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ORIGINAL PAPER

# Heritability of Trail Making Test performance in multiplex schizophrenia families: implications for the search for an endophenotype

**Raúl Mendoza Quiñones · Yuranny Cabral Calderín · Mayelin Domínguez · Tania M. Bravo · Adnelys Reyes Berazaín · Alexander García · Antonio Caballero · Migdyrai Martín Reyes**

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**Abstract** The impairment of the Trail Making Test (TMT) performance as a measure of executive function deficits has been found both in patients with schizophrenia and in their unaffected first-degree relatives, suggesting that it might be considered as a familial vulnerability marker, but its heritability estimates are not well known. This study investigated the genetic heritability of impairments in TMT performance using a sample of 80 schizophrenia patients, 145 unaffected first-degree relatives and 127 healthy controls from families with multiple members with schizophrenia. Consistent with previous reports in the literature, relatives performed in between healthy controls and schizophrenia patients. Based on these results, a variance component-analysis provided small, but significant additive heritability estimates for performance indices relating performance in TMT-version A to TMT-version B. These results showed that this significant but small evidence of heritability on the one hand suggests an association with genetic predisposition to schizophrenia, but that TMT performance is also associated with epigenetic or environmental factors.

**Keywords** Schizophrenia · Heritability · Executive functions · Trail Making Test

R. M. Quiñones · Y. C. Calderín · M. Domínguez · T. M. Bravo · A. R. Berazaín · A. García · M. M. Reyes (✉)
Department of Biological Psychiatry, Cuban Neurosciences Center, 25th Avenue #15202, Cubanacán, P.O. Box 11600, Havana City, Cuba
e-mail: migdyrai@yahoo.com

A. Caballero
Department of Psychiatry, Galis García Hospital, Havana City, Cuba

## Introduction

Schizophrenia (SZ) is associated with a wide range of cognitive impairments, including attention, memory and executive functions as well as a general decline in intellectual functioning [1, 27, 38]. Family studies of schizophrenia have demonstrated that the deficit in executive functions as a measure of dysfunction of the frontal system could be genetically transmitted [4, 19, 31]. In addition, executive function impairments have also been found in unaffected first-degree relatives of probands with schizophrenia when compared with normal control groups suggesting that executive function abnormalities are likely to be produced by genes that increase the risk of the disorder [12, 20]. Accordingly, a number of studies over the past decade have looked for neuropsychological impairments in unaffected relatives of schizophrenia patients to identify quantitative traits that may be useful in increasing the power in genetic linkage and association studies of schizophrenia [11, 30, 33, 41]. In addition, the executive function deficit must be heritable to be considered as a potential vulnerability marker of schizophrenia or a putative endophenotype [16, 34].

Executive function impairment has been widely measured by the Trial Making Test (TMT) [14, 24, 26]. The test consists of two versions: TM-version A (TMA) and TM-version B (TMB). TMA is a measure of visuomotor sequencing involving connection of consecutive numbers randomly arranged on a page and TMB requires the connection of numbers and letters in alternating order. Both versions reflect attention, visual scanning, visuo-spatial memory, working memory for the target sequence, but TMB demands more working memory (keeping two target sequences ready instead of one) and also reflects cognitive flexibility and/or maintaining sets. In addition, TMB–TMA differences or

TMB/TMA ratio scores are proposed to be best indicators of executive control function [5, 24]. TMT deficits appear to reflect disruptions of higher cortical functions including those sensitive to frontal lobe damage [15]. As a component of executive functioning, set-shifting has been hypothesized to be under control of the prefrontal cortex [23]. Abnormal cortical function, particularly in the area of the frontal lobes, has long been recognized to be one important component of a broad spectrum of impairments seen in schizophrenia [22, 28]. Accordingly, Bonilha et al. [8] found a positive correlation between the decreases in gray matter volume with poorer performance of TMT, part B.

