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Latent, genetic, and molecular genetic structure of the Wisconsin Card Sorting Test

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6 Running head: LATENT, GENETIC, AND MOLECULAR GENETIC STRUCTURE OF
7 WCST

8 LATENT, GENETIC, AND MOLECULAR GENETIC STRUCTURE OF THE WISCONSIN
9 CARD SORTING TEST

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28 All data with instructions for their use are available at OSF and can be accessed at OSF link:
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38 LATENT, GENETIC, AND MOLECULAR GENETIC STRUCTURE OF THE WISCONSIN
39 CARD SORTING TEST

40 **Abstract**

41 **Objective:** The main goal of this study was to explore the latent structure and genetic basis of
42 cognitive processes involved in the Wisconsin Card Sorting Task (WCST) within phenotypic,
43 behavioral genetic, and molecular genetic research paradigms.

44 **Method:** The sample used in phenotypic and behavioral genetic analyses comprised 468 twins
45 (154 monozygotic and 80 dizygotic twin pairs), while molecular genetic analyses were
46 performed on 404 twins from the same sample. The zygosity of most twin pairs (96.8%) was
47 determined via DNA analysis of buccal swabs. Trained researchers administered the Wisconsin
48 Card Sorting Test – WCST (Heaton et al., 1993) to the entire sample.

49 **Results:** A phenotypic factor analysis of WCST variables suggested a single-factor solution.
50 Overall heritability ranged from 0.19 to 0.23 across different measures of the WCST. The
51 presence of a single general genetic factor, which could be identified from different measures of
52 the WCST, indicated the unity of various WCST indicators and the existence of a common basic
53 ability. Performance on the WCST did not reveal significant differences between the three
54 genotypes on COMT and DRD2. Carriers of the BDNF Met+ genotype exhibited better
55 performance in cognitive functions in comparison to the BDNF Met- genotype.

56 **Conclusions:** This study highlighted similarities in the phenotypic and genetic structures of the
57 WCST, suggesting one general factor underlying different cognitive functions. The BDNF Met +
58 genotype showed significant main effects on different WCST measures.

59 **Keywords:** behavioral genetics, WCST, COMT, DRD2, BDNF

60 **Key Points**

61 Question: What is the key question this paper addresses?

62 The main goal of this study was to explore the latent structure and genetic basis of cognitive
63 processes involved in the Wisconsin Card Sorting Task (WCST) within phenotypic, behavioural
64 genetic, and molecular genetic research paradigms.

65 Findings: What are the primary findings?

66 In addition to the existence of a single general genetic WCST factor, as suggested by the
67 phenotypic factor analysis and supported by behavioral genetic analyses, the main results of our
68 study include the low heritability of WCST measures, zero evidence for the effects of COMT
69 and DRD2 polymorphisms on WCST measures, and significant main effects of the BDNF Met+
70 genotype on WCST measures.

71 Importance: What are the key scientific and practical implications of the findings?

72 The results point to the existence of a general genetic factor, supporting the thesis on the unity of
73 executive functions measured by the WCST and the existence of a common ability that underlies
74 them, while indicating that the standard WCST performance scores might be insufficient to
75 concurrently assess the distinct cognitive/executive processes required for performing the WCST
76 in healthy adults.

77 Next Steps: What directions should be explored in future research?

78 It is paramount for future research directions to include examinations of the etiology of
79 individual differences in executive functions in clinical population samples as well as
80 explorations of the developmental dynamics of genetic and environmental influences on the
81 etiology of individual differences in executive abilities.

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93 **1 Introduction**

94 “Executive functions” (EFs) is an umbrella term that encompasses a range of interrelated

95 processes involved in purposeful, goal-oriented behavior (Anderson, 2002; Anderson, et al.,

96 2008; Huges & Graham, 2002). EFs are usually defined as a highly complex, integrated set of

97 cognitive abilities and processes critical to adaptive functioning, including planning, time

98 organization of behavior, goal anticipation, activity monitoring, ability to inhibit or delay

99 responses, evaluation of responses, cognitive flexibility, and selection of problem-solving

100 strategies (Anderson, 2002; Damasio & Anderson, 1993; Zelazo et al.,1997).

101 However, there are still theoretical disagreements regarding the contents of executive

102 control (Anderson, 2002; Baddeley, 2007; Damasio & Anderson, 1993; Zelazo et al.,1997;

103 Miyake et al., 2000) arising from the use of different methods and strategies as well as the lack

104 of a unique empirical framework for its study. Understanding the core processes tapped by EF

105 tests is further complicated by the multifaceted nature of the available tasks. Additionally, since

106 executive functions are meta-processes, almost all cognitive performances include executive

107 functions to a certain extent, which contributes to task impurity. Although task impurity

108 complicates the study of EF, latent variable analysis has demonstrated a useful approach to

109 addressing this problem, suggesting that EF tests can be modelled very well in careful

110 convergent and discriminant validity research. Following this approach to studying the

111 organization and function of EFs, Miyake and Friedman (2000) established a model of EF

112 supported by a plethora of empirical evidence (Miyake et al., 2000; Diamond, 2013), indicating

113 that EF is a multi-faceted construct consisting of processes related to response inhibition,

114 working memory updating, and cognitive flexibility (or shifting). More precisely, their

115 theoretical three-factor model of EF (Friedman & Miyake, 2017; Miyake & Friedman, 2012)
116 proposes that individual differences in these EFs can be understood in terms of three different EF
117 components: common EF, shifting-specific, and updating-specific. These three EF abilities are
118 separable (diversity), but are also moderately correlated with one another and thus share a
119 considerable common variance (unity). The unity/diversity pattern has been replicated in several
120 latent-variable studies (Engelhardt et al., 2015; Gustavson et al., 2018, Friedman et al., 2008).

121 One of the established and most widely used tests for measuring EFs is the Wisconsin
122 Card Sorting Test (WCST), considered to provide quantitative measures of abstraction ability
123 and thinking flexibility. The WCST engages various executive processes, such as strategic
124 planning, organized search, ability to use environmental feedback to shift mental sets, goal-
125 directed behavior, and modulation of impulsive response (Heaton et al., 1993; Demakis, 2003;
126 Eling et. al., 2008).

127 1.1 Latent structure of the WCST

128 Although the WCST has been used as a measure of EFs in a large number of clinical and
129 non-clinical studies, only few of them have provided arguments regarding its latent structure and
130 taxonomy of the underlying cognitive processes (e.g., Bowden et al., 1998; Grave et al., 1998;
131 1999; 2002; 2005; Polgár et al., 2010). However, inconsistencies in the samples, test procedures
132 and factor analysis strategies contributed to the lack of consensus regarding the latent structure of
133 the WCST. For example, a review of 15 factor-analytic studies showed that samples from
134 clinical populations differing in symptomatology (neurological patients, psychiatric patients)
135 were often combined with control groups from the non-clinical population (Polgár et al., 2010),
136 whereas only one of them has been conducted on healthy adolescents (Somsen et al., 2000).

137 Furthermore, although exploratory factor analysis (EFA) has been predominantly used,
138 confirmatory factor analysis (CFA) has been performed in some studies (Greve et al., 2005).
139 Significant discrepancies in the selection of WCST measures used in the studies also represent a
140 disruptive factor for the replicability of previous findings. Generally, EFA have indicated
141 solutions ranging from 1 to 3 factors, with the first factor explaining 48 - 71% of the variance
142 (Polgár et al., 2010). The WCST measures that most saturate the first factor are: The Number of
143 Categories, Conceptual Level Responses, Perseverative Errors, Perseverative Response, and The
144 Total Number of Correct Responses, while Non-Perseverative Errors and Failure to Maintain Set
145 most saturate factors 2 and 3 (Polgár et al., 2010). The results of the study by Greve et al. (2005),
146 in which CFA was conducted on a large sample comprising 1221 subjects (neurological patients,
147 psychiatric patients, and a non-clinical control sample), support the three-factor solution obtained
148 in many studies with EFA. However, the results of this study also suggest the instability of the
149 latent structure, since only the first factor (general executive functioning) was statistically
150 significant, while the remaining two were less stable, except in subjects who completed all 128
151 cards. The authors pointed to the fact that early termination of the WCST tasks may lead to loss
152 of information and significantly contributes to the unstable factor structure in research.
153 Additional reason for the instability of the factor structure in previous studies may be relatively
154 small samples, most often ranging from 100 to 200 subjects, which led to a violation of the
155 recommended ratio between the number of variables and sample size in EFA (Greve et al.,
156 2005).

157 Due to the reduced possibility of replication and unreliability of previous results, limited
158 conclusions can be drawn from these methods, especially since both PCA and EFA research
159 techniques have been used to present the observed data, without formal a priori hypothesis

160 testing. Namely, analytic decisions regarding EFA (e.g., the number of factors to extract and
161 rotation) can produce misleading findings and result in a faulty foundation for theory or model
162 building. Furthermore, exploratory model fitting is prone to over-fitting due to sample-specific
163 variance (Byrne, 1989). Using orthogonal rotation has generally been the prior rule in factor
164 analytic studies of the WCST, providing possible artifactual results that indicate the
165 independence of its factors. Orthogonal solutions should never be sought unless the less-
166 prejudicial oblique solution shows factor correlations to be zero (e.g., Floyd and Widamin, 1995;
167 Henson and Roberts, 2006). Further complicating the understanding of WCST structure is the
168 disappointingly low reliability of WCST variables in the nonclinical population (Strauss et al.
169 2006). Inter alia, lower test-retest correlations for executive functioning and memory measures
170 can be explained by non-measurement factors. Namely, Delis, Kramer, Kaplan, and Holdnack
171 (2004) suggest that the complex nature of executive functioning tasks, which involve multiple
172 cognitive processes, may make them more susceptible to performance variability. This was
173 confirmed in a meta-analytic reliability study of neuropsychological measures (Calamia et al.,
174 2013). In this context, specifying the organization of executive functions may necessitate the use
175 of analytical techniques such as latent variable modelling (e.g., confirmatory factor analysis),
176 which can separate measurement error from the measure of individual differences. Latent
177 variable modeling incorporates all of these measurement-related considerations into an analytic
178 strategy, retaining the ability to test relations between important elements in the WCST
179 theoretical model.

180 1.2 Genetic and Environmental Factors of the WCST

181 Behavioral genetic studies of the WCST have yielded inconsistent results, since some
182 studies have shown a hereditary basis (Anokhin et al., 2010, Anokhin et al., 2003, Godinez et al.,
183 2012), while others have failed to identify a genetic contribution to WCST indicators (Chou et
184 al., 2009, Kremen et al., 2007). Previous twin studies that have reported a small to moderate
185 contribution to the genetics of variance of individual WCST indicators have mostly been
186 conducted on adolescent samples (Anokhin et al., 2003; Anokhin et al., 2010; Godinez et al.,
187 2012). In a sample of 58 MZ and 25 DZ twin pairs, aged 17–28 years, for four WCST indices,
188 which included the total number of errors, perseverative errors, perseverative responses, and the
189 trials to complete the first category, 37% to 46% of the variance (respectively) was attributed to
190 genetic influence (Anokhin et al., 2003). The rest of the variance of all indicators was explained
191 by non-shared environmental factors. A longitudinal study conducted on a sample of 166 MZ
192 and 201 DZ twin pairs at the ages of 12 and 14 revealed the existence of a gender effect for
193 genetic and environmental influences on WCST performance, with higher heritability of test
194 indicators for female adolescents (Anokhin et al., 2010). This result was particularly significant
195 for the number of perseverative errors, whose heritability tended to increase from 19% at the age
196 of 12 to 49% at the age of 14 in the female sample. Likewise, a study on a sample of 191 MZ and
197 165 DZ twin pairs with a mean age of 17 years showed a low to moderate heritability for
198 traditionally defined measures such as non-perseverative errors and the number of trials, but also
199 for narrowly defined errors, such as search errors, breaking set errors, and efficient errors (0.10 -
200 0.42 respectively) (Godinez et al., 2012).

