Genes for susceptibility to violence lurk in the brain

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Each year >1.6 million people are killed through violence (1). Preventing violence is one of the most important global concerns. The political, social, or economic causes of violence are well studied, but more recently the awareness has grown that biological causes, which may explain individual differences in predisposition to violence, also need to be investigated. Here it is crucial to distinguish between impulsive reactive violence and predatory violence because the biological bases of these two types of aggression are likely to be different (2). Predatory violence particularly characterizes a smaller group of true psychopaths, whereas reactive violence is common across antisocial groups (3). An important theoretical advance in our knowledge about the brain basis of reactive violence has been made by Meyer-Lindenberg et al. (4) in this issue of PNAS.

A wealth of twin and adoption studies confirms that individual differences in violent/antisocial behavior are heritable (5). It is unlikely that genes directly code for violence; rather, allelic variation is responsible for individual differences in neurocognitive functioning that, in turn, may determine differential predisposition to violent behavior. Genes regulating serotonergic neurotransmission, in particular monoamine oxidase A (MAOA), have been highlighted in the search for a genetic predisposition to violence (6). The MAOA gene is a well-characterized functional polymorphism consisting of a variable number of tandem repeats in the promoter region, with high-activity (MAOA-H) and low-activity (MAOA-L) variants. The MAOA-H variant is associated with a lower concentration of intracellular serotonin, whereas the MAOA-L variant is associated with a higher concentration of intracellular serotonin. It is unclear at present whether MAOA-H or MAOA-L should be considered the risk variant for impulsive violence. Given that existing studies have used very different populations and measures and have not always controlled for concurrent environmental risk or other genetic influences, contradictory findings are perhaps to be expected. Recent research suggests that genetic vulnerability to violence conferred by the low-activity allele of MAOA-L variant may become evident only in the presence of an environmental trigger of maltreatment (7). This research highlights increased serotonin availability (often associated with anxiety) in MAOA-L carriers as a possible predisposition toward neural hyperreactivity to a threat (maltreatment). This much-vaunted example of nature–nurture interaction leads one to expect that genetic predisposition alone may be of little consequence for behavior in favorable conditions. A big question is whether there would also be little consequence for brain function. The study by Meyer-Lindenberg et al. (4) suggests that genotype differences show in the brain.

Individual differences in several brain areas and cognitive functions associated with perception and regulation of emotions have been found to correlate with “impulsive” violent behavior (8). In particular, the orbitofrontal cortex, amygdala, and interconnected regions have shown both structural and functional abnormalities in impulsively violent populations. Conversely, neuropsychological functions associated with these brain regions, such as perception of threat and modulation of affective response, are compromised within impulsively violent individuals (2). Toxic environments may contribute to these abnormalities in brain function. Animal work and studies of clinic samples suggest that maltreatment compromises the functioning of the systems involved in the individual’s response to threat (e.g., amygdala and periaqueductal gray) and the regulation of the threat response once triggered (e.g., orbitofrontal cortex and anterior cingulate) (2, 9–10). The compromised brain function, in turn, is proposed to increase the risk of reactive violence (2). As an example of human studies, neuropsychological data on maltreated youngsters show hyperreactivity to anger (11), an indirect index of amygdala hyperreactivity.

Because genes, even in the presence of toxic environments, do not directly code for violent behavior, investigations of mechanisms for genetic effects on brain and cognition are important. As outlined in the previous paragraph, such work in relation to impulsive violence is advancing quickly. Adding genetic information to brain-imaging data, dubbed imaging genomics, is the next step (12). In this work, it is imperative to establish first a “baseline” of genetic variation within the brain areas of interest before launching into investigations of how gene–environment interaction manifests in brain function or how disordered populations vary in their brain response as a function of genotype. The work of Meyer-Lindenberg et al. (4) in this issue of PNAS demonstrates specifically that for males the MAOA-L genotype is associated with amygdala hyperreactivity during emotional arousal, coupled with diminished reactivity of regulatory prefrontal regions, compared with the high-activity allele (MAOA-H). Volumetric reductions of the limbic areas are also observed in association with MAOA-L genotype. Specific to males (and in line with the X-linked status of this gene), MAOA-L males also show changes in orbitofrontal volume, amygdala and hippocampus hyperreactivity during aversive recall (determining aversive scenes as new or old), and impaired cingulate activation during cognitive inhibition (withholding response to “no go” stimuli).

