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MAOA Levels as a Potential Biological Mechanism in Aggression: A Critical Review

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ABSTRACT

Across cultures and throughout time, human aggression has been conceptualized in various ways. The monoamine oxidase A (MAOA) gene on the X chromosome (Grimsby et al., 1990) has been implicated in aggression from research originating in the 1990s (Cases et al., 1995; Shih & Thompson, 1999). Researchers have sought to create predictive models of aggression, and throughout decades of research have used several different tools to measure the construct such as the Buss-Perry Aggression Questionnaire and the Conners' Teachers Rating Scale. This work will analyze and synthesize current scholarly research; a critical review of this impactful line of inquiry will also be provided.

Keywords: monoamine oxidase A (MAOA), aggression

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Though cultures have conceptualized human aggression in diverse ways throughout time, evolution has periodically preserved seemingly maladaptive human behavior (Freudenberg et al., 2016). Aggression has been studied as a construct comprised of many dimensions (Mentis et al., 2021) that is often separated into premeditated aggression and reactive aggression (Parrott & Giancola, 2007). Both the monoamine oxidase A (MAOA) gene found on the X chromosome (Grimsby et al., 1990) and the left dorsal region of the amygdala, a comparatively minuscule brain structure, have been implicated in manifestations of human aggression (Rosell & Siever, 2015). Studies from the 1990s investigating MAOA revealed genetic links to aggression vulnerability (Cases et al., 1995; Shih & Thompson, 1999).

As researchers have sought to create models to predict aggression in humans, some of these frameworks have mimicked that of a classical drug reward circuit (Flanigan & Russo, 2019). Others have suggested that inhibitory control correlates impact impulsive aggression (Pawliczek et al., 2013; Utendale, et al., 2014). Throughout decades of research, scientists have used many tools to study and measure aggression. In this critical review, in addition to genotyping performed for MAOA level assessment, researchers used several measures to gauge aggression, some of which include the Conners' Teachers Rating Scale, Go/Nogo/Stop task completion and timing, and the Buss-Perry Aggression Questionnaire (BPAQ).

The following review investigated four recent studies that explored the impact of MAOA levels on aggression. A study by Wang et al. (2018) examined associations between serotonin transporter (5-HTT) polymorphisms, MAOA polymorphisms, and oppositional defiant disorder (a behavioral illness associated with aggression). Study results supported a link between MAOA and aggressive behaviors. Ma et al. (2018) investigated whether MAOA polymorphisms affected inhibitory control and aggression in male adolescents, and results showed that MAOA-L gene carriers (those whose gene exhibited less transcription efficiency) experienced greater deactivation of inhibitory control, leading to a greater risk of aggression. A third study by Im and colleagues (2019) examined the functional relationship between aggression and MAOA phenotypes by using electrocardiogram and electroence-phalogram responses after providing aggressive stimuli to participants. Study results indicated aggressive stimuli influenced prominent changes in heart rate for some male MAOA carriers, indicating that MAOA function provides a unique factor in aggression responses. Another study by Khosravian et al. (2020) utilized matched groups to investigate potential associations between violent behavior and MAOA genotypes. Study results did not find a statistically significant relationship between MAOA promoters and uVNTR (Variable Number Tandem Repeat in the upstream of transcriptional initiation region) polymorphisms associated with antisocial behavior, which aligns with some previous research results (Prichard et al., 2007; Widom & Brzustowicz, 2006), but contradicts studies that did find significant associations (Caspi et al., 2002; Tiihonen, 2015; Williams et al., 2009). Further details contained throughout this work will provide clarifying details supporting conclusive recommendations from each study, as well as suggestions for future research.

Neurological structures and elements involved in aggression

While conceptualizations of aggression have evolved throughout varied cultures and time periods (Freudenberg et al., 2016), maladaptive aggressive behaviors have been shown to lead to antisocial behaviors such as rule-breaking and violations of societal norms and personal rights (Frau et al., 2022). Importantly, research has demonstrated that violence and aggression have significant impacts on public health and remain a persistent concern for behavioral health providers (Rosell & Siever, 2015).

Aggression is an evolutionarily preserved, intricate group of behaviors (Mentis et al., 2021) seen in social relations that hold the purpose of inflicting physical or emotional harm to others (Ma et al., 2018; Mentis et al., 2021). Aggression is conceptualized as a multidimensional phenomenon and is often dichotomized into two categories: goal-oriented, premeditated aggression and impulsive, reactive aggression (Parrott & Giancola, 2007). While impulsive aggression often serves as an adaptive reaction to perceived stress, it can also develop into pathological modes when the amount of aggression involved in a response is disproportionate to the stressor presented (Siever, 2008).

Extensive research literature has implicated the amygdala in processes leading to aggression (Rosell & Siever, 2015). As the amygdala is relatively small and maintains a nebulous organization, imaging research tends to investigate the amygdala as an entire structure. More recent research has begun to address the amygdala's functional subdivisions to further understand the relationship between aggression and the amygdala. Repeatedly, in a wide group of populations, inverse associations have been observed between trait aggression and reduced amygdala volumes. Mounting evidence suggests looking at the amygdala's functional subdivisions to elucidate the relationship between aggression and the amygdala. Data suggests the left dorsal region of the amygdala could have a specific role in aggression, but determining precisely how this occurs is an important step for further research (Rosell & Siever, 2015).

