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The Monoamine Oxidase A (MAOA) Genetic Predisposition to Impulsive Violence: Is It Relevant to Criminal Trials?

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Abstract In Italy, a judge reduced the sentence of a defendant by 1 year in response to evidence for a genetic predisposition to violence. The best characterized of these genetic differences, those in the monoamine oxidase A (MAOA), were cited as especially relevant. Several months previously in the USA, MAOA data contributed to a jury reducing charges from 1st degree murder (a capital offence) to voluntary manslaughter. Is there a rational basis for this type of use of MAOA evidence in criminal court? This paper will review in context recent work on the MAOA gene–environment interaction in predisposing individuals to violence and address the relevance of such findings to murder trials. Interestingly, the MAOA genetic variants impact future violence and aggression only when combined with the adverse environmental stimuli of childhood maltreatment. Thus nature and nurture interact to determine the individual's risk. Based on current evidence, I argue there is a weak case for mitigation. But should future experiments confirm the hypothesis that individual differences in impulse control and response to provocation found in MAOA-L men (without abuse) are significantly magnified when combined with childhood maltreatment, the case could turn into a stronger one.

Keywords Violence · Genetic predisposition · MAOA · Monoamine Oxidase A · Criminal responsibility · Neuroethics · Gene × environment interaction

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Genetic Predispositions Enter the Courts

On 18 September 2009, An Italian appeals court triggered controversy when it reduced the defendant's sentence in response to evidence of a genetic predisposition towards violence [1–3]. In a brief editorial published in the European Journal of Human Genetics, Forzano et al. describe the murder case:

> "The convicted man [Abdelmalek Bayout] was an adult male affected by schizophrenia who […] was found guilty at the first level of judgement and was given a reduced sentence (9 years) owing to his mental illness. At the appeal court, a new expert assessment took place, and genetic testing was requested by the defence. […]The judge, however, reduced the sentence from 9 to 8 years, based on the fact that the accused had tested positive for genetic variants that made him particularly prone to be

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aggressive under stressful circumstances and therefore he was even more vulnerable because of that." [1].

The court found especially salient the expert testimony on the effect of Monoamine Oxidase A (MAOA)[1] genetic variants: "In particular, carrying the low activity MAOA gene (MAOA-L) could make the subject more prone to express aggression if provoked or socially excluded. It should be stressed that such "genetic vulnerability" turns out to carry even more significant weight in cases in which an individual grew up in a negative domestic social context, and was, especially in the early decades of life, exposed to adverse, psychologically traumatic environmental factors[2]" [4].

Forzano et al. decry the judge's decision, saying that such action based on genetic testing "[…] might constitute a dangerous precedent [,]" and that "A person should be judged on the basis of his actual condition and mental capacity at the moment of the act, independent of any theoretical predisposition to develop some disease or inappropriate behaviour—even assuming that there is really a link between abnormal behaviour and specific genetic variants" [1].

"I don't think this could have happened in America, where we have the Daubert ruling (which sets out stringent criteria for the admission of scientific evidence)" said Troy Duster, a New York University sociologist, when sought by the Sunday Times (UK) to comment on the case in an article published Nov 17, 2009 [2]. Dr Duster was apparently unaware that 6 months previous to his comment, a US court not only admitted MAOA gene × environment interaction (MAOA-L + childhood abuse) evidence during the guilt phase of the trial of Davis Bradley Waldroup, but the jury took it into account when reducing the charge from 1st degree murder (a capital offense) to voluntary manslaughter (a maximum sentence of 6 years) [5, 6]. Waldroup was sentenced to 32 years total [7], as he also was convicted of especially aggravated kidnapping and attempted first degree murder.

These cases show that molecular behavioral genetics has already entered courts; a discussion of its relevance, therefore, is both warranted and pressing. Did these courts make the right rulings? Is there a well supported link between aggression and specific genetic variants and does it lend support to a case for reduced punishment or charge?

In order to address these questions, I first will paint with broad strokes the historical background of the genetics of crime and then describe in detail what is emerging as the modern stage's principal player: the low activity gene variant of Monoamine Oxidase A (MAOA).

From Lombroso to Molecular-genetic Predispositions: Important Steppingstones[3]

The Italian case described above occurred in an appeals court in Trieste. Two months later in Turin on the opposite side of northern Italy, a museum reopened with rooms lined in prison artifacts—criminal skulls, artwork, handwriting, stories, family trees of criminal families, photographs, and diagrams. The grand reopening of this criminology museum, first established by Italian psychologist and physician Cesare Lombroso, marked the 100th anniversary of Lombroso's death. It has long been noted that the children of criminals seem more likely to commit crimes. Modern epidemiological research estimates that 10% of the families in a given society are responsible for over 50% of crime [8]. It wasn't until 1876, however, that Lombroso published a short volume, *L'Uomo Deliquente* or *The Criminal Man*, the first empirical theory of the biology of criminal behavior [9]. In his preface to this first edition, Lombroso outlines his mission: "To […] decide whether there is a force in nature that causes crime, [by proceeding] to the direct physical and psychological study of the criminal[.]" Lombroso came to argue that some criminals were born, not made, and could be identified by their enrichment in characteristically "primitive" or "atavistic" physical traits—cranial structure, nose size, jaw jutting, jug ears, skin

[1] This gene codes for the MAOA protein, which is important for the degradation of several neurotransmitters including serotonin, dopamine, and noradrenalin.

[2] Translated from the Italian. This quotation, with which the court concurs, is from the testimony of the psychological experts and is written in the court's case report.

[3] A thorough treatment of the period in behavioral genetics from Lombroso to the current work on MAOA is beyond the scope of the paper. I hope with this section to draw a humble outline of some important events that set the context for modern behavioral genetics.

wrinkles, tattoos, etc. These atavistic traits in criminals showed, according to Lombroso, that crime was the result of a regression to a more primitive and violent evolutionary state. Because biology is unlikely to change, he continued, the "born criminals" should be punished in proportion to their threat to society [9]. "Born criminals" composed only one third of the criminal population, however. Of the other types of criminals, Lombroso argued that the "criminaloid" was predisposed to crime by having some—but not many—physical traits of criminality and could be driven to crimes by adverse environments [9].

Though his arguments overstepped their support, reflected racial stereotypes, and have now been rightfully discredited, Lombroso's first attempts to use the scientific method in studies of criminal behavior set the theoretical groundwork for subsequent research on its hereditary nature.

After his death in 1909, Lombroso's physical "anomalies" theory was largely rejected [9]. Nevertheless, the re-publishing of Mendel's pioneering work on the genetics of pea plants ensured that the seeds of the idea of hereditary criminal behavior took root. The success of some researchers, such as Charles Davenport, in finding statistical evidence of Mendelian one-gene-one-trait inheritance in complex behaviors like Huntington's disease reinforced ideas of simple genetic determinism and encouraged others to redouble efforts to look(in vain)for the same simple relationship in behaviors as wide ranging as "feeblemindedness" [10]. These early human studies of behavioral genetics were complemented by work in animal models.

With the rise of human genetics came eugenics, gaining in speed during the interwar period. Twin research, then the cutting edge, blossomed, allowing researchers to form better statistical estimates of the heritability of complex traits; because identical twins are genetically identical, genetic traits should appear with stronger similarity in identical than fraternal twins. Of note, Germany became a major powerhouse in the field of twin research under Verschuer [11]. The mutually-frenzying relationship of eugenics with policy led to forced sterilization laws and immigration quotas for those from "feebleminded origins" in the United States, and reached its abominable zenith in the human genetics laboratories of Nazi Germany [11].

The atrocious human rights violations at Auschwitz in the name of human genetics and the surprising vigor and international voice with which many German geneticists/eugenicists bent their science to the aims of Nazi racial policy combined to strike a large blow to the prestige of behavioral genetics [11]. As McGue [12] succinctly notes, "Behavioral genetics was nearly completely discredited by its early association with the eugenics movement. Few intellectuals wanted to be associated with a scientific Endeavour perceived to have contributed to the Nazi's repressive policies, no matter how indirectly." The inclusion of many of the same Nazi eugenicists at the first meeting of the American society of human genetics in 1949, however, indicates that the true state of events after the war was more complicated [13]. Regardless of the precise cause, in the 1950's competing behaviorist explanations eclipsed hereditary theories of behavior; behaviorists like B.F. Skinner and John B. Watson argued that the baby entered the world as a "blank slate" and that environment, not heredity, determined all behavior [10, 12].

The success of the field of medical genetics in inborn errors of metabolism, which occurred during this period, kept the door open for future behavioral genetics. Of most relevance here is the story of Phenylketonuria (PKU) [14]. Inherited in a simple recessive pattern, PKU is a condition in which the affected child cannot metabolize the phenylalanine present in protein rich foods. Phenylalanine builds to toxic levels that cause irreversible brain damage and mental retardation. In a triumph for molecular science, however, the discovery of the mechanism (build up of phenylalanine) led to a method of early diagnosis and the development of a treatment (a low Phenylalanine diet) that could avert the mentally retarded outcome if immediately applied. Thus PKU became a striking example that we are not "determined exclusively by our genes," but that we have the capacity to modify our environments (diet, here) to overcome previously unavoidable outcomes; genetic knowledge confers empowerment, not helplessness.

