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Exp Biol Med (Maywood) published online 24 April 2014
DOI: 10.1177/1535370214529508

Exp Biol Med (Maywood) OnlineFirst, published on May 20, 2014 as doi:10.1177/1535370214529508

Minireview

Molecular genetics and antisocial behavior: Where do we stand?

Caterina Iofrida, Sara Palumbo and Silvia Pellegrini

Laboratory of Molecular Biology, Department of Surgical, Medical and Molecular Pathology and of Critical Care, University of Pisa, Pisa I-56126, Italy

Corresponding author: Silvia Pellegrini. Email: silvia.pellegrini@med.unipi.it

Abstract

Over the last two decades, it has become increasingly evident that control of aggressive behavior is modulated by the individual genetic profile as well. Several candidate genes have been proposed to play a role in the risk to develop antisocial behavior, and distinct brain imaging studies have shown that specific cortical areas may be functionally and/or structurally impaired in impulsive violent subjects on the basis of their genotypes. In this paper, we review the findings regarding four polymorphisms—*MAOA* (Monoamine oxidase A) uVNTR, *SLC6A4* (solute carrier family 6 (neurotransmitter transporter), member 4) 5HTTLPR, *COMT* (Catechol-O-methyltransferase) Val158Met and *DRD4* (dopamine D4 receptor) VNTR 1–11—that all have been found to be associated with an increased vulnerability for antisocial and impulsive behavior in response to aversive environmental conditions. These results, however, have not been replicated by other studies, likely because of crucial methodological discrepancies, including variability in the criteria used to define antisocial behavior and assessment of environmental factors. Finally, it has been recently proposed that these genetic variants may actually increase the individual susceptibility not merely to the negative environmental factors, but to the positive ones as well. In this view, such alleles would play a wider modulatory role, by acting as ''plasticity'' rather than ''vulnerability'' genes. Overall, these findings have potential important implications that span well outside of neuroscience and psychiatry, to embrace ethics, philosophy, and the law itself, as they pose new challenges to the very notion of Free Will. Novel properly controlled studies that examine multi-allelic genetic profiles, rather than focusing on distinct single variants, will make it possible to achieve a clearer understanding of the molecular underpinnings of the *nature* by *nurture* interaction.

Keywords: COMT, SLC6A4, MAOA, DRD4, antisocial behavior, molecular biology

***Experimental Biology and Medicine* 2014; 0: 1–10. DOI: 10.1177/1535370214529508**

Introduction

Criminal acts, mostly crimes passionnel or instinctive reactions to provocations committed with bewildering cruelty, are often driven by impulsive violence rather than by premeditated actions.[1]

In recent years, the idea that the inability to control aggressive impulses may be partially influenced by the individual genetic profile has been gaining more and more evidence, raising at the same time a large number of ethical issues.[2–4]

The hypothesis that a close linkage between behavior and genetics may exist comes from studies on twins and adoptees,[5] and is supported by several pieces of evidence recently generated by scientific research.[6] A number of candidate genes have been indeed investigated in association with antisocial behavior, especially genes involved in serotonergic[7–11] and dopaminergic[12–14] circuits.

The biological hypothesis of antisocial behavior is also supported by brain imaging studies showing that specific brain regions involved in the control of behavior, including the dorsal and ventral regions of the prefrontal cortex, amygdala, hippocampus, angular gyrus, anterior and posterior cingulate, and temporal cortex, are functionally and/or structurally impaired in impulsive violent subjects [15,16] and in individuals showing non-moral behavior. [17]

Genetic variants implicated in antisocial behavior have been shown to impact brain activation and connectivity, a mechanism that probably concurs to predispose to inflexible emotional processing. The Met allele of *COMT* (Catechol-O-methyltransferase) Val158Met polymorphism, for example, enhances in a dose-dependent manner the reactivity and connectivity of hippocampus and ventrolateral prefrontal cortex during presentation of faces displaying negative emotions.[18] Furthermore, the Met allele homozygous subjects show an inverse correlation between amygdala-orbitofrontal coupling and novelty seeking, an index of temperamental inflexibility.[18] *MAOA* (Monoamine oxidase A) uVNTR (untranslated Variable

