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From Genes to Brain to Antisocial Behavior

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ABSTRACT—*This review summarizes recent brain-imaging and molecular-genetic findings on antisocial, violent, and psychopathic behavior. A “genes to brain to antisocial behavior” model hypothesizes that specific genes result in structural and functional brain alterations that, in turn, predispose to antisocial behavior. For instance, a common polymorphism in the monoamine oxidase A (MAOA) gene has been associated with both antisocial behavior and also reductions in the volume of the amygdala and orbitofrontal (ventral prefrontal) cortex—brain structures that are found to be compromised in antisocial individuals. Here I highlight key brain regions implicated in antisocial behavior, with an emphasis on the prefrontal cortex, along with ways these areas give expression to risk factors for antisocial behavior. Environmental influences may alter gene expression to trigger the cascade of events that translate genes into antisocial behavior. Neuroethical considerations include how responsibility and punishment should be determined given the hypothesis that neural circuits underlying morality are compromised in antisocial individuals.*

KEYWORDS—*brain imaging; genetics; antisocial; moral; treatment*

What specific genes predispose an individual to commit crime? How do they change brain processes to give rise to antisocial behavior? And what role does the environment play? While these questions may seem enigmatic, we are currently witnessing scientific advances that hold the promise of beginning to answer them and revolutionizing our understanding of antisocial, violent, and psychopathic behavior. The key concept highlighted in this review is that specific genes result in structural and functional brain alterations that, in turn, predispose to antisocial behavior. This article summarizes current research

supporting this “genes to brain to antisocial behavior” hypothesis, places that knowledge into the context of the social environment, and explores wider neuroethical considerations for society and the criminal justice system. Antisocial behavior is here viewed as a dimension rather than as a category, and is defined as failure to conform to social norms for lawful behavior.

FROM GENES . . .

Despite strong resistance in many quarters, there is now little scientific doubt that genes play a significant role in antisocial behavior. The question of whether there is a genetic basis is no longer interesting, and it has been replaced by the second-generation question of “How much of antisocial behavior is influenced by genes?” While not all studies show significant effects, reviews of over 100 twin and adoption analyses provide clear evidence that about 50% of the variance in antisocial behavior is attributable to genetic influences (Moffitt, 2005).

From this strong basis, the field is now moving on to the more important, third-generation question: “Which genes predispose to which kinds of antisocial behavior?” Initial answers are starting to emerge from molecular genetic studies. If the monoamine oxidase A (*MAOA*) gene is knocked out (neutralized) in mice, they become highly aggressive, becoming “knock-out” fighters themselves. Knock the gene back in, and they return to their normal behavior patterns (Cases et al., 1995). Break-through family and community studies of humans have also implicated the *MAOA* gene in antisocial behavior (Caspi et al., 2002). One meta-analysis shows replicability of this interaction effect (Kim-Cohen et al., 2006), although inevitably there are environmental complexities that require further clarification.

The important challenge for this third generation of genetic work on antisocial behavior is to identify not just which genes are associated with antisocial behavior but also which among these genes code for the brain impairments found in antisocial groups. At least seven genes to date meet the criteria of being both associated with antisocial/aggressive behavior in humans or animals and of being thought to influence brain structure: *MAOA*, *5HTT*, *BDNF*, *NOTCH4*, *NCAM*, *tlx*, and *Pet-1-ETS*. Taking

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MAOA as an example, the enzyme that this gene codes for breaks down serotonin, a neurotransmitter that is low in antisocial individuals. Males with a common polymorphism (variant) in the *MAOA* gene have an 8% reduction in the volume of the amygdala, anterior cingulate, and orbitofrontal (ventral prefrontal) cortex (Meyer-Lindenberg et al., 2006). These brain structures are involved in emotion and are found to be compromised in antisocial individuals. Thus, while these initial molecular-genetic findings still need to be replicated, it appears that one of the genes linked to antisocial behavior results in structural impairments to brain areas that are compromised in antisocial individuals—from genes, to brain, to antisocial behavior.

... TO BRAIN ...