201 However, in the population of healthy adults, behavioral genetic studies have often
202 shown a complete absence of genetic contributions to achievement on all WCST indicators
203 (Campana et al., 1996; Chou et al., 2010; Kremen et al., 2007; Nicole & Del Miglio 1997;

204 Taylor, 2007). For example, in a sample of 170 MZ and 190 DZ middle-aged male twin pairs,
205 correlations between twins were low on all standard WCST measures and there were no
206 statistically significant differences between MZ and DZ twins (Kremen et al., 2007). To date,
207 only one study (Godinez et al., 2012) has investigated the etiology of covariance between
208 different WCST indicators and found that covariance was best explained by general / common
209 genetic factors, while differences between indicators were caused by specific genetic and
210 environmental factors.

211 In general, it is possible that small samples along with the use of different measures and
212 versions of the WCST (computer and classical) contributed to these inconsistencies. It is also
213 possible that the aforementioned characteristics of the WCST, such as its great complexity and
214 multi-determinism, contributed to the not always clear separation of genetic influences.

215 1.3 The Molecular Genetic Basis of the WCST

216 Although EFs are polygenically determined, there is still no convincing evidence for all
217 gene candidates that could participate in the regulation of this complex phenotype. We selected
218 two genes from the dopamine system that are associated with cognitive and emotional processing
219 – the catechol-O-methyltransferase (COMT) gene and the dopamine receptor D2 (DRD2) gene –
220 and the brain neurotrophic factor (BDNF) gene to examine possible associations with EFs.

221 The COMT gene is located on chromosome 22q11. It predominantly shows gene
222 expression in the prefrontal cortex and affects various cognitive functions (Geller et al., 2017).
223 Functional polymorphism of the COMT gene involves the substitution of one amino acid for
224 another (Valine to Methionine) at codon 158 of the COMT gene, which consequently affects the
225 thermal stability and reduces the activity of COMT enzymes in Met carriers (Klaus et al., 2017;

226 Tunbridge et al., 2019). Previous studies on the association between COMT and executive
227 functions have shown that Met allele carriers tend to perform better in the categories completed
228 score and working memory tests (Bruder et al., 2005), while Val/Met heterozygotes have shown
229 superior cognitive set shifting performance (Khanthiyong et al., 2019). Furthermore, the Val
230 allele has been linked to a higher number of perseverative errors on the WCST (Caldú et al.,
231 2007; Malhotra et al., 2002; Rosa et al., 2004) and a higher number of commission errors on the
232 Continuous Performance Test (Caldú et al., 2007). However, although previous studies have
233 indicated an association between better WCST performance and Met alleles (Barnett et al., 2007;
234 Caldú et al., 2007; Malhotra et al., 2002; Rosa et al., 2004), this result has not been consistently
235 replicated (Geller et al., 2017).

236 The DRD2 gene is located on chromosome 11q23 and it encodes the DRD2 protein,
237 which regulates the functioning of the D2 receptor for dopamine, which may impact motor
238 output in cognitive tasks (Logue & Gould, 2014; Tunbridge et al., 2019). D2 dopamine receptor
239 function has been linked to the regulation of emotional functioning (Barnes et al., 2011), set
240 shifting (Logue & Gould, 2014), and different aspects of cognition (Klaus et al., 2017). The
241 functional polymorphism of the DRD2 gene implies two types of alleles: A1 and A2 (Barnes et
242 al., 2011). In studies conducted thus far, A1 homozygotes have had difficulties in learning from
243 punishment, error processing, and suppressing irrelevant information (Barnes et al., 2011),
244 accompanied by poorer performance on executive function and working memory tasks (Xu et al.,
245 2007), especially special working memory and planning tasks (Klaus et al., 2017) and attention
246 switching tasks (Gurvich & Rossel, 2015).

247 The Brain Neurotrophic Factor (BDNF) gene is located on chromosome 11p14.1. It
248 encodes a small protein that plays a key role in synaptic plasticity, regulating the number of
249 synapses, axon growth, and hippocampal neurogenesis (Kautsky et al., 2019). The dominant
250 expression of the BDNF gene is in the prefrontal cortex and hippocampus (e.g., Wishart et al.,
251 2011). The functional polymorphism of the BDNF gene results from the substitution of one
252 amino acid (Val) for another (Met) at codon 66 of the BDNF gene, which alters BDNF gene
253 expression and leads to smaller hippocampal volume (Kautsky et al., 2019). Previous studies on
254 associations between the BDNF gene polymorphism and cognitive functions have provided
255 inconsistent findings (Sanwald et al., 2020). Despite the predominance of findings showing an
256 association between the BDNF Met allele and poorer working memory performance (Gatt et al.,
257 2009) and executive functions (Benzerouk et al., 2013; Wishart et al., 2011), a growing body of
258 evidence suggests that the BDNF Met allele is associated better executive performance
259 (Alfimova et al., 2012; Harris et al., 2006; Hashimoto et al., 2016).

260

261 1.4 Current Study

262 Since previous studies have indicated many controversies regarding the latent structure of
263 the WCST (e.g., Grave et al., 2005; Polgár et al., 2010), the main goal of our study was to
264 explore possible structural aspects of EFs within the WCST by employing three different
265 methodological and conceptual approaches. Specifically, our research focused on examining the
266 latent structure of the WCST and the hereditary and molecular genetic bases of indicators of
267 executive functions. Our assumption was that these different research paradigms would
268 contribute to the elucidation of an important issue regarding the measures of executive functions
269 covered by the WCST. Therefore, our first research question pertained to examining the latent

270 structure of different WCST indicators using factor analysis, which could contribute to the
271 ongoing debate on whether different measures of the WCST constitute a unique aspect of general
272 executive ability or can be considered as independent cognitive abilities. The second research
273 question pertained to the examination of the relative importance of genetic and environmental
274 influences on individual differences in WCST indices. Moreover, multivariate genetic analyses
275 were expected to determine the extent to which the genes and the environment contribute to the
276 overlap between the indices of the WCST. In general, this goal could contribute to resolving the
277 dilemma of whether the phenotypic structure reflects the basic genetic architecture. The third
278 goal of the present study was to analyze the possible associations between COMT, DRD2, and
279 BDNF genes and WCST performance. Assessing the molecular genetic associations of these
280 phenotypes could enrich our understanding of how DNA variation gives rise to individual
281 differences in executive abilities. Our design was reinforced by the fact that three different
282 research paradigms applied on the same sample of adult twins of both genders could provide new
283 insights into individual differences in performance on the WCST and their biological
284 underpinnings.

285 **2 Method**

286 2.1. Openness and Transparency

287 We follow the guidelines given by JARS (Kazak, 2018) and report on how we determined the
288 sample size, the treatment of missing data, and all measures.

289 All data with instructions for their use are available at OSF and can be accessed at:

290 <https://osf.io/de5u2/> The code behind the quantitative behavioral genetic analysis has been made

291 publicly available at the Zenodo and can be accessed at

292 doi:<https://doi.org/10.5281/zenodo.3514218> (Čolović, 2019). This study's design and its
293 analysis were not pre-registered.

294 2.2 Sample and Procedure

295 The sample was drawn from the Serbian Twin Registry (for detailed recruitment procedures see
296 Authors, 2019), a national and multidisciplinary twin database. The Serbian Twin Registry
297 sample consists of 1,654 participants, including twin pairs and their family members. For the
298 present study, we relied on data from 308 MZ (154 pairs; 75.3% female) and 160 DZ (80 pairs;
299 61.3% female) twins reared together. Among dizygotic twin pairs, there were 35 mixed-gender
300 pairs and 45 same-gender pairs. The respondents were 17 to 58 years old and the average age
301 was 24.08 years (SD = 7.02). Detailed information on the sociodemographic characteristics of
302 the sample is presented in Table 1.

303 < INSERT TABLE 1 ABOUT HERE >>
304

305 After excluding some cases due to failed genotyping, the sample consisted of 404 twins
306 for COMT gene (rs4680), DRD2 gene (rs1800497), and BDNF (rs6265) gene polymorphisms in
307 the subsequent molecular genetic analysis.

308 The zygosity of most twin pairs (96.8%) was determined via DNA analysis of buccal
309 swabs. Buccal swabs were tested using short tandem repeat (STR) megaplex kits – either
310 Investigator 24plex GO! (Qiagen, Valencia, CA, USA) or GlobalFiler (Applied Biosystems,
311 Thermofisher Scientific, Waltham, MA, USA). Both kits detect 21 autosomal STRs. Samples
312 with partial profiles were interpreted if at least 10 loci had results. For a smaller number of twins
313 (3.2%), zygosity was determined using the Twins Physical Resemblance Questionnaire

314 (Oniszczenko et al.,1993). This questionnaire is a self-report measure containing 31 sets of items
315 (plus 19 demographic questions) referring to the similarities and differences in biological and
316 physical indicators (e.g., eye color, body weight, and body height) between twins within a pair.
317 Zygoty measures of this questionnaire proved to be reliable indicators of zygoty in many
318 studies (e.g., Čolović et al., 2018; Reed et al., 2005).

319 The research was approved by the Institutional Ethics Committee of the Faculty of
320 Philosophy (#02-374/15), the Committee for Ethics of Clinical Trials at the Faculty of Medicine
321 (#01-39/229/1) at the University of Novi Sad and the data was collected between 2011 and 2018.
322 Twins were recruited from the whole territory of Serbia. A call for participation in the research
323 was published through the media and press. Data collection was carried out in different sites in
324 Novi Sad, Niš, Novi Pazar, Zrenjanin, and Belgrade. The participation of the twins was
325 voluntary and each respondent signed an informed consent for participation. Executive functions
326 were examined by trained researchers and the entire procedure for collecting data is described
327 elsewhere (for detailed recruitment procedures see Smederevac et al., 2019).

328 2.3 Measures

329 *The Wisconsin Card Sorting Test – WCST* (Heaton et al., 1993). The WCST is the most
330 prominent test for the assessment of set shifting, attention, and inhibition. The test assesses the
331 ability to create and change the principles of categorization, using the task of classifying a series
332 of cards according to one of the three classification criteria (color, form, and the number of
333 elements) related to four target cards. The WCST requires the participant to sort a set of cards
334 according to implicit rules and based on the limited corrective feedback provided by the
335 examiner. The participant's responses can be analyzed to produce separate indices of sources of

336 difficulty on the test. The value of the WCST, therefore, lies in its sensitivity for detecting and
337 characterizing different measures of executive functions: (1) Total Number of Errors: the total
338 number of perseverative and non-perseverative errors during card sorting; (2) Non-Perseverative
339 Errors: the number of errors that are not repetitive during card sorting (3) Perseverative Errors:
340 the number of errors that are repetitive during card sorting, which reflects a tendency towards
341 perseveration; (4) Perseverative Responses: the number of responses that are repetitive, whether
342 or not they are accurate; (5) Categories Completed: the number of series of 10 consecutive
343 correct answers (ranging from 0-6), which reflects the overall success; (6) Conceptual Level
344 Responses: three or more correct answers in a row (individual answers are counted and
345 categories are included), which reflects the insight into the correct pairing principle; (7) Trials to
346 Complete the First Category: the number of attempts to complete the first category (it is counted
347 as 128 if no category is achieved), which reflects the initial conceptual abilities; (8) Failure to
348 Maintain Set: five and more than five – fewer than nine correct answers in a row, which reflects
349 the sorting efficiency. Also included in the analysis was a variable named “Categorizing
350 Efficiency”, which in addition to the number of completed categories concerns the number of
351 attempts to single out these categories. That way, participants were awarded additional points for
352 needing fewer attempts to separate the categories (see Cianchetti et al., 2005).

