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Familial resemblance for executive functions in families of schizophrenic and bipolar patients

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Abstract

Executive dysfunctions are considered to be putative markers of familial/genetic vulnerability to both schizophrenia and bipolar disorder. However, familial resemblance must be demonstrated before executive functions are used as a potential endophenotype. The aim of this study was to investigate familial resemblance for executive functions in families of schizophrenic and bipolar subjects. We assessed executive functions by means of two tests – the Wisconsin Card Sorting Test (WCST) and the Trail Making Test (TMT) - in 351 subjects from five populations: schizophrenic patients, bipolar patients, a group of relatives for each patient group and controls. For both tests, cognitive assessment results were consistent with previous studies: schizophrenic patients showed the greatest impairment, followed by bipolar patients and then the two groups of relatives. In families of bipolar patients we observed familial resemblance for the WCST and part A and part B of the TMT. However, by contrast with the classical point of view, considering executive measures to be markers of genetic vulnerability to schizophrenia, we did not demonstrate familial resemblance for either of the two executive tests in families of schizophrenic patients. Thus, executive measures, as assessed by WCST or TMT, should not be used as endophenotypes in genetic studies of schizophrenia unless confounders are identified and their effects eliminated.

Key-words: executive dysfunction, genetics, endophenotype, cognition

Introduction

Despite the existence of strong evidence for a genetic component in schizophrenia and bipolar disorder, no single gene has convincingly been shown to increase the risk for those disorders. One reason for this is the complexity of psychiatric disorders at the clinical and etiological level. Several authors (Gottesman and Shields, 1973; Leboyer *et al.*, 1998; Freedman *et al.*, 1999; Leboyer, 2003) have advocated the use of the endophenotype approach to circumvent this problem. Endophenotypes are measurable traits, associated with the liability to the disorder and having a simple genetic determinism. As such, they provide a means of reducing clinical and genetic heterogeneity in psychiatric research. Gottesman and Gould (2003) recently summarized criteria for a good (i.e. an useful) endophenotype as follows : a) associated with illness, b) more frequent in non-affected relatives than in general population, c) heritable and d) associated with a candidate gene or gene region. Several authors have suggested that measures of executive functions (EF) could be used as endophenotypes in schizophrenia and bipolar research. EF are cognitive processes that allow the subject to adapt to unusual situations in which automated responses are not sufficient. Among various tests that are used to assess EF, the Wisconsin Card Sorting Test (WCST) and the Trail Making Test (TMT) are of particular interest as they are well standardized and widely used and could represent, at least in families of schizophrenic probands, markers of two distinct risk factors (Yurgelun-Todd and Kinney 1993). Using these two tests, executive dysfunctions were repeatedly found in schizophrenic patients (Koren *et al.* 1998, Bustini *et al.* 1999, Laurent *et al.* 2000), and impairment has also been detected in most studies concerning bipolar patients (Coffman *et al.* 1990, Morice 1990, Ferrier *et al.* 1999), although some exceptions are known (Rubinsztein *et al.* 2000). Several studies of relatives of schizophrenic or bipolar patients have investigated whether executive dysfunctions could be used as a marker of familial vulnerability. Recently, two meta-analyses (Sitskoorn *et al.* 2004, Szöke *et al.* 2005) showed

that relatives of schizophrenic patients have impaired performances on tests of executive functions. The impairments observed were less severe than those observed in patients. Fewer studies have compared the relatives of bipolar patients with controls (Kremen *et al.* 1998, Keri *et al.* 2001) and no firm conclusions can be drawn from the results obtained in these studies. In a previous study, we (Zalla *et al.* 2004) found no significant difference in WCST or TMT scores between relatives of bipolar patients and controls. However, this may reflect the limited statistical power of the study, due to small sample sizes.

The heritability of executive impairments was assessed by calculating relative risk in siblings of schizophrenic patients (Egan *et al.* 2001a). In this population, the authors found an increased risk of impaired performance in Trails B and WCST (4.0 and 2.0 respectively). However, relative risk is not a direct measure of heritability. Instead, as pointed out by Egan *et al.* (2001a) it assesses its upper limit.