Genetic predispositions to complex physical conditions gained credibility and public trust with their success in cardiovascular disease (see [15]), establishing terminology and a way of thinking about risk that was an essential step towards current molecular genetics research on predispositions to violence.

Standing atop these steppingstones, several groups of scientists have begun to reexamine the hypothesis that crime has a genetic basis. What they have found

is a gene × environment interaction, far from Lombroso's born criminal and even farther from "crime genes."

What is a Gene × Environment Interaction?[4]

You take the family car for a spin down Main St. Unbeknownst to you, the computer software that controls the car's anti-lock brakes rounds down when it calculates how many times per second to engage the brakes. About 35% of cars on the road use this sort of anti-lock brakes software, but 65% use one that rounds up. If you were to slam on the brakes with enough force for them to engage the antilock brakes, cars like yours actually pump the brakes fewer times per second and take longer to stop. Given good weather and good driving technique, however, which antilock brakes program you have shouldn't make a difference. If you never slam on the brakes, you never engage the anti-lock system, and your car behaves just like every other.

Now imagine that it begins to snow. Soon, slippery snowflakes blanket the road. Your muscles tense. Combined with this adverse environment, suddenly you have become much more likely to slam on the breaks and unveil the disadvantage in the computer program, which ultimately makes it more likely for you than for the general population to be in a car accident.

Importantly, the combination is not deterministic. By this I mean determined only by your computer program regardless of what else happens. You may never slam on the brakes. Even if you do trigger the antilock brakes, the car will still stop; it will just take longer. Whether you *actually* get into an accident will depend *not only* on the anti-lock brakes program but on your speed, driving experience, alertness, actions of the other drivers, the distance between you and the next car, etc.

But what happens if a car surprises you? It comes down to a nagging fact: if you, or any of 35% of the population like you, drive in the snow, you are more likely than most to get into a car accident and as a group, do. How should we take into account your non-deterministic predisposition to car accidents?

Recent behavioral genetics and neuroscience suggests that we may have unearthed an analogous situation that applies not to car accidents, but to impulsive violence—and there is no possibility of a parts recall. Instead of an adverse environment combining with an antilock-brakes program, it combines with a gene variant coding for monoamine oxidase A (MAOA). One variant confers susceptibility to the negative influence of adverse environmental stimuli like childhood maltreatment to predispose to future violence. The other variant confers resilience. Thus both nature and nurture interact to modify the individual's risk.

The following will review the science linking the MAOA variants to aggression. Though there are other genes associated with violent behavior, I concentrate on MAOA for two reasons 1) the comparative robustness of its supporting evidence and preliminary data on mechanism make it the most promising case for this type of research 2) Both the trials in which molecular genetic predisposition data has had an effect, *Bayout* (2009) and *Waldroup* (2009), the effect was due heavily to MAOA.

A Note on Violence

Before continuing, it is important to clarify that this paper refers to impulsive, reactive violence caused by a stimulus: anger, frustration, or other provocation. I will sometimes use aggression and violence interchangeably, but always I am referring to this reactive form. Although reactive violence can sometimes be adaptive, as in defending oneself, a reaction that is disproportional to the provocation, or in response to perceived and not actual provocation, can become pathological. When it does, this impulsive violence takes major tolls from society. The World Health Organization recently estimated 560,000 people to be dying in a single year as a result of homicide (i.e. greater than 1 person per minute), which is almost 3.5 times the number estimated to be dying as a result of

[4] A similar scenario actually did happen: "February 8, 2010—Toyota […], today announced it will conduct a voluntary safety recall on approximately 133,000 2010 Model Year Prius vehicles to update software in the vehicle's antilock brake system (ABS). [… Some] reported experiencing inconsistent brake feel during slow and steady application of brakes on rough or slick road surfaces when the ABS is activated" http://www.toyota.com/recall/abs.html

collective violence[5] [16]. Most of these homicides represent casualties of impulsive aggression; while some of the most chilling cases in criminology deal with individuals who commit acts of premeditated violence, these cases are of the extreme minority and will not be discussed here [17].

MAOA

First Clues from the Netherlands

Brunner and colleagues [18] found the first evidence that a single gene might be important in violence and aggression. Many of the men in a large Dutch family exhibited a strange behavioral disorder characterized by mild retardation and antisocial behavior: inappropriate aggression, rape, assault, and other violent crime. Brunner and colleagues identified that a single nucleotide (one of the As, Ts, Gs, and Cs that link-up together in the genetic code) in the MAOA gene sequence that was altered in these men artificially terminated the production of MAOA protein leading to its complete absence (C to T, position 936). As mentioned briefly above, MAOA is involved primarily in degradation of the neurotransmitter serotonin and to a lesser extent, noradrenaline and dopamine. Interestingly, mice genetically engineered to be devoid of MAOA protein have increased levels of serotonin and are more aggressive [19]. Because dysregulation of the neurotransmitter, serotonin, had been previously associated with violence [5], a dysregulation of its turnover in these Dutch men was a particularly attractive model for their violent behavior. The MAOA gene's location on the X chromosome carried the potential to explain why violent crime and antisocial personality disorder is observed disproportionately in men in the general population. Men inherit a single X chromosome while females inherit two, which puts men at greater risk for inheriting no functional copy of the MAOA gene.

Because this non-functional mutation in the MAOA gene turned out to be extremely rare in the rest of the population, the results of the Brunner study were of limited use but set the stage for the research that followed.

[5] 170,000 per year were estimated to die of collective violence [16].

A Gene × Environment Interaction

Further research revealed that the MAOA gene exists in several common variations. In the gene's promoter, a region that controls transcription and expression efficiency, there are a variable number of nucleotide tandem repeats (VNTR) arranged much like links of sausage. While the VNTRs range from 1 to 5 repeats, genes with three or four repeats are most common. Approximately 30% of the alleles (gene copies) in the general population contain three repeats while approximately 65% contain 4 [20]. Interestingly, in vitro studies indicate that the variant with three repeats is expressed significantly less efficiently than the variant with four repeats [21], although there is conflicting data about whether this is also true in humans [22].

Caspi and colleagues [21] tested the hypothesis that the low-expressing variant would correlate with antisocial behavior. They tracked a birth cohort of 1037 New Zealand male children at regular intervals as they grew to 26 years of age. Antisocial behavior was measured by convictions for violent crime, diagnosis of adolescent conduct disorder, a psychological assessment of violence-acceptance, and antisocial personality disorder symptoms reported by an informant.

When the children were grouped by the low (three repeats; MAOA-low) or high (four repeats; MAOA-high) activity polymorphisms in the MAOA gene, there was no significant correlation between genotype and antisocial behavior. Consistent with previous studies, however, there was a significant positive correlation between maltreatment and later antisocial behavior (8% had experienced severe maltreatment between the age of 3 and 11 years). Strikingly, boys who had been maltreated AND possessed MAOA-low were significantly more likely to exhibit later antisocial behavior than were maltreated boys with MAOA-high.

Importantly, the boys who were maltreated were not significantly more likely than non-maltreated boys to possess the MAOA low genotype (P=0.82), which suggests that genotype did not predispose the boys to receive maltreatment, but rather impacted their resilience to it. This gene × environment interaction was still seen after correction for socioeconomic status and several other environmental variables. The low MAOA variant seemed to confer sensitivity to maltreatment while the high MAOA conferred a sort

of protection. Although only 12% of the boys in the cohort were maltreated and possessed the low MAOA genotype, they were responsible for 44% of convictions for violent crime. This was the first example of a gene × environment interaction correlating with a behavior and the first time such an interaction was shown to predispose anyone to criminal violence (see Fig. 1 for a diagrammatic representation of the interaction).

MAOA Stands up to Meta-analysis

Several other groups confirmed and expanded upon this research over the next 5 years [23]. Although some groups were not able to repeat the findings of Caspi et al. [21] with their own sample groups, this may have been due to differences in definition of maltreatment or of aggression, or to a lack of statistical power. This critique highlights an important shortcoming in the current literature: exactly what is an adverse environment needs to be better defined and might be the leading reason for discrepancies between trials [24]. Some data, moreover, suggests that the resulting predisposition might be proportional to the severity and duration of the exposure to the adverse environment rather than an all or nothing situation [24, 25]. The developmental window of susceptibility will also need to be systematically investigated. Despite these technological shortcomings, several meta-analyses, which pooled the sample data from up to eight studies to increase statistical power, and attempted to further standardize its variables, were able to show a significant effect for the predisposition of maltreated boys with the low MAOA genotype and aggression [20, 23]. That the interaction held up to the meta-analysis even with the agglomeration of loosely defined "adverse environments" is important and surprising, as few gene–environment interactions in behavioral genetics have done so. For example, the other most studied gene × environment interaction, the one between the 5HTT-LPR (the gene coding for the serotonin transporter), stressful life events, and depression, did not pass testing by a similar meta-analytical method [26].

