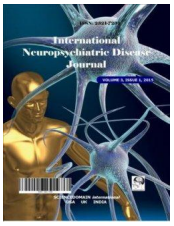

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# MAO-B Activity in Platelets and the MAO-B Gene Polymorphism are Differently Related to Personality Traits in Alcohol Dependent Patients

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Author PN designed the study, wrote the text, performed the statistical evaluations and produced the figures. Authors MR and CM performed the genetic analyses, corrected and proofread the paper. Author JH provided the biochemical analysis of MAO-B with the laboratory help of author DE discussed the interpretation of results. Author MB tested the patients and performed most of the literature search. Authors BG and MJM provided the facilities and helped to recruit patients from their Psychiatric Clinics. All authors read and approved the final manuscript*

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## ABSTRACT

**Aims:** Since monamine oxidase B (MAO-B) platelet activity has been found to be associated with impulsivity, aggression, sensation seeking, and alcoholism, the main goal of the current study to be investigated is the question, if similar associations can be found with the polymorphism rs1799836

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of the MAO B gene coding for activity of the enzyme MAO B.
**Study Design:** The study was an experimental group comparison.
**Place and Duration of Study**: It was carried out at the Psychiatric Giessen University Clinic, the Psychiatric Vitos Clinic and two outpatient psychotherapy treatment centers at the city of Giessen, Germany, between September 2010 and July 2011. Laboratory analyses were only completed in 2012 /2013
**Methodology:** 60 male alcohol dependent patients aged 27 to 68 years were tested individually after detoxification in hospital and subsequent withdrawal. Tests were questionnaires on alcohol history and personality scales (aggression, impulsivity and sensation seeking) followed by a computer test measuring impulsive premature responding and reaction time. In addition, blood samples for determination of platelet MAO B activity and genotyping of the MAO B gene were drawn.
**Results:** Analyses of covariance using genotypes and classes of enzyme activity as independent factors and controlling for age and smoking revealed that the genetic disposition and MAO B activity were not related.(means of MAO B levels, genotype A vs G: P = .228). However, genotype G participants exhibited shorter reaction times (P =.045) and higher aggression scores (P = .043) than A, while genotype A scored higher on experience seeking P= .016) than G. High MAO-B platelet levels were associated with high motor impulsivity (P = .017), but only in genotype A with attentional impulsivity. (interaction: P = .031)
**Conclusion:** The MAO B gene is newly detected to be relevant to personality but is probably not related to MAO B activity .Results are discussed as possibly resulting from different dopamine levels mediated by differences in genotype effects on MAO-B brain activity.

*Keywords: Monoamine oxidase (MAO) B gene polymorphism; MAO B enzyme activity; aggression; impulsivity; reaction time; alcohol dependence.*

## 1. INTRTODUCTION

Different genes and gene sequences have been shown to be directly or indirectly connected with the predisposition to multifactor diseases or disorders as well as with the possibility of their development and degree of clinical signs and may also provide the basis for the development and investigation of novel diagnostic, prophylactic and therapeutic methods and strategies. Neurodegenerative, neurological and psychiatric diseases or disorders belong to the group of diseases targeted by this research. Because genetic, epigenetic and external factors exert combined effects on the predisposition for these diseases and the degree of their clinical symptoms, it is important to determine and characterize gene sequences in combination with possible mediating biochemical characteristics like enzyme activity as well as their associations with personality or behavioural dispositions typical for the specific disease The major goal of the present research paper was therefore to characterise alcohol dependence as an example of neuropsychiatric disorders,-by analysing the associations between a genetic polymorphism, the levels of an associated enzyme (both known to be connected with alcoholism), and alcoholism related personality dispositions.

### 1.1 Molecular Genetics of MAO B

Monoamine oxidases (MAO) s are responsible for the catabolism of monoamines. While the isoform MAO-A is mainly involved in the catabolism of nor-epinephrine and serotonin, .MAO- B is mainly responsible for degradation of dopamine. Both iso-enzymes are found in brain and a number of different tissues, but only MAO-B is also present in platelets [1] the two isoforms of the enzyme are coded by two different genes located in the short arm of the X-chromosome. While the MAO-A polymorphism based on differences in number of tandem repeats (VNTR) has been widely investigated with respect to behaviour [e.g. 2], little is known about effects of genetic variations of the MAO-B gene on psychological dimensions. Three polymorphisms of the MAO-B gene which might be relevant for enzyme activity have been identified, [3] a C-1,114T in the 5' region of the gene, a variable number of GT repeats in intron 2, and a G/A transition in intron 13.

In a study on the functional molecular mechanisms of these polymorphisms the strongest transcriptional effects were observed for the intron 13 region [3], where a single nucleotide polymorphism (SNP) called rs1799836 of the MAO-B gene is represented by

an exchange of adenine (A) to guanine (G). Since the gene is located in the X chromosome, genotypes in male samples are either represented by allele A or allele G. A number of studies investigated, if the two alleles A and G of the MAO-B rs1799836 polymorphism are responsible for differences in platelet enzyme activity. Allele A has been found to be associated with lower enzyme activity than allele G [4]. On the other hand, Balciuniene and colleagues [5] discovered lower MAO-B activity in post-mortem human brains of individuals carrying allele G. This may not be contradictory, because it has been reported that platelet MAO-B activity is not closely related to brain MAO-B activity [6,7].