It has been consistently reported that schizophrenic patients perform worse than controls on the TMT, especially part B [1, 17, 29, 41]. On the other hand, the use of derived indices of the TMT, such as B–A has also produced positive results [5]. Brazo et al. [9] reported that schizophrenia patients performed significantly worse than healthy controls on TMB–TMA index independently of their predominant symptoms. In addition, several authors have shown that the unaffected relatives of schizophrenic patients also perform significantly worse than control subjects on the TMT [6, 12, 18, 35]. In general, these results have demonstrated that probands have longer response times than their unaffected siblings, who in turn have longer response times than normal subjects.

Regarding heritability, it can be defined as the proportion of phenotypic variance attributable to genetic variance across a particular population [2]. In schizophrenia, neuropsychological dysfunctions, particularly in working memory, have consistently shown to be heritable [7, 36]. However, in schizophrenia, there is a lack of studies on heritability of TMT. To our knowledge, only 41% [32] and 50% [39] of heritability estimates have been reported for TMB. Thus, further heritability estimates for TMT should be available to elucidate the underlying genetic variation of this test.

The aim of the present study was first to replicate previous finding of TMT performance deficits in schizophrenia patients and their first-degree relatives and second to estimate the heritability of TMT in a population-based sample of Cuban families with Multiplex Schizophrenia.

## Materials and methods

### Subjects

A total of 374 subjects participated, consisting of 80 patients, 167 relatives and 127 control subjects. The patients were all diagnosed with paranoid schizophrenia and recruited through the Centers of Mental Health of Havana City. The group of schizophrenia patients included 49 men and 31 women, aged 16–66. They were selected from multiplex schizophrenia families based on the presence of two or more schizophrenia-affected subjects in the studied families. Diagnoses were confirmed by experienced psychiatrists in the Spanish version of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) [37]. The Present State Examination (PSE)-10 was carried out on all studied patients. This semi-structured clinical interview is based on DSM-IV criteria [3].

The group of relatives was recruited through the probands of this study. Twenty-two relatives were diagnosed within the schizophrenia spectrum personality traits and were excluded from the study. Diagnoses were confirmed as described for probands. The group of 145 non-affected relatives consisted of 72 parents, 60 siblings, and 13 offspring of affected individuals. A maximum of four first-degree relatives was recruited per family. Familial psychiatric morbidity was investigated using the Family Interview for Genetic Studies, FIGS [21]. A complete family history of first-degree relatives was obtained from each probands and from at least one first-degree relative and it was conducted by psychiatrists formally trained to use the FIGS instrument. The information was supplemented, if required, with data from the medical case notes.

Control subjects were recruited through local recruitment efforts. This group comprised 51 men and 76 women 19–66 years.

The exclusion criteria for relatives and controls subjects were: (1) absence of past or present neurological or psychiatric illnesses, (2) history of traumatic brain injury or body-motor impairments, (3) history of substance abuse, addictions or use of neuroleptics. All subjects reported normal or corrected to normal vision. Written informed consent was obtained from all participants after complete description of the study. The study was performed in accord with the code of ethics of the World Medical Association (Declaration of Helsinki) and the institutional ethics committee.

### Trail Making Test

The Trail Making Test (TMT) [24] requires subjects to complete a tracking task under two conditions. In the first condition (TMA), circles numbered 1–25 are randomly distributed on a page. Starting with number 1, subjects connect all circles successively, as quickly as possible, by a single continuous line, or ‘‘trail’, without lifting the pencil. In the second condition (TMB), 13 randomly designated circles are numbered 1–13, and the remaining 13 are lettered A to M. Subjects draw a line connecting all 26 circles, beginning with 1, and proceeding in the order 1, A, 2, B, 3, C, etc. A practice session preceded the experimental session. For both parts A and B, the score is the total time in seconds required to complete the task.

Total time (in seconds) for TMA and TMB was recorded, representing the direct scores. Then, two derived indices were calculated for all subjects: difference score (B–A) and ratio score (B:A).