Modern Investigations of a Mechanism

These epidemiological findings set off a flurry of neuroscientific inquiry into mechanism of the effect. Unfortunately, these studies were conducted on the MAOA gene variants alone without knowledge of exposure to adverse environment; nevertheless, they provide important insights. A recent study [27] shows that the MAOA gene promoter contains glucocorticoid (stress hormones)/testosterone response elements that govern the gene's transcription, which could further tie MAOA to male violence. Glucocorticoid binding leads to a larger increase in transcription than does testosterone binding, which suggests that an elevated level of testosterone would compete for binding and actually decrease the net rate of transcription. The study went on to show that high

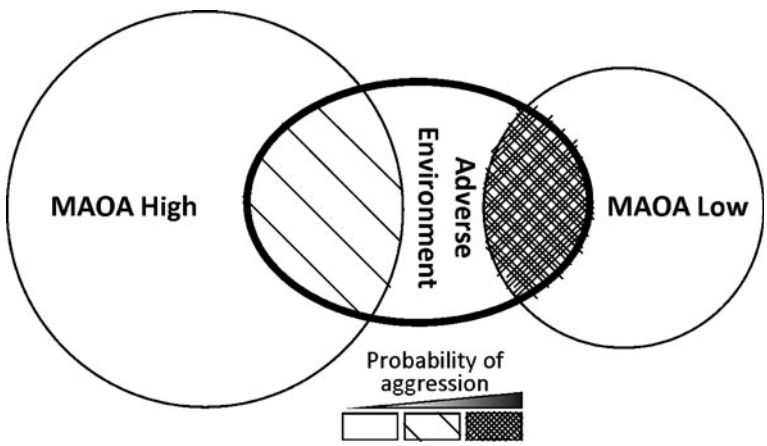

Fig. 1 *Diagramatic representation of the MAOA gene × environment interaction*. Approximately 65% of males (*large circle*) possess the MAOA high gene variant while approximately 30% possess the MAOA Low variant (*small circle*). When equal portions of these groups are exposed to an adverse environment during childhood (the *oval*) only the MAOA low group on average shows a significantly increased probability of aggression (*darker shading*)

testosterone levels, shown previously to correlate with antisocial personality disorder (ASPD), correlated with ASPD and aggression only in males who also possessed the MAOA low genotype. Importantly, there was no significant correlation between MAOA high males producing high testosterone and ASPD or aggression.

Using positron emission tomography (PET) with a radiolabeled MAOA-specific tagging molecule, clorgyline, Alia-Klein et al. [28] showed that differences in the expression of MAOA protein in the human subjects accounted for greater than 30% of variability in trait aggression as assessed by survey.[6] Although they detected no correlation between genotype and MAOA activity, they did not look at whether subjects had a history of childhood maltreatment. It could be feasible that possession of the low MAOA alone would not diminish the amount of protein to levels detectable in this assay unless it had previously been combined with childhood maltreatment.

Buckholtz and colleagues [29] went on to show that functional connectivity between the ventromedial prefrontal cortex (vmPFC), a region implicated in impulse repression, and the amygdala, a region implicated in emotional salience, was increased only in males with the low MAOA gene. Moreover, when performing an emotional face matching task, MAOA low males showed increased activation of the amygdala and decreased activation of the vmPFC as compared to control subjects. Interestingly, decreased activity of vmPFC and increased activity in amygdala had previously been correlated with antisocial behavior, conviction of violent crime, and self reported violence. However, the reverse inference problem of imaging makes it unclear whether the activation pattern (or endophenotype) seen in these previous studies is cause or consequence of the violent behavior. The connection between MAOA-low genotype, this endophenotype, and aggression provides some of the first evidence, however, for a mechanistic role of the gene in this altered brain activation. This neuroimaging study found this effect without differentiating between those who had experienced maltreatment as children. It is intriguing to postulate that the increased activation of the emotional amygdala and decreased activation of the inhibitory input from the cortex could act like the slower-stopping antilock brakes did in our analogy.

The authors note that there is no direct anatomical connective circuitry between the vmPFC and the amygdala. Using a functional connectivity regression analysis, however, they found that this functional connectivity seems to be mediated through the perigenual anterior cingulate, a region with anatomical connections both to the vmPFC and the amygdala. The increased activation of the perigenual anterior cingulate in this circuit is very interesting because of this region's importance in serotonin signaling. The perigenual anterior cingulate contains the highest concentration of the serotonin receptor subtype 5-HT2a, a receptor shown by PET to be even further upregulated in the cingulate in those who have committed violent crime [17]. Moreover, inhibition of the 5-HT2a receptor decreases impulsivity and aggression in animal models while activation increases aggression [30].

Finally, MAOA low subjects show greater activation of the anterior cingulate in response to being excluded from a virtual "ball-passing" game [31] and incidences of aggression become more frequent and of greater magnitude in response to provocation [32] as compared to MAOA high subjects (see Fig. 2 for schematic mechanism).

MAOA on Trial: Legal Implications of an Imperfect Predisposition to Aggression and Violent Crime

Lombroso believed that there was a corporeal seat of violent crime that he could descry in the face of a man. Current research peers behind the face to the genetic building blocks and neuronal networks that enable him to learn and react to an ever changing environment. This research suggests that some people have genetic susceptibilities to adverse environments. Of those children confronted with an adverse environment, only those that carry the low expressing variant of the MAOA gene become more likely to commit future reactive violence. The result, far from "born criminals," is a group of individuals that given the right combination of gene and environment are more vulnerable to act on violent impulses.

[6] PET is an imaging technique that enables researchers to visualize the location and density of a protein of interest by labeling it with a tagged molecule that is injected into the blood.

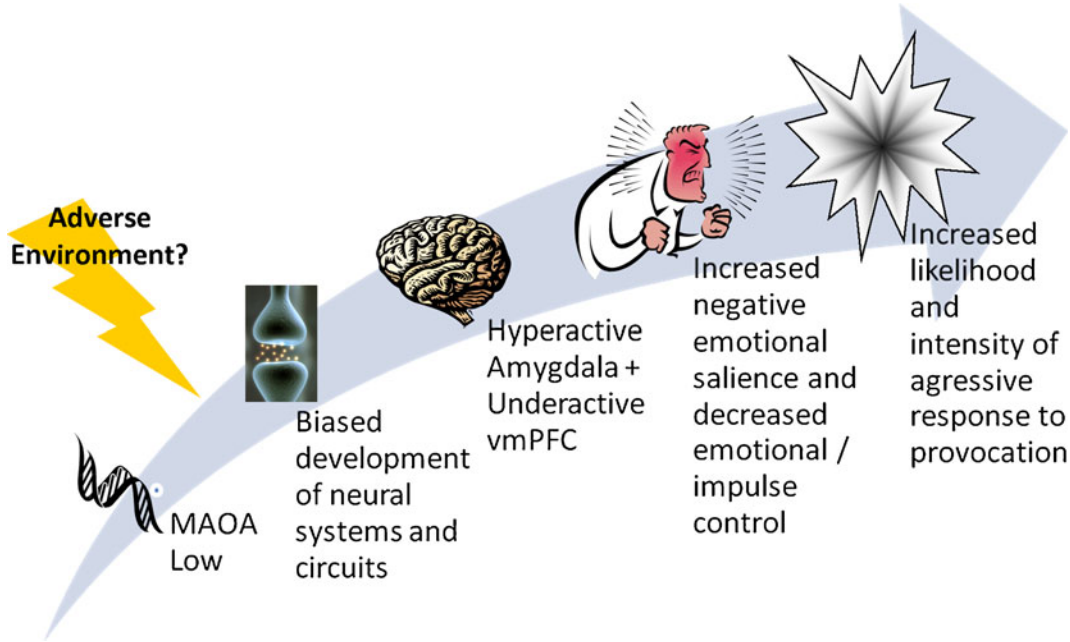

Fig. 2 *Diagramatic representation of proposed mechanism for MAOA variants* (reading from *left* to *right*). The hypothesis follows: presence of the MAOA low variant under normal conditions leads to a slight biasing of the development of neural systems that in turn contribute to a hyperactive amygdala and underactive ventromedial prefrontal cortex (vmPFC) in response to emotional stimuli. This aberrant activation pattern may then contribute to exaggerated emotional salience with decreased impulse control. This creates the risk of provocative stimuli seeming *even more* provocative and contributing to increased likelihood and intensity of response. Though more empirical research is needed, it is hypothesized that the addition of an adverse environment (lightning bolt) supercharges the mechanism, thereby leading to even greater effects

Historical Application

The first appeal to the MAOA gene and violence susceptibility was *Mobley v. State (1995)* [33]. The defense requested MAOA genotyping for the rare mutation found in the Dutch family in the Brunner et al. study of Stephen Mobley, a 29 year old man accused of murder. At this time, the MAOA gene × environment interaction data had yet to surface. Because Mobley's family tree did not fit the proper inheritance pattern for the lack of function MAOA mutation, the judge determined that genotyping was not warranted. Mobley was later executed [34].

