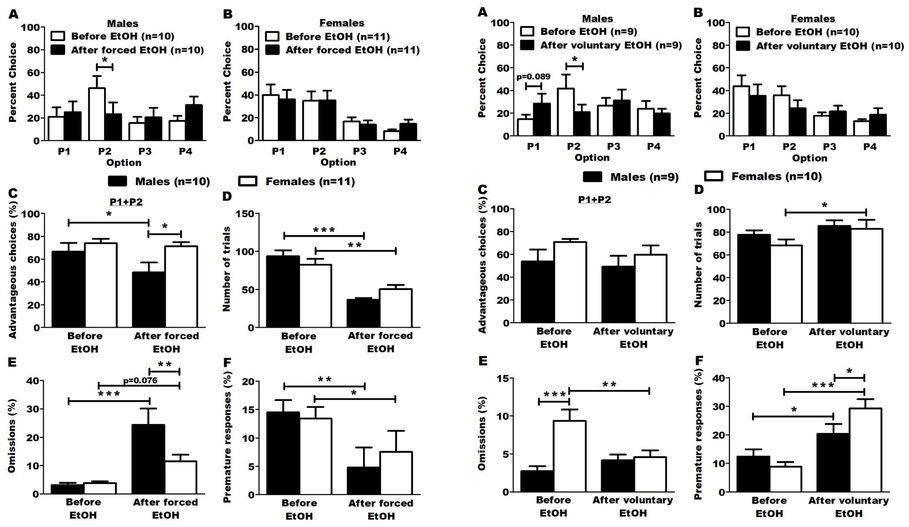
Decision-making before ethanol



(Left) The female rats were faster than the male rats in acquiring the task (reaching 80% of correct trials in the hole associated with the cue)

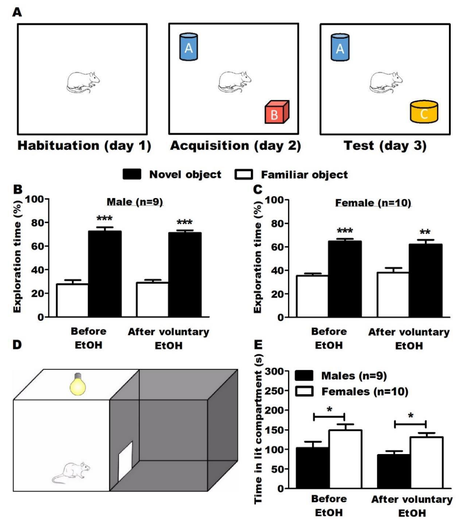
(Right) Male and female rats had a different choice strategy in the RGT before ethanol exposure. The male rats preferred the optimal P2 option, while the female rats preferred both P1 and P2 without distinction. The P1 option can be seen as « risk-averse » as is it associated with low reward and punishment. The male group had significantly more individuals with a poor decision-making level (<33% advantageous choices) than the female group, who was devoid of those.

Decision-making after ethanol



BD history impaired choice process only in males but affected impulse control in both sexes. BD history, whether forced or voluntary, impaired choice behavior specifically in males. The optimal P2 option was decreased by half and their choice behavior became « random » (similar percent choice for each option), suggesting an inability to discern options for their value and adapt from feedback. BD history didnt affect female choice behavior. The forced procedure resulted in a global behavioral suppressing effect in both sexes (↑omissions and premature, ↓trials), while the voluntary procedure resulted in behavioral disinhibition with increased motor impulsivity (↑ premature) in both sexes,

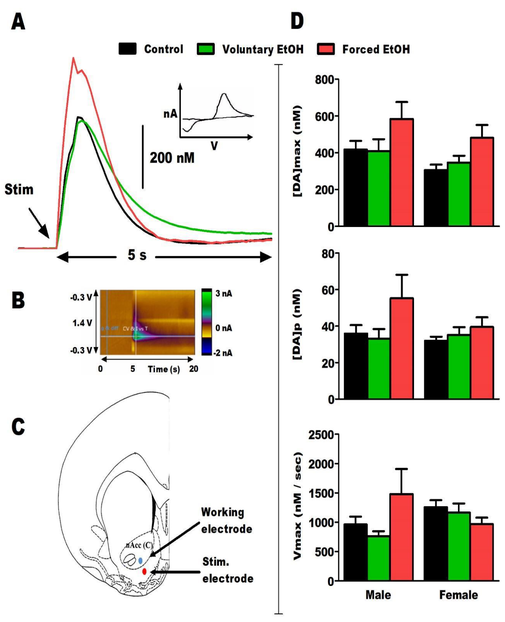
Learning abilities and anxiety



Voluntary BD history didnt affect learning abilities and anxiety. In the NOR task (B and C), male and female rats spent significantly more time on the novel object, showing that they memorized the familiar object, both before and after voluntary ethanol. In the LDB task (E), voluntary ethanol didn't affect the time spent in the lit compartment, associated with stress and anxiety, in both male and female rats. The female rats were overall less anxious than the male rats.