While Pedersen et al. [8], in a twin study, report a strong genetic influence on platelet MAO B activity and a heritability of 76%, other studies failed to find an association between the genetic variants of the MAO-B gene and differences in MAO-B activity [9,10]. These controversial results make it worthwhile to further investigate the relationship between the polymorphism and MAO-B enzyme activity.

### 1.2 MAO B Activity and Personality

MAO-B activity in platelets has been widely shown to be associated with a number of psychopathological disturbances. Among others, low MAO-B activity has been reported to be a marker of alcohol dependence [11,12], primarily of type 2 alcoholism, [13-15] characterised by impulsiveness, sensation seeking, criminal offending and antisocial behaviour [11]. Furthermore, low platelet MAO-B activity has been shown to be associated with these personality traits in non-psychopathological samples, for instance impulsivity [14,16-18], aggression (18) violent offending [16,19], sensation seeking, risk taking and novelty seeking [19-23].

While several studies investigated the relationships between the polymorphism of the MAO-A gene and personality traits [e.g. 24] .little is known about the relationship between the MAO-B polymorphisms and psychological variables. Since frequencies of the two alleles G and A of the MAO-B rs1799836 single nucleotide polymorphism are fairly balanced (A/G = 60/40% in the Caucasian population), this polymorphism seemed suitable for recruiting comparable numbers of participants in each allele group in order to investigate its relation to MAO-B activity and to related personality traits.

Since both the MAO-B gene and the personality traits associated with MAO-B activity in particular aggression, impulsivity and novelty seeking have been found to be associated with alcoholism (see above), a sample of alcohol dependent patients was chosen for investigating the following questions:

### 1.3 Research Questions

1. Is the rs1799836 SNP on intron 13 of the MAO-B gene associated with differences in MAO-B activity in platelets?
2 Can associations between low MAO-B platelet activity and aggression, impulsiveness and sensation/novelty seeking be confirmed in a sample of alcohol dependent patients ?
3. Will carriers of the genotype related to lower enzyme activity of MAO B also score higher on measures of aggression, impulsiveness and sensation/ novelty seeking ?
4. Will the polymorphism and MAO-B activity levels yield potentiating and / or interacrtion effects on the personality variables ?

## 2. MATERTIALS AND METHODS

### 2.1 Participants

The sample of patients included in the present study had to fulfill the following criteria: alcohol dependence as defined by the ICD-10 code F10.2, diagnosed by an experienced psychiatrist, completed detoxification at a psychiatric hospital, male gender, age > 18 years, no additional substance dependence except smoking, no diagnosis of schizophrenia, schizotypal, delusional or bipolar affective disorders according to WHO ICD-10, no treatment with MAO inhibitors, sufficient knowledge of German language, Caucasian ethnicity. Patients were recruited from two German psychiatric hospitals (University Hospital Giessen-Marburg and Vitos Clinic Giessen), after acute withdrawal, and from two outpatient institutions for psychotherapy of alcohol dependent patents after detoxification in one of the two hospitals. All patients signed informed consent and received 20 Euro after completion of the session. The study was approved by the ethics committee of the Medical Faculty of Giessen University, Germany. The resulting sample consisted of 60 males between the age of 27 and 69 years (mean age 47, 9

years (SD = 9.0), level of education: (number of years in school was: ≤ 9 = 35%, 10/11 = 48%, 12/ 13 (A level) = 17%)).

Days of abstinence after detoxification on the day of testing varied between 0 and 30 days for two thirds of the patients. The others, mostly recruited from the institutions of psychotherapeutic treatment, were abstinent for periods between >1 month up to three years. This variation was taken into account upon statistical evaluation (see below).

## 2.2 Procedure

Patients were tested individually between 2 and 5 pm. After filling in two questionnaires (see below) blood samples for determination of MAO-B activity in platelets and for genetic analysis were drawn from an antecubital vein followed by a computer task measuring impulsivity (see below) and then continued to fill in personality questionnaires.

## 2.3 Questionnaires with Respective Subscales

Aggression was assessed by the Freiburg Questionnaire on Factors of Aggression FAF [25]. This questionnaire comprises five subscales (Spontaneous Aggression, Reactive Aggression, Irritability, Inhibition of Aggression, Openness serving as a lie scale). Since low MAO B activity has mostly been claimed to be associated with a violent or criminal type of aggression [e.g. 16,18,19], only the subscale of *Spontaneous Aggression* was selected from the scales of the FAF for evaluation.

Impulsivity was tested by the Scale BIS-11 by Patton et al. [26], a scale comprising Motor, Impulsivity, Cognitive (=Attentional) Impulsivity and Nonplanning.) The scales of *Motor and Attentional Impulsivity* were selected for separate evalutation, because slightly different associations between low MAO-B and these components of impulsivity have been reported in studies investigating Attention Deficit Hyperactivity Disorder (ADHD) [23,27].

Sensation Seeking, another correlate of low MAO B, [e.g.15], is measured by the Sensation Seeking Scales SSS-V [28], comprising the subscales Thrill and Adventure Seeking, Experience Seeking, Boredom Susceptibility, Disinhibition). In studies on the relatisonship with MAO-B activity the subscale most consistently associated with low MAO-B activity was *Experience Seeking* [21,29,30] which closely resembles Novelty Seeking. Therefore Experience Seeking was selected for the present analyses.

