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## **Executive Functions in Children and Adolescents with Turner Syndrome: A Systematic Review and Meta-Analysis**

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## REVIEW

Executive Functions in Children and Adolescents with Turner Syndrome:  
A Systematic Review and Meta-AnalysisClaire Mauger<sup>1,2</sup> · C. Lancelot<sup>1</sup> · A. Roy<sup>1,3</sup> · R. Coutant<sup>4</sup> · N. Cantisano<sup>1</sup> · D. Le Gall<sup>1,5</sup>Received: 23 March 2017 / Accepted: 26 March 2018  
© Springer Science+Business Media, LLC, part of Springer Nature 2018**Abstract**

Turner syndrome (TS) is a genetic disorder, affecting 1/2500 to 1/3000 live female births, induced by partial or total deletion of one X chromosome. The neurocognitive profile of girls with TS is characterized by a normal Verbal IQ and weaknesses in visual-spatial, mathematics, and social cognitive domains. Executive functions (EFs) impairments have also been reported in these young patients. However, methodological differences across studies do not allow determination of which EFs are impaired and what is the magnitude of these impairments. The aim of this review was to clarify the EF profile of children and adolescents with TS. Sixteen samples, from thirteen studies, were included in the current meta-analysis. EFs measures used in these studies were classified into working memory, inhibitory control, cognitive flexibility, or higher-order EFs tasks in accordance with Diamond's model, *Annual Review of Psychology*, 64, 135–168 (2013). Results confirmed that girls with TS had significant executive impairments with effect sizes varying from small (inhibitory control) to medium (cognitive flexibility) and large (working memory, higher-order EFs). Analyses by task revealed that cognitive inhibition may be more impaired than the other inhibitory control abilities. Heterogeneity across cognitive flexibility measures was also highlighted. Between-sample heterogeneity was observed for three tasks and the impact of participants' characteristics on EFs was discussed. This meta-analysis confirms the necessity to assess, in patients living with TS, each EF by combining both visual and verbal tasks. Results also underline the importance of exploring the impact of moderator variables, such as IQ, parental socio-economic status, TS karyotype, psychiatric comorbidities, and hormonal treatment status, upon girls with TS' executive profile.

**Keywords** Turner syndrome · Working memory · Inhibition · Flexibility · Executive functions · Meta-analysis

Turner syndrome (TS) is a common genetic disorder, caused by partial or complete monosomy X, affecting approximately 1/2500 to 1/3000 live female births (Sybert and McCauley 2004). The physical phenotype is commonly characterized by short stature and abnormal pubertal development, as well as a

webbed neck, and cardiovascular, renal, endocrine, and ear abnormalities (Bondy 2007). The neurocognitive profile of children and adolescents living with TS often includes a normal Verbal IQ contrasting with an impaired Performance IQ (see Hong et al. 2009, for a review). Poor mathematics performances (e.g. Mazzocco 1998; Murphy et al. 2006) and deficits in visual-spatial skills (e.g. Green et al. 2014; Romans et al. 1998), social cognition (e.g. Hong et al. 2011; McCauley et al. 2001), and executive functions (e.g. Romans et al. 1997; Temple et al. 1996) have been also described in this pediatric population.

The concept of executive functions (EFs) refers to a set of interrelated abilities mainly mediated by the prefrontal and parietal parts of the brain (Collette et al. 2006), regions in which structural and functional abnormalities have been highlighted in children and adolescents with TS (Bray et al. 2011; Haberecht et al. 2001; Kesler et al. 2004, 2006; Lepage et al. 2013a; Tamm et al. 2003). EF abilities are described as a group of top-down mental processes, acting as a regulation system, which enable people to “formulate goals; to initiate behavior; to anticipate the consequences of actions; to plan and organize behavior

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53 according to spatial, temporal, topical, or logical sequences; and  
 54 to monitor and adapt behavior to fit a particular task or context”  
 55 (Cicerone et al. 2000, p.1605). According to highly influential  
 56 frameworks in current literature (e.g. Lehto et al. 2003; Miyake  
 57 et al. 2000), EF is not a unified construct. Rather, EF is com-  
 58 prised of several correlated yet separable core functions that  
 59 include updating working memory, shifting, and inhibition.  
 60 Such three-factor models of EFs are not comprehensive and  
 61 the inclusion of other EFs has been explored. In this vein,  
 62 Diamond (2013) positioned EFs in a hierarchical framework  
 63 in which results of the three core functions mediate higher-  
 64 order EFs such as planning, problem solving, and reasoning.

65 One of the core EFs is *working memory* (WM) defined by  
 66 Diamond (2013) as the capacity to keep in mind information,  
 67 verbal or visual-spatial, that is not perceptually present and to  
 68 work with it. For example, the Self-Ordered Pointing Task  
 69 (SOPT, Petrides and Milner 1982) is a WM task in which sev-  
 70 eral sheets of paper, containing an identical set of pictures in  
 71 various positions, are presented successively to participants. All  
 72 of these stimuli have to be pointed, but each picture only once  
 73 and one picture at a time per page. Therefore, the participants  
 74 must memorize their previous answers and update information  
 75 at each new sheet to avoid pointing to an item already touched in  
 76 previous pages. Another core function in Diamond’s (2013)  
 77 model is *inhibitory control* which enables both suppression of  
 78 a prepotent representation (*cognitive inhibition*), control of at-  
 79 tention (*selective or focused attention*), and self-control that in-  
 80 volves, among others, not acting impulsively (*response*  
 81 *inhibition*). For instance, the flanker task can be considered as  
 82 a common inhibition task. It requires participants to report the  
 83 direction of an arrow (the target) flanked by irrelevant arrows  
 84 pointing either in the same or in the opposite direction as the  
 85 target. Thus, they have to focus attention on the relevant infor-  
 86 mation and ignore other stimuli. According to Diamond (2013),  
 87 WM and inhibitory control are supposed to be involved in a  
 88 third core EF, *cognitive flexibility*, which refers to the ability to  
 89 switch between mental sets or strategies. In that sense, the Trail-  
 90 Making Test (TMT), which requires participants to draw a line  
 91 between numbered circles in sequential order in the first part of  
 92 the task and between circles that alternate numbers and letters in  
 93 the second part of the task, allows investigation of cognitive  
 94 flexibility. *Higher-level EFs* such as reasoning, problem solving,  
 95 and planning are supposed to be underpinned by these three core  
 96 EFs (Diamond 2013). All of these functions may play a crucial  
 97 role in school success, and more widely, in daily life, allowing to  
 98 adopt appropriate reactions and behaviors. Diamond’s (2013)  
 99 EFs model can be useful to improve our understanding of some  
 100 of the underlying mechanisms behind poor mathematics perfor-  
 101 mances (Baker and Reiss 2016) often reported in children and  
 102 adolescents with TS as well as their difficulties in social and  
 103 interpersonal functioning (Lepage et al. 2013b).

104 Challenges for the investigation of EFs emerge from the fact  
 105 that executive tests involve different types of EFs, yet it remains

106 difficult to determine which executive process contributes most  
 107 to task achievement. For example, the Wisconsin Card Sorting  
 108 Test (WCST), widely used in research and clinical practice as a  
 109 measure of hypothesis generation and ability to shift response  
 110 (Goldstein and Green 1995), was initially introduced to explore  
 111 problem-solving and decision-making abilities (Berg 1948;  
 112 Grant and Berg 1948). In addition, executive tasks are not pure  
 113 measures of a single skill, and as a result, an individual’s exec-  
 114 utive performance can be contaminated by non-executive re-  
 115 quirements of the task (Burgess 1997). Given evidence for im-  
 116 paired visual-spatial ability in patients with TS (see Hong et al.  
 117 2009 for review), which might affect executive tasks requiring  
 118 visual-spatial processing, it could be interesting to consider the  
 119 impact of procedural aspects on EF performance. Furthermore,  
 120 another point to consider is that in some EF tasks participants  
 121 have to provide a response as quickly as possible. The nature of  
 122 the relation between processing speed and EFs is controversial  
 123 and remains to be specified (Lee et al. 2013). As reviewed by  
 124 Mazzocco (2006), a lower processing speed has been described  
 125 in girls with TS. Therefore, it remains unclear if poor perfor-  
 126 mances in executive timed tasks reflect specific EFs difficulties  
 127 or if these results are mediated by deficits in processing speed.

## Executive Functions in Turner Syndrome

128Q2

129 While there has been an increasing interest in EF abilities of  
 130 children with TS over the last two decades, existing studies  
 131 have shown mixed results regarding the nature of these exec-  
 132 utive deficits (Romans et al. 1997; Temple et al. 1996).  
 133 Furthermore, the magnitude of the effect size (ES) of execu-  
 134 tive dysfunction in this population remains unclear.

135 WM impairments in girls with TS were reported in the vast  
 136 majority of studies using digit span tasks (Lepage et al. 2011;  
 137 Loesch et al. 2005; McCauley et al. 1987; McGlone 1985;  
 138 Murphy and Mazzocco 2008; Romans et al. 1997; Romans  
 139 et al. 1998; Ross et al. 1995, 2000; Rovet 1993; Rovet et al.  
 140 1994) or other WM tasks such as n-back tasks (Bray et al.  
 141 2011; Haberecht et al. 2001), or the abstract version of an adap-  
 142 tation of the SOPT (Temple et al. 1996). Results are less conclu-  
 143 sive for the other EFs.

144 Response inhibition, within inhibitory control functions, is  
 145 the most studied in children with TS using tasks assessing im-  
 146 pulsivity. One study (Romans et al. 1998) reported that partici-  
 147 pants with TS responded faster than controls in the Matching  
 148 Familiar Figures Test (MFFT). Moreover, the number of com-  
 149 mission errors was significantly higher in the TS group in the  
 150 Test of Variables of Attention (TOVA: Romans et al. 1997,  
 151 1998). Yet, these findings are not consistent and other studies  
 152 reported no significant difference between girls with TS and  
 153 controls in these same tasks (MFFT: Romans et al. 1997; Ross  
 154 et al. 1998, 1995 – TOVA: Ross et al. 1995), as well as in a Go-  
 155 NoGo task (Tamm et al. 2003). Concerning the other aspects of

156 inhibitory control, these processes have been less often ex- 206  
157 plored. Girls with TS may have cognitive inhibition impair- 207  
158 ments, highlighted by the Stroop task (Temple et al. 1996; 208  
159 Waber 1979). Finally, selective attention deficits were also re- 209  
160 ported on a flanker task (Quintero et al. 2014) and on the 210  
161 Auditory Attention and Response Set subtest and Visual 211  
162 Attention subtest from the NEPSY (Green et al. 2015). 212

163 Evidence for poorer performance on set-shifting tasks appear 213  
164 to be contingent upon task selection. Hence, the majority of stud- 214  
165 ies assessing cognitive flexibility using verbal fluency tasks indi- 215  
166 cated deficient performance among TS samples for phonemic 216  
167 (Bender et al. 1989; Romans et al. 1997, 1998; Temple et al. 217  
168 1996; Temple 2002; Waber 1979) and semantic fluency (Rae 218  
169 et al. 2004; Romans et al. 1998; Temple et al. 1996). Girls with 219  
170 TS had more difficulties than control participants in the TMT 220  
171 (Bender et al. 1993) and in the Same-Opposite world subtest from 221  
172 the Test of Everyday Attention for Children (Skuse et al. 1997). 222  
173 In contrast, some studies using the WCST as an indicator for 223  
174 flexibility revealed no difference between TS and control groups 224  
175 (McGlone 1985; Romans et al. 1997, 1998; Temple et al. 1996), 225  
176 although results are not consistent (Bender et al. 1993; Loesch 226  
177 et al. 2005; Waber 1979). Performance is also heterogeneous with 227  
178 the Contingency Naming Test (CNT), where girls with TS ob- 228  
179 tained lower results than the control group in the two-attribute 229  
180 trials in two studies (Kirk et al. 2005; Mazzocco and Hanich 230  
181 2010) but not in another (Murphy and Mazzocco 2008). 231

182 Higher-level EFs have been assessed in children with TS 232  
183 with the Rey-Osterrieth Complex Figure (ROCF) and different 233  
184 problem-solving tasks such as the Tower of Hanoi (TOH), the 234  
185 Tower of London (TOL) or the Tower subtest from the NEPSY. 235  
186 In most studies (Bishop et al. 2000; Loesch et al. 2005; Reiss 236  
187 et al. 1995; Romans et al. 1997, 1998, 1995, 1997a; Waber 237  
188 1979), but not all (McGlone 1985), girls with TS had more 238  
189 difficulties than controls to reproduce the ROCF. Concerning 239  
190 the TOH and its variants, some studies did not find any differ- 240  
191 ence between the TS group and the controls (Temple et al. 1996; 241  
192 Green et al. 2015; Skuse et al. 1997), while in others, girls with 242  
193 TS obtained lower results (Romans et al. 1997, 1998). 243

194 In TS, differences between studies assessing EFs may be 244  
195 explained, in part, by methodological choices concerning ex- 245  
196 ecutive tasks, for example, visual or verbal modality, or lim- 246  
197 ited response time. Yet, participant characteristics (age, IQ, 247  
198 parental socioeconomic status, karyotype, hormonal 248  
199 treatments, and psychological co-morbidities) could also ex- 249  
200 plain discrepancies in results. 250

## 201 Moderator Variables of Executive Functions 251 202 in Turner Syndrome 252

203 The development of EFs occurs during the first year of life and 253  
204 goes on until the beginning of adulthood, each EF has its own 254  
205 developmental calendar (Best and Miller 2010). It is plausible to 255

206 expect that in TS, developmental changes may not follow the 206  
207 same curve as control children and, as age advances, differences 207  
208 between children with TS and their peers may increase or re- 208  
209 duce. Hence, heterogeneity of results could be explained by 209  
210 variability of participants' age between studies assessing EFs 210  
211 in TS (e.g. Skuse et al. 1997: age range from 6 to 25 years). 211  
212 Even if in the vast majority of studies, TS and control groups 212  
213 have been matched by age, in some studies (e.g. Kirk et al. 213  
214 2005; Murphy and Mazzocco 2008) the two groups were 214  
215 matched by full scale IQ. This IQ-matching criterion could have 215  
216 an impact on the magnitude of the ES on EF tasks. 216

