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**Background:** Autonomic arousal linked to norepinephrine signaling has been found to contribute to reward facilitation — the relative improvement observed on cognitive test trials that are incentivized with performance-based rewards. This study extended that emerging literature by assessing pupillometry-measured arousal during a Stop Signal Reaction-Time (SSRT) behavioral inhibition task for the first time. We hypothesized incorrect trials would prompt relatively greater cognitive effort-related pupil size due to signaling for enhanced cognitive control.

**Methods:** Thirty-five healthy adolescents performed an SSRT with monetarily-incentivized and non-incentivized trials while an infrared eye-tracker sampled binocular pupil sizes. Linear mixed-models (ML estimation) tested main and interaction effects of Reward (reward vs. non-reward) and trial Accuracy (correct vs. incorrect) on mean pupil size, in separate models for Go and Stop conditions.

**Results:** Stop trials showed the predicted Accuracy main effect (p<0.001). In contrast, a Reward × Accuracy interaction (p<0.009) for Go trials found pupil size not only was greater for correct Go trials, it also was relatively greater specifically for rewarded Go trials. Both Go (p<0.0001) and Stop (p=0.0018) mixed-models found pupil size generally was larger on rewarded trials.

**Conclusions:** The partial support for study predictions suggests phasic increases of cognitive effort-based arousal might depend on the congruence between approach (Go) accuracy versus avoidance (Stop) inaccuracy, perhaps strongest when unsuccessfully-countermanded responses engender heightened personal relevance. The results have implications for neuropsychological theories of cognitive effort. They also set the stage for testing hypotheses about possible dysfunction in norepinephrine-mediated arousal neural systems within various psychiatric disorders that have shown abnormal reward facilitation.

**Supported By:** R01MH119815

**Keywords:** Pupillometry, Adolescents, Stop–Signal Task, Reward

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P405. Selective GSK3α and β Inhibition During Early Postnatal Alter Working Memory-Related Behavior in a Sex-Biased Manner in a Mouse Model of 22q11.2 Deletion Syndrome

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**Background:** Overactivation of the Glycogen Synthase Kinase (GSK3) pathway is implicated in a variety of neurological and psychiatric disorders. Non-selective GSK3 (α and β isofoms) inhibitors have been found to rescue cognitive deficits in a variety of preclinical models, but their non-selective profiles hamper their preclinical research utility.

**Methods:** Recently developed selective inhibitors allow targeted inhibition of each isofom, but they impacts on cognition and disease-relevant cognitive dysfunction are unresolved. Here, we tested their potential to rescue spatial working memory deficits in the Df(16)A+/- mouse model of the schizophrenia-predisposing 22q11.2 deletion syndrome.

**Results:** The selective GSK3β inhibitor BRD3731 administered during postnatal development (P7–P28) rescued acquisition deficits in spatial working memory in male but not female Df(16)A+/- mice (n=121, p=0.01, 3-way ANOVA). GSK3β inhibition also rescued deficits in theta-frequency (4–12 Hz) coherence between ventral hippocampus and medial prefrontal cortex, a neurophysiological correlate of spatial working memory performance, in Df(16)A+/- mice (n=98, p=0.02, 3-way ANOVA). Conversely, selective postnatal GSK3α inhibition by BRD0705 failed to rescue task acquisition deficits, but did reverse deficits in task performance under conditions of increased working memory demand in both male and female Df(16)A+/- mice (n=109, p=0.003, 3-way ANOVA).

**Conclusions:** Ongoing transcriptomic analysis of the medial prefrontal cortex and ventral hippocampus of wildtype and Df(16)A+/- mice at various developmental stages stands to inform the molecular basis of our behavioral and neurophysiological findings. Overall, this work indicates differential roles of GSK3αand β isoforms in the development of the neural circuitry supporting spatial working memory and its disease-relevant dysfunction in mice.

**Supported By:** NARSAD 28622, NINDS intramural research program (ZIA NS003168)

**Keywords:** Spatial Working Memory, 22q11.2 Deletion Syndrome, Schizophrenia Risk, GSK-3, Prefrontal Cortex to Hippocampus Synchrony

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P406. Chronic Adolescent Social Instability Stress Leads to Impaired Recognition Memory and Increased Hippocampal FKBP5 and CRHR2 Expression in Adulthood

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**Background:** Recently published studies indicate that the Covid-19 pandemic has dramatically increased rates of anxiety, depression, and suicide in adolescents and young adults. Human and animal studies strongly indicate that early life stress leads to lasting changes to cognition and psychiatric outcomes, but less is known about how chronic adolescent stress may alter brain function across the lifespan.