How does one progress from genes to antisocial behavior? One hypothesis is that gene abnormalities result in structural brain abnormalities that result in emotional, cognitive, or behavioral abnormalities, which in turn predispose to antisocial behavior. There is increasing evidence for brain impairments in antisocial groups, with particularly strong evidence for impairments in the prefrontal cortex (Raine & Yang, 2006). Neurological patients suffering damage to the ventral prefrontal cortex exhibit psychopathic-like disinhibited behavior, reduced autonomic and emotional functioning, and bad decision making (Damasio, 1994). Research using magnetic resonance imaging (MRI) has shown that those with antisocial personality disorder have an 11% reduction in prefrontal gray matter, together with reduced autonomic activity during a social stressor designed to elicit “secondary” emotions of shame, embarrassment, and guilt. (Raine, Lencz, Bihrlé, LaCasse, & Colletti, 2000). The antisocial individuals with the least amount of gray matter also showed the least autonomic stress responsivity. Different clinical neuroscience paradigms are beginning to converge on the conclusion that there is a significant brain basis to antisocial behavior and that these neurobehavioral processes are relevant to understanding violence in everyday society.

Structural prefrontal impairments are paralleled by functional prefrontal impairments (i.e., reduced brain functioning) in a wide range of antisocial populations. Murderers have been found to show reduced glucose metabolism in the prefrontal cortex when this brain region is challenged by a task known to activate it, the continuous-performance task (Raine, Buchsbaum, & LaCasse, 1997). This impairment also specifically characterizes impulsively violent offenders, suggesting that the prefrontal cortex acts as an “emergency brake” on runaway emotions generated by limbic structures. Brain-imaging findings are supported by findings from neuropsychological, neurological, and psychophysiological studies, indicating that the findings are robust. However, the prefrontal cortex is not the only brain area compromised in antisocial populations. Reviews of imaging studies have documented impairments to the cingulate, temporal cortex, angular gyrus, amygdala, and hippocampus (Raine &

Yang, 2006). Specific regions implicated to date are illustrated in Figure 1.

Are the brain impairments illustrated in Figure 1 caused by environmental factors or by genes? A significant role of genetics is hypothesized to operate for two reasons. First, the structural prefrontal impairment found in antisocial individuals was not accounted for by environmental risk factors for antisocial behavior (e.g., history of head injury, child abuse) or by drug or alcohol abuse (Raine et al., 2000). Second, an elegant methodological marriage of structural brain imaging with the behavioral-genetic twin design demonstrated that genes explain 90% of the variation in the volume of prefrontal gray matter in humans (Thompson et al., 2001). These two arguments, taken together, would strongly suggest that the structural impairments in antisocial individuals have a significant genetic basis, although future studies could still identify some role for the environment.

... TO ANTISOCIAL BEHAVIOR

The final step in the “from genes to brain to antisocial behavior” argument is to understand how brain structural and functional impairments give rise to the cognitive, emotional, and behavior risk factors predisposing to antisocial behavior. Table 1 outlines an initial model of brain areas found to be dysfunctional in antisocial individuals, the basic cognitive or affective processes that they give rise to, and how these risk factors translate into outcomes related to antisocial behavior. All of these linkages have an empirical basis, although some links (e.g., prefrontal impairments in antisocial populations) currently have stronger support than others (e.g., angular gyrus and responsibility for actions) and localizations of some elements are not agreed upon in the social science literature.

Table 1 shows that risk factors are not conceptualized as directly causing antisocial or aggressive behavior but that, instead, they bias social behavior in an antisocial direction. For example, the amygdala is centrally involved in fear conditioning. Poor fear conditioning may result in a failure to fully develop a conscience—a set of conditioned emotional responses that motivate individuals to desist from previously punished behavior. Poor conscience development is, in turn, viewed as a predisposition to antisocial behavior. Similarly, ventral prefrontal damage results in disinhibited behavior that predisposes to lawless behavior.

