action underlying ibudilast's effects on the human brain remain largely unknown. Therefore, the current study explored ibudilast's efficacy of improving drinking outcomes and attenuating neural reward signals in individuals with AUD.

Methods: Fifty non-treatment-seeking men and women with AUD were randomized to receive ibudilast ($n = 23$; 16M/7F; age = 34.13 ± 9.30) or matched placebo ($n = 27$; 17M/10F; age = 31.41 ± 7.75). Participants completed a two-week daily diary study during which they filled out daily reports of their past day drinking, mood, and craving (ClinicalTrials.gov identifier: NCT03489850). Participants completed an fMRI alcohol cue-reactivity paradigm half-way through the study (Day 8). The number of heavy drinking days (HDD; ≥5 drinks/day for males, ≥4 drinks/day for females) were calculated over the study period. A set of generalized estimating equations with compound symmetric structure were run to account for repeated measures of drinking. A general linear model was used to evaluate the effect of medication on alcohol cue-elicited ventral striatal activation, which was selected a priori as the region of interest.

Results: Ibudilast, relative to placebo, reduced HDD across time (OR = 0.55, $p = 0.04$). Ibudilast also attenuated alcohol cue-elicited activation in the ventral striatum compared to placebo ($F(1,44) = 7.36$, $p = 0.01$). Reward-related activation in the ventral striatum predicted subsequent drinking in the ibudilast group ($F(1,40) = 6.85$, $p = 0.01$), such that individuals who had attenuated ventral striatal activation and took ibudilast had the fewest number of drinks per drinking day in the week following the scan.

Conclusions: This is the first study to evaluate the effects of ibudilast, a neuroimmune modulator, on drinking outcomes in a clinical sample with AUD. Together, these findings extend preclinical and human laboratory studies of the utility for treating AUD and suggest a biobehavioral mechanism through which ibudilast acts, namely, by reducing the rewarding response to alcohol in the brain leading to a reduction in drinking. This is a critical proof-of-mechanism whereby modulation of neuroimmune signaling via ibudilast's inhibition of PDEs reduced ventral striatal excitability to salient alcohol cues.

Keywords: Alcohol and Substance Use Disorders, Ibudilast, Neuroimmune Mechanisms, Alcohol Use Disorder - Treatment

Disclosure: Nothing to disclose.

T43. An Integrated Multimodal Model of Alcohol Use Disorder Generated by Data-Driven Causal Discovery Analysis

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Background: Alcohol use disorder (AUD) has a lifetime prevalence of nearly 30%, with 14.4 million adults in the US currently in need of treatment. Despite treatment, 50-80% of individuals relapse within a year. Mechanisms underlying recovery are still not very well understood, specifically how multifactorial causes may be driving this disease. The recent emergence of publicly available large datasets with broad phenotyping and high-quality neuroimaging data allows for a new approach of testing traditional addiction models, which generally propose that the maintenance of addiction can be explained through a handful of mechanisms. Here, we develop a multivariate model of AUD by leveraging a recently developed data-driven machine learning framework to model causal factors underlying AUD.

Methods: In the current study, we leveraged the deep behavioral and psychiatric phenotyping and high-resolution neuroimaging data from the Human Connectome Project (HCP; $N = 926$; 54% male, mean age = 29 yrs; alcohol abuse or dependence: 22%), using AUD symptom count as our primary outcome variable. We selected all available self-report, diagnostic and behavioral measures assessing cognition, emotion, social function, psychiatric dysfunction and personality (100 in total). We applied exploratory factor analysis (EFA) to parse phenotypic measures into a set of underlying constructs, using Monte Carlo permutation analysis to determine statistically significant factors. We analyzed resting-state functional connectivity by parcellating the whole brain data into 718 parcels (Cole-Antecevic parcellation) and then computing within-network connectivity within 12 resting-state large-scale brain networks. We then employed data-driven causal discovery analysis (CDA) to generate an integrated model relating phenotypic factors, functional network connectivity, and AUD symptoms. The particular CDA method we applied, Greedy Fast Causal Inference (GFCI; Ogarrio et al., 2016), uses conditional dependence relations to discover when unmeasured variables confound the relationships between measured variables, making this method particularly powerful for real-world datasets that cannot capture every possible variable of interest. We conducted a stability analysis for the estimated causal graph by resampling 95% of the sample without replacement with 1000 repetitions (jackknifing). Recovered edge weights from Structural Equation Modeling (SEM) were presented overlaid on the GFCI graph.

