P.197 Influence of alcohol and acetaldehyde on human psychomotor functions: Findings from the alcohol clamping in healthy young population

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Purpose: Alcohol sensitivity is closely associated with blood acetaldehyde concentrations (BAAC) as acetaldehyde causes a variety of discomforting symptoms. On the other hand, effects of alcohol and acetaldehyde on multiple domains of psychomotor functions have not been thoroughly investigated in a large sample, which was addressed in this study.
Methods: Healthy Japanese students aged 20-24 years without a diagnosis of alcohol dependence were included. Having semi-structured interview for diagnosis and ALDH2 genotyping, they were sorted to one of the three groups based on their ALDH2 genotypes: ALDH2*1/*1 (both active), ALDH2*1/*2 (hetero), and ALDH2*2/*2 (both inactive). Those with ALDH2*2/*2 were excluded from the study since they are extremely sensitive to alcohol. The remaining subjects underwent three neuropsychological tests: the continuous performance test (CPT) for sustained attention, the neuropsychological test (NPT) for reactivity, and the paced auditory serial addition test (PASAT) for working memory. These examinations were conducted at baseline and 60 and 180 minutes after alcohol administration was started. Scores of these tests were compared within subjects by using analysis of variance. Alcohol clamping technique was used to maintain 50 mg% of blood alcohol concentration (BAC) for 180 minutes through the intravenous infusion of diluted ethanol solution. BAAC was assessed 6 times in 240 minutes.
Results: 429 subjects participated in this study; of these, 5 were excluded (ALDH2*2/*2 [n = 3], extremely low body [n = 1], and difficult vascular access [n = 1]). In the remaining 424 subjects, 160 (37.7%) were found to carry inactive ALDH2 (ALDH2*1/*2). Eighteen (4.2%) dropped out because of unpleasant feelings, and 406 completed. Targeted BAC was achieved in 15 minutes and maintained for 180 minutes within the 50±5mg% range. While BAAC in the subjects with ALDH2*1/*1 was stable (mean±SD μg/ml, 0.033±0.005 at baseline; 0.080±0.061 at 60 minutes; and 0.041±0.030 at 180 minutes), it peaked at 60 minutes and then gradually declined in those with ALDH2*1/*2 (0.029±0.007; 2.426±0.087; 0.909±0.043). The ALDH2*1/*2 group showed worsening in the CPT at 60 minutes (correct detection, 38.36±2.81 vs. 36.29±4.80, p = 0.001; omission error, 1.53±2.73 vs. 3.47±4.59, p = 0.014) while there were no differences in the ALDH2*1/*1 group. No significant differences were found between the two groups at baseline and 180 minutes. The reaction time assessed with Task C in the NPT was improved at 60 minutes in the ALDH2*1/*1 group (0.34±0.07 at baseline vs. 0.38±0.11 at 60 minutes, p = 0.001), but not in the ALDH2*1/*2 group whereas no significant differences were observed in the other two tasks in either group. With regard to the PASAT, both groups demonstrated significant improvements at 60 and 180 minutes.
Conclusion: Acetaldehyde seems to have negative impact on sustained attention, BAAC and reactivity may not influence reactivity nor working memory. Moreover, alcohol could improve working memory although a possibility of practice effects cannot be rejected. These findings warrant further investigations, especially neuroimaging studies, to identify the mechanisms underpinning intoxication and possibly beneficial effects of alcohol and acetaldehyde.

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P.198 The neuroanatomy of cannabis use: does gender matter? Findings from the ENIGMA addiction working group

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Background: Cannabis is the most widely used illicit drug globally. Structural neuroimaging (sMRI) studies of cannabis users versus controls show neuroanatomical alterations in areas dense in cannabinoid receptors, but the location and direction of the alterations are inconsistent. These discrepancies may be driven by gender differences that have not

been fully explored given the small-sized and mostly-male samples, as well as by heterogeneous cannabis use levels and confounders that have been inconsistently accounted for (e.g. IQ, nicotine and alcohol use). Here, we aimed to examine the neuroanatomical correlates of cannabis use, and the role of gender and severity of use in the largest cohort of 270 participants examined to date, from the ENIGMA Addiction Working Group.