353 *The Genotyping of COMT, DRD, and BDNF Polymorphisms.* The genotyping of the
354 COMT gene (rs4680), DRD2 gene (rs1800497) and the BDNF gene (rs6265) was carried out
355 using TaqMan assays (TaqMan SNP, Applied Biosystems®, Warrington, UK), as recommended
356 by the manufacturer. The TaqMan SNP Genotyping Assays uses TaqMan 5' -nuclease chemistry
357 for amplifying and detecting specific polymorphisms in purified genomic DNA samples and
358 takes advantage of minor groove-binding probes for superior allelic discrimination. The SNP

359 Genotyping Assays contain a VIC-dye-labelled probe, a FAM-dye-labelled probe with two
360 target-specific primers. PCR was performed using 10 ng of genomic DNA together with 1µl of
361 TaqMan Genotyping assay and 12.5 µl of the genotyping master mix in the final 25µl reaction
362 on a 96-well plate using an ABI Prism 7500 Fast PCR device (Applied Biosystems®, Foster
363 City, California, USA). COMT gene (rs4680), DRD2 gene (rs1800497), and BDNF gene
364 (rs6265) alleles with the specific fluorescence curves were detected and analyzed using the 7500
365 System SDS program, integrated into the ABI Prism 7500 Fast PCR device.

366 The COMT gene polymorphism was defined by 3 groups: 124 high-activity homozygotes
367 (Met/Met carriers), 213 intermediate heterozygotes (Met/Val carriers), and 70 low-activity
368 homozygotes (Val/Val carriers). The COMT gene polymorphism was in the Hardy–Weinberg
369 equilibrium (HWE), with no significant differences between the observed and calculated
370 genotype frequencies ($\chi^2 = 4.13$, $df = 2$, $p > 0.05$).

371 The DRD2 gene polymorphism was defined by 2 groups, according to the presence of the
372 risk allele: A1 homozygotes and A1/A2 heterozygotes were combined into a single group (A1+,
373 127 carriers), and the other group was A1– (280 carriers). The DRD2 gene polymorphism was in
374 the HWE ($\chi^2 = 1.42$, $df = 1$, $p > 0.05$).

375 All analyses of the BDNF gene polymorphism were also performed at the allele level,
376 according to the presence of the risk Met allele. The BDNF gene was defined by 2 groups: 285
377 high-activity homozygotes (Met-) formed one group and Val66Met heterozygotes formed the
378 second group together with Met66Met homozygotes (named Met carriers). This group consisted
379 of 122 Met carriers. BDNF was in the HWE and there were no significant differences between
380 the observed and calculated genotype frequencies ($\chi^2 = 0.20$, $df = 1$, $p > 0.05$).

381 2.4 Data Analysis

382 2.4.1 Preliminary Analysis, Descriptive Analysis, and Twin Intraclass Correlation Analysis

383 The preliminary analysis involved a partialization of the gender effect, as well as a linear
384 and quadratic partialization of the age effect. The partialization of these effects was conducted by
385 using the standard regression procedures proposed by McGue and Bouchard (1984). Descriptive
386 statistical parameters as well as phenotype and intraclass correlations were calculated in the
387 SPSS v.21 software (IBM Corp, 2012).

388 2.4.2 Factor Analysis

389 The latent structure of the WCST indicators was examined via a confirmatory factor analysis
390 (CFA). To provide validation for the obtained latent solutions, the twin sample was split into two
391 cross-validation samples. The Twin 1 subsample comprised all the firstborn twins from the pairs,
392 while the Twin 2 subsample included all the second-born twins from the pairs. The results of the
393 CFA on Twin 1 subsample were then cross-validated in the Twin 2 subsample via a CFA run in
394 the “lavaan” R package (Rosseel, 2012). A robust estimation was used for each model, due to the
395 violation of multivariate normality based on a Mardia’s coefficient greater than 3 (Mardia,
396 1970). Specifically, we performed Satorra–Bentler’s scaled Chi-square testing with robust
397 maximum likelihood estimators (MLM). The model fit of the proposed model was assessed
398 based on the following recommendations: (i) the Tucker-Lewis index (TLI) and the comparative
399 fit index (CFI) >0.9 ; (ii) the standardized root mean square residual (SRMR) and the root mean
400 square error of approximation (RMSEA) <0.08 ; and (iii) a non-significant chi-square (Hu and
401 Bentler 1999).

402 2.4.3 Genetic Analysis

403 Phenotypic similarities between MZ and DZ twins were examined in each WCST
404 dimension by using structural equation modeling (SEM) – employing univariate and multivariate
405 biometric methods. Univariate and multivariate structural equation modeling (SEM) was
406 conducted in the “*lavaan*” R package (Rosseel, 2012). A multivariate genetic analysis was
407 conducted to examine the nature of relationships between WCST factors, by specifying the
408 extent to which they share genetic and environmental influences and the way their influences
409 differ. To specify the form of the observed covariants among WCST factors, multivariate
410 Independent Pathway Models and Common Pathway Models (Rijsdijk & Sham, 2002) were
411 tested in order to estimate: additive (A) and dominance (D) genetic effects, shared (C) and non-
412 shared (E) environmental factors, and specific (s) and common (c) genetic and environmental
413 sources of variance. These models represent different patterns of genetic and environmental
414 influences, which can explain the observed phenotypic correlations between different WCST
415 factors. A comparison of the two model groups and a comparison between the full (ACE, ADE)
416 and reduced (AE, CE) models were carried out by using several fit indicators. Analysis
417 parameters were calculated by using the method of maximum likelihood. Model evaluation was
418 conducted based on the Akaike Information Criterion (AIC: Akaike, 1973), the Bayesian
419 Information Criterion (BIC; Schwarz, 1978), the comparative fit index, the Tucker–Lewis Index
420 (CFI and TLI – optimal values higher than .95, acceptable higher than .90), the root mean square
421 error of approximation (RMSEA - optimal values lower than .05, acceptable lower than .08), and
422 the quotient χ^2/df (recommended < 2) (Ching–Yun, 2002; Kline, 2010). A series of independent
423 and common pathway models were fitted into multivariate covariance matrices. In accordance
424 with parsimony criteria, we selected the model with the smallest number of parameters and a fit

425 not significantly worse than the full model. Additionally, Cholesky behavior genetic analyses
426 (e.g, Neale and Cardon, 2013) were calculated to explore genetic and environmental correlations
427 between WCST scores.

428 2.4.4 Molecular Genetic Analysis

429 The main effects of gene polymorphisms on executive functions were performed using t-
430 test for independent samples (DRD2 and BDNF allelic gene variants as independent variables)
431 and one-way ANOVA (the COMT gene polymorphism as an independent variable). Cohen's *d*
432 and partial eta squared (η_p^2) were used as measures of effect size. A commonly used
433 interpretation is to refer to effect sizes as small ($d = .20$; $\eta_p^2 = .01$), medium ($d = .50$; $\eta_p^2 = .05$),
434 and large ($d = .80$; $\eta_p^2 = .13$), based on the benchmarks suggested by Cohen (1992).

435 **3 Results**

436 3.1 Descriptive Statistics of Phenotypic Characteristics and Twin Intraclass Correlations

437 Means, standard deviations, and univariate cross-twin (intraclass) correlations for each
438 zygosity group are provided in Table 2. The values of skewness and kurtosis indicated that
439 almost all WCST measures were non-normally distributed. Therefore, all measures were first
440 normalized using the rank-based inverse normal (Rankit) transformation (Solomon &
441 Sawilowsky, 2009). However, after the transformation, the magnitude of both skewness and
442 kurtosis did not fall within the range of -1 to 1 for certain measures, indicating that some
443 distributions did not reach normality. Correlations between MZ twins were consistently higher
444 than correlations between DZ twins for all measures. Almost all correlations between MZ twins
445 were positive, significant, and of low-to-moderate strength, with the exception of Failure to

446 Maintain Set and Trials to Complete the First Category. Correlations between DZ twins were
447 non-significant for all WCST variables and approximately twice as low as those between MZ
448 twins. This correlation pattern provided evidence that genetic factors were likely to significantly
449 contribute to the covariance between WCST measures.

450 < INSERT TABLE 2 ABOUT HERE >>

451
452 3.2 Confirmatory Factor Analysis (CFA) of the WCST

453 Total errors were excluded from further analysis since these represented linear
454 combinations of two or more of the obtained variables and provided redundant information.
455 Moreover, the high correlation between perseverative errors and response in the dataset (over
456 0.99) indicated the redundancy of the use of both scores in the same analysis. Based on the
457 results of earlier studies, we tested different factor solutions (Bowden et al., 1998; Greve et al.,
458 1997, 2005; Polgár et al., 2010). The one-factor model used all six scores as indicators (The
459 Number of Categories, Perseverative Errors, Non-Perseverative Errors, Conceptual Level
460 Responses, Trials to Complete the First Category, and Failure to Maintain Set). The second
461 model was a two-factor model. On Factor 1, the indicators were The Number of Categories,
462 Perseverative Errors, Conceptual Level Responses, and Trials to Complete the First Category,
463 while the second factor consisted of two indicators – Non-Perseverative Errors and Failure to
464 Maintain Set. The CFA results revealed that both models showed indications of a lack of fit to
465 the observed data. Table 3. shows fit indices for the comparative models. Both models yielded a
466 significant Chi-square, suggesting that neither described the data fully. Both models showed an
467 unacceptable fit on the CFI and the TLI ($> .95$) and an unacceptable fit according to the RMSEA
468 ($\leq .10$). Since the correlation between the factors in the second model was 0.772 and individual
469 factor loadings exceeded the value of 1, the two- factor model was excluded from further testing
470

471 with the inclusion of the modification index. Further, we explored the potential for obtaining an
472 improved fit by including correlated residuals between like scores. Correlated residuals may be
473 an important element of any factor analysis that includes 'method' variance, as in cases in which
474 multiple scores from one test are included (Millsap, 2011). Thus, we used the modification
475 indices provided by the software to guide model improvement. The one factor-model was
476 improved by allowing for the following modification indices: 1) correlated residuals between
477 Categories Completed and Conceptual Level Responses, 2) correlated residuals between
478 Conceptual Level Responses and Failure to Maintain Set, and 3) correlated residuals between
479 Perseverative Errors and Non-Perseverative Errors. After these refinements, the model's fit was
480 improved, as evidenced by the following goodness-of-fit statistics: $\chi^2(6) = 12.596$, $p = 0.050$,
481 $RMSEA = 0.069$, $SRMR = 0.030$, $CFI = 0.993$, and $TLI = 0.983$. All loadings were significant
482 (Table 3). To validate the CFA results, a subsequent CFA was tested in the Twin 2 subsample
483 (see Table 4). The single-factor solution demonstrated a poor fit to the data; $\chi^2(15) = 102.809$,
484 $p = 0.00$, $RMSEA = 0.211$, $SRMR = 0.067$, $CFI = 0.885$, and $TLI = 0.808$. We then tested the
485 one-factor model with the modifications suggested on Twin 1. Applied to Twin 2, this solution
486 provided a better fit to the data, but still was not within acceptable limits ($\chi^2(6) = 30.178$, $p =$
487 0.000 , $RMSEA = 0.131$, $SRMR = 0.052$, $CFI = 0.973$, $TLI = 0.932$). All loadings were
488 significant (Table 3).

489 As an earlier study concluded, the inadequacy of WCST models may be a result of a number of
490 factors including significant overlap among variables; error due to differences in test length; the
491 relatively rare finding of some WCST scores in the normal normative study; non-linear
492 relationship with another indicator (Grave, 2005; Polgár et al., 2010). We decided to test the
493 fourth CFA model, which excluded some parameters such as Categories Completed. The

494 rationalization for this exclusion was that even after normalization, adequate distribution was not
495 achieved (skewness +1.5). The results of other studies have also shown that the distribution in
496 the normal population is strongly skewed, creating potential problems in statistical evaluation
497 (Obonsavin et al., 1999). Instead of this measure, we included the measures of Categorizing
498 Efficiency, which consider the number of cards used by the subject to complete a maximum of
499 six categories. We also excluded Failure to Maintain Set, since, this variable shows a complex,
500 non-linear association with other WCST scores (Polgár et al., 2010). In the first analysis, Trials
501 to Complete the First Category had very slight loadings (e.g., pattern coefficients greater than or
502 equal to 0.30 were considered salient). We tested the CFA, which included Categorizing
503 Efficiency, Perseverative Error, Non-Perseverative Errors, and Conceptual Level Responses.
504 This solution provided an adequate fit to the data, ($\chi^2(2) = 3.961$, $p = 0.139$, $RMSEA = 0.065$,
505 $SRMR = 0.006$, $CFI = 0.998$, $TLI = 0.994$). All loadings were significant (Table 3). Additionally,
506 parameter estimates are shown in Fig. 1. The CFA model on Twin 2 exhibited excellent fit –
507 $\chi^2(2) = 0.520$, $p = 0.771$, $RMSEA = 0.000$, and $SRMR = 0.003$, $CFI = 1.000$, and $TLI = 1.000$)
508 (Table 4). The model estimated by the CFA analysis on Twin 1 was thus confirmed by the CFA
509 model on Twin 2, in an independent sample.

