astrocyte activation were significantly inhibited by astrocyte-specific deletion of a glutamate transporter, GLT1 (as known as EAAT2, slc1a2) via the expression of GFAP-promoter driven Cre recombinase in the PVT of GLT1 floxed mouse. The changes in eEPSCs were also occluded by the pretreatment of DHK, a GLT1-specific blocker, suggesting that GLT1 is, at least partly, required for astrocyte-induced changes in the neuronal activity in the PVT. In social behavioral evaluation, we found that the astrocyte activation significantly reduced the social recognition in the three-chamber social approach test. Importantly, mice lacking GLT1 selectively in the PVT astrocytes mimicked the astrocyte activation-induced impairment in social behaviors.

Conclusions: Together, our observation indicates that the astrocyte activity in the PVT modulates the adjacent neuronal synaptic events via not only the homeostatic passive activities but the direct modulation of the glutamatergic signaling, at least partly, through the GLT1, leading to shape social behaviors. This implies the importance of astrocytes as another layer to modulate social behaviors and the interaction between astrocytes and neurons via glutamatergic signaling could be a potential therapeutic target for related disorders.

Keywords: Social Behavior, Astrocyte, Glutamate Transporter, Paraventricular Nucleus of the Thalamus

Disclosure: Nothing to disclose.

P415. Cognitive Control Predicts Alleviation of OCD Symptoms by Ketamine

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Background: Obsessive-compulsive disorder (OCD) is a common and impairing illness. First-line pharmacologic treatment with serotonin reuptake inhibitors helps most patients, yet benefit may take weeks to accrue, and many patients don't achieve adequate response. Ketamine and other glutamatergic interventions offer great promise as alternative and more rapidly acting treatments. The growing diversity of treatment options, however, increases the need for data to support goals of precision medicine, matching the right treatment to the right patient.

OCD has been associated with alterations in both cognitive and affective processing, assessed using both neuroimaging and behavioral tests. These alterations include deficits in cognitive control and a valence bias reflected in increased threat responsivity and decreased reward responsivity. In secondary analysis of data from a randomized, active-placebo-controlled trial of intravenous ketamine for treatment of OCD, we explored whether validated behavioral measures of cognitive control and valence processing have utility as predictive biomarkers or as clinically meaningful targets of treatment.

Methods: Data were analyzed from N = 45 unmedicated individuals with DSM-5 obsessive-compulsive disorder who participated in a randomized controlled trial exploring the mechanisms of ketamine as a rapid-acting treatment. Participants were randomized 2:1 to receive a single 40 min intravenous infusion of ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg). Clinical OCD symptoms were assessed using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) at baseline, at post-infusion Day 1, and at post-infusion Day 7. Participants additionally completed a validated, computer-based neurocognitive test battery ('WebNeuro') one day prior to and one day after infusion. Testing included measures of cognitive control (performance on Stroop color-word interference and Go/No-Go tests) and of valence processing (performance on tests of emotion identification and of implicit priming by facial expressions of fear and happiness), quantified as z-scores relative to age-, sex-, and years of education-matched healthy norms. We explored whether baseline performance on cognitive control and valence processing tests moderate symptom alleviation in response to ketamine vs midazolam, and whether pre-post change in test performance is associated with symptom alleviation. MacArthur criteria were used to define potential moderator and mediator variables.

Results: Treatment had a significant effect on OCD symptoms at Day 1 ($\beta = -7.894$, $p = .004$, representing a nearly 8 point mean difference in Y-BOCS change for ketamine vs midazolam) and at Day 7 ($\beta = -6.048$, $p = .005$). In moderation analyses, the interaction between a measure of Stroop interference by response speed and treatment had a significant effect on the change in Y-BOCS at Day 1 ($\beta = -4.0618$, Cohen's $f2 = 0.14$, $p = .04$), but not at Day 7. That is, the effect of treatment at Day 1 was considerably larger for those with faster normalized performance on a color-naming relative to color word-reading task. Performance on the Go/No-Go and valence processing tests did not moderate the treatment effect on outcomes at Day 1 or Day 7. In mediation analyses, treatment did not have a significant effect on pre-post change in cognitive control or valence processing; these measures did not fulfill criteria as potential mediators of Y-BOCS change. Pre-post change in Stroop interference by response speed did, however, correlate with change in Y-BOCS at Day 1 ($r = 0.36$, $p = .03$).