Methods: 145 cannabis users (48 females) and 125 controls (36 females) from seven distinct research sites underwent sMRI. We selected eight regions of interest (ROIs) - amygdala, hippocampus and cerebellum (gray/white matter) volumes, and orbitofrontal (medial/lateral), frontal pole and insular cortical thickness extracted locally, in each site, using standard pipelines from Freesurfer v5.3. Mixed-effect models were run to test the impact of the following variables on the ROIs (i) group, gender, and group-by-gender interaction; (ii) cannabis use level (age of onset and monthly dosage) and (iii) cannabis dependence in a subsample ($n = 228$), comparing 70 dependent users (25 females), 51 non-dependent users (20 females), and 107 controls (34 females). All models were adjusted for assessment site, age, IQ, intracranial volume and alcohol and tobacco monthly use.

Results: Cannabis users showed trend-level thinner medial orbitofrontal cortex ($p<0.08$) than controls. Dependent users had thinner medial ($p<0.01$) and lateral ($p<0.05$) orbitofrontal cortex, and smaller cerebellar white matter volume ($p<0.05$) compared to both non-dependent users and controls. No differences were found between non-dependent users and controls.

Female cannabis users had trend-level smaller cerebellar white matter volume ($p<0.06$) relative to female controls, an effect not found in males. Consistently, female dependent users had smaller cerebellar white matter ($p<0.01$) and thinner orbitofrontal cortex ($p<0.05$) compared to female non-dependent users and controls, while no effect was found among males.

Higher monthly cannabis dosage and earlier cannabis use onset predicted smaller volumes of cerebellar grey ($p<0.05$) and white ($p<0.05$) matter respectively, in male users only. By contrast, in female users, trend-level associations were found between earlier onset of cannabis use and thinner OFC ($p<0.08$) and frontal pole ($p<0.06$).

Conclusions: We showed that overall, cannabis users had marginal neuroanatomical alterations compared to controls limited to the orbitofrontal cortex. Accounting for gender and dependence revealed more marked reductions in the same region (i.e., orbitofrontal cortex) and extended also to other regions (i.e., cerebellar white matter) which appeared driven by women cannabis users and dependent users. Our results warrant a stratified approach to the study of cannabis use neurobiology and point to a neurobiological vulnerability in women cannabis users and dependent cannabis users and suggest that different neurobiological targets for treatment may be required in these groups.

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P.199 Experimental analysis of development of compulsive behavioural disorders due to intravenous fentanyl self-administration

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Objectives: The aim of experiment was to investigate the role of emotion and performance of contingent instrumental responses per se during acquisition for elaboration of Substance-Related Disorders and development of compulsive behaviour induced by drug administration.

Methods: Behavioural model of intravenous self-administration of fentanyl has been used under fixed-ratio schedule in 4 Groups of rats. Two series of experiments were carried out. The first series studied the acquisition of behavioural disorders under self-administration of different doses [0.0006 mg/kg (groups 1, 3) and 0.0012 mg/kg (groups 2, 4)] of drug and different duration [1h (groups 1, 2) and 4h (groups 3, 4)] of session during 10 consecutive days. In the second series, during 4 daily sessions, the same Groups of rats were tested under conditions of equal length of session (45 min) and equal single dose (0.0012 mg/kg) received in response to lever presses with an aim to calculate the number of intravenous self-administration of fentanyl by rats.

Results: Rats in Group 1 and 2 for which daily session lasted 1h and in response to every press obtained different doses of fentanyl, reliably varied by number of lever presses ($T = 3388.5$, $P<0.0001$). Rats in Group 1 performed a stable number (mean $= 13.4 \pm 1.7$) of drug (active) lever presses after the seventh daily session, white those in Group 2, already after the fourth one (mean $= 8.2 \pm 1.6$). Rats in Group 3 and 4 reliably differed from each other by a total number of lever presses ($T = 3319.5$, $P<0.0001$). At the same time, rats in group 3, according to mean values, more frequently (mean $= 29.2 \pm 2.6$) pressed the drug lever than those in Group 4 (mean $= 19.4 \pm 2.7$). According to inactive lever responses, rats in Group 3 and 4 did not differ ($T = 2663$, $P>0.34$) and both Groups ceased inactive lever presses after the second session. Two-way ANOVA analysis of data collected in experimental series 2 has revealed that irrespective the single dose of fentanyl given in response to every contingent press, number of instrumental responses performed during acquisition has an important effect in the development of Substance-Related Disorders (main effect of session duration - $F = 33.79$, $P = 0.0001$). At the same time, the importance of single dose of fentanyl appears to be an important factor for the development of Substance-Related Disorders, (main effect of dose - $F = 7.83$, $P = 0.016$). In addition, this effect of the number of instrumental responses performed in experimental series 1 does not depend on the dose intensity effect (session duration x dose interaction - $F = 4.5$, $P = 0.06$).