Number of Tandem Repeat) modulates both structural and functional brain changes in regions linked to emotion regulation and cognitive control; in low-activity MAOA allele carriers, magnetic resonance imaging (MRI) and functional MRI (fMRI) analyses have shown limbic volume reductions and amygdala hyper-responsiveness during emotional arousal, with diminished reactivity of regulatory prefrontal regions.[19] 5HTTLPR (serotonin-transporter-linked polymorphic region) short allele carriers showed a greater amygdala activation in response to fearful stimuli compared to individuals homozygous for the long allele.[20]

The present paper critically reviews the findings reporting an association between antisocial personality and four polymorphisms that have been extensively studied over the last several years: *MAOA* uVNTR, *SLC6A4* (solute carrier family 6 (neurotransmitter transporter), member 4) 5HTTLPR, *COMT* Val158Met, and *DRD4* (dopamine D4 receptor) VNTR 1–11. We will consider the role of the above polymorphisms in modulating the individual response to adverse environmental factors that have occurred in particular in the early decades of their life.

While the ability to predict whether an individual is likely to commit a crime based on his/her genetic profile obviously remains an utopian plan, as no genetic variant has been found to play any deterministic effect on human behavior, the existence of genetic variants that may affect the individual vulnerability to violence and to the development of antisocial behavior is receiving greater and greater interest, both from a scientific perspective and because of the implications for criminology and potentially for the management of criminal detention and the rehabilitation strategies for convicted people.[21]

Allelic variants for antisocial behavior

MAOA *uVNTR*

The *MAOA* gene, located on the X chromosome, encodes the monoamine oxidase A enzyme, which plays a major role in the metabolism of biogenic amines, including dopamine, noradrenalin, and serotonin.[22]

The *MAOA* has been the first gene to be associated with antisocial behavior since 1993, when a stop codon point mutation, producing a completely not-functioning enzyme, was found in all the male subjects of a Dutch family, who had a severe history of violent acts and impulsive aggression, including homicide, arsonism, and rape.[23]

The causal link between *MAOA* inactivation and aggression was confirmed two years later by knocking-out the *MAOA* gene in mice. These animals, after being genetically modified, become ferociously aggressive against other mice.[24]

While the inactivating mutation running in the Dutch family has never been found so far in the general population, a common uVNTR polymorphism in the promoter region of *MAOA* has been indicated as a moderating factor of the effects of childhood maltreatment on the development of antisocial behavior. This *MAOA* uVNTR consists of a 30-bp repeated sequence present in 2,[25,26] 3, 3.5, 4, 5,[27] or 6[28] copies. The two most common alleles are those with 4 and 3 repeats.[27,28] Alleles with 3.5 or 4 copies of the repeated sequence are transcribed more efficiently than alleles with 2 and 3 repeats, thus being classified as high- and low-activity alleles, respectively.[25–27] Literature on the 5-repeat allele is inconsistent, as it has been classified as low-activity allele by Sabol and colleagues[27] and as high activity allele by Deckert and colleagues.[25] So far, no functional characterization for the rare 6-repeat allele has been published.

Here, we report data on the impact of *MAOA* low-activity alleles, in interaction with childhood maltreatment and abuse, on the development of antisocial behavior in men. In women, data on the association of *MAOA* genotype with aggression are heterogeneous and conflicting.[28–33] It is currently unknown whether, in females, *MAOA* is transcribed from one or both copies of the gene.[34,35] In any case, a MAOA dosage compensation mechanism and a different epigenetic methylation between the sexes have been suggested.[36] Therefore, the role played by *MAOA* on antisocial behavior in women is still to be fully understood.