Results: EFA extracted a set of 18 data-driven factors that represented the wide phenotypic space measured in the HCP dataset. CDA then produced the 30-factor Integrated Multimodal Model of AUD (IMMAUD), which highlighted a multivariate set of causes of AUD, including multiple cognitive, affective, personality, and psychiatric factors, as well as brain network connectivity patterns (12 networks). We found that brain network connectivity measures and phenotypic factors largely separated into two interconnected separate clusters. Brain connectivity intersected with phenotypic variables in a link between fronto-parietal connectivity and fluid cognition. From this point, causal influences propagated from fluid cognition to more specific cognitive measures, including working memory and delay discounting. Lower cognitive scores in turn caused lack-of-agreeableness and lowered social support, which were causally linked to negative affect, internalizing and lack-of-conscientiousness. All of these causes were fully mediated by the sole direct cause of AUD symptoms, externalizing symptoms. A limitation of the used dataset was that approach behavior was not very well characterized, and its role could hence not be described.

Conclusions: Our data-driven model, IMMAUD, provides evidence for a multivariate set of causal pathways underlying AUD. The 30-factor model proposes a hierarchy with causal influence propagating from brain function to cognition to social to affective/psychiatric function and ultimately AUD symptoms. These results underscore that traditional addiction models need to be expanded to highlight the importance of social factors, amongst others. Importantly, the model demonstrated that different pathways exist, which may involve different individuals to different degrees and may hence be targeted separately in personalized treatment approaches. As a consequence, IMMAUD suggests several potential treatment targets for AUD, including neuromodulation of the fronto-parietal network, cognitive/affective interventions, and comorbidity-based interventions.

Keywords: Alcohol Use Disorder, Causal Modeling, Big Data

Disclosure: Nothing to disclose.

T44. Addiction Symptomatology Desensitizes Arousal Response During Impulsive Decision-Making in Opioid Users

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Background: High craving states and increased anxiety are

proximately tied to the decision to seek and consume drugs. In the context of patients with Opioid Use Disorder (OUD) undergoing treatment and intending to reduce their use, this decision implies a risk of relapse, treatment dropout, or even overdose. How can we identify those states in time to act in a preventive manner? Clinical efforts to reduce and prevent relapses are thwarted at least in part by the subjectivity in standard measures used to assess these prodromal symptoms. One alternative is to turn to more objective psychophysiological measures of these states. In this study, we investigate the relationship between a widely used objective measure of arousal (skin conductance response) and impulsive decision-making at different levels of symptom severity in a group of opioid users receiving medication for OUD (MOUD).

Methods: We worked around the methadone schedule of 38 individuals (2 female) under MOUD treatment who endorsed recent craving symptomatology. Participants completed 2 sessions – one before their daily methadone dose and one after (order randomized). In each session, we assessed craving, withdrawal, and anxiety via self-report using validated questionnaires, then asked participants to complete a delay discounting task while skin conductance response (SCR) was measured.

Results: We found SCR to be significantly greater during trials in which subjects made a less as compared to a more impulsive choice in post-methadone ($n = 17$, $p < 0.05$) but not pre-methadone sessions. In post-methadone sessions only, anxiety modulated SCR by increasing it during more impulsive choices and decreasing it during less impulsive choices ($n = 17$, $p < 0.05$). Craving relationship to SCR was differential depending on choice: intensity and episode length were negatively correlated with SCR during impulsive choices (Spearman rho $= -0.626$ and -0.661 respectively, $p < 0.05$, $n = 15$) but positively correlated with SCR during less impulsive choices (Spearman rho=0.777 and 0.759 respectively, $p < 0.05$, $n = 15$). Overall more impulsive individuals showed lower SCR during less impulsive choices (Spearman rho $= -0.719$, $p < 0.05$, $n = 17$).

Conclusions: OUD symptomatology interacts with the relationship between impulsive choice and arousal, desensitizing an individual's arousal response to less impulsive choices when craving and anxiety are high. This result has potentially interesting implications for designing better strategies to aid in detection of symptomatology exacerbation, especially when this may be conducive to more impulsive decisions to resume drug use. Further elucidation of the physiological relationship between craving, anxiety and decision-making could help understand, predict, and prevent relapse in OUD.

