

# **Lack of influence of COMT and NET genes variants on executive functions in schizophrenic and bipolar patients, their first-degree relatives and controls**

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Short title : COMT and NET genes and executive functions

## **Abstract**

**Introduction** Abnormal dopaminergic function in the prefrontal cortex (PFC) may be a key factor in the etiopathogeny of schizophrenia and bipolar disorder. Both schizophrenic and bipolar subjects have executive functions (EF) deficits, thought to reflect abnormal PFC function. The main inactivation pathways for dopamine in the PFC are enzymatic cleavage by the Carboxy-O-Methyl-Transferase (COMT) and reuptake by the nor-epinephrine transporter (NET). Our aim in this study was to replicate previous studies that investigated influence of the COMT genotype on EF in schizophrenic subjects, their relatives and controls and extend their scope by including bipolar patients and their relatives and by exploring NET gene polymorphisms influence on executive performances.

**Methods** We investigated one functional polymorphism of the COMT gene and two polymorphisms of the NET gene. EF were assessed by means of the Trail Making Test and the Wisconsin Card Sorting Test. We assessed the effect of each of the three genotypes on EF for the whole sample (N = 318) and separately in schizophrenic (N = 66), bipolar (N = 94) and healthy subjects (i.e. relatives and controls N = 158). Separate analyses were performed because of the presence, in patients samples, of potentially confounding factors, especially medication.

**Results** Genotype had no significant effect on the cognitive measures in any of the analyses (for the two EF measures, the three polymorphisms and the four groups).

**Conclusion** In our sample we found no evidence in favour of a major effect of COMT or NET polymorphisms on the two tests of EF.

Key words: Cognition, Dopamine, Prefrontal cortex.

## **Introduction**

Importance of genetic factors in the etiology of schizophrenia and bipolar disorder is well established. However, attempts to identify the susceptibility genes involved have been unsuccessful, and this has led to a search for alternative strategies to overcome the limitations of classical association studies. One such strategy is the use of candidate genes in association studies (Leboyer et al., 1998). Candidate genes are genes that code for proteins involved in the normal functioning of the CNS and whose dysfunctions have been implicated in aetiology of psychiatric disorders. As dopaminergic dysfunction was implicated in the pathophysiology of both psychotic and affective disorders, genes coding for proteins that inactivate dopamine (DA) are good candidate genes for both schizophrenia and bipolar disorders.

At the phenotypical level, the limitations of classical association studies can be overcome by the use of endophenotypes i.e. subclinical traits associated with genetic susceptibility to one or more disorders (Gottesman and Gould, 2003, Leboyer, 2003). Endophenotypes are independent of clinical state and heritable. Executive dysfunctions are seen in schizophrenic and bipolar patients in remission (Heinrichs and Zakzanis, 1998, Quraishi and Frangou, 2002) and in their relatives (Szöke et al., 2005, Glahn et al., 2004) and therefore constitute potential endophenotypes.

The fact that DA function influences executive performances suggested the joint use of the two aforementioned strategies. Executive functions depend on the activity of the prefrontal cortex (PFC). DA in the PFC is inactivated primarily by catechol-O-methyl-transferase (COMT). The COMT gene contains a functional polymorphism (Val158Met), resulting in the

generation of two forms of COMT, one of which (the “Met” enzyme) has low activity (Lotta et al., 1995).

Several studies have investigated the association between COMT Val158Met genotypes and EF, as measured by the perseverative errors on the Wisconsin Card Sorting Test (WCST) (Table I). Association was observed in relatives of schizophrenic patients (Rosa et al., 2004), normal controls (Malhotra et al., 2002) and in large, heterogeneous samples in which schizophrenic patients were pooled with their relatives and/or normal controls (Egan et al., 2001, Jooper et al., 2002). However, most studies found no significant association in schizophrenic patients (Rosa et al., 2004, Egan et al., 2001, Jooper et al., 2002, Bilder et al., 2002, Galderisi et al., 2005), normal controls (Tsai et al., 2003, Bruder et al., 2005) or mixed samples (schizophrenic patients and controls) (Ho et al., 2005). The strength of association between the COMT genotype and WCST performances was moderate. Most authors found between 2 % and 5 % of shared variance (Table I).

### **Table I**

There are also many studies investigating the influence of this COMT genotype on other executive or non-executive tasks in different normal or pathologic samples (reviewed in Bilder et al. 2004 and Tunbridge et al. 2006). As most of these studies did not use the WCST it is difficult to say whether other tasks are better than the WCST for determining the effect of the COMT genotype on cognition. The results from these studies are also difficult to compare because the populations used are often different from those in the studies that used WCST (for example, children with ADHD, patients with Parkinson’s disease, subjects with 22q11 deletions, etc.).

One exception is the study by Bilder et al. (Bilder et al., 2002), which used a large range of cognitive tasks in a population of chronic schizophrenics. For the EF, this study suggested that other tests, such as the trail making test (TMT), may be more appropriate than the WCST for investigating the effect of COMT.

