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# MAOA and the neurogenetic architecture of human aggression

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**Antisocial aggression is a widespread and expensive social problem. Although aggressive behaviors and temperament are highly heritable, clinical and trait associations for the most promising candidate gene for aggression, *MAOA*, have been largely inconsistent. We suggest that limitations inherent to that approach might be overcome by using multimodal neuroimaging to characterize neural mechanisms of genetic risk. Herein, we detail functional, structural and connectivity findings implicating the low-expressing allele of the *MAOA* u-VNTR (*MAOA*-L) in adversely prejudicing information processing within a corticolimbic circuit composed of amygdala, rostral cingulate and medial prefrontal cortex. We propose that the MAOA-L, by causing an ontogenic excess of 5-hydroxytryptamine, labilizes critical neural circuitry for social evaluation and emotion regulation (the 'socioaffective scaffold'), thereby amplifying the effects of adverse early-life experience and creating deleterious sociocognitive biases. Our construct provides a neurobiologically consistent model for gene–environment interactions in impulsive aggression.**

## Aggression is familial and heritable

Lifetime prevalence estimates for adult antisocial behavior range as high as 12.3% [1], with each antisocial individual costing society up to ten times more than their healthy counterparts in aggregate healthcare and social service expenditures [2]. Thus, antisociality represents a costly large-scale social problem and a major potential target for policy-based government intervention [3]. A major component of antisocial behavior is aggression. One striking feature of aggression is its familial concentration; it is estimated that in any given community, 10% of the families in that community are responsible for greater than 50% of its crime [4,5]. Such high familiality suggests heritable factors in the intergenerational transmission of risk for antisocial aggression. Indeed, the heritability of antisocial behavior and associated traits has been confirmed by twin and adoption studies [6], with current estimates indicating that genetic factors account for between 40% and 50% of population variance in risk [7]. Like most psychiatric phenotypes, however, antisocial behavior is genetically complex, meaning that multiple genetic variants are likely to contribute to the associated traits in interaction with one another (epistasis) and the environment [5].

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Despite the known heritability of antisocial aggression, little ground was gained in identifying specific genes or sets of genes that comprise the risk architecture of aggression until Brunner's landmark finding of a single, rare, genetic mutation associated with antisocial behavior in a large Dutch kindred [8]. This study implicated the first (and, to date, most compelling) candidate susceptibility gene for human aggression, *MAOA*. With the aid of neuroimaging techniques, several recent studies have begun to elucidate the precise mechanisms by which heritable variation in *MAOA*, through its impact on neural circuitry for affective arousal, emotion regulation and impulse control, might influence human aggression.

## Localization and timing of MAO-A expression

*MAOA* encodes the mitochondrial catabolic enzyme monoamine oxidase A (MAO-A), which catalyzes the oxidative deamination of biogenic amines, making it a critical regulator of neurotransmitter signaling at monoaminergic synapses throughout the brain [9]. *MAOA* and *MAOB* (encoding the isoform MAO-B) each comprise 15 exons and map to adjacent sites on chromosome Xp11.23 [9]. Neuronal localization patterns, substrate preference characteristics and temporal expression dynamics all point to a specific and crucial role for MAO-A in regulating the release and clearance of serotonin (5-hydroxytryptamine; 5-HT) and norepinephrine (NE) during development. MAO-A is localized to the outer mitochondrial membrane in the presynaptic terminal of monoamine projection neurons [10] and is also found in astrocytes [11]; it is thus positioned to govern both the availability of monoamine neurotransmitters for vesicular sequestration and their subsequent extrasynaptic inactivation following release (Figure 1).

The relative importance of MAO-A in regulating 5-HT and NE versus dopamine (DA) is underscored by the finding that *MAOA* knockout mice show drastically increased brain 5-HT and NE compared to wild type, but only negligibly increased DA [12]; these change are accompanied by a distinct behavioral and neuromorphological phenotype (discussed below). No such changes are evident in *MAOB* knockouts [13]. Notably, MAO-A expression precedes MAO-B; whereas MAO-A is present at adult levels at birth, and is the critical enzyme in monoamine catabolism *ante partum*, MAO-B appears only postnatally and subsequently exhibits a striking increase [14].