Since Mobley, discussion about the relevance to criminal courts of the data like that on MAOA has treated it like a distant possibility. In 2008, Pieri and colleagues conducted focus groups of law professionals (social workers, parole officers, judges, law students) in which "almost all participants were skeptical about the possibility that research into the genetics of aggressiveness and violence might benefit, or even enter, their fields of practice, in the foreseeable future or ever" [35]. Perhaps surprising is that by 2007, however, genotyping evidence on MAOA variants (of the gene × environment type) had been submitted in a few U.S. criminal cases and, while it had no effect on outcome, had been tolerated[7] [34]. *Bayout* (2009) and *Waldroup* (2009), force us to acknowledge that it has indeed breached the courts (see Table 1 for summary of MAOA cases).

In *Bayout* (2009), MAOA data was introduced in the sentencing phase. In *Waldroup* (2009), it was introduced in the pre-conviction (liability) phase. These represent the two main phases at which any evidence may act. During the liability phase, a case can be made for a full defense (which if successful will lead to a verdict of not guilty), or a partial defense (which if successful will lead to conviction of a lesser charge) [36]. An example of a full defense is insanity. An example of a partial defense is provocation.

[7] See [34]. Unfortunately, Bernet et al. does not identify the relevant trials by name, but codes them. Note also that Bernet provided the expert evidence in the Waldroup trial [5].

Table 1 MAOA genotyping in court

Case	Brief description	Genotype	Adverse environment?	Result
Mobley (1995)	Charged with murder. During trial, asked for genotyping according to rare Brunner et al. study	Genotyping refused	n/a	Executed
Waldroup (2009)	Charged with murder (capital offense) of estranged wife's friend, attempted murder of wife, and two counts of kidnapping after escalating argument	MAOA L	Childhood Abuse	Voluntary manslaughter (instead of murder); two counts of aggravated kidnapping; attempted 2nd degree murder. 32 year sentence
Bayout (2009)	Defendant assaulted by group of youths, after which he buys a knife and follows victim down street. Kills victim, mistakenly thinking victim was one of the assailants. Possibly delusional at time	MAOA L	Unclear. Culture shock/social isolation? Schizophrenia?	Sentence reduced by 1 year for genetic evidence

The unnamed cases mentioned in [34] are omitted from the table

Evidence that is not strong enough to successfully serve as a full or partial defense can be offered for consideration to mitigate the punishment during the sentencing phase. The Crown Prosecution Services Sentencing Guidelines, for example, lists among its mitigating factors lack of premeditation, mental disorder or disability, provocation less than defense, any element of self defense, age and the West law dictionary also includes childhood abuse.[8] Though it has elements that could be used in several defenses, it might be reasonable to argue that the MAOA interaction could wield most force at the level of sentence determination (See Table 2). While a thorough discussion of relevance of the MAOA data to all the possibilities listed in Table 2 is beyond the reach of this paper, I will focus on provocation as an illustrative example.[9]

"Incapability of Repression" is not Required for Relevance in Court

First, let us dispel what seems to be Forzano et al.'s [1] main argument against the legal use of genetic predispositions: "There is no scientific support to declare that gene variants, claimed to predispose to aggression, would make the carriers incapable of repressing an aggressive behaviour and thus unable to choose appropriate socially acceptable behaviours."[10] Such a declaration would be tantamount to defining the behavior involuntary action similar to spasm or convulsion. In this case, the *actus reus*, or necessary voluntary component of the crime, would be negated and a defense of automatism may be brought forward (see [36]). Forzano et al. are factually correct in pointing out that current scientific evidence is insufficient to argue that MAOA even when combined with severe abuse leads to legally involuntary action. Their argument fails to take into account, however, that the vast majority of defenses and partial defenses—those concerned not with *actus reus* but *mens rea*, the guilty mind—as well as sentencing considerations, do not require the agent to be incapable of repressing the behavior in this strict involuntary sense [36]. Likewise, it is not necessary to prove that MAOA or other genetic variants render an individual *incapable of repressing* his behavior for their effects to be relevant in court.

Can the Framework of Provocation Stretch to Incorporate MAOA?

In concluding their 2008 paper on the MAOA story, Buckholtz et al. [19] propose "that MAOA genotype

[8] Although different jurisdictions accept different criteria for mitigating factors, most of them resemble what I have outlined here. Mitigating factors are most relevant in jurisdictions that still permit capital punishment.

[9] I will leave discussion of Insanity and diminished capacity to another paper, for example.

[10] This comment seems to be reacting against notions of hard genetic determinism, a misinformed stance responsible for phrases like "crime genes."

Table 2 Areas of possible legal relevance for the MAOA interaction

Full defense	Negation of guilt	MAOA	Notes
Duress	Requires threat of grievous bodily harm. Though the strongest cases are where threat is reasonable and immediate, threat can be falsely believed and imminent [36]	Perhaps relevant in so far as MAOA would contribute to a false belief or false appraisal of threat. But likely not so great that it would lead to the full defense	Duress is not a defense to murder. Also subject to reasonable man test
Insanity	M'Naughten Rules: "A defect of reason, from diseases of the mind, as not to know the nature and the quality of the act he was doing; or, if he did know it, that he did not know he was doing what was wrong" [36]	Possible but unlikely: unclear would count as "disease of mind" or that it would have level of interference in knowing wrongness/nature/quality for this defense	Some US jurisdictions have abolished the insanity defense
Partial defense	Murder to manslaughter	MAOA	Notes
Diminished Responsibility (capacity in US)	*HA* 1957s2 "1) Where a person kills or is a party to a killing of another, he shall not be convicted of murder if he was suffering from such abnormality of mind (whether arising from condition of arrested or retarded development of mind or any inherent causes or induced by disease or injury) as substantially impaired his mental responsibility for his acts and omissions in doing or being a party to the killing" [36]	Possible: wording here is remarkably loose. MAOA gene × environment interaction could potentially be thought as abnormality of mind arising out of injury (abuse) or simply "inherent causes."	Not available in many US jurisdictions, especially after reaction to use as basis for the "twinkie defense" in the killing of Harvey Milk
Provocation	*Camplin* (1978) "the reasonable man is a person having the power of self-control to be expected of an ordinary person of the sex and age of the accused, but in other respects sharing such of the accused's characteristics as they think would affect the gravity of the provocation to him [36]."	Possible: stronger if reasonable man subjectified; could thereby include diminished impulse control. As it stands, the over-salience of external social cues may make the defendant more susceptible to provocation (b/c it seems to hold more gravity to him)	Subjectification of reasonable man possible. Roiled in debate
Sentencing	Mitigation of punishment	MAOA	Notes
	Crown prosecution services sentencing guidelines mitigating factors: • Lack of premeditation • Mental disorder or disability • Provocation less than defence • Any extent of self defence • Age • Childhood abuse (west law)	Strongest case. Ticks all the boxes (except for age). Less premeditation, elements of mental disorder, easier provocation, false beliefs of self defense, all combined with childhood abuse	Most relevant in capital trials. Mitigating factors vary somewhat between jurisdictions, but most resemble what is to the left

modifies an individual's 'socioaffective scaffold': the basic neural equipment for social and emotional experience, which subserves cognitive routines for contextualizing social signals, decoding ambiguous social interactions and regulating affective response in the face of perceived interpersonal threat." Cognitive experiments seemed to indicate that MAOA low men are more sensitive to social rejection, have more intense cognitive responses to fearful and negative stimuli, and decreased cognitive control over the

behavioral output from those interactions. Though it remains untested, the hypothesis is that an adverse environment throws that "socioaffective scaffold" even farther of its axis such that the above mechanisms become even more intense. If further work supports this hypothesis, a partial defense that is "provocation-like" may exist for MAOA-L men with childhood maltreatment. Until further work supports it, however, there is a weaker case.

Perceived not Actual Provocation

In their 2006 paper, Eastman et al. [37] suggest that a provocation defense would be implausible: "the mental characteristics cannot be 'proneness to violence' but must be characteristics that made the defendant more susceptible to the particular provocation emitted. This seems infertile ground for neuroscientific evidence." If the above hypothesis is supported, however, these individuals may be "prone to violence" specifically *because they are more susceptible to the particular provocation*. That is, the particular stimulus is perceived as more intense. In practice, the partial defense of provocation if successful reduces a murder charge to manslaughter. The test of provocation is composed of one subjective (was the defendant provoked) and two objective limbs (would a reasonable man have been provoked, would a reasonable man have done as the defendant did). *Camplin* (1978) [38] explained that "the reasonable man is a person having the power of self-control to be expected of an ordinary person of the sex and age of the accused, but in other respects sharing such of the accused's characteristics as they think would affect the gravity of the provocation to him" [36]. The altered evaluation of stimuli due to the MAOA variants, therefore, might reasonably qualify as a characteristic that would affect the gravity of provocation to the accused. It seems also that the increased gravity of the provocation would satisfy even the stringent ruling in *Newell* (1980) [39] that such characteristics would need to have "sufficient degree of permanence to make it part of individual's character and personality. More importantly, there must be some real connection between the nature of the provocation and the particular characteristic of [the defendant] by which it is sought to modify the reasonable man test" [36].

A Subjective Reasonable Man?