Based on these results and on the hypothesis linking EF and catechol-O-methyl transferase (COMT) activity (see Weinberger *et al.* 2001 for further discussion), several studies have looked for an association between executive dysfunctions and COMT gene polymorphisms in schizophrenic patients and their relatives. The Val158Met functional polymorphism of the COMT gene was found to affect WCST performance if schizophrenic patients and controls were pooled together (Egan *et al.* 2001b, Joover *et al.* 2002), but not if schizophrenic patients were assessed separately (Rosa *et al.* 2002, Bilder *et al.* 2002, Ho *et al.* 2005). This effect was also found in the siblings of schizophrenic patients in one study (Rosa *et al.* 2002) but not in another (Egan *et al.* 2001b). It was also found in healthy volunteers (Malhotra *et al.* 2002). In bipolar subjects, a positive association was found between WCST performance and a polymorphism (Val66Met) of another candidate gene, the brain-derived neurotrophic factor (BDNF) gene (Rybakowski *et al.* 2003). Inconsistencies in the results of association studies

using WCST score as the endophenotype may be accounted for by as yet unidentified confounders, which could limit the value of EF as an endophenotype.

The aim of our study was to investigate the causes of discrepancies between the promising results of studies showing impairments in patients and their relatives and the disappointing results of association studies. To do this we assessed familial resemblance for performances on two widely used tests of EF – the WCST and the TMT - in families of schizophrenic and bipolar patients. Familial resemblance, which, unlike relative risk, is sensitive to incorrect individual evaluation and classification (i.e. to confounders not accounted for), is an indicator of actual heritability and, as such, is a more stringent indicator of the usefulness of a putative endophenotype for genetic research.

Discrepancies between studies investigating executive dysfunctions may be partly explained by differences in inclusion criteria for bipolar patients (euthymic or not), for relatives (including or excluding affected relatives) and for controls (including or excluding controls with a positive family history). To limit the probability of identifying spurious differences due to the inclusion of acutely ill patients and of false negative results due to “fuzzy” borders between groups, we used strict inclusion criteria. We included only patients in remission and excluded subjects presenting a personal history of psychotic or bipolar disorders from the non-patient groups, and subjects with affected first-degree relatives from the control group.

Methods

Subjects

Patients meeting DSM-IV (American Psychiatric Association, 1994) criteria for bipolar disorder or schizophrenia were consecutively recruited at two university-affiliated hospitals (the Pitié-Salpêtrière and Albert Chenevier hospitals, Paris). They were included in the study

just before discharge. To confirm the diagnosis of bipolar disorder or schizophrenia in probands, patients were interviewed by an experienced psychiatrist with the French version of the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger *et al.*, 1996; Preisig *et al.*, 1999). First-degree relatives of patients were also contacted and asked to participate in the study. Relatives were interviewed with the DIGS to exclude those presenting psychotic or bipolar disorder. Relatives which met criteria for schizophrenia or bipolar disorder were included in the patients groups. Familial psychiatric morbidity was also investigated using the Family Interview for Genetic Studies (FIGS) (Maxwell, 1992). A complete family history of first-degree relatives was obtained from each proband and from at least one first-degree relative. The information was supplemented, if required, with data from the medical case notes.

Healthy controls were blood donors at the Pitié-Salpêtrière Hospital. Controls were included after being interviewed with the DIGS and the FIGS to confirm the absence of a personal and family history of DSM IV axis I or II disorders.

For inclusion in the study, all subjects (patients, relatives and controls) had to be normothymic, as evaluated by the Montgomery and Asberg depression rating scale (MADRS) (Montgomery and Asberg, 1979) and the Bech and Rafaelsen mania rating scale (MAS) (Bech *et al.*, 1978). Schizophrenic and bipolar patients were also required to be in a stable state, with no change in medication or symptoms for at least two weeks before cognitive evaluation. All patients and some of the relatives were medicated at the time of cognitive assessment. No inclusion or exclusion criteria based on medication were used and as a consequence individual prescriptions varied widely in dosage, number of different molecules and type of medication (antipsychotics – classical or atypical, mood stabilizers, antidepressants, anxiolytics, anticholinergic agents etc.) For this reason description of medication for each subject could not be done in a homogeneous way and was not recorded.

This is the usual situation in studies using cognitive measures as putative endophenotypes in unselected samples of schizophrenic subjects (for example Egan et al 2001, Ho et al 2005). Patients and relatives were included only if they were aged between 18 and 60 years, and had no history of neurological disease or current substance abuse.

The research ethics board of Salpêtrière Hospital reviewed and approved the study. The study was described in detail to the subjects, who then gave written informed consent for participation.