510 The results of the CFA, as the factor score, were used as one of the measures in molecular
511 genetic analyses.

512 << INSERT TABLE 3 ABOUT HERE >>

513 << INSERT TABLE 4 ABOUT HERE >>

514 << INSERT FIGURE 1 ABOUT HERE >>

515

540 The results from the common AE pathway model suggested that genetic and environmental
541 factors had similar effect paths for all WCST phenotypes (Table 6). The overall variance of
542 heredity was better explained by common genetic factors in the case of all four variables (20% -
543 23%). The contribution of the specific genetic factor was only detectable in perseverative errors
544 (3%). In all cases, common environmental effects (56% - 72%) were stronger than specific (5% -
545 23%) environmental effects. The common environmental effect was the highest for Categorizing
546 Efficiency (72%), while the highest specific environmental effect was observed in the case of
547 Non-Perseverative Errors (23%).

548 Cholesky behavior genetic analyses were performed to explore the genetic and
549 environmental correlations of WCST scores. Phenotypic correlations between all WCST
550 measures were moderate-to-high and the same was true for genetic and environmental
551 correlations (Supplement table B).

552 3. 4 Molecular genetic analysis

553

554 The mean scores of WCST dimensions and the factor score in the specific allelic
555 configurations of COMT, DRD2, and BDNF are given in Table 7.

556 << INSERT TABLE 7 ABOUT HERE >>

557 << INSERT TABLE 8 ABOUT HERE >>

558

559 In our sample (Table 8), DRD2 and COMT were not significantly related to any specific
560 measures on the WCST or the factor score. However, BDNF-Met66 carriers showed
561 significantly higher scores on Non-Perseverative Errors ($t = 2.095$; $p = 0.037$; $d_2 = 0.23$), Failure

562 to Maintain Set ($t = 2.233$; $p = 0.026$; $d2 = 0.25$), and Trials to Complete the First Category ($t =$
563 2.376 ; $p = 0.018$; $d2 = 0.26$) and lower scores on Categorizing Efficiency ($t = -2.158$; $p = 0.032$;
564 $d2 = 0.23$) and the WCST factor score ($t = -2.000$; $p = 0.047$; $d2 = 0.21$) than carriers with other
565 genotype combinations. After applying the false discovery rate (FDR) correction for multiple
566 testing, only Trials to Complete the First Category retained statistical significance.

567 **4 Discussion**

568 Although the WCST is widely used in both clinical and research settings, the factors that
569 contribute to the success of its tasks are still controversial. In the present study, we adopted a
570 comprehensive approach, examining phenotypic, behavioral genetic, and molecular genetic bases
571 of the WCST on the same adult twin sample, with the aim of improving the understanding of the
572 structure of these complex phenotypic features.

573 In order to examine the latent structure of the WCST, we used latent variable modeling.
574 This allowed us to incorporate all measurement-related considerations into a single analytic
575 strategy while retaining the ability to test relations between important elements in the theoretical
576 model of the WCST. CFA procedures were applied to six measures of the WCST to determine
577 their latent factor structure on one of the twins in each pair (e.g., the Twin 1 subgroup). One- and
578 two-factor solutions as well as the one-factor model with modification and the reduced one-
579 factor model were examined as possible structures. The results of the CFA were then cross-
580 validated in the second subgroup (e.g., Twin 2). Both basic models, i.e., one- and two-factor
581 models, showed indications of a lack of fit to the observed data on both subsamples. The one-
582 factor model with modifications (correlated residuals) provided a better fit to the data on
583 subsample one but was not cross-validated on the second subsample. Relying on conceptual and

584 statistical criteria, we decided to test the dimensionality of a small number of selected measures,
585 including Categorizing Efficiency, Perseverative Responses, Non-Perseverative Errors, and
586 Conceptual Level Responses. The notably high latent factor loadings for all four WCST
587 variables suggested that the single-factor model provided a good representation of these scores.
588 This one-factor model was cross-validated on the Twin 2 subsample, showing an adequate fit.
589 This factor could represent cognitive flexibility as reflected in the ability to identify the sorting
590 rule, efficient problem-solving as well as the ability to switch from an incorrect sorting concept
591 in response to external feedback. Thus, the results of factor analyses support a unidimensional
592 conceptualization of WCST performance and imply that different aspects of the executive
593 function measured by the WCST cannot be clearly distinguished. More specifically, regardless of
594 the number of indicators included in the factor analysis, the one-factor solution proved to be the
595 most plausible. This result is in line with some previous findings (Bowden et al., 1998, Boone et
596 al., 1998; Pineda & Merchan, 2003) that have shown the unidimensionality of WCST measures.

597 The patterns of inheritance obtained in univariate genetic analysis indicate low genetic
598 conditionality of most of the WCST indicators, which at least partially corresponds to the results
599 of related previous studies (Anokhin et al., 2003; Anokhin et al., 2010; Godinez et al., 2012).
600 Inconsistent results regarding genetic foundations of WCST imply the importance of unifying the
601 basic premises of using the test before explicit conclusions. For example, it is difficult to
602 compare results on samples of different ages, as well as results obtained with different test
603 procedures, such as computer-based testing vs. trained researchers (Anokin et al., 2010; Kremen
604 et al., 2007). Our sample mostly included younger adults and the results support the view that
605 during the life course, most environmental influences on cognitive achievement are non-shared
606 (Finkel & Pedersen, 2001; McCartney et al., 1990). These specific (non-shared) environmental

607 factors might reflect the fact that individuals experience considerable life changes during the
608 transition from adolescence to adulthood, including changes in residence, education, social and
609 employment roles, and behaviors such as substance use. Furthermore, some developmental
610 studies (De Luca et al., 2003) have suggested that peak performance occurs sometime between
611 20 and 29 years of age, when the final differentiation of frontal areas takes place and working
612 memory, strategic planning, goal-setting, and problem-solving reach full maturity. This relatively
613 prolonged development of the prefrontal cortex is often discussed in the context of neural
614 changes, since performance improvements coincide with synaptic pruning and myelination
615 throughout the brain (Fuster, 2002; Lebel & Beaulieu, 2011).

616 Despite the complexity of the test, the expectation that WCST represents a
617 multidimensional measure of executive functions does not have strong empirical support, which
618 is further confirmed by the results of multivariate behavioral genetic analyzes. Namely, the
619 results of multivariate genetic modeling show that the AE common pathway model best explains
620 the covariance of four WCST indicators – Categorizing efficiency, Perseverative responses,
621 Non-Perseverative errors and Conceptual Level Responses. More specifically, high phenotypic
622 correlations among the examined measures can be explained by the common/general non-shared
623 environmental factor, while a smaller part of their covariance is a consequence of a common
624 genetic factor (about 20%). Moreover, specific genetic influences did not make a significant
625 contribution. High genetic correlations (range 0.83 – 0.99) additionally indicate that these
626 different measures shared the same genetic influences. This result largely corresponds to the
627 finding of the previous study (Godinez et al., 2012), demonstrating that the etiology of the
628 covariance between different types of errors in WCST can be explained by one general genetic
629 factor and general non-shared environment.

630 Taken together, the results do not seem to support the classical, clinically justified
631 division into Perseverative and Non-Perseverative Errors, at least when it comes to the non-
632 clinical population, i.e., the population of normal healthy individuals like the ones who
633 participated in this study. In this regard, it seems interesting to examine whether individual
634 differences in achievement in this test (expressed through different WCST scores) explain
635 genetic and environmental influences in the same relationship when it comes to the clinical
636 population (e.g., those with neurological or psychiatric heredity).

637 Finally, the purpose of the molecular genetics analysis was to examine the association
638 between COMT, DRD2, BDNF, and WCST performance. The association between dopamine
639 genes and executive functions has a solid theoretical and empirical foundation (Bruder et al.,
640 2005; Caldú et al., 2007; Khanthiyong et al., 2019). Therefore, the absence of a relationship
641 between COMT and DRD2 gene polymorphisms and WCST measures in this study cannot be
642 generalized with certainty, since this is precluded by the limitations arising from sample size.
643 Namely, the sample size was the main reason for examining only the main effects of genes on
644 WCST indicators, without analyzing their interactions. The basal level of dopamine has a
645 polygenic basis, with probable significant interaction between different genes. Therefore, it is
646 possible that DRD2 and COMT simply did not cover the extent of variability necessary for a
647 relevant calculation of their effect. In other words, this result should not be viewed as an
648 argument against the association between dopamine genes and executive functions, due to the
649 absence of adequate conditions for observing their effects.

650 Significant main effects of BDNF genes were found on Non-Perseverative Errors, Trials to
651 Complete the First Category, Failure to Maintain Set, Categorizing Efficiency, and the WCST

652 factor score. After the correction for multiple testing, only Trials to Complete the First Category
653 still showed significant main effects of BDNF genes. The relatively small sample size may have
654 reduced the statistical power of our analyses. However, in genetics research, overlooking small
655 effects could have substantial consequences on the identification and understanding of the actual
656 determinants of complex psychological phenomena (Götz et al., 2020).

657 These results have important implications. First, they indicate a common genetic basis of
658 different indicators of the WCST, which further confirms its unitarity. Although Non-
659 Perseverative Errors, Trials to Complete the First Category, Failure to Maintain Set, and
660 Categorizing Efficiency represent different indicators of the WCST, it is possible that they all
661 constitute a unique aspect of executive functions. Second, the results represent a direct
662 replication of previous findings (Alfimova et al., 2012; Harris et al., 2006; Hashimoto et al.,
663 2016), providing additional support for the accumulation of evidence on the role of BDNF in the
664 regulation of cognitive processes. In fact, the association between the BDNF Met allele and
665 better achievement on the WCST is not in line with the assumption that this allele contributes to
666 poorer cognitive efficiency. This result primarily refers to aspects of cognition related to the
667 memory domain (e.g., Egan et al., 2003; Hariri et al., 2003).

668 Furthermore, after correction for multiple comparisons, this research highlighted a
669 specific relationship between the BDNF polymorphism and the total number of trials to
670 successfully complete the first category. While this measure can be an indicator of executive
671 dysfunction, it also can reflect conceptual ability. Met group carriers have better performance on
672 this measure of initial conception and abstraction ability than Val/Val homozygotes, with
673 significantly fewer attempts to complete the first category. Since the total number of trials to
674 complete the first category reflects the ability to switch from an incorrect sorting concept, which

675 incorporates set shifting and response inhibition capacity, our finding is consistent with earlier
676 studies that reported that Met carriers had higher average performance in non-hippocampal-
677 based tasks, including the Go/NoGo response inhibition task (Beste et al., 2010) and other
678 executive tasks, such as the Stroop task (Gajewski et al., 2012) and working memory tasks
679 (Alfimova et al., 2012), as well as with better nonverbal reasoning skills (Harris et al., 2006).
680 Although some research does not find any association of the BDNF Val66Met polymorphism
681 with executive function (Mandelman & Grigorenko 2012; Toh et al., 2017), and some find better
682 performance in association with the Val/Val polymorphism (e.g., Altmann et al., 2016;
683 Rybakowski et al., 2003), the Met group in our study mainly included Val-Met heterozygotes,
684 without a representative number of Met homozygotes. Therefore, our result must be considered
685 with great caution. Situational anxiety due to feedback during task solving also may have
686 contaminated the response. An association between anxiety and the BDNF Val allele is a
687 common finding (Lang et al., 2005). Therefore, future studies should clarify how the influences
688 of the BDNF Val66Met polymorphism on cognitive abilities differ depending on the specific
689 neural system and cognitive function, as well as health status, brain development stage, and other
690 potential confounding factors.