Currently, there is vibrant debate about whether individually diminished levels of self-control should modify the reasonable man, making him more subjective [40]. The reasonable person already makes allowances for individual difference for physical attributes; for example, physical size and strength or physical disability [40]. Recent research on impulse control further challenges the physical/mental distinction by revealing that this faculty fatigues much in the same way that a muscle does [41]. It could be argued the reasonable person should take into account significant variations in the size of both the physical muscle and the mental one (which arises from physical processes) or should reject both. An objectively small aggressor could be threatening to another man with even smaller muscles; so could a small impulse to one with even smaller impulse control muscles.

To illustrate this possibility, let us consider a case described by Berns and Swerdlow [42]:

> A man who we will refer to as Tim was convicted of amassing child pornography. After several months in prison, Tim began complaining of painful headaches. Doctors imaged his brain and discovered a large tumor impinging on his orbitofrontal cortex, a region thought to be involved in impulse control. A tumor growth like this can interfere with behavior essentially by compressing and thereby strangling the tissue's normal functions. Interestingly, Tim's pedophilic tendencies disappeared when the tumor was removed. Shortly after the surgery, he was deemed fit for release. Several months later, however, he again began to stockpile child pornography, was discovered, jailed, and a brain image revealed that his brain tumor had grown back. Doctors again removed the tumor, and Tim's pedophilic tendencies again vanished.

In the tumor's absence, Tim behaves in a socially acceptable manner. It is only in its presence that his executive functions, including the ability to control his unacceptable impulses, become reduced below the baseline level that would lead to his refrain from child porn in everyday conditions. Should a tumor pressing on the frontal cortex be incorporated into the reasonable man? In *Luc Thiet Thuan v. R* (1997)

[43], where the defendant had a tumor that may have similarly decreased his self-control, the judge ruled that this condition was not a relevant characteristic. Later that year in *Campbell* (1997) [44], however, the judge overturned the decision, explaining, "If the concept of the reasonable man expressed […] were accepted without any qualification, successful pleas of provocation would be rare indeed, since it is not altogether easy to imagine circumstances in which a reasonable man would strike a fatal blow with the necessary mental intention, whatever the provocation. It is in recognition of human frailty that the scope of the defence of provocation has, to a very limited extent, been enlarged."

A split (3–2) decision in *Smith* (2000) [45] ruled further in favor of the relevance of diminished self control: "a characteristic of the accused, whether temporary or permanent, which affected the degree of control society could reasonably have expected of [the defendant] and which it would be unjust not to take into account" [36]. The dissent, voiced by Lord Millet, responded: "The objective element of provocation should not be eroded and its moral basis subverted in order to provide a defence of diminished responsibility outside the limits within which Parliament has chosen to confine it" [36]. *Rowland* (2003) [46] and *Weller* (2003) [47] embraced the majority approach. Lord Justice Mantell explained that "the judge should not tell the jury that they should, as a matter of law, ignore any aspect. He may give them some guidance as to the weight to be given to some aspects, provided he makes it clear that the question is one which, as the law provides, they are to answer, and not him" [47]. The decision in *Smith* (2000) was questionably overruled by *A-G for Jersey v Holley* (2005) [48] and *Holley* (2005) was subsequently upheld by *James; Karimi* (2006) [49]. The current measure is an ordinary level of self-control. Should the debate swing the other way, however, the MAOA story could pack a double punch with both increased salience and decreased self-control modifying the reasonable man.

Before the age of non-invasive brain imaging, tumors would have gone unnoticed and Tim would have been punished too harshly. It is an ethical imperative, therefore, that legal structures expand to incorporate our understanding of the mind, its abilities, and its weaknesses. Though they are of differing impact magnitudes, Tim's tumor and the MAOA gene × environment interaction share an important similarity. Namely, the MAOA interaction may impair the functional connection between the frontal cortex and the amygdala, which is perhaps equivalent to cutting the power brakes tempering the emotional reaction and decreasing control of violent impulses.

It may be objected that the inclusion of differences in impulse control would create a slippery slope that would lead to even "mere individual differences" in the personal level of impulse control serving in an exculpatory fashion. I counter that keeping in mind the degree of impairment introduces traction. We do not consider all height differences relevant to perceived threat. While two inches might not be relevant, two feet might; the impact of MAOA low alone might not be found relevant by a jury, but that of MAOA low combined with childhood abuse and altered behavioral measures might.[11]

Inferring Mental States: Is MAOA Evidence Really That Different from Other Evidence?

There is understandable reticence to including probabilistic information in criminal trials because of the potential for miscarriages of justice. Forzano et al. voice a version of this concern when they say, "a person should be judged on the basis of his actual condition and mental capacity at the moment of the act, independent of any theoretical predisposition to develop some disease or inappropriate behavior." While it is reasonable to argue that the moment of the act is what matters, demanding one prove the *actual* mental state at any moment is unreasonable and unrealistic. The problem of finding out this mental information is neither new nor restricted to

[11] A reasonable argument is that the jury might overweight this kind of evidence. The basis for overweighting would be a sort of "genetic exceptionalism," or false belief that genetic evidence is in fact inherently different than other evidence. While there is gravity in this risk and it should be taken seriously, excluding genetic information will likely reinforce the very ideas of "genetic exceptionalism" that should be combated. Only by becoming comfortable with talking about and engaging with genetic information can we hope to overcome the specter of "genetic exceptionalism" and the risk of overweighting genetic evidence in trials if it is relevant to the case (see Parens 2010 [53] for "why talking about behavioral genetics is important and difficult"). During the transition period, juries should be guided about how to interpret genetic information.

genetic predispositions, however. In reality, we can do nothing more than *infer* the mental state, yet this is something that courts do all the time. What courts rely on are observed behaviors at the moment (if there is a witness) and after-the-fact psychiatric (or other) evaluations, all "mere" correlates to the "actual" condition and mental capacity, in order to build a case for a certain mental state—in other words, to support the inference. Though courts would be reticent to define them this way, all inferences are by definition probabilistic. Yet courts recognize the problem when they point out that "Beyond reasonable doubt" does not mean "no doubt." In other words, *probabilities do matter* (in so far as they help us make better inferences of mental states). As a corollary, *predispositions matter* (in so far as they provide useful data on probabilities).

Both diagnoses of mental illness in the classical sense (i.e. according to the DSM IV), for example, and genetic predispositions provide useful probabilistic information. They both act as signals that a relevant state is more likely than usual and that the court therefore has a responsibility to look for supporting evidence. MAOA data should be viewed as simply another tool to help in making inferences about mental sates. To illustrate, a diagnosis of schizophrenia can be thought of as a predisposition to (or risk for) hallucinations, delusions, and/or bouts of cripplingly disordered thinking. This would be similar to classifying a person with epilepsy as being predisposed to develop (or at risk for) seizures.[12] In both cases, having a diagnosis would be only probabilistically related to experiencing hallucinations, delusions, seizures, etc. at the time of the crime.[13] Furthermore, experiencing hallucinations, delusions, seizures, etc. at the time of the crime would only be probabilistically relevant for criminal responsibility. For example, consider two delusions that would have differing relevance in a murder trial: 1) Sam believes his child to be replaced by a fairy doppelganger and that if he did not kill this doppelganger, Sam's own child would certainly die; 2) Sam believes he would be paid $10,000 for killing his child. Again, if the court infers that a delusion was present at the time of the crime, it would then be necessary to infer which type of delusion was present. In this way, courts build a tower of nested probabilities to house the inferred mental state. In this framework, there is nothing inherently special about genetic predispositions. Difficulties in proving "actual condition and mental capacity at the moment of the act" are similar in type between risk factors like schizophrenia and risk factors like gene × environment interactions.

At this point, one may bring up the argument, as Forzano et al. do, that "genetic variants associated with schizophrenia do not add to the evaluation of the phenotype itself." I agree that there is an argument for a diagnosis of schizophrenia screening out the usefulness of genetic variants associated with schizophrenia, as the diagnosis provides stronger probabilistic support for a relevant hallucination etc. This does not mean, however, that genetic variants would have no value. Possessing genetic variants associated with schizophrenia—if one had this information but not psychiatric evaluation—would serve as a flag indicating that one should check for the existence of the relevant phenotype. Similarly, if a genetic variant was significantly associated with delusions of persecution or threat (i.e. those delusions particularly pertinent to responsibility as opposed to non-threatening delusions) this information would enrich the diagnosis of schizophrenia in the court. Genetic variants whose effects are relevant via a mechanism distinct from schizophrenia, which seems the case with the MAOA variants, would also be useful. I am not arguing that all predisposing markers—whether psychiatric diagnosis or genetic variant—carry the same level of probabilistic information. They obviously do not. Some genetic variants contain less information than others, or only contain more probabilistic information when combined with a specific environmental stressor like childhood abuse. Similarly, a diagnosis of ADD (attention deficit disorder) would contain lesser probability of a relevant impairment than diagnosis of schizophrenia.

[12] One might reasonably object to my conceptual reorganization by pointing out that a diagnosis of Schizophrenia or Epilepsy requires more than just a predisposition to certain behaviors; rather, it requires one to actually have exhibited those behaviors for some period of time. If the defense claims the first exhibition of the behavior is during or near the moment of the crime, however, a diagnosis—itself an inference made by the psychiatrist—should be investigated and if determined by further psychiatric evaluation to be warranted can further build support for the existence of the claimed mental state at the moment of the crime.