Additional scales related to alcohol dependence for excluding confounders:

- A questionnaire on history and habits of drinking and smoking (Department of Psychology and Psychiatric Hospital University of Giessen, unpublished);
- The Alcohol Craving Questionnaire ACQ [31]

## 2.4 Objective Measurement of Impulsivity (Go/NoGo Discrimination Task)

For measurement of impulsive behavior, a Go/NoGo paradigm was applied on the computer, a modified non-cued version of the cued Go/NoGo task described by Fillmore [32].The participant is instructed to respond as fast and as accurately as possible by pressing a computer button, when the letter Y (= Go stimulus) is presented on the computer screen, and not to respond to the letter O (= NoGo stimulus). Go and NoGo stimuli are presented in random order and at a duration of not more than 800 msec and inter-stimulus intervals between 1100 and 3000ms. The test consists of three sequences: A training period of 10 stimuli followed by a second period comprising 40 Go and 40 NoGo stimuli. In this phase individual reaction times are determined by computing the mean across 90% of the range of reaction times to the 40 Go stimuli. The presentation is continued to test phase III, .in which number of omission errors (responses > 800 ms after a Go stimulus) and commission errors (responses to NoGo stimuli) are recorded. Measures selected were the number of commission errors, (="false alarms"), the classical behavioral measure of impulsivity, and reaction time because shorter decision times in several behavioral tests have been found to be associated with impulsivity [33].

## 2.5 Determination of MAO B Activity

Platelet MAO activity was measured in platelet-rich plasma by a radio enzymatic method with [$^{14}C$]-β-phenylethylamine (β-PEA) "PerkinElmer") as substrate, as described by Hallman et al. [34]. Blood samples were collected by antecubital venipuncture into 4.5 ml Vacutainer® tubes containing EDTA as an anticoagulant. The samples were centrifuged (Jouan BR4i) for 10

min with 800 rpm (114 g) for obtaining platelet-rich plasma. Part of the plasma (100 µl) was used for counting platelets with Sysmex SE-9000 in the biochemical laboratory of the Department of Differential and Biological Psychology at the University of Giessen. One ml of platelet-rich plasma was stored at –80°C until measurement of MAO B activity. After completion of data collection the samples were sent by express on dry ice to the certified clinical laboratory at the University of Tartu, Estonia. After melting the platelet-rich plasma on ice, platelets were sonicated with Bandelin Sonopuls Ultrasonic Homogenizer HD2070 4 x 10 s with intervals for 5 s at 4°C. Then, 50 µl of 0.1 mM [$^{14}$C]-β-PEA were mixed with 50 µl of sonicated plasma, following 4 min incubation in 37°C water bath. After that, 30 µl of 1.0 M HCl was added to stop the reaction and all the tubes were put into an ice bath for another 10 minutes. After adding 750 µl solution of toluene and ethylacetate (1:1), all samples were mixed on a shaker (Vibromax 110, Heidolph) for 30 s at 1700 rpm, and thereafter centrifuged for 5 min at 2000 rpm. From the organic phase 500 µl were pipetted into vials with 8 ml of scintillation liquid (Optiphase "HiSafe"3, Wallac). For standard samples 50 µl of 0.1 mM [$^{14}$C]-β-PEA were added to 8 ml of scintillation cocktail. All samples were analysed in duplicate and blindly corrected using a reference sample.. Radioactivity was measured in a β-counter (Wallac Guardian 1414 Liquid Scintillation Counter). MAO activity was calculated using the following formula: [the amount of the substrate (nmol) x β-count of the sample (cpm) x 1.5]/[β-count of the standard (cpm) x incubation time (min) x the count of platelets in 50 µl of platelet-rich plasma ($10^{10}$ of platelets)], and expressed as nmol of substrate oxidized per $10^{10}$ platelets per min (nmol x min$^{-1}$ x $10^{10}$ platelets$^{-1}$).

## 2.6 Determination of the Genetic Polymorphism. MAO-B rs1799836:

Blood samples were transferred to the Laboratory for Neurogenetics at the Department of Psychology University of Bonn, Germany. DNA was extracted from whole blood samples. Automated purification of genomic DNA was conducted by means of the MagNA Pure® LC system using a commercial extraction kit (MagNA Pure LC DNA isolation kit; Roche Diagnostics, Mannheim, Germany). Genotyping of MAO-B rs1799836 single nucleotide polymorphism (SNP) (an adenine to guanine transition in intron 13 of the MAO-B gene located on the X-chromosome) was performed by real time polymerase chain reaction (RT-PCR) using fluorescence melting curve detection analysis by means of the Light Cycler System (Roche Diagnostics, Mannheim, Germany). The PCR run comprised 48 cycles of denaturation (95°C, 0 s, ramp rate 20°C s-1), annealing (57°C, 18 s, ramp rate 20°C s-1), acquisition of the fluorescence signal (57°C, 1 s, ramp rate 20°C s-1) and extension (72°C, 18 s, ramp rate 20°C s-1) which followed an incubation period of 13 min (95°C) to activate the Taq DNA Polymerase of the reaction mix (Quanti Tect Probe PCR Kit, Qiagen). After amplification a melting curve was generated after an initial denaturation for 20 s at 95°C by keeping the reaction time at 40°C for 20 s and then heating slowly to 80°C with a ramp rate of 0.2°C s-1. The fluorescence signal was plotted against temperature to yield the respective melting points (Tm) of the two alleles. Tm for the A allele was 56.5°C and 63.2°C for the G allele. The primers and hybridization probes used (TIB MOLBIOL, Berlin, Germany) were as follows:

forward primer:
5'- CTCTTATACCACAGGAGAAAGACC -3'; reverse primer:
5'- CATGCAGGATCTGAAATGAA -3'; sensor [G] hybridization probe:
5'- AATAGCAAAAGCGACACCATCTT – fluoresce in-3': anchor hybridization probe:
5'-LCRed640-
CTAATCTGCTCCCTAAAGGACTAAGTAACTG-phosphate 3'.