Antisociality has been measured using a variety of behavioral and psychological scales including evaluation of conduct disorders, conviction for violent offenses, and disposition toward violence and delinquency. Caspi and colleagues provided the first evidence that a large sample of maltreated male children carrying low-activity alleles of *MAOA* were more likely to develop antisocial problems in adulthood as compared to abused children with the high-activity *MAOA* variant.[7] Consistent with these data, Huang and colleagues found a significant correlation between high-activity *MAOA*-uVNTR variants and lower impulsivity in adult males who had suffered early childhood abuse.[28] A number of subsequent studies confirmed these results,[29,31,37–45] while others failed to replicate them.[46–50] Among these papers, two meta-analyses, published in 2006 and 2007, strongly supported the original hypothesis,[40,41] while two very recent studies published in 2013 and conducted in very large samples did not replicate these previous findings. In detail, as part of the Pelotas 1993 Birth Cohort Study, Kieling and colleagues tested 1998 adolescent males from low- and middle-income countries for the interaction between *MAOA* uVNTR genotype and childhood maltreatment in the occurrence of ''externalizing behavior,'' that is a behavior which comprises most antisocial traits including aggression, and represents a major risk factor for later juvenile delinquency, adult crime, and violence.[51] They did not detect any effect attributable to the genotype.[49] Haberstick and colleagues examined the same hypothesis in a sample of 3356 Caucasian and 960 African-Americans participating in the National Longitudinal Study of Adolescent Health.[50] They evaluated the effects of the interaction between *MAOA* uVNTR genotype and maltreatment suffered before the age of 12 on the risk of developing adult antisocial behavior, and reached the same negative results. As we will discuss later, such a discrepancy may be due to the fact that, in the two negative studies, the antisocial behavior was measured by self-reports without any third-party observation. Similarly, the childhood maltreatment was assessed by retrospective reports. Distorted memories may have biased the

evaluation of the environmental contribution producing a significant impact on the data.

SLC6A4 *5HTTLPR*

The serotonin transporter SLC6A4 is a key molecule in the regulation of serotonin levels in the synaptic cleft.[52,53] Serotonin transporter availability is significantly reduced in the anterior cingulate cortex of individuals showing impulsive aggression.[54]

A repeat length polymorphism located in the promoter of *SLC6A4*, named 5HTTLPR, has been associated with various psychiatric disorders and pharmacological treatment response, as well as to behavioral traits.[55–62] 5HTTLPR consists of different lengths of a repetitive sequence containing 20- to 23-bp long repeat elements.[63,64] The most common alleles are a L (long, 16-repeats) and a S (short, 14-repeats) allele.[64] Less common alleles (15-, 18/20- or 22-repeats) have been also reported.[64] Both basal and induced *in vitro* transcription of the L variant of *SLC6A4* are about threefold more efficient than those of the S allele.[63] Consistently, both basal and induced serotonin uptake, in lymphoblast cell lines and platelets from individuals homozygous for the L allele, have been found to be about twofold higher than in cells carrying one or two copies of the S allele.[65,66] In addition, with the G allele of rs25531, a SNP of the L allele, the promoter activity of the long form of 5HTTLPR is comparable to that of the S allele.[67]

A preliminary study on the genetics of moral behavior found an association between the S allele of 5HTTLPR and moral judgment, as the S carriers rated ''unintentional harm'' less acceptable than L–L individuals.[68]

Several studies have described an association between the S allele of 5HTTLPR and impulsivity, aggression, and conduct disorders,[8,69–73] while other studies, including a recent meta-analysis, reported non-replications of these data.[74–76] Contrariwise, an association of the long form of 5HTTLPR to the same behavioral traits has been published.[77]

