

Monoamine oxidase A gene promoter methylation and transcriptional downregulation in an offender population with antisocial personality disorder

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Background

Antisocial personality disorder (ASPD) is characterised by elevated impulsive aggression and increased risk for criminal behaviour and incarceration. Deficient activity of the monoamine oxidase A (MAOA) gene is suggested to contribute to serotonergic system dysregulation strongly associated with impulsive aggression and antisocial criminality.

Aims

To elucidate the role of epigenetic processes in altered MAOA expression and serotonin regulation in a population of incarcerated offenders with ASPD compared with a healthy non-incarcerated control population.

Method

Participants were 86 incarcerated participants with ASPD and 73 healthy controls. MAOA promoter methylation was compared between case and control groups. We explored the functional impact of MAOA promoter methylation on

gene expression *in vitro* and blood 5-HT levels in a subset of the case group.

Results

Results suggest that MAOA promoter hypermethylation is associated with ASPD and may contribute to downregulation of MAOA gene expression, as indicated by functional assays *in vitro*, and regression analysis with whole-blood serotonin levels in offenders with ASPD.

Conclusions

These results are consistent with prior literature suggesting MAOA and serotonergic dysregulation in antisocial populations. Our results offer the first evidence suggesting epigenetic mechanisms may contribute to MAOA dysregulation in antisocial offenders.

Declaration of interest

None.

Antisocial personality disorder (ASPD) is a condition characterised by a persistent pattern of disregard for the rights of others manifesting prior to age 15 as conduct disorder then continuing into adulthood. A core feature of ASPD is an elevated and persistent pattern of impulsive aggression, which places those with the condition at increased risk for criminal offending leading to increased risk for incarceration and recidivism, presenting a significant burden on society and the criminal justice system.¹ As such, ASPD is highly overrepresented in offender populations with upwards of 40% of inmates meeting diagnostic criteria.^{1,2} ASPD is highly heritable with estimates of heritability reaching as high as ($h^2=0.80$).³ Considering the pervasive pattern of impulsive aggression emerging early in life among antisocial populations, convergent genetic and environmental risk factors in early childhood are strongly suggested to contribute to impaired ability to suppress aggressive behaviour.^{4,5} Risk factors including severe physical and/or sexual abuse early in life, as well as parental neglect, represent particularly salient predictors of emergent patterns of impulsive aggression contributing to the development of ASPD.^{4–6} These forms of early-life adversity are suggested to impair social learning and enactment of appropriate prosocial responses to perceived threats, resulting in a greater reliance on aggression.^{7–9} A large body of evidence suggests that impulsive aggression is associated with dysfunction of the serotonin (5-hydroxytryptamine, 5-HT) system.

Studies of impulsive aggression in rodents, non-human primates and human forensic populations suggest a system-wide serotonergic dysregulation manifesting in reduced central 5-HT activity.¹⁰ Altered expression of genes contributing to the regulation of 5-HT have been observed in populations showing high impulsive aggression.^{10,11} Among these genes, the monoamine

oxidase A (MAOA) gene (chrX: 43514155–43606071), which encodes the monoamine oxidase (MAO) enzyme that metabolises 5-HT into 5-hydroxyindoleacetic acid (5-HIAA) following reuptake,¹² has shown a particularly robust association with impulsivity and aggression.¹⁰ Complete inactivation of MAOA through a rare X-linked point-mutation in the gene's eighth exon among the males in a Dutch family was associated with violent impulsive criminal behaviour, mild intellectual disability and dysregulated 5-HT levels.¹³ Knock-out studies of MAOA in rodents have produced similar aggressive phenotypes.^{14–16} A low-expressing variable number tandem repeat (VNTR) in the promoter region of MAOA was associated with increased sensitivity to early-life adversity and risk for antisocial aggression in adulthood.^{17–20} More recently, a longitudinal study spanning 30 years illustrated a moderating role of the low-expressing MAOA variant between exposure to early-life adversity and risk for developing conduct disorder and ASPD.^{5,21} However, attempts to replicate the association between the low-expressing MAOA polymorphism and ASPD risk have yielded inconsistent results.²² Other molecular mechanisms that may contribute to downregulation of MAOA in impulsive aggression are not well understood.

