Editorial

The adaptive brain in mental health: overcoming inherited risk factors

Paul R. Albert, PhD

A primary function of the brain is to drive adaptation of the organism to its environment: learning, memory, attachment, fear, aggression, etc., are all manifestations of how the brain directs adaptation to the environment. One touch of a flame in youth is sufficient to engrain a learned behaviour that lasts a lifetime despite the memory of the specific event having long dissipated. To mediate these behaviours, the brain itself must adapt its transcriptional, structural and neurotransmission functions. This type of imprinted memory has been modelled in young *Caenorhabditis elegans*, where aversive memory is retained throughout the lifetime, while it is forgotten when adults are exposed.[1] This persistent memory retention requires recruitment of new neurons that alone do not mediate memory retrieval, but that must be activated to permit memory retrieval via other neuronal circuits. Similarly, shocking mice in a given context generates a fear memory by recruiting a sparse subset of hippocampal neurons that can be reactivated to recruit the memory of the context. When these neurons are optogenetically inactivated, the fear memory is extinguished; when activated in a different context, this elicits an inappropriate fear response.[2,3] Conversely, activating hippocampal cells that respond to a positive memory can reverse stress-induced depression-like behaviours.[4] Thus, one mechanism of brain adaptation involves cellular adaptation, with recruitment of new sets of neurons.

Despite its potential for adaptation, the greatest risk factor for mental illness remains family history,[5] implicating genes, environment or both, and suggesting a limited capacity of the brain to adapt to these early and lifelong risk factors. The hypothesis that genetic makeup modifies the trajectory of adaptive behaviours underlies current efforts to identify specific genetic changes associated with mental illness. For example, genes associated with schizophrenia, such as *NRG1*, *DISC1*, or *DTNBP1*, undergo positive selection, suggesting that these genes drive a behavioural phenotype that may confer an evo-lutionary advantage in certain environments.[6] The question is whether potentially harmful inherited traits provoke homeostatic compensatory responses and whether these responses can be augmented through early interventions.

Brain adaptation to inherited genetic and nongenetic risk in mice

Studies in mouse models indicate that the brain can adapt to major genetic alterations, such as gene deletions or copy number variations, resulting in "normal" behavioural responses. Focusing on the serotonin (5-HT) system as an example, gene deletion of tryptophan hydroxylase2 (TPH2), the critical enzyme for synthesis of 5-HT in the brain, results in increased aggression and mildly reduced anxiety.[7] Despite a greater than 90% loss of brain 5-HT levels, the TPH2$^{-/-}$ mice show normal development and firing properties of 5-HT neurons, but show altered 5-HT innervation,[8] have compensatory upregulation of postsynaptic 5-HT1A and 5-HT1B receptors[9,10] and reduced 5-HT1A autoreceptor binding,[11] all of which would amplify the 5-HT system. A similar phenotype is observed in mice with a knock-in of human TPH2 (R439H) mutant resulting in 60%–80% loss of 5-HT, with reduced 5-HT1A autoreceptor function with no change in receptor levels.[12] Mouse genetic models with progressive reduction in TPH2 activity resulted in no change in brain 5-HT levels or behaviour due to compensation via reductions in 5-HT metabolism and 5-HT1A autoreceptor function.[13] These studies indicate that molecular adaptation of genes in the 5-HT system compensates for genetic impairments to moderate the behavioural phenotype. This molecular adaptation may involve compensatory gene expression changes that are selected for and engrained by fitness to the environment — in the case of these animal models a low-stress, noncompetitive environment.

