

## Platelet MAO-B, Personality, and Psychopathology

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The article investigates the relationships between platelet monoamine oxidase-B (MAO-B) activity, personality, and psychopathology (*Diagnostic and Statistical Manual of Mental Disorders* [4th ed.; American Psychiatric Association, 1994] diagnoses). These relationships were assessed in 178 incarcerated male juvenile delinquents. Even after controlling for smoking, the authors found that both Internalizing and Externalizing Psychopathology were negatively related to MAO-B activity. In the final reduced model, novelty seeking fully mediated the relationships between MAO-B and Externalizing Psychopathology but not between MAO-B and Internalizing Psychopathology. It was hypothesized that low platelet MAO-B activity does not directly predispose individuals to psychopathology but is related to specific personality traits, which in turn represent a vulnerability factor for psychopathology. Future studies should help clarify the nature of the relationships between personality, biological markers, and psychopathology.

*Keywords:* juvenile delinquents, platelet MAO-B, psychopathology, personality, novelty seeking

An increasing amount of evidence indicates that vulnerability to psychopathology is at least partially related to genetically controlled patterns of neurotransmitter metabolism that are associated, in turn, with particular personality traits. Insight into the mechanisms linking biological markers, personality traits, and vulnerability to psychopathology is crucial for the development of treatment and preventive strategies.

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Monoamine oxidase (MAO) is a biological agent that appears to be of particular interest in understanding the relationships between personality traits, psychopathology, and their biological bases (e.g., Grigorenko, 2002; Oreland, 2003). MAO is an enzyme that facilitates the conversion of a number of neurotransmitters to their metabolites (e.g., Shih & Chen, 1999). Specifically, MAO oxidatively deaminates a number of biogenic amines, including the key neurotransmitters serotonin 5-hydroxytryptamine (5-HT), norepinephrine (NE), and dopamine (DA) and the neuromodulator phenylethylamine (PEA). On the basis of their biochemical properties and functions, two forms of MAO (MAO-A and MAO-B) have been identified. Their common property, most notably, is that DA is a substrate for both MAO-A and MAO-B. As for their unique features, MAO-A exhibits a higher affinity for 5-HT and NE as well as for the inhibitor clorgyline (Johnston, 1968), whereas MAO-B has a higher affinity for PEA, benzylamine, and the inhibitor L-deprenyl (selegiline; Knoll & Magyar, 1972). Although most tissues express both forms of MAO, human placenta and fibroblasts express predominantly MAO-A, and platelets and lymphocytes express only MAO-B (e.g., Shih, Chen, & Ridd, 1999). Bach et al. (1988) demonstrated that MAO-A and MAO-B are encoded by distinct, but closely related, X-linked genes.

The function of MAO-B has been extensively investigated using platelets easily obtainable from whole blood. It has been hypothesized that MAO-B activity in platelets and in the brain is interconnected through the transcription factor activating protein-2 (AP-2) so that high levels of AP-2 drive the expression of target monoamine genes in order to increase monoaminergic activity in various systems (af Klinteberg, von Knorring, & Oreland, 2004).

Platelet MAO-B activity has been linked to susceptibility to a number of psychiatric disorders (for a review, see Volavka, 1999). In particular, low MAO-B activity has been associated with violent criminality (Åsberg, 1997; Belfrage, Lindberg, & Orelund, 1992; Longato-Stadler, af Klinteberg, Garpenstrand, Orelund, & Hallman, 2002) and suicide (Verkes et al., 1998) and has been repeatedly reported in alcoholics and their relatives (Devor, Cloninger, Hoffman, & Tabakoff, 1993; Faraj et al., 1987). When Cloninger's (1994) typology of alcohol abuse is applied, reduced platelet MAO-B activity is considered to be a feature of Type 2 alcoholism, characterized by early onset of alcohol and substance abuse and increased involvement in antisocial activities in both male (Sullivan et al., 1990; von Knorring & Orelund, 1996) and female participants (Hallman, Persson, & af Klinteberg, 2001). Moreover, there is some support for a link between the level of MAO and depression (e.g., Georgotas et al., 1986; Poirier et al., 1987).