[13] Note that one does not need to have schizophrenia to have delusions or hallucinations.

These individual weights are an empirical issue. While the relative risk of a relevant impairment for someone diagnosed with schizophrenia may turn out to be higher than for someone with MAOA low + childhood abuse, the *type* of information (probabilistic) and the difficulty of identifying the *actual* occurrence in each case is similar. A rational agent should either accept both as useful in court or reject both.

If the decision is to accept, then in both cases the court needs corroborating evidence to build its tower towards a good inference of mental state. For the case of schizophrenia, interviews and checklist-questionnaires by forensic psychiatrists help identify continued presence and type of delusions or hallucinations, which would in turn raise the level of confidence about claims of a relevant state at the moment of the crime. It seems possible that one could build similar support in the MAOA case. The same research tools used to establish differential susceptibility of the group to social rejection, negative emotions, and corresponding impulse control could in principle complement the marker data. Such testing might not be warranted, for practical purposes, for every defendant, but might be warranted for those found to have MAOA-L and probable maltreatment. These tests would work to embed a mechanistic story in the otherwise population statistical definition of the gene × environment correlation.[14]

A Brief Address of Harsher Punishments

Though proper examination of a case for harsher punishment is beyond the scope of this paper, it is necessary to mention. The prosecution might argue a person with a predisposition towards violence is a danger to society, a "ticking time-bomb." Punishment should be extended, therefore, not because the person "deserves" greater punishment, but in order to safeguard the community. In effect, this shows how genetic predisposition evidence might cut both ways: decreasing sentence due to less culpability, and increasing sentence due to public safety concerns. Even a successful full excuse can be accompanied by the option of involuntary civil commitment. Which direction wins this tug of war in the MAOA case, however, will depend both on political environment and practical considerations. While the political environment in the UK at least seems to be growing more intolerant of deviance,[15] our increasing appreciation of workings of the brain and the surprisingly dynamic malleability of its neurons[16] raise the possibility that behaviors might be successfully altered in new ways that safeguard the community without the need for continued imprisonment. The advent of non-invasive brain imaging, for example, enabled the identification and removal of the tumor that influenced Tim's undesirable behavior, after which his behavior improved to the point that he was deemed safe to return to the community. With the development of a mechanistic understanding comes the potential to harness the power of modern medicine, neuroscience, and psychology necessary to drive toward effective rehabilitation. We need to protect the public, but this might be achieved through effective treatment combined with a shorter prison sentence. Though I will address this possibility only briefly in the case of MAOA, mindfulness training,[17] Omega-3 supplementation (found in oily fish),[18] and

[14] Some point menacingly to its statistical nature and the observation that a majority of those with MAOA-L and childhood maltreatment do not go on to commit violence (see [1]). While these things are important to remember, they do not form a sound basis upon which to argue that MAOA data should have no effect in criminal court. The majority of those with schizophrenia, epilepsy, etc. do not commit crimes. If they do, however, the court has a responsibility to investigate whether these markers are relevant to the crime. The same should be true in the MAOA case.

[15] The possibility of punishment based solely on risk to society hovers in the British skies where a person deemed to pose a greater than 50% risk to commit future violent crime is proposed to be diagnosed with Dangerous and Severe Personality Disorder (DSPD). DSPD would support an optional extension of a criminal sentence to life or permanent monitoring [54, 55].

[16] Modern research on epigenetics (in which environmental influences dynamically modify the accessibility and transcription rates of genes) shows that even genes themselves are less static than we had previously thought (see [24]). The MAOA gene–environment interaction itself may be mediated by such a mechanism: the MAOA promoter region contains sites for one mechanism (addition of a methyl group—methylation) of metaplasticity and has been shown to be methylated in response to components in tobacco smoke [56, 57].

[17] Mindfulness training is an adaptation of a type of Buddhist meditation that helps individuals recognize and tolerate impulses and seems especially suited to angry impulses [58]

[18] Omega-3 fatty acids are essential for proper development and function of the prefrontal cortex, the area of the brain most directly involved in impulse control, and supplementation shows promises of decreasing impulsive aggression [35, 59]

5HT2a receptor antagonists[19] all show potential for specifically addressing effects of MAOA-L (see Table 3) and should be investigated in a rigorous, evidence-based manner. While it seems intuitive that the MAOA interaction would lead to higher rates of reoffending, moreover, it is important to remember that this has yet to be shown empirically and may not necessarily turn out to be the case.

Table 3 Treatments to be investigated

Treatment	Rationale
5HT2a receptor antagonists	• Overactive perigenual nucleus may mediate the disrupted amygdala/PFC circuit • Perigenual nucleus rich in 5HT2a receptors • MAOA deficiency might indicate surplus of 5HT and overstimulation of area • 5HT2a antagonists decrease aggression in mouse model
Omega-3 supplements	• Underactive PFC and impulse control • Omega-3 important for proper PFC function • Omega-3 decrease incidence of violence in children and prisoners
Mindfulness training	• Overactive amygdala and overly salient emotional content • Mindfulness training helps subjects recognize emotions and let them pass • Mindfulness training decreases incidence of aggression in certain studies

Returning to Trieste: *Bayout* (2009)

On the day of the murder, the defendant was accosted by a group of South American youths, who insulted him (calling him a "faggot") for wearing black eyeliner (kohl), which the defendant said he wore for religious reasons [4]. The youths then beat him up, giving him cuts and bruises. The defendant changed his bloodied clothes at a nearby cultural center, bought a knife, followed down a street and killed the victim, whom he believed (falsely) to be one of the South American youths. The trial judge was convinced that on the balance of probabilities there was some diminution of rational capacity; the defendant had a history of mental disorder, stopped taking medication 6 months prior to the offence, and intended to kill one of his assailants, but mistakenly killed a random South American person.[20] The judge deemed the evidence not strong enough to support an insanity defense, however.

Did the defendant experience an adverse environment? The case proceedings make no mention of childhood abuse or maltreatment. But as we saw earlier, there is considerable ambiguity about what could count as an adverse environment. Buckholtz [19] suggest a very inclusive definition "one typified by persistent uncertainty, unpredictable threat, poor behavioral modeling and social referencing, and inconsistent reinforcement for prosocial decision making." The defense spends significant time arguing that the defendant was unsettled by the shock of uprooting from his native Algerian to Italian culture. Could culture shock and subsequent social isolation count as an adverse environment? Or could schizophrenia itself count as an adverse environment, one typified by illogical, unpredictable threats and uncertainty? Also, the defendant moved to Italy when he was 24 years old, not when he was a child. Schizophrenia does not typically onset until 17–21 years; also not exactly childhood. Is this too old for an adverse environment to have an impact? These questions highlight the need for more research (see Table 4). The prefrontal cortex does not finish maturing until the early-mid twenties (coincident with schizophrenia onset) and the brain remains immensely plastic throughout life, however, both of which suggest room for influence [50].

Though theoretically possible, it remains to be shown empirically whether and to what degree these potential adverse environments could have impacted the defendant's brain. MAOA as marker in this case, therefore, contains very uncertain probabilistic information. The case for MAOA mitigation would certainly be stronger if Bayout had the "classical" physical abuse during early childhood. Bayout was

[19] Remember from the review of the science that MAOA-L subjects had increased activation of the perigenual anterior cingulate, which could be responsible for the aberrant coupling between the amygdala and prefrontal cortex. This region is rich in 5HT2a receptors and an antagonist applied to an animal model decreased aggression.

[20] [2] mistakenly claims that the victim was one of the defendant's assailants.

put through a modified Stroop test, however, which suggested, according to the trial document, that he had trouble inhibiting his motor impulses (most cues signaled that the defendant should reach out and touch a button; on the cues that signaled to hold back, Bayout failed to do so 23 out of 60 times).[21] It is difficult to estimate the extent of the defendant's behavioral disinhibition without knowing the exact parameters of the behavior task, but it may provide some independent support of decreased inhibitory control. Again, this would be more relevant if the reasonable man went down the subjective route. Moreover, the provocation seems quite distant to the crime (~1.5 h). The South American youths created a hostile, stressful environment and though influence of such an environment of perceived threat and persecution should not be all-together ruled out, it remains to be shown whether hypersensitivity due to MAOA variants could impact an action so far removed from the stimulus.

It is questionable though not completely outlandish that Bayout experienced an adverse environment during a relevant window that could combine with his MAOA-L gene. Thus it should count at most a weak argument that there is impairment above that of MAOA-L alone. Behavioral evidence corroborated the proposition of impaired impulse control, however, which suggests that at least one component of the MAOA-L effects may be present. Such an association may have limited relevance in biasing, via an environment of persecution, the channeling of the psychotic episode to a violent response, and *perhaps* would support the minor reduction in the sentence (1 year). At this point, it is worth remembering that the defense screened for several other genes of potential relevance, all with less empirical support than the MAOA case; together, however, one could argue that the minor reduction in sentence is better supported.[22] If his potential adverse environments and developmental windows were supported by empirical evidence, however, the decision would certainly rest on firmer ground. At its current strength, introduction at the sentencing phase seems most relevant.