691 Our results diverged from the specificity of the traditional WCST scores posited by
692 authors and indicated an overlap of most of the variance shared between WCST variables. They
693 were inconsistent with the interpretation that these measures represent distinct constructs.
694 Instead, the measures appear to reflect the same dimension of various aspects of WCST
695 performance. The authors' definitions suggest several factors underlying the different types of
696 errors in the WCST, which represent indices of more independent abilities. However, the results
697 of this study seem to support the claim that different WCST scores can be explained by a single

698 common genetic factor, which would in turn suggest the use of the WCST as a unique measure
699 of a certain general executive function. In other words, the existence of a general genetic factor
700 supports the thesis on the unity of different executive functions measured by the WCST and the
701 existence of a common ability that underlies them.

702 4.1 Constraints on generality

703 Limitations arising from our study do not allow for a simple generalization of the results,
704 since the sample size can certainly contribute to the reduced reliability of findings. On average,
705 the sample used in our research encompassed upper-level education participants. Such a sample
706 structure resulted in the reduced variability of executive functions, which somewhat affected the
707 mutual relationships of WCST variables, reducing the magnitude of the correlations of different
708 measures. Furthermore, the study included a greater number of female pairs relative to male pairs
709 and a higher proportion of MZ pairs relative to DZ pair. However, it should be noted that these
710 two disproportions are quite typical in volunteer twin samples (Lykken et al., 1987). Because of
711 this imbalance in sex, we were unable to examine the genetic influences of sex differences. The
712 largest percentage of twins belonged to the young adult category ($M = 24.5$ and about 80% of the
713 twins in the sample were up to 30 years of age). Considering these limitations, all WCST
714 measures were corrected for sex and age effects by applying McGue and Bouchard's (1984)
715 regression technique, i.e., entering sex and age as predictors and taking each specific WCST
716 measure as a criterion, while retaining the residuals. Since participants in our study were all
717 White, they are unlikely to be representative of the broader population. Moreover, although
718 trained researchers administered the WCST, it is possible that small inconsistencies affected the
719 quality of responses, which could not be controlled as a method factor due to the sample size.

720 Furthermore, in the era of GWAS, the examination of the associations of single nucleotide
721 polymorphisms yields findings of limited representativeness. Despite all the limitations, our
722 study provides robust arguments from three research paradigms for the conclusion that the
723 WCST encompasses general executive processes in healthy adults.

724

725 **References**

- 726 Alfimova, M. V., Korovaitseva, G. I., Lezheiko, T. V., & Golimbet, V. E. (2012). Effect of
727 BDNF Val66Met polymorphism on normal variability of executive functions. *Bulletin of*
728 *experimental biology and medicine*, 152(5), 606–609. [https://doi.org/10.1007/s10517-](https://doi.org/10.1007/s10517-012-1587-x)
729 012-1587-x
- 730 Altmann, V., Schumacher-Schuh, A. F., Rieck, M., Callegari-Jacques, S. M., Rieder, C. R., &
731 Hutz, M. H. (2016). Val66Met BDNF polymorphism is associated with Parkinson's
732 disease cognitive impairment. *Neuroscience letters*, 615, 88-91.
733 <https://doi.org/10.1016/j.neulet.2016.01.030>
- 734 Anderson, P. (2002). Assessment and development of executive function during childhood.
735 *Child Neuropsychology*, 8, 71-82.
- 736 Anderson, V., Jacobs, R., & Anderson, P.J. (2008). *Executive functions nad the frontal lobes: A*
737 *lifespan perspective*. Taylor & Francis Group, New York, London
- 738 Anokhin, A. P., Golosheykin, S., Grant, J. D., & Heath, A. C. (2010). Developmental and genetic
739 influences on prefrontal function in adolescents: a longitudinal twin study of WCST
740 performance. *Neuroscience letters*, 472(2), 119–122.
741 <https://doi.org/10.1016/j.neulet.2010.01.067>

- 742 Anokhin, A. P., Heath, A. C., & Ralano, A. (2003). Genetic influences on frontal brain function:
743 WCST performance in twins. *Neuroreport*, *14*(15), 1975–1978.
744 <https://doi.org/10.1097/00001756-200310270-00019>
- 745 Baddeley, A. D. (2007). Working memory, thought and action. Oxford: Oxford University Press.
- 746 Barnes, J. J., Dean, A. J., Nandam, L. S., O'Connell, R. G., & Bellgrove, M. A. (2011). The
747 molecular genetics of executive function: role of monoamine system genes. *Biological*
748 *psychiatry*, *69*(12), e127–e143. <https://doi.org/10.1016/j.biopsych.2010.12.040>
- 749 Barnett, J. H., Jones, P. B., Robbins, T. W., & Müller, U. (2007). Effects of the catechol-O-
750 methyltransferase Val 158 Met polymorphism on executive function: a meta-analysis of
751 the Wisconsin Card Sort Test in schizophrenia and healthy controls. *Molecular*
752 *psychiatry*, *12*(5), 502–509. <https://doi.org/10.1038/sj.mp.4001973>
- 753 Benzerouk, F., Gierski, F., Gorwood, P., Ramoz, N., Stefaniak, N., Hübsch, B., ... & Limosin, F.
754 (2013). Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism and its
755 implication in executive functions in adult offspring of alcohol-dependent probands.
756 *Alcohol*, *47*(4), 271–274. <https://doi.org/10.1016/j.alcohol.2013.03.001> bib/3.2.119.
- 757 Beste, C., Baune, B. T., Domschke, K., Falkenstein, M., & Konrad, C. (2010). Paradoxical
758 association of the brain-derived-neurotrophic-factor val66met genotype with response
759 inhibition. *Neuroscience*, *166*(1), 178-184.
760 <https://doi.org/10.1016/j.neuroscience.2009.12.022>
- 761 Boone, K. B., Pontón, M. O., Gorsuch, R. L., González, J. J., & Miller, B. L. (1998). Factor
762 analysis of four measures of prefrontal lobe functioning. *Archives of Clinical*
763 *Neuropsychology*, *13*(7), 585–595. [https://doi.org/10.1016/S0887-6177\(97\)00074-7](https://doi.org/10.1016/S0887-6177(97)00074-7)

- 764 Bowden, S. C., Fowler, K. S., Bell, R. C., Whelan, G., Clifford, C. C., Ritter, A. J., & Long, C.
765 M. (1998). The reliability and internal validity of the Wisconsin Card Sorting Test.
766 *Neuropsychological Rehabilitation*, 8(3), 243-254. <https://doi.org/10.1080/713755573>
- 767 Bowden, S. C., Fowler, K. S., Bell, R. C., Whelan, G., Clifford, C. C., Ritter, A. J., Long, C. M.
768 (1998). The reliability and internal validity of the Wisconsin Card Sorting Test.
769 *Neuropsychological Rehabilitation*, 8, 243-254.
- 770 Bruder, G. E., Keilp, J. G., Xu, H., Shikhman, M., Schori, E., Gorman, J. M., & Gilliam, T. C.
771 (2005). Catechol-O-methyltransferase (COMT) genotypes and working memory:
772 associations with differing cognitive operations. *Biological psychiatry*, 58(11), 901–907.
773 <https://doi.org/10.1016/j.biopsych.2005.05.010>
- 774 Byrne, B.M. (1989). *A primer of LISREL*. New York: Springer-Verlag
- 775 Calamia, M., Markon, K., & Tranel, D. (2013). The robust reliability of neuropsychological
776 measures: meta-analyses of test-retest correlations. *The Clinical neuropsychologist*,
777 27(7), 1077–1105. <https://doi.org/10.1080/13854046.2013.809795>
- 778 Caldú, X., Vendrell, P., Bartrés-Faz, D., Clemente, I., Bargalló, N., Jurado, M. A., Serra-
779 Grabulosa, J. M., & Junqué, C. (2007). Impact of the COMT Val108/158 Met and DAT
780 genotypes on prefrontal function in healthy subjects. *NeuroImage*, 37(4), 1437–1444.
781 <https://doi.org/10.1016/j.neuroimage.2007.06.021>
- 782 Campana, A., Macciardi, F., Gambini, O., & Scarone, S. (1996). The Wisconsin Card Sorting
783 Test (WCST) performance in normal subjects: a twin study. *Neuropsychobiology*, 34(1),
784 14–17. <https://doi.org/10.1159/000119284>
- 785 Ching–Yun, Y. (2002). Evaluating Cut off Criteria of Model Fit Indices for Latent Var-iable
786 Models with Binary and Continuous Outcomes. (Doctoral thesis, Univer-sity of

- 787 California, Los Angeles, USA). Retrieved from:
788 <http://www.statmodel2.com/download/Yudissertation.pdf>.
- 789 Chou, L. N., Kuo, P. H., Lin, C. C., & Chen, W. J. (2010). Genetic and environmental influences
790 on the Wisconsin Card Sorting Test performance in healthy adolescents: a twin/sibling
791 study. *Behavior genetics*, 40(1), 22–30. <https://doi.org/10.1007/s10519-009-9299-3>
- 792 Cianchetti, C., Corona, S., Foscoliano, M., Contu, D., & Sannio-Fancello, G. (2007). Modified
793 Wisconsin Card Sorting Test (MCST, MWCST): normative data in children 4-13 years
794 old, according to classical and new types of scoring. *The Clinical neuropsychologist*,
795 21(3), 456–478. <https://doi.org/10.1080/13854040600629766>
- 796 Cohen, J. (1992). *Statistical Power Analysis for the Behavioral Sciences*, 4th ed., New Jersey:
797 Lawrence Erlbaum Associates, Inc.
- 798 Čolović, P. (2019). Petarcolovic/R_CqBG 1.0.0-Beta. Zenodo, 2019. Zenodo,
799 [doi:https://doi.org/10.5281/zenodo.3514218](https://doi.org/10.5281/zenodo.3514218).
- 800 Čolović, P., Branovački, B., & Bosić, D. Z. (2018). Validation of zygosity assessment by a self-
801 report questionnaire in a sample of adult Serbian twins. *Primenjena psihologija*, 11(4),
802 419-432.
- 803 Damasio, A. R., & Anderson, S.W. (1993). The frontal lobes. In K. M. Heilman & E. Valenstein
804 (Eds.), *Clinical neuropsychology* (3rd ed., pp.409-460.). New York: Oxford University
805 Press.
- 806 De Luca, C. R., Wood, S. J., Anderson, V., Buchanan, J. A., Proffitt, T. M., Mahony, K., &
807 Pantelis, C. (2003). Normative data from the CANTAB. I: development of executive
808 function over the lifespan. *Journal of clinical and experimental neuropsychology*, 25(2),
809 242–254. <https://doi.org/10.1076/jcen.25.2.242.13639>

- 810 Delis, D. C., Kramer, J. H., Kaplan, E., & Holdnack, J. (2004). Reliability and validity of the
811 Delis-Kaplan Executive Function System: an update. *Journal of the International*
812 *Neuropsychological Society*, 10(2), 301-303.
813 <https://doi.org/10.1017/S1355617704102191>
- 814 Demakis, G. J. (2003). A meta-analytic review of sensitivity of the Wisconsin Card Sorting Test
815 to frontal and lateralized frontal brain damage. *Neuropsychology*, 17, 255-264.
- 816 Diamond A. (2013). Executive functions. *Annual review of psychology*, 64, 135–168.
817 <https://doi.org/10.1146/annurev-psych-113011-143750>
- 818 Dobson, P. (2000). An investigation into the relationship between neuroticism, extraversion and
819 cognitive test performance in selection. *International Journal of Selection and*
820 *Assessment*, 8(3), 99–109. <https://doi.org/10.1111/1468-2389.00140>
- 821 Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A.,
822 Zaitsev, E., Gold, B., Goldman, D., Dean, M., Lu, B., & Weinberger, D. R. (2003). The
823 BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human
824 memory and hippocampal function. *Cell*, 112(2), 257–269. [https://doi.org/10.1016/s0092-](https://doi.org/10.1016/s0092-8674(03)00035-7)
825 [8674\(03\)00035-7](https://doi.org/10.1016/s0092-8674(03)00035-7)
- 826 Eling, P., Derckx, K., & Meas, R. (2008). On the historical and conceptual background of the
827 Wisconsin Card Sorting Test, *Brain and Cognition*, 67, 247-253.
- 828 Engelhardt, L. E., Briley, D. A., Mann, F. D., Harden, K. P., & Tucker-Drob, E. M. (2015).
829 Genes Unite Executive Functions in Childhood. *Psychological science*, 26(8), 1151–
830 1163. <https://doi.org/10.1177/0956797615577209>
- 831 Erickson, K. I., Kim, J. S., Suever, B. L., Voss, M. W., Francis, B. M., & Kramer, A. F. (2008).
832 Genetic contributions to age-related decline in executive function: a 10-year longitudinal

