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## A Molecular Signature of Depression in the Amygdala

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**OBJECTIVE:** Major depressive disorder is a heterogeneous illness with a mostly uncharacterized pathology. Recent gene array attempts to identify the molecular underpinnings of the illness in human postmortem subjects have not yielded a consensus. The authors hypothesized that controlling several sources of clinical and technical variability and supporting their analysis with array results from a parallel study in the unpredictable chronic mild stress (UCMS) rodent model of depression would facilitate identification of the molecular pathology of major depression. **METHOD:** Large-scale gene expression was monitored in postmortem tissue from the anterior cingulate cortex and amygdala in paired male subjects with familial major depression and matched control subjects without major depression (N=14–16 pairs). Area dissections and analytical approaches were optimized. Results from the major depression group were compared with those from the UCMS study and confirmed by quantitative

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polymerase chain reaction and Western blot. Gene coexpression network analysis was performed on transcripts with conserved major depression-UCMS effects. **RESULTS:** Significant and bidirectional predictions of altered gene expression were identified in amygdala between major depression and the UCMS model of depression. These effects were detected at the group level and also identified a subgroup of depressed subjects with a more homogeneous molecular pathology. This phylogenetically conserved "molecular signature" of major depression was reversed by antidepressants in mice, identified two distinct oligodendrocyte and neuronal phenotypes, and participated in highly cohesive and interactive gene coexpression networks. **CONCLUSIONS:** These studies demonstrate that the biological liability to major depression is reflected in a persistent molecular pathology that affects the amygdala, and support the hypothesis of maladaptive changes in this brain region as a putative primary pathology in major depression.

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