In addition, studies on MAO and personality have demonstrated that individuals with low platelet MAO-B activity score higher on such traits as risk taking, sensation seeking, novelty seeking (af Klinteberg, Schalling, Edman, Orelund, & Åsberg, 1987; Holschneider & Shih, 1998; Howard, Cowley, Roy-Byrne, & Hopfenbeck, 1996), impulsiveness, and monotony avoidance (Schalling, Åsberg, Edman, & Levander, 1984). These personality traits have also been linked to severe and more violence-related alcohol problems and drug use in young adulthood (Cloninger, Sigvardsson, & Bohman, 1988). Other studies have found high levels of novelty seeking predictive of criminality (Howard, Kivlahan, & Walker, 1997; Sigvardsson, Bohman, & Cloninger, 1987) and substance abuse (Wills, Windle, & Cleary, 1998). Individuals who might be described as impulsive, exploratory, curious, excitable, disorderly, and distractible and as having a high level of behavior activation are likely to have reduced platelet MAO-B activity and are at higher risk for predominantly Externalizing Psychopathology, such as antisocial involvement and early-onset substance abuse (Cloninger, 1994). Thus, there are reasons to believe that low platelet MAO-B activity is not necessarily connected with psychopathology per se, but with personality traits that make the individual more vulnerable to psychopathology (Belfrage et al., 1992; Orelund & Shaskan, 1983).

Recently, however, the significance of the association between platelet MAO-B, psychopathology, and psychopathology-associated personality traits has been questioned; the association between low MAO and Externalizing Psychopathology has been suggested to occur because of smoking, which often co-occurs with externalizing problems and, most important, inhibits platelet MAO activity (Fowler et al., 1996; Simpson et al., 1999; Whitfield et al., 2000).

The present study sought to explore the associations between platelet MAO-B activity, personality, and psychopathology in male juvenile delinquents while controlling for the youths' levels of smoking.

## Method

### Participants

This study represents a partial overlap with a larger study that assessed psychopathology in incarcerated juvenile delinquents (Ruchkin, Kuposov, Vermeiren, & Schwab-Stone, 2003a, 2003b). Over a period of 6 months,

we recruited delinquent youth volunteers ( $N = 178$ ) from a group of male adolescent inmates who were between 14 and 18 years old (mean age, 16.2 years,  $SD = 0.8$  years). These young men had been court-ordered after trial to the only juvenile prison facility in the Arkhangelsk region of northern Russia, a catchment area with a population of 1.5 million. The region is ethnically homogeneous, with approximately 98% of the population being of Russian ancestry. Most of the participants had multiple convictions that included property crimes (theft, car theft, and so on; 51%), violence-related crimes (e.g., assault or robbery; 38%), and in some cases rape or other forms of sexual violence (6%) or murder (5%). At the time of the study, the mean length of sentence was 4.3 years, and all participants had been incarcerated for at least 6 months.

### Procedure

After receiving a detailed description of the study, all participants were informed of the voluntary and confidential nature of their involvement with the study and consented to participate. Eight participants refused to participate because of an unwillingness to provide personal information. The appropriate ethics committees in Russia, Sweden, and the United States approved the study. Psychopathology was assessed through a semistructured psychiatric interview, the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997), conducted by two psychiatrists blind to the results of self-reports. Each psychiatrist received standard K-SADS training from one of the authors of the instrument (Joan Kaufman) and determined the diagnoses according to criteria in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., [DSM-IV], American Psychiatric Association, 1994). Novelty seeking was assessed by means of a self-report questionnaire, the Temperament and Character Inventory (TCI; Cloninger, Przybeck, Svrakic, & Wetzel, 1994). Self-report data were obtained during small group sessions (5–8 participants), with each participant seated at a separate table. In addition, two nurses obtained blood samples from participants' arm veins. Because of the limited capacity of Lars Orelund's laboratory to process many samples simultaneously, blood samples were obtained in several collection waves and within 24 hr of collection were transported, with appropriate clearance from Russian customs, to the laboratory at the Department of Medical Pharmacology, Uppsala University, Sweden, where the analyses of platelet MAO-B activity were carried out.