- 833 study of COMT and BDNF polymorphisms. *Frontiers in human neuroscience*, 2, 11.
834 <https://doi.org/10.3389/neuro.09.011.2008>
- 835 Finkel, D., & Pedersen, N. L. (2004). Processing speed and longitudinal trajectories of change
836 for cognitive abilities: The Swedish Adoption/Twin Study of Aging. *Aging,*
837 *Neuropsychology, and Cognition*, 11(2-3), 325–345.
838 <https://doi.org/10.1080/13825580490511152>
- 839 Floyd, F. J., & Widaman, K. F. (1995). Factor analysis in the development and refinement of
840 clinical assessment instruments. *Psychological Assessment*, 7(3), 286-299.
841 <https://doi.org/10.1037/1040-3590.7.3.286>
- 842 Friedman, N. P., & Miyake, A. (2017). Unity and diversity of executive functions: Individual
843 differences as a window on cognitive structure. *Cortex*, 86, 186-204.
- 844 Friedman, N. P., Miyake, A., Young, S. E., DeFries, J. C., Corley, R. P., & Hewitt, J. K. (2008).
845 Individual differences in executive functions are almost entirely genetic in origin. *Journal*
846 *of experimental psychology. General*, 137(2), 201–225. [https://doi.org/10.1037/0096-](https://doi.org/10.1037/0096-3445.137.2.201)
847 [3445.137.2.201](https://doi.org/10.1037/0096-3445.137.2.201)
- 848 Fuster, J. M. (2002). Prefrontal cortex in temporal organization of action. *The Handbook of*
849 *Brain Theory and Neural Networks*, 2nd edn. MIT Press, Cambridge, 905-910.
- 850 Gajewski, P. D., Hengstler, J. G., Golka, K., Falkenstein, M., & Beste, C. (2012). The Met-
851 genotype of the BDNF Val66Met polymorphism is associated with reduced Stroop
852 interference in elderly. *Neuropsychologia*, 50(14), 3554-3563.
853 <https://doi.org/10.1016/j.neuropsychologia.2012.09.042>
- 854 Gatt, J. M., Nemeroff, C. B., Dobson-Stone, C., Paul, R. H., Bryant, R. A., Schofield, P. R., ... &
855 Williams, L. M. (2009). Interactions between BDNF Val66Met polymorphism and early

- 856 life stress predict brain and arousal pathways to syndromal depression and anxiety.
857 *Molecular psychiatry*, 14(7), 681–695. <https://doi.org/10.1038/mp.2008.143>
- 858 Geller, S., Wilhelm, O., Wacker, J., Hamm, A., & Hildebrandt, A. (2017). Associations of the
859 COMT Val158Met polymorphism with working memory and intelligence—A review and
860 meta-analysis. *Intelligence*, 65, 75–92. <https://doi.org/10.1016/j.intell.2017.09.002>
- 861 Godinez, D. A., Friedman, N. P., Rhee, S. H., Miyake, A., & Hewitt, J. K. (2012). Phenotypic
862 and genetic analyses of the Wisconsin Card Sort. *Behavior genetics*, 42(2), 209–220.
863 <https://doi.org/10.1007/s10519-011-9502-1>
- 864 Götz, F. M., Gosling, S. D., & Rentfrow, J. (2021, January 10). Small effects: The indispensable
865 foundation for a cumulative psychological science. <https://doi.org/10.31234/osf.io/hzrxf>
- 866 Grave, K. W., Bianchini, K. J., Hartley, S. M., Adams, D. (1999). The Wisconsin Card Sorting
867 Test in stroke rehabilitation: Factor structure and relationship to outcome. *Archives of*
868 *Clinical Neuropsychology*, 14, 497-509.
- 869 Grave, K. W., Ingram, F., Bianchini, K. J., (1998). Latent structure of the Wisconsin Card
870 Sorting Test in clinical sample. *Archives of Clinical Neuropsychology*, 13, 597-609.
- 871 Grave, K. W., Love, J. M., Sherwin, E., Mathias, C. W., Ramzinski, P., Levy, J. (2002).
872 Wisconsin Card Sorting Test in chronic severe traumatic brain injury: Factor structure
873 and performance subgroups. *Brain Injury*, 16, 29-40.
- 874 Grave, K. W., Stickle, T. R., Love, J. M., Bianchini, K. J., Stanford, M. S. (2005). Latent
875 structure of the Wisconsin Card Sorting Test: A confirmatory factor analytic study.
876 *Archives of Clinical Neuropsychology*, 20, 355-364.

- 877 Gurvich, C., & Rossell, S. L. (2015). Dopamine and cognitive control: sex-by-genotype
878 interactions influence the capacity to switch attention. *Behavioural brain research*, *281*,
879 96–101. <https://doi.org/10.1016/j.bbr.2014.11>.
- 880 Gustavson, D. E., Panizzon, M. S., Elman, J. A., Franz, C. E., Reynolds, C. A., Jacobson, K. C.,
881 Friedman, N. P., Xian, H., Toomey, R., Lyons, M. J., & Kremen, W. S. (2018). Stability
882 of genetic and environmental influences on executive functions in midlife. *Psychology*
883 and aging, *33*(2), 219–231. <https://doi.org/10.1037/pag0000230>
- 884 Hariri, A. R., Goldberg, T. E., Mattay, V. S., Kolachana, B. S., Callicott, J. H., Egan, M. F., &
885 Weinberger, D. R. (2003). Brain-derived neurotrophic factor val66met polymorphism
886 affects human memory-related hippocampal activity and predicts memory performance.
887 *The Journal of neuroscience: the official journal of the Society for Neuroscience*, *23*(17),
888 6690–6694. <https://doi.org/10.1523/JNEUROSCI.23-17-06690.2003>
- 889 Harris, S. E., Fox, H., Wright, A. F., Hayward, C., Starr, J. M., Whalley, L. J., & Deary, I. J.
890 (2006). The brain-derived neurotrophic factor Val66Met polymorphism is associated with
891 age-related change in reasoning skills. *Molecular psychiatry*, *11*(5), 505–513.
892 <https://doi.org/10.1038/sj.mp.4001799>
- 893 Harrisberger, F., Smieskova, R., Schmidt, A., Lenz, C., Walter, A., Wittfeld, K., Grabe, H. J.,
894 Lang, U. E., Fusar-Poli, P., & Borgwardt, S. (2015). BDNF Val66Met polymorphism and
895 hippocampal volume in neuropsychiatric disorders: A systematic review and meta-
896 analysis. *Neuroscience & Biobehavioral Reviews*, *55*, 107–118.
897 <https://doi.org/10.1016/j.neubiorev.2015.04.017>
- 898 Hashimoto, T., Fukui, K., Takeuchi, H., Yokota, S., Kikuchi, Y., Tomita, H., Taki, Y., &
899 Kawashima, R. (2016). Effects of the BDNF Val66Met Polymorphism on Gray Matter

- 900 Volume in Typically Developing Children and Adolescents. *Cerebral cortex*, 26(4),
901 1795–1803. <https://doi.org/10.1093/cercor/bhw020>
- 902 Heaton, R. K. (1981). Wisconsin card sorting test manual. Psychological assessment resources.
- 903 Heaton, R. K., Chelune, G. J., Tallei, J. L., Key, G. G. & Curtiss, G. (1993). *Wisconsin Card*
904 *Sorting Test manual: Revised and Expanded*. Odessa, FL: Psychological Assessment
905 Resources.
- 906 Henrich, J., Heine, S. J., & Norenzayan, A. (2010). Most people are no WEIRD. *Nature*,
907 466(7302), 29. <https://doi.org/10.1038/466029a>
- 908 Henson, R. K., & Roberts, J. K. (2006). Use of Exploratory Factor Analysis in Published
909 Research: Common Errors and Some Comment on Improved Practice. *Educational and*
910 *Psychological Measurement*, 66(3), 393-416. <https://doi.org/10.1177/0013164405282485>
- 911 Hu, L. T., & Bentler, P. M. (1999). Cutoff criteria for fit Indexes in covariance structure
912 analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling*,
913 6(1), 1–55. <https://doi.org/10.1080/10705519909540118>.
- 914 Huges, C. & Graham, A. (2002). Measuring executive functions in childhood: Problems and
915 solutions? *Child and Adolescent Mental Health*, 7, 131-142.
- 916 IBM SPSS statistics for windows, version 21.0. Armonk, NY: IBM Corp.
- 917 Kautzky, A., James, G. M., Philippe, C., Baldinger-Melich, P., Kraus, C., Kranz, G. S., ... &
918 Wadsak, W. (2019). Epistasis of HTR1A and BDNF risk genes alters cortical 5-HT1A
919 receptor binding: PET results link genotype to molecular phenotype in depression.
920 *Translational psychiatry*, 9(1), 1–10. <https://doi.org/10.1038/s41398-018-0308-2>
- 921 Kazak, A. E. (2018). Editorial: Journal article reporting standards. *American Psychologist*, 73(1),
922 1–2. <https://doi.org/10.1037/amp0000263>

- 923 Khanthiyong, B., Thanoi, S., Reynolds, G. P., & Nudmamud-Thanoi, S. (2019). Association
924 study of the functional Catechol-O-Methyltransferase (COMT) Val158Met
925 polymorphism on executive cognitive function in a Thai sample. *International journal
926 of medical sciences, 16*(11), 1461. <https://doi.org/10.7150/ijms.35789>
- 927 Klaus, K., Butler, K., Durrant, S. J., Ali, M., Inglehearn, C. F., Hodgson, T. L., ... & Pennington,
928 K. (2017). The effect of COMT Val158Met and DRD 2 C957T polymorphisms on
929 executive function and the impact of early life stress. *Brain and behavior, 7*(5), e00695.
930 <https://doi.org/10.1002/brb3.695>
- 931 Kline, R. B. (2010). Principles and practice of structural equation modeling. New York, NY:
932 Guilford
- 933 Lang, U. E., Hellweg, R., Kalus, P., Bajbouj, M., Lenzen, K. P., Sander, T., Kunz, D., &
934 Gallinat, J. (2005). Association of a functional BDNF polymorphism and anxiety-related
935 personality traits. *Psychopharmacology, 180*(1), 95–99. [https://doi.org/10.1007/s00213-
936 004-2137-7](https://doi.org/10.1007/s00213-004-2137-7)
- 937 Lebel, C., & Beaulieu, C. (2011). Longitudinal development of human brain wiring continues
938 from childhood into adulthood. *The Journal of neuroscience: the official journal of the
939 Society for Neuroscience, 31*(30), 10937–10947.
940 <https://doi.org/10.1523/JNEUROSCI.5302-10.2011>
- 941 Logue, S. F., & Gould, T. J. (2014). The neural and genetic basis of executive function:
942 attention, cognitive flexibility, and response inhibition. *Pharmacology, biochemistry, and
943 behavior, 123*, 45–54. <https://doi.org/10.1016/j.pbb.2013.08.007>