## 2.7 Statistical Evaluation

Since in alcohol dependent patients MAO B levels decline within the first 4-5 weeks after detoxification and period of abstinance varied considerably in our sample (see above), a non-linear regression between MAO B levels and days of abstinence was computed. There was a clear negative regression up to day 30, levelling off thereafter. Therefore, residuals of MAO B values (differences between predicted and observed MAO B levels) were computed and used for further statistical analysis.

Since, furthermore, MAO-B is reduced by smoking and increases with age, (correlations in our sample r= -.310 P=.017 and r= +.375, P=.003 respectively), age and number of cigarettes smoked per day were included as covariates in univariate analyses of covariance (ANCOVA) Question 1 was answered by an ANCOVA using the genetic factor (genotype A vs

G) as the independent factor and MAO-B activity as the dependent variable.

Questions 2-4 were analysed in one step by two-way analyses of covariance (covariates age and number of cigarettes smoked per day) with the independent factors genotype (A/G) and classes of MAO-B activity. Classes of activity were defined by trichotomizing the values of activity (nmol of substrate oxidized per $10^{10}$ platelets/min, corrected for duration of abstinence), into low (≤5.5), intermediate (5,6-7.9) and high (≥8.0) levels of activity according to percentage of distribution. Dependent variables were the subscale of Spontaneous Aggression of the FAF, the scales Motor and Attentional Impulsivity of the BIS 11, the Experience Seeking scale of the SSS.and Reaction Time in the Go/NoGo task. Number of commission errors in this task emerged as an unsuitable parameter because of its extremely skewed distribution with almost no variance due to bottom effects and was not included in the evaluation.

Post hoc tests were performed by one.way ANCOVA to test for differences between classes of MAO B activity in each genotype and LSD tests were used for comparison of single groups. Level of significance was set at alpha = .05. In case of significant correlations between the questionnaire scores (Spontaneous Aggression, Motor and Attentional Impulsitiy, Experience Seeking) Bonferroni corrections for multiple testing were performed where applicable.

## 3. RESULTS

### 3.1 Association between the MAO- B Polymorphism and MAO- B Activity in Platelets

Our sample consisted of 34 carriers of allele A (in males = genotype A) and 26 carriers of allele G of the MAO-B rs1799836 polymorphism, which is in line with the percentages in the general male Caucasian population (see above).The activity of MAO-B in platelet rich plasma was 7.98±.592 SEM nmol per $10^{10}$ platelets/min in carriers of genotype A and 6.819 ±.674 SEM in genotype G (total group : mean = 7.49±.720 SEM). The analysis of covariance yielded no significant difference between the two groups ($F_{1/55}$ = 1.479, P = .23). Yet it seems worthwhile to tests for similarities between psychological correlates of the polymorphism and of MAO-B enzyme activity.

### 3.2 Associations of the MAO-B Polymorphism and Classes of MAO-B Platelet Activity with the Psychological Variables

#### 3.2.1 Overview

Two-way analyses of covariance performed on each of the questionnaire scores and the behavioural measure of impulsivity described above yielded the results in Table 1.

#### 3.2.2 Spontaneous aggression

While there was no difference in aggression between levels of MAO-B activity, the main effect of the polymorphism revealed that carriers of genotype G showed significantly higher scores on Spontaneous Aggression than genotype A ($F_{2/51}$ = 4.315,P = .043) . Fig. 1 depicting means for each of the 2x3 groups, illustrates that carriers of genotype G who show the lowest levels of MAO B activity were the most aggressive.

Fig1.

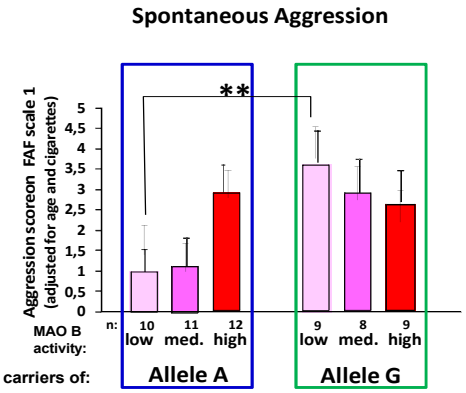


**Fig. 1. Effects of MAO B polymorphism and MAO B activity on scores of Spontaneous Aggression combined (age and number of cigarettes used as covariates)**

*Effect of MAO B polymorphism: P=.043, MAO B activity: not significant, interaction: P =.116; **P<.01 in LSD post hoc test*

#### 3.2.3 Motor Impulsivity

Motor Impulsivity was significantly associated with MAO-B activity in platelets but unexpectedly, high impulsives had higher levels ($F_{2/51}$ = 4.41, P=.017), while it was not related to variations of the MAO-B gene ($F_{1/51}$ = 0.75, P = .786). As illustrated in Fig. 2, the effect is more pronounced in carriers of allele A, Since Motor

Impulsivity is positively correlated with Spontaneous Aggression (r=.366 P=.004), Attentional Impulsivity (r= .512, P=<.001), and Experience Seeking (r=.410, P=.001), Bonferroni correction was performed by dividing the significance level by 3 which still yields a significant result at the.5% level (P=.017).