Epigenetic investigation has allowed for greater insight into how environmental factors may interact with the genome to facilitate altered gene expression and induce behavioural phenotypes, which in turn increase risk of mental illness.²³ Studies in animals and humans indicate that early-life adversity is associated with epigenetic changes in expression of genes that are critical to regulate important biological systems, such as the stress response.^{24,25} Recent work suggests that early-life adversity may also contribute to epigenetic alteration of serotonergic genes

in aggressive populations. For instance, hypermethylation of the serotonin transporter gene (5-HTT) promoter region has been associated with ASPD among women who had experienced sexual abuse in childhood.^{26,27} Similarly, another study illustrated that promoter hypermethylation of the same gene is associated with reduced brain 5-HT synthesis in childhood aggression.²⁸

This suggests that genes critical in regulating 5-HT may be epigenetically regulated in populations prone to high aggression. Recent work in rodents and humans also suggests that MAOA is poised for epigenetic regulation.²⁹ In a peripubertal stress model of aggression in rats, enrichment of H3ac in the MAOA promoter was associated with altered gene expression and highly aggressive behaviour among stressed rats.³⁰ The authors also showed treatment with the MAO inhibitor clorgyline led to reduced aggression among rats exposed to stress during the peripubertal period.³⁰ Further, MAOA promoter methylation was recently shown to correlate inversely with MAO enzymatic activity in the brains of healthy males.³¹ Together, this work suggests that genes involved in regulating 5-HT may fall under epigenetic influence in antisocial populations, although epigenetic regulation of MAOA has not yet been investigated. As such, the current study explores the potential role of epigenetic regulation of MAOA in a population of incarcerated offenders with ASPD.

Method

Participants

The case participants were incarcerated men ($n=86$, mean age 27.1) who met DSM-IV-TR³² criteria for ASPD from the Epidemiology of Mental Disorders, Personality Disorders, and Intellectual Disabilities in Prison Settings cohort. In this study, a representative sample of offenders in Quebec who received a federal sentence (i.e. 2 years or more) requiring incarceration were recruited over a 4-year period through the Regional Reception Center at the Correctional Service of Canada complex in Sainte-Anne-des-Plaines. Following recruitment, inmates were assessed for DSM-IV-TR Axis I and II diagnoses using the Structured Clinical Interview (SCID).³³ Sociodemographic and judicial information was gathered. Following psychiatric and sociodemographic assessments, participants were asked to provide a blood sample. Following informed consent, whole blood samples were obtained and provided the basis for downstream epigenetic and analytic chemistry experiments. As a result of the high rate of comorbidity representative of offender populations with ASPD,^{1,2} participants with Axis I and II comorbidities were also included into the study (online Table DS1).

Control participants were healthy non-incarcerated individuals ($n=73$) derived from the Québec Longitudinal Study of Kindergarten Children (QLSKC)³⁴ and gender- and age-matched to the case participants. Briefly, the QLSKC cohort consists of 3018 participants initially recruited from kindergarten classes in French-speaking schools across the province at the age of 6. Random and proportional recruitment according to the 11 administrative districts of the province yielded a representative sample of the Quebec population. Multiple behavioural and psychiatric assessments are available from this cohort at different time points during development as well as adulthood.³⁵ For the current study, we selected a random sample of QLSKC participants who had no DSM-III-R Axis I and II diagnoses³⁶ at any assessment point, and whose aggression scores did not deviate from the population mean.

The study was approved by the research ethics boards of the University of Montreal, McGill University, Université du Québec à Trois-Rivières, Institut Philippe-Pinel de Montréal, and

Correctional Services Canada at both provincial and federal levels. Written informed consent was obtained from all participants.

Analysis of MAOA promoter methylation

DNA was extracted from whole blood using QIAGEN's QIAmp DNA Mini Kit according to the manufacturer's instructions (Qiagen, Germantown, Maryland, USA; www.qiagen.com). The extracted genomic DNA was then bisulfite-treated using QIAGEN's Epitect Bisulfite Kit following manufacturer guidelines. Methylation analysis of a region within the MAOA promoter spanning ~1.5 kb (chrX: 43514507-43515991) comprised of 71 CpGs was performed using Sequenom's EpiTYPER at Genome Quebec's Innovation Centre.

