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A New, Blue Gene Highlights Glutamate and Hippocampus in Depression

Heike Tost[1] and Andreas Meyer-Lindenberg[1,*]
[1]Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, University of Heidelberg, Medical Faculty Mannheim, Mannheim, Germany
*Correspondence: a.meyer-lindenberg@zi-mannheim.de
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Depression is a common and debilitating psychiatric syndrome with a complex risk architecture marked by interacting genetic and environmental factors. In this issue of *Neuron*, the study by Kohli et al. (2011) reports a novel genome-wide supported risk variant for depression that affects hippocampal gene expression, anatomy, and biochemistry.

Major depressive disorder (MDD) is a common illness with a lifetime prevalence of 17% in the general population and a leading cause of disability worldwide (McKenna et al., 2005). Enormous direct and indirect costs, the severe burden on those afflicted and their families, and strongly increased mortality from suicide and complicating somatic illnesses underscore the urgent need for better diagnosis and treatment. Since depression was recognized as a complex brain disorder in the 1950s, early research often focused on neurochemical aspects of the condition such as monoaminergic neurotransmission. This strategy was suggested by the mechanisms of action of antidepressant drugs discovered serendipitously during that time (Ketter et al., 1996). In recent years, the availability of novel research technologies has enabled a broader view of MDD that integrates additional neurobiological dimensions, in particular those derived from molecular genetics and neuroimaging. In line with this conceptual shift, depression is now conceptualized as a biologically heterogeneous behavioral endpoint of the adverse interaction of susceptibility genes and environmental factors. This risk constellation, in turn, triggers a complex cascade of intermediate biological changes in gene expression, cellular physiology, and neurochemistry that impacts on multiple interconnected neural networks (Meyer-Lindenberg and Weinberger, 2006).

On the systems level, converging neuroimaging evidence points to a prominent role of the cortical-limbic circuits in the pathophysiology of the disease. Specifically, milestone work by the Mayberg group has identified a key neural node for depression in the subgenual anterior cingulate cortex (ACC), which regulates downstream limbic sites such as hippocampus and amygdala. This research has been successfully translated into new interventional strategies, notably deep-brain stimulation near the subgenual ACC of patients with a poor response to conventional pharmacotherapy (Mayberg, 2009). Given the heritable component of the disorder, the question has been asked whether candidate risk gene variants modulate the function of these cortical-limbic networks (Munafò et al., 2008). Often, the answer has been yes: for example, abnormalities in the interregional coupling of ACC and amygdala have been found in short-allele carriers of the 5′ promoter polymorphism of the serotonin transporter gene (Pezawas et al., 2005). Properties of this neural circuit also predicted trait anxiety, a temperamental feature associated with depression, indicating that this genetic variant affects a systems-level mechanism linked to the disease. Importantly, the cortical-limbic circuitry is not only modulated by genetic but also environmental risk factors: chronic stress impacts on the amygdala, hippocampus, medial prefrontal cortex, and their regulatory interactions, which are important for neural plasticity functions such as neural extinction, a crucial coping mechanism for environmental adversity (Pezawas et al., 2005).

Candidate gene studies, however, have been criticized because the evidence for association with the illness phenotype is ambiguous. This objection can be partly addressed through genome-wide association (GWA) studies, which provide hypothesis-free support for susceptibility variants that survive the severe statistical correction procedures necessary with this approach. Genome-wide significant variants associated with other mood disorders have in fact been found to impact limbic and medial prefrontal regulatory regions (Wessa et al., 2010). In the optimal case, a genome-wide study will identify a truly novel genome-wide supported risk variant for psychiatric illness, demonstrate its functional impact in key neural systems of the disease, aim to address the impact of environmental factors, and provide clues about future treatment targets.

Many of these hopes are realized in the work by Kohli at al. (2011) in this issue of *Neuron*. Following a GWA strategy in a Caucasian sample of 353 index cases and 366 healthy controls, the authors identify a new genome-wide supported risk variant (rs1545843) for MDD on chromosome 12q21.31. Through replication in a meta-analysis across six independent samples, confidence in the robustness of the reported disease association is considerable. This finding is all the more important as prior GWA studies failed to identify susceptibility variants of MDD on a genome-wide supported level of significance (Lewis et al., 2010; Shi et al., 2011).