In addition to genetic transmission of traits, nongenetic mechanisms are being uncovered that highlight the complexity of mental illness. For example, transgenerational transmission of 5-HT1A receptor genotype (*HTR1A*) in prenatal mice has been shown to strongly influence the adult anxiety phenotype.[14] Embryonic implantation of wild-type *HTR1A* embryos in *HTR1A*^{−/−} mothers transmitted the anxiety phenotype to the first- and second-, but not the third-generation offspring,[15] suggesting transgenerational adaptation of the behavioural phenotype. This nongenetic maternal transmission of anxiety to wild-type mice appears to involve altered immune function in the offspring, resulting in reduced ventral hippocampal function, associated with altered DNA methylation and expression of lipid and synaptic signalling genes.[15,16] In humans, the C(-1019)G *HTR1A* promoter polymorphism associated with depression and suicide prevents regulation by *Deaf1*, altering brain-wide 5-HT1A receptor expression.[17,18] In *Deaf1* knockout mice, despite similar alterations in 5-HT1A expression, adaptations in the signalling of 5-HT1A receptors across generations led to the development of a mild behavioural phenotype.[19] Thus, transgenerational molecular adaptation involving changes in gene expression appears to reduce the impact of genetic and nongenetic changes in the *HTR1A* gene with succeeding generations. By contrast, a mouse model of unpredictable maternal stress and separation from offspring leads to transgenerational transmission across 3 generations of a behavioural phenotype, including impaired social interaction and cognition and increased stress resilience, with persistent changes in pre- and postsynaptic 5-HT1A receptor activity and circuitry.[20,21] Thus, maternal stress and separation appear to reprogram molecular adaptation to a different affective state that persists for generations.

Enhancing adaptation to inherited risk for depression in humans

Inter- and transgenerational transmission of depression in humans has been well documented. Children of depressed mothers have higher rates of depression, and children with both depressed mothers and grandmothers had the highest rates compared with children with nondepressed mothers.[5] Successful treatment of mothers' depression reduces depression in their children, while relapse worsens depression.[22,23] Interestingly, a 5-HT risk allele for depression (5-HTTLPR s-allele) was 4-fold over-represented in children of mothers with depression, suggesting that genetic risk factors increase susceptibility to maternally transmitted depression.[24] Similarly, healthy young men with multigenerational history of depression were more susceptible to reducing 5-HT using acute tryptophan depletion (ATD) than those without this family history.[25] Patients in remission from depression remain vulnerable to ATD, particularly those treated with 5-HT-directed antidepressants.[26] Thus the ability of the human brain to adapt to inherited risk is incomplete, and the risk of depression persists even after recovery.

How can beneficial brain adaptation to stabilize behaviour be enhanced? One strategy uses pharmacological or other treatments of depression in the mothers, which can enhance the interaction with the child and improve the child's behavioural symptoms.[27,28] Early treatment of children whose symptoms do not improve despite the mother's remission is another potential strategy.[27] However, pharmacological approaches to early life treatment in mothers or children may elicit long-term adverse effects. In animal studies, early postnatal (p4 to p21, equivalent to third trimester [7–9 mo of pregnancy] to 2 yr postnatal in humans[29]) treatment with selective serotonin reuptake inhibitors (SSRIs) results in a strong and persistent anxiety- and depression-like phenotype,[30] and SSRI treatment of children during an analogous developmental window could be detrimental. In animal studies, the effects of treatment of mothers during gestation may also result in anxiety or depression in the offspring[31] or may lack efficacy.[32] Treatment of breast-feeding women during the early postpartum period may result in 20% antidepressant transfer through the milk, but is considered a relatively safe option.[33,34] However, there is some evidence of behavioural or psychomotor impairment in human infants following prenatal exposure to SSRIs, but further study is needed.[35] Exposure of children to maternal depression from age 2–5 years appears to be a critical period for transmission of behavioural disturbances,[36] hence this period may be the most important and perhaps safer to target for treatment. It remains unclear whether antidepressant treatment at these early developmental stages results in cellular, molecular or both forms of brain adaptation.

An attractive alternative to pharmacological treatment of children is nonpharmacological treatment to enhance the child's developmental environment. The finding that children of depressed mothers are at high risk for depression, and that this risk is diminished with successful treatment of the mother suggests that, while genetic transmission of risk may play a role, a key determinant of the child's mental health is a nurturing maternal environment. Thus, a major approach to enhancing brain adaptation to genetic risk would be to effectively treat the mother as early as possible (with antidepressants and/or psychotherapy) and to enhance the mother–child relationship during the critical developmental period between ages 2–5 years. The latter nonpharmacological approach could include family support and education to ensure that the child receives quality parenting while the mother is depressed, careful monitoring of the child for signs of anxiety or depression, and psychotherapy should such signs emerge — all of which may enhance brain adaptation.

Conclusion

There is evidence for molecular brain adaptations to inherited vulnerability to anxiety and depression that can sometimes occur over generations. These processes can be accelerated by interventions that improve the environment, or that directly target brain plasticity. Future studies of the mechanisms underlying early intervention strategies to enhance brain adaptation may provide new approaches to treat vulnerable populations.

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