In this study, we included also 137 subjects (25 schizophrenic patients, 22 relatives of schizophrenic patients, 37 bipolar patients, 33 relatives of bipolar patients and 20 controls), for whom cognitive evaluation, with a larger battery of cognitive tests, has already been reported (Zalla *et al.* 2004).

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 remained.

The two measures most often used to assess WCST performance are the number of categories completed and number of perseverative errors. However, as the number of categories shows an important ceiling effect, the only measure we used in our analysis was number of perseverative errors.

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.

In this study we used three measures derived from the TMT : time to complete Part A, time to complete Part B and the difference between the two parts of the test (time B-A) The time taken to complete Part A depends mainly on visual scanning and motor speed. Because Part B of the TMT is influenced by cognitive flexibility the time taken to complete Part B is considered a measure of EF. The difference between the two parts of the test is used to eliminate performance variation due to psychomotor speed (Lezak 1995), and the resulting value is considered a more specific measure of EF.

Statistical methods

Group comparison, for executive performances, was done by analysis of covariance (ANCOVA), with sex, age, and study level used as the covariates. Bilateral comparisons of interest (between schizophrenic and bipolar patients, between the groups of patients and their respective relatives, between the two groups of relatives and between controls and each of the other groups) were carried out using contrasts. We used Bonferroni correction for eight comparisons to reduce type I errors due to multiple tests, setting the threshold for significant results at 0.00625.

Familial resemblance was assessed in families for which two or more members, affected or not, had completed the cognitive tests. To ensure that this assessment was independent of factors likely to influence cognitive performance, we calculated residuals by subtracting the predicted performance from the actual performance. Performance was predicted by means of a generalized linear model in which we included all significant explanatory variables.

Finally, we carried out an ANOVA, with family membership as an independent variable, to assess the effect of family membership on the residuals calculated in the previous step. This procedure was used for the total sample and separately for schizophrenic and bipolar families.

All analyses were carried out with the SAS[®] V8 package.

Results

The final sample consisted of 351 subjects: 74 schizophrenic patients, 68 of their relatives, 97 bipolar patients, 64 of their relatives and 48 controls. Their demographic characteristics are summarized in Table 1. Highest completed school grade was recorded, according to the usual conventions (Pichot *et al.* 1993) as a trichotomous variable (1 = elementary school; 3 = at least high school completed; 2 = intermediate between 1 and 3). However, as no level 1 subjects were present in three groups and as such subjects were also rare in the other groups, we decided to pool the first two levels together in subsequent analysis.

Insert Table 1

The results of cognitive assessment are summarized in table 2.

Insert Table 2.

Familial resemblance was assessed in 75 families (37 schizophrenic and 38 bipolar pedigrees), for a total of 196 subjects.

TMT

As sex had no significant effect on any of the TMT scores, all comparisons were adjusted only for age and school grade.

Part A. Significant differences were found between groups ($p < 0.0001$). Schizophrenic patients differed significantly from their relatives ($p < 0.0001$), from bipolar patients ($p = 0.0004$) and from controls ($p < 0.0001$) and bipolar patients differed significantly from controls ($p < 0.0001$). No significant difference emerged in comparisons of the groups of relatives with controls or of bipolar patients and their relatives.

Familial resemblance was significant in the total sample ($F = 1.51$, $df = 72$, $p = 0.025$) and in BP pedigrees ($F = 2.37$, $df = 36$, $p = 0.0017$), but not in schizophrenic pedigrees ($F = 0.83$, $df = 36$, $p = 0.72$).

Part B. The five groups significantly differed in their results ($p < 0.0001$). Contrasts showed that schizophrenic subjects had significant impairments when compared to their relatives ($p < 0.0001$), controls ($p < 0.0001$) and bipolar subjects ($p < 0.0001$). Significant differences were also observed when controls were compared to bipolar patients ($p < 0.0001$), with relatives of schizophrenic subjects ($p = 0.0018$) and with relatives of bipolar subjects ($p = 0.0045$)

For part B of the TMT there was no significant familial resemblance in the total sample ($F = 1.32$, $df = 72$, $p = 0.093$) or in schizophrenic pedigrees ($F = 1.11$, $df = 36$, $p = 0.36$). However in BP pedigrees significant familial resemblance was observed ($F = 1.86$, $df = 36$, $p = 0.017$).

B-A difference. Significant differences were found between groups ($p < 0.0001$). Schizophrenic patients differed significantly from their relatives ($p = 0.0006$), from bipolar patients ($p = 0.0053$) and from controls ($p < 0.0001$) and bipolar patients differed significantly from controls ($p = 0.0005$). No significant difference emerged in comparisons of the groups of relatives with controls or of bipolar patients and their relatives.