217 Processing speed, likely to have an impact on EFs, and 217  
218 other aspects of EFs, such as WM abilities, are considered as 218  
219 part of intelligence constructs (Floyd et al. 2010; McGrew 219  
220 2009). Thus, these processes are assessed in intelligence test 220  
221 batteries (e.g. Wechsler 2014). When the TS group and con- 221  
222 trols were matched on IQ, differences between the two groups 222  
223 in some EF tasks may be lower in comparison to other studies 223  
224 in which controls had higher IQ than girls with TS. Moreover, 224  
225 considering IQ scores as matching criteria could lead to the 225  
226 inclusion of unrepresentative participants. For example, in- 226  
227 cluding healthy children with slightly lower IQ scores than 227  
228 expected (Dennis et al. 2009) can be misleading. 228

229 Another variable, which may also have an impact on EFs, 229  
230 is parental socioeconomic status (SES). Depending on the EF 230  
231 tasks (Ardila et al. 2005), children from families with low SES 231  
232 have more EF difficulties than children from well-off families 232  
233 (Hackman and Farah 2009; Sarsour et al. 2011). If girls with 233  
234 TS present some EF impairments, differences between these 234  
235 girls and control participants may be lower in studies in which 235  
236 participants with TS have significantly higher SES than con- 236  
237 trols. Inversely, differences between the control and TS groups 237  
238 may increase if controls are from well-off families and patients 238  
239 with TS are not. 239

240 Other characteristics, specific to children and adolescents 240  
241 with TS, should be also taken into account in EF assessment. 241  
242 In TS, the anomaly affecting one of the two X chromosomes 242  
243 can be present in all cells or only one part (mosaicism). The 243  
244 hypothesis of cognitive differences between different TS kar- 244  
245 yotypes has been explored in several studies in which girls 245  
246 with 45,X monosomy were compared to girls with mosaic 246  
247 karyotypes and girls with other TS karyotypes (e.g. X partial 247  
248 deletion or X translocation). Regarding intellectual abilities, 248  
249 girls with a ring X chromosome had more verbal and non- 249  
250 verbal difficulties than girls with 45,X monosomy (Kuntsi 250  
251 et al. 2000). These latter obtained significantly lower scores 251  
252 than girls with mosaicism on the Wechsler Intelligence Scale 252  
253 for Children, Fourth Edition (WISC-IV)'s perceptual reason- 253  
254 ing and WM indexes (Bray et al. 2011). Children with struc- 254  
255 tural abnormalities of X chromosome (translocation, isochro- 255  
256 mosome, partial deletion) had higher Verbal IQ than ones with 256  
257 X monosomy or mosaicism (Messina et al. 2007). Compared 257  
258 to the other karyotypes, 45,X monosomy has been associated 258

259 with an increase of visual-constructive and visual-perceptual  
 260 deficits (Ross et al. 1997a; Temple and Carney 1995), verbal  
 261 episodic memory impairments (Ross et al. 1995) and visual-  
 262 spatial WM difficulties (Buchanan et al. 1998; Temple et al.  
 263 1996). However, several studies reported that karyotype did  
 264 not significantly impact IQ (Lahood and Bacon 1985; Temple  
 265 2002; Zhao et al. 2013) or cognitive flexibility abilities  
 266 (Temple 2002). In children with 45,X monosomy, the influ-  
 267 ence of X chromosome parental origin has been explored and,  
 268 as the impact of karyotype, results were heterogeneous  
 269 (Bishop et al. 2000; Ergür et al. 2008; Kesler et al. 2004;  
 270 Larizza et al. 2002; Lepage et al. 2012, 2013c; Loesch et al.  
 271 2005; Skuse et al. 1997).

272 Several hormonal treatments are prescribed to children and  
 273 adolescents with TS, such as growth hormone (GH) to in-  
 274 crease adult height and estrogen therapy (around 12 years of  
 275 age) to induce puberty (Bondy 2007). Regarding cognitive  
 276 profile, no difference was highlighted between girls with TS  
 277 receiving GH and girls receiving placebo (Ross et al. 1997b),  
 278 yet, another study (Rovet and Holland 1993) highlighted im-  
 279 provement of social abilities in the GH group. Furthermore,  
 280 oxandrolone, an anabolic steroid, is used with GH in children  
 281 with extreme short stature or when GH treatment is not com-  
 282 menced before 9 years of age (Bondy 2007). After several  
 283 years of treatment, compared to placebo group, girls with TS  
 284 receiving oxandrolone had better WM abilities (Ross et al.  
 285 2003) and a lower frequency of severe arithmetic learning  
 286 disabilities (Ross et al. 2009). Moreover, positive effects of  
 287 an early estrogen treatment on nonverbal processing time,  
 288 motor speed (Ross et al. 1998), verbal WM, verbal and non-  
 289 verbal episodic memory (Ross et al. 2000) were emphasized  
 290 in young girls with TS receiving low doses of estrogen com-  
 291 pared to girls receiving placebo.

292 Finally, children with TS reported more depressive and  
 293 anxiety symptoms (Kiliç et al. 2005; McCauley et al. 2001;  
 294 Saad et al. 2015) but also a higher prevalence of attention  
 295 deficit-hyperactivity disorder (ADHD; Russell et al. 2006).  
 296 As these symptoms are known to be associated with executive  
 297 impairments in children and adolescents (Han et al. 2016;  
 298 Ursache and Raver 2014; Wagner et al. 2015; Willcutt et al.  
 299 2005), it would be interesting to consider these psychological  
 300 comorbidities in order to improve our understanding of the  
 301 heterogeneous nature of EF tasks performances.

302 **Aims**

303 Based on Diamond's (2013) hierarchical model of EFs, the  
 304 present meta-analysis addresses the following research ques-  
 305 tions (1) When comparing girls with TS and controls, are there  
 306 ES differences across tasks depending on EF abilities tested?  
 307 (2) Did children with TS fail only in visual modality EF tasks?  
 308 (3) Did participants with TS have lower performance than

controls only in EF tasks that require a rapid response? To 309  
 answer these questions, study results, in which EF abilities 310  
 of girls with TS were compared to age-matched control girls' 311  
 EF abilities, will be analyzed. 312

**Methods** 313

The search was conducted following the PRISMA (Preferred 314  
 Reporting Items for Systematic review and Meta-Analyses) 315  
 guidelines (Moher et al. 2009) and Gates and March's 316  
 (2016) recommendations. 317

**Study Eligibility Criteria** 318

To be retained in the current meta-analysis, studies had to meet 319  
 seven criteria (1) all of the patients included were diagnosed 320  
 with TS, (2) participants were aged between 6 to 18 years, (3) 321  
 the TS group had to be compared to a control group matched 322  
 at least by age and sex, (4) children included in the control 323  
 group had no pediatric or neurological disease, (5) at least one 324  
 neuropsychological task was used to assess WM, inhibitory 325  
 control, cognitive flexibility or higher-order EFs, (6) data re- 326  
 ported were sufficient to calculate an ES, (7) the article was 327  
 published in English or French. 328

**Search Strategy** 329

A systematic literature search was performed in September 330  
 2015 and updated in September 2017 without any restriction 331  
 of publication date. Five electronic databases (*Pubmed*, 332  
*PsycARTICLES*, *PsycINFO*, *Web of Science Core* 333  
*Collection*, and *Cochrane Central Register of Controlled* 334  
*Trials*) were examined. The following combination of key- 335  
 words was used: ("executive" or "cognitive" or "cognition" 336  
 or "neurocognitive" or "neuropsychological" or "inhibitory 337  
 control" or "inhibition" or "attention" or "cognitive flexibili- 338  
 ty" or "working memory" or "planning" or "decision mak- 339  
 ing") and ("child\*" or "adolescenc\*") and ("Turner syndrome" 340  
 or "X monosomy" or "sex chromosome abnormalities" or 341  
 "45,X" or "Ullrich-Turner syndrome" or "X chromosome ab- 342  
 normalities" or "X chromosome deletion"). Subsequently, the 343  
 reference section of publications found through our search 344  
 was checked to identify additional studies that may have been 345  
 missed. In addition, when data reported in the article were not 346  
 sufficient to calculate an ES, the authors were contacted to 347  
 collect missing data and unpublished results. 348

**Study Selection** 349

Initial searches were carried out by two authors (\*\* and \*\*). 350  
 Both authors were responsible for the exclusion of duplicated 351  
 records and the screening of titles and abstracts to check 352

353 eligible studies according to the inclusion criteria. Any dis-  
 354 crepancies were resolved by consensus. These studies were  
 355 further assessed for eligibility using the full text. Seven au-  
 356 thors were contacted to obtain missing data and unpublished  
 357 results. Unfortunately, none could respond positively to our  
 358 request.

## 359 Data Extraction

360 **Sample Characteristics** For each sample, means and standard  
 361 deviation (SD) of age, Verbal IQ (VIQ) and Performance IQ  
 362 (PIQ) were extracted for TS group and its matched controls. In  
 363 several studies, the number of participants could vary depend-  
 364 ing on the tasks, thus, sample size was extracted for each task.  
 365 For TS groups, when data were available, the proportion of  
 366 patients with 45,X karyotype and information concerning hor-  
 367 monal treatment (estrogen therapy and growth hormone ther-  
 368 apy) were also extracted.

369 **Executive Function Tasks** Neuropsychological measures of  
 370 EFs were coded separately when assessing one of the follow-  
 371 ing EF components: WM, inhibitory control, cognitive flexi-  
 372 bility, higher-order EFs. For each task, one variable was se-  
 373 lected as the most appropriate measure of EF. The chosen  
 374 variable had to be available in all studies included in the me-  
 375 ta-analysis. If data from several variables were present in the  
 376 retained studies, we have selected the one described as the  
 377 most pertinent measure to assess the targeted EF. This issue  
 378 was raised for three tasks, the TOVA, WCST and SOPT. For  
 379 the TOVA, the variable “commission errors” has been chosen  
 380 because, according to Greenberg and Waldman (1993), it al-  
 381 lows the assessment of impulsivity or response inhibition.  
 382 Concerning the WCST, the percent of perseverative errors,  
 383 which “may be a better metric of executive function if a single  
 384 score from the WCST is to be used” (Rhodes 2004, p.488),  
 385 has been retained. For the SOPT, used in one study, the vari-  
 386 able “number of pages before error” has been chosen because  
 387 it seemed to be the most adequate in the assessment of WM  
 388 abilities compared to the two others (total item perseveration,  
 389 total position perseveration). Whenever possible, a time vari-  
 390 able was also extracted. For each TS group and its control  
 391 group, sample size, mean and SD of each variable (or  $F$ -  
 392 value when such data were not available) were extracted.  
 393 Two studies (Ross et al. 1998, 2000) have examined the ef-  
 394 fects of an early estrogen treatment on girls with TS cognitive  
 395 profile by comparing two subgroups (one group with hormonal  
 396 treatment and one group without). In these studies, the age  
 397 ranges were 7 to 9 years (Ross et al. 2000) and 10 to 12 years  
 398 (Ross et al. 1998). Several other studies retained for the meta-  
 399 analyses included participants in the same age ranges, yet  
 400 patients with TS did not receive estrogen treatment.  
 401 Therefore, only placebo subgroup results were extracted from  
 402 these two studies.

## Data Analysis

Data analysis was carried out with R software, version 3.2.4. 404  
 (R Core Team 2016) using the packages “compute.es” (Del 405  
 Re 2013), “MAAd” (Del Re and Hoyt 2014), “metaSEM” 406  
 (Cheung 2015a), and “metafor” (Viechtbauer 2010). This last 407  
 one was also applied to create forest plots. 408

The ES was calculated for each variable. As Cohen’s  $d$  409  
 tends to lead to an overestimation of the ES due to the small 410  
 samples sizes, Hedge’s  $g$  correction formula was used to avoid 411  
 this bias (Borenstein et al. 2009; Hedges 1981). When means 412  
 and SD were missing, the ES was calculated using  $F$ -value. 413  
 The direction of ES was coded in such a way that a negative 414  
 score corresponded to a greater executive dysfunction of TS 415  
 group. To avoid obtaining a positive  $g$  when girls with TS 416  
 made more errors than control group or had longer response 417  
 time, the sign of ES had to be reversed for error and time 418  
 variables. Cohen’s criteria (Cohen 1992) were employed to 419  
 interpret ES. Thus, ES is “small”, “medium” or “large” when 420  
 $g$  value is respectively equal to 0.2, 0.5 or 0.8. For several 421  
 tasks (verbal fluency tasks, TOL in Temple et al. 1996; digit 422  
 span subtest in Ross et al. 2000), it was necessary to compute a 423  
 total score from subscores. Therefore, subscore ESs were 424  
 pooled using Borenstein et al.’s (2009) method. The latter uses 425  
 the correlation coefficient value to calculate  $g$  variance. In line 426  
 with Scammacca et al. (2014)’s recommendations, this corre- 427  
 lation coefficient value, unknown in the studies included in 428  
 this meta-analysis, was considered to be equal to 1. 429

In some studies, several tasks have been used to assess EFs. 430  
 Therefore, data extracted from a same group of participants 431  
 would be included several times in the meta-analysis. It was 432  
 necessary to consider the dependence between these ES. A 433  
 three-level meta-analysis was conducted using the 434  
 maximum-likelihood method to estimate heterogeneity. An 435  
 overall ES was calculated with all the ES. Three different 436  
 levels of heterogeneity are taken into account in this analysis 437  
 (1) sampling variance of all the ES at level 1, (2) variance 438  
 between ES extracted from the same sample at level 2 and 439  
 (3) variance between ES extracted from different samples at 440  
 level 3 (Assink and Wibbelink 2016). To test the hypothesis of 441  
 the homogeneity of ES, the Cochran’s  $Q$ -test was applied 442  
 (Cochran 1954). The  $p$ -value threshold was fixed to 10%. If 443  
 $p$ -value is less than 0.10, the heterogeneity cannot be consid- 444  
 ered as exclusively due to within-sample error. The level 2 an 445  
 level 3 heterogeneity variances were estimated with  $\tau^2_{(2)}$  and 446  
 $\tau^2_{(3)}$ , respectively. To quantify the heterogeneity, the  $I^2$  index 447  
 was calculated.  $I^2_{(2)}$  and  $I^2_{(3)}$  allow to estimate the proportion 448  
 of the total heterogeneity of the ES due to the level 2 (within- 449  
 sample) and level 3 (between-sample) heterogeneity. The ef- 450  
 fect of moderators (task modality, type of assessed EF) was 451  
 investigated using a mixed-effects model. In these analyses, 452  
 $R^2_{(2)}$  and  $R^2_{(3)}$  estimate the percentage of variance of the het- 453  
 erogeneity explained by the moderator at level 2 and level 3 454

455 (Cheung 2015b). Following the method introducing by  
 456 Cheung (2015b), the three-level model has been compared  
 457 to a model in which  $\tau^2_{(3)}$  is set to zero and to a model in  
 458 which  $\tau^2_{(2)}$  is set to zero. To complete the three-level meta-  
 459 analysis, a univariate meta-analysis was conducted for each  
 460 EF task. The random-effects model, which takes into account  
 461 within-sample and between-sample variances, was used to  
 462 conduct these different univariate analyses.

