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Jelena Radulovic
Bratislav Stankovic

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GENETIC DETERMINANTS OF EMOTIONAL BEHAVIOR: LEGAL LESSONS FROM GENETIC MODELS

Jelena Radulović* & Bratislav Stanković**

INTRODUCTION

The past decade of neuroscience research has been dedicated to the exploration of the genetic heritability of mental processes and the role of specific genes in their regulation. A long reluctance to tackle questions related to the molecular basis of behavior has been overcome; genetic technologies and approaches to these questions have developed and expanded. Psychology, which historically belonged to the social sciences, became more and more connected to the biological sciences, not only on a neuroanatomical level but also on a genetic level. By using animal models—rodents, in particular—the genetic basis of behavior has been examined in a large number of experiments.¹

This Article attempts to summarize what we have learned from animal models, and suggests which critical questions still need to be answered if we are to further elucidate the relationship between genetics and behavior. We focus predominantly on the genetic determinants of stress-induced behavior, such as fear and anxiety, and we explain how these behaviors relate to aggression in rodents. Although convincing evidence demonstrates the role of genes in evolutionary-conserved or species strains and gender-specific behavior, it has become increasingly clear that the gene-environment interactions shaping emotional behavior are extremely complex. The rules that apply to these interactions seem to be diverse and flexible, enabling adaptation to the external demands of our social environment and the rigid rules of our legal system. Genetic abnormalities, however, may cause

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maladaptive behavior that significantly impairs the ability of some individuals to integrate into the social system. A society’s capacity for emotion may even influence the evolution of social norms—and thus the law itself.

II. WHAT ARE GENES?

The entire genetic material of a cell is located, in the form of a densely packed deoxyribonucleic acid (DNA), within a specific compartment called the nucleus. The structure of DNA is relatively simple, allowing for only four bases (adenine, guanine, thymine, and cytosine) to encode all the body’s structural and functional proteins (Figure 1). The order of these bases (DNA sequence) is the same in every cell of a complex organism. But defined DNA segments are distinctively regulated (expressed or silenced) in particular cell types, thereby enabling the development of many different tissues and organs, including the brain.

**FIGURE 1: THE NERVE CELL**

3. Figure 1 depicts a nerve cell containing input fibers (dendrites), an output fiber (axon), and a cell body. It also presents a magnified cell body, which reveals a nucleus containing DNA with genes as segments coding for single proteins.
Genes are the smallest hereditary units containing information for the structure of a specific protein. Depending on this information, a specific receptor, ion channel, transporter, enzyme, or any other protein is synthesized during development or in response to a sudden or prolonged environmental challenge. Each organism contains two parental copies of the same gene, except for genes located in the sex chromosomes. These are usually not identical copies because each parent contributes a slightly different genetic sequence.

III. HOW DO GENES AFFECT BRAIN FUNCTIONING?

The brain contains a dense network of neuronal cells containing input branches (dendrites) and an output fiber (axon). These cells are highly polymorphic and interconnected in loops that excite or inhibit signal propagation (Figure 2). Two main features of the brain cells are their ability to rapidly transmit impulses over long distances by electrochemical processes and to slowly remodel their networks by gene regulation. Molecules released at nerve endings—such as amino acids, neurotransmitters, and neuropeptides acting at their receptors—play a crucial role in the initiation of both processes and affect many brain functions, including behavior. In general, a balance between excitation and inhibition of neuronal excitability is achieved by the coordinated activities of amino acids, neurotransmitters, and neuropeptides (Figure 2).

Dysregulation of their interactions in particular areas of the brain may have significant consequences for the expression of specific types of behavior. Genes directly encode the information on the structure of all neuropeptides, receptors, transporters, and enzymes responsible for the generation and degradation of neurotransmitters. When small alterations in the genetic sequence occur in parts of the brain that are critical for the function of its protein, they may have profound effects on the brain and behavior.

IV. How We Measure Emotional Behavior in Rodents

A. Anxiety

In rodents, anxiety is measured by a number of paradigms that evaluate different sets of behaviors under defined environmental condi-

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6. Figure 2 presents an image of the brain. A particular brain area, such as the amygdala, is highly involved in the regulation of emotional behaviors. It contains a dense network of interconnected neurons whose activity reflects a balance between excitatory and inhibitory activity.

The most commonly applied tests measure the preference for dark over light environments (elevated plus-maze test, dark-light emergence task), the intensity of muscle contraction in response to sensory stimuli (startle), or contacts during social interactions. In the shock-probe burying test, an animal encounters an electrified probe and copes with it by burying or avoiding it. This test has been regarded as a model for fear as well as anxiety.