We found no statistically significant familial resemblance in executive performance, assessed as the difference between Trail B and Trail A results, in the total sample ($F = 1.17$, $df = 72$, $p = 0.22$) or in the schizophrenic ($F = 1.13$, $df = 36$, $p = 0.43$) and bipolar ($F = 1.33$, $df = 36$, $p = 0.20$) pedigrees assessed independently.

WCST

Sex had no significant effect on perseverative errors scores in the WCST. ANCOVA adjusted for age and school grade showed significant differences between the five groups ($p < 0.0001$).

Bilateral comparisons revealed that schizophrenic patients differed from their relatives ($p = 0.0028$), from bipolar patients ($p = 0.0013$) and from controls ($p < 0.0001$). No significant difference was identified between bipolar patients and control, between groups of relatives and controls or between bipolar patients and their relatives.

For the number of perseverative errors, we found a familial resemblance in the total sample ($F = 1.79$, $df = 71$, $p = 0.003$) and in BP pedigrees ($F = 2.94$, $df = 36$, $p = 0.0001$), but not in schizophrenic pedigrees ($F = 1.14$, $df = 35$, $p = 0.76$).

One possible reason for the negative results obtained when assessing familial resemblance for EF in schizophrenic families, in contrast with significant familial resemblance in bipolar families for TMT B and WCST is that the models used to predict performances on those tests are not as good for schizophrenic as for bipolar pedigrees. We therefore calculated the SD of residuals as a rough estimate of the fit of the models. For the WCST the values obtained for this estimator were higher for schizophrenic patients (21.0) than for the three other groups (16.1 for schizophrenic relatives, 15.7 for bipolar relatives and 12.6 for bipolar patients). Similar results were obtained for the TMT B (59.7 in schizophrenic patients, 30.1 in their relatives, 43.8 for bipolars and 31.8 in the group of relatives of bipolar patients) thus suggesting that the models used may predict performance less accurately for schizophrenic patients.

Discussion

By contrast with the classical point of view considering executive dysfunctions to be markers of genetic vulnerability to schizophrenia, we did not demonstrate familial resemblance for two widely used tests (WCST and Trail) in the families of schizophrenic patients. However, we observed familial resemblance for WCST and for Trails A and B performances in BP families.

The lack of familial resemblance within the families of schizophrenic patients was unexpected as there is strong evidence for executive dysfunction in schizophrenic patients (Heinriks and Zakzanis 1998, Johnson-Selfridge and Zalewski 2001) and their relatives (Snitz *et al.* 2003, Szöke *et al.* 2005). There are two possible explanations for our findings: either performances in these two tests are not influenced by familial factors, or the limitations of our study prevented us from demonstrating familial resemblance. Several lines of evidence from this and previous studies suggest that the two EF tests used are influenced by familial factors. First, impairments have been demonstrated in the relatives of schizophrenic patients for both TMT and WCST in most studies and have been validated by a meta-analysis of published data (Szöke *et al.* – 2005). Second, several studies using the WCST as an endophenotype have demonstrated associations between candidate genes (COMT or BDNF) in general population (Malhotra *et al.* 2002), in bipolar patients (Rybakowski *et al.* 2003), and in the relatives of schizophrenic patients (Rosa *et al.* 2002), but not in schizophrenic probands (Rosa *et al.* 2002, Bilder *et al.* 2002, Ho *et al.* 2005). Finally, we observed, in this study, familial resemblance in the families of bipolar patients. Thus, performances in EF tests, as shown by these data obtained in different populations, are clearly influenced by familial factors. However, we detected no familial resemblance in the families of schizophrenic patients. This apparent discrepancy may be accounted for by several potential limitations of this study.