One pathway by which dysfunctional brain circuits can give rise to antisocial behavior is in breakdown of moral feeling. This neural moral theory of antisocial behavior (Raine & Yang, 2006) posits that antisocial individuals have a breakdown in the neural circuit normally activated during moral decision making. Areas include the medial prefrontal cortex (PFC), ventral PFC, angular gyrus, posterior cingulate, and amygdala—all areas implicated in antisocial behavior. The overlap of structures implicated in antisocial populations and moral-judgment tasks generates the hypothesis that *some* of the brain impairments in antisocial individuals disrupt moral emotion and decision making, in

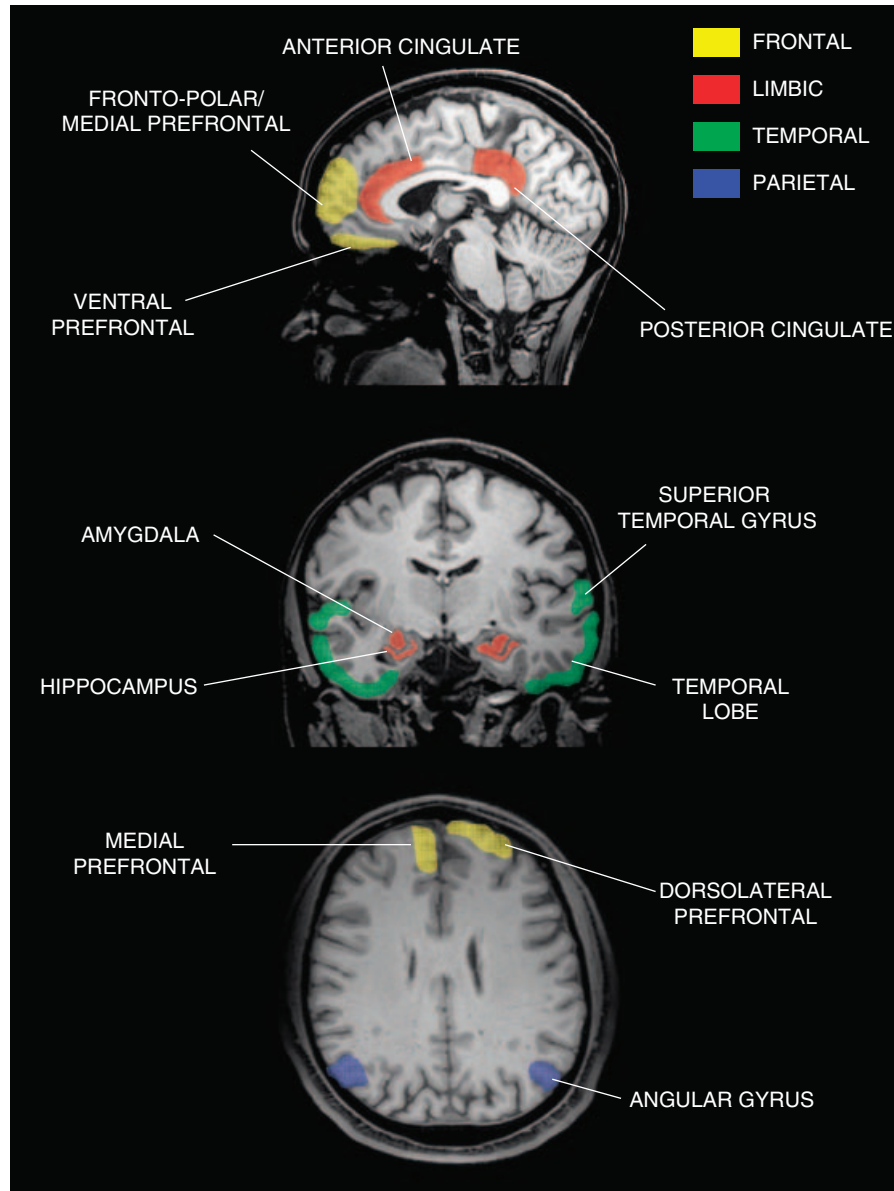


Fig. 1. Illustration based on midsagittal (top), coronal (middle), and axial (bottom) MRI slices of the brain regions found to be structurally or functionally impaired in antisocial, violent, and psychopathic populations (see Table 1).

turn predisposing the individual to rule-breaking, antisocial behavior.

FROM ENVIRONMENT TO GENES TO BRAIN TO ANTISOCIAL BEHAVIOR?