In vitro functional analysis of MAOA promoter methylation and gene expression

A 678 bp region of the MAOA promoter was cloned into the pCpG free-basic Lucia vector using primer sequences: Forward 5'-TATA GGATCC CGGGTATCAGCTGAAACATCA-3' and Reverse 5'-TATA AAGCTT GGTGATTTCGACCTCAAGAGAGT-3' containing BAMHI and HINDIII restriction sites, respectively (underlined in sequences). The addition of BAMHI and HINDIII restriction sites in the primers ensured that the region of interest (ROI) was cloned into the vector in correct orientation relative to the Lucia reporter gene. The plasmid was then submitted to SssI methylase (New England Biolabs, Ipswich, Massachusetts, USA; www.neb.ca) treatment involving a 4 h incubation period at 37°C. This process facilitates the addition of a methyl group to each of the 16 CpG sites within the ROI, thus generating a fully methylated construct. HEK293 cells were seeded in 24 well-plates for a period of 24 h. Following this period, native vector, unmethylated and methylated constructs were co-transfected with pGL3 control vector used for normalisation in HEK293 cells for an additional 24 h. The impact of native vector, unmethylated and methylated constructs on luciferase reporter gene activity in cell-extract and cell media was quantified by Berthold Luminometer using a dual-luciferase assay reporter kit (Promega, Madison, Wisconsin, USA; www.promega.com). Data were collected using Simplicity 4.2 software for Windows XP.

Analysis of 5-HT serum levels in blood

Analysis of 5-HT serum levels in blood was available for a subsample of 80 case participants. It was performed using a high-pressure liquid chromatography (HPLC) system (Shimadzu LC-10AD, Columbia, Maryland, USA; www.shimadzu.com) coupled to a fluorometric detector (Shimadzu RF-10AXL) according to the method of Comai *et al.*³⁷ Briefly, HPLC analysis of 5-HT relied on selective fluorometric detection via an online HPLC retention of the protein fraction in a precolumn system and subsequent elution via isocratic gradient phosphate buffer (0.004 M, pH 3.5)/acetonitrile (80/20, v/v). The separation was performed at a flow rate of 1 mL/min using an analytical Platinum EPS C18 100A column (5 µm; 250 × 4.6 mm; Alltech, Deerfield, Illinois, USA; www.alltech.com). The fluorometric detector was set at the excitation and emission wavelengths of 285 and 345 nm, respectively.

Statistical analyses

Statistical analyses were performed using SPSS software version 20 for Windows 8. Analysis of MAOA promoter methylation differences between case and control participants was performed by two-way mixed-model ANOVA with *post hoc* least significant

difference (LSD) correction for multiple comparisons. Results from this analysis also provided the basis for subsequent functional analysis. To determine the relative *in vitro* impact of native vector, unmethylated and methylated constructs on luciferase reporter gene activity, data were analysed using a one-way ANOVA with Bonferroni *post hoc* correction for multiple comparisons. Finally, multiple regression analysis was used to determine whether MAOA promoter CpG methylation, as measured by EpiTYPER, was associated with variance in serum 5-HT levels in a subset of 80 case participants.

Results

MAOA promoter methylation

To assess the MAOA methylation status in our groups, we investigated a 1.5 kb region of the promoter region. This region contains a total of 71 CpGs, and was selected to gain maximum coverage of the MAOA promoter region. It also included a 466 bp region where methylation has previously been correlated with MAO enzymatic function in the brain.³¹ We first extracted DNA from whole blood then bisulfite-treated the DNA in preparation for methylation analysis. For methylation mapping, we used EpiTYPER, which is a method that uses uracil-specific enzymatic base cleavage of bisulfite treated DNA followed by a mass spectrometry based quantification of methylation with single CpG dinucleotide resolution. A two-way mixed-model ANOVA revealed a significant main effect of group ($F(1,1650) = 16.866$, $P = 0.000042$), as well as a significant main effect of CpG site ($F(52,365) = 567.5$, $P < 0.001$) and a significant interaction between group and CpG site ($F(52,365) = 6.617$, $P < 0.001$). More specifically, our results indicated significant overall hypermethylation of the MAOA promoter region among the case group compared with the control group (Fig. 1(a)). *Post hoc* LSD analysis for multiple-testing revealed significant group differences in methylation levels for 34 of the 71 MAOA promoter CpGs assessed by EpiTYPER, 31 of which were hypermethylated among the case participants (Fig. 1(b) and (c)).