463 An overall ES was calculated for each EF task  
 464 employed in several studies. To assess processing speed  
 465 in girls with TS, an ES was calculated for the response  
 466 time variable of EF tasks when data were available. In  
 467 some of these meta-analyses, only a little number of  
 468 studies could be included. Hence, the results should be  
 469 interpreted with caution. As for the three-level meta-  
 470 analysis, Cochran's  $Q$ -test was used to assess the pres-  
 471 ence of heterogeneity among the ES (Cochran 1954).  
 472 The parameter  $\tau^2$ , using DerSimonian and Laird meth-  
 473 od, estimates the between-sample heterogeneity variance  
 474 (Borenstein et al. 2009). The  $I^2$  index was calculated to  
 475 quantify the proportion of total variation due to true  
 476 variability between samples rather than chance. The  $I^2$   
 477 index estimates what percentage of the observed vari-  
 478 ance would remain if the sampling error could be elim-  
 479 inated (Borenstein et al. 2017). For each univariate me-  
 480 ta-analysis, a funnel plot was produced. The number of  
 481 studies included in this meta-analysis was too low to  
 482 statistically test funnel plot asymmetry (Higgins and  
 483 Green 2011). Therefore, the funnel plots were visually  
 484 inspected to detect outliers. The leave-one-out method  
 485 was used to verify the robustness of each univariate  
 486 meta-analysis' results and to assess the impact of out-  
 487 liers on the overall ES. Hence, each analysis was con-  
 488 ducted repeatedly removing one study at a time  
 489 (Viechtbauer 2010).

490 **Results**

491 **Characteristics of the Samples**

492 Thirteen articles met the seven selection criteria cited  
 493 above. Among these, two publications (Romans et al.  
 494 1997; Ross et al. 1995) included several independent  
 495 patients groups, each of them being compared to their  
 496 own control group (matched by age and sex). As a  
 497 result, sixteen independent samples were retained in  
 498 the meta-analysis. See Fig. 1 for a flow diagram sum-  
 499 marizing the study's selection process.

500 Sample characteristics are summarized in Table 1. In  
 501 each sample, the TS group and its control group were  
 502 matched by age and sex. The mean age range was from  
 503 8.1 to 14.2 years of age for TS groups and 8.4 to

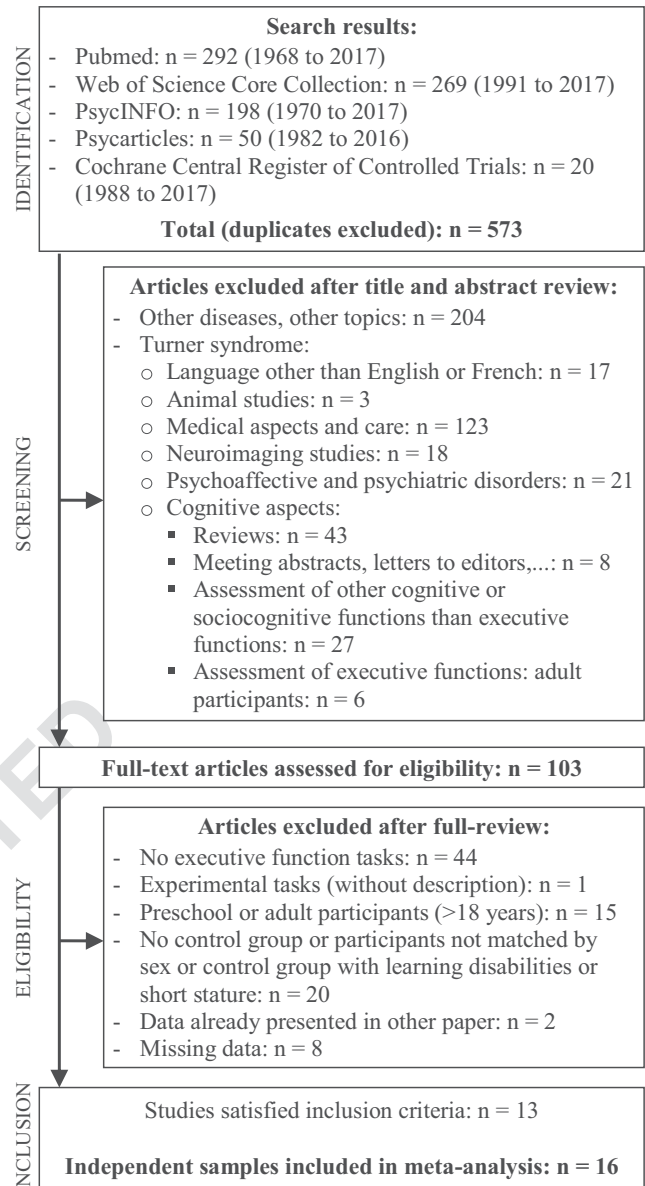


Fig. 1 Flow diagram of selection of studies

14.3 years of age for control groups. Concerning IQ, data were missing in several studies (Bray et al. 2011; Rae et al. 2004; Ross et al. 1997a; Temple et al. 1996; Temple 2002). The mean VIQ ranged between 96 and 107 in TS groups and between 101.5 and 115.3 in control groups, whereas the mean PIQ ranged between 87.7 and 95 in TS groups and between 102 and 113 in control groups.

TS groups' characteristics considerably varied between studies. Thus, three studies included only patients with 45,X karyotype (Quintero et al. 2014; Rae et al. 2004; Ross et al. 1997a), whereas in other samples, different TS karyotypes (45,X, partial deletion of the second X, different mosaic karyotypes) were mixed. Concerning estrogen therapy, five studies did not

**Table 1** Summary of samples characteristics

Studies	Turner syndrome group		Patients with GH therapy				Control group				Number of EF tasks	
	Patients with 45,X karyotype	Estrogen therapy	Patients with Estrogen therapy	Mean age (SD)	VIQ (SD)	PIQ (SD)	Mean age (SD)	VIQ (SD)	PIQ (SD)	Mean age (SD)		VIQ (SD)
t1.1	Bray et al. 2011	10/14	—	10.6 (1.6)	—	—	10.6 (1.5)	—	—	—	—	2
t1.2	Quintero et al. 2014	31/31	—	10.7 (2.31)	— <sup>a</sup>	— <sup>a</sup>	10.2 (2.27)	— <sup>a</sup>	— <sup>a</sup>	— <sup>a</sup>	— <sup>a</sup>	2
t1.3	Rae et al. 2004	9/9	0/9	9.92 (1.5)	—	—	9.92 (1.25)	—	—	—	—	2
t1.4	Reiss et al. 1995	27/30	3/23 <sup>b</sup>	10.5 (3.42)	99 (15.4)	87.7 (13.7)	10.75 (2.83)	115.3 (16.4)	110.3 (15.5)	—	—	1
t1.5	Romans et al. 1997	3 samples confounded: 65/105	0/30	8.4 (0.8)	107 (15)	94 (13)	8.5 (0.8)	102 (10)	102 (12)	—	—	7
t1.6	Romans et al. 1997	10.0 to 12.49	0/37	11.2 (0.8)	102 (12)	94 (14)	11.4 (0.7)	102 (10)	106 (15)	—	—	7
t1.7	Romans et al. 1997	12.5 to 16.9	38/38	14.2 (1.6)	102 (11)	91 (12)	14.2 (1.2)	105 (8)	108 (12)	—	—	7
t1.8	Romans et al. 1998	2 samples confounded: 63/99 <sup>c</sup>	2 samples confounded: 99/99 <sup>c</sup>	14.2 (0.83)	98.5 (12.4)	89.4 (12.8)	14.3 (0.8)	101.5 (10.4)	106.9 (14.1)	—	—	8
t1.9	Ross et al. 1995 younger	2 samples confounded: 36/56	0/35	8.8 (1.3)	103 (14)	92 (14)	8.7 (0.9)	107 (11)	107 (11)	—	—	4
t1.10	Ross et al. 1995 older	2 samples confounded: 36/56	0/35	12.3 (0.5)	103 (10)	93 (11)	12.2 (0.8)	104 (10)	106 (14)	—	—	4
t1.11	Ross et al. 1997a	83/83	0/83	11.1 (2.7)	102 (12)	—	11.3 (2.6)	102 (9)	—	—	—	1
t1.12	Ross et al. 1998	18/23	0/23	11.9 (0.5)	102 (13)	93 (14)	11.9 (0.7)	104 (11)	105 (16)	—	—	1
t1.13	Ross et al. 2000	36/54 <sup>d</sup>	0/30	8.1 (0.6)	104 (16)	95 (14)	8.4 (0.6)	104 (9)	105 (14)	—	—	2
t1.14	Rovet et al. 1994	25/45	—	11.5 <sup>e</sup>	97.6 (12)	91.7 (14.8)	11.9 <sup>e</sup>	106.6 (12)	113 (14.4)	—	—	1
t1.15	Temple et al. 1996	8/16	—	10.42 (1.2)	96 (—)	92 (—)	10.58 (0.87)	—	—	—	—	7
t1.16	Temple 2002	9/19	—	10.79 (0.91)	99.4 (—)	91.3 (—)	10.92 (0.48)	—	—	—	—	1

GH Growth Hormone, SD Standard deviation, VIQ Verbal Intellectual Quotient, PIQ Performance Intellectual Quotient, EF executive function

<sup>a</sup>The WISC-IV, in which subtests are not any more organized into VIQ and PIQ, was used in this study

<sup>b</sup>Information was not known for 7 participants

<sup>c</sup>Participants were divided into two sub-groups: adolescents (13–16.9 years) and young adults (17.09–21.9 years). Only adolescents ( $n = 64$ ) were included in the analysis

<sup>d</sup>Participants were divided into two sub-groups: estrogen-treated participants and placebo-treated participants. Only placebo group ( $n = 30$ ) was included in the analysis

<sup>e</sup>Standard deviation of age was missing but authors specified that groups were age-matched. The age range was from 7.4 to 16.8 years

538 provide information about treatment received by partic- 604  
 555 ipants (Bray et al. 2011; Quintero et al. 2014; Rovet 605  
 556 et al. 1994; Temple et al. 1996; Temple 2002) and these 606  
 557 data were unknown for several girls in another study 607  
 558 (Reiss et al. 1995). In several samples, none of the girls 608  
 559 with TS received this treatment (Rae et al. 2004; Ross  
 560 et al. 1995, 1997a, 1998, 2000, 1997), whereas, in other  
 561 studies, all participants were treated with estrogen (12.5  
 562 to 16.9 years old group in Romans et al. 1997, 1998).  
 563 For GH therapy, information was available in six studies  
 564 (Romans et al. 1997, 1998, 1995, 1997a, 1998, 2000).  
 565 The proportion of participants receiving GH was be-  
 566 tween 0% and 59%. Concerning EF assessment, the  
 567 number of tasks used varied from one to eight among  
 568 studies. The executive tasks, and related variables, used  
 569 in samples included in the current meta-analysis are  
 570 presented on Table 2.

### 571 Three-Level Meta-Analysis

572 **Overall Score** Fifty-six variables assessing performances 622  
 573 on EF tasks were extracted from fifteen samples. The  
 574 overall ES was medium and significant ( $g = -0.67$ , 95%  
 575 C.I.  $[-0.77, -0.56]$ ,  $Z = -12.19$ ,  $p < 0.001$ ). The Q sta-  
 576 tistic indicated significant heterogeneity among the ES  
 577 ( $Q(55) = 124.97$ ,  $p < 0.001$ ). The estimated within-sample  
 578 heterogeneity variance ( $T^2_{(2)}$ ) was 0.077 and the esti-  
 579 mated between-sample heterogeneity variance ( $\tau^2_{(3)}$ )  
 580 was 0.002. According to  $I^2_{(2)}$  and  $I^2_{(3)}$  values, 54.04%  
 581 and only 1.34% of the total heterogeneity were ex-  
 582 plained by level 2 and level 3, respectively. See Fig. 2  
 583 for the forest plot.

584 **Effects of Moderators** The impact of task modality was  
 585 assessed. Overall ES were significant and large for tasks  
 586 in verbal modality ( $g = -0.86$ , 95% C.I.  $[-1.03, -0.70]$ ,  
 587  $Z = -10.38$ ,  $p < 0.0001$ ) and medium in visual modality  
 588 ( $g = -0.57$ , 95% C.I.  $[-0.69, -0.45]$ ,  $Z = -9.36$ ,  
 589  $p < 0.001$ ). With this moderator, the estimated heteroge-  
 590 neity variance  $\tau^2$  was 0.052 at level 2 and only  
 591 0.003 at level 3. Task modality explained almost 33%  
 592 of the heterogeneity at level 2 ( $R^2_{(2)} = 32.65\%$ ), whereas  
 593 the level 3  $R^2_{(3)}$  was equal to zero.