Other polymorphisms, especially of genes with related functions, may affect EF, thereby masking the effect of the COMT Val158Met polymorphism. In the PFC, the second most important mechanism of DA inactivation is re-uptake by the norepinephrine transporter (NET) (Tzschentke, 2001). The NET contributes to inactivation of both DA and norepinephrine. These neurotransmitters have been implicated in the pathophysiology of both schizophrenia and bipolar disorder. Therefore, the NET gene is a functional candidate gene in schizophrenia and bipolar disorder. As several studies have suggested a linkage between markers situated in the immediate vicinity of the NET gene and bipolar disorder (Ekholm et al. 2003, Segurado et al., 2003) or schizophrenia (DeLisi et al. 2002, Lewis et al., 2003) the NET gene may also be a positional candidate.

We therefore investigated the effect of the COMT gene polymorphism not only on the results obtained for the WCST but also on those obtained for the TMT. In addition, we investigated the effect of two NET gene polymorphisms on these two tests of EF.

The first NET gene polymorphism (A1287G) is the only known exonic polymorphism with a high frequency (Stober et al., 1996). The second (T-182C) is located in the promoter region (Zill et al., 2002) and may therefore affect the expression of the NET gene.

## **Aim of the study**

The aim of this study was to replicate previous studies investigating the effect of the COMT gene on EF in schizophrenic subjects, their relatives and controls and to extend their scope by including bipolar patients and their relatives. We also aimed to explore the effect on EF of polymorphisms of a second gene involved in DA inactivation in the PFC (the NET gene).

## **Methods**

### **Subjects**

Probands suffering from schizophrenia, schizoaffective or bipolar disorder were consecutively recruited at two university-affiliated hospitals (the Henri Mondor and Albert Chenevier Hospitals, Créteil). They were included in the study just before discharge. To be included, patients had to meet DSM-IV (American Psychiatric Association, 1994) criteria for bipolar disorder, schizoaffective disorder or schizophrenia. Patients were interviewed by an experienced psychiatrist, with the French version of the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994, Preisig et al., 1999), to confirm the diagnosis according to DSM IV criteria.

We also asked first-degree relatives of patients to participate in the study. Relatives were interviewed with the DIGS to exclude those presenting a diagnosis of psychotic or bipolar disorder. The information obtained was supplemented, for probands and relatives, if required, with medical case notes.

Healthy controls were blood donors at the Pitié-Salpêtrière Hospital. Controls were included after being interviewed with the DIGS and the Family Interview for Genetic Studies (FIGS) (Maxwell, 1992), to confirm the absence of personal and family histories of DSM IV, axis I or II, disorders.

For inclusion in this study, all subjects (patients, relatives and controls) had to be normothymic, as evaluated by the MADRS (Montgomery and Asberg, 1979) and the Bech and Rafaelsen mania rating scale (MAS) (Bech et al., 1979). Schizophrenic and bipolar patients also had to be in a stable state, with no change in medication or symptoms for a period of at least two weeks before the cognitive evaluation. Patients and relatives were included only if aged between 18 and 60 years, and if they had no history of neurological disease or current substance abuse. All the subjects included in the study were Caucasian of West European origin.

The research ethics board of Salpêtrière Hospital reviewed and approved the study. Written informed consent was obtained from all subjects after the complete description of the study.

### **Cognitive assessment**

We used the classic form of the WCST (Heaton, 1981), with four stimulus cards differing in three characteristics: color (yellow, green, red, blue), shape (triangle, star, cross, circle) and number (one to four) and two identical sets of 64 response cards. The test was discontinued after the completion of six categories or when no more response cards were left. The two measures most often used to assess WCST performance are number of categories completed and number of perseverative errors. However, as the number of categories displays a major ceiling effect, we used only perseverative errors score.

The Trail Making Test (Reitan and Wolfson, 1985) is a pencil and paper test assessing psychomotor speed, attention and set alternation. Part A requires the subjects to connect 25 consecutively numbered circles as quickly as possible. In Part B, the subjects have to connect 25 consecutively numbered and lettered circles by alternating between the two sets. The time taken to complete Parts A and B of the TMT is recorded in seconds. As set alternation is required only in Part B, the time taken to complete Part A is subtracted from the time taken to complete Part B to eliminate performance variation due to psychomotor speed (Lezak, 1995), and this value is used as a measure of EF. As some authors report differences between the two parts of the test and others have reported the separate scores for the TMT A and B, we decided to use all three variables in order to facilitate comparison of the data.

The tests were carried out in standardized conditions and scored by three of the authors (two clinical neuropsychologists, A.T. and C.A., and one MD, A.S.) who have extensive practice in these tests.

As schizoaffective subjects show cognitive impairments similar to those of schizophrenic subjects (Evans et al., 1999, Gooding and Tallent, 2002) those two populations were considered together, as routinely done in other studies (Egan et al, 2001, Krabbendam et al., 2001).

### **Genetic analysis**

Genomic DNA was extracted from B lymphoblastoid cell lines and the fragments containing the polymorphisms of interest were amplified by polymerase chain reaction (PCR). For COMT, we used the primers COMT F: 5'-CTC ATC ACC ATC GAG ATC AAC and COMT R: 5'-GAT AGT GGG TTT TCA GTG AAC G to generate a 528 bp fragment.

