# Sex-specific Neural Responses to Acute Psychosocial Stress in Depression

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## Background

Major depressive disorder (MDD) is a stress-related mental disorder characterized by high morbidity, high recurrence and high suicide rate. Increased stress sensitivity has been implicated in depression. Preclinical studies highlight possible sex-specific effects in neural stress responses in limbic/striatal-frontal regions [1]. In light of this evidence, we speculated stress response abnormalities in MDD might be further modulated by sex.

Notably, a recent study in healthy controls indicated that timing of stress exposure affects neural stress responses of limbic structures including the amygdala, hippocampus and medial prefrontal cortex [2]. These findings suggest that it might be important to take stress exposure time into account when conducting stress research.

In the current study, our goal was to investigate potential interaction effects among stress exposure time, sex and diagnosis in limbic/striatal-frontal regions during psychosocial stress.

## Methods and Materials

The Montreal Imaging Stress Task (MIST; three runs, each run lasting 7min) [3] was administered to 124 patients with first-episode MDD (48 males/76 females, mean age ± SD = 25.32 ± 6.96) and 243 heathy controls (HCs, 106 males/137 females, mean age ± SD = 20.98 ± 3.52) in conjunction with fMRI scanning. Subjective stress and cortisol levels were collected throughout the task. All fMRI data were preprocessed using the fMRIPrep pipeline version 1.5.8.

For individual-level analysis, a general linear model including control, stress and rest conditions was conducted for each participant using SPM12. Amygdala, hippocampus, medial orbitofrontal cortex, nucleus accumbens and dorsolateral prefrontal cortex (DLPFC) were selected as a priori regions of interest. Contrast values of stress condition relative to control condition over three runs were extracted for each person.

For group-level analysis, a repeated measures ANCOVA with *Hemisphere* (left, right) and *Time* (run 1, run 2, run 3) as within-subject factors, *Sex* and *Diagnosis* (HC, MDD) as between-subject factors, and age as covariate was run on contrast values (stress vs. control) extracted from five regions of interest.

## Results

### ❖ *Sex * Diagnosis* interaction

A significant *Diagnosis* × *Sex* interaction emerged for the amygdala, hippocampus and nucleus accumbens (amygdala, F(1,362) = 5.76, $p$ = 0.017; hippocampus, F(1,362) = 4.73, $p$ = 0.030; nucleus accumbens, F(1,362) = 4.755, $p$ = 0.030).

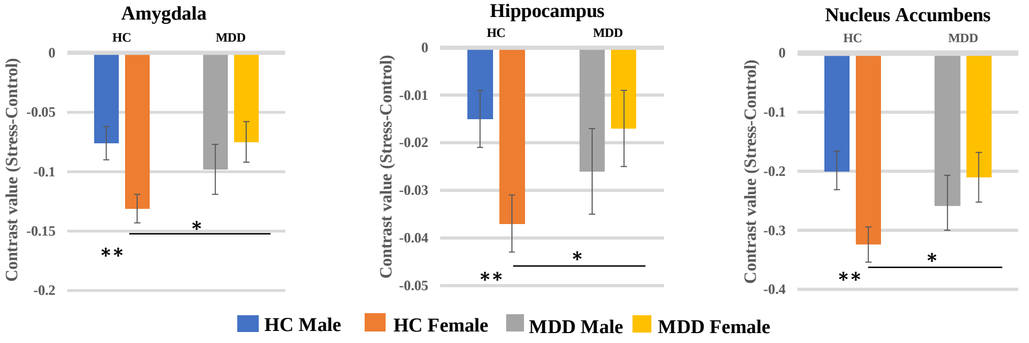


**Figure 1 *Sex * Diagnosis* interaction in the amygdala, hippocampus and nucleus accumbens**

### ❖ *Sex * Diagnosis * Time* interaction

A significant *Sex * Diagnosis * Time* interaction emerged for the amygdala, medial orbitofrontal cortex and nucleus accumbens (amygdala, F(1,362) = 11.249, $p$ = 0.001; medial orbitofrontal cortex, F(1,362) = 6.786, $p$ = 0.010; nucleus accumbens, F(1,362) = 4.776, $p$ = 0.009). Further analyses showed that *Time * Diagnosis* interaction only emerged in females.

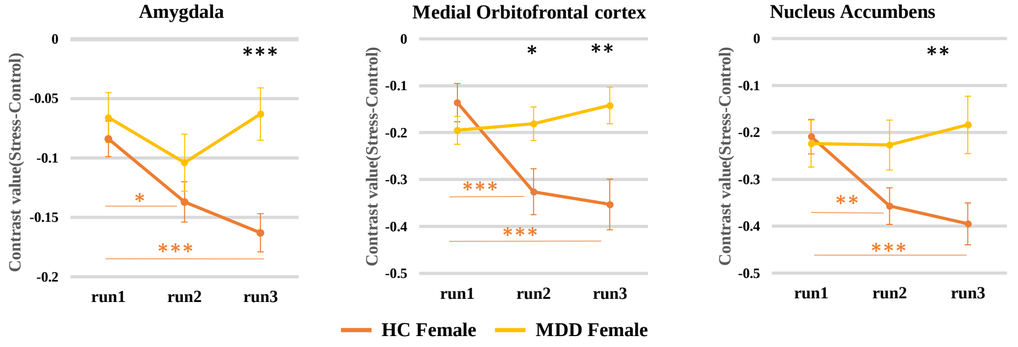


**Figure 2 *Time * Diagnosis* interaction in the amygdala, medial orbitofrontal cortex and nucleus accumbens in females**

### ❖ Main effect of *Sex*

A significant main effect of *Sex* was observed in the dorsolateral prefrontal cortex (F(1,362) = 8.434, $p$ = 0.004).

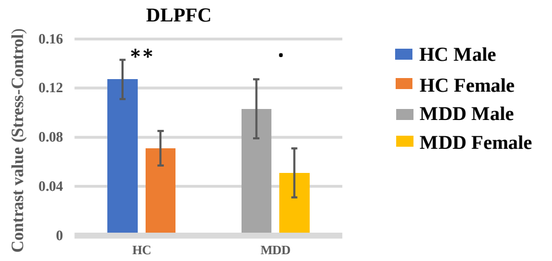


**Figure 3 Sex differences in dorsolateral prefrontal cortex**

## Conclusions

- Observed sex differences in HCs may reveal sex-specific stress coping strategies and highlight the importance of considering sex differences in stress research.
- Case-control differences in neural stress responses observed in females may provide evidence for sex differences in the etiology and pathophysiology of depression.
- The failure to deactivate limbic regions in females with depression may implicate the dysfunction of adaptive stress responses over stress exposure in female depressed patients.
- The observed changes in activation over the course of the stressor emphasize the importance of stress timing in neuroimaging research.

## References

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