- 944 Lykken, D. T., McGue, M., & Tellegen, A. (1987). Recruitment bias in twin research: the rule of
945 two-thirds reconsidered. *Behavior genetics*, 17(4), 343–362.
946 <https://doi.org/10.1007/BF01068136>
- 947 Malhotra, A. K., Kestler, L. J., Mazzanti, C., Bates, J. A., Goldberg, T., & Goldman, D. (2002).
948 A functional polymorphism in the COMT gene and performance on a test of prefrontal
949 cognition. *The American journal of psychiatry*, 159(4), 652–654.
950 <https://doi.org/10.1176/appi.ajp.159.4.652>
- 951 Mandelman, S. D., & Grigorenko, E. L. (2012). BDNF Val66Met and cognition: all, none, or
952 some? A meta-analysis of the genetic association. *Genes, Brain and Behavior*, 11(2),
953 127-136. <https://doi.org/10.1111/j.1601-183X.2011.00738.x>
- 954 Mardia, K. V. (1970). Measures of multivariate skewness and kurtosis with applications.
955 *Biometrika*, 57(3), 519-530.
- 956 McCartney, K., Harris, M. J., & Bernieri, F. (1990). Growing up and growing apart: A
957 developmental meta-analysis of twin studies. *Psychological Bulletin*, 107(2), 226–237.
958 <https://doi.org/10.1037/0033-2909.107.2.226>
- 959 McGue, M., & Bouchard, T. J. (1984). Adjustment of twin data for the effects of age and sex.
960 *Behavior Genetics*, 14(4), 325–343. <https://doi.org/10.1007/BF01080045>
- 961 Millsap, R. E. (2012). *Statistical approaches to measurement invariance*. Routledge.
- 962 Miyake, A., & Friedman, N. P. (2012). The nature and organization of individual differences in
963 executive functions: four general conclusions. *Current Directions in Psychological*
964 *Science*, 21, 8–14.
- 965 Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D.
966 (2000). The unity and diversity of executive functions and their contributions to complex

- 967 "Frontal Lobe" tasks: a latent variable analysis. *Cognitive psychology*, 41(1), 49–100.
968 <https://doi.org/10.1006/cogp.1999.0734>
- 969 Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., Wager, T. D. (2000).
970 The unity and diversity of executive functions and their contributions to complex
971 “frontal lobe” tasks: A latent variable analysis. *Cognitive Psychology*, 41, 49–100.
- 972 Neale, M. C. C. L., & Cardon, L. R. (2013). *Methodology for genetic studies of twins and*
973 *families* (Vol. 67). Springer Science & Business Media.
- 974 Nicole, S., & Del Miglio, C. (1997). Abstraction skillfulness in monozygotic and dizygotic twin
975 pairs. *Acta geneticae medicae et gemellologiae*, 46(1), 57–67.
976 <https://doi.org/10.1017/s0001566000000751>
- 977 Obonsawin, M. C., Crawford, J. R., Page, J., Chalmers, P., Low, G., & Marsh, P. (1999).
978 Performance on the Modified Card Sorting Test by normal, healthy individuals:
979 relationship to general intellectual ability and demographic variables. *The British*
980 *journal of clinical psychology*, 38(1), 27–41. <https://doi.org/10.1348/014466599162647>
- 981 O'Connor B. P. (2000). SPSS and SAS programs for determining the number of components
982 using parallel analysis and velicer's MAP test. *Behavior research methods, instruments,*
983 *& computers: a journal of the Psychonomic Society, Inc*, 32(3), 396–402.
984 <https://doi.org/10.3758/bf03200807>
- 985 Oniszczenko, W., Angleitner, A., Strelau, J., & Angert, T. (1993). The questionnaire of twins'
986 physical resemblance. Unpublished questionnaire, University of Warsaw, Warsaw,
987 Poland, and University of Bielefeld, Bielefeld, Germany.

- 988 Pineda, D. A., & Merchan, V. (2003). Executive function in young Colombian adults.
989 *International Journal of Neuroscience*, 113(3), 397–410.
990 <https://doi.org/10.1080/00207450390162164>
- 991 Polgár, P., Réthelyi, J. M., Bálint, S., Komlósi, S., Czobor, P., Bitter, I. (2010). Executive
992 function in deficit schizophrenia: What do the dimensions of the Wisconsin Card Sorting
993 Test tell us? *Schizophrenia Research*, 122, 85-93.
- 994 R Core Team (2016). R: A Language and Environment for Statistical Computing. Vienna,
995 Austria: R Foundation for Statistical Computing <https://www.R-project.org/>.
- 996 Reed, T., Plassman, B. L., Tanner, C. M., Dick, D. M., Rinehart, S. A., & Nichols, W. C. (2005).
997 Verification of self-report of zygosity determined via DNA testing in a subset of the
998 NAS-NRC twin registry 40 years later. *Twin research and human genetics: the official*
999 *journal of the International Society for Twin Studies*, 8(4), 362–367.
1000 <https://doi.org/10.1375/1832427054936763>
- 1001 Rijdsdijk, F. V., & Sham, P. C. (2002). Analytic approaches to twin data using structural equation
1002 models. *Briefings in bioinformatics*, 3(2), 119–133. <https://doi.org/10.1093/bib/3.2.119>
- 1003 Rosa, A., Peralta, V., Cuesta, M. J., Zarzuela, A., Serrano, F., Martínez-Larrea, A., & Fañanás,
1004 L. (2004). New evidence of association between COMT gene and prefrontal
1005 neurocognitive function in healthy individuals from sibling pairs discordant for
1006 psychosis. *American Journal of Psychiatry*, 161(6), 1110–1112.
1007 <https://doi.org/10.1176/appi.ajp.161.6.1110>
- 1008 Rosseel, Y. (2012). Lavaan: An R package for structural equation modeling. *Journal of*
1009 *Statistical Software*, 48, 1–36. Retrieved from <http://www.jstatsoft.org/v48/i02/>

- 1010 Rybakowski, J. K., Borkowska, A., Czerski, P. M., Skibińska, M., & Hauser, J. (2003).
1011 Polymorphism of the brain-derived neurotrophic factor gene and performance on a
1012 cognitive prefrontal test in bipolar patients. *Bipolar disorders*, 5(6), 468-472.
1013 <https://doi.org/10.1046/j.1399-5618.2003.00071.x>
- 1014 Sanwald, S., Montag, C., & Kiefer, M. (2020). Depressive Emotionality moderates the influence
1015 of the BDNF Val66Met polymorphism on executive functions and on unconscious
1016 semantic priming. *Journal of Molecular Neuroscience*, 70(5), 699–712.
1017 <https://doi.org/10.1007/s12031-020-01479-x>
- 1018 Smederevac, S., Mitrović, D., Sadiković, S., Milovanović, I., Branovački, B., Dinić, B. M., ...
1019 Milutinović, A. (2019). Serbian twin registry. *Twin Research and Human Genetics*,
1020 22(6), 660–666. <https://doi.org/10.1017/thg.2019.114>.
- 1021 Solomon, S. R., & Sawilowsky, S. S. (2009). Impact of rank–based normalizing transformations
1022 on the accuracy of test scores. *Journal of Modern Applied Statistical Methods*, 8, 448–
1023 462. <https://doi.org/10.22237/jmasm/1257034080>.
- 1024 Somsen, R. J., Van der Molen, M. W., Jennings, J. R., van Beek, B. (2000). Wisconsin Card
1025 Sorting in adolescents: Analysis of performance, response times and heart rate. *Acta*
1026 *Psychologica*, 104, 227-257.
- 1027 Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A compendium of neuropsychological tests:*
1028 *Administration, norms, and commentary* (3rd ed.). Oxford University Press.
- 1029 Suchy (2009). Executive functioning: Overview, assessment, and reasearch issues for non-
1030 neuropsychologists. *Annals of Behavioral Medicine*, 37, 106-116.
- 1031 Taylor J. (2007). Heritability of Wisconsin Card Sorting Test (WCST) and Stroop Color-Word
1032 Test performance in normal individuals: implications for the search for endophenotypes.

- 1033 *Twin research and human genetics: the official journal of the International Society for*
1034 *Twin Studies*, 10(6), 829–834. <https://doi.org/10.1375/twin.10.6.829>
- 1035 Toh, Y. L., Ng, T., Tan, M., Tan, A., & Chan, A. (2018). Impact of brain-derived neurotrophic
1036 factor genetic polymorphism on cognition: A systematic review. *Brain and*
1037 *behavior*, 8(7), e01009. <https://doi.org/10.1002/brb3.1009>
- 1038 Tunbridge, E. M., Narajos, M., Harrison, C. H., Beresford, C., Cipriani, A., & Harrison, P. J.
1039 (2019). Which dopamine polymorphisms are functional? systematic review and meta-
1040 analysis of COMT, DAT, DBH, DDC, DRD1–5, MAOA, MAOB, TH, VMAT1, and
1041 VMAT2. *Biological psychiatry*, 86(8), 608–620.
1042 <https://doi.org/10.1016/j.biopsych.2019.05.014>
- 1043 Wishart, H. A., Roth, R. M., Saykin, A. J., Rhodes, C. H., Tsongalis, G. J., Pattin, K. A., ... &
1044 McAllister, T. W. (2011). COMT Val158Met genotype and individual differences in
1045 executive function in healthy adults. *Journal of the International Neuropsychological*
1046 *Society*, 17(1), 174–180. <https://doi.org/10.1017/s1355617710001402>
- 1047 Xu, H., Kellendonk, C. B., Simpson, E. H., Keilp, J. G., Bruder, G. E., Polan, H. J., ... & Gilliam,
1048 T. C. (2007). DRD2 C957T polymorphism interacts with the COMT Val158Met
1049 polymorphism in human working memory ability. *Schizophrenia research*, 90(1-3), 104–
1050 107. <https://doi.org/10.1016/j.schres.2006.10.001>
- 1051 Zelazo, P. D., Carter, A., Reznick, J. S., & Frye, D. (1997). Early development of executive
1052 function: A problem-solving framework. *Review of General Psychology*, 1, 198-226.

1053

1054 Table 1

1055

1056 *Sociodemographic characteristics of study subjects*

1057

Age (years)	Range (17-58) 24.08 ± 7.02
Gender	
male	28.63%
female	71.37%
Race	
White/Caucasian	100.0%
Education level	
Primary education (8 years in total)	0.86%
Secondary (11-12 years in total)	27.16%
Higher School and University (16-17 years in total)	21.12%
Student	47.84%
Other	3.02%
Employment status	
Unemployed	34.87%
Employed	26.97%
Retired	0.88%
Student	32.24%
Other	5.04%
Material status	
Very bad	0.64%
Bad	4.29%
Average	33.05%
Good	49.36%
Very good	12.66%

1058

1059 Table 2
1060
1061 *Descriptive Statistics and Twin Intraclass Correlation Coefficients for the Used Measures With*
1062 *95% Confidence Intervals*

WCST measure	<i>M (SD)</i>	MZ	DZ
Total Number of Errors	22.575 (17.229)	0.229** (0.073; 0.373)	-0.042 (-0.262; 0.180)
Non-Perseverative Errors	10.601 (9.891)	0.279** (0.126; 0.419)	-0.169 (-0.377; 0.055)
Perseverative Errors	12.215 (9.197)	0.213** (0.056; .359)	0.041 (-0.182; 0.259)
Perseverative Responses	13.676 (11.405)	0.207** (0.050; 0.353)	0.056 (-0.167; 0.273)
Categories Completed	5.485 (1.268)	0.296** (0.144; 0.434)	-0.116 (-0.330; 0.109)
Conceptual Level Responses	71.930 (17.191)	0.273** (0.120; 0.413)	-0.143 (-0.354; 0.081)
Trials to Complete the First Category	14.911 (10.618)	0.101 (-0.058; 0.255)	0.140 (-0.082; 0.349)
Failure to Maintain Set	0.526 (0.969)	0.143 (-0.016; 0.294)	-0.145 (-0.356; 0.079)
Categorizing Efficiency	68.441 (26.919)	0.292** (0.141; 0.431)	-0.159 (-0.369; 0.064)

1063 *Note.* *M* – mean, *SD* – standard deviation; MZ – monozygotic twins, DZ – dizygotic twins; * $p <$
1064 $.05$. ** $p < .01$.