### Estimation of Platelet MAO-B Activity

Blood samples of approximately 5 ml were drawn into Vacutainer tubes (BD Diagnostics) containing ethylenediaminetetraacetic acid. Within 24 hr, platelet-rich plasma was prepared by low-speed centrifugation, 200 g for 10 min, and approximately 1 ml of platelet-rich plasma was removed by careful suctioning. Thereafter, platelet concentrations of the plasma samples were estimated electronically, and the plasma was stored at  $-80^{\circ}\text{C}$ . Catalytic activity of platelet MAO-B was analyzed by a radiometric assay with  $^{14}\text{C}$ -labeled beta-phenylethylamine (B-PEA) as a substrate (Hallman, Orelund, Edman, & Schalling, 1987). All samples were analyzed blindly and in duplicate.

### Smoking

Data on smoking status (the average number of cigarettes smoked by the participant per day) were collected twice from all participants in the study—first during the course of the psychological and psychiatric assessment and again before collection of the blood samples (correlated at .60), with the average calculated on the basis of both assessments to minimize potential response biases. The number of cigarettes per day ranged from 0 (6 participants, 3.4%) to 20 (28 participants, 15.7%), with a mean of 10.1 ( $SD = 5.28$ ).

### Assessment Instruments

**K-SADS-PL.** A widely used, extensively validated semistructured psychiatric interview, K-SADS-PL, was used to yield current and past *DSM-IV* diagnoses. The measure consists of introductory and screen interviews and five diagnostic supplements, including Affective Disorders; Psychotic Disorders; Anxiety Disorders; Behavioral Disorders; and Substance Abuse, Eating, and Tic Disorders. The psychiatric diagnoses were based on the information collected from adolescents only. Interrater reliability for this measure is high, with interrater agreement in scoring screens and diagnoses ranging from 94% to 100% (Kaufman et al., 1997).

**TCI.** The TCI is based on Cloninger's unified biosocial theory of personality (Cloninger, Svrakic, & Przybeck, 1993). Within this approach, temperament dimensions are independent and largely genetically determined (Cloninger, 1994). In particular, novelty seeking is viewed as a trait that reflects the tendency toward behavior activation in response to novel stimuli or cues. Participants scoring high on novelty seeking tend to show high levels of exploratory behavior, impulsive decision making, quick loss of temper, and active avoidance of frustration. The novelty-seeking scale includes 20 items, with true or false response alternatives. In our sample, Cronbach's alpha for novelty seeking was .60.

## Results

### Psychiatric Diagnoses, Platelet MAO-B, and Novelty Seeking: Descriptive Analyses

Juvenile delinquents reported high rates of lifetime psychiatric diagnoses, with particularly high levels of Externalizing Psychopathology (conduct disorder, alcohol and substance abuse), suicide attempts, and posttraumatic stress disorder (PTSD). The prevalence of psychopathology was 26 (14.3%) for anxiety disorder, 21 (11.5%) for separation anxiety, 58 (32.6%) for lifetime suicide ideations or attempts, 49 (26.9%) for PTSD, 26 (14.3%) for major depressive disorder, 50 (27.5%) for substance abuse (other than alcohol), 104 (57.1%) for alcohol abuse, 133 (73.1%) for conduct disorder, and 29 (15.9%) for attention-deficit/hyperactivity disorder (ADHD).

Previous research (e.g., Krueger, Caspi, Moffitt, & Silva, 1998) has suggested a taxonomy in which psychopathological symptoms could be grouped into moderately correlated Internalizing and Externalizing factors. In the present study, a confirmatory factor analysis using structural equation modeling techniques was used to confirm these two factors for the lifetime psychiatric diagnoses. The first factor, representing Internalizing Psychopathology, consisted of all anxiety disorders, including PTSD and separation anxiety, lifetime history of suicide ideations and attempts, and major depression. The second factor, representing Externalizing Psychopathology, consisted of conduct disorder, alcohol abuse, substance abuse, and ADHD. All psychiatric diagnoses loaded significantly on one of these two factors, with loadings ranging from .27 (for ADHD) to .68 (for anxiety disorders). The factors were moderately correlated at .35. The model had a good overall fit:  $\chi^2(26, N = 178) = 35.74$ , root-mean-square error of approximation (RMSEA) = .046 (range: .000–.080), comparative fit index (CFI) = .93 supporting the proposed grouping of the diagnoses.

The mean level of platelet MAO activity in this sample was 9.06 ( $SD = 3.43$ ); the mean value for the trait of novelty seeking was 11.31 ( $SD = 2.74$ ).

