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The role of monoamine oxidase A in aggression: current translational developments and future challenges

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Abstract

Drawing upon the recent resurgence of biological criminology, several studies have highlighted a critical role for genetic factors in the ontogeny of antisocial and violent conduct. In particular, converging lines of evidence have documented that these maladaptive manifestations of aggression are influenced by monoamine oxidase A (MAOA), the enzyme that catalyzes the degradation of brain serotonin, norepinephrine and dopamine. The interest on the link between *MAOA* and aggression was originally sparked by Han Brunner's discovery of a syndrome characterized by marked antisocial behaviors in male carriers of a nonsense mutation of this gene. Subsequent studies showed that *MAOA* allelic variants associated with low enzyme activity moderate the impact of early-life maltreatment on aggression propensity. In spite of overwhelming evidence pointing to the relationship between *MAOA* and aggression, the neurobiological substrates of this link remain surprisingly elusive; very little is also known about the interventions that may reduce the severity of pathological aggression in genetically predisposed subjects. Animal models offer a unique experimental tool to investigate these issues; in particular, several lines of transgenic mice harboring total or partial loss-of-function *Maoa* mutations have been shown to recapitulate numerous psychological and neurofunctional endophenotypes observed in humans. This review summarizes the current knowledge on the link between *MAOA* and aggression; in particular, we will emphasize how an integrated translational strategy coordinating clinical and preclinical research may prove critical to elucidate important aspects of the pathophysiology of aggression, and identify potential targets for its diagnosis, prevention and treatment.

Keywords

Aggression; Monoamine oxidase A; animal models; Antisocial behavior

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Conflicts of Interest.
None

1. Introduction

Aggression is characterized by a multifaceted array of adaptive responses aimed at inflicting harm to another organism for offensive or defensive purposes. From an evolutionary perspective, aggressive behaviors are instrumental to a large number of vital functions, including the attainment of resources, determent of competitors and organization of social hierarchies (Buss and Shackelford, 1997). Given the relevance of these tasks for survival and offspring fitness, it is not surprising that human aggression is deeply rooted in genetic foundations (Ferguson, 2010). Consistent with this premise, multiple studies have documented the high heritability of pathological aggression, defined as a set of maladaptive and exaggerated hostile manifestations, such as antisocial and violent behaviors (Grove et al., 1990; diLalla and Gottesman, 1991; Miles and Carey, 1997; Rhee and Waldman, 2002). The best-validated genetic basis of aggression and antisocial behavior is the gene *MAOA*, located on the short arm of the X chromosome (Xp11.4-p11.23) (Bach et al., 1988; Grimsby et al., 1990) and encoding monoamine oxidase A. This enzyme catalyzes the degradation of key brain neurotransmitters involved in pathological aggression, such as serotonin (5-hydroxytryptamine; 5-HT), and the two catecholamines norepinephrine and dopamine (Bortolato et al., 2008). While other genes involved in monoamine neurotransmission pathways have been implicated in antisocial behaviors (Ferguson and Beaver, 2009), the unique reputation of *MAOA* lies in the large number of independent studies supporting its role in aggression. For all the popularity of this gene - which has even led to occasional misinterpretations from the media and criminal justice system (Crampton and Parkin, 2007; Forzano et al., 2010) - the neurobiological underpinnings of the link between *MAOA* and aggression remain surprisingly elusive. A unique tool to address this issue is afforded by animal models, and in particular by lines of transgenic mice with total or partial loss-of-function mutations for this enzyme (Cases et al., 1995; Scott et al., 2008; Bortolato et al., 2011). The goal of this review article is to present a holistic view of the available knowledge on the relationship between *MAOA* and aggression pathophysiology, and underscore the multiple elements of convergence between human and animal findings. To this end, we conducted a systematic review of the scientific literature in the past 30 years (1985–2015), focused on the relations between MAOA and aggression, antisocial behavior, violence and psychopathy (for details on the literature search, see the PRISMA Flow Diagram in Fig. 1). We will particularly emphasize how emerging evidence from preclinical models may help inform future lines of research on the molecular bases of aggression and antisocial behavior, and assist in the identification of diagnostic markers and therapeutic targets for these conditions.

2. Clinical and phenomenological classifications of aggression

The socioeconomic repercussions of pathological aggression are nothing short of devastating. In the U.S. alone, more than 5.4 million non-fatal violent crimes occurred in 2014 (Langton and Truman, 2014), with total costs estimated to exceed $180 billion/year (McCollister et al., 2010), including direct (such as legal and medical expenses, perpetrator incarceration, etc.) and indirect costs (including lost earnings, time, productivity, etc.) (Miller et al., 2001; Waters et al., 2004).

To compound this grim scenario, current strategies to treat pathological aggression are based on empirical approaches, often relying on the combination of antidepressant and anticonvulsant medications with cognitive/behavioral therapy, which are only moderately effective (Fava, 1997; Volavka et al., 2006).

One of the major critical barriers to the improvement of our clinical approaches lies in our inadequate understanding of the dimensional nature of the spectrum of aggressive behaviors and other externalizing disorders (Krueger et al., 2005). A glaring example of this shortcoming comes from the diagnostic criteria defined by the DSM-5, which fail to discern the dimensional commonalities among the conditions characterized by predominant aggressive psychopathology (such as antisocial personality disorder and intermittent explosive disorder in adulthood, as well as conduct disorder and oppositional defiant disorder in childhood and adolescence).

In the attempt to overcome these conceptual restrictions and identify biological subtypes of pathological aggression, the Research Domain Criteria (RDoC) initiative promoted by the National Institute of Mental Health (NIMH) has laid out a number of preliminary standards to study different pathophysiological aspects of this phenomenon, as indicated by research in neuroscience and psychology. The RDoC framework regards aggression as a core frustrative, non-reward construct within the broader group of negative valence systems. The RDoC has also recognized a preliminary distinction between *proactive* and *reactive* aggression, based on the motivational and emotional state of the perpetrators (Dodge and Coie, 1987; for reviews see Vitaro and Brendgen, 2011; Fite, et al. 2012), as well as different information-processing mechanisms and autonomic responses (Connor et al., 2004).

Proactive aggression is typically initiated by the offender in an instrumental fashion, and directed towards a rewarding and/or positive outcome, such as power or dominance status (Vitaro et al., 1998); accordingly, this construct is associated with a *positive outcome expectancy* for aggression (Dodge et al., 1997; Marsee and Frick, 2007; Vitaro and Brendgen, 2011). Proactive aggression has also been linked to *callous-unemotional traits*, characterized by a lack of empathy and remorse, as well as flattened emotional responses for others' suffering (Frick et al., 2003). This temperament has been shown to have robust genetic (Viding et al., 2007) and environmental bases. For example, this construct has been linked to social learning from models of violent behavior and substance abuse (Dodge et al., 1997; Connor et al., 2004).

In contrast, reactive aggression consists in the uncontrollable and/or exaggerated defensive responses to perceived provocation or threat (Dodge and Coie, 1987; Eisenberg and Fabes, 1992). Accordingly, individuals with reactive aggression exhibit a *hostile attribution bias*, i.e. higher propensity to perceive provocation or threat in response to neutral stimuli (Vitaro and Brendgen, 2011). The hostile nature of reactive aggressive responses is typically associated with impairments in social information processing, emotion regulation, verbal intelligence, impulse control and executive functioning (Dodge et al., 1997; Lemerise and Arsenio, 2000; Connor et al., 2003; Dodge and Pettit, 2003; Marsee and Frick, 2007; Arsenio et al., 2009). Reactive aggression is also associated with child abuse and maltreatment (Dodge et al., 1997; Shields and Cicchetti, 1998; Connor et al., 2004). The

severity and prevalence of this subtype follow a developmental trajectory, with a peak at young ages, followed by a gradual remission; this decline signifies a progressively greater ability to suppress emotional outbursts.

3. *MAOA* deficiency and aggression

MAOA has been largely associated with impulsive and reactive aggression, particularly in relation to overt, physical manifestations of violence. The first indication of a key role of this gene in antisocial behavior came from the identification of a point nonsense mutation (C936T) in exon 8 of the *MAOA* gene within a large Dutch kindred (Brunner et al., 1993; Brunner, 1996). The corresponding X-linked recessive disorder, named Brunner syndrome, was found to be characterized by abnormal levels of disruptive, violent outbursts in the affected males; these responses, which were reportedly triggered by frustration, anger and/or fear, would often lead to criminal acts, including attempted murder, rape and arson. Other symptoms and clinical signs included borderline intellectual disability, sleep disturbances and stereotyped hand movements. Although this breakthrough was instrumental for the resurgence of biological criminology, progress on the clinical characterization of the phenotypic consequences of *MAOA* deficiency lagged behind for several years, due to the lack of nosographic details on the psychological and cognitive characteristics of these patients (Hebebrand and Klug, 1995) as well as the rarity of Brunner syndrome. Indeed, several attempts to identify other cases of this disorder proved unsuccessful (Mejia et al., 2001), and a second case of Brunner syndrome was described in the literature only in 2014, approximately twenty years after the first report (Piton et al., 2014).

In contrast with clinical evidence, progress on the characterization of the neurobehavioral correlates of *MAOA* deficits came from studies on mutant mice. In 1995, Cases and colleagues reported the development of the first transgenic line of *Maoa* knockout (KO) mice. This mutation resulted from the serendipitous deletion of exons 2 and 3 of the *Maoa* gene in C3H/HeJ mice, following the integration of an interferon β cassette. Similarly to the phenotypes of Brunner syndrome, MAOA deficiency in mice resulted in high levels of aggressive behavior towards both familiar and foreign conspecifics. The analysis of the neurochemical correlates of these alterations revealed increased levels of 5-HT, norepinephrine and dopamine in the brain; however, the elevations in each monoamine were found to be age-dependent. In particular, 5-HT concentrations were 900–1000% greater than the corresponding levels in wild-type (WT) littermates during the first three postnatal weeks; conversely, significant increases in catecholamines were only recorded after the second week of life, possibly attesting to different functional roles of monoamine neurotransmitters (and their metabolism) throughout the development of the central nervous system. In correspondence to these time-sensitive changes, the comparisons of neurobehavioral phenotypes between KO and WT pups at multiple ages pointed to a complex set of developmental alterations. In particular, KO pups in the first week of life exhibited intense head nodding, trembling and deficits in posture and gait. These alterations were followed by hyperlocomotion and hyperreactivity during the second week of life, time-locked with the onset of aggressive biting.

The lack of evidence on early-life abnormalities in Brunner syndrome patients raised the question of whether the neurodevelopmental aberrances in *Maoa* KO mice may result from their artificial mutation and/or by the interaction of the phenotypical consequences of *Maoa* deficiency with other congenital problems in the C3H/HeJ strain, such as blindness. These doubts were essentially dispelled by the development of a second line of 129S6 mice harboring a spontaneous mutation of exon 8 (in a position adjacent to the site of the nonsense codon in Brunner syndrome) (Scott et al., 2008). Indeed, the spectrum of alterations exhibited by these mice overlaps with those of C3H mice.

Our group and others have investigated whether the aggression in adult KO mice may be underpinned by specific cognitive and emotional endophenotypes. These studies elucidated that KO mice display a marked reduction in social and environmental exploration (Bortolato et al., 2011; Godar et al., 2011). In particular, KO mice showed exaggerated defensive and neophobic responses to minor or innocuous stimuli (such as unfamiliar objects in their home cage or a mild footshock) (Kim et al., 1997; Godar et al., 2011); furthermore, they displayed lower response to stressful and threatening contingencies, including predator cues, physical restraint and cold temperature (Popova et al., 2006; Godar et al., 2011; Godar et al., 2015). KO mice were also found to exhibit a marked reduction in other measures of risk assessment and threat appraisal (Popova et al., 2001; Bortolato et al., 2011; Godar et al., 2011), as well as greater retention of aversive memories (Kim et al., 1997; Dubrovina et al., 2006).