First, our sample of relatives may be unrepresentative as not all the relatives approached agreed to participate in the study. Familial resemblance for EF may therefore be obscured because the relatives included may be preferentially those who do not carry the cognitive endophenotype and may have EF measures similar to controls. This seems unlikely as our results for controls and relatives are similar to those already published in the literature. A lack of statistical power may also account for the lack of detection of familial resemblance in schizophrenic families, but this also seems unlikely as we obtained significant results for bipolar families with a similar sample size. Finally, confounders not accounted for in our study may explain this negative result. The absence of familial resemblance for WCST in schizophrenic families may result from some sources of heterogeneity in executive performances not being taken into account, in particular in probands. Indeed, the SD of residuals were larger in schizophrenic probands than in the other groups of subjects. Further support for this hypothesis is provided by the observation that, if WCST score is used as an endophenotype in association studies, positive results are obtained in BP patients (Rybakowski *et al.* 2003), in general population (Malhotra *et al.* 2002), in the relatives of schizophrenic patients (Rosa *et al.* 2002) and in mixed samples (Egan *et al.* 2001b, Joover *et al.* 2002) but not in schizophrenic probands alone (Egan *et al.* 2001b, Bilder *et al.* 2002, Rosa *et al.* 2002, Joover *et al.* 2002, Ho *et al.* 2005). Altogether, we suggest that confounding factors usually not taken into account influence executive measures in patients with schizophrenia and could be the cause of negative association studies. These potential confounders in schizophrenic patients may include treatment, illness duration, motivation and symptoms. In a meta-analysis of EF studies in schizophrenic patients, Johnson-Selfridge and Zalewski (2001) found that positive and negative symptoms and number of hospital admissions influenced EF. In future studies testing cognitive endophenotypes as markers of vulnerability to schizophrenia, such variables should therefore be taken into account.

Another potential problem concerns the statistical methods. Different methods could be used to calculate the residuals. First, normative data from large normal samples are available (for example Taubaugh 2004, Drane et al 2002) and could be used to calculate residuals. However, there is not enough evidence to support the use of these data in pathological samples and/or in their relatives.

Another method consists in calculating separate residual curves for each sample (schizophrenic subjects, bipolar and their relatives). To be reliable such method necessitate large individual samples, not usually available.

In our study we used all available subjects to calculate the influence of demographic and diagnostic variables. This is the method usually used in studies on cognition in schizophrenic and bipolar subjects and their relatives (see for example Laurent et al 1999, Krabbendam et al. 2001). We chose this method because our aim was to assess if cognitive measures, as currently used, are good potential endophenotypes. Further studies are needed to evaluate the impact of the different methods used to calculate the influence of demographic variables in non-normal samples.

We detected familial resemblance for WCST in BP families. Nevertheless, two caveats should be placed on the use of this measure as an endophenotype in genetic studies of bipolar disorder. The first is that the origin of familial resemblance may be genetic and/or environmental. Larger samples, and possibly particular types of samples (e.g. adoptees) are required to separate these two types of effect. A more important limitation is that, to date, few data are available supporting the association of executive dysfunctions with bipolar disorder and, especially, the presence of impairments in relatives. In our study, differences between controls and bipolar patients and between controls and relatives of bipolar patients were not statistically significant for the WCST. Although previous studies (reviewed in Quraishi and Frangou 2002) have suggested that bipolar patients display mild impairments in both WCST

and TMT, three studies using these tests found no difference between the relatives of bipolar patients and controls (Kremen *et al.* 1998, Keri *et al.* 2001, Zalla *et al.* 2004). This suggests that impairment may be more state- than trait-related.

The absence of familial resemblance for the TMT the B-A difference in bipolar families suggests that either this measure of EF is not subject to familial influence, or the familial effect is obscured by confounders that do not influence WCST results. This suggests that these two measures of EF have different determinants.

The separate analyses of Trails A and B provided significant familial resemblance in bipolar families. These results and the negative result for the B-A difference suggest that visual scanning and motor processes, but not cognitive flexibility, are influenced by familial factors. As for WCST results, more research is needed before scores of Trail A and B could be considered potential endophenotypes for bipolar disorder.

In conclusion, in this study we did not find familial resemblance in families of schizophrenic subjects for two measures of EF considered as potential endophenotypes. This negative result was observed using the usual methods for the inclusion of subjects and for the statistical analysis of data. This implies that efforts have to be made to address the present methodological limitations before these EF measures could be successfully used as endophenotypes in schizophrenia research.

In contrast in bipolar families several cognitive measures (TMT part A and B, perseverative errors on the WCST) showed familial resemblance. Before they could be considered potential for bipolar disorder more research is needed to establish the association between executive dysfunction and vulnerability to bipolar disorder.

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References

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association, 1994.

Bech P., Bolwig T.G., Kramp P., Rafaelsen O.J. 1979. The Bech-Rafaelsen Mania Scale and the Hamilton Depression Scale. *Acta Psychiatrica Scandinavica* 59, 420-430.