594 The impact of the type of assessed EF on the ES was  
 595 also explored (see Fig. 2). Overall ES varied from small  
 596 for inhibitory control ( $g = -0.44$ , 95% C.I.  $[-0.60,$   
 597  $-0.28]$ ,  $Z = -5.52$ ,  $p < 0.001$ ) to medium for cognitive  
 598 flexibility ( $g = -0.57$ , 95% C.I.  $[-0.75, -0.40]$ ,  $Z =$   
 599  $-6.17$ ,  $p < 0.001$ ) and large for working memory ( $g =$   
 600  $-0.89$ , 95% C.I.  $[-1.07, -0.70]$ ,  $Z = -9.42$ ,  $p < 0.001$ )  
 601 and higher-order EFs ( $g = -0.87$ , 95% C.I.  $[-1.04,$   
 602  $-0.70]$ ,  $Z = -10.05$ ,  $p < 0.001$ ). With this moderator, the  
 603 estimated heterogeneity variance  $\tau^2$  at level 2 and level

3 were 0.026 and 0.007, respectively. The type of 604  
 assessed EF explained almost 66% of the heterogeneity 605  
 at the level-2 ( $R^2_{(2)} = 65.85\%$ ), whereas this variable did 606  
 not explain between-sample heterogeneity ( $R^2_{(3)} =$  607  
 0.00%). 608

**Comparison between Models** The model where between- 609  
 sample heterogeneity variance  $\tau^2_{(3)}$  was set to zero was 610  
 statistically more suitable than the three-level model 611  
 ( $\chi^2(df = 1) = 0.02$ ,  $p = 0.88$ ). The three-level model was 612  
 statistically better than the model where within-sample 613  
 heterogeneity variance  $\tau^2_{(2)}$  was fixed to zero ( $\chi^2(df =$  614  
 1) = 19.24,  $p < 0.001$ ). Hence, the ES extracted from the 615  
 same study cannot be considered homogeneous. In a 616  
 same sample, the ES magnitude could depend on the 617  
 EF task. Therefore, to explore girls with TS' results 618  
 for each EF task, several univariate meta-analyses by 619  
 task have been conducted. In each meta-analysis, each 620  
 sample was included only once. 621

### Working Memory Tasks

622 Three tasks were used to assess WM, namely, the Digit 623  
 Span subtest from the WISC-R ( $k = 8$ ), the SOPT ( $k =$  624  
 1), and a n-back task ( $k = 1$ ). Two versions of the SOPT 625  
 were used in Temple et al.'s study (Temple et al. 1996), 626  
 a concrete-objects version in which stimuli are drawings 627  
 of everyday objects and an abstract-objects version in 628  
 which stimuli are black-and-white patterns. Girls with 629  
 TS had more difficulties than matched controls, particu- 630  
 larly in the abstract version ( $g = -1.04$ ), whereas the 631  
 difference between the two groups was smaller in the 632  
 concrete version ( $g = -0.21$ ). In the experimental n-back 633  
 task (Bray et al. 2011), ES was large in the two modal- 634  
 ities (visual-spatial:  $g = -0.98$ ; phonological:  $g = -1.11$ ). 635

636 A meta-analysis was conducted for the digit span 637  
 subtest. See Fig. 3 for the visual representation of the 638  
 results. The ES was large and significant for this task 639  
 ( $g = -0.91$ , 95% CI  $[-1.07, -0.75]$ ,  $Z = -10.96$ , 640  
 $p < 0.001$ ) and there was no significant difference across 641  
 the samples ( $Q(6) = 2.15$ ,  $p = 0.91$ ,  $\tau^2 = 0.00$ ,  $I^2 =$  642  
 0.00%). There was no outlier in the funnel plot (see 643  
 Appendix). According to the leave-one-out analysis, 644  
 none of the studies had a significant impact on the 645  
 overall ES (ES range from  $-0.94$  to  $-0.87$ ). Only two 646  
 studies detailed scores for each part of the test, forward 647  
 and backward digit span (Romans et al. 1998, 2000). 648  
 Girls with TS were more impaired when they had to 649  
 recall digits in reversal order. Forward recall ES was 650  
 small or medium (Romans et al. 1998:  $g = -0.56$ ; Ross 651  
 et al. 2000:  $g = -0.48$ ), whereas ES was large for back- 652  
 ward recall (Romans et al. 1998:  $g = -0.91$ ; Ross et al. 653  
 2000:  $g = -1.06$ ).

**Table 2** Tasks used to assess executive functions

t2.1	EF tasks	k	EF variables	RT variables	EF tested, based on Diamond's model (2013)	Main abilities tested
t2.2	WISC-R Digit span	8	Standard score <sup>a</sup>	–	Verbal working memory	working memory (backward recall part), short-term retention capacity, auditory attention
t2.3	n-back task	1	For each modality: mean accuracy for 1-back +2-back conditions	–	Verbal working memory VS working memory	working memory, VS or auditory attention (depending on stimuli used)
t2.4	SOPT	1	Pages before err.	–	VS working memory	working memory, strategy use, self-monitoring
t2.5	Stroop	1	Time (Name colored ink) – time (Name colored dots) <sup>b</sup>	Mean RT for each of the three parts <sup>b</sup>	Inhibitory control: interference control (cognitive inhibition)	inhibition of a prepotent response, focused attention, reading level, processing speed
t2.6	Adaptation of the ANT	1	Mean RT for each condition (executive control) <sup>b</sup>	Mean RT for each condition (alerting and orienting) <sup>b</sup>	Inhibitory control: interference control (selective or focused attention)	VS focused attention, inhibition of distractors
t2.7	MFFT	6 <sup>c</sup>	Number of correct answers	Mean RT <sup>b</sup>	Inhibitory control: response inhibition (self-control and discipline)	impulsivity, visual perception
t2.8	TOVA	6	Number of commission err. <sup>b</sup>	Mean RT <sup>b</sup>	Inhibitory control: response inhibition (self-control and discipline)	impulsivity, focused attention
t2.9	WCST	5	Number of perseverative err. <sup>b</sup>	–	Cognitive flexibility	reactive flexibility, ability to form abstract concepts, ability to consider the examiner's feedback
t2.10	Phonemic fluency	8	Total number of words named	–	Cognitive flexibility	spontaneous flexibility, search strategy, retrieval of lexical items, short-term memory, processing speed
t2.11	Semantic fluency	3	Total number of words named	–	Higher-order EF: planning	planning, perceptual organization, visual constructional skills
t2.12	ROCF	8	Copy score	–	Higher-order EFs: planning and problem solving	planning, problem solving, VS abilities, working memory, inhibition
t2.13	Tower of Hanoi	4	Score <sup>d</sup>	Average Time <sup>b</sup>		
	Tower of London	1	Number of correct problems	Mean RT <sup>b</sup>		

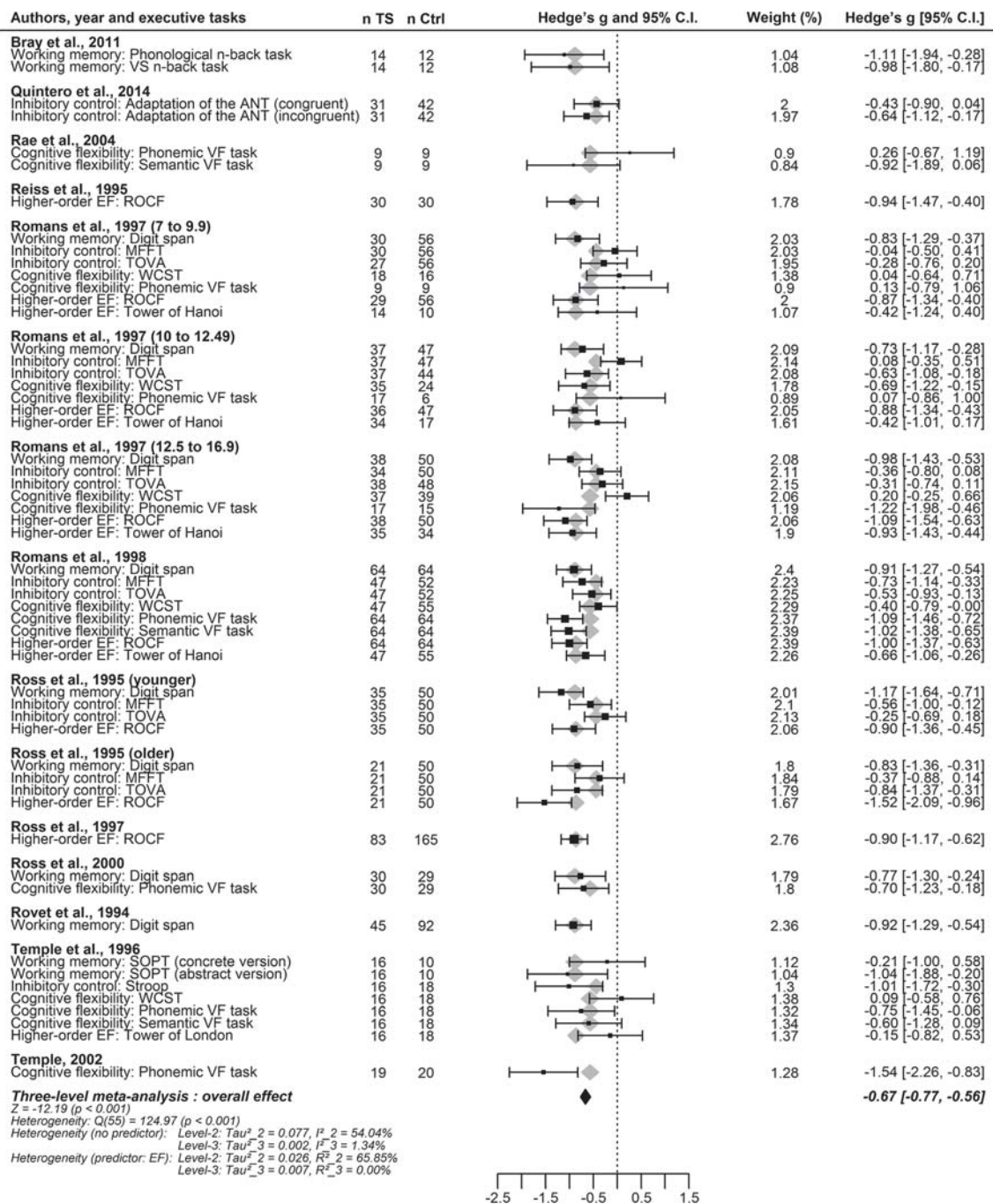
EF executive functions, k number of samples, RT Response Time, WISC-R Wechsler Intelligence Scale for Children-Revised, VS visual-spatial, SOPT Self-Ordered Pointing Test, err: Errors, ANT Attention Network Test, MFFT Matching Familiar Figures Test, TOVA Test of Variables of Attention, WCST Wisconsin Card Sorting Test, ROCF Rey-Osterrieth Complex Figure

<sup>a</sup> One study (Ross et al. 2000) used forward and backward digit spans. This study was not included in the univariate meta-analysis by task

<sup>b</sup> The sign of effect size was reversed

<sup>c</sup> There were seven samples for response time variable

<sup>d</sup> This composite score takes into account accuracy, completion time and problem difficulty



**Fig. 2** Forest plot of individual effect sizes and overall effect size estimate. *n TS* number of participants with Turner syndrome, *n Ctrl* number of control participants, *C.I.* Confidence Interval, *VS* visual-spatial, *ANT* Attention Network Test, *VF* verbal fluency, *ROCF* Rey-Osterrieth Complex Figure, *MFFT* Matching Familiar Figures Test,

*TOVA* Test of Variables of Attention, *WCST* Wisconsin Card Sorting Test. Note: A negative Hedge's *g* value means that the TS group has underperformed when compared to its control group. The grey diamonds represent the average estimated effect size for the executive function assessed by the task

**680 Time Variables** None of the studies retained in the current meta-analysis used response time variables in WM tasks.