One of the most robustly validated genetic contributors to impulsive aggression is the monoamine oxidase A (MAOA) gene on the X chromosome short arm (Grimsby et al., 1990). This gene is responsible for encoding the MOAO enzyme which catalyzes monoaminergic neurotransmitters related to impulsive aggression (serotonin, norepinephrine, and dopamine; Seo et al., 2008). Research on MAOA knockout mice begun in the 1990s produced evidence for human and mice genetic links to aggression vulnerability (Cases et al., 1995; Shih & Thompson, 1999). A 1993 study by Brunner et al. demonstrated impulsive and overt aggression in five male Dutch extended family members with a common mutation on the eighth exon of their MAOA gene. Cases et al. (1995) performed a study with MAOA knockout mice and found that when MAOA was eliminated, serotonin and norepinephrine increased, as did aggressive, offensive behaviors and socio-communicative deficits.

A study with an American sample demonstrated that when testing males with both lower MAOA levels (MAOA-L) and with higher levels (MAOA-H) in Flanker-GoNogo tasks, MAOA-L males showed attenuated anterior cingulate cortex (ACC) responses as compared to MAOA-H males (Meyer-Lindenberg et al., 2006). Interestingly, females showed no difference in brain activation, suggesting this genetic polymorphism may affect medial prefrontal cortex (MPFC) and ACC performance and aggression solely in males. The study results indicated that low MAOA was associated with reduced limbic volume and diminished prefrontal reactivity. In a related study by Holz et al. (2016), neuroimaging was used to find a sex-specific interaction between childhood life stress and MAOA genotype in a fairly large sample (n = 125, 72 males). The study results demonstrated that men with MAOA-L showed reduced activation as childhood stress lessened, while MAOA-H males showed increased neural responses. These studies combined suggest MAOA-L carriers with a propensity for impulsive aggression experience prefrontal dysfunction when undergoing response inhibition (Ma et al., 2018).

Explanatory neurological models of aggression

Researchers have constructed several animal models of proactive or goal-driven aggression. One such paradigm mirrors that of classical models describing drug reward type and

conditioned place preference, which are based on classical reward circuits (Flanigan & Russo, 2019). Additional models of impulsive aggression, more like that akin to the investigation in this review, have been suggested. Such animal models suggest reactive aggression develops like alcohol exposure and anabolic steroid exposure models. These models lead to hyperarousal-associated aggression. Importantly, many instances of aggression may not be cleanly identified as exclusively proactive or reactive (Flanigan & Russo, 2019).

Neuroscientists have studied neural correlates associated with inhibitory control, which is theorized to impact impulsive aggression. Some research has demonstrated that inhibitory control deficits have been implied to facilitate impulsive aggression (Pawliczek et al., 2013; Utendale, et al., 2014). Research by Passamonti and colleagues. (2006, 2008) in small samples (n = 24 and 35, respectively) with an inhibitory Go/NoGo task generated results showing that male carriers of the MAOA-L gene experienced less activation in the ventral anterior cingulate cortex. These results support the model that dysfunction occurs in the prefrontal cortex for those who carry MAOA-L genes and maintain a propensity for impulsive aggression (Ma et al., 2018). As will be seen in the following research study review, these models describing the development of aggression may be useful in understanding the implications of MAOA levels in those responding to aggressive impulses and tendencies.

Measuring aggression

This review of recent studies will discuss several methods used to measure aggression. While many instruments are available, the studies included in this review used the following tools to measure aggression, as well as antisocial behaviors and inhibitory lack of control: psychological measures assessing antisocial personality disorder and violence propensities, EEG and ECG readings, the Conners' Teachers Rating Scale, Go/Nogo/Stop task completion and timing, the Chinese version of the Buss-Perry Aggression Questionnaire (BPAQ), Korean Buss-Durkee Hostility Inventory, the Korean-BPAQ, and the Korean-Peer Conflict Scale.

Critical review

Limited recent research has investigated the relationship between aggression and MAOA. One such study, conducted in 2018 by Wang et al., surveyed the potential association between monoamine oxidase A (MAOA) polymorphisms, serotonin transporter (5-HTT) polymorphisms, and oppositional defiant disorder (ODD) in a population of Han Chinese children. Youth with ODD tend to display defiant, negative, and hostile behaviors (e.g., aggression and violence) toward authority figures (Gomez, 2017; Riley et al., 2016). Additionally, ODD is seen as an emotional adjustment disorder (Cavanagh et al., 2016) that suggests an underlying genetic component, as research has demonstrated that ODD retains moderate heritability and familial clustering (Riley, 2016). Previous research had found strong relationships between serotonin (5-HT) and behaviors such as aggression, indicating a deficiency in 5-HT function may be found to increase impulsivity (Coccaro & Lee, 2010) and aggression (Park et al., 2013). Relatedly, MAOA is an enzyme that supports the synthesis, transmission, and disintegration of 5-HT, suggesting it may play a critical role in aggressive tendencies, such as those exhibited in ODD.

