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Serotonin transporter and depression: from the emotional to the social brain

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PERSONALITY TRAITS OF EMOTIONALITY-BASIS FOR THE HERITABILITY OF DEPRESSION?

Considerable evidence implicates personality traits of the anxiety-related cluster (Neuroticism) comprising fearfulness, negative emotionality, and stress reactivity interacting with specific environmental factors in the neurobiological mechanisms leading to an increased risk for depression, an etiologically heterogeneous group of brain disorders that are characterized by a wide range of symptoms that reflect alterations in cognitive, psychomotor, and emotional processes[9,13]. Definition of the clinical phenotype is only vaguely rooted in neurobiology, boundaries of diagnostic subtypes are ambiguous, and animal models of behavioral dispair have considerable limitations. Although research on the neurobiology of depression is still in its infancy, several milestones have already been reached: *a)* variation in gene expression was confirmed to play a predominant role in individual differences in complex traits including personality and behavior; *b)* gene x environment interaction was established in nonhuman primate and rodent models as well as in humans; *c)* gene-phenotype correlation was substantiated by functional neuroimaging, and *d)* the notion that both genes and environmental factor impact on brain development and thus set the stage for the susceptibility to depression is increasingly appreciated. Given the etiological and psychobiological complexity of depression, it is not surprising that the identification of vulnerability genes and elucidation of their interaction with environmental stressors is extremely difficult and continues to be among the last challenges of genomics, epigenetics, behavioral neurosciences, and psychiatry.

Investigation of subtle alterations in the expression of genes of the serotonergic pathway, such as the serotonin (5-HT) transporter (5-HTT, SLC6A4), of correlations between 5-HTT genotype, brain activity and cognition, as well as of environmental variables interacting with 5-HTT variants currently strengthen research on the genetics of depression. A variation in the gene encoding the 5-HTT, the master controller in the fine-tuning of 5-HT signaling, recurring independently during anthropoid and hominoid evolution, is not only associated with anxiety-related personality traits but also with disorders of emotion regulation, yet the molecular and neural mechanisms underlying the interplay of genes and environmental adversity constituting disease risk are still poorly understood[1,2,4,13]. Here, innate variability of brain function is discussed from an interdisciplinary viewpoint blending cognitive, social, and psychiatric neuroscience on top of behavioral genetics and evolutionary psychology. Neural modularity of social cognitive processes and emotion regulation is also taken into consideration. Following an appraisal of brain imaging correlates of genomic variation and epigenetic programming as strategies for disease risk assessment, future challenges for biosocial sciences are dicussed in perspective of the evolving genetic architecture of emotional behavior and social interaction in nonhuman primates and humans.

In the decade ensuing the first report linking 5-HTT variation to emotionality, numerous clinical cohorts have been studied for association with disorders of emotion regulation, including depression. Although modest effect sizes typical of non-Mendelian traits, polygenic patterns of inheritance, epistatic and epigenetic interactions, and heterogeneity between studies considerably confounded attempts to reach agreement regarding the role of 5-HTT in the pathophysiology of these conditions, the 5-HTT has nevertheless become a model par excellence in cognitive, biosocial, and psychiatric neurosciences. Recent studies suggest that 5-HTT variation interacts with deleterious early rearing experience in rhesus macaques to influence attentional and emotional resources, sensitivity to ethanol, and stress response. The demonstration that early life stress and resulting mechanisms of gene × environmental interaction uniquely reinforce or even uncover links between 5-HTT variation, behavior, and psychopathology in both humans and nonhuman primates is particularly outstanding and seem to

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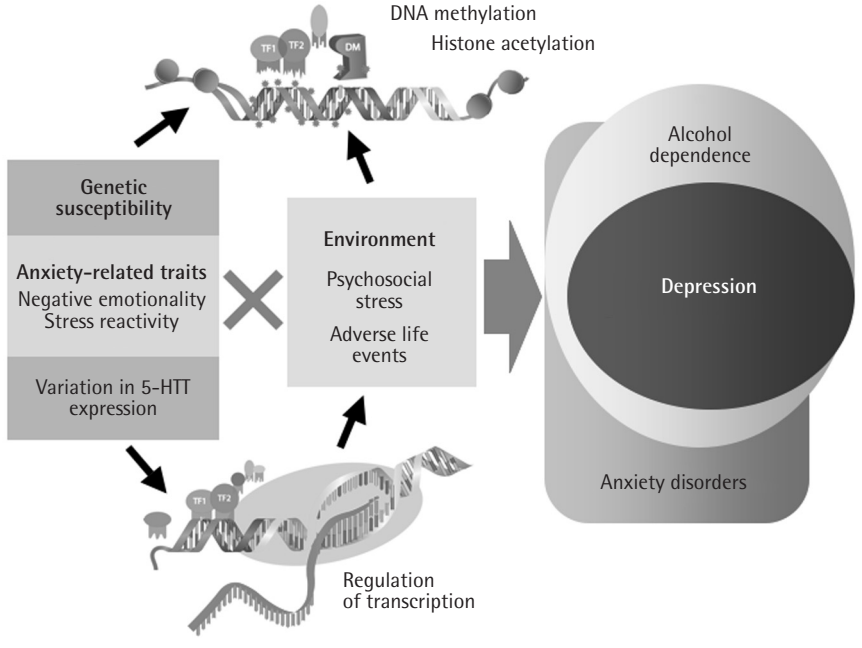