However, among these studies, only Reif and colleagues and Sakai and colleagues have investigated a Gene × Environment (G × E) interaction with childhood maltreatment.[8,74] Interestingly, as van IJzendoorn and colleagues have reviewed in their meta-analysis paper, a considerable number of recent (2004–2012) studies conducted on children and adolescents have highlighted a strong association between the S allele of 5HTTLPR and a differential susceptibility to the environment, showing that the S allele carriers are both more vulnerable to negative environments and profit significantly more from positive environmental conditions.[78] Negative environments included being physically bullied, lack of maternal care, and similar measures, while negative developmental outcome comprised emotional difficulties, conduct problems, relational aggression, and lower scores of moral internalization.[79,80] On the other hand, positive environments were represented by caregiver communicative parenting, proper maternal care, and similar measures, as well as positive outcomes by school and social competence, and by avoiding risky behavior.[80,81]

COMT *Val158Met (alias G472A or rs4680)*

COMT is a catecholamine-metabolizing enzyme with a pivotal role in the regulation of dopamine levels in synapses, particularly in the prefrontal cortex where the Dopamine Transporter (DAT) is poorly expressed.[82] Due to this reason and to its localization on the chromosome 22q11, deleted in velo-cardio-facial syndrome, *COMT* has raised great interest in mental illness research.[83] The G/A rs4680 polymorphism results in a functional single amino acid substitution in exon IV consisting in a valine to methionine change (Val158Met), with consequent reduction of the enzymatic activity.[84] The average frequency of the low activity allele (Met) in the overall population amounts to 0.39 (ranging from 0.01 to 0.62) according to 1000 Genome database (http://www.1000genomes.org), with the Europeans having nearly equal frequencies of the two alleles and the high activity allele being more common in all the other parts of the world.[85]

The *COMT* Val158Met polymorphism has been indicated as a possible risk factor for neuropsychiatric diseases including schizophrenia, substance dependence, bipolar disorder, obsessive-compulsive disorder, anorexia nervosa, and attention deficit hyperactivity disorder (ADHD).[86,87] Interestingly, there is evidence of the Met allele association with behavioral traits such as emotionality, impulsivity, hostility, anger, violence, and aggression and the risk of committing homicides and suicides by violent means.[88–97] Animal studies support the implication of the low activity of COMT enzyme in aggressive behavior.[98]

Most of the human association studies between the *COMT* genetic variants and violence-related traits involve schizophrenics and schizoaffective patients, as recently reported in a meta-analysis showing that males carrying the low activity Met allele, particularly the Met/Met genotype, are at risk for violent behavior.[12] However, since the sample included in the meta-analysis comprised primarily men (80%), its power was limited and a possible relationship in females cannot be excluded. In detail, the Met/Met genotype was associated to higher risk for aggressive and dangerous behavior in schizophrenics with a history of aggressive behavior and in schizophrenics with high scores at the Overt Aggression Scale or the Corrigan Agitated Behavior Scale.[93–95,97,99–101]

In line with these data, schizophrenic patients indicted for homicide, or who had attempted suicide, had a higher frequency of Met allele and Met/Met genotype.[96,97] The same association was found in a sample of non-schizophrenic individuals who had attempted suicide.[92] Conversely, some studies did not find the association between the Met allele and violence in schizophrenics,[102–107] but found an association with verbal aggression[106] and violence and physical aggression against objects in epistasis with two other SNPs in the *COMT* gene.[107] On the other hand, one single study associated the Val/Val genotype to higher scores of aggression in schizophrenia.[108]

Violent behavioral traits associated with *COMT* Val158Met include hostility (in a sample of schizophrenics),[91] neuroticism,[109] novelty-reward seeking,[110,111] and motor impulsivity within a simulated real-life decision-making.[89]