In their study, Wang et al. (2018) used random group sampling to gather data from 2,000 pupils in Henan Province China between 2007 and 2009. Teachers completed the Conners' Teachers Rating Scale, and two physicians interviewed both teachers and parents. Diagnoses of ODD were made based on the criteria in the Diagnostic and Statistical Manual of Mental Disorders -IV (DSM-IV; American Psychiatric Association, 2000). The final sample included 123 ODD participants and 134 healthy controls matched for age and gender (M_{age} ODD participants = 10.4 years; M_{age} healthy control

participants = 10.1 years). Regarding 5-HT, genotyping was performed for the serotonin-transporter-linked promoter region (5-HTTLPR), a degenerate repeat polymorphic region in the SLC6A4 gene responsible for coding for the serotonin transporter (5-HTT). Genotyping was also executed for the MAOA-uVNTR (Variable Number Tandem Repeat in the upstream of transcriptional initiation region) polymorphism, a genetic variation of the MAOA gene.

SPSS PASW Statistics 13.0 software (SPSS Inc., Chicago, IL, USA) was employed to determine differences in genotype and allele frequencies between the ODD and control groups (Wang et al., 2018). A Chi-Square goodness-of-fit analysis inspected present deviation from the Hardy-Weinberg equilibrium separately in two groups with a significance level of $p = 0.025$. Results in comparisons between groups of the 5-HTTLPR genotype indicated no significant differences; however, statistically significant differences were found in the allele distributions. Regarding the results in comparing MAOA-uVNTR genotypes and allele frequencies between groups, significant differences were observed in both cases for the entire sample (male and female) and for the sub-group of male participants, but not for the female-only sub-group. Interestingly, the influence of the uVNTR polymorphism on aggression may be explained by the polymorphism's effect on MAOA activity: 2-, 3-, and 5- repeat alleles are linked to less transcriptional efficiency (MAOA-L) than the 3.5- and 4- repeat alleles (MAOA-H), implying that MAOA-L alleles are associated with high risk for impulsive aggression in several studies, especially if childhood maltreatment is present (Caspi et al., 2002; Chester et al., 2015).

This work by Wang et al. (2018) was the first study to show an association between ODD, 5-HTTLPR and MAOA-uVNTR polymorphisms, suggesting a link between MAOA and aggressive tendencies or behaviors. Additional analysis in the study demonstrated that a high activity allele of MAOA-uVNTR could augment risk of ODD development for children, while a low activity allele may prove to be a protective factor. This corroborates additional research that has shown MAOA-uVNTR maintains an association with aggressive behaviors (Zhang et al., 2016). However, some studies show contradictory results indicating that aggressive behaviors are associated with low-activity alleles of MAOA-uVNTR (Caspi et al., 2002; Chester et al., 2015).

Interestingly, study authors highlight that violence is often considered a male-driven trait, and is controlled by a gene on the Y chromosome; however, the gene that produces MAOA is only present on the X chromosome (Wang et al., 2018). Additional statistical analyses were performed to determine the significance of differences between the distributions alleles and genotypes of MAOA-uVNTR. Results indicated that high-activity alleles of the MAOA-uVNTR increased the risk of ODD only for males, from which one might infer that the MAOA-uVNTR gene polymorphism is a risk factor for developing ODD only in male children. This observation supports a previous study in which a similar association between male aggressive behavior and MAOA-VNTR was observed (Schlüter et al., 2016).

This study by Wang et al. (2018) investigated two important potential contributors to aggression, and the results corroborated additional research on the topic. However, limitations must also be considered. Samples were taken from one geographical location and were chiefly Chinese, limiting the generalizability of the results. Additionally, the sample size was limited, impacting the statistical power available for the analyses. Future studies are recommended to increase the sample size and sample diversity.

In another study conducted by Ma et al. (2018), researchers attempted to determine MAOA polymorphism influences on inhibitory control neurophysiological correlates through the use of a GoStop task and a Go/Nogo task, adapted via functional MRI (fMRI). Only male adolescent participants were selected, as MAOA is an X-

linked gene and it is not yet clear how the MAOA genotype executes gene transcription in females (Carrel & Willard, 2005). Efforts to reduce confounding factors in the study necessitated that females not be selected, as inferences are challenging to make regarding MAOA activity in females with heterozygous gene expression. In the study, the pure Go/Nogo task was included to support the measurement of action restraint, which structure permitted testing for MAOA genotype differential effects of neural correlates in processes involving subtle inhibition (Ma et al., 2018).

Due to previously-conducted research presented earlier (Holz et al., 2016; Meyer-Lindenberg et al., 2006; Passamonti et al., 2006, 2008) and the evidence that the VPFC and ACC experienced impaired functioning in carriers of MAOA-L alleles, researchers predicted that those with MAOA-L would experience reduced activation of inhibition in the VPFC and ACC. Ma et al. (2018) also examined differential genotype effects taking place during response inhibition, as measured in brain responses via correlations between self-reported aggression and a neural index of the aggression-MAOA gene relationship.

Study participants (*n* = 74) included male adolescents randomly chosen from a senior high school in China (Ma et al., 2018). Participants had no hearing or vision abnormalities or emotional disorders, and their intelligence quotients were above 80. All participants were right-handed and were of Han Chinese ethnicity. Genomic DNA was obtained via blood samples, and MAOA polymorphisms were detected with polymerase chain reaction assays via a modified protocol (Sabol et al., 1998). Following the standard published methods (Sabol et al., 1998), individuals with an X chromosome 3-repeat allele repeat sequence were placed in the MAOA-L group, while those with a 4-repeat sequence observed on the X chromosome were grouped in the MAOA-H group (Ma et al., 2018).

