**Early Adverse Life Events: Interaction with Glucocorticoid [NR3C1] and Proinflammatory Cytokine [IL-1β] Polymorphisms to Influence Grey Matter Variations in Females with and without Abdominal Pain**

**Arpana Gupta1-3, Lisa A. Kilpatrick1-3, Jennifer Labus1-3, Mariam Bonyadi1, Cody Ashe-McNailey1,3, Nuwanthi Heendeniya1-3, Sylvie Bradesi1-3, Lin Chang1-3, Emeran A. Mayer1-4**

1-3: Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress and Pain and Interception Network (PAIN); UCLA.

1-2: David Geffen School of Medicine, UCLA; 3: Division of Digestive Diseases, UCLA; 4: Ahmanson-Loovelace Brain Mapping Center, UCLA.

**Abstract**

To examine the influence of gene polymorphisms of the glucocorticoid receptor (NR3C1) and proinflammatory cytokines (IL-1β) in influencing cortical thickness (CT) in the sgACC in premenopausal female IBS patients and healthy control (HC) subjects.

**Methods**

**Subjects**
- MRI data was gathered in 210 right handed premenopausal female subjects consisting of 73 IBS and 137 HCs.
- IBS diagnosis was made using the ROME I and II symptom criteria.
- Childhood traumatic and adverse life events were assessed using the Early Traumatic Inventory (ETI-Global Score and Sub-scores: Emotional, Physical, Sexual, General).
- Aims: To evaluate the interactions of early environmental (EALs) and gene polymorphisms (glucocorticoids (NR3C1) and proinflammatory cytokines (IL-1β)) in influencing the cortical thickness (CT) of the subgenual anterior cingulate cortex (sgACC) in premenopausal female IBS patients.
- Hypothesis: Early traumatic and adverse life events may play a role in shaping somatosensory cortex have also been reported in healthy subjects, where they are positively correlated with pain sensitivity, suggesting a possible role of genetic or epigenetic factors in determining such changes.

**Results**

- No significant main effects for EALs were demonstrated with greater EALs for IBS compared to HCs. Subjects as a group had significant reductions in cortical thickness of the sgACC, regardless of ETI.
- The prevalence of ETI total score (cut-off score ≥ 9) was significantly greater in IBS (22%) compared to HCs (12%) (F (1)=4.900, p<0.049).
- CT of the left sgACC was lower in IBS compared to HCs (F (1)=4.753, p=0.030).
- Reduction in CT of the left sgACC was associated with higher ETI on the emotional subscale (r=-.150, p=.025).
- Individuals homozygous for the most common NR3C1 haplotype have increased CT in the left sgACC compared to individuals with lesser common NR3C1 haplotypes.

**Legend:**
- LC (left): homozygous/hetereozygous with lesser common NR3C1 haplotypes (non-CAC/G)
- MC (left): homozygous with most common NR3C1 haplotype (CAC/G)

**Summary and Conclusions**

- Early adverse life events are associated with reduced cortical thickness in the sgACC, a key region in emotional regulation circuits in both IBS and HCs.
- Interactions between GC NR3C1 and IL-1β are associated with decreased cortical thickness of the sgACC.
- GC receptor binding regulates the ability of NF-kB to bind to DNA and enhance cytokine gene transcription resulting in a pro-inflammatory state.
- Our findings are consistent with the concept that interactions between increased GC signaling (related to epigenetic modification of the HPA axis) and neuroinflammation play a role in grey matter reduction in the sgACC.

**Supported by NIH grants:** P30 DK041301, R01 DK048351, P50DK64539, K01 DK085133. UCLA Ahmanson-Loovelace Brain Mapping Center (Pilot Scans). UCLA Brain Research Institute (Support Funds)