Most of these anxiety tests also measure additional behaviors—such as exploration, locomotion, and risk assessment—that may be directly linked to anxiety. Because the interdependence of these behaviors and anxiety is difficult to evaluate, anxiety is ideally identified and quantified when those behaviors are not affected. With the exception of the startle test, the tests for anxiety evaluate acute anxiety responses and are optimally carried out only once. Multiple exposures to the test are associated with the strong interference of habituation, which adds learning components to anxious behavior.

**B. Fear**

Apart from inborn fears—such as the fear of predators—an evaluation of fear responses requires a two-step procedure. Classical fear conditioning occurs when the animal learns that an originally neutral stimulus (conditioned stimulus, CS) is predictive of danger. For training, the animal is placed in a novel environment (context); after an exploratory period, a foot shock (unconditioned stimulus, US) is delivered. If a tone or light is presented as a CS before the shock, the animal learns to associate the CS with the US (Figure 3).

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After exposure to the tone or light, the fear response is evaluated by measuring the freezing behavior that reflects conditioned fear. Alternatively, a conditioned light or tone may be presented when the animals are in a startle box, and in response to the CS exhibit, the animal displays a fear-potentiated startle.

The listed models have been extremely advantageous for the preclinical evaluation of anxiolytic drugs and for the identification of brain areas and molecular mechanisms that regulate fear and anxietal behavior. The main limitation of these models is their uncertain relationship to human diseases, but they do allow the study of specific endophenotypes that might occur across different mental disorders.

C. How Do We Study Genetic Effects on Behavior?

Ample evidence demonstrates that heritability is significantly associated with particular emotional behaviors. There are several approaches commonly used to establish such an association. Studies with different rodent strains and substrains clearly demonstrate heri-
table differences in stress responses and associated neuroendocrine and behavioral alterations. More focused approaches consist of the selective inbreeding of rodents displaying high or low anxiety, depression, or aggressive behavior. The linkage of particular sets of genes with specific behaviors has been performed by quantitative trait loci analyses. All of these approaches can be successfully employed in human studies as well. A unique advantage of rodent models, however, is the option to specifically insert or remove single genes (knockouts) and study their behavioral effects in the newly generated transgenic animals (Figure 4). Most experiments have employed a constitutive genetic defect that was present throughout the development and adulthood in the whole brain. Recent technologies allow for space-limited (regional) and time-limited (inducible) genetic manipulations.

**Figure 4: Gene Knockout**

![Gene Knockout Diagram]


18. Figure 4 depicts how current genetic technologies enable researchers to selectively remove any single gene (gene x) from a chromosome and thereby create a mouse containing all but the deleted genetic information.
The main advantage of the single gene manipulations is the potential to establish the relationship between a specific gene and a specific type of behavior. The limitations of this approach, such as developmental compensation or early postnatal mortality, are likely to be overcome by inducible and regional knockouts. Thus, the roles of some genes that might have been overlooked due to their critical role in development can be reassessed with these models. Another problem is the application of these data to human situations, where gene alterations are likely to consist of subtle sequence changes rather than overexpression or deletion of an entire gene. Therefore, candidate genes from animal experiments need to be further analyzed for relevance to the human population. It appears that this task will be less challenging than one might anticipate, because the brain circuits and genes that regulate emotional behavior are highly evolutionary-conserved.

D. What Have We Learned So Far?

1. Genes Significantly Affect Emotional Behavior

Single gene mutations affect fear, anxiety, aggression, and a number of other emotional behaviors. Research shows that genes that code for specific receptors, enzymes, serotonin, norepinephrine, corticotropin-releasing factor, and transporters of neurotransmitters such as gamma-amino-butyric acid (GABA) profoundly affect behaviors associated with fear, anxiety, addiction, and aggression. These effects, however, are unexpectedly complex.

2. Genetic Effects on Behavior Are Redundant: Many Genes Affect One Behavior

Classic genetic disorders are typically caused by a single gene. A defect in a single gene coding for a coagulation factor may cause hemophilia, a disease characterized by lethal bleeding. As soon as the genetic defect has been overcome by introducing the responsible factor, the disease symptoms disappear. So far, such a relationship between a single gene and a single behavioral symptom, mental process, or disease has not been established. In contrast, many genes may affect a single behavior if those genes are located in brain networks crit-

19. See Martin E. Keck et al., Listening to Mutant Mice: A Spotlight on the Role of CRF/CRF Receptor Systems in Affective Disorders, 29 NEUROSCIENCE & BIOBEHAVIORAL REV. 867 (2005); Klaus-Peter Lesch, Serotonergic Gene Inactivation in Mice: Models for Anxiety and Aggression?, 268 NOVARTIS FOUND. SYMP. 111 (2005); Stefano Vicini & Pavel Ortinski, Genetic Manipulations of GABA\textsubscript{A} Receptor in Mice Make Inhibition Exciting, 103 PHARMACOLOGY & THERAPEUTICS 109 (2004).
ical for the generation of this behavior. For example, any imbalance of excitatory and inhibitory neurotransmission in the area of the brain called the amygdala will affect fear and anxiety, because this region is central to the regulation of these behaviors (Figure 2).