Results: neurobiology

Baseline DA phasic transmission

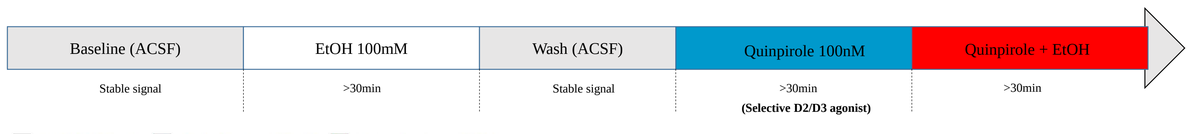


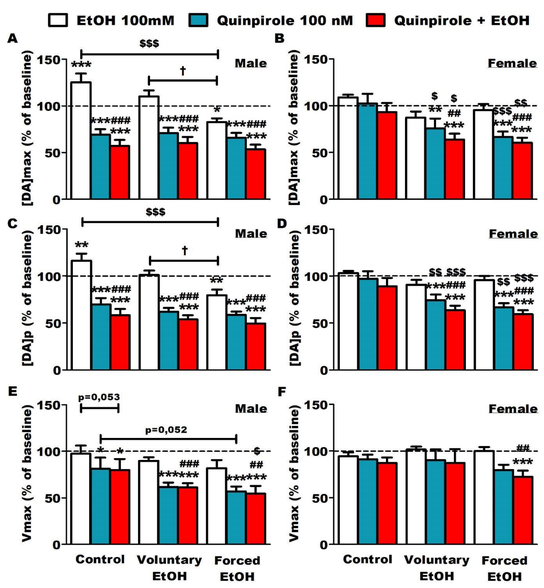
(A, B and C) Extracellular dopamine was recorded in the nucleus accumbens core (NAc) by applying a triangular waveform (-0,4 to +1,2 to -0,4V vs Ag/AgCl, 400 V/s) to a carbon-fiber working electrode. Phasic release of DA was evoked every 5min using a monophasic stimulation (24 pulses, 2ms width) for 0,5 ms with a 200 µA intensity and a 60Hz frequency. Pharmacology was performed using ethanol and quinpirole.

BD history, whether forced or voluntary, didnt affect baseline DA phasic transmission. (D) BD didnt modify [DA]max (instant maximal extracellular concentration of DA released), [DA]p (DA concentration released per pulse) and Vmax (velocity of the dopamine transporter).

Baseline DA phasic transmission wasnt different depending on sex.

Response to pharmacology





	♂	♀
EtOH-induced DA release	+	0
DA release inhibition by quinpirole	+	0
Blockade of EtOH-induced DA release by quinpirole	+	0
Blockade of DA release by BD history	+	0
Increase in quinpirole sensitivity after BD history	0	+

Different pharmacological sensitivity to acute ethanol, quinpirole and BD history depending on sex.

Acute ethanol increased phasic DA release specifically in male rats. This effect was blocked by quinpirole in male control rats, and blunted / reversed depending on BD history in binger rats, suggesting a reward deficit syndrome.

Acute ethanol had no effect in female rats of all groups. BD history increased sensitivity to quinpirole specifically in female rats, with an increase of quinpirole-mediated DA inhibition of release.

Those results overall suggest the involvement of D2/D3 autoreceptors in the effects of BD, depending on sex.

Conclusion: This preclinical longitudinal study examined the impact of BD on DM capacities taking into account for sex and BD-exposure paradigm and assessing changes in DA signaling in the core of the NAc. Choice processes were impaired specifically in males, after either passive or active BD history, however, decrease in impulse control was highlighted in both sexes. Thus, the binge history differentially affected two of the main factors known to underly DM behavior in both sexes. Behavioral changes were associated with changes in the DA signaling in the core of the NAc with a blunting or reversal of the enhancing effect of acute alcohol in males, and an increase in the sensitivity of quinpirole-mediated inhibition of dopamine release in females but not in males. The observed changes in DA signaling after the binge history may involve adaptations of the D2/D3 autoreceptors in both sexes. Overall, our study demonstrated that BD exposure affected both DM processes and DA signaling in the core of the NAc in a sex-related manner, further suggesting that these effects may play a role in the vicious cycle leading to BD perpetuation and the early onset of AUD and dependence.