Bilder R.M., Volavka J., Czobor P., Malhotra A.K., Kennedy J.L., Ni X., Goldman R.S., Hoptman M.J., Sheitman B., Lindenmayer J.-P., Citrome L., McEnvoy J.P., Kunz M., Chakos M., Cooper T.B., Lieberman J.A. 2002. Neurocognitive correlates of COMT Val158Met polymorphism in chronic schizophrenia. *Biological Psychiatry*. 52, 701-707.

Bustini M., Stratta P., Daneluzzo E., Pollice R., Prosperini P., Rossi A. 1999. Tower of Hanoi and WCST performance in schizophrenia: problem-solving capacity and clinical correlates. *Journal of Psychiatry Research* 33, 285-290.

Coffman J.A., Bornstein R.A., Olson S.C., Schwarzkopf S.B., Nasrallah H.A. 1990. Cognitive impairment and cerebral structure by MRI in bipolar disorder. *Biological Psychiatry*. 27, 1188 – 1196.

Drane et al 2002

Egan M.F., Goldberg T.E., Gsheidle T., Bigelow L.B., Weinberger D.R. 2001a. Relative risk for cognitive impairments in siblings of patients with schizophrenia. *Biological Psychiatry* 50, 98-107.

Egan M.F., Goldberg T.E., Kolachana B.S., Callicott J.H., Mazzanti C.M., Straub R.E., Goldman D., Weinberger D.R. 2001b. Effect of COMT Val108/158 Met genotype on frontal

lobe function and risk for schizophrenia. *Proceedings of the National Academy of Science USA*. 98, 6917-6922.

Ferrier I.N., Stanton B.R., Kelly T.P., Scott J. 1999. Neuropsychological function in euthymic patients with bipolar disorder. *British Journal of Psychiatry*. 175, 246-251.

Franke P., Maier W., Hardt J., Hain C. 1993. Cognitive functioning and anhedonia in subjects at risk for schizophrenia. *Schizophrenia Research* 10, 77-84.

Freedman R., Adler L.E., Leonard S. 1999. Alternative phenotypes for the complex genetics of schizophrenia. *Biological Psychiatry*. 45, 551-558.

Gottesman I.I., Gould T.D. 2003 The endophenotype concept in psychiatry: etymology and strategic intentions. *American Journal of Psychiatry*. 160, 636-645.

Gottesman I.I., Shields J., 1973. Genetic theorizing and schizophrenia. *British Journal of Psychiatry* 122, 15-30.

Heaton R. 1981. *The Wisconsin Card Sorting Test manual*. Psychological Assessment Resources, Odessa, FL;

Heinrichs R. W., Zakzanis K.K. 1998. Neurocognitive deficit in schizophrenia: a quantitative review of evidence. *Neuropsychology*. 12, 426-445.

Ho B, Wassink TH, O'Leary DS, Sheffield VC, Andreasen NC. 2005. Catechol-O-methyltransferase Val (158) Met gene polymorphism in schizophrenia: working memory, frontal lobe MRI morphology and frontal cerebral blood flow. *Molecular Psychiatry* 10, 287-298.

Johnson-Selfridge M., Zalewski C. 2001. Moderator variables of executive functioning in schizophrenia: meta-analytic findings. *Schizophrenia Bulletin*. 27, 305-316.

Joober R., Gauthier J., Lal S., Bloom D., Lalonde P., Rouleau G., Benkelfat C, Labelle A. 2002. Catechol-O-Methyltransferase Val- 108/158 – Met gene variants associated with performance on the Wisconsin Card Sorting Test. *Archives of General Psychiatry*. 59, 662.

Keri S., Kelemen O., Benedek G., Janka Z. 2001. Different trait markers for schizophrenia and bipolar disorder: a neurocognitive approach. *Psychological Medicine* 31, 915-922.

Koren D., Seidman L.J., Harrison R.H., Lyons M.J., Kremen W.S., Caplan B., Goldstein J.M., Faraone S.V., Tsuang M.T. 1998. Factor structure of the Wisconsin Card Sorting Test: dimensions of deficit in schizophrenia. *Neuropsychology*. 12, 289-302.

Krabbendam

Kremen WS, Faraone SV, Seidman LJ, Pepple JR, Tsuang MT. 1998. Neuropsychological risk indicators of schizophrenia: a preliminary study of female relatives of schizophrenic and bipolar probands. *Psychiatry Research* 79, 227-240.