For the NET T-182C polymorphism, we used primers T182C-F: 5'-ACC TGA GCT GGG GAG GGG GTC and T182C-R: 5'-GAA GCC GAC TAC GGA CAG CAG to generate a 600 bp fragment.

For NET G1287A polymorphism, we used the primers G1287A-F: 5'- TCC AGG GAG ACC CTA ATT CC and G1287A-R: 5'- TTG ACT TTA TTG AAA TGC GGC to generate a 241 bp fragment.

Details of the PCR for the COMT polymorphism are provided below. A similar method was used for NET polymorphisms, with slight differences indicated in brackets.

PCR was carried out in a volume of 20 µl containing 150 ng genomic DNA, Taq Invitrogen 1X buffer, 1.5 mmol/l MgCl<sub>2</sub>, 200 µmol dNTP, 0.5 µmol of each primer and 1.5 (1.25) units of Invitrogen *Taq* polymerase. The initial denaturation step - 30 seconds (3 minutes) at 95 °C was followed by 35 cycles of 30 seconds at 95°C, 30 seconds at 55°C, 30 seconds at 72°C and a final elongation step for 10 minutes at 72 °C. The purified fragments were analyzed in a 16-lane capillary automated 3100 DNA sequencer (PE 3100, Applied Biosystems).

## **Statistical methods**

Groups of subjects were compared using Chi-square test or Fisher's Exact test for categorical data, and ANOVA for continuous data.

We assessed the effect of each genotype on the results obtained in the two EF tests, with correction for the influence of other significant variables, by means of stepwise, backward regression. In the regression model, the cognitive measure was the dependent variable. The genotype was the independent variable of interest, and was, as such, forced in the final solution. Demographic variables (sex, age, education level) and group membership were used

as covariables and were retained in the final model only if their influence was significant at the 0.1 threshold. We assessed whether the effect of genotype on cognitive measures was affected by group membership by adding a genotype x group interaction factor to the model as a covariable.

As in the groups of patients several factors (such as medication, illness duration etc.) may influence DA metabolism, cognition or both, we analyzed the whole sample and then separately the schizophrenic, bipolar and “healthy” (i.e. relatives and controls) subsamples. Because we had no a priori reasons to consider that the influence of COMT and NET polymorphisms is different in the three groups of healthy individuals we did not analyze those groups separately unless the genotype x group interaction factor was significant. This strategy avoided unnecessary loss of statistical power (due to smaller samples) and the increase of risk of false positive results (due to multiple statistical tests). Family membership was added as a random effect factor to take into account the lack of independence between family members in analyses including relatives.

Based on previous reports of the influence of the COMT genotype on WCST perseverative errors, we assessed the power of our study to detect similar effects (i.e. 2-5% of shared variance) in our samples. The shared variance ( $R^2$ ) in previous published studies was computed based on the reported F value (when not available this value was calculated from the reported data i.e. means and SD), number of subjects, and degrees of freedom – see table I.

All statistical analyses were carried out with SAS V8 software.

## **Results**

We included 318 subjects: 66 schizophrenic or schizoaffective patients (SZ), 57 first-degree relatives of schizophrenic or schizoaffective patients (SZ-Rel), 94 bipolar patients (BP), 51 first-degree relatives of bipolar subjects (BP-Rel) and 50 normal controls (NC). The SZ group included 45 schizophrenic subjects and 21 (30.3 %) schizoaffective subjects.

We observed significant differences in demographic variables (age, sex, education level) between the five groups, mainly due to the SZ group, which was younger, and contained a higher proportion of male subjects and individuals with low educational levels (see Table II). For the two tests of EF used: the worst results were obtained for the SZ group and the best for the NC group (Table II). For all cognitive measures (WCST perseverative errors, TMT A, B and B-A), significant differences (at the 0.01 threshold) were observed between schizophrenic patients and their relatives, between the SZ and BP and between SZ and NC groups. BP patients had significantly lower performances than the NC on Trail A and B but not on the WCST or on the TMT B-A. No significant differences were observed between the BP group and their relatives, between the groups of relatives (BP-Rel vs SZ-Rel) or between the groups of relatives and the NC group.

### **Table II**

For each group (total sample, healthy subjects i.e. the SZ-Rel, BP-Rel and NC groups combined, SZ patients, BP patients), the genotypes for the three polymorphisms were in Hardy-Weinberg equilibrium. In the total sample and in the subsamples (healthy subjects,

schizophrenic patients and bipolar patients), for all three polymorphisms, there were no statistically significant differences in demographic variables when groups defined on the basis of genotype were compared (data not shown).

Tables III to V summarize the cognitive tests results according to specific genotype, for the four groups analyzed. The results are presented as least squares means. These values reflect the effect of genotype after correction for significant demographic variables. As the genotype by group interaction factor was not retained in any of the final models we did not make separate analyses for the two groups of relatives or for controls.

