Results: Lenrispodun induced increases in IFG activity during the stop signal task ($n = 24$) at 1.0mg (Cohen's $d = .63$) but not 10.0 mg (Cohen's $d = .07$) versus saline. Lenrispodun did not induce changes in dAI activity during fear extinction ($n = 22$) at the 1.0 mg (Cohen's $d = -0.052$) or 10.0 mg (Cohen's $d = 0.242$) doses. Lenrispodun administration was well-tolerated. Lenrispodun and three metabolites were present in blood samples taken 45 and 210 minutes after administration (drug, time, and drug*time interaction, all p's < 0.001), and post-hoc tests confirmed a dose-dependent response at each timepoint after administration.

Conclusions: A low dose (1.0 mg) of lenrispodun increased BOLD fMRI signals in the IFG during the stop signal task consistent with improved neural inhibitory control. However, lenrispodun did not induce an attenuating effect on BOLD fMRI signals in the dAI during the extinction phase of a fear conditioning task. Collectively, these results support the hypothesis that PDE 1 inhibition affects neural inhibitory control. Future investigations should determine whether lenrispodun improves neural inhibitory control in target populations such as individuals with attention deficit hyperactivity disorder.

Keywords: Pharmacology, Neuropharmacology, pharmaco-BOLD, Cognitive Control, Fear Conditioning and Extinction

Disclosure: Nothing to disclose.

P210. Impulsive Aggression: Serotonergic Neural Pathways and Neural Targets of the Anti-Aggressive Effects of Fluoxetine

Harold Koenigsberg*, Daniel Rosell, Kurt Schulz, M. Mercedes Perez-Rodriguez, Cameryn Cooley, Antonia New, Mark Slifstein, Richard Carson, Anissa Abi-Dargham, Judy Thompson, Erin Hazlett, Nabeel Nabulsi, Yiyun Huang, Margaret McClure, Xiaoyan Xu

Icahn School of Medicine at Mount Sinai, Bronx, New York, United States

Background: Impulsive aggression (IA) is an unplanned intense aggressive reaction to a psychosocial precipitant. Recurrent acts of impulsive aggression are often seen in borderline personality disorder (BPD), intermittent explosive disorder (IED) and posttraumatic stress disorder (PTSD). The serotonergic system has been implicated in IA, but its neural mechanisms have not been well characterized.

Methods: We will report on our findings from a PET study comparing the regional binding of the 5-HTT ligand, [11C]DASB, in a group of 18 subjects with IED, who have current impulsive aggression to 11 healthy controls. Following baseline PET scans, IED subjects received 12 weeks of treatment with fluoxetine.

Results: While there were no significant differences in regional [11C]DASB binding between groups, in the IED group, trait aggression was positively associated with [11C]DASB binding in the anterior cingulate (ACC) ($r = 0.64$, $p = .01$)and ventral striatum (VST) ($r = .68$, $p = .005$). Greater state aggression was associated with greater [11C]DASB binding in the ACC ($r = 0.724$, $p = .002$). Furthermore, greater [11C]DASB binding in the VST predicted a greater decrease in state aggression with fluoxetine treatment ($p = .0007$, uncorrected). .

Conclusions: Binding of the serotonin transporter ligand in the anterior cingulate cortex ACC) is associated with state aggression and binding in the ACC and ventral striatum is associated with trait aggression. Teh anti-aggressive effects of fluoxetine appear to be mediated by serotonergic activity in the ventral striatum.

Keywords: Aggression, Serotonin Transporter, PET Imaging

Disclosure: Nothing to disclose.

P211. Markers of Oxidative Stress, Cell-Free Mitochondrial DNA and F2-Isoprostanes, are Elevated With Ongoing Caregiving Stress, Perceived Stress, and With Depressive Symptoms

Kathryn Ridout*, Daniel Lindqvist, Samuel Ridout, Aric Prather, Elissa Epel

The Permanente Medical Group, Santa Rosa, California, United States

Background: Oxidative stress is increased in psychiatric disorders and psychological stress. Two reliable markers of oxidative stress are cell-free mitochondrial DNA (mtDNA) and F2-isoprostanes. Previous studies of these markers in depression have been limited in sample size and lack longitudinal findings. Further, relations between F2-isoprostanes and psychological or chronic stress is unknown. This study aimed to examine the association of cell-free mtDNA and F2-isoprostanes with stress and depressive symptoms over time.

Methods: One-hundred and eighty-three community- and clinic-recruited women with chronic caregiving stress ($N = 92$) or low-stress controls ($N = 91$) were included in this longitudinal case-control study. High-stress maternal caregivers had at least one child diagnosed with autism spectrum disorder and reported a score of ≥13 on the Perceived Stress Scale (PSS), while low-stress maternal control subjects were characterized as caring for a neurologically typical child and reported a PSS score of ≤19 at baseline (in line with national norms). Exclusion criteria included current psychiatric conditions, major chronic diseases, and regular use of steroid prescription medications. Active major depressive disorder or antidepressant use at baseline was an additional exclusion criterion for control participants only. Participants reported depressive symptoms (Inventory of Depressive Symptomatology), perceived stress (PSS), and provided a fasting morning blood sample at baseline, 9, 18, and 24 months. Cell-free mtDNA and F2-isoprostane levels were measured from plasma. Plasma cell-free mtDNA was determined using quantitative real time polymerase chain reaction; F2-isoprostanes were measured by gas chromatography-mass spectrometry.

Results: The average age was 42 + /-5.1; 76% identified as White, 92.3% as non-Hispanic. In a repeated measure mixed regression model, there was a significant effect of caregiver group on cell-free mtDNA ($F(1,590) = 4.20$, $p = .041$) and F2-isoprostane levels ($F(1,441) = 5.70$, $p = .017$), with caregivers having significantly higher levels of oxidative stress. Perceived stress ($F(1,560) = 5.35$, $p = .021$) and depressive symptoms ($F(1,578) = 8.96$, $p = .003$) were significantly associated with cell-free mtDNA regardless of caregiving group. In subjects with low perceived stress, cell-free mtDNA was significantly higher in subjects that were depressed compared to those without depression ($p = .050$), whereas cell-free mtDNA levels did not stratify by depressive symptoms in subjects with high perceived stress.

Conclusions: These longitudinal data reveal that both stress and depression are associated with durable increases in oxidative stress. Understanding the mechanisms by which depression, stress, and oxidative stress are related may help elucidate new biomarkers and treatment targets for depressive disorders.

Keywords: Circulating Cell-Free Mitochondrial DNA, Prostaglandin, Oxidative Stress, Depression, Perceived Stress

Disclosure: Nothing to disclose.

P212. Neural Substrates Underlying Stress-Induced Changes in Female Infant-Directed Behavior

Brenda Abdelmesih, Robyn Anderson, Anita Autry*

Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York, United States

Background: Decades of research have focused on the neurobiology of maternal behavior, revealing common mechanisms and