The study measured aggression via a Chinese version of a 21-item tool, the Buss-Perry Aggression Questionnaire (BPAC-C; Yang, 2007). Participants were instructed to complete two inhibition tasks, a GoStop task measuring action cancellation and a Go/Nogo task measuring action restraint. The GoStop task involved Stop, Go, and Nogo trials which measured action cancellation, through several trials of participant responses to a variable 5-digit black number appearing on a white screen. For Go/Nogo tasks, only Go/Nogo responses were allowed. An fMRI scan was implemented during the GoStop and GoNogo tasks, with 70-second task blocks followed by 20-second rest blocks. The effect of genotype was computed by using a two-sample t-test with GoStop versus Go/Nogo contrasts; these were accounted for in each genotype group with the goal of assessing differential effects of genotypes on inhibition types (Ma et al., 2018).

In the study analysis, none of the 72 participants were observed to manifest a 2-, 3.5-, or 5-repeat allele (Ma et al., 2018). Ages ranged from 14-17 years, and the two groups were similar in both age and intelligence quotient. In the MAOA-L group, the BPAQ-C scores and anger subscale scores showed a significantly higher range than the MAOA-H group. Technical issues allowed behavioral analysis of only 41 participants, for which subsample, researchers compared task performance between genotype subgroups. No significant group differences were observed in the accuracy of inhibited Go, Nogo, and Stop trials (Ma et al., 2018). As fMRI results were analyzed, no significance was observed for task type main effect or group main effect. Additionally, no interaction effect between groups was present. These results suggest no difference occurred in framewise displacement between groups or tasks (Ma et al., 2018).

Inhibition-related activity (activation and deactivation) was observed across genotype and inhibition types (Ma et al., 2018). A one-sample t-test regarding brain responses throughout GoStop and Go/Nogo versus baseline across inhibition types and genotypes demonstrated inhibition-related activation in a chiefly bilateral prefrontal-subcortical circuit

throughout the precentral gyrus, supplemental motor area, interior frontal gyri, middle frontal gyri, striatum, insula, and bilateral supramarginal gyri/inferior parietal lobes. In comparison, inhibition-related deactivation occurred in midline brain areas including the posterior cingulate cortex (PCC), the ventromedial prefrontal cortex, the precuneus, the subgenual ACC, and the cuneus (areas associated with the default mode network, DMN; Ma et al., 2018). Brain regions also showed differences in inhibition types across genotype groups. Go/Nogo tasks showed greater activation in the PCC, the ventro-medial PFC and the precuneus than did the GoStop tasks. This indicated decreased activation in action cancellation compared to the action restraint condition. Brain regions also revealed differences across tasks. This was seen in two-sample t-tests with GoStop + Go/Nogo tasks. Differences were observed in decreased responses for MAOA-L participants (compared to those with MAOA-H) in the following areas: the precuneus, the PCC, the mid-cingulate cortex, and the bilateral precentral gyri. No interaction effects were observed for genotype by inhibition types.

Study authors then correlated BPAQ-C total scores, subscale scores, and inhibition-related activation in the precuneus/PCC within the entire sample. A negative correlation between inhibition-related brain responses in the precuneus/PCC and the BPAQ-C total scores was observed; in the BPAQ-C subscales, only anger scores showed negative correlations with precuneus/PCC brain responses. In further analyses for both the MAOA-L and MAOA-H groups, no significant correlations were found between BPAQ-C scores or anger scores and PCC/precuneus brain responses.

While the study by Ma et al. (2018) found significant effects for group and inhibition type in the PCC/precuneus, no interaction between them was observed, and inhibitory control periods showed brain responses were negatively correlated across groups for BPAQ-C total scores. However, the deactivation of the DMN and inhibition-related activation of the front-subcortical network suggest that the study touched on neural correlates related to inhibitory control. The study also demonstrated that MAOA-L carriers experienced more deactivation in the precuneus/PCC than did MAOA-H participants. These findings may suggest that those with a greater risk for aggressive behavior have a greater need to suppress the DMN to deploy resources on goal-oriented inhibition tasks. Pronounced DMN suppression was observed during action cancellation compared to action restraint. Differences were not observed in prefrontal-subcortical response inhibition circuits in the adolescent sample during inhibitory control; however, greater DMN suppression was seen in MAOA-L participants as compared to MAOA-H participants.

While the research conducted by Ma et al. (2018) provided information that may one day support identifying adolescents at greater risk for developing maladaptive aggression, some limitations to this research were observed. Study limitations included the restriction to only male adolescents in a limited geographical region, the study design neglected inter-trial jittering of intervals to separate brain responses for Stop versus Go versus Nogo trials, and a lack of motion censoring approach which should improve task-based fMRI quality, and is especially recommended for adolescent samples (Siegel et al., 2014).