Conclusions: Ketamine robustly reduced symptoms of OCD at Day 1 and Day 7 post-infusion, compared to the active-placebo midazolam. Our data suggest that the short-term effect of ketamine vs midazolam on Y-BOCS may be influenced by baseline inhibitory cognitive control, such that greater control (less Stroop interference for color-naming) predicted greater benefit from ketamine vs midazolam. Our data may accord with published findings suggesting that Stroop task performance moderates the effectiveness of other OCD treatment modalities (e.g., cognitive behavioral therapy vs fluoxetine).

Keywords: Obsessive-Compulsive Disorder, Ketamine, Neurocognitive Assessment, Moderators, RCT

Disclosure: Nothing to disclose.

P416. Efficacy of Ketamine in Unmedicated Adults With Obsessive-Compulsive Disorder: A Randomized Controlled Trial

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Background: Developing novel, robust Obsessive Compulsive Disorder (OCD) treatments is an urgent public health need, given OCD typically starts in childhood, leads to lifelong morbidity, and costs the economy $2.1 billion (direct costs) and $6.2 billion (indirect costs such as lost productivity) annually. OCD is characterized by an inability to inhibit intrusive thoughts (obsessions) and repetitive behaviors (compulsions). Serotonin reuptake inhibitor (SRI) treatment of OCD exhibits a long lag time (2-3 months) before clinical benefit, and this benefit is typically only partial. Identifying effective, fast-acting treatments will help reduce OCD morbidity and its life effects. We previously reported the rapid OCD symptom reduction of ketamine, a glutamate N-methyl-d-aspartate (NMDA) receptor antagonist, versus saline infusions in a proof-of-concept crossover trial (n = 15) in

unmedicated adults with OCD. Building on this initial finding, we evaluated the efficacy of ketamine in a larger group of unmedicated OCD patients with improved control conditions (active placebo control condition).

Methods: This was a randomized controlled trial of a single infusion of ketamine compared to an active placebo condition (midazolam, an anesthetic). With institutional review board approval, unmedicated adult patients (age 18-65) with OCD were randomly assigned under double-blind conditions to receive a single intravenous infusion of ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg) in a 2:1 ratio (total n = 45). Participants met DSM-5 criteria for OCD with at least moderate symptoms (Yale-Brown Obsessive Compulsive Rating Scale score of at least 16). Exclusion criteria included severe depression (17-item Hamilton Depression Rating Scale was less or equal to 18 to enter the study) and comorbid psychiatric or medical conditions that made participation unsafe. The primary outcome was change in OCD severity 1 week after drug administration, as assessed by the Y-BOCS. Duration of effect was explored with weekly Y-BOCS up to 4 weeks post-infusion. We focused on estimating intention to treat effects based on longitudinal mixed effects modeling. For both moderator and mediator investigation, we employed the MacArthur approach embedded in mixed effects modeling.

Results: Regarding the primary outcome, the ketamine group had significantly greater improvement in Y-BOCS score than the midazolam group 1 week after treatment (Cohen's $d = 1.25$, $p < 0.001$). The effects from a single intravenous infusion of ketamine persist up to 3 weeks post-infusion (Cohen's $d = 0.59$, $p = 0.007$), gradually reducing each week and then becoming insignificant by Week 4. We examined age, sex, and race as potential moderators of treatment effects, although none were identified as significant moderators. We also examined change in dissociation as a potential mediator of treatment effect, although it did not turn out to be a significant mediator.

Conclusions: To our knowledge, this is the largest clinical trial to date of ketamine in unmedicated OCD patients. Ketamine demonstrated rapid and durable OCD symptom improvement compared to the active control condition. By using an optimized active placebo design to control for nonspecific anesthetic effects, this study provides new supporting evidence for the specific OCD therapeutic effects of ketamine.