### Statistical analysis

We compared demographic characteristics between groups using chi-squared tests for categorical variables and analysis of variance (ANOVA) for continuous variables. Concerning the years of education variable, comparison among the three groups was best conducted by the Kruskal–Wallis *H* test. Before analysis data were examined for normality and univariate outliers. The distributions of the TMA and TMB raw scores found not to conform to the assumptions of normalcy (Shapiro–Wilk test $(W) = 0.830$, $p > 0.01$) were skewed to the right (toward higher impairment). Reflected log transformations improved the distributions and were used in further analysis.

Differences between patients, first-degree relatives and normal controls on all TMT variables were tested using a mixed General Linear Model (GLM) defined by between-subjects group factor and number of family as a random variable with age and years of education as covariates. We used family number as between factor to correct for family relatedness in our analysis because the relatives are related (to each other and to the patients), while the controls are not related. In case of significant effects, comparisons by planned contrast analysis were performed to verify significant differences between three groups with an accepted level of significance of $p < 0.05$. Heritability analysis was performed using the variance component-based program SOLAR [2]. Heritability is defined as the phenotypic variance explained by additive genetic factors. Components of variance were estimated by maximum likelihood including variation caused by the covariates age and sex in a multistep procedure. The significance of the heritability estimate was computed by comparing the polygenic model with the significant covariates to a sporadic model that had the genetic component removed.

## Results

### Demographic sample characteristics

Demographic data are provided in Table 1. The three groups differed in age ($F$ (2,348) = 37.9, $p < 0.000$), with the relatives being older than the patients ($p < 0.000$) and the controls ($p < 0.000$), who did not differ from each other ($p = 0.724$) (Table 1). The groups differed significantly in terms of years of education ($H$ (2,351) = 28.0, $p < 0.000$). The group of patients showed a lower level of education than the relatives' group ($p = 0.025$) and the group of controls ($p < 0.000$). Relatives also showed lower level of education than controls ($p = 0.021$).

### Comparison of TM performance between groups

The GLM analysis showed that the effect of group was significant for both conditions: TMA ($F = 14.17$, $p < 0.001$) and TMB ($F = 36.0$, $p < 0.001$). Also the two

**Table 1** Demographic sample characteristics

| Variable | SZ patients | Relatives | Controls | Statistic test | *p* |
|---|---|---|---|---|---|
| *N* | 80 | 145 | 127 | | |
| Age (years) | | | | | |
| Mean ± SD | 36.2 ± 11.1 | 47.4 ± 14.0 | 34.8 ± 12.1 | $F = 37.9$ $df = 2$ | 0.000 |
| Gender | | | | | |
| Male (%) | 49 (61.2) | 62 (42.8) | 51 (40.2) | $\chi^2 = 9.84$ $df = 2$ | 0.007 |
| Education (years) | | | | | |
| Mean ± SD | 11.3 ± 3.0 | 12.6 ± 3.7 | 13.9 ± 2.8 | $H = 28.0$ $df = 2$ | 0.000 |
| Age of onset (years) | | | | | |
| Mean ± SD | 22.6 ± 6.3 | – | – | | |
| Duration of disease (years) | | | | | |
| Mean ± SD | 12.6 ± 8.1 | – | – | | |
| Antipsychotic treatment *n* (%) | | – | – | | |
| Typical neuroleptics | 71 (89.5) | | | | |
| Atypical neuroleptics | 5 (6.8) | | | | |
| Both neuroleptics | 4 (3.6) | | | | |

*SD* standard deviation

*H* represents non-parametric Kruskal–Wallis test

set shifting scores showed a significant effect of groups: TMB–A ($F = 12.74$, $p = 0.009$) and TMB/A ($F = 8.69$, $p > 0.001$), indicating that the overall TMT performance differed between the three studied groups (see Table 2).

Planned contrast analysis test provided in Table 3 demonstrated that SZ non-affected relatives performed significant poorer than controls on TMB; TMB–A and TMB/A. Results indicated that SZ patients were significantly impaired on all measures of TMT relative to controls. Schizophrenia patients also took longer to complete the TM in comparison to the relatives group. The mean of TMB–A and TMB/A scores were not significantly different between SZ patients and their relatives, suggesting poor TMT performances in both group.