**Methods:** The current study examines the effects of chronic social instability stress (SIS) on male and female mice from 4 to 11 weeks of age. SIS mice (n=52) experienced twice weekly cage changes, preventing the formation of stable social hierarchies, while control mice (n=48) remained with their original
cage mates. Mice were subsequently assessed throughout adulthood for changes in behavior associated with anxiety, affect, aggression, motivation, and recognition memory. At 66 weeks of age, levels hippocampal mRNA expression of genes associated with human early life stress were also compared (CRHR1, CRHR2, FKBP5, SLCA4).

Results: Mice exposed to SIS showed decreased novel object recognition (p=0.002) and responded more during the progressive ratio task (p=0.033). At 66 weeks, SIS mice had increased hippocampal FKBP5 (p=0.03) and CRHR2 (p=0.005) expression relative to controls; furthermore, these measures negatively correlated with novel object recognition (FKBP: p=0.007; CRHR2: p=0.04).

Conclusions: Chronic adolescent social instability stress led to persistent memory deficits and increased hedonic seeking in adulthood, possibly due to hippocampal damage resultant from lasting alterations to the stress cascade. Future studies will determine the cellular, molecular and circuit-level changes underlying these effects.

Supported By: Support from an institutional grant from USC department of Psychiatry and Keck School of Medicine

Keywords: Early Life Stress, FKBP5, Memory Deficit

P407. Neuropsychological Profiles and Risk for Psychiatric Diagnoses in Individuals With Nonverbal Learning Disability/Developmental Visual-Spatial Disorder

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Background: We used Louvain community detection (LCD) to characterize neuropsychological and academic profiles of NonVerbal Learning Disability (NVLD) subtypes and risk for psychiatric diagnoses.

Methods: LCD was applied to 180 individuals meeting criteria for NVLD within the Healthy Brain Network (N=1640). Clustering parameters were those used to make a provisional NVLD diagnosis: Individual IQ index scores from the Wechsler Intelligence Scale for Children-5 (Verbal Comprehension Index [VCI], Fluid Reasoning Index [FRI], Visual-Spatial Index [VSI]), the discrepancy between VCI and FRI, or VSI, as well as performance on tests of functional impairment including math (WIAT-III Numerical Operations), motor (Purdue Pegboard), social (CBCL Social Problems), or executive functioning, specifically inhibitory control (IC; NIH Toolbox Flanker) and cognitive flexibility (CF; NIH Toolbox Dimensional Card Sort). Clusters were validated by testing differential associations with academic achievement, risk for psychiatric diagnoses, and level of psychiatric symptoms, Bonferroni adjusted for multiple comparisons.

Results: Profile 1 had differences between VCI and both VSI and FRI, impairment in all four areas of functional outcomes, more symptoms of inattention than profile 1, and more aggression than profiles 2 and 3. Profile 2 had differences between VCI and VSI and significantly higher risk for Anxiety disorder and lower risk for Specific Learning Disorder than other profiles. VSI and FRI were associated with math, social, motor and EF skills in profiles 1, 2, 3, but not 4.

Conclusions: LCD identified four neuropsychological profiles characterized by patterns of deficits in visual-spatial reasoning and differential risk for anxiety or specific learning disorder.

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Keywords: Visual-Spatial Processes, Psychiatric Risk, Academic Impairment

P408. An Exploration of Social Cognition in Pregnancy and Postpartum

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Background: There is little research that examines changes in social cognition with pregnancy and postpartum. This domain of cognition is particularly important as it may be related to maternal caregiving behaviors and the ability to interpret the infant’s mental states and anticipate their needs. The current study aimed to explore social cognitive performance in women during prenatal and postpartum periods.

Methods: Pregnant participants (N=68) (mean age 34.21, SD 5.3) and age matched non-pregnant controls (n=20) (mean age 38.70, SD 12.8) completed two social cognition measures assessing mentalizing, the Movie for the Assessment of Social Cognition (MASC) and the Reading of the Mind in the Eyes (RMET). The pregnant group completed assessments at 36 weeks prenatal (n=54, n=65) and four months postpartum (n=11, n=17). A subset of pregnant participants completed the MASC (n=10) or RMET (n=16) at both time points.

Results: There were no significant differences in MASC or RMET accuracy scores among pregnant, postpartum, and non-pregnant participants. In the subset of participants who completed the RMET and MASC at prenatal and postpartum periods, there was no significant difference on a paired sample t-test in prenatal and postpartum mean accuracy scores for the RMET or the MASC.

Conclusions: We report preliminary evidence of intact social cognitive ability (mentalizing accuracy similar to non-pregnant healthy controls) during pregnancy and postpartum, however an investigation of prenatal and postpartum social cognitive performance should be further explored in a larger sample.