In a related research study conducted by Im et al. (2019), Im and colleagues investigated the influences of the MAOA genotype on aspects of aggression, looking at both cardiac and neural activities. The sample included a Korean population, and transcriptional efficiency was measured with in vitro reporter gene assays founded on full MAOA promoter sequences to determine uVNTR transcriptional contribution. The functional relationship between aggression and MAOA genotypes was investigated by inspecting electrocardiogram (ECG)- and electroencephalogram (EEG)-related neurobiological responses performed after

aggression stimuli were encountered by both females and males. Both EEG and ECG readings offer useful mechanisms to investigate neural activity due to real-time response collection and fine temporal resolution. However, this study is one of few that have utilized this helpful research approach (Im et al., 2019).

Of 524 college and high school students, 84 right-handed participants (48 women and 36 men) were selected to complete self-report questionnaires and receive measurements of their neurobiological signals via EEG and ECG readings (Im et al., 2019). In the sample, seven unique genotypes were identified in the population, two in men (3.5R/Y and 4.5R/Y) and five in women (3.5R/3.5R, 4.5R/4.5R, 2.5R/3.5R, 2.5R/4.5R, 3.5R/4.5R). Self-report questionnaires included the K-BDHI, K-BPAQ, and K-PCS, all validated for Korean populations (Han, 2008; Jeong, 1995; No, 1983). Neurobiological signals were measured while participants watched videos (118 seconds in duration) with both neutral stimuli and scenes related to aggression as stimuli: one with verbal abuse, one with peer conflict and bullying, and one with a person scratching a blackboard with their nails (shown to cause irritability).

Noted in previous research, frontal alpha asymmetry in EEG is a common signal pattern in response to aggression; greater left frontal alpha asymmetry in resting states indicates approach motivation, and greater right asymmetry indicates avoidance motivation. Due to differences in emotional expression and EEG responses to stimuli, researchers chose to focus on individual differences in EEG signals in the right frontal regions of the brain (Fp2 and F8) which have shown relation to aggression.

Statistical analyses were performed to detect statistically significant differences in the allelic groups' and the control group's transcriptional efficiency values (Im et al., 2019). Groups of females and males were analyzed separately due to chromosomal differences; a two-way analysis of variance (ANOVA) and Bonferroni posthoc test were used. Frequencies of 3.5 R and 4.5R allele groups were 63.8% and 34.8% respectively, which differs greatly from those observed in Caucasians. However, that observed in this Korean sample was similar to those reported previously for Japanese (Kunugi et al., 1999) and Chinese individuals (Pai et al., 2007).

In the study analysis, researchers discovered three main MAOA alleles in a Korean population: the rarer 2.5R allele, and the predominant 3.5R and 4.5R alleles. While a minor difference was observed in the transcriptional efficiencies of the 3.5R and 4.5R alleles, the greatest value (contradicting existing research) was found in the 2.5R allele. Interestingly, researchers found that psychological indices of aggression were not different among disparate MAOA genotypes. However, EEC and EEG results found through aggression-related stimulation demonstrated that oscillatory changes for novel phenotypes might vary due to the MAOA genotype. Of interest, researchers found prominent changes in heart rate and frontal γ power in male 4.5R carriers. These findings offer genetic insights regarding MAOA function and supply a neurobiological basis to assist in understanding varied socio-emotional mechanisms at work in healthy individuals (Im et al., 2019).

A study by Khosravian et al. (2020) aimed to learn of associations between MAOA genotypes and propensities for violent behavior between two matched groups: one with violent histories and one without violent records. Specifically, the researchers endeavored to learn associations between antisocial behavior and MAOA uNVTR polymorphisms in incarcerated male adults in Central Iran. Study authors recognized that no genetic polymorphisms had been found to have definite influences on human behavior, and using genetic profiles to determine the propensity of criminal behavior was not feasible. However, the researchers believed that understanding an individual's vulnerability to commit violent acts may have important implications for rehabilitation and criminology fields; thus, this study sought to answer whether

such vulnerability may be empirically ascertained.

The research by Khosravian et al. (2020) included 183 adult males, 88 of whom were violent (imprisoned) and 95 of whom were non-violent controls; group members were matched for age (range = 18-60 years old). The antisociality of participants was measured using behavioral and psychological measures that assessed antisocial personality disorder (ASPD) and propensity toward violence and infarction (Iofrida et al., 2014). ASPD of incarcerated participants was assessed using DSM-IV criteria, and healthy controls were assessed to screen out individuals with backgrounds including substance abuse, psychiatric illness, and personality disorder. All participants were also assessed for current mental status and schizophrenia. Participants' DNA was extracted from blood samples using agarose gel electrophoresis, and spectrophotometry. A three-step analysis was used to determine relationships between MAOA 30-bp VNTR variants and antisocial behavior. In the first step, the number of 30-bp repeats in MAOA genes for both cases and controls was determined. Secondly, allelic and genotype frequencies for each participant were calculated. Last, a Chi-Square test was performed to determine MAOA allelic frequencies among the control and case groups (Khosravian et al., 2020).

The results of the study showed three MAOA uNVTR allelic groups, including 3.5, 4.5, and 5.5 variants (Khosravian et al., 2020). The association between MAOA gene allele variants and antisocial behavior was tested using the Chi-Square test. The results did not show a statistically significant association between allele frequencies and antisocial behavior in the sample. Of the three observed repeat variants, 3.5R, 4.5R, and 5.5R, 5.5 R was the rarest found in 1.14% of antisocial subjects and 1.05% of healthy controls, and the most frequent was the 4.5 repeat variant (61.05% in controls and 56.825 of cases). These results varied from other studies' findings of genotype distributions (Huang et la., 2004; Sabol, 1998).