Despite arguments for a direct causal pathway from genes to brain to antisocial behavior, psychosocial processes cannot be ruled out and could be critical. Environmental influences early in development could directly change gene expression (the way in which a gene's DNA sequence is translated into neuronal structure and function), in turn altering brain functioning and

resulting in antisocial behavior. Separating rat pups from the mother in the first 3 weeks of life results in fearlessness and a reduced stress response in adulthood, resulting in an increase in glucocorticoid gene expression in the hippocampus and prefrontal cortex, two brain areas critically involved in regulation of the HPA stress response (Weaver, Meaney, & Szyf, 2006). Conduct-disordered children have a reduced cortisol stress response and a more fearless temperament. As such, early environmental influences can alter gene expression, which then gives rise to the cascade of brain and behavior events outlined above. The exciting idea is that, although 50% of the variance in antisocial behavior is genetic in origin, genes are not fixed,

TABLE 1
The Translation of Brain Impairments to Risk Factors for Antisocial Behavior

Impaired brain region	Processes/risk factors	Outcome
Frontal cortex		
Dorsolateral	Response perseveration Poor planning/organization Theory of mind	Failure to desist from punished behavior Occupational and social dysfunction, low income Misperception of others intentions/behavior
Ventral–orbitofrontal	Decision making Emotion regulation Mediation of emotional responses guiding behavior	Bad life judgments Poor anger control Poor behavioral control
Medial-polar prefrontal	Empathy/concern for others Moral judgment Self-reflection	Callous disregard for others' feelings/situation Noncompliance with societal rules Lack of self-insight
Limbic structures		
Anterior cingulate	Inhibition Errors /conflict processing	Failure to withhold an antisocial response Difficulty in dealing with conflictual situations
Posterior cingulate	Moral decision-making Self-referencing	Noncompliance with societal rules Poorer attribution of negative life outcomes to self
Amygdala	Fear conditioning Social-emotion judgments Moral emotion Judging trustworthiness	Lack of affect and poor conscience development Misinterpreting others' motives/feelings Noncompliance with societal rules Hypersociability and victimization
Hippocampus	Contextual fear conditioning	Not placing punished responses into social context
Temporal cortex		
Temporal pole–superior temporal gyrus	Theory of mind, social perception	Misattribution of other's motives
Posterior superior temporal gyrus	Moral judgment	Noncompliance with societal rules
Parietal cortex		
Angular gyrus	Moral judgment Sense of responsibility for actions	Noncompliance with societal rules Irresponsible behavior

static, and immutable; psychosocial influences can result in structural modifications to DNA that have profound influences on neuronal functioning and, hence, antisocial behavioral outcome.

The social environment can interact with genetics and biological risk factors for antisocial behavior in other ways (Raine, 2002). Antisocial behavior is exponentially increased when social and biological risk factors combine. Studies from several countries have shown that birth complications (including anoxia, known to particularly damage the hippocampus) interact with negative home environments (e.g., early maternal rejection of the child) in predisposing to adult violent offending. There is also replicated evidence that an abnormality in the *MAOA* gene interacts with early child abuse in predisposing to adult antisocial behavior (Caspi et al., 2002).

Social processes can also moderate the relationship between biology and antisocial behavior. Reduced prefrontal glucose metabolism particularly predisposes to violence in those from benign home backgrounds. Low physiological arousal is particularly associated with antisocial behavior in individuals from benign home backgrounds. In these cases, where the individual lacks social risk factors that “push” them toward antisocial behavior, biological factors have a greater explanatory role (Raine, 2002). In contrast, the link between antisocial behavior and

biological risk factors in those from negative home environments may be weaker because social causes of crime “camouflage” the biological contribution.

TREATMENT, MORAL JUDGMENT, AND NEUROETHICS

Biology is not destiny and it should ultimately be possible to remediate neurobiological risk factors. The fundamental question is: “If antisocial individuals have broken brains, can they be fixed?” Ultimate solutions could be both natural and surprisingly simple. Poor nutrition in the first 3 years of life has been associated with long-term antisocial behavior throughout childhood and late adolescence (Liu, Raine, Venables, Dalais, & Mednick, 2004). Low IQ was associated with both poor nutrition and antisocial behavior, and controlling for IQ abolished the relationship between poor early nutrition and later antisocial behavior. This mediating effect of IQ supports the model that poor nutrition leads to poor brain functioning, resulting in neurocognitive (brain) impairments that predispose to antisocial behavior. Fish oil is rich in omega-3, a long-chain fatty acid making up 40% of cell membrane, and dietary supplementation has been associated both with increased IQ and reduced antisocial behavior in prisoners (Gesch, Hammond, Hampson, Eves,

& Crowder, 2002). Prevention programs that manipulate nutrition early in life have resulted in reduced delinquency (Olds et al., 1998) and criminality (Raine, Mellingen, Liu, Venables, & Mednick, 2003). Environmental manipulations can in theory reverse brain risk factors for antisocial behavior.