Building on this background, we explored whether the developmental changes in KO mice may correspond to a generalized inability to process environmental information. These studies led to the discovery that *Maoa* mutants exhibit a broad number of deficits akin to core autistic symptoms, namely social deficits, communication impairments, perseverative behaviors, poor reversal learning and reduced auditory and tactile sensitivity (Bortolato et al., 2013a). Notably, this preclinical evidence was strikingly confirmed by the recent characterization of a new cases of Brunner syndrome in a boy with low-functioning autism-spectrum disorder, exhibiting severe cognitive impairments and episodic self-aggression in response to stress (Piton et al., 2014). Other loss-of-function *MAOA* mutations were recently identified in males with mild intellectual disability, introverted and obsessive traits, attentional deficits and episodic explosive aggression (Palmer et al., 2015). The early onset of the behavioral symptoms in these patients confirm that the clinical abnormalities in Brunner syndrome are underpinned by dysregulations in early neurodevelopmental processes.

The possibility that *MAOA* deficiency is conducive to impairments that may be related to aggression and autism-related alterations is particularly intriguing, in consideration of the frequency of aggressive manifestations in autistic children (Lecavalier, 2006; Farmer and Aman, 2011). Recent studies have shown that *MAOA* may play a key role in the ontogenesis of sensory and communication deficits, as well as arousal regulation problems and aggressiveness in autistic boys (Cohen et al., 2011). These findings may suggest a potential relationship between aggression and sensory-communicative problems, even raising the intriguing possibility that aggression may arise as a defensive response driven by poor social information processing (Crick and Dodge, 1996). Future work will be needed to verify

whether the severity of aggression in *MAOA*-deficient individuals may correlate with the intensity of communicative and sensory deficits.

In summary, the total congenital deficiency of *MAOA*, termed Brunner syndrome, has been shown to result in antisocial behavior and abnormally high levels of aggression in patients; these findings have been paralleled by similar results in mouse models harboring null-allele mutations of the *Maoa* gene. In particular, these investigations have begun to reveal that the behavioral phenotype of MAOA deficiency also encompasses autistic-related characteristics, which have been recently confirmed in recently-discovered cases of Brunner syndrome.

4. Role of *MAOA* allelic variants in the ontogeny of aggression

The bulk of clinical evidence on the link between *MAOA* and aggression comes from genetic studies on the numerous polymorphic variants of this gene (Table 1). The richest source of evidence on the functional role of *MAOA* in aggression has come from an upstream variable-number tandem repeat (uVNTR) polymorphism, featuring alleles with different numbers (2, 3, 3.5, 4, 5 and 6) of 30-bp repeats 1.2 kb upstream of the transcription initiation site (Sabol et al., 1998; Huang et al., 2004). The two most common uVNTR alleles, harboring 3 and 4 repeats, are estimated to be present in 35–39% and 59–63% of Caucasians, respectively; conversely, 3-repeat variants are present in the majority of African (52–59%) Asian (53–61%), and Hispanic (70%) Americans (Sabol et al., 1998; Rosenberg et al., 2006; Widom and Brzustowicz, 2006; Beaver et al., 2013). The particular importance of the uVNTR polymorphism arises from its functional nature: the 3-repeat allele (and, to an even greater extent, the 2-repeat allele) is associated with low transcriptional efficiency of the *MAOA* promoter, resulting in lower enzyme activity than that of the 4-repeat variant (Sabol et al., 1998; Deckert et al., 1999; Denney et al., 1999; Jonsson et al., 2000).

Several studies have shown an association between the 2- and 3-repeat alleles and multiple facets of aggression, including hostility and antisocial personality (Oreland et al., 2007; Buckholtz and Meyer-Lindenberg, 2008; Weder et al., 2009; Williams et al., 2009). This predisposition is accompanied by a set of impairments of neurocognitive functions, such as processing of facial expressions (Lee and Ham, 2008), as well as blunted stress response (Brummett et al., 2008). Other studies have investigated whether *MAOA* uVNTR variants may be related to other personality traits, including conscientiousness, straightforwardness, and neuroticism, but results have been largely inconsistent (Garpenstrand et al., 2002; Samochowiec et al., 2004; Jacob et al., 2005; Contini et al., 2006; Kim et al., 2006; Rosenberg et al., 2006; Tochigi et al., 2006), possibly suggesting a specific involvement of *MAOA* in aggression.

An interesting aspect of the research on the psychological phenotypes associated with different *MAOA* uVNTR alleles involves the specific subtypes of aggression. Numerous lines of evidence have shown that the low-activity variants are associated with reactive, rather than proactive aggression. For example, carriers of 3-repeat variants exhibit a greater proclivity to engage in hostile retaliatory acts against the provocations of perceived opponents and competitors (McDermott et al., 2009; Kuepper et al., 2013). More recently,

these individuals were shown to display a significantly higher tendency to engage in impulsive aggressive reactions to negative affect (Chester et al., 2015).

A number of studies have found a robust association between low-activity *MAOA* variants (and particularly 2-repeat alleles) and psychopathy and criminal behavior (Guo et al., 2008; Beaver et al., 2009; Beaver et al., 2010; Beaver et al., 2013; Beaver et al., 2014; Armstrong et al., 2014; Stetler et al., 2014; Tiihonen et al., 2015). The link with psychopathy, which has garnered this allele the questionable moniker of "psycho gene", is particularly surprising, given the consolidated link of this trait with proactive aggression and callous-unemotional traits, rather than reactive aggression (Raine et al., 2006; Nouvion et al., 2007). Nevertheless, it is worth noting that the definition of psychopathy is not entirely aligned with that of proactive aggression; for example, this trait is associated with several aspects of impulsivity (Morgan et al., 2011). In addition, several authors have recognized a distinction between *primary* psychopathy, characterized by low anxiety and lack of conscience, and *secondary* psychopathy, associated with negative affect, high anxiety and impulsivity (Blackburn, 1975; Newman et al., 2005a; Skeem et al., 2007). Recent work has shown that these two subtypes are underpinned by different genetic and environmental factors (Blonigen et al., 2005; Hicks et al., 2012); in particular, secondary psychopathy is highly associated with environmental risk factors (Skeem et al., 2003). This background suggests that the acquisition of psychopathic traits in carriers of low-activity *MAOA* alleles may result from social learning: in other terms, while these variants lead to a greater propensity for reactive aggression, the repeated engagement in violent acts (if associated with perceived advantages) may in turn facilitate the development of instrumental antisocial behaviors. With respect to this possibility, it is interesting to note that, although the distinction between reactive and proactive aggression is well supported by clinical evidence (Card and Little, 2006), several studies point to a moderate concurrence of both subtypes (see Polman et al., 2007 for a meta-analysis of this relationship in children and adolescents), and indicate a sizable overlap of their genetic predisposition factors (Brendgen et al., 2006).

In keeping with the multifactorial nature of aggression, multiple lines of evidence have documented that the influence of *MAOA* on antisocial behavior is shaped by interactions with other vulnerability factors. In a seminal study on New Zealanders, Caspi and coworkers (2002) reported that male carriers of the 3-repeat allele with a history of child abuse or neglect had a significantly higher prevalence of antisocial behaviors than individuals with only one risk factor. This breakthrough, which documented the first gene x environment (GxE) interaction in antisocial conduct, was confirmed and extended by multiple subsequent studies in US, UK and Sweden (Foley et al., 2004; Huang et al., 2004; Nilsson et al., 2006; Frazzetto et al., 2007; Weder et al., 2009; Beach et al., 2010; Derringer et al., 2010; Edwards et al., 2010; Åslund et al., 2011; Fergusson et al., 2011; but see also Prichard et al., 2008 and Haberstick et al., 2014 for contrasting evidence), and validated by three meta-analyses (Kim-Cohen et al., 2006; Byrd and Manuck, 2014; Ficks and Waldman, 2014). A particularly remarkable replication of this result came from a 30-year longitudinal study, showing that abused children with low-activity *MAOA* variants developed conduct problems and hostility at around 16 years of age (Fergusson et al., 2011). Interestingly, low-activity *MAOA* alleles have been recently found to interact with maternal stress to influence negative emotionality

in infants (Hill et al., 2013), pointing to the fact that the synergistic effects of stress and *MAOA* may also occur throughout prenatal development.

An interesting interpretation of the psychological processes underlying GxE interaction has been recently provided by Nillson and colleagues (2014), who reported that low-activity *MAOA* variants may interact with early maltreatment by shaping the susceptibility to negative events. In line with this idea, the interaction of these genetic variants with social exclusion has been shown to result in higher aggression scores in the point subtraction aggression paradigm, a common experimental task used to simulate aspects of aggression in a laboratory setting (Gallardo-Pujol et al., 2013).

It is worth noting that the nature of the GxE interaction is sex-dimorphic. Indeed, most lines of evidence have shown that, in women, high-activity *MAOA* variants and their interactions with early adversities, predict for externalizing behaviors and aggression (Kinnally et al., 2009; Beach et al., 2010; Åslund et al., 2011; Verhoeven et al., 2012; McGrath et al., 2012; Holz et al., 2014; but see also Ducci et al., 2008 for evidence pointing to homozygous low-activity genotype as a risk factor for antisocial behavior in females). Further studies are warranted to examine how *MAOA* may impact aggression risk in a sex-dependent fashion.

Taken together, the evidence on the *uVNTR* variants of *MAOA* has unequivocally shown that male carriers of low-activity alleles of this gene are predisposed to a negative bias in the interpretation of social stimuli, which results in a greater propensity for aggressive and impulsive reactions to provocation and stress. Building on this premise, several independent studies have shown that the synergism of this psychological substrate with early-life traumas or stressors markedly increases the susceptibility to develop antisocial behaviors from adolescence onwards. A potential tool to investigate the mechanistic bases of this GxE interaction may be afforded by animal models. Most of the preclinical studies on the role of *MAOA* genotypic variants have been produced in non-human primates (Barr and Driscoll, 2014). Sequence analysis studies have revealed the presence of functional VNTRs in the transcriptional control region of *MAOA* across several species of monkeys (such as Rhesus macaques and Gelada baboon) as well as apes (including gorillas, orangutans, chimpanzees and bonobos) (Wendland et al., 2006). In particular, the alleles in the rh*MAOA*-LPR (an upstream functional polymorphism regulating *MAOA* transcription) in Rhesus monkeys show a great degree of variability, particularly in societies with high levels of intermale conflicts for dominance, suggesting a likely homology with the uVNTR polymorphism (Wendland et al., 2006). These variants have also been shown to participate in GxE interactions with early rearing experiences; for instance, male macaques raised with or without their mothers were found to exhibit competitive behavior and social group aggression in a *MAOA*-dependent fashion. In striking resemblance with the human data, carriers of low-activity alleles reared in small groups or without mothers were found to exhibit higher aggression and other anxiety-related maladaptive behaviors (Newman et al., 2005b; Karere et al., 2009).

While no direct equivalent of uVNTR alleles exist in rodents, our group has begun studying the impact of early stress in a novel line of *Maoa* hypomorphic mice, generated through the insertion of a neomycin resistance cassette into the eighth intron of the gene *Maoa*

(Bortolato et al., 2011). These mice, termed *Maoa*^{Neo}, display reduced normal levels of *Maoa* transcript and very low levels of MAOA activity. Similar to *Maoa* KO mice, *Maoa*^{Neo} mice display impairments in social behavior, as well as communication deficits and perseverative behaviors (Bortolato et al., 2011 and unpublished data). In addition, we found that these animals feature alterations in their cerebellar morphology (Alzghoul et al., 2012) reminiscent of abnormalities documented in autism-spectrum disorder patients. In contrast with KO mice, however, their *Maoa*^{Neo} counterparts display no spontaneous aggression, affording a unique experimental platform to test the effects of early adversities on the development of this trait. Collectively, these premises argue in favor of the utilization of animal models as a unique experimental tool to verify the role of MAOA in the neurobiological bases of GxE interactions in antisocial behavior and aggression.

5. Role of MAOA enzymatic activity in aggression

Although the majority of clinical studies on the role of *MAOA* in aggression has focused on the genetic bases of this relationship, a number of investigations have targeted the specific role of the enzyme and its catalytic activity in antisocial and violent behaviors. One of the key limitations of this approach is that peripheral MAOA activity is typically measured in platelets, which only express MAOB (Bortolato et al., 2008). It is worth noting, however, several studies have highlighted that MAO platelet activity is low in aggressive and violent individuals (Belfrage et al., 1992; Skondras et al., 2004); the significance of these findings, however, remains unclear, given that *Maob* deficiency in mice is associated with behavioral disinhibition, but not aggression (Grimsby et al., 1997; Bortolato et al., 2009).