**691 Inhibitory Control Tasks**

692 Different aspects of inhibitory control were assessed  
693 with the MFFT (*k* = 6), the TOVA (*k* = 6), an adaptation

of the children's ANT (*k* = 1), and the Stroop task (*k* = 694  
1). In the Stroop task used only by Temple et al. 695  
(1996), the difference in time between the interference 696  
condition and the baseline condition was more impor- 697  
tant in the TS group than in the control group. The ES 698  
was large for this task (*g* = -1.01). In the adaptation of 699  
the ANT used in Quintero et al.'s study (Quintero et al. 700

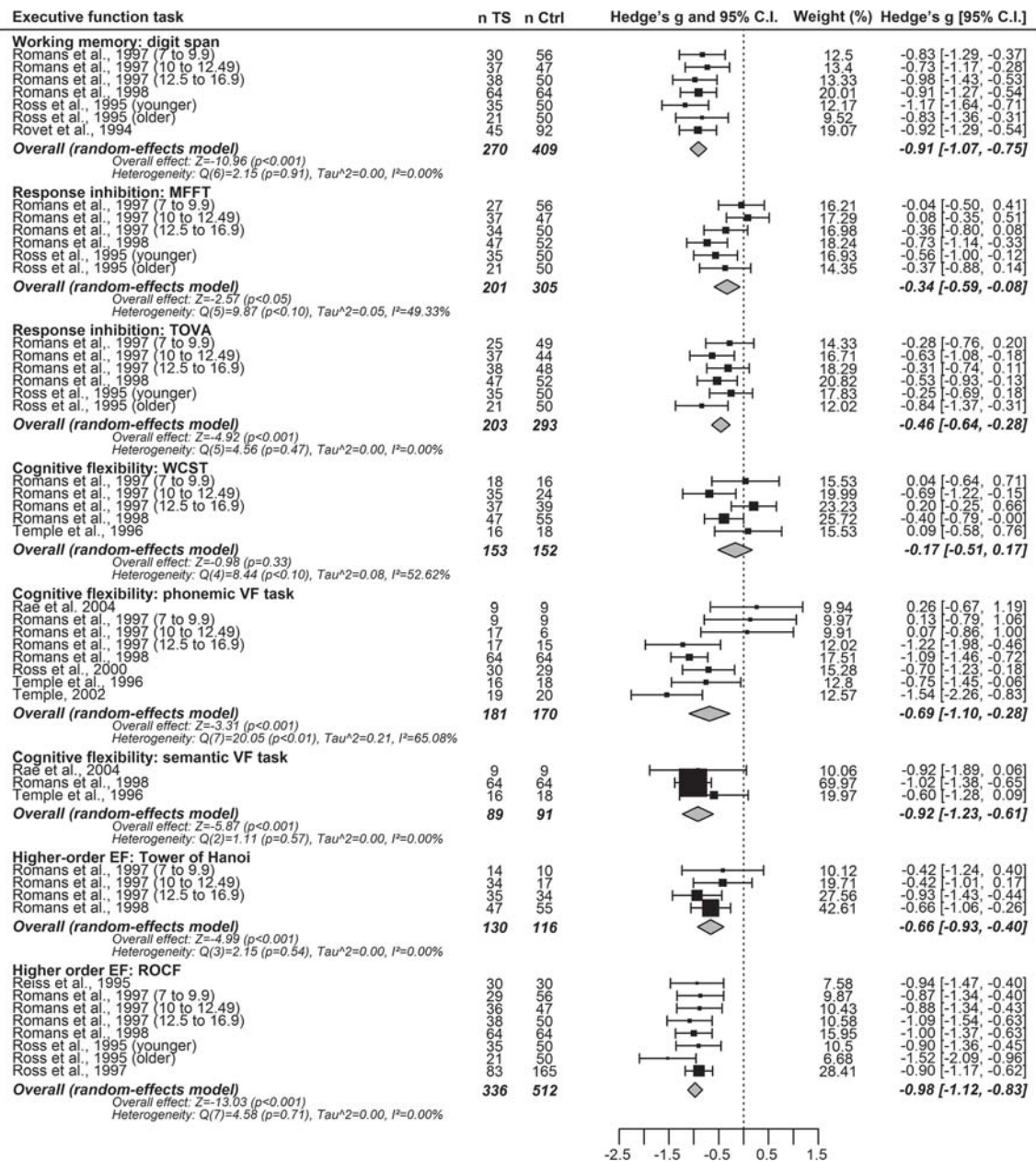


Fig. 3 Forest plots of overall effect size estimate for executive function tasks. *n TS* number of participants with Turner syndrome, *n Ctrl* number of control participants, *C.I.* Confidence Interval, *MFFT* Matching Familiar Figures Test, *TOVA* Test of Variables of Attention, *WCST*

Wisconsin Card Sorting Test, *VF* verbal fluency, *ROCF* Rey-Osterrieth Complex Figure. Note: A negative Hedge's *g* value means that the TS group has underperformed when compared to its control group

2014), the mean reaction time was higher in the TS group with a small ES in the congruent condition ( $g = -0.43$ ) and a medium ES in the incongruent condition ( $g = -0.64$ ).

Conducting a meta-analysis was possible for the TOVA and the MFFT (see Fig. 3). Compared to control participants, girls with TS had less correct answers in the MFFT and made more commission errors in the TOVA. For these two tasks, the ES was small but significant (MFFT:  $g = -0.34$ , 95% CI [-0.59; -0.08],  $Z = -2.57$ ,  $p < 0.05$ ; TOVA:  $g = -0.46$ , 95% CI [-0.64; -0.28],  $Z = -4.92$ ,

$p < 0.001$ ). The *Q*-test did not reveal evidence of heterogeneity between studies for the TOVA ( $Q(5) = 4.56$ ,  $p = 0.47$ ,  $\tau^2 = 0.00$ ,  $I^2 = < .01\%$ ) but it was significant for the MFFT ( $Q(5) = 9.87$ ,  $p < 0.10$ ,  $\tau^2 = 0.05$ ,  $I^2 = 49.33\%$ ). Thus, near 50% of total heterogeneity would be due to between-sample heterogeneity in this task. For the MFFT, two samples were close to the funnel plot limits (see Appendix, Romans et al. 1998; the 10 to 12.5 years old group from Romans et al. 1997). The overall ES range obtained with the leave-one-out method was from -0.43 (without the 10 to 12.5 years old group from Romans et al. 1997) to -0.25

723 (without Romans et al. 1998). When the younger sample  
 724 from Ross et al. (1995) was removed, the results remained  
 725 no longer significant ( $g = -0.29$ , 95% C.I. [-0.58; 0.01],  
 726  $Z = -1.92$ ,  $p = 0.06$ ). For the TOVA, no outlier has been  
 727 observed and the results seemed robust. The overall ES  
 728 range obtained with the leave-one-out method was from  
 729  $-0.50$  to  $-0.41$ .

730 **Response Time** In the Stroop task, slower responding was  
 731 observed in the TS group with a medium ES for the reading  
 732 part ( $g = -0.53$ ) and large ES for the color-naming ( $g = -0.99$ )  
 733 and the interference ( $g = -0.97$ ) parts.

734 Concerning the ANT, reaction time was higher in the  
 735 TS group for both incongruent and congruent conditions  
 736 (see previous part Analysis by task). In the same way,  
 737 participants with TS were slower than controls in the  
 738 other conditions for this attentional task (neutral cue:  
 739  $g = -0.45$ ; no cue:  $g = -0.55$ ; valid cue:  $g = -0.49$ ; inva-  
 740 lid cue:  $g = -0.45$ ). For each condition, response time  
 741 differences between the TS group and its control group  
 742 were small or, for the no cue condition and the congru-  
 743 ent condition, medium. The difference between the TS  
 744 group and the control group slightly increased with task  
 745 difficulty (neutral cue vs no cue, congruent vs  
 746 incongruent).

747 For the MFFT, the response time variable can be  
 748 used to assess impulsivity (Messer 1976). Compared to  
 749 the previous MFFT meta-analysis, one additional study  
 750 (Ross et al. 1995), which did not provide the number of  
 751 correct responses but only the mean response time, was  
 752 added to this analysis. There was no significant differ-  
 753 ence between the TS and control groups ( $g = 0.13$ , 95%  
 754 CI [-0.04; 0.30],  $Z = 1.55$ ,  $p = 0.12$ ). There was no sig-  
 755 nificant heterogeneity across the seven samples ( $Q(6) =$   
 756  $6.02$ ,  $p = 0.42$ ,  $\tau^2 = 0.00$ ,  $I^2 = 0.00\%$ ). No outlier was  
 757 identified in the funnel plot (see Appendix). In the  
 758 leave-one-out method, the overall ES range was from  
 759  $0.07$  to  $0.20$ . The meta-analysis results became signifi-  
 760 cant when one sample was removed (the 10 to  
 761 12.5 years old group from Romans et al. 1997) but  
 762 the ES remained small ( $g = 0.20$ , 95% CI [0.01; 0.38],  
 763  $Z = 2.08$ ,  $p < 0.05$ ).

764 In the TOVA, response time variable may assess in-  
 765 formation processing speed and motor response speed  
 766 (Greenberg and Waldman 1993). Girls with TS were  
 767 faster than control participants and the difference be-  
 768 tween TS and control groups was small and significant.  
 769 ( $g = 0.32$ , 95% CI [0.11; 0.54],  $Z = 2.96$ ,  $p < 0.01$ ). The  
 770 results were not significantly different across the six  
 771 samples ( $Q(5) = 6.90$ ,  $p = 0.23$ ,  $I^2 = 27.50\%$ ). One outlier  
 772 (youngest group from Ross et al. 1995) was observed in  
 773 the funnel plot (see Appendix). When this sample was  
 774 removed, overall ES value increased but remained small

( $g = 0.42$ , 95% CI [0.22; 0.62],  $Z = 4.08$ ,  $p < 0.001$ ). The  
 775 meta-analysis results seemed to be robust. The range of  
 776 overall ES obtained with the leave-one-out method was  
 777 from  $0.27$  to  $0.42$ .  
 778

**Cognitive Flexibility Tasks** 779

780 The WCST ( $k = 5$ ), the phonemic ( $k = 8$ ) and semantic  
 781 verbal fluency tasks ( $k = 3$ ) were used to assess cogni-  
 782 tive flexibility abilities. In the WCST (see Fig. 3), girls  
 783 with TS did not make significantly more perseverative  
 784 errors than control participants. The ES was small and  
 785 non-significant ( $g = -0.17$ , 95% CI [-0.51; 0.17],  $Z =$   
 786  $-0.98$ ,  $p = 0.33$ ). The  $Q$ -test was significant ( $Q(4) =$   
 787  $8.44$ ,  $p < 0.10$ ,  $\tau^2 = 0.08$ ). The  $I^2$  index indicated that  
 788 52.62% of the total variation would be due to heteroge-  
 789 neity between samples. One sample (the 10 to 12.5 years  
 790 old group from Romans et al. 1997) was close to funnel  
 791 plot limits (see Appendix.). When this sample was re-  
 792 moved, overall ES got closer to zero ( $g = -0.06$ , 95%  
 793 CI [-0.53; 0.34],  $Z = -0.43$ ,  $p = 0.67$ ). According to the  
 794 leave-one-out method (ES range from  $-0.30$  to  $-0.06$ ),  
 795 the meta-analysis results were consistent. The ES  
 796 remained small and non-significant regardless of the re-  
 797 moved study.

798 Concerning the verbal fluency tasks (see Fig. 3), girls with  
 799 TS named significantly less words than controls in the two  
 800 conditions (phonemic:  $Z = -3.31$ ,  $p < 0.001$ ; semantic:  $Z =$   
 801  $-5.87$ ,  $p < 0.001$ ). For the phonemic tasks, ES was medium  
 802 ( $g = -0.69$ , 95% CI [-1.10; -0.28]), whereas it was large for  
 803 the semantic tasks ( $g = -0.92$ , 95% CI [-1.23; -0.61]). The  $Q$ -  
 804 test did not reveal heterogeneity between studies for semantic  
 805 fluency tasks ( $Q(2) = 1.11$ ,  $p = 0.57$ ,  $\tau^2 = 0.00$ ,  $I^2 = 0.00\%$ ),  
 806 while the results were significantly heterogeneous for the pho-  
 807 nemic fluency tasks ( $Q(7) = 20.05$ ,  $p < 0.01$ ,  $\tau^2 = 0.21$ ).  
 808 According to the  $I^2$  index, 65.08% of the total variability  
 809 among ES would be caused by heterogeneity across the eight  
 810 samples. Three outliers were identified in the funnel plot  
 811 representing phonemic tasks' ES (Rae et al. 2004; Romans  
 812 et al. 1998; Temple 2002). Without Rae et al. (2004), overall  
 813 ES became large ( $g = -0.81$ , 95% CI [-1.19; -0.42],  $Z =$   
 814  $-4.10$ ,  $p < 0.001$ ) whereas when the two other outliers were  
 815 removed, overall ES remained medium and close to the over-  
 816 all ES value calculated with all samples' results (without  
 817 Romans et al. 1998:  $g = -0.60$ , 95% CI [-1.08; -0.11],  $Z =$   
 818  $-2.41$ ,  $p < 0.05$ ; without Temple 2002:  $g = -0.58$ , 95% CI  
 819 [-0.99; -0.16],  $Z = -2.70$ ,  $p < 0.01$ ). Concerning semantic  
 820 verbal fluency task, no outlier was observed in the funnel plot  
 821 (see Appendix), but this task has been used in only three  
 822 samples. The meta-analysis results should be interpreted with  
 823 caution. Indeed, the overall ES became medium when one  
 824 sample (Romans et al., Romans et al. 1998) was removed  
 825 ( $g = -0.70$ , 95% CI [-1.26; -0.14],  $Z = -2.45$ ,  $p < 0.05$ ).

826 **Time Variables** There was no time variable in the WCST.  
 827 For the verbal fluency tasks, response time limit is 60 s.  
 828 Thus, the number of correct responses may reflect pro-  
 829 cessing speed. In a same period, the girls with TS pro-  
 830 duced significantly less words than controls (see previ-  
 831 ous section Analysis by task).

### 832 Higher-Order Executive Functions Tasks

833 Three tasks were used to assess higher-level EFs, namely, the  
 834 ROCF ( $k=8$ ), the TOL ( $k=1$ ), and the TOH ( $k=4$ ). In the  
 835 TOL used in Temple et al.'s study (Temple et al. 1996), the TS  
 836 group obtained lower scores than its matched controls but the  
 837 ES was small ( $g=-0.15$ ).

838 A meta-analysis was conducted using results obtained in  
 839 the TOH (see Fig. 3), another problem solving task. Girls with  
 840 TS scored significantly lower than the control participants  
 841 resulting in a medium ES ( $g=-0.66$ , 95% CI  $[-0.93$ ;  
 842  $-0.40]$ ,  $Z=-4.99$ ,  $p<0.001$ ). The  $Q$ -test did not indicate sig-  
 843 nificant heterogeneity between samples ( $Q(3)=2.15$ ,  $p=$   
 844  $0.54$ ,  $\tau^2=0.00$ ,  $I^2=0.00\%$ ). No outlier was identified in the  
 845 funnel plot (see Appendix). The overall ES obtained with the  
 846 leave-one-out method were close to the ES obtained when all  
 847 samples were included (ES range from  $-0.72$  to  $-0.56$ ).  
 848 Hence, the meta-analysis results could be considered as  
 849 robust.

850 In the ROCF (see Fig. 3), the TS group's copy score was  
 851 lower than control group's score and the ES was large and  
 852 significant ( $g=-0.98$ , 95% CI  $[-1.12$ ;  $-0.83]$ ,  $Z=-13.03$ ,  $p$   
 853  $<0.001$ ). The results were homogeneous ( $Q(7)=4.58$ ,  $p=$   
 854  $0.71$ ,  $\tau^2=0.00$ ,  $I^2=0.00\%$ ). In the funnel plot (see  
 855 Appendix), one study (the older group in Ross et al. 1995)  
 856 was close to the funnel limits. Removing this sample did not  
 857 have an impact on the overall ES ( $g=-0.94$ , 95% C.I.  $[-1.09$ ;  
 858  $-0.78]$ ,  $Z=-12.08$ ,  $p<0.001$ ). According to the leave-one-  
 859 out method (ES range from  $-1.01$  to  $-0.94$ ), the meta-  
 860 analysis results were consistent.