Keywords: Delay Discounting, Skin Conductance Response, Opioid addiction, Anxiety, Craving

Disclosure: Nothing to disclose.

T45. Morphine Evokes a Neuroimmune Response in Healthy Volunteers

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Background: There is tremendous need to investigate novel treatment targets for opioid use disorder (OUD), such as the neuroimmune system. In preclinical studies, opioid administration reliably evokes pro-inflammatory responses in the periphery and brain. These pro-inflammatory responses have been shown to influence appetitive (e.g., craving and opioid-seeking) and dysphoric (e.g., pain and withdrawal symptoms) addiction processes and thus, may contribute to the development of OUD and/or perpetuate continued opioid use among OUD patients. In this paradigm development pilot study, we investigated the neuroimmune effects of acute opioid administration using Positron Emission Tomography (PET) imaging with [11C]PBR28, a radiotracer that binds to the 18kDa translocator protein (TSPO), a marker sensitive to immune stimuli. We hypothesized that opioid administration would increase whole-brain TSPO availability and pain tolerance on the Cold Pressor Task.

Methods: Healthy individuals with prior medical opioid exposure ($N = 4$; 3M; 2 'high-affinity' binders; Age=30 years [range = 26–38]; BMI = 26.5 [range = 24–30]) completed two 120-minute [11C]PBR28 PET scans in one day: before and 2-hours after intramuscular morphine administration (0.07mg/kg). Arterial blood was acquired to measure the metabolite-corrected input function. Volumes of distribution (VT), i.e., TSPO availability, were calculated in 10 regions of interest (ROIs) using multilinear analysis–1 (MA-1; t*=30). Regional [11C]PBR28 VT values were evaluated using a repeated-measures analysis of variance with rs6971 genotype as a fixed factor ('high' vs. 'mixed affinity' TSPO binders). Subjective, behavioral, and physiological effects were assayed before and after morphine.

Results: Morphine increased TSPO availability by 28%-39% across ROIs, $F(1,2) = 9.56$, $p = 0.09$, partial $\eta 2 = 0.83$, 'very large' effect. Morphine increased hand withdrawal latency on the Cold Pressor Task, i.e., pain tolerance, $F(1,2) = 3.98$, $p = 0.18$, partial $\eta 2 = 0.66$, 'very large' effect. Morphine decreased systolic and diastolic blood pressure by 11mmHg and 7mmHg, respectively (ps < 0.09).

Conclusions: Preliminary findings for this ongoing pilot study suggest that a side effect of morphine administration is neuroimmune stimulation. If confirmed, this would be the first study to demonstrate a mechanistic relationship between opioid administration and neuroimmune signaling in people, thus providing initial evidence for a plausible role of the neuroimmune system in OUD. The morphine dose administered (<6mg) is comparable to a standard-of-care post-operative analgesic dose. Epidemiological data indicate that 3-10% of healthy individuals treated with opioids for management of surgical pain become long-term opioid users and thus, are high risk for developing OUD. We hypothesize that opioid-induced neuroimmune signaling influences the propensity for long-term opioid use and OUD. The clinical relevance of our findings will be borne out in future studies which will investigate whether pretreatment with a glial modulator, e.g., ibudilast, attenuates morphine's neuroimmune effects and whether supplementing opioids with glial modulators after surgery reduces long-term opioid use (i.e., 'opioid-sparing' effect) and thus, risk for OUD.

Registered Clinical Trial: NCT03801629

Keywords: Neuroimmune Mechanisms, Opioid Side-Effects, Opioid Use Disorder, TSPO and [11C]PBR-28 PET, Pain Analgesia

Disclosure: Nothing to disclose.

T46. Psilocybin-Assisted Psychotherapy for Alcohol Use Disorder: A Randomized Controlled Trial

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Background: Several lines of evidence suggest that classic psychedelics (5-HT2A receptor agonists or partial agonists) such as psilocybin might facilitate behavior change in individuals with substance use disorders.

Methods: We are conducting a multi-site, double-blind, randomized controlled trial to assess the effects of psilocybin-