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Abstract

Objective: Efforts to promote the cessation of harmful alcohol use are hindered by the affective and physiological components of alcohol withdrawal (AW), which can include life-threatening seizures. Although previous studies of AW and relapse have highlighted the critical importance of the N-methyl-D-aspartate receptor (NMDAR) subunit GluN2B and the detrimental role of stress, little is known about genetic risk factors. We therefore conducted genetic and neurobiological studies to identify and characterize novel risk loci.

Methods: We performed a genome-wide association study (GWAS) of AW symptom count in uniformly assessed subjects with histories of serious AW, followed by additional genotyping in independent subjects, and bioinformatic analyses. We used genetically modified mouse neuronal cultures to conduct electrophysiological and pharmacological studies of neurobiological systems implicated by the GWAS.

Results: The top association signal for AW severity was in sortilin-related gene SORCS2 on chromosome 4 (European-American meta-analysis $n = 1,478$, $P = 4.3 \times 10^{-9}$), and the same risk allele also predicted more severe clinical outcomes in seizure disorder patients participating in a randomized trial of anticonvulsant effectiveness ($n = 654$, $P = 3.2 \times 10^{-3}$). In humans, SORCS2 is most highly expressed in the nervous system, and bioinformatic analyses showed that the SORCS2 risk haplotype disrupts transcription factor (TF) binding motifs within a stress hormone-regulated enhancer element active in human hippocampus. In mouse hippocampal preparations, we demonstrate that SorCS2 is a key regulator of GluN2B-mediated synaptic responses.

Conclusion: These translational findings identify new synaptic regulatory processes, and provide novel targets for managing the aversive consequences of abrupt alcohol cessation.

PM297

High-dose zolpidem dependence and detoxification from withdrawal symptoms using diazepam

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Abstract

Objective of the study: Zolpidem is a nonbenzodiazepine hypnotic for the treatment of insomnia, and known as a relatively safe medication. However, there have been several case reports of zolpidem abuse and dependence these days. Even though some withdrawal symptoms like seizures can occur, there was no standard detoxification method until now.

Methods used: We reviewed the previous researches about high-dose zolpidem addiction and proposed treatment, and the clinical case.

Summary of results: A high dose of zolpidem has similar pharmacologic properties as the rest of benzodiazepines, even though the usual dose of zolpidem has a selectivity to type 1 benzodiazepine receptor. So, some cases of high-dose Zolpidem dependence can be treated by conventional benzodiazepines, such as diazepam. Actually, diazepam tends to be avoided because of complicated pharmacological properties and potential risks like respiratory suppression, iatrogenic dependence. But diazepam is still one of candidate medication for managing

withdrawal symptoms of benzodiazepine dependence, and also, nonbenzodiazepine hypnotics in the clinical setting.

Conclusions reaches: We report a rare case of high-dose addiction and successful detoxification by cross-titration with diazepam.

Key words: addiction, dependence, detoxification, diazepam, withdrawal, zolpidem.

PM298

Dissociable effects of cannabinoids on anticipatory and consummatory reward processing

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Running title: 'cannabis and musical reward'

Abstract

Reward processing can be parsed into dissociable components of anticipation (e.g. wanting) and consummation (e.g. liking). Dysfunctional reward anticipation is a transdiagnostic pathology spanning depression, schizophrenia and addiction. The rewarding effects of cannabis may be caused by its primary psychoactive constituent, delta-9-tetrahydrocannabinol (THC). Cannabidiol (CBD) is another cannabis constituent that can inhibit some effects of THC. This study had the following objectives: 1) to investigate the acute effects of cannabis on reward anticipation and consummation, 2) to establish whether these effects are blocked by CBD.

Across 3 sessions, 16 healthy cannabis users inhaled vaporized cannabis preparations containing 8mg THC, 8mg THC + 10mg CBD, and placebo. Reward consummation was indexed using functional Magnetic Resonance Imaging, evidenced by greater signal whilst listening to classical music versus scrambled sound. Regions of interest were selected from a meta-analysis of music-evoked emotion, and all results were False Discovery Rate corrected. Reward anticipation was recorded using the visual analogue scale 'want to listen to music'; post-hoc tests were Bonferroni-corrected.

Analysis of consummatory reward showed that cannabis containing THC only reduced activation in bilateral temporal gyrus (right: $p=0.005$, left: $p=0.008$), right hippocampus ($p=0.025$), right amygdala ($p=0.025$), right insula ($p=0.026$) and right medial orbitofrontal cortex (OFC, $p=0.033$). Cannabis containing THC and CBD did not alter signal in any regions. Across all scans, OFC activation correlated with subjective pleasure ratings ($r(48)=0.463$, $p<0.001$). Both types of cannabis increased reward anticipation to a similar extent (THC: $p=0.001$, THC+CBD: $p=0.006$).