The most prominent line of evidence for the association between *MAOA* activity and aggression comes from PET studies employing radiolabeled *MAOA* inhibitors (Fowler et al., 2007; Alia-Klein et al., 2008). In particular, it was shown that, in healthy adult males, *MAOA* activity in multiple subcortical and cortical brain regions was inversely correlated with indices of trait aggression in the Multidimensional Personality Questionnaire (MPQ) (Alia-Klein et al., 2008). This finding has been confirmed by Independent studies showing that anger and hostility are negatively correlated with *MAOA* binding in multiple sub-regions of the prefrontal cortex (PFC) (Soliman et al., 2011). These results underscore the importance of MAOA in antisocial behavior and point to this enzyme as a biomarker for aberrant aggression. In support of this idea, recent studies have documented lower MAOA distribution volume in patients affected by antisocial personality disorder (Kolla et al., 2015).

While these findings appear to be in line with the abundant evidence on the role of uVNTR genotypes in aggression, it is worth noting that no direct association between these alleles and MAOA brain levels in adults has been found (Fowler et al., 2007). This lack of direct relationship was also confirmed by post-mortem analyses, which documented that, although the enzyme activity of 3-repeat carriers is numerically lower than that of 4-repeat controls, this comparison was not statistically significant (Balciuniene et al., 2002). Taken together, this background suggests that, while uVNTR variants are likely to predispose to different levels of MAOA catalytic activity in the brain, this effect may be particularly important in early life stages, when this enzyme reaches its peak concentrations (Tong et al., 2013).

Future studies are warranted to investigate the association between uVNTR alleles and brain MAOA activity in childhood and adolescence.

It is also worth noting that MAOA enzyme activity is influenced by multiple environmental factors, including exercise (Morishima et al., 2006), diet (Jahng et al., 1998) and stress (Marquez et al., 2013), raising the possibility that the importance of the genetic influence on this index may become progressively weaker with time. Two important corollaries of this idea are that the nature of the link between *MAOA* and aggression is neurodevelopmental, and that early-life exposure to environmental factors that may reduce *MAOA* activity may lead to a greater predisposition to aggression.

Indeed, this possibility has been hypothesized to explain the well-documented association between maternal smoking and conduct disorder (Baler et al., 2008; Wakschlag et al., 2010), in consideration of the reduction of MAOA activity following exposure to smoke (Fowler et al., 1996; Berlin and Anthenelli, 2001).

The importance of contextual factors in the regulation of MAOA activity is also supported by evidence documenting that brain MAOA activity is predicted by the levels of methylation of *MAOA* promoter (Shumay et al., 2012), suggesting that environmental factors, especially during early stages, influence MAOA activity through epigenetic mechanisms. The relevance of this result is highlighted by the recent discovery of higher levels of *MAOA* promoter methylation in violent offenders (Checknita et al., 2015).

In summary, recent evidence has shown that *MAOA* genetic variants may not be a robust predictor of the catalytic activity of the corresponding enzyme, likely due to a wide array of environmental influences. This finding notwithstanding, the catalytic activity of MAOA in the brain may serve as an even more reliable and accurate biological index to measure the predisposition to antisocial behavior and aggression.

Rodent models have been extensively used to verify how and when chronic pharmacological blockade of MAOA may lead to aggressive responses. These investigations have shown that prenatal inhibition of MAOA leads to increased proclivity for aggression and stereotyped behaviors in rats (Whitaker-Azmitia et al., 1994; Mejia et al., 2002). In addition, *MAOA* inhibition in adolescence and juvenile stages (between the third and sixth week of life) has been recently found to result in aggression in mice, while the same treatment during the first three postnatal weeks leads to anxiety-like behaviors, but not aggression (Yu et al., 2014). Finally, several studies have shown that chronic inhibition of *MAOA* in adult rodents reduces, rather than increases, aggression (Griebel et al., 1998; Datla et al., 1991). In conformity with the antidepressant effects of MAOA inhibitors, this latter regimen was found to reduce defensive responses towards predators and block stress-induced aggression in adult rodents. Taken together, these data suggest that low MAOA activity may have distinct and complementary outcomes across different developmental stages, the combination of which may lead to enduring increases in aggression.

6. Neuroanatomical bases of the link between *MAOA* and aggression

The primary approach to identify the biological underpinnings of the link between *MAOA* and aggression in humans is currently based on neuroimaging studies conducted on carriers of different functional classes of uVNTR alleles. As mentioned above, low-activity genotypes have been shown to predispose for reactive aggression by facilitating the dysregulation of affective information processing and altering the emotional response to provocation (McDermott et al., 2009; Gallardo-Pujol et al., 2013; Kuepper et al., 2013). Several studies on reactive aggressive individuals have shown that these behavioral alterations reflect dysregulations in corticolimbic networks, and particularly in the connectivity between the amygdala and different parts of the PFC (Ongur and Price, 2000; Best et al., 2002; Ghashghaei and Barbas, 2002; Machado and Bachevalier, 2006; Coccaro et al., 2007; New et al., 2009; Coccaro et al., 2011; Rosell and Siever, 2015). Specifically, the impaired communication between these areas is often based on a diminished activity of prefrontal regions and an increased responsiveness of the amygdala and other limbic structures to social cues (Sterzer et al., 2005; Coccaro et al., 2007; Marsh et al., 2011; Motzkin et al., 2011). Indeed, the activities of the PFC and amygdala are inversely correlated in reactive aggressive individuals during emotional appraisal (Coccaro et al., 2011; Dorfman et al., 2014), probably indicating the impairment of top-down inhibitory controls from the cortex to limbic areas.

In confirmation of the link between low *MAOA* activity and aggression, similar neurofunctional alterations have been reported in male carriers of 3-repeat *MAOA* uVNTR alleles. Specifically, these subjects exhibit elevated and reduced volumes of the orbitofrontal cortex and amygdala, respectively; these morphological changes are accompanied by diminished prefrontal activity during tasks of inhibitory control as well as heightened limbic responsiveness to emotional arousal (Meyer-Lindenberg et al., 2006; Buckholtz et al., 2008; Nymberg et al., 2013). Furthermore, these individuals showed a significant enhancement of neural activity in the PFC, in correspondence of their high responsiveness to social rejection, insults and facial affect (Eisenberger et al., 2007; Denson et al., 2014). These data support the possibility that *MAOA* in the PFC modulates both the ability to properly assess the emotional salience of contextual cues (towards a less severe hostile attribution bias), and the selection of appropriate adaptive responses; early disruptions of this system may enhance the sensitivity to adverse-life experience and result in a negative socio-cognitive bias (Buckholtz and Meyer-Lindenberg, 2008; Dorfman et al., 2014).

In addition to clinical studies, the neuroanatomical underpinnings of the link between *Maoa* and aggression have been extensively investigated in mouse models. The indirect proof of the importance of cortico-amygdalar connectivity in these mutants came from the finding that the behavioral and metabolic effects of *Maoa* deletion could be rescued by genetic reinstatement of human *MAOA* in forebrain areas (Chen et al., 2007). Further studies by our group and others helped understand the cellular bases of the behavioral dysfunctions associated with low MAOA activity. Both *Maoa* KO and $Maoa^{Neo}$ males exhibit functional deficits of the PFC, which are accompanied by higher dendritic arborization of its pyramidal cells (Bortolato et al., 2011); conversely, opposite morphological and functional changes were documented in amygdala (Kim et al., 1997; Bortolato et al., 2011; Godar et al., 2015).

Notably, the combination of hypofrontality and amygdalar hyperactivity in *Maoa* mutants parallels the well-documented dysregyulation of corticolimbic connectivity observed in reactive aggressive subjects (Coccaro et al., 2011).

Another morphological abnormality featured in *Maoa* KO mice concerns the reduced thickness of the rostral portion of the corpus callosum (Bortolato et al., 2013a). This aberrance, which further suggests connectivity impairments in the frontal pole of the cortex, may lead to impairments in the interhemispheric processing of emotional responses to conflict and social cues (Paul et al., 2007; Schutter and Harmon-Jones, 2013), thereby contributing to the maladaptive responses to neutral and threatening cues in these animals (Godar et al., 2011). Reductions in callosal thickness have been evidenced in psychopathic, antisocial subjects (Raine et al., 2003).

Finally, *Maoa*-deficient mice exhibit a marked dysmorphogenesis of the barrel fields in layer IV of the somatosensory cortex (Cases et al., 1995; Bortolato et al., 2011). These structures serve the sensory representation of the mystacial vibrissae in the rodent snout (Erzurumlu and Jhaveri, 1990), and are optimal proxy substrates for the analysis of columns, basic functional units of cortical organization in the brain (Lubke and Feldmeyer, 2007; Lokman and Garel, 2014). While columnarity alterations are usually regarded as prominent cytoarchitectural correlates of autism-related impairments (Courchesne and Pierce, 2005; Buxhoeveden et al., 2006; Stoner et al., 2014), these studies suggest that region-specific alterations in cortical columns may underpin not only autistic symptoms, but also contribute to the pathogenesis of antisocial and violent behavior. To the best of our knowledge, little is currently known about changes in dendritic arborization and columnarity in carriers of low-activity *MAOA* variants and antisocial individuals. Based on animal findings, future studies on post-mortem brain samples are warranted to address this potentially important translational link.

7. Neurochemical bases of the link between *MAOA* and aggression

The clinical evidence on the neurochemical mechanisms supporting the link between *MAOA* and aggression is very limited and based on indirect indices, such as the levels of monoamine metabolites in peripheral fluids and/or CSF. For example, Brunner syndrome patients exhibit very low urinary concentrations of 5-hydroxyindoleacetic acid (5-HIAA) as well as homovanillic acid (HVA) and vanillylmandelic acid (VMA), the key products of oxidative metabolism of 5-HT and catecholamines, respectively (Brunner et al., 1993), signifying the marked reduction in monoamine degradation. *MAOA* uVNTR variants were also found to affect monoamine metabolism; for example, the high-activity alleles are associated with greater CSF concentrations of 5-HIAA and HVA (Williams et al., 2003; Zalsman et al., 2005). Of note, low 5-HIAA levels have long been regarded as a sensitive biomarker for hostility, aggression and impulsive violence (Linnoila et al., 1983; Virkkunen and Linnoila, 1990; Soderstrom et al., 2001; Moore et al., 2002; Duke et al., 2013), in correspondence of the key role of 5-HT in the regulation of aggression (Bortolato et al., 2013b; Coccaro et al., 2015).

Most of our current knowledge on the biochemical processes mediating the link between *MAOA* and aggression comes from evidence gathered on animal models. The main neurotransmitter implicated in the aggressive behavior of *Maoa* KO mice is 5-HT. The bulk of evidence has shown that impulsive aggression is consequent to a reduction of 5-HT content; for example, dietary restriction of the 5-HT precursor tryptophan impairs emotional processing and increases the susceptibility for outbursts in aggressive patients (Lee et al., 2012; Passamonti et al., 2012; Grady et al., 2013). As noted above, however, *Maoa* KO mice exhibit pronounced *elevations* of synaptic 5-HT levels; this apparent conundrum may be explained by the multifaceted contributions of 5-HT to the ontogeny of aggression across multiple developmental stages and different brain regions. Given that the concentrations of brain 5-HT are consistently higher in *Maoa* KO than WT mice, this persistent elevation in 5-HTergic tone may desensitize neurons to the changes in neurotransmitter release caused by environmental stimuli. In line with this idea, we recently found that the aggression of *Maoa* KO mice is paradoxically *reduced* by inhibition of 5-HT reuptake (Godar et al., 2014), which leads to a drastic reduction of firing of 5-HTergic neurons as well as a marked enhancement in 5-HT synaptic content (Evrard et al., 2002). In line with these findings, Palmer and colleagues (2015) recently reported that administration of selective 5-HT reuptake inhibitors reduced aggressive outbursts and improved mood in Brunner syndrome patients.