### Psychiatric Diagnoses, MAO-B, and Personality: Analyses of Associations

To investigate the links among the variables of interest, we applied structural equation modeling techniques. Because of the cross-sectional nature of the study, the findings suggest a possible causal pathway but do not explicitly test one. For inclusion in the models, the psychiatric diagnoses were combined into two factors, Internalizing Psychopathology and Externalizing Psychopathology, as described earlier. Three types of models were tested: direct effects models (with and without controlling for smoking), the mediated model (with novelty seeking as mediator between platelet MAO and psychopathology), and the reduced mediated model (with Internalizing Psychopathology excluded). Each model was estimated in two steps. First, a fully saturated model, with all possible paths among variables, was estimated. Subsequently, all nonsignificant paths were excluded from the model, and the fit of the modified model was assessed.

In the first model (not presented as a figure),  $\chi^2(31, N = 178) = 39.5$ , RMSEA = .04 (range: .00–.07), CFI = .94, the relationships between platelet MAO and psychopathology were considered without controlling for the level of smoking. Both factors were significantly negatively related to the level of MAO-B (Internalizing Psychopathology at  $-.20, p < .05$ , and Externalizing Psychopathology at  $-.15, p < .05$ , standardized coefficients), with lower MAO-B activity associated with higher levels of psychopathology. After we had controlled for smoking (significant negative association between smoking and MAO-B activity at  $-.20, p < .01$ ), the described relationships remained significant, (see Figure 1)  $\chi^2(42, N = 178) = 53.1$ , RMSEA = .04 (range: .00–.07), CFI = .92. No significant relationships between smoking and psychopathology were obtained. Controlling for smoking only slightly decreased the fit of the model,  $\Delta\chi^2(11, N = 178) = 13.6, ns$ , and this covariate was preserved in further analyses, corresponding to the evidence in the literature regarding the connection between platelet MAO-B and smoking intensity.

Second, a mediated model was assessed with novelty seeking serving as a mediator of the relationships between platelet MAO and psychopathology (not presented as a figure),  $\chi^2(50, N = 178) = 60.4$ , RMSEA = .03 (range: .00–.06), CFI = .94. The MAO-B activity was related to novelty seeking (at  $-.22, p < .01$ ), which in turn was related to Externalizing (at  $.41, p < .01$ ), but not to Internalizing (.09, *ns*), Psychopathology. Direct relationship from MAO-B remained significant to Internalizing ( $-.19, p < .05$ ), but not to Externalizing, Psychopathology ( $-.07, ns$ ). Thus, novelty

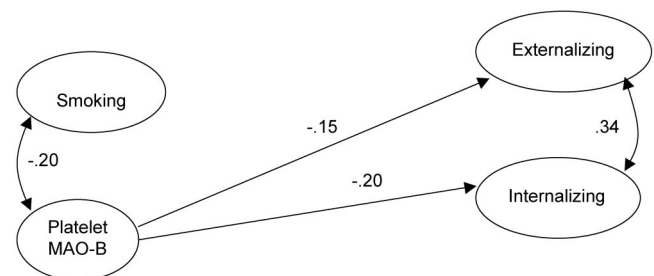


Figure 1. Direct effects model, controlling for smoking (significant paths only).

seeking appeared to fully mediate the relationships between MAO-B and Externalizing Psychopathology.

Subsequently, the Internalizing factor was removed from the model, and the model fit was reassessed,  $\chi^2(13, N = 178) = 16.2$ , RMSEA = .04 (range: .00–.08), CFI = .94, demonstrating no significant impact on the model fit,  $\Delta\chi^2(37, N = 178) = 44.2, ns$ . As Figure 2 shows, in this final model the relationships between MAO-B and Externalizing Psychopathology remained fully mediated by novelty seeking. Low levels of MAO-B activity were related to high levels of novelty seeking, which in turn was related to greater levels of Externalizing Psychopathology.

### Discussion

The present study analyzes, in a single model, psychiatric factors, personality traits, and levels of MAO-B and not only supports the relationships between MAO-B and Externalizing Psychopathology but also demonstrates that they are fully mediated by the personality trait of novelty seeking. Although the present data confirmed the negative link between the level of smoking and MAO-B activity, with the number of cigarettes per day negatively correlating with MAO activity, the relationships between MAO-B and psychopathology remained significant even after controlling for the effects of smoking.