Reward anticipation is primed by cannabis, regardless of its CBD content. By contrast, cannabis reduces neural activation to reward consummation, and this effect is blocked by CBD. These

dissociable effects support a role of the endocannabinoid system in reward dysfunction seen in depression, schizophrenia and addiction.

PM299

Cortical thickness of resting state networks in the brain of male patients with alcohol dependence

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Abstract

Problem drinking is related to brain damage. At the same time, there are evidences that alcohol-induced brain damage can be recovered by abstaining for enough time. Brain functions associated with alcohol consumption can be assessed by the resting state functional connectivity in diverse resting state networks (RSNs). This study aims to ascertain the alcohol effect on the structures forming established RSNs by assessing their thickness.

Twenty-six abstinent male patients with alcohol dependence and the same number of age-matched healthy control were recruited from an inpatient mental hospital and community. All participants underwent a 3T MRI scan. Averaged cortical thickness of areas constituting default mode, cognitive control and other RSNs were determined by using FreeSurfer with Yeo atlas derived from cortical parcellation estimated by intrinsic functional connectivity.

Mean cortical thicknesses of all networks were differed between groups significantly. However, their effect size of group difference is most prominent in ventral attention network (closely relate to cingulo-opercular network of control network, Cohen's $d = 1.00$), and default mode network had the lowest effect size (Cohen's $d = 0.67$).

There are differences in degree and pattern of structural recovery after abstinence across areas forming RSNs. Considering previous observation with same participants that group differences of connectivity was significant only in cingulo-opercular network, we can explain recovery pattern of cognition and emotion related to default mode network and the mechanisms for craving and relapse associate with control network.

Reference

Yeo et al. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, 106(3), 1125–1165.

PM300

Impaired fronto-insular activation during risky decision making in young adults with internet gaming disorder

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Abstract

Objectives: Internet gaming disorder (IGD) is defined as the excessive and compulsive internet gaming behavior despite negative psychosocial consequences. We tested the hypothesis that subjects with internet gaming disorder would be less

sensitive to high-risk situations and exhibit aberrant brain activation related to risk prediction processing.

Methods: 24 young male adults with IGD (IGD group; mean age=24.8±2.8) and 24 age-matched male healthy controls underwent functional MRI while performing a risky decision-making task (Odd-Even-Pass task). Task stimuli consisted of sets of white, solid-colored circles on a black background. The participants were asked to estimate whether the total number of coins was odd or even. The task consisted of 2 conditions: 1) a certain condition, in which the participants could easily estimate the correct answer; and 2) an uncertain condition, in which the coins were overlapped and the borders were blurred, so the participants could only make a guess. The trials with uncertainty were designed to give the feedback "correct" at a fixed rate of 16.6%, regardless of the participants' responses, so the feedback indicated the same prediction error to every participant.

Results: The IGD group, compared with the healthy control group, exhibited attenuated fronto-insular activation in response to high-risk uncertain conditions. Additionally, the healthy control group showed stronger activations within the dorsal attention network, including the dorsal prefrontal cortex and posterior parietal cortex.

Conclusion: We found that fronto-insular activation was impaired under uncertain, high-risk conditions in young adults with internet gaming disorder. This impairment might lead to impaired sensitivity to the negative adverse consequences of excessive internet gaming and a more generalized inability to adopt new behavioral strategies, even when realizing the risk is higher than predicted.

PM301

Neuroanatomical pathways associated with post-stroke affective and apathetic depression

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Abstract

Objectives: Our goal was to localize lesions in post-stroke depression patients using magnetic resonance imaging (MRI), based on the statistical parametric maps (SPM) image analysis technique that can be used to combine image data from multiple participants and correlate these images with other data sets.

Methods: Magnetic resonance imaging acquisitions were obtained from 149 post stroke patients, who were assessed for affective and apathetic symptoms using the Hospital Anxiety and Depression Scale (HADS) and the Apathy Scale (AS) respectively. We created a SPM that displayed an association between lesion location and affective and apathetic symptoms.

Results: Among the patients with higher depressive scores, the lesion overlap centered on the brainstem, left basal ganglia and left frontal cortex. Among the patients with higher apathy scores, the lesion overlap centered on the brainstem and bilateral striatum. The overlap lesion for both affective and apathetic depression centered mainly on the brainstem, however the two types of depression often did not overlap.

Conclusions: Two core symptoms that can occur after stroke, affective and apathetic symptoms, appear to be associated with different monoaminergic neuroanatomical pathways (serotonergic and dopaminergic).