Another mechanism that may contribute to the pathogenesis of aggression in *MAOA*-deficient subjects is the elevation in brain dopamine content. Although dopamine levels are only mildly increased in the central nervous system of *Maoa* KO mice, recent studies have shown that the direct optogenetic stimulation of dopaminergic neurons in the mesocorticolimbic system leads to a marked enhancement of aggressive behaviors (Yu et al., 2014). Given that cortical dopamine is predominantly metabolized by catechol-O-methyltransferase (COMT), it is possible that low MAOA activity may lead to selective changes in dopamine signaling in the nucleus accumbens. Accordingly, studies in rodents have shown that the accumbal concentrations of this neurotransmitter are increased before, during and after an aggressive encounter (de Almeida et al., 2005). Clinical evidence has also shown the implication of hyperactive dopaminergic limbic transmission in reactive aggression (Comai et al., 2012). Furthermore, given the importance of accumbal dopamine signaling in habit formation, it is likely that this substrate may play a role in the formation of aggressive habits and the perpetuation of antisocial behaviors.

In addition to monoaminergic changes, we have documented that *Maoa* KO mice exhibit functional deficits of the glutamatergic system, and in particular of the N-methyl-D-aspartate receptors (NMDARs) in the PFC (Bortolato et al., 2012). *Maoa* mutants show stoichiometric changes of NMDAR subunit composition, with reduced glycosylation of NR1 and increased expression of NR2A and NR2B. The resulting reduction in NMDAR conductance is posited to result in functional impairments of the PFC (Bortolato et al., 2012), which may account for the maladaptive processing of contextual cues in individuals with low *MAOA* activity (Sterzer et al., 2005; Godar et al., 2011). The relevance of NMDARs in the aggression of *MAOA*-deficient individuals is consistent with prior evidence pointing to this receptor in the modulation of neurofunctional processes implicated in the assessment of environmental and social cues (Seeburg et al., 1995; Jackson et al., 2004; Rolls et al., 2008). Recent clinical

studies have identified a correlation between elevated cerebrospinal glutamate levels and aggressive behaviors in healthy volunteers (Coccaro et al., 2013). Although the exact mechanisms underpinning aggressiveness in individuals with low MAOA activity remains unclear, it is possible that changes in glutamate signals from the PFC may switch off inhibitory cortical control over subcortical circuits. Thus, pharmacological compounds that rectify glutamatergic alterations of the PFC and/or the limbic circuitry may be beneficial as potential therapies. From this perspective, it is worth noting that NMDAR subunit antagonism was found to result in a dramatic amelioration of aggression in MAOA KO mice (Bortolato et al., 2012); given that memantine, a low-potency NMDAR antagonist, exerts therapeutic properties in patients with high levels of aggression and agitation (Wilcock et al., 2008), these results may provide important leads for the development of novel treatment for antisocial behaviors in aggressive patients with low MAOA activity variants.

In conclusion, findings from animal models strongly suggest that the role of MAOA in the pathophysiology of aggression and antisocial behavior is based on the cross-talk of several neurotransmitter systems in the corticolimbic system, including 5-HT, dopamine and glutamate (with its attending NMDAR receptor). The reciprocal interactions of these systems may vary across different brain regions and developmental stages, further highlighting the high neurobiological complexity of the underpinnings of aggressive behavior.

8. Future challenges and conclusions

The evidence presented in this review shows the close alignment between clinical and preclinical findings with respect to the phenotypic consequences of low MAOA activity, across a number of complementary lines of evidence encompassing genetic, neuroimaging and psychological analyses. In particular, studies on patients and animal models converge in indicating that MAOA plays a cardinal role in the orchestration of reactive aggression, through the modulation of corticolimbic circuits serving social information processing and emotional responsiveness.

In both humans and animals, the impact of *MAOA* on aggressive behavior appears to depend on similar factors, including stress exposure, as well as sex- and age-specific processes. MAOA may be particularly critical in modifying the cortical and amygdalar responses to adverse environmental contingencies during early developmental stages, and the combination of these endophenotypes with other dysregulations may lead to enduring modifications of socio-affective reactivity through the engagement of epigenetic processes.

These premises point to the unique possibility of establishing a solid translational platform, based on the integration of clinical and preclinical research, in order to address the following unresolved challenges concerning the pathophysiology of antisocial behavior associated with low MAOA activity:

- *What are the behavioral characteristics of subjects with low MAOA allelic variants at different developmental stages?* Although it is known that reactive aggression follows a developmental trajectory, the specific contribution of MAOA to this process remains unclear. To elucidate this aspect, future studies are needed to

profile the behavioral characteristics of carriers of low *MAOA* activity variants, as well as animals with MAOA deficiency during early developmental stages. In particular, these investigations should ascertain whether specific neurobehavioral changes may be associated with alterations in neuroendocrinological indices, also in relation to different degrees of exposure to various environmental contingencies.

- *What elements of stress interact with low MAOA alleles to affect aggression?* Ample evidence has shown that low MAOA activity allelic variants interact with childhood maltreatment, but the specific factors of stress that may influence this phenotype are elusive. Future studies in humans and rodents should verify whether different stressors may interact with *MAOA* genotypes to increase risk for antisocial behaviors.
- *Do individuals with low MAOA allelic variants (with or without exposure to early maltreatment) exhibit alterations in cortical columnarity, dendritic arborization or NMDAR function in the PFC?* Our findings indicate that *Maoa*-deficient mice exhibit a number of functional and histoarchitectural changes in the PFC. Post-mortem studies are warranted to verify whether antisocial behaviors in humans may be underpinned by similar deficits.
- *Does low MAOA activity interact with early stress in animals to increase the risk for aggression?* Preliminary observational studies have begun analyzing what specific modalities and degrees of severity of stress interact with MAOA variants to facilitate the development of antisocial behavior and aggression (Weder et al., 2009; Derringer et al., 2010). It is clear, however, that these studies can only be performed from a correlational perspective. To address these issues from an experimental standpoint, future studies on animal models are needed; furthermore, these investigations would be fundamental to understand the molecular bases of GxE interactions and identify novel putative therapeutic targets to prevent and/or treat antisocial behavior.
- *How do sex differences impact MAOA activity and protect or predispose towards aggression?* Clinical data suggest that the link between low-activity MAOA polymorphisms and aggression is sex-dependent. Indeed, antisocial behaviors in females appear to be mostly associated with high-activity MAOA alleles. The mechanisms of this dimorphism, however, are still unknown. Future preclinical investigations should explore whether different sex factors (such as testosterone, adrenal androgens and/or estrogens) may influence the pathogenesis of aggressive responses in *Maoa*-deficient mice.
- *Is psychological stress the only environmental factor that interacts with low MAOA activity alleles?* Most studies have focused on psychological traumas and stressors as the key environmental factor interacting with MAOA. Nevertheless, recent evidence indicates that the neural effects of stress are based on similar processes as those caused by other forms of environmental damage, such as the oxidative stress induced by smoking and/or neuroinflammation. It is unclear, however, whether any of these factors may predispose to aggression by interacting with specific genetic variants of MAOA.

- *Does MAOA genotype affect vulnerability to drug abuse?* Ample evidence has shown that substance abuse and dependence are highly comorbid with aggression, raising the possibility that MAOA may be a risk factor for drug abuse. Future clinical and preclinical studies are needed to address this interesting hypothesis and verify whether *MAOA* may influence the complex relationship between addiction, negative emotionality and aggressive psychopathology.

Taken together, these questions highlight a translational framework for clinical and preclinical researchers to begin unraveling the specific mechanisms by which MAOA contributes to the pathogenesis of aggression. The integration of data and ideological concepts from both sources of research is fundamental for future theoretical developments on the ontogeny of antisocial behavior, and may assist with the identification of premorbid signs and diagnostic biomarkers for this disorder. In addition, this research will be instrumental to the development of future preventative measures and novel therapeutic strategies for this devastating condition.

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List of abbreviations

5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin
COMT	catechol-O-methyltransferase
CSF	cerebro-spinal fluid
DSM-5	Diagnostic and statistical manual of mental disorders, fifth edition
GxE	gene × environment
HVA	homovanillic acid
KO	knockout
MAOA	Monoamine oxidase A (human and other primate genes)
Maoa	Monoamine oxidase A (mouse gene)
MAOA	Monoamine oxidase A (protein)
Maob	Monoamine oxidase B (mouse gene)
MAOB	Monoamine oxidase B (protein)
MPQ	Multidimensional Personality Questionnaire
NIMH	National Institute of Mental Health
NMDAR	N-methyl-D-aspartate receptor

PET	positron emission tomography
PFC	prefrontal cortex
RDoC	Research Domain Criteria
uVNTR	upstream variable-number tandem repeat
VMA	vanillylmandelic acid
VNTR	variable-number tandem repeat
WT	wild-type

REFERENCES

Alia-Klein N, Goldstein RZ, Kriplani A, Logan J, Tomasi D, Williams B, et al. Brain monoamine oxidase A activity predicts trait aggression. J Neurosci. 2008; 28:5099–5104. [PubMed: 18463263]

Alzghoul L, Bortolato M, Delis F, Thanos PK, Darling RD, Godar SC, et al. Altered cerebellar organization and function in monoamine oxidase A hypomorphic mice. Neuropharmacology. 2012; 63:1208–1217. [PubMed: 22971542]

Armstrong TA, Boutwell BB, Flores S, Symonds M, Keller S, Gangitano DA. Monoamine oxidase A genotype, childhood adversity, and criminal behavior in an incarcerated sample. Psychiatr Genet. 2014; 24:164–171. [PubMed: 24983833]

Arsenio WF, Adams E, Gold J. Social information processing, moral reasoning, and emotion attributions: relations with adolescents' reactive and proactive aggression. Child Dev. 2009; 80:1739–1755. [PubMed: 19930349]

Aslund C, Nordquist N, Comasco E, Leppert J, Oreland L, Nilsson KW. Maltreatment, MAOA, and delinquency: sex differences in gene-environment interaction in a large population-based cohort of adolescents. Behav Genet. 2011; 41:262–272. [PubMed: 20734127]

Bach AW, Lan NC, Johnson DL, Abell CW, Bembenek ME, Kwan SW, et al. cDNA cloning of human liver monoamine oxidase A and B: molecular basis of differences in enzymatic properties. Proc Natl Acad Sci USA. 1988; 85:4934–4938. [PubMed: 3387449]

Balciuniene J, Emilsson L, Oreland L, Pettersson U, Jazin E. Investigation of the functional effect of monoamine oxidase polymorphisms in human brain. Hum Genet. 2002; 110:1–7. [PubMed: 11810289]

Baler RD, Volkow ND, Fowler JS, Benveniste H. Is fetal brain monoamine oxidase inhibition the missing link between maternal smoking and conduct disorders? J Psychiatry Neurosci. 2008; 33:187–195. [PubMed: 18592036]

Barr CS, Driscoll C. Neurogenetics of aggressive behavior: studies in primates. Curr Top Behav Neurosci. 2014; 17:45–71. [PubMed: 24368617]

Beach SR, Brody GH, Gunter TD, Packer H, Wernett P, Philibert RA. Child maltreatment moderates the association of MAOA with symptoms of depression and antisocial personality disorder. J Fam Psychol. 2010; 24:12–20. [PubMed: 20175604]

Beaver KM, Barnes JC, Boutwell BB. The 2-repeat allele of the MAOA gene confers an increased risk for shooting and stabbing behaviors. Psychiatr Q. 2014; 85:257–265. [PubMed: 24326626]

Beaver KM, DeLisi M, Vaughn MG, Barnes JC. Monoamine oxidase A genotype is associated with gang membership and weapon use. Compr Psychiatry. 2010; 51:130–134. [PubMed: 20152292]

Beaver KM, Holtfreter K. Biosocial influences on fraudulent behaviors. J Genet Psychol. 2009; 170:101–114. [PubMed: 19492728]

Beaver KM, Sak A, Vaske J, Nilsson J. Genetic risk, parent-child relations, and antisocial phenotypes in a sample of African-American males. Psychiatry Res. 2010; 175:160–164. [PubMed: 20004478]

Beaver KM, Wright JP, Boutwell BB, Barnes JC, DeLisi M, Vaughn MG. Exploring the association between the 2-repeat allele of the MAOA gene promoter polymorphism and psychopathic

personality traits, arrests, incarceration, and lifetime antisocial behavior. Pers Indiv Differ. 2013; 54:164–168.