3. A Single Gene May Affect Several Behaviors

The deletion of a single gene may also affect a variety of behaviors. For example, the 5-HT_{1B} subunit of the serotonin receptor affects anxiety and aggressive behavior,\(^{20}\) while genetic manipulations of the receptors for corticotropin-releasing factor (a key stress mediator) affect emotional, motivational, and consumatory behavior.\(^{21}\) The main reason for these pleiotropic effects lies in the widespread distribution of these neurotransmitter systems in areas of the brain that regulate different behaviors.

4. Gene Mutation Effects Are Strain-Dependent and Gender-Dependent

Genes interact with one another in unique ways. Mouse models have shown that a specific genetic manipulation can profoundly impact the emotional behavior of one mouse strain while proving completely ineffective in another. Thus, even within the same species, a single gene may distinctively affect behavior by interacting with other strain-specific genes that enhance or neutralize its effects. Several examples of the strain-dependent role of genes affecting anxiety have recently been highlighted.\(^{22}\) Notably, the effects of several genes related to the function of serotonin—one of the best-characterized mediators of anxiety, alcohol preference, and aggression—show remarkable strain dependency. Thus, in mouse strains that are closely related genetically, a knockout of the serotonin transporter and receptor (5-HT_{1B}) enhanced anxiety and alcohol drinking, respectively.\(^{23}\)

Increasing evidence also shows that single gene manipulation can profoundly affect fear or anxiety-like behavior in one gender but not the other. We have shown earlier that deleting the gene coding for a

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corticotropin-releasing factor results in anxiety-like behavior in male but not female mice.\textsuperscript{24} Rather, the same gene knockout increases depression-like behavior predominantly in females.\textsuperscript{25}

5. \textit{Gene-Environment Interactions}

It has been shown that the effect of several genes on anxiety, depression, aggression, or alcohol consumption depends on the prior history of stressful experiences and specific environmental situations. Mice lacking a corticotropin-releasing factor did not show elevated alcohol preference relative to their littermates containing the receptor. After exposure to a repeated stress, however, these mice developed a delayed and persistent increase in alcohol consumption.\textsuperscript{26} Another model consisted of mice lacking a transporter for the neurotransmitter norepinephrine. These mice showed that norepinephrine actions do not cause anxiety or depression in the environment in which the animal experiences stress, but they do increase depression in novel stressful situations.\textsuperscript{27}

Taken together, these studies suggest that the genetic effects on behavior cannot be averaged. Instead, a systematic characterization within a population and gender, together with detailed evaluation of an individual's environment, seem to be required to understand how genes affect behavior and when their effects are likely to occur (Figure 5).

\textsuperscript{24} See Toshimitsu Kishimoto et al., \textit{Deletion of Crhr2 Reveals an Anxiolytic Role for Corticotropin-Releasing Hormone Receptor-2}, 24 \textit{Nature Genetics} 415 (2000).


\textsuperscript{26} See Inge Sillaber et al., \textit{Enhanced and Delayed Stress-Induced Alcohol Drinking in Mice Lacking Functional CRH1 Receptors}, 296 \textit{Science} 931 (2002).

\textsuperscript{27} József Haller et al., \textit{Behavioral Responses to Social Stress in Noradrenaline Transporter Knockout Mice: Effects on Social Behavior and Depression}, 58 \textit{Brain Res. Bull.} 279 (2002).
LESSONS FROM GENETIC MODELS

Figure 5: Gene-Environment Interactions

Susceptibility genes

Gender-specific genes

Strain-specific genes

EMOTIONAL BEHAVIOR

Environment

V. Perspective

Although accumulating evidence demonstrates that single genes or sets of genes clearly affect emotional behavior, their roles appear to be much more complex than originally anticipated. A great deal of work is still being performed to isolate the genes that are critical to regulating emotional behavior and causing mental disorders.