A subsequent planned comparison analysis was performed to minimize potential confounding results by the unequal sample size and differences in age and years of educations effects. The analysis was repeated with a subsample consisting of 60 SZ patients, 60 unaffected relatives of probands and 60 controls matched for age, sex and years of education (results shown in Table 4).

When this same analysis was conducted with the subsample, the same results were obtained. SZ patients and their unaffected relatives differed significantly from controls in TMT performance demonstrating an impairment of the executive functions distributed along a continuum with relatives, showing intermediate impairment when comparing patients, relatives and controls.

**Table 2** Trail Making Test (TMT) performance by groups, mean (±SD)

| | SZ patients | Relatives | Controls | $F$ ($df = 2$) | $p$ |
|---|---|---|---|---|---|
| TMA | 4.46 (±0.53) | 4.27 (±0.47) | 4.07 (±0.42) | 14.7 | <0.001 |
| TMB | 5.57 (±0.56) | 5.23 (±0.60) | 4.78 (±0.52) | 36.04 | <0.001 |
| TMB–A | 1.10 (±0.55) | 0.96 (±0.45) | 0.71 (±0.37) | 12.74 | 0.005 |
| TMB/A | 1.25 (±0.14) | 1.22 (±0.11) | 1.17 (±0.09) | 8.69 | <0.001 |

*SD* standard deviation; *TMA*, TMT part A; *TMB*, TMT part B

Log transformation of TMT raw scores are showed and used in the ANCOVA analysis with age and years of education as covariates

**Table 3** Summary statistic for planned contrast analysis

| | TMA | | TMB | | TMB–A | | TMB/A | |
|---|---|---|---|---|---|---|---|---|
| | $F$* | $p$ | $F$* | $p$ | $F$* | $p$ | $F$* | $p$ |
| P vs. C | 21.75 | <0.001 | 71.04 | <0.001 | 23.77 | <0.001 | 14.69 | <0.001 |
| P vs. R | 23.56 | <0.001 | 34.61 | <0.001 | 3.54 | 0.060 | 0.98 | 0.320 |
| R vs. C | 0.06 | 0.806 | 7.84 | 0.005 | 11.06 | <0.001 | 9.99 | 0.001 |

$F$* Test of significance for planned contrast analysis, $F(1,346)$

P vs. C = SZ patients versus Controls

P vs. R = SZ patients versus Unaffected relatives of probands

R vs. C = Unaffected relatives of probands versus Controls

**Table 4** Summary statistic for planned contrast analysis with a subsample

| | TMA | | TMB | | TMB–A | | TMB/A | |
|---|---|---|---|---|---|---|---|---|
| | $F$* | $p$ | $F$* | $p$ | $F$* | $p$ | $F$* | $p$ |
| P vs. C | 34.24 | <0.001 | 94.84 | <0.001 | 37.30 | <0.001 | 22.02 | <0.001 |
| P vs. R | 9.04 | <0.001 | 19.06 | <0.001 | 5.47 | 0.019 | 2.90 | 0.089 |
| R vs. C | 11.67 | <0.001 | 41.17 | <0.001 | 20.09 | <0.001 | 12.59 | <0.001 |

$F$* Test of significance for planned contrast analysis, $F(1,346)$

P vs. C = SZ patients versus Controls

P vs. R = SZ patients versus Unaffected relatives of probands

R vs. C = Unaffected relatives versus Controls

**Table 5** Heritability of TMT performance from the Additive Genetic Model

| Scores | Covariate: age, sex | | Covariate: age, sex, status affected | |
|---|---|---|---|---|
| | $h^2$ (SD) | $p$ | $h^2$ (SD) | $p$ |
| TMA | 0.000 (0.000) | 0.500 | 0.015 (0.107) | 0.445 |
| TMB | 0.105 (0.113) | 0.168 | 0.136 (0.115) | 0.110 |
| TMB–A | 0.192 (0.116) | 0.041 | 0.220 (0.117) | 0.025 |
| TMB/A | 0.212 (0.108) | 0.019 | 0.242 (0.110) | 0.010 |

*TMA*, TMT version A; *TMB*, TMT version B

Estimation of heritability

Significant heritability estimates were found for TMB/A ($h^2 = 0.212$, $p = 0.019$) and TMB–A ($h^2 = 0.192$, $p = 0.041$). TMA and TMB did not show evidence of heritability (Table 5). When affected status was added as an additional covariate, the heritability estimate for TMB/A remained similar ($h^2 = 0.242$, $p = 0.010$), and increased slightly for TMB–A ($h^2 = 0.220$, $p = 0.025$).