**Table III.**

**Table IV.**

**Table V.**

As detailed in tables III to V, in all the analyses carried out (for the two EF measures, the three polymorphisms and the four groups) genotype had no significant effect on cognitive measures (at the 0.05 threshold). No significant differences in the effect of genotype on executive measures were observed when all demographic variables (age, sex, education level and when appropriate group) were retained in the model.

Similar results (not shown, tables VI to VIII, available on line) were obtained when genotype influence on TMT A and B was assessed.

We also calculated the power of our study to detect a similar sized association between genotypes and cognitive measures as those found in previous studies (i.e. between 2 and 5 % of shared variance). The study power was limited for individual subgroups (0.20 for 2% shared variability and 0.45 for 5% in SZ, 0.27 and respectively 0.60 for BP), but better for the healthy subjects group (0.42 and 0.83) and for the whole sample (0.70 and 0.99).

## **Discussion**

In this study, we analyzed the effects of three polymorphisms of two genes involved in DA metabolism in the PFC, on the results obtained in two tests exploring EF (the WCST and the TMT) in schizophrenic, bipolar patients, their relatives and controls. Overall, in our sample we did not find arguments in favor of a significant effect of these polymorphisms on the results obtained on the two cognitive tests. The power calculations suggested that although the combined samples were sufficient to detect a 5 % shared variance between the genotypes and cognitive performances, the individual samples were not. Therefore, we could not rule out a false negative result in the presence of a small effect of genotype on these cognitive measures or whether the effect was limited to one of the sub-samples.

Egan et al. (2001) suggested that the effect of the COMT Val/Met polymorphism on performance in the WCST might depend on the number of alleles present, with Met/Met subjects having the best performances. Our results are not consistent with this hypothesis. The only group in which Met/Met subjects performed best and Val/Val subjects worst was the BP group, but differences were small and, even before correction for multiple testing, far from significant ( $p=0.33$ ). Thus, although lack of statistical power for analysis of the BP group may account for the lack of significance observed, this explanation is improbable for the other groups. Three studies on schizophrenic patients showed that Met/Met subjects performed best in the WCST (Egan et al., 2001, Joober et al., 2002, Bilder et al., 2002), but none of these differences were statistically significant. Our data, and those of Rosa et al. (2004) are at variance with these results as schizophrenic subjects homozygous for the Met allele obtained the worst results (statistically non significant differences).

In schizophrenic subjects, other dopaminergic changes and/or treatment effects may mask the effect of the COMT genotype. For this reason, we and other authors studied this effect in normal subjects (Malhotra et al., 2002, Tsai et al., 2003), relatives of patients (Rosa et al., 2004) and mixed (i.e. controls and/or relatives and/or patients) samples (Egan et al., 2001, Joober et al., 2002, Ho et al., 2005), but conflicting results were once again obtained. This divergence in results may be accounted for by: a) false negative results due to low statistical power, b) false positive results or c) true genetic variability (Lohmueller et al., 2003). It is currently difficult to draw clear conclusions on this point as too few studies, which included too few subjects, have yet been carried out. However, false negative results are unlikely to account for the observed differences between studies as, with the exception of the princeps study (Egan et al., 2001), studies finding no significant effect (Tsai et al., 2003, Ho et al., 2005, our study) have included larger samples of subjects than those reporting significant effects. True genetic variability is also unlikely to account for the differences as all studies but one (Tsai et al., 2003), were carried out in populations containing a large majority of Caucasian subjects of West European origin.

Bilder et al. (2002) suggested that the TMT might be more appropriate than the WCST for investigating the effect of the COMT Val/Met polymorphism on EF. Our data do not confirm this hypothesis in the SZ group or in any of the other groups and are consistent with those of other authors who found no significant differences in TMT performances between groups defined on the basis of COMT Val158Met genotype in schizophrenic subjects or in their siblings (Rosa et al. 2002) or in a mixed (schizophrenic and normal subjects) sample (Ho et al., 2005).

We also analyzed, for the first time, the effect of two polymorphisms of another gene (the NET gene) involved in DA metabolism in the PFC. The first polymorphism (A1287G) is the only exonic polymorphism of the NET gene occurring at high frequency. This polymorphism had no effect, in any of the groups, on the results obtained in the WCST or the TMT.

The second NET gene polymorphism (C-182T) is located in the promoter region and, as such, may affect NET gene expression. This polymorphism had no significant effect on either task, in any of the groups, but the results obtained were close to the significance threshold ( $p=0.053$ ) in the SZ group, for the difference score (B-A) of the TMT. The lack of significance of the results may be due to low statistical power. The absence of such effect in the other groups suggests that, if this polymorphism really does have an effect, it is mediated by characteristics present only in schizophrenic patients (for example, treatment with dopaminergic agents). However, this finding should be interpreted with caution for several reasons. First, multiple statistical tests increase the risk of type 2 error (false positives due to chance finding). Second, this result is mainly the consequence of differences between very low performances in heterozygous subjects and those of the rare C/C subjects. Finally, the lack of *in vitro* or *in vivo* data concerning the influence of this polymorphism on NET gene expression limits the possibilities for interpreting this result.