### 3.2.4 Attentional impulsivity

Attentional Impulsivity was not significantly associated with either MAO-B activity or the genetic variable, but the interaction ($F_{2;50}$= 3.704, P=.032) revealed that increasing levels of MAO B activity were significantly associated with increasing scores of Attentional Impulsitvity only in carriers of allele A (see Fig. 3). This was confirmed by a post hoc ANCOVA within genotype A ($F_{2;31}$ = 11.18, P<.001) yielding means of Attentional Impulsivity of 12.86, 14.75 and 18.76 for low, intermediate and high MAO B levels respectively. After Bonferroni correction results were still highly significant (P = .003).

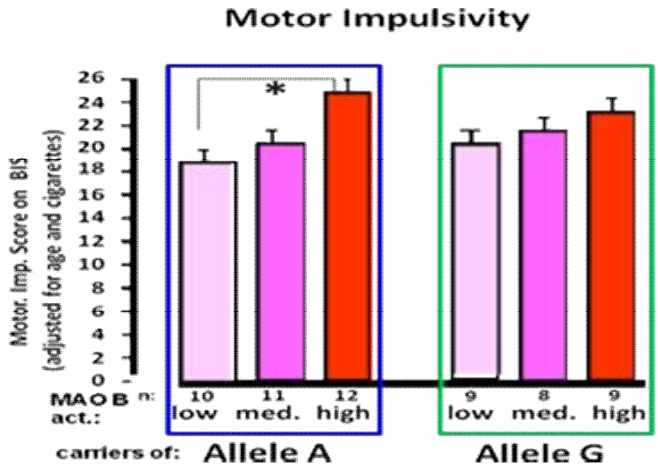


**Fig. 2. Effect of MAO- B polymorphism and MAO B activity on Motor Impulsivity combined (age and number of cigarettes used as covariates)**

*Effect of MAO- B activity: P = .017, effect of MAO- B polymorphism and interaction: not significant; *P<.05 in post-hoc test*

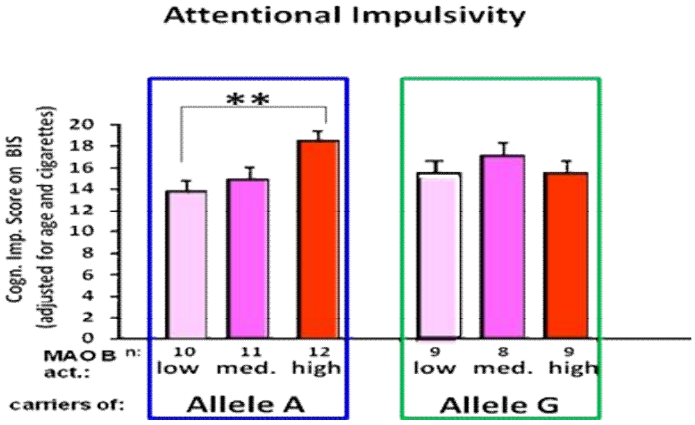


**Fig. 3. Interaction of MAO- B polymorphism with MAO- B activity for Attentional Impulsivity (age and number of cigarettes used as covariates)**

*Effect of MAO- B activity: P=.113, effect of MAO B polymorphism; not significant; interaction: P= .031; **P<.01 in LSD post hoc test*

**Table 1. Results obtained by analysis of covariance. Independent factors: MAO B activity (low, intermediate, high) and MAO B genotype (G/A). (Covariates: age +number of cigarettes smoked/day). Adjusted means of questionnaire scores for main effects (+/¯SEM) N= 60 alcohol dependent males**

| Dependent Variable | MAO B Activity ++ | | | | | Genotype | | | | Interaction | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | low | intermediate | high | | | A | G | | | | |
| | n+ 19 | 19 | 21 | F | P | 34 | 26 | F | P | $F_{int}$ | $P_{int}$ |
| Spontaneous Aggression | 2.146 | 1.988 | 2.746 | .547 | .582 | 1.653 | 2.931 | 4.315 | .**043** | 2.25 | .116 |
| | (.594) | (.543) | (.536) | | | (.406) | (.457) | | | | |
| Motor Impulsivity | 19.53 | 21.43 | 23.95 | 4.41 | .**017** | 21.79 | 21.49. | .075 | .786 | 1.32 | .275 |
| | (1.057) | (.967) | (.954) | | | (.722) | (814) | | | | |
| Attentional Impulsivityl | 14.28 | 15.57 | 16.85 | 3.16 | .113 | 15.65 | 14.49 | .034 | .855 | 3.70 | .**031** |
| | (.896) | (.773) | (.763) | | | (.578) | (1.65) | | | | |
| Experience Seeking | 4.020 | 5.35 | 5.127 | 3.18 | .051 | 5.341 | 4.32 | 6.247 | .**016** | .097 | .389 |
| | (.392) | (.359) | (.354) | | | (.268) | (.302) | | | | |
| Reaction Time (ms) | 436.5 | 426.9 | 430.0 | .072 | .930 | 450.6 | 411.7 | 4.239 | .**045** | .093 | .911 |
| | (17.92) | (17.0) | (16.25) | | | (12.28) | (14.22) | | | | |

*$F_{int}$ $P_{int}$ = interaction effect; bold type: P≤.05, ++units = nmol/ $10^{10}$ platelets/minute, low= <5.5, intermediate = 5.6-7.9, high = >8.0, + one missing value due to technical problems*

### 3.2.5 Experience Seeking

Experience Seeking showed a close to significant association with MAO-B activity ($F_{2/51}$=3.321 P=.051) and a significant association with the polymorphism of the MAO-B gene ($F_{1/51}$ =6.248, P = .016). Higher scores on the Experience Seeking Scale were observed in genotype A as compared to genotype G as well as in high and intermediate MAO-B enzyme levels as compared to the low level group (Fig. 4). Bonferroni correction of the significance level would have required a minimal P value of 017, for the 5% level of significance, so that the association with MAO B levels was no longer significant, but the association with the genotype remained significant at the 5% level.