Figura 1 *Vulnerability to depression and molecular mechanisms of epigenetics: neither genes nor environment act alone.*

herald a new era of behavioral genetics. Moreover, identification of 5-HTT as a susceptibility gene for depression is a first step en route for an explanation of the molecular dimension of personality and behavior at risk, outlines strategies to identify physiologic pathways and mechanisms that lead to other disorders of cognitive function and emotion regulation, provides tools to dissect the interactive effects of genes and environment in the development of affective spectrum disorders, and holds the potential to predict response to antidepressant therapy.

IMAGING OF EMOTIONALITY: A RISK ASSESSMENT STRATEGY FOR DEPRESSION?

Early small steps of behavioral genetics are contrasted by giant leaps in a postgenomic era still in its infancy. The application of paradigms novel to neurogenetic approaches including neurophysiology, neuropsychology, and functional neuroimaging as well as inclusion of a more extensive phenotypic spectrum (higher cognitive functions, communication skills, social competence, etc.) have strengthened the connection between 5-HTT, social cognition and emotionality, and continue to enable a more profound understanding of how common genetic variation modulates human behavior[5-7,10,11]. Finally, studies in genetically modified mice have begun to underscore the central role of 5-HT and its fine-tuning by 5-HTT function in embryonic patterning events, brain development, and synaptic plasticity, particularly in neurocircuitries related to social cognitive and emotional processes. Potential relevance of 5-HTT variation in social cognition, the construct comprising processes employed to conform with essential norms and procedures of the social world, is currently transcending the boundaries of behavioral genetics to embrace biosocial science.

SEROTONIN TRANSPORTER DEFICIENT MOUSE: A MODEL FOR MOLECULAR AND NEURAL MECHANISMS OF EPIGENETICS?

As analyses of the genomes of humans, nonhuman primates, and other species has contributed fundamentally to understanding how humans have evolved, the next level of complexity concerns the nature of genetic variation among humans and its influence on interindividual differences as well as the relative impact of genetic and environmental determinants on social competence and behavior. The 5-HTT knockout mouse provides a model to study the impact of genetic mechanisms on development and plasticity of the brain including regionalization of the cortex and its connectivity to subcortical structures[3,12,14,15]. Despite growing evidence for a critical role of the 5-HTT in the integration of synaptic connections in the raphe-amygdala-medial prefrontal cortex circuit during critical periods of development and adult life, knowledge of the machinery involved in these fine-tuning processes remain fragmentary. Although the molecular mechanisms by which early life stress increases disease risk in adulthood are not known, they are presumed to include epigenetic programming of gene expression[8]. Epigenetic programming of anxiety-like behavior underscores the view that environmental influences can persistently