In conclusion, we obtained no evidence that the three polymorphisms studied have an effect on EF in the two tests used here. Despite theoretical considerations, evidence that genes encoding enzymes inactivating DA in the PFC significantly affect EF is weak, and there is even less evidence to suggest that these genes are involved in the etiology of schizophrenia or bipolar disorder by modifying cognition. Despite these disappointing results, we believe that approaches combining cognitive endophenotypes and candidate genes strategies should be

pursued. The choice of other genes and polymorphisms, of other cognitive tests, and the development of more complex interaction models may lead to more consistent positive results.

## **Acknowledgments**

This research was supported by grants from "Délégation à la Recherche Clinique de l'AP-HP" (PHRC AOM 98152) and INSERM. A.S., A.M. and C.A. received grants from the "Fondation pour la Recherche Médicale".

We thank the staff of the "Banque de cellules – Service de Biochimie génétique et moléculaire" of the Cochin Hospital (Paris) for generating and maintaining the lymphoblastoid cell lines.

We also thank M.J. Pereira-Gomes and E. Abadie for technical assistance.

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**Table I.** Percentage of shared variance between the COMT genotype and WCST perseverative errors results in the previously published samples

| Author/year      | Population <sup>a</sup> | Number of subjects | F (df)                | R2       | % Shared variance |
|------------------|-------------------------|--------------------|-----------------------|----------|-------------------|
| Tsai (2003)      | C                       | 120                | 0,28 <sup>b</sup> (2) | 0,004806 | 0,48              |
| Rosa (2004)      | S                       | 67                 | 0,37(2)               | 0,011430 | 1,14              |
| Ho (2005)        | S+C                     | 243                | 1,74(2)               | 0,014293 | 1,43              |
| Egan (2001)      | S+R+C*                  | 449                | 6(2)                  | 0,026201 | 2,62              |
| Galderisi (2005) | S                       | 106                | 2,13 <sup>b</sup> (2) | 0,039770 | 3,98              |
| Egan (2001)      | S+C*                    | 230                | 4,93(2)               | 0,041628 | 4,16              |
| Bilder (2002)    | S                       | 45                 | 0,92(2)               | 0,041971 | 4,20              |
| Joober (2002)    | S+C*                    | 125                | 2,79(2)               | 0,043737 | 4,37              |
| Joober (2002)    | S                       | 94                 | 2,71(2)               | 0,056212 | 5,62              |
| Malhotra (2002)  | C*                      | 73                 | 4,43(2)               | 0,112351 | 11,24             |
| Rosa (2004)      | R*                      | 76                 | 5,5(2)                | 0,130952 | 13,10             |

<sup>a</sup> C = controls, S = schizophrenics, R= relatives;

<sup>b</sup> computed using available (mean and standard deviation) data

\* statistically significant association

**Table II.** Demographic characteristics and results of cognitive assessment with the Wisconsin Card Sorting Test (WCST) and Trail Making Test (TMT)

|  | Schizophrenic subjects | Relatives of schizophrenic subjects | Bipolar subjects | Relatives of bipolar subjects | Normal controls |
|--|------------------------|-------------------------------------|------------------|-------------------------------|-----------------|
| N  | 66                     | 57                                  | 94               | 51                            | 50              |
| Age (Mean +/- SD)                                | 34.1 +/-8.9            | 43.8 +/- 13.2                       | 40.4 +/-11.0     | 40.4 +/-13.3                  | 42.2 +/- 12.9   |
| Sex (% male)                                     | 65.2                   | 59.6                                | 39.4             | 37.3                          | 52.0            |
| Education level (At least high school completed) | 40.9 %                 | 82.5 %                              | 86.2 %           | 78.4 %                        | 64.0 %          |
| WCST-PE <sup>a</sup> (Mean +/- SD)               | 23.9 ± 20.5            | 14.8 ± 18.5                         | 13.5 ± 12.8      | 13.7 ± 18.9                   | 10.4 ± 8.3      |
| TMT A (Mean +/- SD)                              | 50.5 ± 18.1            | 38.2 ± 12.9                         | 41.7 ± 16.0      | 38.1 ± 16.3                   | 32.3 ± 11.6     |
| TMT B (Mean +/- SD)                              | 126.2 ± 69.5           | 86.3 ± 36.4                         | 88.6 ± 48.1      | 82.2 ± 42.1                   | 63.5 ± 24.2     |
| TMT B-A <sup>b</sup> (Mean +/- SD)               | 75.7 ± 60.1            | 48.2 ± 30.5                         | 46.9 ± 44.7      | 44.1 ± 36.5                   | 31.2 ± 17.9     |