DRD4 *VNTR (alias 1–11)*

DRD4 is a G protein coupled receptor that inhibits adenylyl cyclase and adenosine triphosphate production upon interaction with dopamine. It is highly expressed in the cerebellum and pituitary gland, followed by thalamus, amygdala, and hypothalamus.[112] The *DRD4* gene is located on chromosome 11 and comprises a 48 bp VNTR in exon III. This polymorphic region ranges from 1 to 11 repeats (r): the 1–5 r are commonly known as short group (DRD4-s), while the 6–8r are called long (DRD4-l). The s-alleles are in general more common, even though the most frequent alleles are the 4r and 7r.[113] Ebstein and colleagues in 2006 reported evidence for the *DRD4* VNTR as a functional polymorphism.[114] The polymorphic repeated segment codes for the third intra-cytoplasmic loop of the receptor, which couples with the G protein to mediate intracellular signaling; the length of the variable region seems to affect the efficiency of transcription, translation, and second messenger generation, with the DRD4-l alleles lowering these processes.[114]

The *DRD4* VNTR has been linked to antisocial behavioral traits and also to attention, verbal abilities,[115] ADHD,[116] and bipolar disorder.[117] The DRD4-7r allele has been associated with higher scores of novelty seeking in a group of healthy adult subjects,[118] as well as with higher novelty seeking, smoking, and alcohol consumption in male teenagers from a high-risk community sample.[119–122]

The DRD4-7r and 2r alleles have been also associated with out-of-Africa migration distance of human population about 50,000 years ago, which correlates with increased exploratory, novelty seeking and risk-taking behavior.[123]

The DRD4-7r allele, especially in presence of adverse social constraints and low parental quality, has been consistently associated with externalizing behavior.[13,124–126] Even prenatal maternal stress predisposes to childhood antisocial behavior in offspring carrying the DRD4-7r allele.[127] The same allele has been associated with lower effortful control (EC), i.e. the ability to inhibit dominant responses[128] that are core features of antisocial behavior, in the context of negative parenting.[129] Consequently, adolescent males carrying the DRD4-7r allele showed significantly higher delinquency, short temper, and thrill seeking.[130]

Evidence also exists for the implication of the DRD4-2r allele in predisposing to anger in college students tested with the State-Trait Anger Expression Inventory,[131] while the DRD4-3r allele has been associated with worth impulsive behavior in ADHD children, measured by ''Conners'' and ''Strengths and Difficulties parent and teacher'' questionnaires.[132]

Behavioral genetics in trials

The earliest genetic evidence in a criminal case dates back to 1968 in France when murderer Daniel Hugon was convicted for the homicide of an elderly prostitute that took place in 1965 in the Pigalle district of Paris. Since Hugon carried an additional Y chromosome, a condition known as XYY syndrome, he was reputed to be prone to aggression and thus to have an innate predisposition to crime. The defense and the court permitted the use of the defendant's karyotype to mitigate the sentence.[133]

Seven years later, in the USA, in the famous case known as *People v. Yukl* (372 N.Y.S.2 d 715, Sup. Ct., 1975), the defendant was indicted and charged for the murder of a 23-year-old woman inside his apartment. The judge agreed to submit the evidence of the XYY condition to the jury, but the jurors rejected the insanity defense. Both the legal and the scientific community agreed that the association between this chromosomal condition and violent behavior was not reliable, as subsequently confirmed.

In 1994, in the USA, in *Mobley v. State* (426 S.E. 2 d 150, Ga., 1993), the defense lawyer asked the murderer Stephen Mobley to be tested for *MAOA* genetic mutation as a mitigating factor. However, the court declined the request even though there was indisputable evidence of family history of violence.

In a case published in 2010 by Rigoni and colleagues,[134] a young woman, J.F., was convicted for killing her newborn child immediately after his birth. Her genotype showed five genetic variants reported as associated with violence and impulsivity[135] and a structural MRI examination revealed reduced gray matter volume in the left prefrontal cortex, a region specifically associated with response inhibition.[136] Given that the defendant also had a history of multidrug and alcohol abuse, the experts' evaluation concluded for a diagnosis of borderline personality disorder characterized by high impulsivity and aggressive tendencies. However, the experts' testimony was not included in the sentence because the woman was acquitted for lack of evidence.