Functional assessment

To analyse the potential functional impact of the MAOA promoter hypermethylation observed in the case group on gene transcription, we cloned a 678 bp ROI into a CpG-free promoterless vector (pCpGfree-Basic Vector). Selection of this 678 bp (chrX: 43515313-43515991) ROI within the MAOA promoter for functional assays was based on the following. *In silico* analysis using Transfac revealed several predicted binding domains for transcription factors based on transcription factor consensus sequence (online Table DS2). As such, methylation in this region is more likely to affect binding of transcription factors leading to altered transcriptional activity of MAOA. Second, this ROI represented the region showing the most pronounced differences in CpG methylation between the case and control groups (Fig. 2). Thus, the ROI represented a strong candidate for *in vitro* functional assays. Finally, methylation within a 466 bp region of the selected ROI has been previously correlated to brain MAO enzymatic levels in healthy human participants by others.³¹

Native vector, unmethylated, and fully-methylated ROI constructs were produced and transfected into HEK293 cells for a period of 24 h. Following this period, the impact of each construct on luciferase reporter gene activity was quantified. A one-way ANOVA analysis was used to compare the effect of native vector, unmethylated and fully methylated constructs on reporter gene activity. Analysis revealed a significant between-group effect ($F(2,11) = 1206.9$, $P < 0.0001$). The unmethylated construct

showed a 12-fold increase of luciferase reporter activity (23.90, s.d. = 0.60) compared with the native vector construct (1.95, s.d. = 0.07) ($P = 9.2 \times 10^{-14}$). The methylated construct showed a significant 53% decrease in reporter activity (11.19, s.d. = 0.39) compared with the unmethylated construct ($P = 5.9 \times 10^{-10}$) (Fig. 3). Thus, our results suggest that the selected 678 bp ROI has clear promoter activity, and that methylation in this region leads to a significant decrease in this activity.

As the functional study results suggested that methylation of our ROI may be contributing to downregulation of MAOA gene expression in our case group, we sought to determine whether MAOA promoter methylation would be significantly associated with blood 5-HT levels in these participants. To this end, we assessed 5-HT blood serum levels using HPLC. Regression analysis indicated that methylation at 45 CpGs in the MAOA promoter was associated with blood 5-HT levels, and explained 88.8% of its variance ($R^2 = 0.888$, $F(44,13) = 2.34$, $P = 0.048$). Our analysis suggested that increased MAOA promoter methylation was positively associated with 5-HT levels in blood. These results suggest that MAOA promoter methylation may play a role in 5-HT dysregulation among offenders with ASPD.

Discussion

Main findings

Deficient activity of the MAOA gene has been frequently associated with increased impulsivity and aggression. Work spanning the past decade has suggested that a low expressing functional polymorphism of MAOA may play a mediating role between early-life adversity and the development of ASPD.^{6,17,20-22} However, efforts to replicate these findings have yielded inconsistent and inconclusive results.²² As such, this study sought to explore the potential impact of epigenetically altered expression of MAOA, offering novel insight into molecular mechanisms contributing to dysregulated MAOA expression in a population of offenders with ASPD. Our results suggest that hypermethylation in the MAOA promoter, particularly in its sequence proximal to the transcription start site, is associated with ASPD and may contribute to a downregulation of MAO activity and increased 5-HT levels, a finding consistent with prior work among antisocial offenders.²¹

Dysregulation of 5-HT is strongly associated with elevated impulsive aggression.¹⁰ This association represents one of the most consistently reported associations between biological factors and behavioural phenotypes acting as risk factors for mental illness.¹⁰ Typically, reduced 5-HT activity in the central nervous system is linked to elevated impulsive aggression.¹⁰ Our results suggest that increased MAOA promoter methylation results in decreased MAO production, and increased 5-HT levels in blood serum among offenders with ASPD. This finding is consistent with previous literature indicating decreased MAOA activity among antisocial offenders and elevated peripheral 5-HT in aggression.³⁸ Several studies suggest reduced central 5-HT correlates with increased peripheral 5-HT levels in blood platelets in behavioural phenotypes including increased aggression.³⁸⁻⁴¹ Although the biological mechanisms underlying this inverse relationship are not yet understood, this phenotype may be suggestive of a broader system-wide dysregulation of 5-HT observable in central and peripheral pathways underlying aggression and impulsivity.³⁸