<sup>a</sup> Number of perseverative errors in the WCST

<sup>b</sup> Difference between times to complete parts B and A of the TMT

**Table III.** Influence of the Val158Met polymorphism of the COMT gene on Wisconsin Card Sorting Test (WCST) and Trail Making Test B-A (TMT B-A) results

| Test                 | Sample                                    | Genotype |                         |         |                         |         |                         | F    | p    | Covar. retained <sup>a</sup> |
|----------------------|---|----------|-------------------------|---------|-------------------------|---------|-------------------------|------|------|------------------------------|
|                      |   | Met/Met  |                         | Met/Val |                         | Val/Val |                         |      |      |                              |
|                      |   | N        | Least square means (SE) | N       | Least square means (SE) | N       | Least square means (SE) |      |      |                              |
| WCST <sup>b</sup>    | Total                                     | 68       | 17.69 (1.99)            | 165     | 17.24 (1.35)            | 70      | 16.11 (1.95)            | 0.19 | 0.82 | A, L, G                      |
|                      | Schizophrenic subjects                    | 15       | 29.22 (5.04)            | 33      | 20.21 (3.40)            | 10      | 24.50 (6.14)            | 1.13 | 0.33 | L                            |
|                      | Bipolar subjects                          | 30       | 12.17 (2.10)            | 43      | 15.17 (1.83)            | 20      | 16.68 (2.50)            | 1.14 | 0.33 | A, S                         |
|                      | Healthy subjects (relatives and controls) | 23       | 12.03 (3.11)            | 89      | 16.91 (1.70)            | 40      | 12.73 (2.50)            | 1.72 | 0.18 | A, L, S                      |
| TMT B-A <sup>c</sup> | Total                                     | 69       | 55.87 (4.91)            | 172     | 52.48 (3.17)            | 76      | 60.01 (4.60)            | 1.02 | 0.36 | A, L, G                      |
|                      | Schizophrenic subjects                    | 17       | 73.95 (12.89)           | 35      | 64.05 (9.05)            | 14      | 90.56 (14.07)           | 1.31 | 0.28 | A, L                         |
|                      | Bipolar subjects                          | 29       | 57.17 (8.60)            | 44      | 65.69 (7.42)            | 20      | 66.76 (9.09)            | 0.64 | 0.53 | A, L                         |
|                      | Healthy subjects (relatives and controls) | 23       | 48.42 (5.53)            | 93      | 43.52 (2.99)            | 42      | 49.88 (4.37)            | 0.98 | 0.37 | A, L, G                      |

<sup>a</sup> Covar. retained = covariables retained in the final regression model; A= age, L=education level, G= group, S=sex (the interaction factor genotype x group was not significant for any of the analyses);

<sup>b</sup> Number of perseverative errors in the WCST

<sup>c</sup> Difference between times to complete parts B and A of the TMT

**Table IV.** Influence of the C-182T polymorphism of the NET gene on Wisconsin Card Sorting Test (WCST) and Trail Making Test B-A (TMT B-A) results

| Test                 | Sample                                    | Genotype |                         |     |                         |     |                         | F    | p     | Covar. retained <sup>a</sup> |
|----------------------|---|----------|-------------------------|-----|-------------------------|-----|-------------------------|------|-------|------------------------------|
|                      |   | C/C      |                         | C/T |                         | T/T |                         |      |       |                              |
|                      |   | N        | Least square means (SE) | N   | Least square means (SE) | N   | Least square means (SE) |      |       |                              |
| WCST <sup>b</sup>    | Total                                     | 32       | 14.16 (2.56)            | 122 | 16.62 (1.35)            | 135 | 15.43 (1.36)            | 0.47 | 0.62  | A, L, G                      |
|                      | Schizophrenic subjects                    | 5        | 25.60 (7.22)            | 20  | 21.80 (3.61)            | 26  | 20.88 (3.16)            | 0.18 | 0.83  | -                            |
|                      | Bipolar subjects                          | 11       | 13.23 (2.85)            | 35  | 14.72 (1.96)            | 44  | 15.22 (1.93)            | 0.21 | 0.81  | A, S                         |
|                      | Healthy subjects (relatives and controls) | 16       | 13.13 (3.46)            | 67  | 14.90 (1.78)            | 65  | 13.31 (1.87)            | 0.26 | 0.77  | A, L, S                      |
| TMT B-A <sup>c</sup> | Total                                     | 34       | 45.66 (6.67)            | 126 | 59.37 (3.65)            | 140 | 52.86 (3.54)            | 1.99 | 0.14  | A, L, G                      |
|                      | Schizophrenic subjects                    | 6        | 38.83 (21.79)           | 22  | 92.01 (11.09)           | 31  | 63.80 (9.56)            | 3.07 | 0.053 | A, L                         |
|                      | Bipolar subjects                          | 11       | 65.98 (10.00)           | 36  | 65.98 (7.86)            | 43  | 61.01 (7.98)            | 0.20 | 0.82  | A, L                         |
|                      | Healthy subjects (relatives and controls) | 17       | 45.87 (6.60)            | 68  | 44.93 (3.46)            | 66  | 43.78 (3.72)            | 0.05 | 0.94  | A, L, G                      |

<sup>a</sup> Covar. retained = covariables retained in the final regression model; A= age, L=education level, G= group, S=sex (the interaction factor genotype x group was not significant for any of the analyses);