861 **Time Variables** The time required to reproduce the ROCF  
 862 was not reported in the studies included in this meta-  
 863 analysis. Concerning the tower tasks, in the four sam-  
 864 ples using the TOH, girls with TS had slower perfor-  
 865 mances when resolving items. The difference between  
 866 TS and control groups was large and significant ( $g=$   
 867  $-0.95$ , 95% CI  $[-1.22$ ;  $-0.68]$ ,  $Z=-6.93$ ;  $p<0.001$ ).  
 868 There was no significant between-sample heterogeneity  
 869 ( $Q(3)=2.86$ ;  $p=0.41$ ,  $\tau^2=0.00$ ,  $I^2=0.00\%$ ). No outlier  
 870 was identified (see Appendix) and the results seemed  
 871 robust according to the leave-one-out method (ES range  
 872 from  $-1.00$  to  $-0.84$ ). In the TOL task used only by  
 873 Temple et al. (1996), girls with TS were also slower  
 874 than controls but, in this task, the difference between  
 875 the two groups was small ( $g=-0.16$ ).

## Discussion

876 The aim of this review was to explore EF profile char- 877  
 878 acteristics in children and adolescents with TS. Even if 878  
 879 these girls' EF abilities have been assessed in several 879  
 880 studies, methodologies previously used present some 880  
 881 limitations and vary from one publication to another. 881  
 882 The current meta-analysis results provide evidence that 882  
 883 girls with TS suffer from executive impairments and 883  
 884 support the argument suggesting the fractionation of 884  
 885 EFs processes (Diamond 2013; Lehto et al. 2003; 885  
 886 Miyake et al. 2000). WM and higher-order EFs seem 886  
 887 to be the most affected processes, whereas some aspects 887  
 888 of inhibitory control and cognitive flexibility may be 888  
 889 more preserved in these young patients. 889

### Executive Functions Impairments in Turner Syndrome

890 In the three-level meta-analysis, the overall ES was neg- 891  
 892 ative and medium, corroborating the argument that girls 892  
 893 with TS have executive impairments. However, this re- 893  
 894 sult should be interpreted in light of the within- and 894  
 895 between-sample variability. Indeed, between-sample het- 895  
 896 erogeneity was surprisingly lower than the within- 896  
 897 sample heterogeneity. Only fifteen studies have been 897  
 898 included in this meta-analysis and, among them, the 898  
 899 number of outcome variables ranged from one to eight. 899  
 900 A negative and large ES was obtained for each of the 900  
 901 studies in which only one variable was extracted (Reiss 901  
 902 et al. 1995: ROCF:  $g=-0.94$ ; Ross et al. 1997a, b: 902Q3  
 903 ROCF:  $g=-0.90$ ; Rovet et al. 1994: Digit span subtest: 903  
 904  $g=-0.92$ ; Temple 2002: phonemic verbal fluency task: 904  
 905  $g=-1.54$ ). Between-sample heterogeneity would have 905  
 906 been higher if, in some of these studies, the authors 906  
 907 had used a task in which small differences between girls 907  
 908 with TS and controls have been observed (e.g. MFFT). 908  
 909 Moreover, four studies, in which seven or eight vari- 909  
 910 ables were extracted, were conducted by the same re- 910  
 911 search team (Ross et al. 1997a, b; Romans et al. 1998). 911Q4  
 912 The authors investigated different EFs, used the same 912  
 913 tasks and obtained heterogeneous results in the four 913  
 914 studies. Within-sample heterogeneity would have been 914  
 915 lower if, in some studies, the authors had explored only 915  
 916 one EF with several tasks (such as Bray et al. 2011). 916  
 917 Indeed, according to moderator analysis, the type of 917  
 918 assessed EF might explain a large part of within- 918  
 919 sample heterogeneity. 919

920 In the present study, large WM deficits in children 920  
 921 and adolescents with TS were highlighted through tasks 921  
 922 used to assess visual-spatial or verbal WM, except for 922  
 923 one, the concrete version of the SOPT (Temple et al. 923  
 924 1996). There are at least three possible hypotheses to 924  
 925 explain this performance in the SOPT. One proposed 925

926 by Temple et al. (1996) suggests that girls with TS may  
 927 have difficulties when stimuli are non-verbal or when  
 928 they cannot adopt a verbal strategy to support executive  
 929 processes. However, the results did not totally confirm  
 930 this hypothesis: impairments have been highlighted both  
 931 on executive non-verbal tasks (visual-spatial n-back  
 932 task, abstract version for the SOPT) and verbal ones  
 933 (digit span and auditory n-back tasks in which a verbal  
 934 strategy could be used). A second possible explanation  
 935 of the concrete version of SOPT results is that, in this  
 936 task, other processes are involved such as self-  
 937 monitoring which could be preserved in girls with TS.  
 938 Yet, this hypothesis cannot explain performances dis-  
 939 crepancies between the two versions of SOPT. A third  
 940 explanation is to suppose that self-monitoring might be  
 941 efficient in girls with TS only in tasks where double-  
 942 coding could be involved (Paivio 1971).

943 The association between TS and inhibition impair-  
 944 ment varied across inhibitory measures. In the three  
 945 Stroop conditions, a cognitive inhibition task, girls with  
 946 TS were slower than controls. The Stroop effect value  
 947 ( $g = -1.01$ ) may suggest that these girls have signifi-  
 948 cantly more difficulties inhibiting a prepotent response when  
 949 compared to controls. The other inhibitory processes  
 950 described by Diamond (2013), focused attention and re-  
 951 sponse inhibition, seem to be more preserved in girls  
 952 with TS. Thus, they were slower than controls in the  
 953 ANT (a focused-attention task), but this difference in  
 954 response time was quite similar among the six condi-  
 955 tions of ANT despite different difficulty levels (ES  
 956 range from  $-0.64$  to  $-0.45$ ). Therefore, a slower pro-  
 957 cessing speed in girls with TS compared to their  
 958 matched controls may explain differences observed be-  
 959 tween the two groups. As for response inhibition, even  
 960 if children with TS had more difficulties than their  
 961 healthy peers to inhibit impulsive behaviors, differences  
 962 with controls were small for the accuracy and response  
 963 time variables in tasks assessing impulsivity.

964 Concerning cognitive flexibility, a discrepancy was  
 965 found between the tasks used to explore this function.  
 966 Compared to healthy controls, girls with TS had signif-  
 967 icantly lower performance on verbal fluency tasks with  
 968 medium to large ES, whereas there was no significant  
 969 difference between groups in the WCST. Two hypothe-  
 970 ses can be advanced to explain these differences. First,  
 971 maybe these tasks do not assess the same aspects of  
 972 cognitive flexibility. Eslinger and Grattan (1993) distin-  
 973 guished spontaneous flexibility, assessed by fluency  
 974 tasks that require generation of diverse answers, versus  
 975 reactive flexibility, assessed by the WCST where partic-  
 976 ipants need to adapt their answers to the examiner's  
 977 demands or to stimuli. In TS, spontaneous flexibility  
 978 may be impaired whereas reactive flexibility may be

979 more preserved. The second explanation is that the im-  
 980 pairment observed in verbal fluency tasks could be due  
 981 to the fact that participants have a limited period of  
 982 time to generate as many words as possible. In the  
 983 present meta-analysis, this time constraint was absent  
 984 in the WCST in which the chosen variable was the  
 985 number of perseverative errors. Differences observed  
 986 across cognitive flexibility tasks may be attributed, at  
 987 least in part, to a slowdown in information processing  
 988 speed.

989 According to Diamond's model (2013), the three core  
 990 EFs contribute to higher-order EFs. However, conflict-  
 991 ing results have been reported under the type of plan-  
 992 ning task used. Hence, children with TS took more time  
 993 to complete the TOH and could not reach the same  
 994 level as that of controls (a medium ES was found). In  
 995 contrast, in the case of TOL a small difference was  
 996 found between the TS group and the control group  
 997 concerning both the accuracy score and response time.  
 998 While these two tasks appear to be very similar, they  
 999 may involve different cognitive processes. For instance,  
 1000 it has been suggested that WM and inhibition may be  
 1001 related to TOL results, whereas only inhibition may  
 1002 contribute to TOH performance (Welsh et al. 1999). In  
 1003 contrast, Zook et al. (2004) have proposed that only  
 1004 fluid intelligence measure was related to scores of the  
 1005 TOL, whereas WM, inhibitory response, fluid intelli-  
 1006 gence, and TOH performances were correlated. The cur-  
 1007 rent meta-analysis results are congruent with those ob-  
 1008 tained by Zook et al. (2004). Planning abilities have  
 1009 also been assessed with the ROCF. Large differences  
 1010 between girls with TS and healthy controls were ob-  
 1011 served, yet, this could be explained by impairments ob-  
 1012 served in patients with TS in visual constructional abil-  
 1013 ities which are necessary in succeeding this task.

1014 **Visual-Spatial Impairment and EFs in Girls with Turner**  
 1015 **Syndrome**

1016 According to Temple and Carney (1995) who assessed  
 1017 different aspects of visual functions in TS, difficulties  
 1018 may affect more specifically visual-perceptual and  
 1019 visual-constructional abilities but visual-spatial capaci-  
 1020 ties seem to be preserved. However, this hypothesis  
 1021 has not been supported by clinical data. Several studies  
 1022 have suggested that underperformance of girls with TS  
 1023 on Benton's Judgement of Line Orientation task or the  
 1024 Arrows subtest from the NEPSY may suggest that they  
 1025 also present visual-spatial deficits (Bray et al. 2013;  
 1026 Green et al. 2014; Kesler et al. 2004). When task mo-  
 1027 dality was used as moderator, the estimated ES was  
 1028 large for verbal tasks ( $g = -0.86$ , 95% C.I.  $[-1.03$ ,  
 1029  $-0.70]$ ), whereas it was medium for visual tasks ( $g =$

1030  $-0.57$ , 95% C.I.  $[-0.69, -0.45]$ ). Hence, even if visual-  
1031 spatial difficulties could explain poor performances on  
1032 executive tests which involve visual stimuli, it may not  
1033 fully explain impairments reported in other tasks  
1034 assessing verbal WM or verbal fluency. Moreover,  
1035 Bray et al. (2011) have proposed an innovative method-  
1036 ology which contrasts two versions of a WM task, one  
1037 based on phonological processing and one based on  
1038 visual-spatial processing. This method has highlighted  
1039 that girls with TS were impaired in both modalities.  
1040 Unfortunately, it was the only study included in the  
1041 current analysis allowing the comparison of modality  
1042 specificity within the same EF.

1043 Links between visual-spatial impairments and EFs have  
1044 been explored in other studies, which did not meet the  
1045 inclusion criteria for this meta-analysis. In Lepage et al.  
1046 (2011), girls with TS had significantly lower scores than  
1047 controls on the Attention-Executive Domain of the  
1048 NEPSY. Performances of patients with TS on Tower and  
1049 Visual Attention subtests were significantly and positively  
1050 correlated to subtests from Perceptual Reasoning Index  
1051 score of the WISC-IV. This association was not observed  
1052 in the control group. These results are interesting but it is  
1053 unclear if the TS results on EF tasks were due exclusively  
1054 to EF impairment or if the visual nature of stimuli accent-  
1055 uated impairments. In another study (Green et al. 2015),  
1056 girls with TS were divided in two sub-groups according to  
1057 the severity of ADHD-associated behaviors and were  
1058 compared to neurotypical children as well as to children  
1059 with idiopathic ADHD. All girls with TS had lower re-  
1060 sults than neurotypical controls in all the NEPSY do-  
1061 mains. The two TS groups had the same profile compared  
1062 to children with idiopathic ADHD, except for visual-  
1063 spatial tasks in which girls with TS had poorest results.  
1064 There was no difference between the two TS groups in  
1065 visual-spatial EF tasks but girls with TS with ADHD-  
1066 associated behaviors had lower results on auditory EF  
1067 tasks than the other ones without ADHD. Therefore, an  
1068 EF deficit, at least partially independent of visual-spatial  
1069 impairments, could be observed in girls with TS and may  
1070 be associated with the ADHD profile, a variable, among  
1071 others, that should be considered when performances in  
1072 EF tasks are analyzed.

### 1073 **Moderator Variables of Executive Functions** 1074 **in Children with Turner Syndrome**

1075 In the current meta-analysis, heterogeneous results across  
1076 samples were observed for three EF tasks, the MFFT, the  
1077 phonemic fluency verbal task, and the WCST. Several  
1078 variables could explain these ES differences between  
1079 samples.

As suggested in the Introduction, some aspects of  
EFs are considered as part of the intelligence construct.  
Heterogeneous results could be explained by IQ differ-  
ences between the different samples in which these EF  
tasks have been used. Indeed, correlations between IQ  
and EF tasks, including MFFT, WCST and phonemic  
verbal fluency task, have been previously highlighted  
in developmental data (MFFT: Messer 1976; Fluency  
verbal tasks: Anderson et al. 2001; WCST: Ardila  
et al. 2000). Given the lack of relevant data, this hy-  
pothesis could not be explored in this meta-analysis.

In the current review, seven studies found no significant  
difference in SES between TS and control groups (Reiss  
et al. 1995; Romans et al. 1997, 1998; Ross et al. 1995,  
1997a, 1998, 2000). Two studies specified that children in-  
cluded were from mainstream schools (Temple et al. 1996;  
Temple 2002) and three studies did not mention this variable  
(Bray et al. 2011; Quintero et al. 2014; Rae et al. 2004). Due  
to the lack of information, it was not possible to statistically  
control for SES influence on ES in the current meta-analysis.  
However, given that in the majority of studies there was no  
significant difference in SES between the two groups, an ef-  
fect of this variable on the meta-analysis results seems to be  
unlikely.