Polk County, Tennessee: *Waldroup* (2009)

The case for the relevance of the MAOA data is stronger in Waldroup's trial, as it seems he was both abused as a child and possessed the MAOA-L variant [5]. There was no delay between the triggering stressful incident and the violent action, moreover. The violence was especially brutal however: a discussion between Waldroup and his wife about their marital problems escalated and all of a sudden, Waldroup fired his rifle (killing the wife's female friend, who he believed had had an affair with her) and shot his fleeing wife in the back. A struggle ensued: the wife kicked the gun away, but Waldroup pulled a pocket knife and cut her. This exchange was repeated with a shovel and a machete before the wife submitted and was dragged inside the home. Police arrived shortly thereafter and the wife was saved [6].

No corroborating behavioral tests on impulse control or emotional sensitivity were performed. Waldroup's lawyers, however, did argue that he suffered from both intermittent explosive disorder and acted in passion, both conditions that could be related to the MAOA story. Should the increased emotional sensitivity and lowered impulse control indeed be magnified when combined with abuse, a case may be made for a partial defense according to the criteria above (temporary and severe perceived emotional threat and, if the reasonable man is subjectified, diminished self-control). Until research corroborates that hypothesis, however, we will not know whether the court made the right decision in considering the MAOA evidence during the liability phase or whether it should have been restricted to the sentencing phase.

A Cautious Conclusion

I recalled a brief history of genetics of crime and behavior up to the probabilistic association between the MAOA gene × environment interaction and impulsive violence. I argued that this genetic evidence is similar to current psychiatric diagnoses as a marker

[21] The details of the procedure were not provided in the legal document.

[22] This argument leaves itself open to a challenge that might arise if we continue down this road: courts may soon be faced with cases in which the defense presents whole genomes and points out thousands of genetic variants each with small but non-zero associations with violence (and with varying levels of empirical support).

Table 4 Future research needed

Practical concern	Research needed	Notes
Mechanism of MAOA gene × environment interaction exaggerates effect of the gene alone on cognitive measures?	Repeat current cognitive neuroscience studies with both MAOA genotype and childhood abuse as independent variables	Urgent. Much stronger case for relevance if interaction follows the hypothesized mechanism
What counts as an adverse environment?	Abuse: • Nuclear family only? • Continual or single case? • Severity? • Bullying at school? • Exposure to gang violence? • Cultural conflict (i.e. Israel-Palestine)? Neglect: • Maternal rejection only? • Social isolation? • Culture shock? Other: • Uncertainty in environment? • Mental or physical illness? • Maternal smoking during pregnancy? • Poor nutrition?	All these need not be investigated. The goal should be to identify relevant environments while knocking down arguments based on irrelevant environments. For example, should Bayout's move from Algerian to Italian society or onset of schizophrenia be considered an adverse environment?
A critical period for relevant adversity? If so, what is it?	• Young childhood? • Pre-puberty? • Before brain fully developed (18–24)?	Possible that certain adverse environments serve as triggers during specific windows only—maybe different windows for different environments
To whom does the data apply?	• White males only?	Important for validity of evidence in court
How strong is the impulse control deficit?	• Like flashing-light induced seizure? • Like mosquito-bite induced scratch?	Impacts how relevant info is to guilt phase of trial
What tests could complement the genetics in a legal setting?	• Stop-signal test for motor impulse control • Reaction to negatively valenced faces • Reaction to simulated social exclusion • Tendency and degree of punishment in "hot sauce" task [3]	Critical in building a case for a relevant impairment of impulse control, or emotional arousal at the time of the crime

of a potentially relevant condition and could with future research form the rational basis for mitigation of criminal responsibility. Before we can know whether the decisions in the only two trials in which this data has had an effect, *Bayout* (2009) and *Waldroup* (2009), were correct, however, we need further research (see Table 4), especially corroboration that the deficits in emotional regulation and impulse control seen in those with MAOA-L alone are magnified upon addition of an adverse environment; we also need to better delineate the type and window of adverse environment that is relevant.

As we move forward toward this goal of building a rigorous evidence base, we should keep in mind that it was less than 100 years ago (during the interwar period) that Yale Psychologist Robert Yerkes stated in an address to the American Eugenics Council that "the safe development of eugenics is indeed assured by [our] insistence that we should not let application outstrip knowledge" [51]. Despite the energies of some of the brightest minds of the time, the heritability of crime was overestimated, was poorly and too generally defined, and resulted in a definition of the "unfit" that closely mimicked existing racial and ethnic prejudices.[23]

[23] The possibility of discrimination exists with the MAOA data as well and should be safeguarded against in any application: the MAOA-L gene is differentially represented across ethnicities (see [60–62]).

Application outpaced knowledge without anyone realizing it. As a result, the sterilizations and immigration laws that aimed to improve society actually damaged it.

The journalist, Walter Lippmann, who lived at the time, warned, "If [the expert's] advice is followed, and he is wrong, the consequences may be incalculable." For "except on a few subjects where our knowledge is great, we cannot choose between true and false accounts [52]." The people rely on the expert. They have learned to trust the prestige of science in order to form public opinion. Scientists have a great responsibility, consequently, to ensure that any application is reasonably justified by the data.

In light of this history, it is worth noting that the investigation of the mechanism of the MAOA × environment predisposition has advanced farther than any of its contemporaries or predecessors in the association with impulsive violence. It is linked to a neurotransmitter system and functional differences in brain areas known to be involved in anger production and control. Nonetheless, it will be extremely important to ensure that application of the data on MAOA × environment predispositions toward violence does not outpace a realistic understanding of mechanism.

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References

1. Forzano, F., P. Borry, A. Cambon-Thomsen, S.V. Hodgson, A. Tibben, P. De Vries, C. Van El, and M. Cornel. 2010. Italian appeal court: A genetic predisposition to commit murder. *European Journal of Human Genetics* 18(5): 519–521.
2. Ahuja, A. The get out of jail free gene. *The Sunday Times (UK)* 2009, (November 17).
3. Feresin, E. 2009. Lighter sentence for murderer with 'bad genes'. *Nature* 10(1038)/news.2009.1050.
4. Bayout v. Francesco. 2009, RGAssise App. 6/2008 RGNR 1685/2007, RG. sent 5, dd 18 settembre 2009.
5. Hagerty, B. 2010. Can your genes make you murder? *National Public Radio* (July 1): [http://www.npr.org/templates/story/story.php?storyId=128043329]
6. Waldroup Guilty, will not face death penalty. *Polk News* 2009 (March 25): [http://www.polknewsonline.com/2009/03/25/Top_News/Waldroup_guilty,_will_not_face_death_penalty/4158.html]
7. Waldroup gets 32 years. *Polk News* 2009 (May 13): [http://www.polknewsonline.com/2009/05/13/Top_News/Waldroup_gets_32_years/4493.html]
8. Alia-Klein, N., R.Z. Goldstein, D. Tomasi, P.A. Woicik, S. J. Moeller, B. Williams, I.W. Craig, F. Telang, A. Biegon, G.J. Wang, J.S. Fowler, and N.D. Volkow. 2009. Neural mechanisms of anger regulation as a function of genetic risk for violence. *Emotion* 9(3): 385–396.
9. Lombroso, C., M. Gibson, and N.H. Rafter. 2006. *Criminal man*. Durham: Duke University Press.
10. Greenspan, R.J. 2008. The origins of behavioral genetics. *Current Biology* 18(5): R192–8.
11. Weiss, S.F. 2006. Human genetics and politics as mutually beneficial resources: The case of the Kaiser Wilhelm Institute for Anthropology, Human Heredity and Eugenics during the Third Reich. *Journal of the History of Biology* 39(1): 41–88.
12. McGue, M. 2010. The end of behavioral genetics? *Behavior Genetics* 40(3): 284–296.
13. Hirschhorn, K. 2008. A short history of the American Society of Human Genetics. *American Journal of Human Genetics* 83(3): 307–310.
14. Centerwall, S.A., and W.R. Centerwall. 2000. The discovery of phenylketonuria: The story of a young couple, two retarded children, and a scientist. *Pediatrics* 105(1 Pt 1): 89–103.
15. Arnett, D.K., A.E. Baird, R.A. Barkley, C.T. Basson, E. Boerwinkle, S.K. Ganesh, D.M. Herrington, Y. Hong, C. Jaquish, D.A. McDermott, C.J. O'Donnell, and American Heart Association Council on Epidemiology and Prevention, American Heart Association Stroke Council, Functional Genomics and Translational Biology Interdisciplinary Working Group. 2007. Relevance of genetics and genomics for prevention and treatment of cardiovascular disease: a scientific statement from the American Heart Association Council on Epidemiology and Prevention, the Stroke Council, and the Functional Genomics and Translational Biology Interdisciplinary Working Group. *Circulation* 115 (22): 2878–2901.
16. Brown, D., A. Butchart, A. Harvey, K. Bartolomeos, D. Meddings, L. Sminkey. 2007. World Health Organization: Third Milestones of a Global Campaign for Violence Prevention Report 2007: scaling up.
17. Siever, L.J. 2008. Neurobiology of aggression and violence. *The American Journal of Psychiatry* 165(4): 429–442.
18. Brunner, H., M. Nelen, X. Breakefield, H. Ropers, and B. van Oost. 1993. Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. *Science* 262(5133): 578–580.
19. Buckholtz, J.W., and A. Meyer-Lindenberg. 2008. MAOA and the neurogenetic architecture of human aggression. *Trends in Neurosciences* 31(3): 120–129.
20. Kim-Cohen, J., A. Caspi, A. Taylor, B. Williams, R. Newcombe, I.W. Craig, and T.E. Moffitt. 2006. MAOA, maltreatment, and gene–environment interaction predicting children's mental health: New evidence and a meta-analysis. *Molecular Psychiatry* 11(10): 903–913.
21. Caspi, A., J. McCray, T.E. Moffitt, J. Mill, J. Martin, I.W. Craig, A. Taylor, and R. Poulton. 2002. Role of genotype in