First, scientists are searching for genes that may have been overlooked. The generation of mice in which single gene manipulations are performed after the development may help to identify novel genes that regulate behavior, because such manipulations are not expected to induce lethality. Second, scientists are also trying to identify reliable and objective biomarkers of emotional behaviors. Such markers may be mutations, polymorphisms, or recombinations of specific genes that regulate emotional behavior.

Third, ongoing research is striving to isolate critical sets of genes and characterize in more detail their susceptibility to environmental factors. This is probably the greatest challenge considering the infinite number of possible interactions between a large number of genes.

28. Figure 5 depicts a scheme that shows multiple interactions—among genes as well as between genes and environment—that affect emotional behavior.
and an even larger number of environmental variations. Nevertheless, major adaptive responses, such as stress, are likely to unravel significant linkages of specific genes with stress-induced changes of anxiety or aggressive behavior. Importantly, most cases of exaggerated emotionality and associated behaviors occur in response to acute or chronic stress.

Finally, researchers are trying to determine the extent to which a genetic predisposition for a particular unwanted behavior may be overcome by other biological systems within the individual, including the compensatory activation of genes that oppose such behavior or enhance utilization of cortical brain areas that commonly keep emotional behavior under control. This aspect is particularly relevant for establishing when emotional behaviors are out of control.

VI. LEGAL IMPLICATIONS

The idea of a possible connection between the brain, culture, and law is not new.29 Fueled by advances in molecular biology and genetic engineering, we have seen an explosion of interest in biology and its implications for the social sciences. The discussions have frequently explored the connections of biological evolution to mind and culture, stirring up colorful debates on the relevancy of biology to law.30 Generally speaking, the capacity for emotion and learning may lead to the evolution of social norms on both individual and societal levels. Law, which is essentially a social norm that penalizes destructive behavior, is directly affected by biological evolution.31

The influence that genetic makeup exerts on an individual’s behavior clashes with certain fundamental ideas in our system of justice. The key question turns on the degree to which our actions are caused


31. See Wilson, Consilience, supra note 29.
by our genes. Our social and legal institutions place great emphasis and value on self-determination. Self-determination "deeply affect[s] . . . our conception of ourselves as responsible agents and . . . as morally and legally responsible for our actions." Western philosophy has long viewed people as autonomous individuals free to make their own decisions. This view has influenced our definitions of crime, including the mens rea requirement, which lies at the center of criminal culpability. A more thorough understanding of our genetic blueprint might make us reconsider our mechanistic definitions of crime in favor of a more evaluative doctrine of justice.

Information about an individual's genetic makeup can be used by society in a variety of ways. For example, it appears that some human beings may be naturally predisposed toward violence and rape. Should society regulate individuals with genetic predispositions toward crime? As in any other area that deals with genetic information and genetic testing, the potential for abuse exists. Warnings have already been issued about the potential of genetic testing for creating new groups of disadvantaged people who might need the same protections now accorded to those suffering from race and sex discrimination. Any regulation of the genetic determinants underlying an individual's behavior must be approached with caution.

Whether a particular behavior is normatively good or bad cannot be established by determining simply that an individual is inclined to behave in such a manner. Certain behaviors are viewed as good or bad only according to an external normative standard. Thus, human beings may be naturally predisposed to engage in trade, act compassionately, and enter into reciprocal arrangements for mutual benefit. By almost any moral code, all of these behaviors are normatively good.

Scientific findings show some of the ways in which genetic determinants may influence emotional behavior, which consequently serves as the bases for norms and laws. The identification of specific genes that

correlate with basic human emotions such as fear, anger, and anxiety\textsuperscript{38} will help in our search for the moral roots of legal obligation. Perhaps hatred, in the form of prejudice, results from the tensions among individual genotypes and cultures that have driven the evolution of species.\textsuperscript{39} Science could provide information to answer that question.

VII. Conclusion

Founded in the genotype, an individual's capacity for emotion may dictate an individual's behavior and have legal ramifications. The legal system tends to assume either that people are purely rational actors, or that their brains are blank slates on which cultural behavior is written. The reality is much more complicated, and it can only be appreciated with a deeper understanding of behavioral biology. As we continue to reveal the molecular mysteries underlying the genetic determinants of emotional behavior, we must cope with new questions. The best approach is to become cognizant about the ways in which the genetic makeup of the individual influences the development of societal norms. That knowledge will help us understand how to best construct laws that balance the advances of science with emotional and social development, while providing feedback that encourages the development of positive normative behavior.

\textsuperscript{38} Wayne Weiten \& Margaret A. Lloyd, Psychology Applied to Modern Life: Adjustment in the 90s, at 78 (4th ed. 1994).

\textsuperscript{39} Id. at 155-56.