Different types of X chromosome abnormalities lead  
to a diagnosis of TS, and differences across karyotypes  
could explain variability in EF profiles. Unfortunately, it  
was not possible to assess the impact of karyotype on  
ES in the current meta-analysis. The proportion of pa-  
tients with 45,X karyotype was unknown in several  
samples. Among the studies included in the current  
analysis, three compared the 45,X group to the other  
karyotypes groups (Bray et al. 2011; Ross et al. 1995;  
Temple et al. 1996). These studies did not find a sig-  
nificant effect of karyotype on EF except for the SOPT  
(Temple et al. 1996). In the abstract version of this task,  
girls with a 45,X karyotype had poorer performances  
than the group including participants with TS with var-  
ious karyotypes (mosaic patterns, partial deletions, trans-  
locations). Significant differences were mentioned be-  
tween 45,X and mosaic groups in subtests of perceptual  
reasoning index and WM index from the WISC-IV  
(Bray et al. 2011) where the mosaic group was less  
impaired in several measures but the authors did not  
detail the results. In light of the possible impact of  
karyotype upon cognitive profile, it may be relevant  
(when the number of participants allows to conduct sol-  
id statistical analysis) to create different sub-groups un-  
der the TS karyotype.

Girls with TS receive GH treatment and, several  
years later, estrogen therapy. The influence of GH could  
not be explored in the current analysis due to the lack  
of relevant data. In a study not included in this review

1133 (absence of control group; Ross et al. 1997b), partici-  
 1134 pants who received GH and those who received placebo  
 1135 obtained similar performances on all cognitive tasks in-  
 1136 cluding EF tasks (MFFT, TOVA, ROCF, digit span sub-  
 1137 test). Concerning the potential impact of estrogen treat-  
 1138 ment on EF abilities, only two samples among the six-  
 1139 teen included in the present analysis (Ross et al. 1998,  
 1140 2000) detailed results regarding estrogen status. Three  
 1141 EF tasks were used – a digit span subtest, a phonemic  
 1142 verbal fluency task (Ross et al. 2000), and the MFFT  
 1143 (Ross et al. 1998) – and a difference was observed  
 1144 across the participants with TS only on the digit span  
 1145 backward. There was no difference between healthy  
 1146 controls and estrogen-treated TS group whereas  
 1147 placebo-treated TS group had significantly lower results  
 1148 than controls (Ross et al. 2000). However, the lack of  
 1149 information in the other included samples ( $k=14$ ) is a  
 1150 barrier when further exploring the impact of this treat-  
 1151 ment upon EFs in girls with TS. The role played by  
 1152 estrogen in brain development and neuroplasticity, as  
 1153 well as its neuroprotective effects (Crider and Pillai  
 1154 2016), strengthens the argument that estrogen therapy  
 1155 could improve cognition in TS. Therefore, compliance  
 1156 regarding this therapy, prescribed in most patients with  
 1157 TS (Bondy 2007), must be taken into account when  
 1158 cognitive processes are assessed. Some cognitive differ-  
 1159 ences across adolescents with TS may be partially ex-  
 1160 plained by the variation in compliance behaviors. These  
 1161 hormonal treatments may also have positive effects on  
 1162 psychological well-being in girls with TS (Ross et al.  
 1163 1996; Rovet and Holland 1993), another moderator var-  
 1164 iable that may have an impact on EF abilities.

1165 The prevalence of psychiatric disorders, such as anx-  
 1166 iety, depression, or ADHD, is higher in patients with TS  
 1167 (Kiliç et al. 2005; McCauley et al. 2001; Russell et al.  
 1168 2006; Saad et al. 2015). Among the studies retained,  
 1169 depression, anxiety, and ADHD symptoms were  
 1170 assessed in only one study (Reiss et al. 1995). There  
 1171 was no significant difference between the TS group and  
 1172 the control group on depression or anxiety items of the  
 1173 Child Behavior Checklist but the children with TS had  
 1174 significant higher scores than the control group on the  
 1175 attention and social problem scales. Authors did not  
 1176 analyze the association between these scores and perfor-  
 1177 mances on EF tasks. To our knowledge, the impact of  
 1178 depression or anxious symptoms upon cognitive skills  
 1179 has never been explored in children and adolescents  
 1180 with TS. Considering negative effects observed in pop-  
 1181 ulations presenting these symptoms (Han et al. 2016;  
 1182 Ursache and Raver 2014; Wagner et al. 2015), these  
 1183 aspects should also be considered in TS to improve  
 1184 the understanding of these girls' cognitive profiles and  
 1185 to adapt their psychological care and rehabilitation.

**Impact of Executive Functions Impairments  
 in Children with Turner Syndrome**

1186  
 1187

1188 Children and adolescents with TS present mathematical  
 1189 impairments (Baker and Reiss 2016; Mazzocco 1998;  
 1190 Mazzocco and Hanich 2010; Murphy and Mazzocco  
 1191 2008). Many studies highlighted significant associations  
 1192 between EFs, most particularly WM abilities, and math-  
 1193 ematics (e.g. De Smedt et al. 2009; Gathercole et al.  
 1194 2004). In children with TS, there was no correlation be-  
 1195 tween Calculations score from Woodcock-Johnson  
 1196 Psychoeducational Battery-Revised and executive tasks  
 1197 such as a digit span backward subtest (Murphy and  
 1198 Mazzocco 2008). Another study explored the impact of  
 1199 increasing WM demand on tasks which assess automa-  
 1200 ticity and accuracy of participants to compose and de-  
 1201 compose numbers. It appeared that, in girls with TS,  
 1202 WM abilities may be involved in numerical tasks which,  
 1203 in contrast, are supposedly effortless in control children  
 1204 (Mazzocco and Hanich 2010). Furthermore, a positive  
 1205 correlation between visual-spatial results and those ob-  
 1206 tained in a symbolic numerical magnitude comparison  
 1207 task has been also described in girls with TS but not in  
 1208 control participants (Brankaer et al. 2016). Associations  
 1209 between WM, or other EFs, and mathematic disabilities  
 1210 in TS are not yet clear and need to be further explored in  
 1211 future researches.

1212 Many studies highlighted social disabilities in girls with  
 1213 TS (Hong et al. 2011; Lepage et al. 2013b; Lesniak-  
 1214 Karpiak et al. 2003; McCauley et al. 1995, 2001; Reiss  
 1215 et al. 1995). A deficit in emotion recognition has been  
 1216 described (McCauley et al. 1987; Romans et al. 1998;  
 1217 Hong et al. 2014), yet theory of mind abilities have been  
 1218 assessed in only two studies and the results were conflict-  
 1219 ing (Hong et al. 2011; Yamagata et al. 2012). Theory of  
 1220 mind abilities play a crucial role to adopt behaviors appro-  
 1221 priate to social situations and several EFs, such as inhibi-  
 1222 tion and WM could be involved in theory of mind abilities  
 1223 (e.g. Austin et al. 2014; Carlson et al. 2002). Thus, WM  
 1224 and cognitive inhibition impairments observed in girls with  
 1225 TS might be associated with theory of mind weaknesses  
 1226 and social difficulties in these young girls.

**Limitations and Future Directions**

1227

1228 Even if this meta-analysis improves knowledge of EF pro-  
 1229 file of children and adolescents with TS, these results  
 1230 should be interpreted in light of some limitations. This  
 1231 syndrome is a heterogeneous rare disorder and, unfortu-  
 1232 nately, few research teams have been interested in EF abil-  
 1233 ities of patients with TS. The number of studies respecting  
 1234 all inclusion criteria was small and the methodology var-  
 1235 ied. It was not possible to explore the potential effects of

1236 the participant characteristics upon EF performances.  
 1237 Insufficient information regarding variables which can  
 1238 have an effect on observed findings (i.e. IQ, age, karyo-  
 1239 type, co-morbid psychiatric disease, hormonal status) was  
 1240 available in the majority of the studies included in the  
 1241 current review. The small number of studies did not allow  
 1242 elimination of those conducted by the same research team.  
 1243 Therefore, the possibility that some girls with TS were  
 1244 included in several studies at different ages or that same  
 1245 results were used in different studies cannot be rejected.

1246 Another limitation comes from the nature of EF tasks.  
 1247 The different tasks retained in the current analysis could  
 1248 reflect different cognitive abilities. It was the case for  
 1249 example in the Tower tasks, as previously indicated, this  
 1250 task may target different cognitive processes depending  
 1251 on the version. Some tasks using different type of stimuli  
 1252 (e.g. the SOPT) would be more discriminant than simpler  
 1253 EF tasks. In addition, in the current analysis, planning and  
 1254 inhibitory control have been assessed exclusively with  
 1255 tasks in which visual-spatial abilities operate. Therefore,  
 1256 the role played by the visual-spatial deficit on executive  
 1257 impairments must be considered. It is plausible to suggest  
 1258 that EF assessment in this population includes both verbal  
 1259 and visual tasks for each EF. Another possibility to dif-  
 1260 ferentiate the visual-spatial deficit and EFs impairments  
 1261 would be to decompose EF tasks, as Roy et al. (2010)  
 1262 have done to assess planning abilities in children with  
 1263 neurofibromatosis type 1. These authors used two condi-  
 1264 tions of the ROCF copy, namely, the “Formulation” condi-  
 1265 tion (similar to the classic task) and the “Execution” con-  
 1266 dition. In this last condition, planning abilities play a less  
 1267 important role. Five sheets are successively presented to  
 1268 children. In each sheet, different elements of the ROCF  
 1269 are progressively added. Therefore, the children reproduce  
 1270 the figure by including progressively in their drawings the  
 1271 elements that appear in each new sheet presented. A sig-  
 1272 nificantly higher score in the “Execution” condition when  
 1273 compared to the “Formulation” condition provides argu-  
 1274 ments in favor of planning impairments.

1275 Finally, the present meta-analysis was focused exclusively  
 1276 in pencil-and-paper EF tasks or computerized EF tasks. To  
 1277 our knowledge, only one study explored the impact of exec-  
 1278 utive dysfunctions in daily lives of girls with TS (Lepage  
 1279 et al. 2013b) where authors administrated the Behavior  
 1280 Rating Inventory of Executive Function (BRIEF; Gioia  
 1281 et al. 2002). The BRIEF is a questionnaire which assesses  
 1282 executive impairments in daily life at home, with the Parent  
 1283 Form, and at school, with the Teacher Form. Lepage et al.  
 1284 (2013b) used the Parent Form and the results revealed that  
 1285 there were more complaints concerning EF difficulties in the  
 1286 TS group in comparison with the control group. It would be  
 1287 interesting to confirm these results, with Parents and Teacher  
 1288 forms, and compared them to EF task performances.

**Conclusion**

1289

1290 This systematic review and meta-analysis confirms the pres-  
 1291 ence of EF impairments in girls with TS. Difficulties seem to  
 1292 affect particularly WM and higher-order EFs. Self-regulation  
 1293 and reactive flexibility abilities appear to be less impaired. Girls  
 1294 with TS were slower than controls in several EF tasks yet this  
 1295 slower processing speed did not totally explain poor perfor-  
 1296 mances observed in cognitive inhibition and problem-solving  
 1297 timed tasks. Given visual-spatial impairments described in TS,  
 1298 in order to improve our understanding of these patients’ EF  
 1299 profile, each EF should be assessed through tasks in visual-  
 1300 spatial modality and tasks in verbal modality. Moreover, the  
 1301 use of decomposed EF tasks could help distinguish the different  
 1302 processes involved. Several moderator variables should be con-  
 1303 trolled, such as SES, IQ, karyotype, presence of psychological  
 1304 comorbidities, or compliance to the hormonal treatment. A bet-  
 1305 ter understanding of EF impairments could help to explore  
 1306 difficulties encountered by girls living with TS, such as math-  
 1307 ematical difficulties or social disabilities.

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 1309 program EnJeu[x] Enfance & Jeunesse financed by the region Pays de la  
 1310 Loire, France. Authors would like to thank Alexandre Laurent for his  
 1311 assistance in statistical analyses.

**Compliance with Ethical Standards**

1313

1314 **Conflict of Interest** The authors declare that they have no conflict of  
 1315 interest.