Belfrage H, Lidberg L, Oreland L. Platelet monoamine oxidase activity in mentally disordered violent offenders. Acta Psychiatr Scand. 1992; 85:218–221. [PubMed: 1561894]

Berlin I, Anthenelli RM. Monoamine oxidases and tobacco smoking. Int J Neuropsychopharmacol. 2001; 4:33–42. [PubMed: 11343627]

Best M, Williams JM, Coccaro EF. Evidence for a dysfunctional prefrontal circuit in patients with an impulsive aggressive disorder. Proc Natl Acad Sci USA. 2002; 99:8448–8453. [PubMed: 12034876]

Blackburn R. Am empirical classification of psychopathic personality. Br J Psychiatry. 1975; 127:456–460. [PubMed: 1203635]

Blonigen DM, Hicks BM, Krueger RF, Patrick CJ, Iacono WG. Psychopathic personality traits: heritability and genetic overlap with internalizing and externalizing psychopathology. Psychol Med. 2005; 35:637–648. [PubMed: 15918340]

Bortolato M, Chen K, Godar SC, Chen G, Wu W, Rebrin I, et al. Social deficits and perseverative behaviors, but not overt aggression, in MAOA hypomorphic mice. Neuropsychopharmacol. 2011; 36:2674–2688.

Bortolato M, Chen K, Shih JC. Monoamine oxidase inactivation: from pathophysiology to therapeutics. Adv Drug Deliver Rev. 2008; 60:1527–1533.

Bortolato M, Godar SC, Alzghoul L, Zhang J, Darling RD, Simpson KL, et al. Monoamine oxidase A and A/B knockout mice display autistic-like features. Int J Neuropsychopharmacol. 2013a; 16:869–888. [PubMed: 22850464]

Bortolato M, Godar SC, Davarian S, Chen K, Shih JC. Behavioral disinhibition and reduced anxiety-like behaviors in monoamine oxidase B-deficient mice. Neuropsychopharmacology. 2009; 34:2746–2757. [PubMed: 19710633]

Bortolato M, Godar SC, Melis M, Soggiu A, Roncada P, Casu A, et al. NMDARs mediate the role of monoamine oxidase A in pathological aggression. J Neurosci. 2012; 32:8574–8582. [PubMed: 22723698]

Bortolato M, Pivac N, Muck Seler D, Nikolac Perkovic M, Pessia M, Di Giovanni G. The role of the serotonergic system at the interface of aggression and suicide. Neuroscience. 2013b; 236:160–185. [PubMed: 23333677]

Brendgen M, Vitaro F, Boivin M, Dionne G, Perusse D. Examining genetic and environmental effects on reactive versus proactive aggression. Dev Psychol. 2006; 42:1299–1312. [PubMed: 17087562]

Brummett BH, Boyle SH, Siegler IC, Kuhn CM, Surwit RS, Garrett ME, et al. HPA axis function in male caregivers: effect of the monoamine oxidase-A gene promoter (MAOA-uVNTR). Biol Psychol. 2008; 79:250–255. [PubMed: 18639608]

Brunner HG, Nelen M, Breakefield XO, Ropers HH, van Oost BA. Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. science. 1993; 262:578–580. [PubMed: 8211186]

Brunner HG. MAOA deficiency and abnormal behaviour: perspectives on an association. Ciba Found Symp. 1996; 194:155–164. discussion 64-7. [PubMed: 8862875]

Buckholtz JW, Callicott JH, Kolachana B, Hariri AR, Goldberg TE, Genderson M, et al. Genetic variation in MAOA modulates ventromedial prefrontal circuitry mediating individual differences in human personality. Mol Psychiatry. 2008; 13:313–324. [PubMed: 17519928]

Buckholtz JW, Meyer-Lindenberg A. MAOA and the neurogenetic architecture of human aggression. Trends Neurosci. 2008; 31:120–129. [PubMed: 18258310]

Buss DM, Shackelford TK. Human aggression in evolutionary psychological perspective. Clin Psychol Rev. 1997; 17:605–619. [PubMed: 9336687]

Buxhoeveden DP, Semendeferi K, Buckwalter J, Schenker N, Switzer R, Courchesne E. Reduced minicolumns in the frontal cortex of patients with autism. Neuropath Appl Neurol. 2006; 32:483–491.

Byrd AL, Manuck SB. MAOA, childhood maltreatment, and antisocial behavior: meta-analysis of a gene-environment interaction. Biol Psychiatry. 2014; 75:9–17. [PubMed: 23786983]

Card NA, Little TD. Proactive and reactive aggression in childhood and adolescence: A meta-analysis of differential relations with psychosocial adjustment. Int J Behav Dev. 2006; 30:466–480.

Cases O, Seif I, Grimsby J, Gaspar P, Chen K, Pournin S, et al. Aggressive behavior and altered amounts of brain serotonin and norepinephrine in mice lacking MAOA. science. 1995; 268:1763–1766. [PubMed: 7792602]

Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, et al. Role of genotype in the cycle of violence in maltreated children. science. 2002; 297:851–854. [PubMed: 12161658]

Checknita D, Maussion G, Labonte B, Comai S, Tremblay RE, Vitaro F, et al. Monoamine oxidase A gene promoter methylation and transcriptional downregulation in an offender population with antisocial personality disorder. Br J Psychiatry. 2015; 206:216–222. [PubMed: 25497297]

Chen K, Cases O, Rebrin I, Wu W, Gallaher TK, Seif I, Shih JC. Forebrain-specific expression of monoamine oxidase A reduces neurotransmitter levels, restores the brain structure, and rescues aggressive behavior in monoamine oxidase A-deficient mice. J Biol Chem. 2007; 282:115–123. [PubMed: 17090537]

Chester DS, DeWall CN, Derefinko KJ, Estus S, Peters JR, Lynam DR, et al. Monoamine oxidase A (MAOA) genotype predicts greater aggression through impulsive reactivity to negative affect. Behav Brain Res. 2015; 283:97–101. [PubMed: 25637908]

Coccaro EF, Fanning JR, Phan KL, Lee R. Serotonin and impulsive aggression. CNS Spectr. 2015; 20:295–302. [PubMed: 25997605]

Coccaro EF, McCloskey MS, Fitzgerald DA, Phan KL. Amygdala and orbitofrontal reactivity to social threat in individuals with impulsive aggression. Biol Psychiatry. 2007; 62:168–178. [PubMed: 17210136]

Coccaro EF, Sripada CS, Yanowitch RN, Phan KL. Corticolimbic function in impulsive aggressive behavior. Biol Psychiatry. 2011; 69:1153–1159. [PubMed: 21531387]

Cohen IL, Liu X, Lewis ME, Chudley A, Forster-Gibson C, Gonzalez M, et al. Autism severity is associated with child and maternal MAOA genotypes. Clin Genet. 2011; 79:355–362. [PubMed: 20573161]

Comai S, Tau M, Gobbi G. The psychopharmacology of aggressive behavior: a translational approach: part 1: neurobiology. J Clin Psychopharmacol. 2012; 32:83–94. [PubMed: 22198449]

Connor DF, Steingard RJ, Anderson JJ, Melloni RH Jr. Gender differences in reactive and proactive aggression. Child Psychiatry Hum Dev. 2003; 33:279–294. [PubMed: 12723901]

Connor DF, Steingard RJ, Cunningham JA, Anderson JJ, Melloni RH Jr. Proactive and reactive aggression in referred children and adolescents. Am J Orthopsychiatry. 2004; 74:129–136. [PubMed: 15113242]

Contini V, Marques FZ, Garcia CE, Hutz MH, Bau CH. MAOA-uVNTR polymorphism in a Brazilian sample: further support for the association with impulsive behaviors and alcohol dependence. Am J Med Genet B Neuropsychiatr Genet. 2006; 141b:305–308. [PubMed: 16526025]

Courchesne E, Pierce K. Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. Curr Opin Neurobiol. 2005; 15:225–230. [PubMed: 15831407]

Crampton P, Parkin C. Warrior genes and risk-taking science. N Z Med J. 2007; 120:U2439. [PubMed: 17339895]

Crick NR, Dodge KA. Social information-processing mechanisms in reactive and proactive aggression. Child Dev. 1996; 67:993–1002. [PubMed: 8706540]

Datla KP, Mitra SK, Bhattacharya SK. Serotonergic modulation of footshock induced aggression in paired rats. Ind J Exp Biol. 1991; 29:631–635.

de Almeida RM, Ferrari PF, Parmigiani S, Miczek KA. Escalated aggressive behavior: dopamine, serotonin and GABA. Eur J Pharmacol. 2005; 526:51–64. [PubMed: 16325649]

Deckert J, Catalano M, Syagailo YV, Bosi M, Okladnova O, Di Bella D, et al. Excess of high activity monoamine oxidase A gene promoter alleles in female patients with panic disorder. Hum Mol Genet. 1999; 8:621–624. [PubMed: 10072430]

Denney RM, Koch H, Craig IW. Association between monoamine oxidase A activity in human male skin fibroblasts and genotype of the MAOA promoter-associated variable number tandem repeat. Hum Genet. 1999; 105:542–551. [PubMed: 10647887]

Denson TF, Dobson-Stone C, Ronay R, von Hippel W, Schira MM. A functional polymorphism of the MAOA gene is associated with neural responses to induced anger control. J Cogn Neurosci. 2014; 26:1418–1427. [PubMed: 24564461]

Derringer J, Krueger RF, Irons DE, Iacono WG. Harsh discipline, childhood sexual assault, and MAOA genotype: an investigation of main and interactive effects on diverse clinical externalizing outcomes. Behav Genet. 2010; 40:639–648. [PubMed: 20364435]

DiLalla LF, Gottesman II. Biological and genetic contributors to violence- Widom's untold tale. Psychol Bull. 1991; 109:125–129. discussion 30-2. [PubMed: 2006224]

Dodge KA, Coie JD. Social-information-processing factors in reactive and proactive aggression in children's peer groups. J Pers Soc Psychol. 1987; 53:1146–1158. [PubMed: 3694454]

Dodge KA, Lochman JE, Harnish JD, Bates JE, Pettit GS. Reactive and proactive aggression in school children and psychiatrically impaired chronically assaultive youth. J Abnorm Psychol. 1997; 106:37–51. [PubMed: 9103716]

Dodge KA, Pettit GS. A biopsychosocial model of the development of chronic conduct problems in adolescence. Dev Psychol. 2003; 39:349–371. [PubMed: 12661890]

Dorfman HM, Meyer-Lindenberg A, Buckholtz JW. Neurobiological mechanisms for impulsive-aggression: the role of MAOA. Curr Top Behav Neurosci. 2014; 17:297–313. [PubMed: 24470068]

Dubrovina NI, Popova NK, Gilinskii MA, Tomilenko RA, Seif I. Acquisition and extinction of a conditioned passive avoidance reflex in mice with genetic knockout of monoamine oxidase A. Neurosci Behav Physiol. 2006; 36:335–339. [PubMed: 16583159]

Ducci F, Enoch MA, Hodgkinson C, Xu K, Catena M, Robin RW, et al. Interaction between a functional MAOA locus and childhood sexual abuse predicts alcoholism and antisocial personality disorder in adult women. Mol Psychiatry. 2008; 13:334–347. [PubMed: 17592478]

Duke AA, Begue L, Bell R, Eisenlohr-Moul T. Revisiting the serotonin-aggression relation in humans: a meta-analysis. Psychol Bull. 2013; 139:1148–1172. [PubMed: 23379963]

Edwards AC, Dodge KA, Latendresse SJ, Lansford JE, Bates JE, Pettit GS, et al. MAOA-uVNTR and early physical discipline interact to influence delinquent behavior. J Child Psychol Psychiatry. 2010; 51:679–687. [PubMed: 19951362]

Eisenberg, N.; Fabes, RA. Emotion, regulation, and the development of social competence. In: Clark, M., editor. Emotion and social behavior: Vol. 14. Review of personality and social psychology. Newbury Park, CA: Sage; 1992. p. 119-150.