Alterations in DNA methylation are associated with early-life adversity and are thought to be aetiologically related to development of psychopathology, including mood disorders and suicide, commonly observed among individuals who have been exposed to difficult early-life environments.⁴²⁻⁴⁴ The possibility

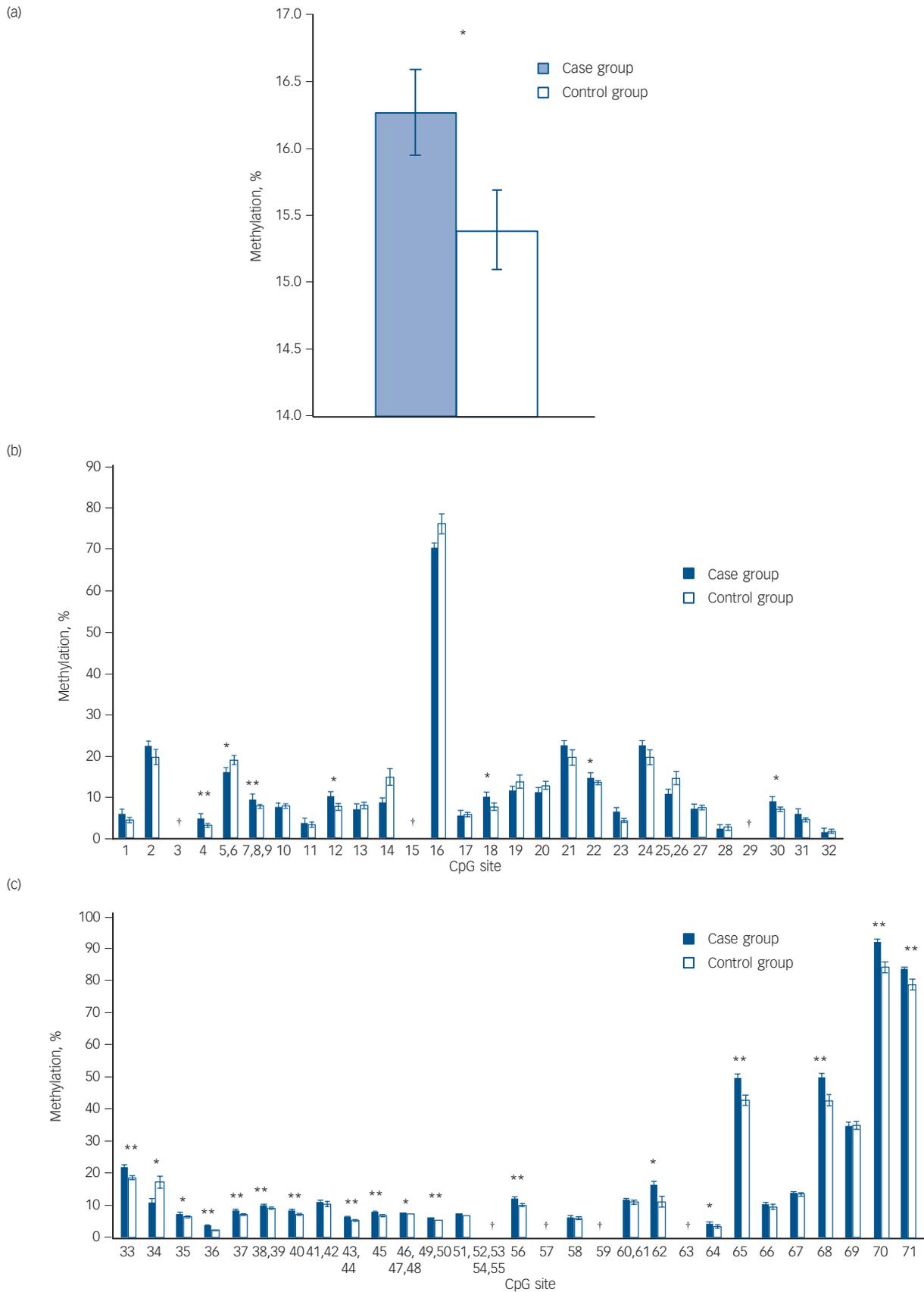


Fig. 1 Methylation of monoamine oxidase A (MAOA) promoter region assessed by EpiTYPER.