<sup>b</sup> Number of perseverative errors in the WCST

<sup>c</sup> Difference between times to complete parts B and A of the TMT

**Table V.** Influence of the A1287G polymorphism of the NET gene on Wisconsin Card Sorting Test (WCST) and Trail Making Test B-A (TMT B-A) results

| NET A1287G           |   | Genotype |                         |     |                         |     |                         | F    | p    | Covar. retained <sup>a</sup> |
|----------------------|---|----------|-------------------------|-----|-------------------------|-----|-------------------------|------|------|------------------------------|
| Test                 | Sample                                    | A/A      |                         | A/G |                         | G/G |                         |      |      |                              |
|                      |   | N        | Least square means (SE) | N   | Least square means (SE) | N   | Least square means (SE) |      |      |                              |
| WCST <sup>b</sup>    | Total                                     | 30       | 16.97 (2.62)            | 111 | 15.94 (1.47)            | 149 | 16.23 (1.33)            | 0.07 | 0.94 | A, L, G                      |
|                      | Schizophrenic subjects                    | 9        | 26.89 (6.13)            | 17  | 19.71 (4.46)            | 27  | 23.63 (3.54)            | 0.49 | 0.61 | -                            |
|                      | Bipolar subjects                          | 8        | 13.67 (2.91)            | 39  | 16.87 (1.86)            | 43  | 13.29 (1.91)            | 1.70 | 0.20 | A, S                         |
|                      | Healthy subjects (relatives and controls) | 13       | 10.41 (3.82)            | 55  | 14.59 (1.98)            | 79  | 14.67 (1.67)            | 0.56 | 0.57 | A, L, S                      |
| TMT B-A <sup>c</sup> | Total                                     | 31       | 53.98 (7.15)            | 119 | 56.44 (3.79)            | 154 | 54.22 (3.40)            | 0.12 | 0.89 | A, L, G                      |
|                      | Schizophrenic subjects                    | 10       | 70.90 (17.28)           | 22  | 71.83 (12.05)           | 29  | 73.08 (10.61)           | 0.01 | 0.99 | A, L                         |
|                      | Bipolar subjects                          | 8        | 73.10 (11.27)           | 40  | 69.86 (7.62)            | 42  | 61.28 (8.33)            | 0.61 | 0.55 | A, L                         |
|                      | Healthy subjects (relatives and controls) | 13       | 38.76 (7.27)            | 57  | 43.74 (3.74)            | 83  | 46.73 (3.19)            | 0.61 | 0.54 | A, L, G                      |

<sup>a</sup> Covar. retained = covariables retained in the final regression model; A= age, L=education level, G= group, S=sex (the interaction factor genotype x group was not significant for any of the analyses);

<sup>b</sup> Number of perseverative errors on the WCST

<sup>c</sup> Difference between times to complete parts B and A of the TMT

**Table VI.** Influence of the Val158Met polymorphism of the COMT gene on Trail Making Test (TMT) A and B results

| Test               | Sample                                    | Genotype |                         |         |                         |         |                         | F    | p    | Covar. retained <sup>a</sup> |
|--------------------|---|----------|-------------------------|---------|-------------------------|---------|-------------------------|------|------|------------------------------|
|                    |   | Met/Met  |                         | Met/Val |                         | Val/Val |                         |      |      |                              |
|                    |   | N        | Least square means (SE) | N       | Least square means (SE) | N       | Least square means (SE) |      |      |                              |
| TMT A <sup>b</sup> | Total                                     | 69       | 42.68 (1.82)            | 172     | 40.23 (1.24)            | 76      | 43.62 (1.74)            | 1.81 | 0.17 | A, L, G                      |
|                    | Schizophrenic subjects                    | 17       | 55.47 (4.01)            | 35      | 45.63 (2.78)            | 14      | 52.20 (4.41)            | 2.3  | 0.11 | A, L                         |
|                    | Bipolar subjects                          | 29       | 43.96 (2.85)            | 44      | 39.63 (2.33)            | 20      | 42.92 (3.43)            | 0.76 | 0.47 | A                            |
|                    | Healthy subjects (relatives and controls) | 23       | 34.56 (2.59)            | 93      | 37.31 (1.46)            | 42      | 39.15 (2.09)            | 1.01 | 0.38 | A, L, G                      |
| TMT B <sup>c</sup> | Total                                     | 69       | 98.73 (5.50)            | 172     | 91.85 (3.65)            | 76      | 103.93 (5.23)           | 2.20 | 0.12 | A, L, G, S                   |
|                    | Schizophrenic subjects                    | 17       | 129.15 (15.01)          | 35      | 110.84 (10.40)          | 14      | 142.61 (16.47)          | 1.49 | 0.23 | A, L                         |
|                    | Bipolar subjects                          | 29       | 107.76 (9.88)           | 44      | 106.42 (8.39)           | 20      | 105.37 (10.81)          | 0.02 | 0.98 | A, L                         |
|                    | Healthy subjects (relatives and controls) | 23       | 82.19 (6.24)            | 93      | 80.20 (3.47)            | 42      | 89.26 (5.00)            | 1.37 | 0.27 | A, L, G, S                   |

<sup>a</sup> Covar. retained = covariables retained in the final regression model; A= age, L=education level, G= group, S=sex (the interaction factor genotype x group was not significant for any of the analyses);