Eisenberger NI, Way BM, Taylor SE, Welch WT, Lieberman MD. Understanding genetic risk for aggression: clues from the brain's response to social exclusion. Biol Psychiatry. 2007; 61:1100–1108. [PubMed: 17137563]

Erzurumlu RS, Jhaveri S. Thalamic axons confer a blueprint of the sensory periphery onto the developing rat somatosensory cortex. Brain Res Dev Brain Res. 1990; 56:229–234. [PubMed: 2261684]

Evrard A, Malagié I, Laporte AM, Boni C, Hanoun N, Trillat AC, Seif I, De Maeyer E, Gardier A, Hamon M, Adrien J. Altered regulation of the 5-HT system in the brain of MAO-A knock-out mice. Eur J Neurosci. 2002; 15:841–851. [PubMed: 11906526]

Farmer CA, Aman MG. Aripiprazole for the treatment of irritability associated with autism. Expert Opin Pharmacother. 2011; 12:635–640. [PubMed: 21294670]

Fava M. Psychopharmacologic treatment of pathologic aggression. Psychiatr Clin North Am. 1997; 20:427–451. [PubMed: 9196923]

Ferguson CJ, Beaver KM. Natural born killers: The genetic origins of extreme violence. Aggress Violent Behav. 2009; 14:286–294.

Ferguson CJ. Genetic contributions to antisocial personality and behavior: a meta-analytic review from an evolutionary perspective. J Soc Psychol. 2010; 150:160–180. [PubMed: 20397592]

Fergusson DM, Boden JM, Horwood LJ, Miller AL, Kennedy MA. MAOA, abuse exposure and antisocial behaviour: 30-year longitudinal study. Br J Psychiatry. 2011; 198:457–463. [PubMed: 21628708]

Ficks CA, Waldman ID. Candidate genes for aggression and antisocial behavior: a meta-analysis of association studies of the 5HTTLPR and MAOA-uVNTR. Behav Genet. 2014; 44:427–444. [PubMed: 24902785]

Fite, PJ.; Rathert, J.; Colder, CR.; Lochman, JE.; Wells, K. Proactive and reactive aggression. In: Levesque, RJR., editor. Encyclopedia of Adolescence. New York, NY: Springer; 2012. p. 2164-2170.

Foley DL, Eaves LJ, Wormley B, Silberg JL, Maes HH, Kuhn J, et al. Childhood adversity, monoamine oxidase a genotype, and risk for conduct disorder. Arch Gen Psychiatry. 2004; 61:738–744. [PubMed: 15237086]

Forzano F, Borry P, Cambon-Thomsen A, Hodgson SV, Tibben A, de Vries P, et al. Italian appeal court: a genetic predisposition to commit murder. Eur J Hum Genet. 2010; 18:519–521. [PubMed: 20216573]

Fowler JS, Alia-Klein N, Kriplani A, Logan J, Williams B, Zhu W, et al. Evidence that brain MAOA activity does not correspond to MAOA genotype in healthy male subjects. Biol Psychiatry. 2007; 62:355–358. [PubMed: 17141746]

Fowler JS, Volkow ND, Wang GJ, Pappas N, Logan J, Shea C, et al. Brain monoamine oxidase A inhibition in cigarette smokers. Proc Natl Acad Sci USA. 1996; 93:14065–14069. [PubMed: 8943061]

Frazzetto G, Di Lorenzo G, Carola V, Proietti L, Sokolowska E, Siracusano A, et al. Early trauma and increased risk for physical aggression during adulthood: the moderating role of MAOA genotype. PloS one. 2007; 2:e486. [PubMed: 17534436]

Frick PJ, Cornell AH, Barry CT, Bodin SD, Dane HE. Callous-unemotional traits and conduct problems in the prediction of conduct problem severity, aggression, and self-report of delinquency. J Abnorm Child Psychol. 2003; 31:457–470. [PubMed: 12831233]

Gallardo-Pujol D, Andres-Pueyo A, Maydeu-Olivares A. MAOA genotype, social exclusion and aggression: an experimental test of a gene-environment interaction. Genes Brain Behav. 2013; 12:140–145. [PubMed: 23067570]

Garpenstrand H, Norton N, Damberg M, Rylander G, Forslund K, Mattila-Evenden M, Gustavsson JP, Ekblom J, Oreland L, Bergman H, Owen MJ, Jönsson EG. A regulatory monoamine oxidase a promoter polymorphism and personality traits. Neuropsychobiol. 2002; 46:190–193.

Ghashghaei HT, Barbas H. Pathways for emotion: interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. Neuroscience. 2002; 115:1261–1279. [PubMed: 12453496]

Godar SC, Bortolato M, Castelli MP, Casti A, Casu A, Chen K, et al. The aggression and behavioral abnormalities associated with monoamine oxidase A deficiency are rescued by acute inhibition of serotonin reuptake. J Psychiatr Res. 2014; 56:1–9. [PubMed: 24882701]

Godar SC, Bortolato M, Frau R, Dousti M, Chen K, Shih JC. Maladaptive defensive behaviours in monoamine oxidase A-deficient mice. Int J Neuropsychopharmacol. 2011; 14:1195–1207. [PubMed: 21156093]

Godar SC, Bortolato M, Richards SE, Li FG, Chen K, Wellman CL, et al. Monoamine Oxidase A is Required for Rapid Dendritic Remodeling in Response to Stress. Int J Neuropsychopharmacol. 2015:18.

Grady CL, Siebner HR, Hornboll B, Macoveanu J, Paulson OB, Knudsen GM. Acute pharmacologically induced shifts in serotonin availability abolish emotion-selective responses to negative face emotions in distinct brain networks. Eur Neuropsychopharmacol. 2013; 23:368–378. [PubMed: 22739125]

Griebel G, Curet O, Perrault G, Sanger DJ. Behavioral effects of phenelzine in an experimental model for screening anxiolytic and anti-panic drugs: correlation with changes in monoamine-oxidase activity and monoamine levels. Neuropharmacology. 1998; 37:927–935. [PubMed: 9776388]

Grimsby J, Lan NC, Neve R, Chen K, Shih JC. Tissue distribution of human monoamine oxidase A and B mRNA. J Neurochem. 1990; 55:1166–1169. [PubMed: 2398352]

Grimsby J, Toth M, Chen K, Kumazawa T, Klaidman L, Adams JD, et al. Increased stress response and beta-phenylethylamine in MAOB-deficient mice. Nat Genet. 1997; 17:206–210. [PubMed: 9326944]

Grove WM, Eckert ED, Heston L, Bouchard TJ Jr, Segal N, Lykken DT. Heritability of substance abuse and antisocial behavior: a study of monozygotic twins reared apart. Biol Psychiatry. 1990; 27:1293–1304. [PubMed: 2364118]

Guo G, Ou XM, Roettger M, Shih JC. The VNTR 2 repeat in MAOA and delinquent behavior in adolescence and young adulthood: associations and MAOA promoter activity. Eur J Hum Genet. 2008; 16:626–634. [PubMed: 18212819]

Haberstick BC, Lessem JM, Hewitt JK, Smolen A, Hopfer CJ, Halpern CT, et al. MAOA genotype, childhood maltreatment, and their interaction in the etiology of adult antisocial behaviors. Biol Psychiatry. 2014; 75:25–30. [PubMed: 23726513]

Hebebrand J, Klug B. Specification of the phenotype required for men with monoamine oxidase type A deficiency. Hum Genet. 1995; 96:372–376. [PubMed: 7649563]

Hicks BM, Carlson MD, Blonigen DM, Patrick CJ, Iacono WG, Mgue M. Psychopathic personality traits and environmental contexts: Differential correlates, gender differences, and genetic mediation. Personal Disord. 2012; 3:209–227. [PubMed: 22452762]

Hill J, Breen G, Quinn J, Tibu F, Sharp H, Pickles A. Evidence for interplay between genes and maternal stress in utero: monoamine oxidase A polymorphism moderates effects of life events during pregnancy on infant negative emotionality at 5 weeks. Genes Brain Behav. 2013; 12:388–396. [PubMed: 23480342]

Holz N, Boecker R, Buchmann AF, Blomeyer D, Baumeister S, Hohmann S, et al. Evidence for a Sex-Dependent MAOA × Childhood Stress Interaction in the Neural Circuitry of Aggression. Cereb Cortex. 2014

Huang YY, Cate SP, Battistuzzi C, Oquendo MA, Brent D, Mann JJ. An association between a functional polymorphism in the monoamine oxidase a gene promoter, impulsive traits and early abuse experiences. Neuropsychopharmacology. 2004; 29:1498–1505. [PubMed: 15150530]

Jacob CP, Müller J, Schmidt M, Hohenberger K, Gutknecht L, Reif A, Schmidtke A, Mössner R, Lesch KP. Cluster B personality disorders are associated with allelic variation of monoamine oxidase A activity. Neuropsychopharmacology. 2005; 30:1711–1718. [PubMed: 15870836]

Jackson ME, Homayoun H, Moghaddam B. NMDA receptor hypofunction produces concomitant firing rate potentiation and burst activity reduction in the prefrontal cortex. Proc Natl Acad Sci U S A. 2004; 101:8467–8472. [PubMed: 15159546]

Jahng JW, Houpt TA, Joh TH, Son JH. Differential expression of monoamine oxidase A, serotonin transporter, tyrosine hydroxylase and norepinephrine transporter mRNA by anorexia mutation and food deprivation. Brain Res. 1998; 107:241–246.

Jonsson EG, Norton N, Gustavsson JP, Oreland L, Owen MJ, Sedvall GC. A promoter polymorphism in the monoamine oxidase A gene and its relationships to monoamine metabolite concentrations in CSF of healthy volunteers. J Psychiatr Res. 2000; 34:239–244. [PubMed: 10867119]

Karere GM, Kinnally EL, Sanchez JN, Famula TR, Lyons LA, Capitanio JP. What is an “adverse” environment? Interactions of rearing experiences and MAOA genotype in rhesus monkeys. Biol Psychiatry. 2009; 65:770–777. [PubMed: 19103441]

Kim JJ, Shih JC, Chen K, Chen L, Bao S, Maren S, et al. Selective enhancement of emotional, but not motor, learning in monoamine oxidase A-deficient mice. Proc Natl Acad Sci USA. 1997; 94:5929–5933. [PubMed: 9159177]

Kim SJ, Kim YS, Kim SY, Lee HS, Kim CH. An association study of catechol-O-methyltransferase and monoamine oxidase A polymorphisms and personality traits in Koreans. Neurosci Lett. 2006; 401:154–158. [PubMed: 16584839]

Kim-Cohen J, Caspi A, Taylor A, Williams B, Newcombe R, Craig IW, et al. MAOA, maltreatment, and gene-environment interaction predicting children’s mental health: new evidence and a meta-analysis. Mol Psychiatry. 2006; 11:903–913. [PubMed: 16801953]

Kinnally EL, Huang YY, Haverly R, Burke AK, Galfalvy H, Brent DP, et al. Parental care moderates the influence of MAOA-uVNTR genotype and childhood stressors on trait impulsivity and aggression in adult women. Psychiatr Genet. 2009; 19:126–133. [PubMed: 19357553]

Kolla NJ, Matthews B, Wilson AA, Houle S, Bagby RM, Links P, et al. Lower Monoamine Oxidase-A Total Distribution Volume in Impulsive and Violent Male Offenders with Antisocial Personality

Disorder and High Psychopathic Traits: An [(11)C] Harmine Positron Emission Tomography Study. Neuropsychopharmacology. 2015; 40:2596–2603. [PubMed: 26081301]

Krueger RF, Markon KE, Patrick CJ, Iacono WG. Externalizing Psychopathology in Adulthood: A Dimensional-Spectrum Conceptualization and Its Implications for DSM-V. J Abnorm Psychol. 2005; 114:537–550. [PubMed: 16351376]

Kuepper Y, Grant P, Wielpuetz C, Hennig J. MAOA-uVNTR genotype predicts interindividual differences in experimental aggressiveness as a function of the degree of provocation. Behav Brain Res. 2013; 247:73–78. [PubMed: 23499704]

Langton, L.; Truman, J. Socio-emotional impact of violent crime, Special Report, US Department of Justice, Office of Justice Programs, Bureau of Justice Statistics. Washington, DC: 2014 Sep.