Laurent et al 1999,

Laurent A, Biloa-Tang M, Bougerol T, Duly D, Anchisi AM, Bosson JL, Pellat J, d'Amato T, Dalery J. 2000. Executive/attentional performance and measures of schizotypy in patients with schizophrenia and in their nonpsychotic first-degree relatives. *Schizophr Research* 46, 269-283.

Leboyer M., 2003. Searching for alternative phenotypes in psychiatric genetics. *Methods in Molecular Medicine* 77, 145-161.

Leboyer M., Bellivier F., Nosten-Bertrand M., Jouvent R., Pauls D., Mallet J. 1998. Psychiatric genetics: search for phenotype. *Trends in Neurosciences*. 21, 102-105.

Lezak M.D. 1995. *Neuropsychological assessment*. 3th ed., Oxford University Press, Oxford.

Malhotra A.K., Kestler L.J., Mazzanti C., Bates A.J., Goldberg T., Goldman D. 2002. A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. *American Journal of Psychiatry*. 159, 652-654.

Maxwell M.E., 1992 Family Interview for genetic Studies. Clinical Neurogenetic Branch, Intramural Research Program, NIMH

Montgomery S.A., Asberg M. 1979. A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* 134, 382-389.

Morice R. 1990 Cognitive inflexibility in schizophrenia and mania. *British Journal of Psychiatry*. 157, 50-54.

Nurnberger J.I.Jr., Blehar M.C., Kaufmann C.A., York-Cooler C., Simpson S.G., Harkavy-Friedman J., Severe J.B., Malaspina D., Reich T. 1996. Diagnostic interview of genetic studies; rationale, unique features and training. *Archives of General Psychiatry*. 51, 249-259.

Pichot P., Lebeaux M.O., Penhouët C., Simon M. 1993. L'estimation du niveau intellectuel prémorbide à la WAIS-R. Comparaison entre ;a méthode de Barona et l'Index de détérioration de Wechsler. *Revue Européenne de Psychologie appliquée*. 43, 291-301.

Preisig M., Fenton B.T., Matthey M.L., Berney A., Ferrero F. 1999. Diagnostic interview for genetic studies (DIGS): inter-rater and test-retest reliability of the French version. *European Archives of Psychiatry and Clinical Neuroscience* 249, 174-179.

Quraishi S., Frangou S. 2002. Neuropsychology of bipolar disorder: a review. *Journal of Affective Disorders* 72, 209-226.

Reitan RM. & Wolfson D. (1985). *The Halstead-Reitan Neuropsychological test battery: theory and clinical interpretation.*, Neuropsychology Press, Tucson.

Rosa A., Zarzuela A., Cuesta M.J., Peralta V., Martinez-Larrea A., Serrano F., Fananas L. COMT gene variability and prefrontal neurocognitive functions in discordant sib pairs for schizophrenia spectrum disorder. *American Journal of Medical Genetics* 114, 867.

Rubinsztein J.S., Micahel A., Paykel E.S., Sahakian B.J. 2000. Cognitive impairment in remission in bipolar affective disorder. *Psychological Medicine* 30, 1025-1036.

Rybakowski J.K., Borkowska A., Czerski P.M., Skibinska M. Hauser J. 2003 Brain-derived neurotrophic gene polymorphism and prefrontal function in bipolar patients. *Bipolar Disorders*. 5, supplement 1, 78

Sitskoorn M.N., Aleman A., Ebisch S.J., Appels M.C., Kahn R.S. 2004 Cognitive deficits in relatives of patients of patients with schizophrenia: a meta-analysis. *Schizophrenia Research* 71, 285-295.

Snitz B.E., MacDonald A.W., Carter C.S. 2003 Cognitive impairments in adult first-degree relatives of schizophrenia patients: a meta-analytic review. *Schizophrenia Research (Supplement)*. 60, 158.

Stratta P., Daneluzzo E., Mattei P., Bustini M., Casacchia M., Rossi A. 1997. No deficit in Wisconsin Card Sorting Test performance of schizophrenic patients' first-degree relatives. *Schizophrenia Research*. 26, 147-151.

Szöke A., Schürhoff F., Mathieu F., Meary A, Ionescu S, Leboyer M. 2005 Tests of executive functions in first-degree relatives of schizophrenic patients – a meta-analysis. *Psychological Medicine*. 35, 771 – 782.

Taubaug 2004,

Weinberger D.R., Egan M.F., Bertolino A., Callicott J.H., Mattay V.S., Lipska B.K., Berman K.F., Goldberg T.E., 2001 Prefrontal neurons and the genetics of schizophrenia. *Biological Psychiatry* 50, 825 – 844.