In 2009, a judge of the Italian Appeal Court in Trieste decided to reduce by one year the condemnation of Abdelmalek Bayout, an Algerian citizen who stabbed and killed a man in Udine, initially sentenced to 9 years and 2 months of prison. Together with the other evidence, including psychiatric assessment, neuropsychological evaluation, structural and functional brain imaging examination, the sentence included, for the first time in the world, the defendant genetic profile. The offender was, in fact, carrier of one or both copies of the risk alleles for *MAOA* uVNTR, *SLC6A4* 5HTTLPR, *COMT* Val158Met, and *DRD4* VNTR.[137] This sentence triggered a wide debate all over the world that still involves philosophers, psychologists, psychiatrists, lawyers, and neuroscientists.[138]

In 2011, another judge from the Italian Court in Como decided to accept an expert testimony that included neuroimaging and genetic tests in sentencing a young woman, Stefania Albertani, charged with the murder of her sister and the attempted murder of her mother. The sentence was mitigated from 30 to 20 years of prison, preceded by a period of at least three years in a mental hospital for a therapeutic and rehabilitation program.[139]

Again in 2011, in the USA, Bradley Waldroup, who had brutally killed his wife's friend and attempted to kill his wife, was sentenced to 32 years imprisonment instead of death penalty, because he carried a *MAOA*-low activity allele. This deficiency, added to his history of severe child abuse, convinced jurors to decline the death sentence (State v. Waldroup, No. E2010-01906-CCA-R3-CD, 2011 WL 5051677, at *1-3).

Discussion

Over the last decade, following the decoding of the human genome, the debate about the potential role played by distinct genetic variants in the origin of antisocial behavior has received a renewed interest. A recent meta-analysis by Vassos and colleagues systematically reviewed the literature on the genetic association with aggression and violence, raising some concerns. These authors did not identify any major effect by single genes on aggression, and concluded that the candidate gene approach has not succeeded in identifying genes associated with aggression and violence.[76] However, they did not include G × E studies in their analysis, as they examined only the main effects of single gene variants on antisocial behavior. Negative environmental conditions do play a crucial role in exacerbating the vulnerability effects associated with distinct genetic variants, especially the low-*MAOA* alleles. Thus, the lack of consideration for the environmental effects may contribute to explain the negative findings of this study. As a matter of fact, most of the studies on the genetic association with antisocial behavior reached statistical significance in groups of individuals who had been subjected to child abuse and maltreatment, low parenting, maternal distress, and/or low socio-economic status.[13,78,125–127,140]

On the other hand, previous G × E association studies demonstrating that single gene variants in combination with the adverse environment are associated to aggression and conduct disorders, like the groundbreaking work of Caspi and colleagues on *MAOA* uVNTR,[7] failed to be replicated in larger samples of individuals by very recent publications,[49,50] raising again some doubts about such an association.

Several factors may contribute to explain these discrepancies among individual studies. First, the lack of selective scales to measure each antisocial trait separately has not facilitated the identification of the associations with genotype. Second, the vast majority of the studied has focused each on a single gene variant; however, recent papers suggest that genetic profiles rather than single gene variants should be taken into consideration to obtain more robust results.[141,142] Simons and colleagues, for example, described a cumulative effect of three genetic variants, the S allele of *SLC6A4* 5HTTLPR, the *DRD4*-l alleles, and the low-activity alleles of *MAOA* uVNTR, in interaction with adverse social environment, on commitment to the ''street code'' and aggression in African-Americans.[142] Initial results from our own lab, though limited in numbers, show a remarkable different distribution of these alleles in criminal offenders as compared to individuals with no history of criminal behavior (unpublished data).