Lecavalier L. Behavioral and emotional problems in young people with pervasive developmental disorders: relative prevalence, effects of subject characteristics, and empirical classification. J Autism Dev Disord. 2006; 36:1101–1114. [PubMed: 16897387]

Lee BT, Ham BJ. Monoamine oxidase A-uVNTR genotype affects limbic brain activity in response to affective facial stimuli. Neuroreport. 2008; 19:515–519. [PubMed: 18388730]

Lee RJ, Gill A, Chen B, McCloskey M, Coccaro EF. Modulation of central serotonin affects emotional information processing in impulsive aggressive personality disorder. J Clin Psychopharmacol. 2012; 32:329–335. [PubMed: 22544009]

Lemerise EA, Arsenio WF. An integrated model of emotion processes and cognition in social information processing. Child Dev. 2000; 71:107–118. [PubMed: 10836564]

Linnoila M, Karoum F, Miller T, Potter WZ. Reliability of urinary monoamine and metabolite output measurements in depressed patients. Am J Psychiatry. 1983; 140:1055–1057. [PubMed: 6191580]

Lokmane L, Garel S. Map transfer from the thalamus to the neocortex: inputs from the barrel field. Semin Cell Dev Biol. 2014; 35:147–155. [PubMed: 25020201]

Lubke J, Feldmeyer D. Excitatory signal flow and connectivity in a cortical column: focus on barrel cortex. Brain Struct Funct. 2007; 212:3–17. [PubMed: 17717695]

Machado CJ, Bachevalier J. The impact of selective amygdala, orbital frontal cortex, or hippocampal formation lesions on established social relationships in rhesus monkeys (Macaca mulatta). Behav Neurosci. 2006; 120:761–786. [PubMed: 16893284]

Marquez C, Poirier GL, Cordero MI, Larsen MH, Groner A, Marquis J, et al. Peripuberty stress leads to abnormal aggression, altered amygdala and orbitofrontal reactivity and increased prefrontal MAOA gene expression. Transl Psychiatry. 2013; 3:e216. [PubMed: 23321813]

Marsee MA, Frick PJ. Exploring the cognitive and emotional correlates to proactive and reactive aggression in a sample of detained girls. J Abnorm Child Psych. 2007; 35:969–981.

Marsh AA, Finger EC, Fowler KA, Jurkowitz IT, Schechter JC, Yu HH, et al. Reduced amygdala-orbitofrontal connectivity during moral judgments in youths with disruptive behavior disorders and psychopathic traits. Psychiatr Res. 2011; 194:279–286.

McCollister KE, French MT, Fang H. The Cost of Crime to Society: New Crime-Specific Estimates for Policy and Program Evaluation. Drug Alcohol Depen. 2010; 108:98–109.

McDermott R, Tingley D, Cowden J, Frazzetto G, Johnson DD. Monoamine oxidase A gene (MAOA) predicts behavioral aggression following provocation. Proc Natl Acad Sci USA. 2009; 106:2118–2123. [PubMed: 19168625]

McGrath LM, Mustanski B, Metzger A, Pine DS, Kistner-Griffin E, Cook E, et al. A latent modeling approach to genotype-phenotype relationships: maternal problem behavior clusters, prenatal smoking, and MAOA genotype. Arch Women Ment Health. 2012; 15:269–282.

Mejia JM, Ervin FR, Baker GB, Palmour RM. Monoamine oxidase inhibition during brain development induces pathological aggressive behavior in mice. Biol Psychiat. 2002; 52:811–821. [PubMed: 12372653]

Mejia JM, Ervin FR, Palmour RM, Tremblay RE. Aggressive behavior and Brunner syndrome: no evidence for the C936T mutation in a population sample. Am J Med Genet. 2001; 105:396–397. [PubMed: 11378857]

Meyer-Lindenberg A, Buckholtz JW, Kolachana B, A RH, Pezawas L, Blasi G, et al. Neural mechanisms of genetic risk for impulsivity and violence in humans. Proc Natl Acad Sci USA. 2006; 103:6269–6274. [PubMed: 16569698]

Miles DR, Carey G. Genetic and environmental architecture of human aggression. J Pers Soc Psychol. 1997; 72:207–217. [PubMed: 9008382]

Miller TR, Fisher DA, Cohen MA. Costs of juvenile violence: policy implications. Pediatrics. 2001; 107:E3. [PubMed: 11134467]

Moore TM, Scarpa A, Raine A. A meta-analysis of serotonin metabolite 5-HIAA and antisocial behavior. Aggress Behav. 2002; 28:299–316.

Morgan JE, Gray NS, Snowden RJ. The relationship between psychopathy and impulsivity: A multi-impulsivity measurement approach. Pers Indiv Differ. 2011; 51:429–434.

Morishima M, Harada N, Hara S, Sano A, Seno H, Takahashi A, et al. Monoamine oxidase A activity and norepinephrine level in hippocampus determine hyperwheel running in SPORTS rats. Neuropsychopharmacology. 2006; 31:2627–2638. [PubMed: 16421512]

Motzkin JC, Newman JP, Kiehl KA, Koenigs M. Reduced prefrontal connectivity in psychopathy. J Neurosci. 2011; 31:17348–17357. [PubMed: 22131397]

New AS, Hazlett EA, Newmark RE, Zhang J, Triebwasser J, Meyerson D, et al. Laboratory induced aggression: a positron emission tomography study of aggressive individuals with borderline personality disorder. Biol Psychiatry. 2009; 66:1107–1114. [PubMed: 19748078]

Newman JP, MacCoon DG, Vaughn LJ, Sadeh N. Validating a distinction between primary and secondary psychopathy with measures of Gray's BIS and BAS constructs. J Abnorm Psychol. 2005a; 114:319–323. [PubMed: 15869363]

Newman TK, Syagailo YV, Barr CS, Wendland JR, Champoux M, Graessle M, et al. Monoamine oxidase A gene promoter variation and rearing experience influences aggressive behavior in rhesus monkeys. Biol Psychiatry. 2005b; 57:167–172. [PubMed: 15652876]

Nilsson KW, Comasco E, Hodgins S, Oreland L, Aslund C. Genotypes do not confer risk for delinquency but rather alter susceptibility to positive and negative environmental factors: gene-environment interactions of BDNF Val66Met, 5-HTTLPR, and MAOA-uVNTR. Int J Neuropsychopharmacol. 2014:18.

Nilsson KW, Sjoberg RL, Damberg M, Leppert J Ohrvik J, et al. Role of monoamine oxidase A genotype and psychosocial factors in male adolescent criminal activity. Biol Psychiatry. 2006; 59:121–127. [PubMed: 16125147]

Nouvion SO, Cherek DR, Lane SD, Tcheremissine OV, Lieving LM. Human proactive aggression: association with personality disorders and psychopathy. Aggress Behav. 2007; 33:552–562. [PubMed: 17654689]

Nymberg C, Jia T, Lubbe S, Ruggeri B, Desrivieres S, Barker G, et al. Neural mechanisms of attention-deficit/hyperactivity disorder symptoms are stratified by MAOA genotype. Biol Psychiatry. 2013; 74:607–614. [PubMed: 23746540]

Ongur D, Price JL. The organization of networks within the orbital and medial PFC of rats, monkeys and humans. Cereb Cortex. 2000; 10:206–219. [PubMed: 10731217]

Oreland L, Nilsson K, Damberg M, Hallman J. Monoamine oxidases: activities, genotypes and the shaping of behaviour. J Neural Transm. 2007; 114:817–822. [PubMed: 17426915]

Palmer EE, Leffler M, Rogers C, Shaw M, Carroll R, Earl J, et al. New insights into Brunner syndrome and potential for targeted therapy. Clin Genet. 2015

Passamonti L, Crockett MJ, Apergis-Schoute AM, Clark L, Rowe JB, Calder AJ, Robbins TW. Effects of acute tryptophan depletion on prefrontal-amygdala connectivity while viewing facial signals of aggression. Biol Psychiatry. 2012; 71:36–43. [PubMed: 21920502]

Paul LK, Brown WS, Adolphs R, Tyszka JM, Richards LJ, Mukherjee P, Sherr EH. Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. Nat Rev Neurosci. 2007; 8:287–299. [PubMed: 17375041]

Piton A, Poquet H, Redin C, Masurel A, Lauer J, Muller J, et al. 20 ans apres: a second mutation in MAOA identified by targeted high-throughput sequencing in a family with altered behavior and cognition. Eur J Hum Genet. 2014; 22:776–783. [PubMed: 24169519]

Polman H, Orobio de Castro B, Koops W, van Boxtel HW, Merk WW. A meta-analysis of the distinction between reactive and proactive aggression in children and adolescents. J Abnorm Child Psych. 2007; 35:522–535.

Popova NK, Maslova LN, Morosova EA, Bulygina VV, Seif I. MAOA knockout attenuates adrenocortical response to various kinds of stress. Psychoneuroendocrinology. 2006; 31:179–186. [PubMed: 16112493]

Popova NK, Skrinskaya YA, Amstislavskaya TG, Vishnivetskaya GB, Seif I, de Meier E. Behavioral characteristics of mice with genetic knockout of monoamine oxidase type A. Neurosci Behav Physiol. 2001; 31:597–602. [PubMed: 11766896]

Prichard Z, Mackinnon A, Jorm AF, Easteal S. No evidence for interaction between MAOA and childhood adversity for antisocial behavior. Am J Med Genet B Neuropsychiatr Genet. 2008; 147b:228–232. [PubMed: 18023041]

Raine A, Dodge K, Loeber R, Gatzke-Kopp L, Lynam D, Reynolds C, et al. The Reactive-Proactive Aggression Questionnaire: Differential Correlates of Reactive and Proactive Aggression in Adolescent Boys. Aggress Behav. 2006; 32:159–171. [PubMed: 20798781]

Rhee SH, Waldman ID. Genetic and environmental influences on antisocial behavior: a meta-analysis of twin and adoption studies. Psychol Bull. 2002; 128:490–529. [PubMed: 12002699]

Rolls ET, Loh M, Deco G. An attractor hypothesis of obsessive-compulsive disorder. Eur J Neurosci. 2008; 28:782–793. [PubMed: 18671737]

Rosell DR, Siever LJ. The neurobiology of aggression and violence. CNS Spectr. 2015; 20:254–279. [PubMed: 25936249]

Rosenberg S, Templeton AR, Feigin PD, Lancet D, Beckmann JS, Selig S, et al. The association of DNA sequence variation at the MAOA genetic locus with quantitative behavioural traits in normal males. Hum Genet. 2006; 120:447–459. [PubMed: 16896926]

Sabol SZ, Hu S, Hamer D. A functional polymorphism in the monoamine oxidase A gene promoter. Hum Genet. 1998; 103:273–279. [PubMed: 9799080]

Samochowiec J, Syrek S, Michał P, Ryzewska-Wódecka A, Samochowiec A, Horodnicki J, Zakrzewska M, Kucharska-Mazur J. Polymorphisms in the serotonin transporter and monoamine oxidase A genes and their relationship to personality traits measured by the Temperament and Character Inventory and NEO Five-Factor Inventory in healthy volunteers. Neuropsychobiology. 2004; 50:174–181. [PubMed: 15292674]

Schutter DJ, Harmon-Jones E. The corpus callosum: a commissural road to anger and aggression. Neurosci Biobehav Rev. 2013; 37:2481–2488. [PubMed: 23911937]

Scott AL, Bortolato M, Chen K, Shih JC. Novel monoamine oxidase A knock out mice with human-like spontaneous mutation. Neuroreport. 2008; 19:739–743. [PubMed: 18418249]

Seeburg PH, Burnashev N, Kohr G, Kuner T, Sprengel R, Monyer H. The NMDA receptor channel: molecular design of a coincidence detector. Recent Prog Horm Res. 1995; 50:19–34. [PubMed: 7740157]

Shields A, Cicchetti D. Reactive aggression among maltreated children: the contributions of attention and emotion dysregulation. J Clin Child Psychol. 1998; 27:381–395. [PubMed: 9866075]

Shumay E, Logan J, Volkow ND, Fowler JS. Evidence that the methylation state of the monoamine oxidase A (MAOA) gene predicts brain activity of MAOA enzyme in healthy men. Epigenetics. 2012; 7:1151–1160. [PubMed: 22948232]

Skeem J, Johansson P, Andershed H, Kerr M, Louden JE. Two subtypes of psychopathic violent offenders that parallel primary and secondary variants. J Abnorm Psychol. 2007; 116:395–409. [PubMed: 17516770]

Skeem JL, Poythress N, Edens JF, Lilienfeld SO, Cale EM. Psychopathic personality or personalities? Exploring potential variants of psychopathy and their implications for risk assessment. Aggress Violent Beh. 2003; 8:513–546.