As is often the case, the identified polymorphism in the Kohli study maps to a chromosomal "desert area" outside any annotated gene, which complicates the process of finding a biologically meaningful interpretation of the finding. This highlights the crucial relevance of implementing multiple, interrelated intermediate

phenotype studies to help assign a function to the initial genetic result. Based on the relative proximity, the authors hypothesized a regulatory effect of the variant on the expression of a gene of the solute carrier 6 family (*SLC6A15*), a sodium-dependent high-affinity transporter for large amino acids in the central nervous system (Bröer et al., 2006). In line with their expectations, the authors demonstrate a significant decrease in expression of the full-length SLC6A15 mRNA isoform in rs1545843 risk allele carriers by using a valuable resource, human premortem hippocampal tissue.

The access to this material is especially useful because prior evidence relates stress-induced impairments in hippocampal neuroplasticity to the expression of cognitive and affective deficits in MDD. Notably, these processes have been convincingly linked to alterations in glutamate neurotransmission, which is critical for the neuroplasticity and anatomy of the hippocampus (Fuchs et al., 2004). Interestingly, proline, a precursor for glutamate synthesis, is the substrate with the highest affinity for the SLC6A15 transporter. Thus, these findings may indicate a potential risk mechanism linking *SLC6A15* genotype and environmental stressors to limbic dysregulation in glutamate neurotransmission and ultimately to psychopathology.

To probe the theory of a modulation of *SLC6A15* function by environmental factors such as chronic stress, the authors expand their analysis to the examination of gene expression in the hippocampus of an established mouse model of stress vulnerability and resilience. In line with their hypothesis, Kohli et al. (2011) demonstrate a significant and specific reduction of SLC6A15 mRNA expression in stress-susceptible mice.

Finally, by adding yet two other intermediate phenotype levels, Kohli et al. (2011) extend their scope from genetic association and gene expression to in vivo biomarkers of the human brain and examine the impact of the identified susceptibility variant on hippocampus anatomy and neurochemistry. By using automated brain morphometry, the authors provide evidence for significant genotype-by-diagnosis interaction effects of rs1545843 on hippocampus volume: a disproportionally pronounced gray matter decrease in the bilateral cornus ammonis was seen in MDD patients carrying the risk allele (A/A). This finding is supported by evidence from a proton magnetic resonance spectroscopy study, where the authors demonstrate lower levels of the molecules N-acetyl-aspartate and glutamate and/or glutamine in the hippocampus of healthy risk-allele carriers. These molecules are thought to be markers of neuronal viability and glutamate signaling. It is interesting to speculate that these measures of glutamate metabolism, altered already in healthy controls, may index an effect close to the action of the risk gene identified in the present study, whereas hippocampal volume deficits, visible only in patients, could require additional genetic or environmental risk factors that must, by definition, have been more numerous in the participants with MDD.

Overall, the work by the consortium reported in Kohli at al. (2011) provides a remarkable body of neuroscience evidence linking rs1545843, a novel genome-wide supported risk variant, to the pathophysiology of MDD. In doing so, the authors cover several interconnected intermediate phenotype levels that provide, in their entirety, new insights into the pathophysiology of depression. Notably, this genetic approach ended up defining a system susceptible to environmental risk factors such as chronic stress, which re-emphasizes the crucial relevance of gene-environmental interactions to the pathophysiology of depression. Given this premise, future studies should further extend this research, for example from testing regionally driven hypotheses to the examination of entire functional networks, such as investigation of dynamic aspects of neural circuits involving the hippocampus. The effects of gene-environment interactions on cortical-limbic processing circuits to which glutamate is a critical contributor should also be examined. Because the work by Kohli et al. (2011) points to glutamate dysfunction as likely mediator of these complex susceptibility effects, these functional biomarkers may aid both the development and neuroimaging-guided evaluation of innovative new pharmacological approaches, which modulate, directly or indirectly, the adverse downstream effects of glutamate dysfunction in mood regulatory circuits.

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