Study findings were not able to show a relationship between uVNTR polymorphisms in antisocial behavior and MAOA promoters (Khosravian et al., 2020), which aligns with some similar studies (Prichard et al., 2007; Widom & Brzustowicz, 2006), and contradicts others that did find remarkable and significant associations (Caspi et al., 2002; Tiihonen, 2015; Williams et al., 2009). The failure of the study by Khosraivan and colleages (2020) to support a relationship between uVNTR polymorphisms and antisocial behavior may be due to variations in population characteristics, including a distinctive profile of the uVNTR polymorphism of the MAOA gene.

Conclusion and recommendations

Aggression has been studied as a multidimensional construct (Mentis et al., 2021) and various neurobiological mechanisms have been investigated to determine their impact upon aggression outcomes (Frau et al., 2022; Grimsby et al., 1990; Im et al., 2018; Khosravian et al., 2020; Ma et al., 2018; Pawliczek et al., 2013; Wang et al., 2018). This work has focused primarily on the effect of MAOA polymorphisms on aggression and has investigated how such polymorphisms may impact aggression experienced in humans. The review also considered research into therapeutic approaches that may optimize the reduction of aggression in MAOA-deficient individuals.

While one study produced contradictory results (Khosravian et al., 2020), the bulk of the study results reviewed support that a relationship exists between low MAOA levels, lack of inhibitory control, and aggression (Im et al., 2019; Wang et al., 2018). Limitations experienced in each study suggest that future work should focus on additional populations including females, increase study sample sizes, generate samples from geographical regions with greater ethnic diversity, and address differences in enzyme expression and neurotransmitter levels, as well as assess ECG and EEG oscillatory activity from emotional and

cognitive perspectives. Additionally, when investigating MAOA levels as an underlying mechanism of aggression, several potential confounds exist, including associations of MAOA with substance use, depression, and schizophrenia. Addressing these considerations and confounds in future studies may provide additional insight and confirmatory evidence of the impact of MAOA polymorphisms on human aggression.

References

[1]. American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (4th ed., text rev.).

[2]. Brunner, H. G., Nelen, M., Breakefield, X. O., Ropers, H. H., & van Oost, B. A. (1993). Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. *American Association for the Advancement of Science, 262* (5133), 578-580. https://doi.org/10.1126/science.8211186

[3]. Carrel, L., & Willard, H. F. (2005). X-inactivation profile reveals extensive variability in X-linked gene expression in females. *Nature, 434*, 400–404.

[4]. Cases, O., Seif, I., Grimsby, J., Gaspar, P., & al, et. (1995). Aggressive behavior and altered amounts of brain serotonin and norepinephrine in mice lacking MAOA. *Science*, *268*(5218), 1763.

[5]. Caspi, A., McClay, J., Moffitt, T. E., Mill, J., Martin, J., Craig, I. W., Taylor, A., & Poulton, R. (2002). Role of genotype in the cycle of violence in maltreated children. *Science: American Association for the Advancement of Science, 297*(5582), 851-854.

[6]. Cavanagh, M., Quinn, D., Duncan, D., Graham, T., & Balbuena, L. (2017). Oppositional defiant disorder is better conceptualized as a disorder of emotional regulation. *Journal of Attention Disorders, 21*(5), 381–389. https://doi-org.fgul.idm.oclc.org/10.1177/1087054713520221

[7]. Chester, D. S., DeWall, C. N., Derefinko, K. J., Estus, S., Peters, J. R., Lynam, D. R., & Jiang, Y. (2015). Monoamine oxidase A (MAOA) genotype predicts greater aggression through impulsive reactivity to negative affect. *Behavioural Brain Research, 283*, 97–101. https://doi.org/10.1016/j.bbr.2015.01.034

[8]. Coccaro, E. F., & Lee, R. (2010). Cerebrospinal fluid 5-hydroxyindolacetic acid and homovanillic acid: Reciprocal relationships with impulsive aggression in human subjects*. Journal of Neural Transmission, 117*(2), 241–248. https://doi.org/10.1007/s00702-009-0359-x

[9]. Flanigan, M. E., & Russo, S. J. (2019). Recent advances in the study of aggression. *Neuropsychopharmacology, 44*(2), 241–244. https://doi.org/10.1038/s41386-018-0226-2

[10]. Frau, R., Pardu, A., Godar, S., Bini, V., & Bortolato, M. (2022). Combined Antagonism of 5-HT_2 and NMDA receptors reduces the aggression of monoamine oxidase A knockout mice. *Pharmaceuticals*, *15*(2), 213. https://doi.org/10.3390/ph15020213

[11]. Freudenberg, F., Carreño Gutierrez, H., Post, A. M., Reif, A., & Norton, W. H. J. (2016). Aggression in non-human vertebrates: Genetic mechanisms and molecular pathways. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 171*(5), 603–640. https://doi.org/10.1002/ajmg.b.32358

[12]. Gomez, R. (2017). Factor structure of parent and teacher ratings of the ODD symptoms for Malaysian primary school children. *Asian Journal of Psychiatry, 25*, 22–26. https://doi.org/10.1016/j.ajp.2016.10.013

[13]. Grimsby, J., Lan, N. C., Neve, R., Chen, K., & Shih, J. C. (1990). Tissue distribution of human monoamine oxidase A and B mRNA. *Journal of Neurochemistry, 55*, 1166–1169.