Three characteristics of our samples should be mentioned here. First, because we studied a specific population in which the levels of Externalizing Psychopathology tend to be particularly high and the levels of MAO-B activity tend to be lower than in the general population, the link between these factors may be stronger than in some of the previously published work (e.g., Whitfield et al., 2000). Second, in contrast to other studies, we assessed the relationships of MAO-B activity not to any particular psychiatric diagnosis but rather to two major groups of diagnoses, which is likely to have an impact on the magnitude of the relationships. Third, and most important, the present data demonstrate that the paths from MAO-B activity to the Externalizing factor appear to be fully mediated by the personality trait of novelty seeking. In sum, we suggest that low MAO-B activity does not predispose an individual to particular types of psychopathology per se. Rather, low MAO-B activity is related to a specific personality profile with high levels of novelty seeking, characterized by impulsivity, sensation seeking, and increased exploratory activity (e.g., Zuckerman, 1994). This personality trait, in turn, might predispose an

individual to Externalizing Psychopathology but is not sufficient for its development (Cloninger et al., 1994). Whether psychopathology occurs depends on the influence of other psychosocial or biological risk factors.

The negative link between MAO-B and Internalizing Psychopathology was not surprising, considering earlier demonstrated relationships between platelet MAO-B and suicide attempts (Verkes et al., 1998), PTSD (Davidson, Lipper, Kilts, Mahorney, & Hammett, 1985), and depression (Georgotas et al., 1986; Poirier et al., 1987). This finding, together with the associations between MAO and Externalizing Psychopathology, suggests that low MAO may represent a nonspecific marker indicating predisposition to distress or psychopathology in general, rather than to a specific type or group of disorders. To obtain a more comprehensive picture of the associations between the functions of neurotransmitters, personality, and psychopathology will require careful assessment of other biological markers or personality traits. In addition, recent research (e.g., Oreland, Hallman, & Damberg, 2004) presents data suggesting a complex structure of relationships between MAO and monoamine agents, with the former possibly being a marker of the activity of various transcriptional factors regulating systems of monoamine genes (e.g., DA, NE, and 5-HT). Today, the degree and specificity of such regulation and its reflection in the levels of MAO-B are neither sufficiently understood nor quantified. Thus, this study provides data and generates hypotheses that incrementally contribute to our understanding of the relationships between genes, genetically controlled and environmentally sensitive biochemical agents (such as MAO-B), personality traits, and behaviors.

Relatively low levels of relationship between the variables in the model most likely can be explained by a ubiquitous role of neurotransmitters in various personality traits and different kinds of psychopathology. Because many genes are involved in the metabolic cycles of any given neurotransmitter and, in turn, many neurotransmitters appear to be relevant to complex human behaviors, the individual contributions of specific functional polymorphisms in genes involved in neurotransmitter metabolisms may be relatively small. Thus, it is possible that a consideration of a single neurotransmitter cycle provides only a partial perspective on the relationships, whereas assessment of several neurotransmitter systems (or several genes involved in a neurotransmitter turnover) can potentially provide substantially better explanatory power (e.g., Ebstein & Belmaker, 2002). It should be mentioned, however, that the increasing number of variables considered inevitably results in higher demands for statistical power. Thus, large data sets will need to be acquired to further unveil the complexity of these relationships.

In summary, future studies should assess these associations more specifically, within a framework of a longitudinal approach, and in large populations with high risk because studies of the general population are not always able to capture these relationships, probably as a result of the low prevalence of psychopathology. Even in the present study, which involves the biological assessment of one of the largest groups of delinquent youth ever described in the literature, the effects were very modest, suggesting a large variability of psychopathology and MAO-B levels within this population.

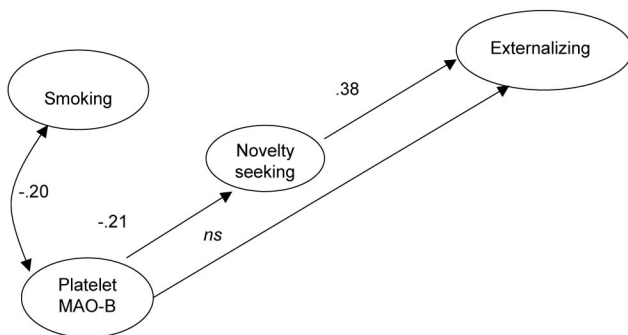


Figure 2. Final mediated model, reduced.

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