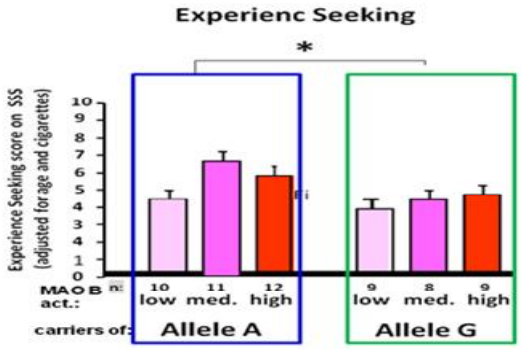


**Fig. 4. Combined effect of MAO B polymorphism and MAO- B activity on Experience Seeking (age and number of cigarettes used as covariates)**

*Effect of MAO-B activity: P = .051; effect of MAO- B polymorphism: P =.016, interaction: not significant*
**P = .016 by ANCOVA*

### 3.2.6 Reaction time

Reaction Time in the Go/NoGo paradigm turned out to be shorter in carriers of allele G than in carriers of allele A ($F_{1/51}$= 4.239, P =.043), and was not associated at all with platelet activity. ($F_{2/51}$=.072, P=.930 (see Fig. 5). Since Reaction Time was not significantly correlated with any of the questionnaire scores, bias due to multiple testing can be excluded and therefore no alpha adjustment was performed.

## 4. DISCUSSDION

The aim of the present paper was to investigate the link between MAO-B enzyme activity and a genetic variation of the rs1799836 polymorphism of the MAO-B gene with respect to associations with impulsiveness related personality variables. and aggression in a sample of alcohol dependent patients.

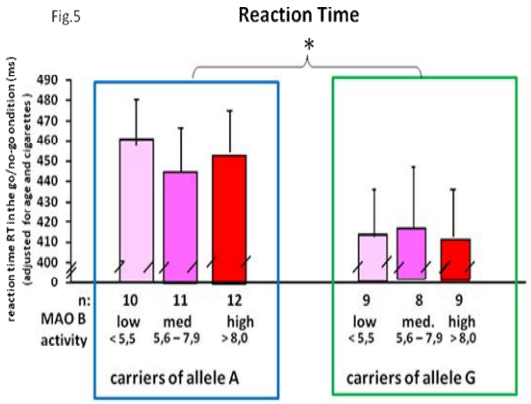


**Fig. 5. Means of Reaction Time in the Go/No-Go task according to classification of MAO-B activity and genotype) (age and number of cigarettes used as covariates)**

*Effect of MAO-B activity and interaction not significant; effect of MAO-B polymorphism: P = .043; * P =.036 by ANCOVA*

### 4.1 Question 1

The first question concerning the association between the MAO-B enzyme activity and the MAO-B SNP polymorphism of the gene has to be answered negatively. The results indicated that carriers of allele A did not show lower platelet MAO-B activity as claimed by Garpenstrand et al. [4]. Our data would rather confirm results of studies reporting a missing association between the genetic variable and MAO-B activity [9,10]) This may be due to the fact that MAO B levels in the periphery are mediated by numerous additional genetic factors like other polymorphisms of the gene mentioned in the introduction or transcription factor AB-2ß emphasized by Damberg et al [1,35], and there may be more environmental factors than the ones we controlled (age, smoking, duration of alcohol abstinence).

### 4.2 Question 2

The association between impulsivity /aggression related personality dimensions and low MAO B levels can not be confirmed in our sample of alcohol dependent patients either. Neither measures of impulsivity nor spontaneous aggression or experience seeking were found to be associated with low platelet activity as

expected from previous studies [14,16,17, 18].Instead, higher MAO B activity levels indicated higher scores on *Motor Impulsivity.* In spite of significant positive correlations with Motor Impulsivity. (see results section), none of the other questionnaire scores was significantly associated with MAO B platelet activity. High instead of low enzyme activity in high Motor impulsives may be specific for alcohol dependent patients. On the other hand, a study by Paaver et al. [36]. indicated that a subtype of impulsivity, self reported risky behavior, was associated with higher platelet MAO activity This finding would match our results obtained with Motor Impulsivity which significantly correlates with for instance the Disinhibition Scale of the SSS (r= .371 P=.004), a scale associated with risk taking. Moreover, Harro et al. [37] assumed a bimodal association between MAO-B activity and aspects of impulsivity, because in a study on adolescents, performed to predict the probability to become a smoker, participants with high as well as low MAO-B activity in platelets developed into smokers as adults.

Therefore, the association between impulsivity and platelet MAO B activity may depend on the subtype of impulsive behavior.

As to the missing association between Spontaneous Aggression and low MAO B levels, assumed from results reported on associations with conduct disorders and violence [e.g. 19], it may be argued that in alcoholic patients, a softer type of aggression represented by the subscale Reactive Aggression of the FAF questionnaire may rather be associated with MAO-B levels, but an ANCOVA performed on this subscale did not yield any significant association with MAO-B activity either ($F_{2/51}$; P = .915).

As a whole, the sample of alcohol dependent patients probably does not represent the typical violent type 2 alcoholics described to show low MAO B activity, but evidently rather consists of cooperative patients willing to be transferred to psychotherapy after detoxification.