Wolf L. E., Cornblatt B.A., Roberts S.A., Maminski Shapiro B., Erlenmeyer-Kimling L. 2002. Wisconsin Card Sorting deficits in offspring of schizophrenics in the New York high-risk project. *Schizophrenia Research*. 57: 173-82.

Yurgelun-Todd D.A., Kinney D.K. 1993. Patterns of neuropsychological deficits that discriminate schizophrenic individuals from siblings and control subjects. *Journal of Neuropsychiatry and Clinical Neuroscience* 5, 294-300.

Zalla T., Joyce C., Szöke A., Schürhoff F., Pillon B., Komano O., Perez-Diaz F., Bellivier F., Alter C., Dubois B., Rouillon F., Houdé O., Leboyer M. 2004. Executive dysfunctions as potential markers to bipolar disorders and schizophrenia. *Psychiatry Research* 121, 207-217.

Laurent, A., Moreaud, O., Bosson, J.L., Naegele, B., Boucharlat, J., Saoud, M., d'Amato, T., Dalery, J. (1999). Neuropsychological functioning among non-psychotic siblings and parents of schizophrenic patients. *Psychiatry Research* **87**,147-157.

Krabbendam, L., Marcelis, M., Delespaul, P., Jolles, J., van Os, J. (2001). Single or multiple familial cognitive risk factors in schizophrenia? *American Journal of Medical Genetics* **105**, 183-188.

Drane D.L., Yuspeh R.L., Huthwaite J.S., Klingler L.K. Demographic characteristics and normative observations for derived-trail making test indices. *Neuropsychiatry Neuropsychol Behav Neurol*. 2002 Mar;15(1):39-43

Table 1. Demographic characteristics of the five groups of subjects (schizophrenic patients, relatives of schizophrenic patients, bipolar patients, relatives of bipolar patients and controls)

	Schizophrenic patients	Relatives of schizophrenic patients	Bipolar patients	Relatives of bipolar patients	Controls	F (df)	p
N	73	67	95	63	48		
Age (mean +/- SD)	33.0 +/- 9.0 ^a	44.7 +/- 12.9 ^b	40.5 +/- 11.0	40.7 +/- 13.0	42.2 +/- 13.2	9.31 (4)	<0.0001
Sex (% men)	67.6 ^a	47.1	38.1	39.1	50.0	15.93 (4)	0.0031
Education (% high school)	41.9 ^a	79.4	86.6	82.8	62.5 ^a	48.59 (4)	<0.0001

a. significantly different, at 0.05 threshold, from the other groups;

b. significantly different, at 0.05 threshold, from the bipolar subjects

Table 2. Results of cognitive assessment, WCST and TMT, in the five groups of subjects (schizophrenic patients, relatives of schizophrenic patients, bipolar patients, relatives of bipolar patients and controls)

		Schizophrenic patients	Relatives of schizophrenic patients	Bipolar patients	Relatives of bipolar patients	Controls	F (df)	p
TMT	N	73	67	95	63	48		
	Part A (mean +/- SD) ^a	50.8 +/- 17.8 ^{b,c,d}	39.4 +/- 14.3	41.4 +/- 16.0 ^b	37.1 +/- 15.9	32.6 +/- 11.5	15.84 (7)	<0.00001
	Part B (mean +/- SD) ^a	123.4 +/- 67.0 ^{b,c,d}	85.1 +/- 35.0 ^b	88.7 +/- 47.8 ^b	78.3 +/- 33.7 ^b	63.4 +/- 24.1	23.27 (7)	<0.00001
	B-A (mean +/- SD) ^a	72.6 +/- 58.1 ^{b,c,d}	45.8 +/- 29.8	47.3 +/- 44.6 ^b	41.2 +/- 34.3	30.9 +/- 18.3	14.36 (7)	<0.00001
WCST	N	66	63	96	63	48		
	Perseverative errors (mean +/- SD) ^a	24.6 +/- 21.6 ^{b,c}	15.1 +/- 17.5	13.6 +/- 12.8	12.8 +/- 17.1	9.7 +/- 7.6	9.37 (7)	<0.00001

c. p for group effect < 0.0001,

d. significantly different, at 0.00625 threshold, from controls,

e. significantly different, at 0.00625 threshold, from their relatives

f. significantly different, at 0.00625 threshold, from bipolar patients