the cycle of violence in maltreated children. *Science* 297 (5582): 851–854.
22. Willeit, M., and N. Praschak-Rieder. 2010. Imaging the effects of genetic polymorphisms on radioligand binding in the living human brain: A review on genetic neuroreceptor imaging of monoaminergic systems in psychiatry. *Neuroimage* 53(3): 878–892.
23. Taylor, A., and J. Kim-Cohen. 2007. Meta-analysis of gene–environment interactions in developmental psychopathology. *Development and Psychopathology* 19(4): 1029–1037.
24. Tremblay, R.E., and M. Szyf. 2010. Developmental origins of chronic physical aggression and epigenetics. *Epigenomics* 2(4): 495–499.
25. Weder, N., B.Z. Yang, H. Douglas-Palumberi, J. Massey, J. H. Krystal, J. Gelernter, and J. Kaufman. 2009. MAOA genotype, maltreatment, and aggressive behavior: The changing impact of genotype at varying levels of trauma. *Biological Psychiatry* 65(5): 417–424.
26. Risch, N., R. Herrell, T. Lehner, K. Liang, L. Eaves, J. Hoh, A. Griem, M. Kovacs, J. Ott, and K.R. Merikangas. 2009. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: A meta-analysis. *JAMA* 301(23): 2462–2471.
27. Sjöberg, R.L., F. Ducci, C.S. Barr, T.K. Newman, L. Dell'Osso, M. Virkkunen, and D. Goldman. 2008. A non-additive interaction of a functional MAO-A VNTR and testosterone predicts antisocial behavior. *Neuropsychopharmacology* 33(2): 425–430.
28. Alia-Klein, N., R.Z. Goldstein, A. Kriplani, J. Logan, D. Tomasi, B. Williams, F. Telang, E. Shumay, A. Biegon, I. W. Craig, F. Henn, G.J. Wang, N.D. Volkow, and J.S. Fowler. 2008. Brain monoamine oxidase A activity predicts trait aggression. *The Journal of Neuroscience* 28(19): 5099–5104.
29. Buckholtz, J.W., J.H. Callicott, B. Kolachana, A.R. Hariri, T.E. Goldberg, M. Genderson, M.F. Egan, V.S. Mattay, D.R. Weinberger, and A. Meyer-Lindenberg. 2008. Genetic variation in MAOA modulates ventromedial prefrontal circuitry mediating individual differences in human personality. *Molecular Psychiatry* 13(3): 313–324.
30. Tsiouris, J.A. 2010. Pharmacotherapy for aggressive behaviours in persons with intellectual disabilities: Treatment or mistreatment? *Journal of Intellectual Disability Research* 54(1): 1–16.
31. Eisenberger, N.I., B.M. Way, S.E. Taylor, W.T. Welch, and M.D. Lieberman. 2007. Understanding genetic risk for aggression: Clues from the brain's response to social exclusion. *Biological Psychiatry* 61(9): 1100–1108.
32. McDermott, R., D. Tingley, J. Cowden, G. Frazzetto, and D.D.P. Johnson. 2009. Monoamine oxidase A gene (MAOA) predicts behavioral aggression following provocation. *Proceedings of the National Academy of Sciences of the United States of America* 106(7): 2118–2123.
33. Mobley v. State. (1995) 455S.E.2d 61. Ga. Sup. Ct.
34. Bernet, W., C.L. Vnencak-Jones, N. Farahany, and S.A. Montgomery. 2007. Bad nature, bad nurture, and testimony regarding MAOA and SLC6A4 genotyping at murder trials. *Journal of Forensic Sciences* 52(6): 1362–1371.
35. Pieri, E., and M. Levitt. 2008. Risky individuals and the politics of genetic research into aggressiveness and violence. *Bioethics* 22(9): 509–518.
36. Padfield, N. 2008. *Criminal Law*, 6th ed. New York: Oxford University Press.
37. Eastman, N., and C. Campbell. 2006. Science and society: Neuroscience and legal determination of criminal responsibility. *Nature Reviews. Neuroscience* 7(4): 311–318.
38. Camplin. (1978) AC 705, (1978) 2 WLR 679, 67 Cr App Rep 14, (1978) 2 All ER 168, HL
39. Newell. (1980) 71 Cr App Rep 331, (1980) Cr LR 576.
40. Beecher-Monas, E., and E. Garcia-Rill. 2006. Genetic predictions of future dangerousness: Is there a blueprint for violence? *Law and Contemporary Problems* 69(1–2): 301–342.
41. Baumeister, R.F., K.D. Vohs, and D.M. Tice. 2007. The strength model of self-control. *Current Directions in Psychological Science* 16(6): 351–355.
42. Burns, J.M., and R.H. Swerdlow. 2003. Right orbitofrontal tumor with pedophilia symptom and constructional apraxia *sign*. *Archives of Neurology* 60(3): 437–440.
43. Luc Thiet Thuan v. R. (1997) AC 131, (1996) 2 All ER 1033, (1996) 3 WLR 45, (1996) 2 Cr App Rep 178, (1996) Crim LR 820, PC.
44. Campbell. (1997) 1 Cr App Rep 1999, (1997) Crim LR 227, CA.
45. Smith (Morgan James). (1999) QB 1079, affd (2001) 1AC 146, (2000) 4 All ER 289, (2000) 3 WLR 654, (2001) 1 Cr App Rep 31, (2000) Crim LR 1004, HL.
46. Rowland. (2003) EWCA Crim 3636, 148 Sol Jo LB 26, (2003) All ER (D) 237 (Dec).
47. Weller. (2003) EWCA Crim 815, (2004) 1 Cr App Rep 1, (2003) Crim LR 724.
48. A-G for Jersey v Holley. (2005) UKPC 23; (2005) Crim LR 966.
49. James; Karimi. (2006) EWCA Crim 14.
50. Crews, F., J. He, and C. Hodge. 2007. Adolescent cortical development: A critical period of vulnerability for addiction. *Pharmacology, Biochemistry and Behavior* 86(2): 189–199.
51. Yerkes, R. *Robert M. Yerkes Papers*. *Manuscripts & Archives, Yale University.*
52. Lippmann, W. 1922. *Public Opinion*. New York: Free.
53. Parens, E. 2004. Genetic differences and human identities: On why talking about behavioral genetics is important and difficult. *Hastings Center Report* 34(1 SUPPL.).
54. Maden, T., and P. Tyrer. 2003. Dangerous and severe personality disorders: A new personality concept from the United Kingdom. *Journal of Personality Disorders* 17(6): 489–496.
55. Corbett, K., and T. Westwood. 2005. 'Dangerous and severe personality disorder': A psychiatric manifestation of the risk society. *Critical Public Health* 15(2): 121–133.
56. Shumay, E., and J.S. Fowler. 2010. Identification and characterization of putative methylation targets in the MAOA locus using bioinformatic approaches. *Epigenetics* 5(4): 325–342.
57. Berlin, I., C. Heilbronner, S. Georgieu, C. Meier, J.M. Launay, and O. Spreux-Varoquaux. 2009. Reduced monoamine oxidase A activity in pregnant smokers

and in their newborns. *Biological Psychiatry* 66(8): 728–733.
58. Wright, S., A. Day, and K. Howells. 2009. Mindfulness and the treatment of anger problems. *Aggression and Violent Behavior* 14(5): 396–401.
59. Hibbeln, J.R., T.A. Ferguson, and T.L. Blasbalg. 2006. Omega-3 fatty acid deficiencies in neurodevelopment, aggression and autonomic dysregulation: Opportunities for intervention. *International Review of Psychiatry* 18(2): 107–118.
60. Lea, R.A., G. Chambers. Monoamine oxidase, addiction, and the "warrior" gene hypothesis. *Journal of the New Zealand Medical Association*. 2007, 120(1250): U2441.
61. Merriman, T., V. Cameron. Risk-taking: Behind the warrior gene story. *Journal of the New Zealand Medical Association*. 2007, 120(1250): U2440.
62. Way, B.M., and M.D. Lieberman. 2010. Is there a genetic contribution to cultural differences? Collectivism, individualism and genetic markers of social sensitivity. *Social Cognitive and Affective Neuroscience* 5(2–3): 203–211.