## 4.3 Questions 3 and 4

In looking for similarities in associations according to questions 3 and for combined effects according to question 4, the overall impression is that MAO-B levels and allele variants of the gene are not correlated with the same psychological variables. Concerning the questionnaires, it is surprising that not the enzyme activity but the polymorphism is associated with *Spontaneous* A*ggression* Although the interaction between genotype and enzyme levels did not reach significance ($F_{2/51}$=2.25,P=.116), Fig 1 had revealed that low MAO B levels add to the genetic effects of allele G on aggression. In spite of a significant correlation between Spontaneous Aggression and Motor Impulsivity (r=.410, P=001), Motor Impulsivity was not associated with the genotype at all. (see Table 1) Therefore, mutual confounding by causing pseudo-correlations can be excluded because Spontaneous Aggression was not related with MAO B activity and Motor Impulsivity was not related with the polymorphism.

The polymorphism was also relevant for Attentional Impulsivity*,* as shown by the significant interaction between enzyme activity levels and genotype. (Table 1) Highest scores on attention deficit were observed in participants of genotype A who in addition had highest levels of MAO B activity (Fig.3 and ANCOVA performed within participants of genotype A) .A similar modifying effect of a genetic disposition on the association of MAO B activity with attention deficits was observed by Paaver et al. [38] who reported that a measure of attentional impulsivity on a visual computer test was associated with low MAO B activity predominantly in carriers of the short allele of the polymorphism of the serotonin transporter gene HTTLPR. Since this short allele is associated with anxiety, authors concluded that attention deficits may particularly be associated with low MAO B in anxious impulsives.

Since Attentional Impulsivity is significantly correlated with Motor Impulsivity (r=.508, P<.001), possible confounding was tested in our sample by adding Motor Impulsivity as an additional covariate in the ANCOVA performed on the sub-sample of genotype A. This did not reduce the highly significant association of Attentional Impulsivty with MAO B activity ($F_{2/27}$= 5.524, P=.01) and confirms the modifying effect of the gene on the association with platelet activity. The differences between Motor and Attentional Impulsivity in associations with MAO B confirm that there may be different biological mechanisms underlying the two subtypes of impulsivity relevant to ADHD.

Experience Seeking had been shown to be significantly higher in participants of genotype A than G, but was only marginally affected by MAO

B levels So the dimension Experience Seeking is evidently more specific for the genotype than for low MAO B levels reported in previous publications [21,29,30]. Although relationships between MAO-B levels and Sensation Seeking had been reported by previous researchers [20,21]. It is interesting that in our sample neither the total scale of Sensation Seeking nor its other subscales yielded significant associations with the genotype, when controlling for Experience Seeking .by analysis of covariance. This indicates that only the aspect of being attracted by novel stimuli, but not risky or impulsive behavior (as represented by the Thrill and Adventure Seeking and Disinhibititon subscales) are influenced by the polymorphism. This would match findings by Ersche et al. [39] who report an independent association of sensation seeking and impulsivity with drug addiction.

Experience Seeking is evidently typical for genotype A and very different from spontaneous Aggression which had been found to be higher in carriers of genotype G. Independence between the two traits is confirmed by their zero-correlation (r = -.030, P = 823).

It was surprising to observe the influence of the polymorphism on Reaction Time which on the one hand represents decision time as a measure of impulsivity [33] and, on the other hand, indicates general psychomotor speed. So the interpretation is not easy, because the other behavioral task assessing impulsivity, number of “false alarms” was evidently too easy as to yield enough variance for group comparisons. Faster Reaction Time is evidently not associated with the other variable which characterizes genotype G, namely Spontaneous Aggression (r = .076, P = .576) and is also not at all associated with levels of MAO B activity (Table 1), perhaps indicating a finding independent of the other personality variables.

In order to test for further confounding influences possibly responsible for associations between the biological factors and the personality variables reported, additional analyses on relationships between the MAO-B variables with history of alcohol dependence (number of glasses of beer, wine and hard drinks consumed before detoxification, age at onset, years of dependence, and number of previous detoxifications) or scores on the Alcohol Craving Questionnaire (31) were performed. None of them yielded any significant associations with either the enzyme activity or the MAO-B gene polymorphism.

### 4.4 Possible Underlying Mechanisms

So, if we try to interpret our results by putative underlying functional mechanisms**,** we can probably not base our assumptions on lower MAO-B platelet activity in carriers of allele A in our sample, as postulated by Garpenstr and et al. [4]. However, lower MAO-B brain levels in carriers of allele G according to Balciunieni et al [5] with the consequence of higher brain levels in carriers of allele A might explain some of our associations reported. Although direct genetic influences of the genotypes on psychological functions cannot be excluded, associations may most probably be seen as mediated by MAO B dependent different dopamine levels. A model considering dopamine as a mediator for the relationships reported in our study is depicted in Fig. 6.

In carriers af allele G low brain MAO-B activity would result in higher dopamine activity (DA) which increases speed of perception, as shown in studies on cognitive performance and dopamine [e.g. 40]. But high DA may also be the link to aggression. High dopamine activity has not only been reported to indicate expectation of external rewards, but may also be related with aggression, at least in animal models [41,42] where aggression has been reported to have rewarding properties [43,44]. However, in humans usually low dopamine synthesis and transmission, assessed by PET studies, have been found to be associated with aggressive responses in a behavioral provocation paradigm [44]. The Authors explain the controversy among others by the type of aggression, investigated and the biological significance of rewarding properties of aggression in animals and not in humans. Our result of higher aggression in individuals with possibly lower MAO-B brain activity resulting from the influence of genotype G match findings obtained for the low activity allele of the MAO-A gene, which could be shown to truly result in lower MAO-A levels in brain which was associated with aggression in humans [24].