(a) Mean methylation for 1.48 kb region of MAOA promoter. Results indicate significant hypermethylation among the case group compared with the control group ($P < 0.001$).
 (b) Methylation profile for CpGs 1–32 of the MAOA promoter region. Results indicate significant group differences in methylation at 7 sites representing 11 CpGs (* $P < 0.05$, ** $P < 0.005$).
 (c) Methylation profile for CpGs 33–71 of the MAOA promoter region. Results indicate significant group differences in methylation at 18 sites representing 23 CpGs (* $P < 0.05$, ** $P < 0.005$).
 † Data unavailable.

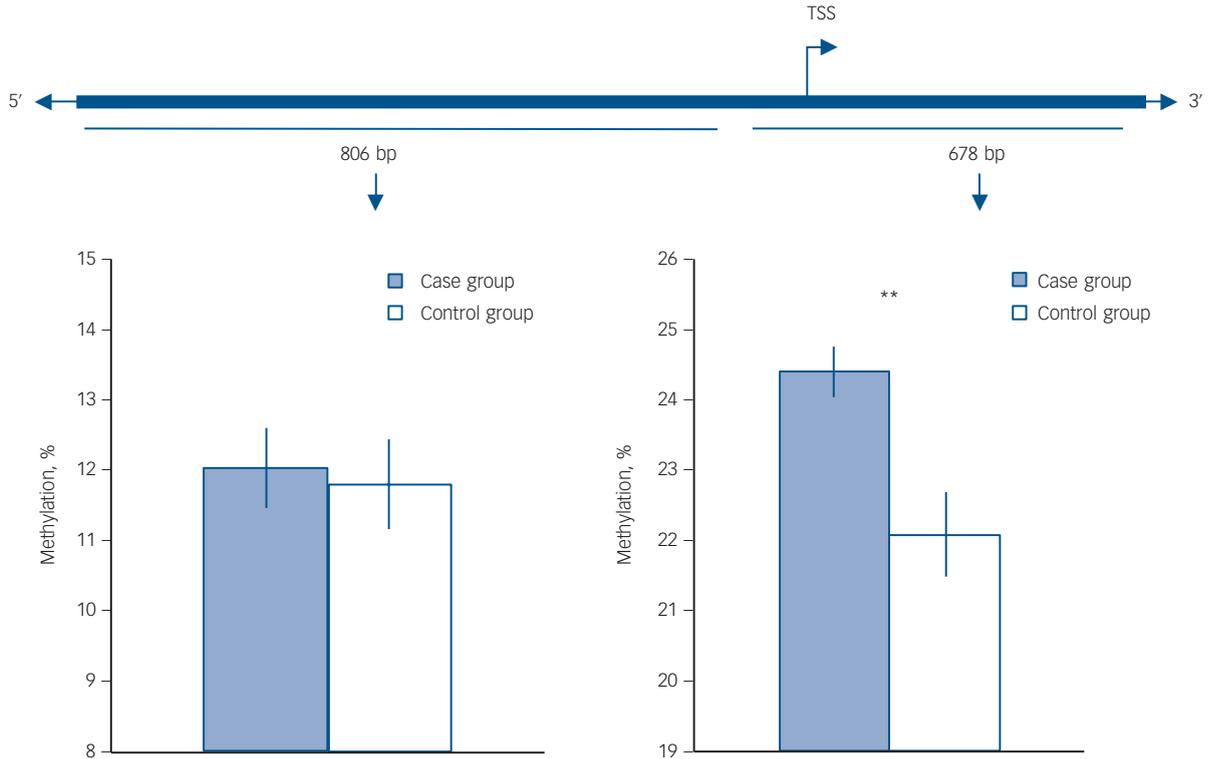


Fig. 2 Comparison of group mean methylation differences between the region of interest (ROI) and pre-ROI regions of monoamine oxidase A (*MAOA*) promoter relative to the transcription start site (TSS). Results suggest no significant group difference in pre-ROI CpG methylation (bottom left) and significant hypermethylation in the post-ROI region among the case group compared with the control group ($P < 0.005$) (bottom right).