An alternative approach is to remediate the neurotransmitter abnormalities produced by gene abnormalities, although it must be recognized that such treatments are downstream from genes—we do not yet know how to directly reverse genetic predispositions to antisocial behavior. Nevertheless, genes regulating serotonin's transportation back to the cell body from the synaptic cleft have recently been linked to antisocial-aggressive behavior in children and adults. Given that antisocial-aggressive individuals have low serotonin, medications that increase the availability of serotonin, such as Prozac (an SSRI, or selective serotonin reuptake inhibitor), ought to lower antisocial behavior *if* there is a causal connection. There is evidence to support this prediction in both aggressive adults and children (Connor, Boone, Steingard, Lopez, & Melloni, 2003).

Despite this positive evidence, the fact remains that society is reluctant to use medication to treat antisocial behavior, while at the same time being comfortable in medicating other behavioral conditions. Paradoxically, because the environment influences gene expression, our neurobiological makeup is ever-changing, whether we like it or not. Should society move toward grasping the biological nettle in order to snuff out crime and violence and reduce suffering? Or should it instead turn a blind eye to new clinical neuroscience knowledge and prohibit tampering with humankind's biological essence, even if this results in lives being lost which could have been saved by biological prevention efforts?

An additional neuroethical concern is that of responsibility and punishment. If a murderer suffers brain impairments predisposing him to commit impulsive violence, are we to hold him fully accountable for his behavior? From a moral-judgment standpoint, given the evidence that the neural circuits underlying moral feeling and decision making are impaired in antisocial populations (Raine & Yang, 2006), are such individuals as capable as the rest of us to know—and do—what is right? Psychopaths may know the legal difference between right and wrong, but do they have the *feeling* of what is right and wrong? Emotions are believed to be central to moral judgment, and they provide the driving force to act morally. In this context, how moral is it for us to punish many criminals as harshly as we do? On the other hand, are there not significant dangers in loosening our concept of accountability? The very concept of “from genes to brain to antisocial behavior” raises neuroethical questions that need to be aired in order for prevention science to progress.

CONCLUSIONS AND FUTURE DIRECTIONS

A new generation of clinical neuroscience research that encapsulates brain imaging and molecular genetics is giving rise to

the concept that specific genes result in structural and functional brain impairments that predispose to antisocial, violent, and psychopathic behavior. A critical next step in testing the “from genes to brain to antisocial behavior” hypothesis is to conduct molecular-genetic and brain-imaging research on the same population in order to identify the genes coding both for brain structural and functional abnormalities and for antisocial behavior. The next empirical step is to ascertain whether antisocial, psychopathic individuals evidence abnormal processing of moral dilemmas. How we will deal with this new knowledge at societal and legal levels is a significant neuroethical challenge. The more we learn about the neurobiological causes of criminal behavior, the more difficult questions arise concerning culpability, punishment, and freedom of will. The future scientific and neuroethical challenges for the emerging field of neuro-criminology can best be met by integrative cross-disciplinary research that bridges traditional macrosocial theories (emphasizing broad social constructs) with new perspectives from clinical and social neuroscience to better understand, and ultimately prevent, antisocial behavior in both children and adults.

Recommended Reading

- Damasio, A. (1994). (See References). A ground-breaking book linking the ventral prefrontal cortex with emotion, cognition, and antisocial behavior.
- Kim-Cohen, J., Caspi, A., Taylor, A., Williams, B., Newcombe, R., Craig, I.W., & Moffitt, T.E. (2006). (See References). A review of molecular genetic studies indicating replicability of the antisocial-*MAOA* association.
- Moffitt, T.E. (2005). (See References). A key review of gene-environment interactions in relation to antisocial behavior.
- Raine, A. (2002). (See References). A review of studies demonstrating an interaction between biological factors and social factors in predisposing to antisocial behavior.
- Raine, A., & Yang, Y. (2006). (See References). A review of brain imaging research on antisocial populations arguing for impairments in the circuitry underlying moral decision making in psychopaths.
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REFERENCES

- Cases, O., Seif, I., Grimsby, J., Gaspar, P., Chen, K., Pourmin, S., et al. (1995). Aggressive behavior and altered amounts of brain serotonin and norepinephrine in mice lacking *MAOA*. *Science*, *268*, 1763–1766.
- Caspi, A., McClay, J., Moffitt, T., Mill, J., Martin, J., Craig, I.W., et al. (2002). Role of genotype in the cycle of violence in maltreated children. *Science*, *297*, 851–854.