As indicated in Fig.6, the influence of the G allele may partly, but not significantly be supported by additional high DA levels resulting from low platelet MAO-B activity (green arrows and bracket).

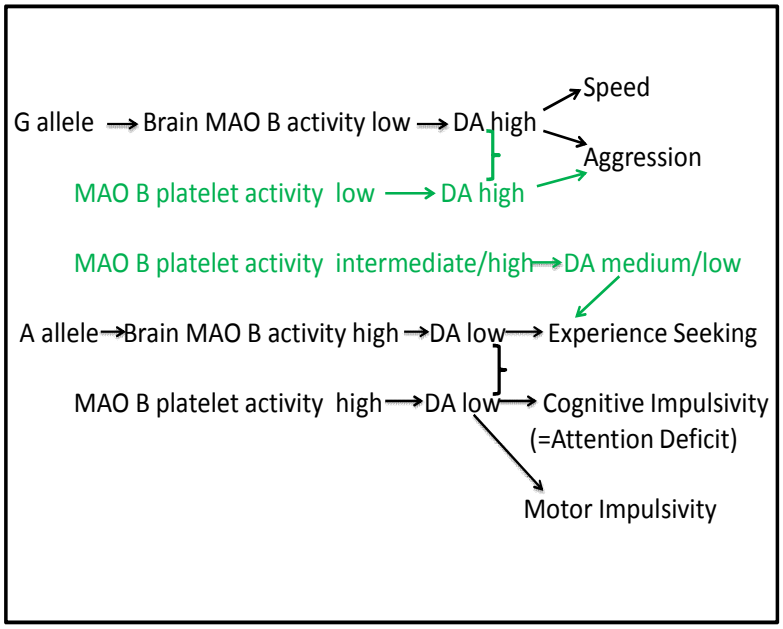


**Fig. 6. Underlying mechanisms assumed for the results**
*(Green lines = week associations, combined effects indicated by vertical brackets)*

If we assume higher MAO-B activity and hence lower DA for allele A, it would mean that lower DA is associated with Experience Seeking. This reminds of the old idea that according to Eysenck [45] extraversion and according to Zuckerman [46] sensation seeking result from under-arousal and represent the need for self stimulation, i.e, the effort to increase DA. This phenomenon is slightly supported by a moderate DA level resulting from average to high activity of platelet MAO-B (green arrow).

This relationship differs from the one observed for Attentional Impulsivity. This trait is only indirectly affected by allele A, because only in its presence high platelet activity leading to DA reduction seems to produce the typical symptoms of attention deficit. This would confirm why symptom reduction in ADHD patients is achieved by dopamine-agonistic substances, but is not always effective.

Motor Impulsivity, however, seems to be affected in the total sample by high platelet MAO- B leading to low DA, independent of the gene variant. This type of behavior is also positively influenced by dopaminergic drugs in ADHD patients.

In Summary, it is not clear, how the effects of platelet levels of MAO-B actually feed back to the brain to modulate behavior, and if a causal mechanism may be assumed, or if the gene as well as the tendency to develop certain MAO-B levels in platelets are just associated with psychological traits independently of their functional relationship with DA.

A major limitation of the present study is, of course, the rather small sample size, which makes it hard to observe robust genetic associations. The influence of one SNP on psychological phenotypes is usually rather small, and therefore large sample sizes are needed to detect those effects [e. g. 47,48]. Given the experimental nature of the present study and the assessment of MAO-B activity besides the investigation of a genetic variation clearly makes it difficult to recruit large samples for a study like this especially when investigating a clinical group, so that the results obtained can rather be taken as representing a pilot study for the development of hypotheses.

Further limitations, of course, are: that the results are only based on males, that assessment of traits was achieved by self reports, and that the study does not provide measures of MAO-B brain activity or dopamine levels which could have helped to elucidate differences and similarities between brain and platelet MAO-B activity.

## 5. CONCLUSION

New findings in our results point to rather separate influences of the genetic factor and the activity of MAO-B on personality, (genotype G being associated with aggression and psychomotor speed, genotype A with Experience Seeking, and MAO B platelet activity with Motor Impulsivity). Furthermore, rather high than the expected low MAO-B activity was associated with impulsivity which can be explained by a U-shaped relationship. Finally, the association of higher enzyme activity with attention deficits merely in carriers of genotype A indicates a moderating effect of the gene on platelet activity.

Taken together, the results rather point to the independence between brain and platelet MAO-B activity as claimed by Young et al [6]. When interpreting MAO-B brain levels as being mediated by the gene, and DA levels as resulting from differences in MAO B brain activity, the results may be interpreted as resulting from differences in dopamine availability.

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## PATIENT CONSENT

Each single patient was thoroughly informed about the aim and procedure of the study and data protection. Patients signed consent forms which are kept as confidential material in a safe place at the Department of Psychology, University of Giessen. Texts of patient information and consent forms had been approved by the ethics committee of the Medical Faculty of the University of Giessen. All authors hereby declare that the experiment has been examined and approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

## COMPETING INTERESTS

All authors have declared that they do not have any conflict of interest. `No financial support was provided from companies or commercial institutions, but expenses were covered by the authors´ department accounts of the Universities of Giessen, Bonn and Tartu.

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