Keywords: Ketamine, OCD, Midazolam

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P417. Investigating the Role of Medial Orbitofrontal Cortex (mOFC) in Deterministic and Probabilistic Negative Reinforcement

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Background: Obsessive compulsive disorder (OCD) is a chronic, severe psychiatric illness that is characterized by obsessions – recurrent intrusive thoughts and images – and compulsions – repetitive behaviors performed to relieve anxiety associated with obsessive thoughts. Negative reinforcement-based theories of OCD suggest that the manifestation and maintenance of compulsions may be driven by this temporary relief from obsession-evoked anxiety. A recent clinical study by our group (Panny et al., under review, Biological Psychiatry) found heightened activity in the medial orbitofrontal cortex (mOFC) when OCD patients removed compulsion-related images in a novel negative reinforcement paradigm. To further dissect the cellular responses contributing to these bulk regional changes in mOFC activity, we measured neural activity via single-photon calcium imaging in wild-type mice during a negative reinforcement task in this exploratory study.

Methods: C57Bl6/J mice (n = 6; 4 male, 2 female) were trained on a novel negative reinforcement task. During the task, a light cue predicted a foot shock, and mice could avoid shocks with 100% probability by pressing a lever within the 20 sec cue period ("avoid response"). If mice did not press the lever during the cue period, a series of shocks commenced. Mice could escape remaining foot shocks by lever pressing during this period ("escape response"). Mice performed 50 trials per day for 7 days. This was followed by 5 days of probabilistic reinforcement of responses, in which lever pressing led to shock avoidance on 50% of trials. Prior to training, mice were injected with virus encoding GCaMP6f (AAV5-CaMKII-GCaMP6f-WPRE-SV40, titer 2.2×10^12) into mOFC and implanted with gradient-index (GRIN) lenses to visualize mOFC activity using miniature microscopes (Inscopix). Single-cell calcium activity was extracted using CNMF-e algorithm, converted to ΔF/F, and time-locked to several timepoints within each trial (i.e. presentation of avoidance cue, lever extension, lever press, shock onset). Calcium transients aligned to behavioral events of interest that exceeded >1 SD from null distribution were considered significant.

Results: Mice quickly learned to avoid foot shocks, showing significantly more avoidance responses (59.3%) than either escape responses (29.3%) or trial failures (11.3%) beginning on the first day of training (avoid vs. escape: $p < .05$; avoid vs. failure: $p < .005$). By day 7 of training, mice avoided 99.8% of potential shocks, performing an avoid response on 97.3% of trials. Calcium imaging on day 1 of training demonstrated that 13.3% of neurons (69/518) were activated at onset of lever pressing to initiate an avoidance response; this effect was maintained over time, with 15.3% of neurons (107/699) activated at onset of avoidance responses on day 7. Ongoing analyses of cells tracked over days will determine whether activity of individual mOFC neurons changes as 1) avoidance behaviors become well-learned and maintained over time and 2) after changing from deterministic to probabilistic negative reinforcement.

Conclusions: In OCD, compulsive behaviors are reinforced by the temporary relief provided from anxiety brought on by intrusive thoughts and images. Preliminary findings from our lab show that patients with OCD display heightened activity in mOFC in response to removal of compulsion-related images, suggesting this may be a key locus of negative reinforcement in OCD. Here, we developed a novel task which leads to rapid acquisition of active avoidance responses in mice and coupled it with single-photon in vivo calcium imaging in mOFC. Preliminary analyses show that a subset of neurons in mOFC are selectively responsive during engagement in an active avoidance behavior. Further analyses will establish how mOFC responses are modulated throughout negative reinforcement training and following changes in task contingencies.

Keywords: Active Avoidance, Negative Reinforcement, Medial Orbitofrontal Cortex, Obsessive-Compulsive Disorder (OCD), In Vivo Calcium Imaging

Disclosure: Nothing to disclose.

P418. Precision Functional Mapping in Obsessive-Compulsive Disorder Using Dense Sampling Scanning

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