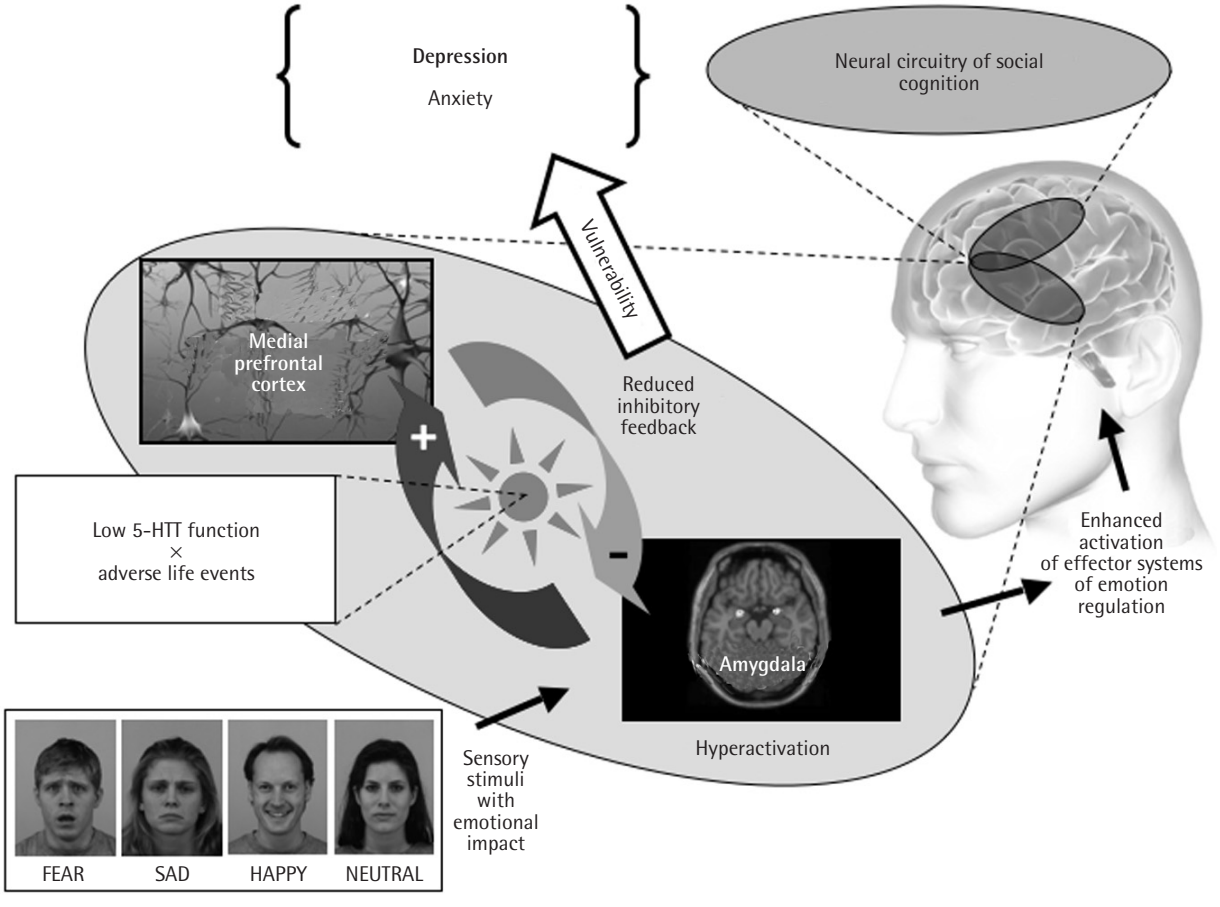

Figura 1 *Influence of 5-HTT gene × environment interaction on neural networks of social cognition and emotion regulation.*

remodel neuronal units during early development, rendering 5-HTT modified mice indispensable for the dissection of the molecular and neural mechanisms of epigenetic programming at the neurodevelopmental-behavioral interface. As investigations have begun to refine the methodologies for capturing epigenetic effects on the brain in genetically modified mice and humans, we may before long better understand the mechanisms that leave some individuals susceptible and others resilient to depression.

FUTURE CHALLENGES

We are clearly a long way from completely understanding the evolutionary and neural mechanisms of social cognitive phenomena and effective social functioning. Yet, the potential impact of 5-HTT variation on social cognition is currently transcending the boundaries of behavioral genetics to embrace biosocial science, thus resulting in a new microcosm of «social neurogenetics of behavior». Biosocial science has been conceptualized to transforms our understanding of problems ranging from gender-specific behavior, marriage and the family as a social institution, to «freedom of will» and legal responsibility, as well as to the natural history of moral obligation. As analyses of genomes of humans, nonhuman primates, and other species has contributed fundamentally to understanding how humans have evolved and how they (mal)function, biosocially focused genomics is about to provided insight into phenomena such as prehistoric migrations of human populations. It has matured to explore the nature of genetic variation among humans and its influence on interindividual differences as well as the relative impact of genetic and environmental determinants on cognition, emotionality, and behavior. Neurosocial science increasingly uses imaging to study the neural basis of economic, social, and political behavior, examining such phenomena as social conformity, decision-making, empathy, and time preference. The integration of biosocial paradigms in behavioral genetics to test for species generality contributes observations that will eventually tear down some long-standing myths about the uniqueness of human behavior. Although the increasing impact of neurogenetics on social sciences has long been anticipated and represents an inevitable, though preferred development, the transition from complicated correlations to useful prediction is the future challenge.

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