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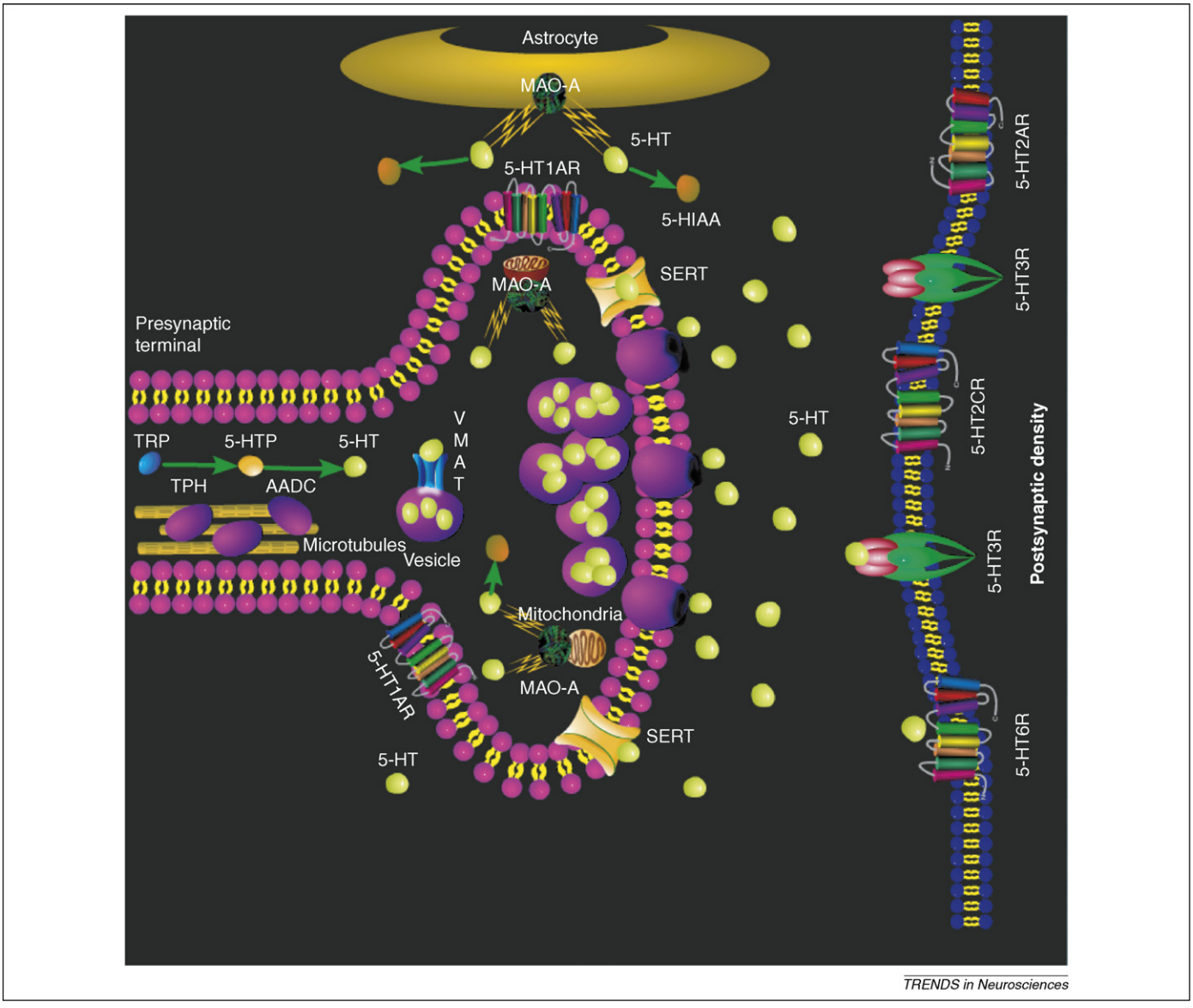


**Figure 1**. Idealized serotonergic synapse depicted here demonstrates the role of MAO-A in the catabolism of serotonin. Serotonin (5-hydroxytryptamine; 5-HT) is synthesized from tryptophan (TRP) by hydroxylation to 5-hydroxytryptophan (5-HTP) via tryptophan hydroxylase (TPH) and decarboxylation of the intermediate 5-HTP by amino acid decarboxylase (AADC). Serotonin is packaged into synaptic vesicles by the vesicular monoamine transporter (VMAT). Serotonin can be degraded presynaptically by mitochondrial monoamine oxidase A (MAO-A) or extrasynaptically by glially expressed MAO-A into 5-hydroxyindoleacetic acid (5-HIAA). Once released, synaptic serotonin can be cleared by the serotonin transporter (SERT) or bind to one of seven classes of serotonin receptors residing on both the pre- and postsynaptic membranes.

## Human and animal *MAOA* knockouts

Human and preclinical work indicate an important role for *MAOA* in impulsive-aggressive behavior. Brunner and colleagues examined a large Dutch kindred notorious for the persistent and extreme reactive aggression demonstrated by some of its males. This multigenerational phenotype included mild mental retardation; predisposition to aggressive outbursts, especially in response to frustration, anger and fear; and violent impulsive behavior, such as rape, assault and attempted murder, arson and exhibitionism [8]. Sequencing and linkage revealed a missense mutation (C936T) that produces a premature stop codon in the eighth exon of the *MAOA* gene, present in all affected individuals and representing, in hemizygous males, a functional *MAOA* knockout [8].

Subsequent genetic deletion studies have recapitulated this aggressive phenotype in animal models and, by showing alterations in brain structure and function that relate to developmentally specific changes in serotonergic and noradrenergic metabolism, suggest mechanisms for the influence of *MAOA* on behavior. Male *MAOA* knockout mice are hyperaggressive, demonstrate enhanced fear responses [15] and show dramatically elevated 5-HT and NE levels with much smaller increases in DA [12]. Several findings implicate an adverse influence of excess 5-HT during development in the manifestation of pathological aggression in these animals. Notably, this behavioral phenotype is dose-dependently blocked by the 5-HT2A antagonist ketanserin [16]. In addition, *MAOA*-deficient mice show developmentally specific cytoarchitectonic