Finally, a novel perspective is emerging from recent behavioral genetics studies. Differently from the classic view, restricted to the hypothesis that some variants of ''risk genes'' may confer a genetic *predisposition to aggression*,[7,143–145] recent studies have suggested that such alleles may rather be variants of ''plasticity genes,'' responsible for a higher environmental susceptibility *to better and to worse*.[78,141,146,147] Interestingly, concerning *MAOA* uVNTR, Belsky and colleagues have highlighted that, in many studies,[7,38-40] the low-activity allele carriers, who had not experienced maltreatments, had even lower scores in antisocial behavior as compared to the high-activity MAOA carriers.[146]

The idea of a differential genetic susceptibility to both negative and positive environments definitely supports a non-deterministic concept of behavior and, at the same time, opens up to new possibilities of intervention to rehabilitate convicted people.

The genetics of criminal behavior is a very delicate issue due to its considerable impact on society and, consequently, on law. It has been often argued that behavior does not follow deterministic rules, so that no genetic variant may lead to the expression of a given behavior. If behaviors were under strict genetic control, then individuals would have very limited, if any at all, Free Will. In turn, nobody could be held responsible for their acts, as Free Will is the *conditio sine qua non* for the penal system. While there are indeed clinical conditions due to a single genetic mutation that lead to a disruption of mental function, including decision-making abilities and impulse control, such as in some fronto-temporal dementias[148–150] or familiar Alzheimer's disease[151,152] or yet in Huntington's Chorea,[153] the more general question of the relation between genes and behavior is way more complex. What appears to emerge from the studies in the literature, in spite of the methodological heterogeneity and the somewhat discrepant conclusions, is that some genetic alleles—alone or, more likely, in combination—may modulate the individual risk toward violence and antisocial behavior. For this increased vulnerability to manifest, adverse environmental factors are required. This is a well-known and commonly accepted concept in general medicine, in which the presence of a given risk factor—say high blood pressure or high cholesterol—is not *sufficient* nor *necessary* for a clinical condition to occur—in the example, a cardiovascular accident—but it does increase the likelihood that such a condition may actually occur as compared to individuals without those risk factors. Thus, some individuals who have one or more of the genetic variants described earlier appear to be at increased risk to enact a violent/impulsive conduct when confronted with a provocative situation that others would approach in a different way.

Whether or not such considerations may be relevant for the penal system is becoming more and more a subject of intense debates, as in recent years evaluation of genetic factors has been utilized to claim mitigating conditions for a defendant.[154]

As a matter of fact, not only molecular genetics but also neuroscience and brain imaging in particular are shedding new light on the neural underpinnings of mental functions, including moral judgment, decision-making processes, control of behavior, and instincts.[155] Altogether, these studies are bringing up with a renovated vigor the issue whether (some) criminals are ''bad or mad.''[156,157] This is indeed an ancient question, suffice it to think to what the Greek philosopher Plato wrote over 2000 years ago: *No one is willingly evil, but one can become evil for a bad disposition in his body and for a training without a true education; this is hideous for everyone and happens against his will*.[158]

In our opinion, further studies on the genetics of antisocial behavior, including a more objective evaluation of the environmental influence, more selective scales to evaluate different behavioral traits, and, last but not least, the analysis of multi-allelic genetic profiles, will allow scientists to achieve a more comprehensive understanding of the role of genetics on violence. This will likely lead behavioral genetics to become an important component of forensic evaluations.

Author Contributions: All authors contributed in the design, interpretation of the studies and review of the manuscript. Caterina Iofrida and Sara Palumbo collected all the literature, critically reviewed it, and drafted the manuscript. Silvia Pellegrini conceived and supervised the entire work.

ACKNOWLEDGEMENTS

Caterina Iofrida was supported by IRIS Foundation (Castagneto Carducci, Livorno, Italy). This work was supported by a grant from the Italian Minister of Education, University and Research (PRIN 2010-2011) to Silvia Pellegrini.

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