[14]. Han, Y. K. (2008). The relation of psychological variables to relational aggression in early adolescence. Unpublished master's thesis, Ajou University, Suwon, Korea.

[15]. Holz, N., Boecker, R., Buchmann, A. F., Blomeyer, D., Baumeister, S., Hohmann, S.,Jennen-Steinmetz, C., Wolf, I., Rietschel, M., Witt, S. H., Plichta, M., Meyer-Lindenberg, A., Schmidt, M. H., Esser, G., & Banaschewski, T., Brandeis, D., & Laucht, M. (2016). Evidence for a sex-dependent MAOA × childhood stress interaction in the neural circuitry of aggression. *Cerebral Cortex, 26*(3), 904-914.

[16]. Huang Y*.,* Cate, S. P., Battistuzzi, C., Oquendo, M. A., Brent, D., & Mann, J.J. (2004). An association between a functional polymorphism in the monoamine oxidase A gene promoter, impulsive traits and early abuse experiences. *Neuropsychopharmacology, 29*(8):1498–505.

[17]. Im, S., Jeong, J., Jin, G., Yeom, J., Jekal, J., Lee, S., Cho, J. A., Lee, S., Lee, Y., Kim, D.-H., Bae, M., Heo, J., Moon, C., & Lee, C.-H. (2019). MAOA variants differ in oscillatory EEG & ECG activities in response to aggression-inducing stimuli. *Scientific Reports*, *9*(1), 2680. https://doi.org/10.1038/s41598-019-39103-7

[18]. Iofrida, C., Palumbo, S.,, & Pellegrini, S., (2014). Molecular genetics and antisocial behavior: Where do we stand? *Experimental Biology and Medicine, 239*(11):1514–23.

[19]. Jeong, D. (1995). A buffering effects of social support on children's school stress and maladjustments. Department of Education Graduate School Korea University.

[20]. Khosravian, M., Nikpour, P., Emadi-Baygi, M., Soleimanpour, A., & Moghadam, F. Y. (2020). Association analysis of monoamine oxidase-A gene promoter polymorphism (MAOA uVNTR) for antisocial behavior: Absence of the counting number repeats in central Iran. *Archives of Neuroscience*, *7*(4), Article 4. https://doi.org/10.5812/ans.102247

[21]. Kunugi, H., Ishida, S., Kato, T., Tatsumi, M., Sakai, T., Hattori, M., Hirose, T., & Nanko, S. (1999). A functional polymorphism in the promoter region of monoamine oxidase A gene and mood disorders. *Molecular Psychiatry, 4*(4), 393-395. https://doi.org/10.1038/sj.mp.4000558

[22]. Ma, R., Gan, G., Zhang, J., Ming, Q., Jiang, Y., Gao, Y., Wang, X., & Yao, S. (2018). MAOA genotype modulates default mode network deactivation during inhibitory control. *Biological Psychology*, *138*, 27–34. https://doi.org/10.1016/j.biopsycho.2018.08.006

[23]. Mentis, A.-F. A., Dardiotis, E., Katsouni, E., & Chrousos, G. P. (2021). From warrior genes to translational solutions: Novel insights into monoamine oxidases (MAOs) and aggression. *Translational Psychiatry*, *11*(1), 130. https://doi.org/10.1038/s41398-021-01257-2

[24]. Meyer-Lindenberg, A., Buckholtz, J. W., Kolachana, B., Hariri, A. R., Pezawas, L., Blasi, G., Wabnitz, A., Honea, R., Verchinski, B., Callicott, J., Egan, M., Mattay, V., & Weinberger, D. (2006). Neural mechanisms of genetic risk for impulsivity and violence in humans. *Proceedings of the National Academy of Sciences of the United States of America, 103*, 6269–6274.

[25]. No, A. N. (1983). The effects of assertive training on the reduction of aggression and anxiety in juvenile delinquents [master's thesis]. Seoul: Seoul National University, 1-87.

[26]. Pai, C., Chou, S. & Huang, F. (2007). Assessment of the role of a functional VNTR polymorphism in MAOA gene promoter: a preliminary study. *Forensic Science Journal, 6*, 37–43.

[27]. Park, T. W., Park, Y. H., Kwon, H. J., & Lim, M. H. (2013). Association between TPH2 gene polymorphisms and attention deficit hyperactivity disorder in Korean children. *Genetic Testing and Molecular Biomarkers, 17*(4), 301–306. https://doi.org/10.1089/gtmb.2012.0376

[28]. Parrott, D. J., & Giancola, P. R. (2007). Addressing "The criterion problem" in the assessment of aggressive behavior: Development of a new taxonomic system. *Aggression and Violent Behavior, 12*(3), 280-299. https://doi.org/10.1016/j.avb.2006.08.002

[29]. Passamonti, L., Cerasa, A., Gioia, M. C., Magariello, A., Muglia, M., Quattrone, A., & Fera, F. (2008). Genetically dependent modulation of serotonergic inactivation in the human prefrontal cortex. *Neuroimage, 40*(3), 1264–1273.