<sup>b</sup> Time to complete Trail A

<sup>c</sup> Time to complete Trail B

**Table VII.** Influence of the C-182T polymorphism of the NET gene on Trail Making Test (TMT) A and B results

| Test               | Sample                                    | Genotype |                         |     |                         |     |                         | F    | p    | Covar. retained <sup>a</sup> |
|--------------------|---|----------|-------------------------|-----|-------------------------|-----|-------------------------|------|------|------------------------------|
|                    |   | C/C      |                         | C/T |                         | T/T |                         |      |      |                              |
|                    |   | N        | Least square means (SE) | N   | Least square means (SE) | N   | Least square means (SE) |      |      |                              |
| TMT A <sup>b</sup> | Total                                     | 34       | 43.72 (2.57)            | 126 | 39.92 (1.40)            | 140 | 42.74 (1.38)            | 1.67 | 0.19 | A, L, G                      |
|                    | Schizophrenic subjects                    | 6        | 55.19 (6.91)            | 22  | 46.52 (3.51)            | 31  | 51.64 (3.02)            | 0.89 | 0.42 | A, L                         |
|                    | Bipolar subjects                          | 11       | 45.19 (4.68)            | 36  | 40.26 (2.58)            | 43  | 42.71 (2.35)            | 0.50 | 0.61 | A                            |
|                    | Healthy subjects (relatives and controls) | 17       | 37.77 (3.22)            | 68  | 36.31 (1.68)            | 66  | 38.07 (1.82)            | 0.34 | 0.72 | A, L, G                      |
| TMT B <sup>c</sup> | Total                                     | 34       | 90.44 (7.67)            | 126 | 98.73 (4.16)            | 140 | 94.91 (4.07)            | 0.56 | 0.58 | A, L, G                      |
|                    | Schizophrenic subjects                    | 6        | 94.00 (25.72)           | 22  | 139.10 (13.10)          | 31  | 115.29 (11.26)          | 1.57 | 0.22 | A, L                         |
|                    | Bipolar subjects                          | 11       | 102.8 (14.34)           | 36  | 110.99 (8.81)           | 43  | 104.37 (8.63)           | 0.26 | 0.77 | A, L                         |
|                    | Healthy subjects (relatives and controls) | 17       | 85.30 (7.67)            | 68  | 81.43 (4.01)            | 66  | 80.26 (4.33)            | 0.17 | 0.84 | A, L, G                      |

<sup>a</sup> Covar. retained = covariables retained in the final regression model; A= age, L=education level, G= group, S=sex (the interaction factor genotype x group was not significant for any of the analyses);

<sup>b</sup> Time to complete Trail A

<sup>c</sup> Time to complete Trail B

**Table VIII.** Influence of the A1287G polymorphism of the NET gene on Trail Making Test (TMT) A and B results

| Test               | Sample                                    | Genotype |                         |     |                         |     |                         | F    | p    | Covar. retained <sup>a</sup> |
|--------------------|---|----------|-------------------------|-----|-------------------------|-----|-------------------------|------|------|------------------------------|
|                    |   | A/A      |                         | A/G |                         | G/G |                         |      |      |                              |
|                    |   | N        | Least square means (SE) | N   | Least square means (SE) | N   | Least square means (SE) |      |      |                              |
| TMT A <sup>b</sup> | Total                                     | 31       | 39.03 (2.57)            | 119 | 42.70 (1.43)            | 154 | 41.21 (1.32)            | 1.00 | 0.37 | A, L, G                      |
|                    | Schizophrenic subjects                    | 10       | 52.70 (5.32)            | 22  | 50.43 (3.68)            | 29  | 47.03 (3.19)            | 0.51 | 0.60 | A, L                         |
|                    | Bipolar subjects                          | 8        | 35.74 (5.38)            | 40  | 41.17 (2.41)            | 42  | 42.85 (2.35)            | 0.75 | 0.48 | A                            |
|                    | Healthy subjects (relatives and controls) | 13       | 32.03 (3.38)            | 57  | 39.29 (1.82)            | 83  | 37.40 (1.57)            | 2.04 | 0.15 | A, L, G                      |
| TMT B <sup>c</sup> | Total                                     | 31       | 92.47 (8.00)            | 119 | 98.71 (4.32)            | 154 | 95.28 (3.92)            | 0.34 | 0.71 | A, L, G                      |
|                    | Schizophrenic subjects                    | 10       | 122.48 (20.43)          | 22  | 121.99 (14.13)          | 29  | 121.66 (12.23)          | 0.00 | 0.99 | A, L                         |
|                    | Bipolar subjects                          | 8        | 114.53 (16.66)          | 40  | 111.88 (8.41)           | 42  | 103.36 (8.94)           | 0.45 | 0.64 | A, L                         |
|                    | Healthy subjects (relatives and controls) | 13       | 71.80 (8.26)            | 57  | 82.64 (4.36)            | 83  | 83.97 (3.73)            | 0.94 | 0.40 | A, L, G                      |

<sup>a</sup> Covar. retained = covariables retained in the final regression model; A= age, L=education level, G= group, S=sex (the interaction factor genotype x group was not significant for any of the analyses);

<sup>b</sup> Time to complete Trail A

<sup>c</sup> Time to complete Trail B