## Discussion

We found that relatives of schizophrenic patients performed worse on TMT than controls, but significantly better than the group of schizophrenia patients. This result of TMT deficit in unaffected first-degree relatives is consistent with the criterion that a putative endophenotype should be found at a higher rate in the unaffected relatives of probands than the general population [30, 39]. Previous meta-analyses have also shown that TMB may effectively discriminate between siblings of patients and controls [29, 35]. However, some studies have failed to find significant differences in executive functioning impairment measured with TMT in parents of schizophrenia patients compared to controls [11] or no differences were found between siblings and controls [40], suggesting that the analysis of TMT performance should take into account several factors such as sampling and statistical variation, type of family members studied and the type of control subjects enrolled [12]. In this study, we studied a large sample of probands and their relatives from multiplex schizophrenia families. This design has the advantage of heightening the effect of familial loading and the lever of cognitive impairments. This strategy has led us to replicate previous results in observing significant deficits of TM performance in relatives compared to controls [13, 18, 25].

It is assumed that positive heritability estimates would be the most likely to enhance molecular genetics studies [10]. We estimated the heritability using variance component methods implemented in SOLAR to know how much of the variation in the performance of TMT can be attributed to inherited genetic factors. The present study provided significant additive heritability estimated for TM (B–A) and TM (B/A). The presence of evidence of heritability in agreement with the finding of TMT performance impairment in unaffected relatives suggests an association with genetic predisposition to schizophrenia. However, low estimates of heritability of TMT (TMB–A = 0.22 and TMB/A = 0.24) that we found in our study, may be indicative of the fact that environmental factors may contribute more than the genetic effects to the performance of TMT. Egan et al. [12] reported an increased relative risk for impaired performance on TMB and suggested that, although relative risk estimates upper limits of heritability, TMT abnormalities may be heritable. Relatively few studies have examined heritability estimates for TMT in schizophrenia [7]. Additional studies have investigated the genetic and environmental influences on TMT as index of executive control. Waldman [39] found higher twin correlations for monozygotic than for dizygotic twins for both Trail A and Trail B on Attention-deficit/hyperactivity disorder (ADHD) and also found longer TMT response times in unaffected relatives than normal subjects.

A limitation of this study is that age and education levels were not matched among three groups (patients, relatives, and controls). Relatives of probands were older than schizophrenia patients and controls. Controls were better educated than the other two groups. It has been suggested that age and education may be confounding factors regarding neuropsychological performance. Therefore, although age and education years were adjusted as covariates in this study, it might have improved the strength of the study if those variables had been better matched.

For clarity purposes, we repeated the analyses with a subsample consisting of 60 SZ patients, 60 unaffected relatives of probands and 60 controls matched for age, sex and years of education. In the reanalysis with a smaller sample we obtained the same results diminishing the potential confounding effects caused by the possible inhomogeneous within-group-regression in combination with the unequal sample sizes (see Table 4).

In summary, we found those with schizophrenia and their nonpsychotic relatives to be impaired on TMT and provided data to round out the evidence for positive heritability on TMT performance, providing support that TMT appears to meet the heritability criterion. However, the small values of heritability estimates suggest that TMT performance is also associated with epigenetic or environmental factors. Thus, this finding suggests that TMT impairment, as a measure of executive functioning deficit, may be a valid vulnerability marker in high-risk subjects of schizophrenia. More studies of heritability estimates for TMT performance deficit are needed to investigate the

usability of this deficit as an endophenotypic marker for schizophrenia.

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