These findings are extremely exciting for several reasons. As we see differences at the neural level, in the absence of behavioral differences, this finding gives rise to the possibility that MAOA-L contributes to a vulnerable neural signature that could turn “nasty” given adverse environmental circumstances. No brain-imaging studies to date exist with both MAO-A genotype and maltreatment information, but the study by Meyer-Lindenberg et al. (4) implicates the precise brain regions previously shown to be affected by maltreatment in animal studies (13) and human neuropsychological studies (11). The authors are thorough in unpacking the meaning of their findings. For example, the finding of reduced cingulate reactivity, coupled with heightened amygdala reactivity in MAOA-L carriers, is taken to suggest poor regulation of amygdala by cingulate cortex. Another exciting finding that is discussed in detail is the male specificity of some of the MAOA-L neural signature. Meyer-Lindenberg et al. (4) suggest that this finding provides some evidence for a physiological consequence of X-inactivation in the human brain. The finding of an intermediate response in

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female heterozygotes further supports this explanation. These preliminary findings are particularly interesting in relation to the postulated link with impulsive violence, because there is a gender imbalance on this trait.

Meyer-Lindenberg et al. (4) emphasize that their sample is not composed of antisocial individuals with violent aggression, and they are not studying the relationship of MAOA and violence per se. They also emphasize that by itself, the MAOA gene is likely to contribute only a small amount of risk in interaction with other important factors, such as other genes and toxic environments. We welcome this emphasis, as any behavioral trait is the product of many predisposing genes (most of which have not yet been found) and a host of relevant environmental factors. Importantly, the two MAOA groups were matched on 5-HTTLPR genotype, which could have otherwise been argued to account for at least some of the observed structural/functional differences. The possible effects of other genes were not analyzed in this data set. As more is understood about gene–gene interactions and how they influence different brain circuits, the background genotype effects on MAOA-confounded brain differences will become clearer. An interesting direction for future research that directly arises from this study is a genotype (high/low risk) by environment (high/low risk) study of brain structure and function. A factorial design is needed where individuals from each quadrant of any proposed genotype–environmental risk combination are included. Such a study design might reveal how environmental risk potentiates the response of an already-vulnerable system. A possible influence of environmental risk on gene-brain-cognition-behavior pathways is sketched out in Fig. 1.

We are reminded here of the cross-language study of dyslexia by Pauls et al. (14), which showed that English-speaking dyslexics demonstrated stark evidence of reading failure on standard reading tests, whereas Italian-speaking dyslexics did not, because of the transparency of Italian orthography. Yet, the brain-imaging data showed that both groups had the same neurophysiologically abnormal brain response to print. Interestingly, sensitive behavioral measures, although hitherto not standardly used, showed just as clear deficits in the Italian-speaking dyslexics as in the English-speaking ones. The parallel we would like to suggest is that the MAOA-L carriers may also be distinguished reliably from the MAOA-H carriers given sufficiently sensitive behavioral measures. The environmental contribution in this case might not necessarily be thought to act at the biological level but might act at the behavioral level in the sense of being hidden in some conditions but obvious in others.

Clearly the explanation of predatory violence will be different. Here the indications are that the true psychopaths who exhibit this type of violence show somewhat different brain responses (2) and even may be more genetically predisposed to violence (15). It would be interesting to consider whether empathic responsiveness would distinguish these populations, with true psychopaths deficient in empathy. In contrast, individuals who show reactive/impulsive violence might not be deficient, and paradigms to study empathy responses at the brain level to pain (16) and to fairness (17) are now available to answer these questions.

Sadly, the distinction between premeditated predatory and reactive impulsive violence is lacking in many behavioral genetic and imaging genomics studies, as is the study of empathy. We hope this study of Meyer-Lindenberg et al. (4) will encourage people to articulate clearer hypotheses from genes to brain, mind, and behavior.