Skondras M, Markianos M, Botsis A, Bistolaki E, Christodoulou G. Platelet monoamine oxidase activity and psychometric correlates in male violent offenders imprisoned for homicide or other violent acts. Eur Arch Psychiatry Clin Neurosci. 2004; 254:380–386. [PubMed: 15538603]

Soderstrom H, Blennow K, Manhem A, Forsman A. CSF studies in violent offenders I. 5-HIAA as a negative and HVA as a positive predictor of psychopathy. J Neural Transm. 2001; 108:869–878. [PubMed: 11515752]

Soliman A, Bagby RM, Wilson AA, Miler L, Clark M, Rusjan P, et al. Relationship of monoamine oxidase A binding to adaptive and maladaptive personality traits. Psychol Med. 2011; 41:1051–1060. [PubMed: 20810002]

Sterzer P, Stadler C, Krebs A, Kleinschmidt A, Poustka F. Abnormal neural responses to emotional visual stimuli in adolescents with conduct disorder. Biol Psychiatry. 2005; 57:7–15. [PubMed: 15607294]

Stetler DA, Davis C, Leavitt K, Schriger I, Benson K, Bhakta S, et al. Association of low-activity MAOA allelic variants with violent crime in incarcerated offenders. J Psychiatr Res. 2014; 58:69–75. [PubMed: 25082653]

Stoner R, Chow ML, Boyle MP, Sunkin SM, Mouton PR, Roy S, et al. Patches of disorganization in the neocortex of children with autism. New Engl J Med. 2014; 370:1209–1219. [PubMed: 24670167]

Tiihonen J, Rautiainen MR, Ollila HM, Repo-Tiihonen E, Virkkunen M, Palotie A, et al. Genetic background of extreme violent behavior. Mol Psychiatry. 2015; 20:786–792. [PubMed: 25349169]

Tochigi M, Otowa T, Hibino H, Kato C, Otani T, Umekage T, Utsumi T, Kato N, Sasaki T. Combined analysis of association between personality traits and three functional polymorphisms in the tyrosine hydroxylase, monoamine oxidase A, and catechol-O-methyltransferase genes. Neurosci Res. 2006; 54:180–185. [PubMed: 16360899]

Tong J, Meyer JH, Furukawa Y, Boileau I, Chang LJ, Wilson AA, et al. Distribution of monoamine oxidase proteins in human brain: implications for brain imaging studies. J Cereb Blood Flow Metab. 2013; 33:863–871. [PubMed: 23403377]

Verhoeven FE, Booij L, Kruijt AW, Cerit H, Antypa N, Does W. The effects of MAOA genotype, childhood trauma, and sex on trait and state-dependent aggression. Brain Behav. 2012; 2:806–813. [PubMed: 23170243]

Viding E, Frick PJ, Plomin R. Aetiology of the relationship between callous-unemotional traits and conduct problems in childhood. Br J Psychiatry Suppl. 2007; 49:33–38.

Virkkunen M, Linnoila M. Serotonin in early onset, male alcoholics with violent behaviour. Ann Med. 1990; 22:327–331. [PubMed: 2291840]

Vitaro, F.; Brendgen, M. Subtypes of aggressive aggressive behaviors: Etiologies, development and consequences. In: Bliesener, TBA., editor. Antisocial behavior and crime: Contributions of theory and evaluation research to prevention and intervention. Germany: Hogrefe; 2011.

Vitaro F, Gendreau PL, Tremblay RE, Oligny P. Reactive and proactive aggression differentially predict later conduct problems. J Child Psychol Psyc. 1998; 39:377–385.

Volavka J, Citrome L, Huertas D. Update on the biological treatment of aggression. Actas Esp Psiquiatr. 2006; 34:123–135. [PubMed: 16552640]

Wakschlag LS, Kistner EO, Pine DS, Biesecker G, Pickett KE, Skol AD, et al. Interaction of prenatal exposure to cigarettes and MAOA genotype in pathways to youth antisocial behavior. Mol Psychiatry. 2010; 15:928–937. [PubMed: 19255579]

Waters, HHA.; Rajkotia, Y.; Basu, S.; Rehwinkel, JA.; Butchart, A. The economic dimensions of interpersonal violence. Department of Injuries and Violence Prevention WHO. , editor. Geneva: 2004. p. 4

Weder N, Yang BZ, Douglas-Palumberi H, Massey J, Krystal JH, Gelernter J, et al. MAOA genotype, maltreatment, and aggressive behavior: the changing impact of genotype at varying levels of trauma. Biol Psychiatry. 2009; 65:417–424. [PubMed: 18996506]

Wendland JR, Hampe M, Newman TK, Syagailo Y, Meyer J, Schempp W, Timme A, Suomi SJ, Lesch KP. Structural variation of the monoamine oxidase A gene promoter repeat polymorphism in nonhuman primates. Genes Brain Behav. 2006; 5:40–45. [PubMed: 16436187]

Whitaker-Azmitia PM, Zhang X, Clarke C. Effects of gestational exposure to monoamine oxidase inhibitors in rats: preliminary behavioral and neurochemical studies. Neuropsychopharmacology. 1994; 11:125–132. [PubMed: 7840864]

Widom CS, Brzustowicz LM. MAOA and the “cycle of violence:” childhood abuse and neglect, MAOA genotype, and risk for violent and antisocial behavior. Biol Psychiatry. 2006; 60:684–689. [PubMed: 16814261]

Wilcock GK, Ballard CG, Cooper JA, Loft H. Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer’s disease: a pooled analysis of 3 studies. J Clin Psychiatry. 2008; 69:341–348. [PubMed: 18294023]

Williams LM, Gatt JM, Kuan SA, Dobson-Stone C, Palmer DM, Paul RH, et al. A polymorphism of the MAOA gene is associated with emotional brain markers and personality traits on an antisocial index. Neuropsychopharmacology. 2009; 34:1797–1809. [PubMed: 19194374]

Williams RB, Marchuk DA, Gadde KM, Barefoot JC, Grichnik K, Helms MJ, et al. Serotonin-related gene polymorphisms and central nervous system serotonin function. Neuropsychopharmacology. 2003; 28:533–541. [PubMed: 12629534]

Yu Q, Teixeira CM, Mahadevia D, Huang Y, Balsam D, Mann JJ, et al. Dopamine and serotonin signaling during two sensitive developmental periods differentially impact adult aggressive and affective behaviors in mice. Mol Psychiatry. 2014; 19:688–698. [PubMed: 24589889]

Zalsman G, Huang YY, Harkavy-Friedman JM, Oquendo MA, Ellis SP, Mann JJ. Relationship of MAOA promoter (u-VNTR) and COMT (V158M) gene polymorphisms to CSF monoamine metabolites levels in a psychiatric sample of caucasians: A preliminary report. Am J Med Genet B Neuropsychiatr Genet. 2005; 132B:100–103. [PubMed: 15457497]

Highlights

- The enzyme monoamine oxidase A (MAOA) is one of the best-characterized molecular underpinnings of antisocial behavior and aggression
- Low-activity *MAOA* variants moderate the effect of environmental adversity in the pathogenesis of aggression
- Herein, we review clinical and animal models of MAOA deficiency and aggression
- We highlight translational approaches for solving current challenges

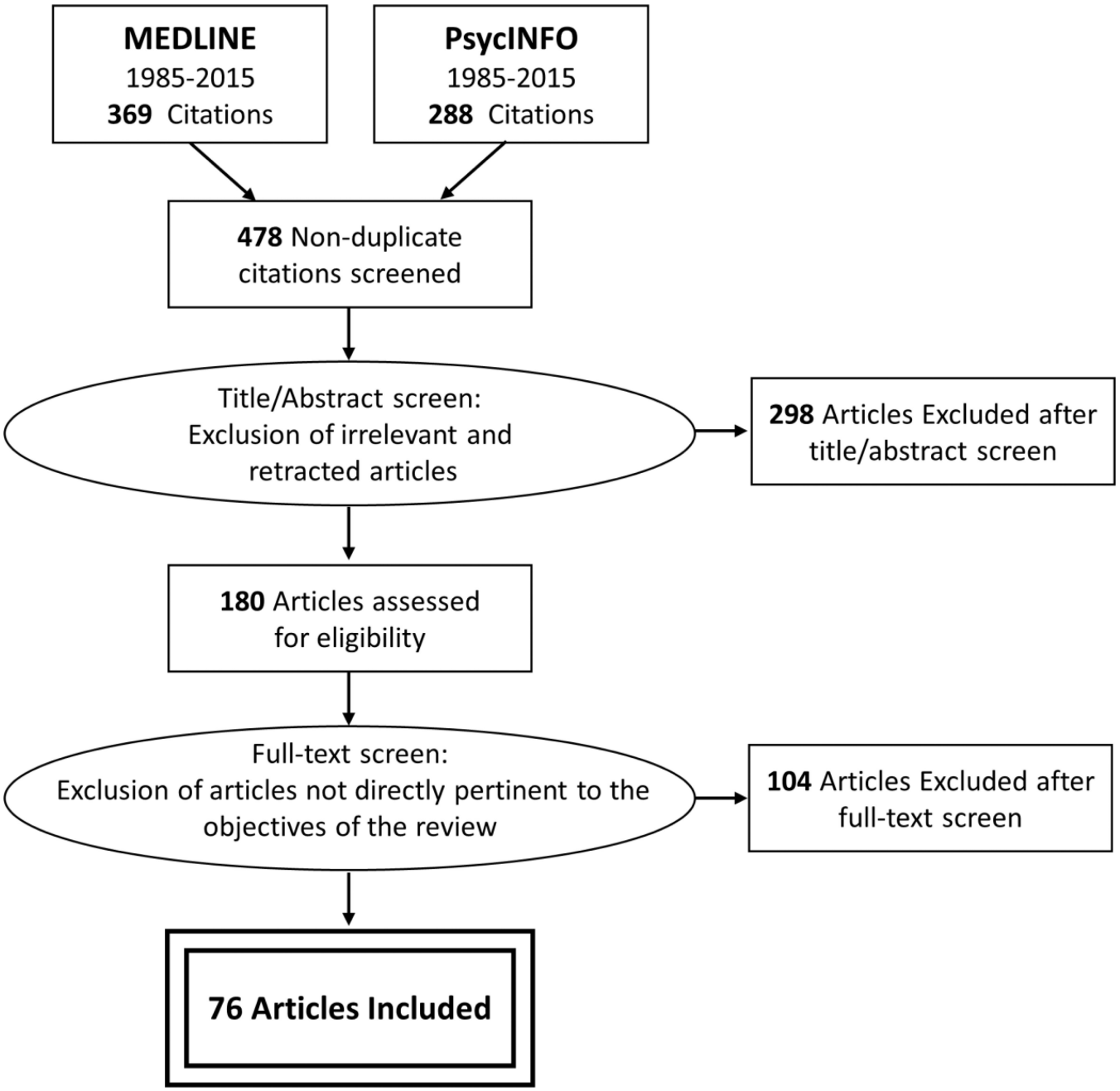

Figure 1.
PRISMA Flow Diagram summarizing the literature search used for the present review. Only studies written in English were included.

Table 1

List of major *MAOA* polymorphisms.

VNTR	uVNTR Ca(n)
SNP	Rs1137070
	Rs1465107
	Rs1801291
	Rs2072743
	Rs2235186
	Rs2283725
	Rs3027400
	Rs3027407
	Rs5906883
	Rs5906957
	Rs5953210
	Rs6323
	Rs6609257
	Rs72554632
	Rs909525
	Rs979606