- Connor, D.F., Boone, R.T., Steingard, R.J., Lopez, I.D., & Melloni, R.H. (2003). Psychopharmacology and aggression: II. A meta-analysis of nonstimulant medication effects on overt aggression-related behaviors in youth with SED. *Journal of Emotional and Behavioral Disorders, 11*, 157–168.
- Damasio, A. (1994). *Descartes' error: Emotion, reason, and the human brain*. New York: GP Putnam's Sons.
- Gesch, C.B., Hammond, S.M., Hampson, S.E., Eves, A., & Crowder, M.J. (2002). Influence of supplementary vitamins, minerals and essential fatty acids on the antisocial behaviour of young adult prisoners: Randomised, placebo-controlled trial. *British Journal of Psychiatry, 181*, 22–28.
- Kim-Cohen, J., Caspi, A., Taylor, A., Williams, B., Newcombe, R., Craig, I.W., & Moffitt, T.E. (2006). MAOA, maltreatment, and gene–environment interaction predicting children's mental health: New evidence and a meta-analysis. *Molecular Psychiatry, 11*, 903–913.
- Liu, J.H., Raine, A., Venables, P.H., Dalais, C., & Mednick, S.A. (2004). Malnutrition at age 3 years and externalizing behavior problems at ages 8, 11 and 17 years. *American Journal of Psychiatry, 161*, 2005–2013.
- Meyer-Lindenberg, A., Buckholtz, J.W., Kolachana, B., Hariri, A.R., Pezawas, L., Blasi, G., et al. (2006). Neural mechanisms of genetic risk for impulsivity and violence in humans. *Proceedings of the National Academy of Sciences, U.S.A., 103*, 6269–6274.
- Moffitt, T.E. (2005). The new look of behavioral genetics in developmental psychopathology: Gene–environment interplay in antisocial behaviors. *Psychological Bulletin, 131*, 533–554.
- Olds, D., Henderson, C.R.J., Cole, R., Eckenrode, J., Kitzman, H., Luckey, D., et al. (1998). Long-term effects of nurse home visitation on children's criminal and antisocial behavior: 15-year follow-up of a randomized controlled trial. *JAMA: The Journal of the American Medical Association, 280*, 1238–1244.
- Raine, A. (2002). Biosocial studies of antisocial and violent behavior in children and adults: A review. *Journal of Abnormal Child Psychology, 30*, 311–326.
- Raine, A., Buchsbaum, M., & LaCasse, L. (1997). Brain abnormalities in murderers indicated by positron emission tomography. *Biological Psychiatry, 42*, 495–508.
- Raine, A., Lencz, T., Bihrl, S., LaCasse, L., & Colletti, P. (2000). Reduced prefrontal gray matter volume and reduced autonomic activity in antisocial personality disorder. *Archives of General Psychiatry, 57*, 119–127.
- Raine, A., Mellingen, K., Liu, J.H., Venables, P.H., & Mednick, S.A. (2003). Effects of environmental enrichment at 3–5 years on schizotypal personality and antisocial behavior at ages 17 and 23 years. *American Journal of Psychiatry, 160*, 1627–1635.
- Raine, A., & Yang, Y. (2006). Neural foundations to moral reasoning and antisocial behavior. *Social, Cognitive, and Affective Neuroscience, 1*, 203–213.
- Thompson, P.M., Cannon, T.D., Narr, K.L., van Erp, T., Poutanen, V.P., & Huttunen, M. (2001). Genetic influences on brain structure. *Nature Neuroscience, 4*, 1253–1258.
- Weaver, I.C.G., Meaney, M.J., & Szyf, M. (2006). Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. *Proceedings of the National Academy of Sciences, U.S.A., 103*, 3480–3485.