[30]. Passamonti, L., Fera, F., Magariello, A., Cerasa, A., Gioia, M. C., Muglia, M., et al. (2006). Monoamine oxidase–A genetic variations influence brain activity associated with inhibitory control: New insight into the neural correlates of impulsivity. *Biological Psychiatry, 59*, 334–340.

[31]. Pawliczek, C. M., Derntl, B., Kellermann, T., Kohn, N., Gur, R. C., & Habel, U. (2013). Inhibitory control and trait aggression: Neural and behavioral insights using the emotional stop signal task. *Neuroimage, 79*, 264-274.

[32]. Prichard, Z. M., Jorm, A. F., Mackinnon, A., & Easteal, S. (2007). Association analysis of 15 polymorphisms within 10 candidate genes for antisocial behavioural traits. *Psychiatric genetics, 17*(5), 299-303.

[33]. Riley, M., Ahmed, S., & Locke, A. (2016). Common questions about oppositional defiant disorder. *American Family Physician, 93*(7), 586–591

[34]. Rosell, D. R., & Siever, L. J. (2015). The neurobiology of aggression and violence. *CNS Spectrums, 20*(3), 254–279. https://doi.org/10.1017/S109285291500019X

[35]. Sabol, S. Z., Hu, S., & Hamer, D. (1998). A functional polymorphism in the monoamine oxidase A gene promoter. *Human Genetics, 103*, 273–279.

[36]. Schlüter, T., Winz, O., Henkel, K., Eggermann, T., Mohammadkhani-Shali, S., Dietrich, C., Heinzel, A., Decker, M., Cumming, P., Zerres, K., Piel, M., Mottaghy, F., & Vernaleken, I. (2016). MAOA-VNTR polymorphism modulates context-dependent dopamine release and aggressive behavior in males. *NeuroImage, 125*, 378-385. doi:https://doi-org.fgul.idm.oclc.org/10.1016/j.neuroimage.2015.10.031

[37]. Seo, D., Patrick, C. J., & Kennealy, P. J. (2008). Role of serotonin and dopamine system interactions in the neurobiology of impulsive aggression and its comorbidity with other clinical disorders. *Aggression and Violent Behavior, 13*, 383–395.

[38]. Shih, J. C., & Thompson, R. F. (1999). Monoamine oxidase in neuropsychiatry and behavior. *American Journal of Human Genetics, 65*(3), 593-598. https://doi.org/10.1086/302562

[39]. Siegel, J. S., Power, J. D., Dubis, J. W., Vogel, A. C., Church, J. A., Schlaggar, B. L., et al. (2014). Statistical improvements in functional magnetic resonance imaging analyses produced by censoring high-motion data points. *Human Brain Mapping, 35*, 1981–1996.

[40]. Siever, L. J. (2008). Neurobiology of aggression and violence. *The American Journal of Psychiatry, 165*, 429–442.

[41]. Tiihonen, J., Rautiainen, M. .R, Ollila, H. M., Repo-Tiihonen, E., Virkkunen, M., Palotie, A., Pietiilinen, O., Kristiansson, K., Joukamaa, M. , Lauerma, H., Saarela, J., Tyni, S., Vartiainen, H., Paananen, J., Goldman, D. & Paunio, T. (2015). Genetic background of extreme violent behavior. *Molecular Psychiatry, 20*(6):786.

[42]. Utendale, W. T., Nuselovici, J., Saint-Pierre, A. B., Hubert, M., Chochol, C., & Hastings, P. D. (2014). Associations between inhibitory control, respiratory sinus arrhythmia, and externalizing problems in early childhood. *Developmental Psychobiology, 56*(4), 686-699.

[43]. Wang, C.-H., Ning, Q.-F., Liu, C., Lv, T.-T., Cong, E.-Z., Gu, J.-Y., Zhang, Y.-L., Nie, H.-Y., Zhang, X.-L., Li, Y., Zhang, X.-Y., & Su, L.-Y. (2018). Associations of serotonin transporter gene promoter polymorphisms and monoamine oxidase A gene polymorphisms with oppositional defiant disorder in a Chinese Han population. *Behavioral and Brain Functions*, *14*(1), 15. https://doi.org/10.1186/s12993-018-0147-6

[44]. Widom, C. S., & Brzustowicz, L. M. (2006). MAOA and the “cycle of violence:” Childhood abuse and neglect, MAOA genotype, and risk for violent and antisocial behavior. *Biological psychiatry, 60*(7), 684-689.

[45]. Williams, L. M., Gatt, J. M., Kuan, S. A., Dobson-Stone, C., Palmer, D. M., Paul, R. H., Song, L., Costa, P. T., Schofield, P. R., Gordon, E. (2009). A polymorphism of the MAOA gene is associated with emotional brain markers and personality traits on an antisocial index. *Neuropsychopharmacology (7)*:1797.

[46]. Yang, W. (2007). The study of reliability and validity of the aggression questionnaire (revised edition). *Applied Psychology*. Guangzhou, Guangdong: Jinan University.

[47]. Zhang, Y., Ming, Q., Wang, X., & Yao, S. (2016). The interactive effect of the MAOA-VNTR genotype and childhood abuse on aggressive behaviors in Chinese male adolescents. *Psychiatric Genetics, 26*(3), 117–123. https://doi.org/10.1097/YPG.0000000000000125