Table 3

Factor Loadings From the One-Factor Result of the CFA on the Measures of the WCST

Model 3. One-factor with correlated residuals	Twin1	Twin2	Model 4. Reduced one-factor model	Twin1	Twin2
Number of WCST Categories	0.675	0.805	Categorizing Efficiency	0.971	0.973
Perseverative Errors	-0.918	-0.837	Perseverative Errors	-0.892	-0.884
Non-Perseverative Errors	-0.909	-0.820	Non-Perseverative Errors	-0.895	-0.856
Failure To Maintain Set	-0.455	-0.595	Conceptual Level Responses	0.959	0.953
Trials to Complete the First Category	-0.313	-0.294			
Conceptual Level Responses	0.930	0.988			

Table 4

Fit indices for CFA models Twin 1 and Twin 2.

Model	$\chi^2(df)$	<i>p-level</i>	AIC	BIC	CFI	TLI	SRMR	RMSEA (95% CI)	
Model 1.	102.355 (9)	0.000	14007.928	140049.391	0.893	0.822	0.059	0.211 (0.177-0.246)	
Twin 1	Model 2.	86.180 (8)	0.000	13987.631	14032.550	0.914	0.838	0.064	0.204 (0.168- 0.243)
	Model 3.	11.397 (6)	0.077	13909.838	13961.668	0.994	0.985	0.030	0.062 (0.000-0.114)
	Model 4.	3.961 (2)	0.136	8321.871	8349.514	0.998	0.995	0.006	0.065 (0.000-0.156)
Model 1.	102.809 (9)	0.000	14057.995	14099.459	0.886	0.811	0.067	0.211 (0.179-0.245)	
Twin 2	Model 2.	99.531(8)	0.000	14051.808	14096.727	0.893	0.799	0.073	0.221 (0.186- 0.258)
	Model 3.	30.178 (6)	0.000	13972.265	14024.094	0.973	0.932	0.052	0.131 (0.089-0.177)
	Model 4.	0.520 (2)	0.771	8427.141	8454.784	1.000	1.005	0.003	0.000 (0.000-0.085)

Note-model 1. One-factor model; Model 2. Two- factor model; Model 3. One-factor model with correlated residuals; Model 4. Reduced one-factor model

Table 5
Fit Indices for Multivariate Models

	Model	χ^2/df	AIC	BIC	CFI	TLI	RMSEA (95% CI)
Independent pathways model	ACE	72.526 (48)	16777	16915.274	0.989	0.987	0.066 (0.031 – 0.096)
	ADE	70.255 (48)	16775	16913.003	0.990	0.988	0.063 (0.026 – 0.093)
	AE	74.193 (56)	16763	16873.299	0.992	0.992	0.053 (0.000 – 0.083)
	CE	78.296 (56)	16767	16877.402	0.990	0.990	0.058 (0.021 – 0.087)
Common pathways model	ACE	74.904 (53)	16769	16890.375	0.990	0.990	0.059 (0.022 – 0.089)
	ADE	73.103 (53)	16768	16888.575	0.991	0.991	0.057 (0.016 – 0.087)
	AE	74.904 (58)	16759	16863.099	0.993	0.993	0.050 (0.000 – 0.080)
	CE	78.714 (58)	16763	16866.909	0.991	0.991	0.055 (0.015 – 0.084)

Notes. A – additive genetic variance. D – non-additive genetic variance. C – shared environmental variance. E – non-shared environmental variance and measurement error.

Table 6

Specific and Common Genetic and Environmental Contributions for the Common AE Multivariate Model With 95% Confidence

Intervals

Measures	Ac	As	h2	Ec	Es	e2
Categorizing Efficiency	0.232 (0.070 - 0.375)	0.001 (0.000 - 0.002)	0.233	0.712 (0.572 - 0.869)	0.055 (0.081 - 0.034)	0.767
AE Common pathways model						
Perseverative Errors	0.174 (0.310 - 0.028)	0.025 (0.000 - 0.052)	0.199	0.616 (0.790- .464)	0.185 (0.228 - 0.144)	0.801
Non-Perseverative Errors	0.211 (0.386 - 0.081)	0.000 (0.000 - 0.000)	0.211	0.557 (0.669 - 0.381)	0.232 (0.193- 0.294)	0.789
Conceptual Level Responses	0.217 (0.063- 0.362)	0.000 (0.024 - 0.000)	0.217	0.697 (0.549 - 0.845)	0.086 (0.114 - 0.066)	0.782

Note. Ac – common genetic variance. As – specific genetic variance. h2 – hereditary variance. Ec – common environmental variance.

Es – specific environmental variance. e2 – environmental variance.

Table 7

Mean Scores of WCST Dimensions in the Seven Allelic Configurations of Interest

	Categories Completed	Perseverative Errors	Perseverative Responses	Non-Perseverative Errors	Failure to Maintain Set	Trials to Complete the First Category	Total Errors	Conceptual Level Responses	Categorizing Efficiency	Factor score on the WCST
COMT										
Met+	8.081 (34.181)	8.900 (42.893)	9.006 (43.417)	10.757 (42.555)	5.619 (40.710)	2.298 (42.850)	11.097 (44.937)	-0.623 (14.983)	-1.412 (25.088)	-1.587 (23.506)
Met+/Met-	4.275 (34.279)	0.218 (45.254)	0.229 (45.145)	-0.369 (45.065)	1.174 (38.275)	0.805 (43.573)	0.001 (48.118)	0.986 (16.974)	1.480 (25.399)	1.641 (24.577)
Met-	-2.720 (35.589)	4.596 (47.048)	4.410 (46.655)	2.934 (49.296)	6.364 (40.980)	13.186 (46.769)	1.505 (51.819)	-1.572 (19.169)	-2.582 (30.419)	-2.112 (28.963)
DRD2										
A1+	2.616 (34.188)	4.791 (44.088)	4.653 (44.219)	4.318 (44.617)	2.819 (38.464)	-0.623 (41.559)	4.656 (47.433)	-0.831 (17.665)	-1.537 (26.885)	-1.270 (25.813)
A1-	4.963 (34.793)	3.121 (45.354)	3.192 (45.341)	3.301 (45.586)	3.718 (39.998)	5.236 (45.082)	3.219 (48.298)	0.448 (16.395)	0.535 (25.950)	0.576 (24.751)
BDNF										
Met66-	2.586 (35.372)	5.975 (45.748)	5.717 (45.693)	6.707 (45.873)	6.308 (40.836)	6.814 (44.120)	5.910 (48.860)	-0.732 (17.141)	-1.866 (27.059)	-1.568 (25.740)
Met66+	8.033 (32.499)	-1.751 (42.622)	-1.137 (42.967)	-3.521 (43.058)	-3.197 (35.430)	-4.463 (43.027)	-1.515 (45.638)	1.853 (15.871)	3.943 (23.819)	3.623 (23.142)

Table 8

Allelic Effects of COMT, DRD2, and BDNF Polymorphisms on WCST Dimensions

	Categories Completed	Perseverative Errors	Perseverative Responses	Non-Perseverative Errors	Failure to Maintain Set	Trials to Complete the First Category	Total Errors	Conceptual Level Responses	Categorizing Efficiency	Factor score on the WCST
COMT	2.196 (2)	1.479 (2)	1.503 (2)	2.384 (2)	0.726 (2)	2.143 (2)	2.184 (2)	0.751 (2)	0.849 (2)	0.947 (2)
DRD2	-0.632 (1)	0.346 (1)	0.303 (1)	0.209 (1)	-0.212 (1)	-1.239 (1)	.0279 (1)	-0.708 (1)	-0.735 (1)	-0.685 (1)
BDNF	-1.505 (1)	1.590 (1)	1.409 (1)	2.095 (1)*	2.361 (1)*	2.376 (1)*	1.430 (1)	-1.422 (1)	-2.158(1)*	-2.000 (1)*

Note. Values in the cells are values of **t** and **F** tests with df (degrees of freedom) shown in brackets; ** $p < .01$, * $p < .05$. Correlations that remained significant after the False Discovery Rate (FDR) correction are bolded (for 30 correlation coefficients, with the default critical p-value set on .05, the corrected critical value was $p = .01798$).

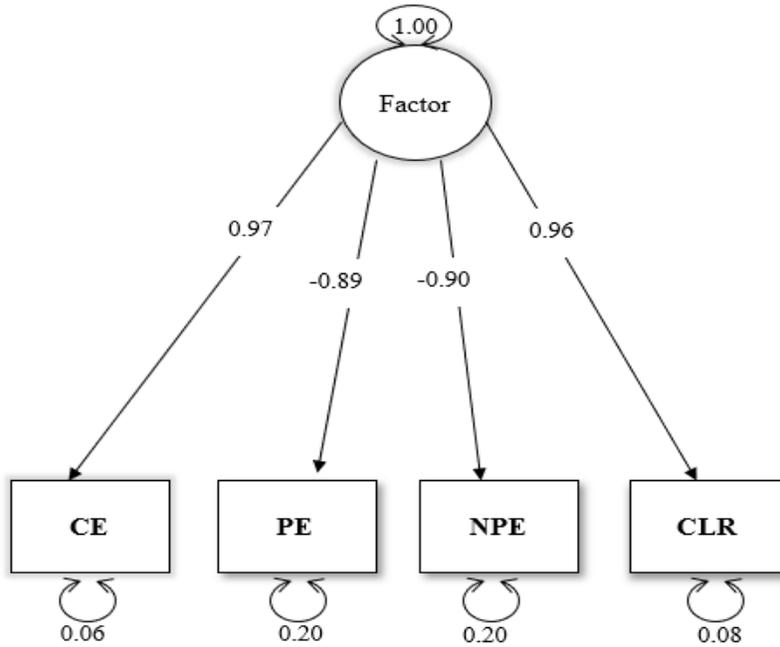


Fig. 1 Best-fitting (most parsimonious) CFA model twin 1. CE-Categorizing Efficiency PE- Perseverative errors; NPE- nonperseverative errors; CLR-Conceptual Level Responses

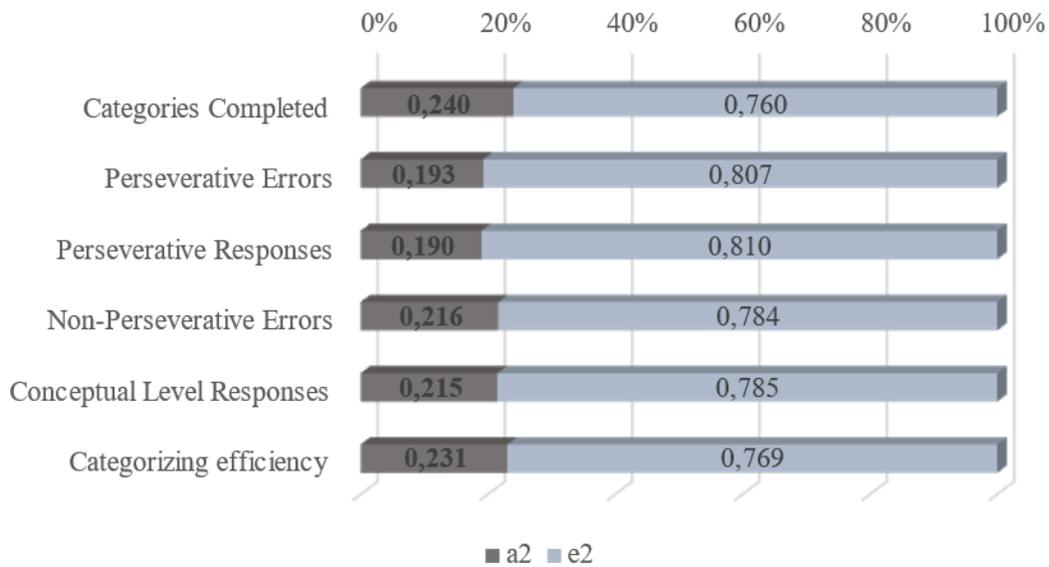


Fig. 2 Variance explained by additive genetic (a^2) and non-shared environmental factors (e^2) for WCST indexes.

Data availability statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.