that *MAOA* promoter hypermethylation is associated with early-life adversity is consistent with prior literature illustrating that associations between *MAOA* sequence variants and childhood maltreatment confer risk for antisocial behaviour. Epigenetic alteration of genes involved in serotonergic regulation is also associated with aggression. Recent work has indicated that hypermethylation of the serotonergic transporter gene (5-HTT) promoter is associated with the development of ASPD among individuals who had experienced sexual abuse during childhood.^{28,45,46} Results from the same group also suggest that the

magnitude of 5-HTT promoter methylation change relative to controls positively correlates with the presence of parental psychopathology.²⁶ Recent work has also indicated that markers of chromatin remodelling may also contribute to altered *MAOA* expression in aggression.³⁰ Together, these studies offer further support of a role for epigenetically altered regulation of 5-HT genes and highlight the importance of pre- and perinatal environmental factors as potential catalysts. Future work should further examine the potential role early-life adversity plays in epigenetic modulation of *MAOA*.

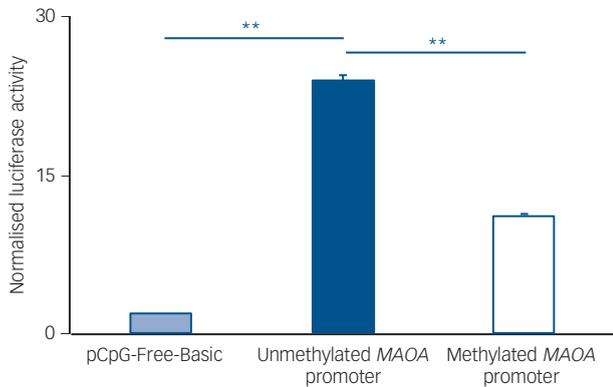


Fig. 3 Luciferase assay comparing transcriptional activity driven by methylated, unmethylated and empty pCpG-free-basic vector monoamine oxidase A (*MAOA*) region of interest (ROI) constructs. Results indicate significantly lower transcriptional activity for the methylated construct and empty pCpG-free-basic constructs compared with the unmethylated *MAOA* ROI construct (** $P < 0.005$).

Limitations

Limitations of this study include the unavailability of peripheral 5-HT measures among the control group and measures of MAO enzymatic levels for both group. As such, inference of a direct causal relationship between *MAOA* promoter hypermethylation and altered MAO and 5-HT activity between case and control groups cannot be made. However, our results are consistent with such a possibility, as well as with prior work suggesting a direct relationship between peripheral *MAOA* promoter methylation and positron emission tomography estimated MAO enzymatic activity in the brain of healthy men.³¹ Further, our experimental design prohibits us from determining whether the *MAOA* promoter methylation observed is directly attributable to ASPD or to environmental antecedents such as early-life adversity. Inclusion of a group with ASPD without presence of early-life adversity could help to clarify this relationship in subsequent studies. Since brain tissue cannot be obtained from living participants, whole blood was used as a proxy tissue for methylation analysis. Although the relationship between central and peripheral methylation patterns is not yet understood, recent

studies have illustrated associations between methylation patterns in peripheral tissue and antisocial phenotypes.^{28,45,46} Finally, ASPD is a developmental condition typified by significant psychiatric comorbidity. As such, the specificity of our results to ASPD may be limited by the retrospective case–control design of the study, although there is a considerable amount of evidence supporting this link in the literature. Future studies should explore the specificity of MAOA promoter methylation and ASPD.

Implications

To our knowledge, the current study presents the first evidence suggesting epigenetic mechanisms may play a functional role in modulating MAOA expression and regulating 5-HT levels in a population of offenders with ASPD. Thus, the results presented offer crucial insight into molecular mechanisms underlying impulsive aggression, a phenotype also linked to increased risk for mental illness. It is our hope that the current study provides a foundation for understanding the role of epigenetic processes in the biology of aggression.

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words

Out-of-body experiences

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Out-of-body experiences, in which the person feels they are viewing the world from outside their body, may be spontaneous or triggered by pain or fear, due to failure to integrate proprioceptive, tactile and visual information in the right parieto-temporal junction. They are similar to autoscopia, namely seeing your body in extra-personal space. But out-of-body experiences can occur in a near-death state during a cardiac arrest and be remembered even though brain processes are distorted or absent. Reliable accounts of patients who have acquired verifiable information while clinically dead suggest that consciousness may not after all be limited to the brain.

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