**Appendix**

1316

**Working Memory Task**

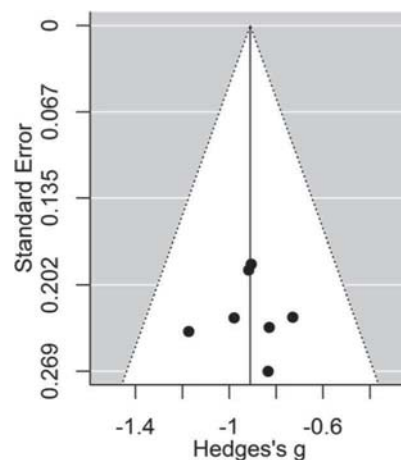
1317

*Digit Span Subtest*

1318

Funnel Plot of the Digit Span Subtest

1319  
1320



Leave-One-Out Method's Results

1321

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau <sup>2</sup>	I <sup>2</sup>
Romans et al. 1997 (7 to 9.9)	-0.92	[-1.10; -0.75]	-10.38	0.000	2.01	0.85	0.00	0.00
Romans et al. 1997 (10 to 12.5)	-0.94	[-1.11; -0.76]	-10.51	0.000	1.41	0.92	0.00	0.00
Romans et al. 1997 (12.5 to 16.9)	-0.90	[-1.08; -0.73]	-10.09	0.000	2.04	0.84	0.00	0.00
Romans et al. 1998	-0.91	[-1.09; -0.73]	-9.81	0.000	2.15	0.83	0.00	0.00
Ross et al. 1995 (younger)	-0.87	[-1.05; -0.70]	-9.86	0.000	0.76	0.98	0.00	0.00
Ross et al. 1995 (older)	-0.92	[-1.09; -0.75]	-10.52	0.000	2.06	0.84	0.00	0.00
Rovet et al. 1994	-0.91	[-1.09; -0.73]	-9.84	0.000	2.15	0.83	0.00	0.00

1322

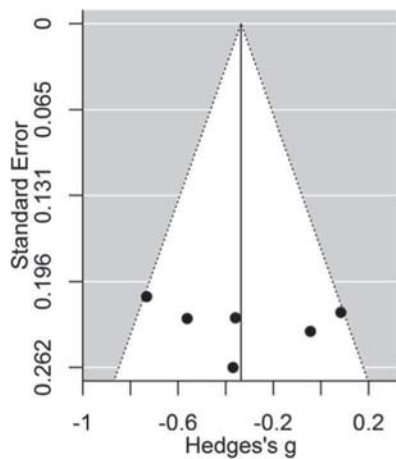
1323 **Inhibitory Control Tasks**

1324 *Matching Familiar Figures Test*

1325

1326 Funnel Plot of the Matching Familiar Figures Test (Correct  
1327 Answers)

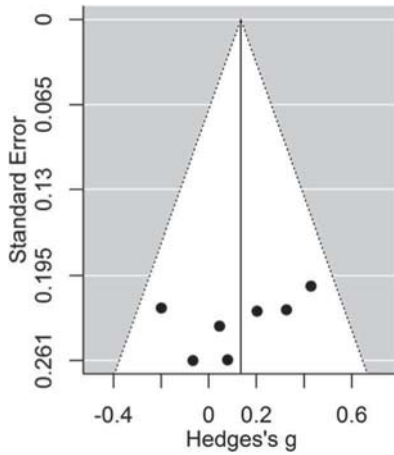
1328



1329 Leave-One-Out Method's Results

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau <sup>2</sup>	I <sup>2</sup>
Romans et al. 1997 (7 to 9.9)	-0.39	[-0.67; -0.11]	-2.74	0.006	7.96	0.093	0.05	49.76
Romans et al. 1997 (10 to 12.5)	-0.43	[-0.66; -0.20]	-3.62	0.000	5.32	0.255	0.02	24.87
Romans et al. 1997 (12.5 to 16.9)	-0.33	[-0.64; -0.01]	-2.05	0.040	9.86	0.043	0.08	59.43
Romans et al. 1998	-0.25	[-0.48; -0.01]	-2.03	0.042	5.45	0.244	0.02	26.62
Ross et al. 1995 (younger)	-0.29	[-0.58; -0.01]	-1.92	0.055	8.70	0.069	0.06	54.03
Ross et al. 1995 (older)	-0.33	[-0.63; -0.02]	-2.11	0.035	9.85	0.043	0.07	59.41

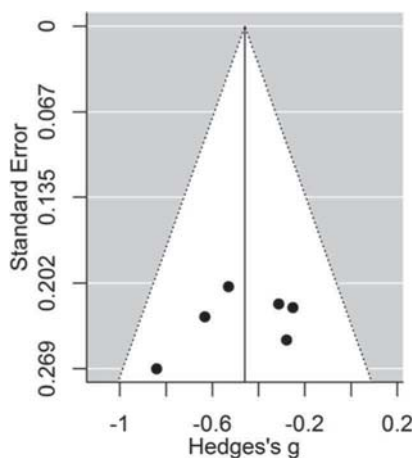
1330 Funnel Plot of the Matching Familiar Figures Test (Response  
 1331 Time Variable)  
 1332



1333 Leave-One-Out Method's Results  
 1334

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau <sup>2</sup>	I <sup>2</sup>
Romans et al. 1997 (7 to 9.9)	0.15	[-0.05; 0.34]	1.44	0.150	5.85	0.321	0.01	14.58
Romans et al. 1997 (10 to 12.5)	0.20	[0.01; 0.38]	2.08	0.038	3.29	0.656	0.00	0.00
Romans et al. 1997 (12.5 to 16.9)	0.12	[-0.08; 0.32]	1.16	0.246	5.92	0.314	0.01	15.47
Romans et al. 1998	0.07	[-0.12; 0.26]	0.72	0.469	3.47	0.627	0.00	0.00
Ross et al. 1995 (younger)	0.10	[-0.09; 0.29]	1.04	0.298	5.15	0.398	0.00	2.91
Ross et al. 1995 (older)	0.14	[-0.06; 0.34]	1.37	0.169	5.97	0.309	0.01	16.27
Ross et al. 1998	0.16	[-0.03; 0.35]	1.67	0.095	5.35	0.375	0.00	6.51

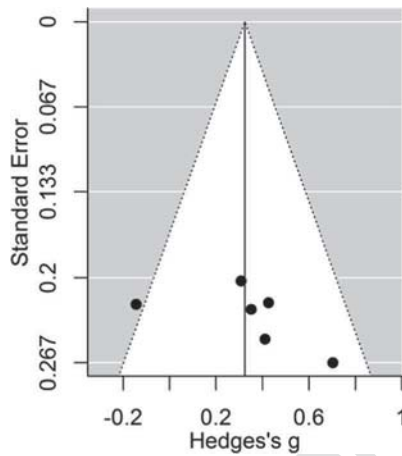
1335 *Test of Variables of Attention*  
 1336  
 1337 Funnel Plot of the Test of Variables of Attention (Commission  
 1338 Errors)



Leave-One-Out Method's Results

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau <sup>2</sup>	I <sup>2</sup>
Romans et al. 1997 (7 to 9.9)	-0.49	[-0.69; -0.29]	-4.85	0.000	3.94	0.414	0.00	0.00
Romans et al. 1997 (10 to 12.5)	-0.42	[-0.63; -0.22]	-4.15	0.000	3.87	0.424	0.00	0.00
Romans et al. 1997 (12.5 to 16.9)	-0.49	[-0.70; -0.29]	-4.76	0.000	4.01	0.405	0.00	0.28
Romans et al. 1998	-0.44	[-0.66; -0.23]	-4.01	0.000	4.41	0.354	0.01	9.24
Ross et al. 1995 (younger)	-0.50	[-0.71; -0.30]	-4.90	0.000	3.48	0.480	0.00	0.00
Ross et al. 1995 (older)	-0.41	[-0.60; -0.21]	-4.09	0.000	2.28	0.684	0.00	0.00

1339 Funnel Plot of the Test of Variables of Attention (Response  
 1340 Time Variable)



1341  
 1342 Leave-One-Out Method's Results

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau <sup>2</sup>	I <sup>2</sup>
Romans et al. 1997 (7 to 9.9)	0.31	[0.02; 0.06]	2.38	0.017	6.74	0.151	0.03	40.63
Romans et al. 1997 (10 to 12.5)	0.32	[0.06; 0.59]	2.39	0.017	6.87	0.143	0.04	41.79
Romans et al. 1997 (12.5 to 16.9)	0.31	[0.05; 0.57]	2.30	0.021	6.60	0.158	0.03	39.42
Romans et al. 1998	0.33	[0.06; 0.60]	2.41	0.016	6.89	0.142	0.04	41.97
Ross et al. 1995 (younger)	0.42	[0.22; 0.62]	4.08	0.000	1.53	0.821	0.00	0.00
Ross et al. 1995 (older)	0.27	[0.06; 0.47]	2.52	0.011	4.53	0.340	0.01	11.62

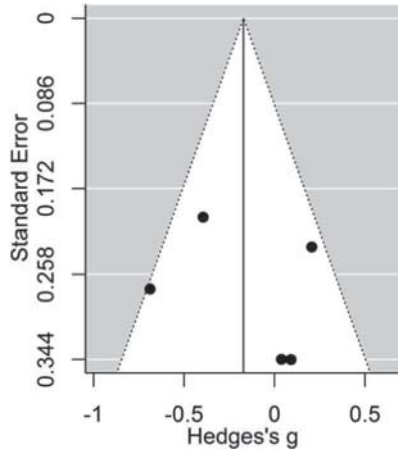
1343 **Cognitive Flexibility Tasks**

1344 *Wisconsin Card Sorting Test*

1345

1346 Funnel Plot of the Wisconsin Card Sorting Test

1347



1348 Leave-One-Out Method's Results

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau <sup>2</sup>	I <sup>2</sup>
Romans et al. 1997 (7 to 9.9)	-0.21	[-0.62; 0.20]	-1.00	0.314	7.94	0.047	0.11	62.22
Romans et al. 1997 (10 to 12.5)	-0.06	[-0.37; 0.26]	-0.35	0.725	4.37	0.225	0.03	31.29
Romans et al. 1997 (12.5 to 16.9)	-0.30	[-0.63; 0.03]	-1.76	0.079	4.48	0.214	0.04	33.00
Romans et al. 1998	-0.09	[-0.53; 0.34]	-0.43	0.670	6.88	0.076	0.11	56.38
Temple et al. 1996	-0.22	[-0.62; 0.18]	-1.07	0.283	7.69	0.053	0.10	60.98

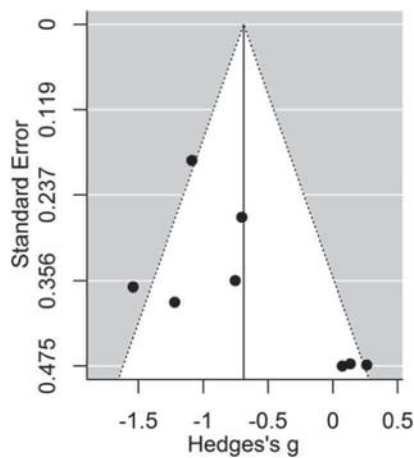
1349

1350 *Phonemic Verbal Fluency Task*

1351

1352 Funnel Plot of the Phonemic Verbal Fluency Task

1353



1354 Leave-One-Out Method's Results

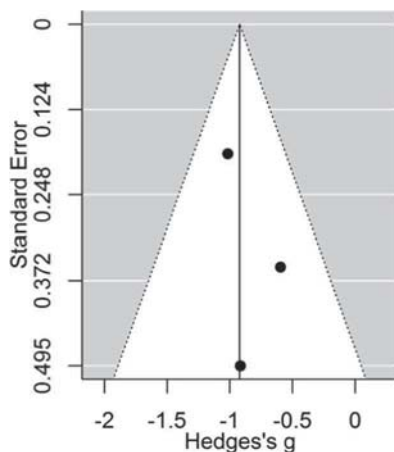
	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau <sup>2</sup>	I <sup>2</sup>
Rae et al. 2004	-0.81	[-1.19; -0.42]	-4.10	0.000	14.4	0.025	0.15	58.49
Romans et al. 1997 (7 to 9.9)	-0.79	[-1.19; -0.39]	-3.85	0.000	15.7	0.016	0.17	61.68
Romans et al. 1997 (10 to 12.5)	-0.78	[-1.19; -0.37]	-3.73	0.000	16.3	0.012	0.18	63.10
Romans et al. 1997 (12.5 to 16.9)	-0.61	[-1.06; -0.16]	-2.65	0.010	18.9	0.004	0.24	68.26
Romans et al. 1998	-0.60	[-1.08; -0.11]	-2.41	0.016	17.0	0.009	0.27	64.72
Ross et al. 2000	-0.67	[-1.16; -0.18]	-2.67	0.008	19.8	0.003	0.29	69.69
Temple et al. 1996	-0.67	[-1.14; -0.20]	-2.79	0.005	20.0	0.002	0.26	70.00
Temple 2002	-0.58	[-0.99; -0.16]	-2.70	0.007	15.8	0.015	0.18	61.99

1355

1356 *Semantic Verbal Fluency Task*

1357

1358 Funnel Plot of the Semantic Verbal Fluency Task



1359

1360 Leave-One-Out Method's Results

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau <sup>2</sup>	I <sup>2</sup>
Rae et al. 2004	-0.91	[-1.27; -0.55]	-5.00	0.000	1.11	0.291	0.01	10.16
Romans et al. 1998	-0.70	[-1.26; -0.14]	-2.45	0.014	0.28	0.598	0.00	0.00
Temple et al. 1996	-1.00	[-1.35; -0.66]	-5.71	0.000	0.04	0.850	0.00	0.00

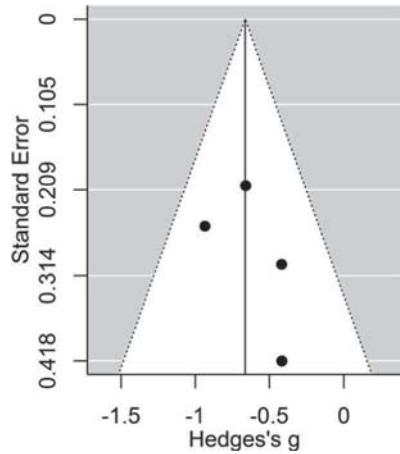
1361 **Higher-Order Executive Function Tasks**

1362 *Tower of Hanoi*

1363

1364 Funnel Plot of the Tower of Hanoi (Score Variable)

1365



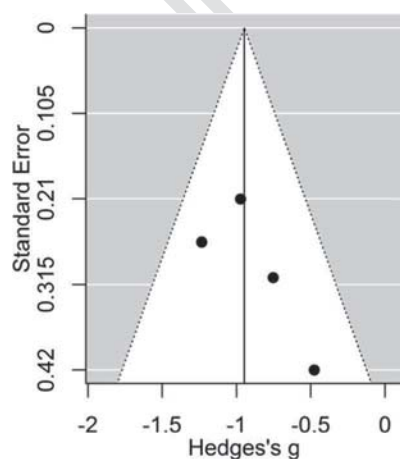
1366 Leave-One-Out Method's Results

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau <sup>2</sup>	I <sup>2</sup>
Romans et al. 1997 (7 to 9.9)	-0.69	[-0.97; -0.42]	-4.93	0.000	1.77	0.413	0.00	0.00
Romans et al. 1997 (10 to 12.5)	-0.72	[-1.02; -0.43]	-4.88	0.000	1.32	0.517	0.00	0.00
Romans et al. 1997 (12.5 to 16.9)	-0.56	[-0.87; -0.25]	-3.59	0.000	0.58	0.747	0.00	0.00
Romans et al. 1998	-0.66	[-1.02; -0.30]	-3.60	0.000	2.15	0.341	0.01	7.05

1367

1368 Funnel Plot of the Tower of Hanoi (Average Time Variable)

1369



1370 Leave-One-Out Method's Results

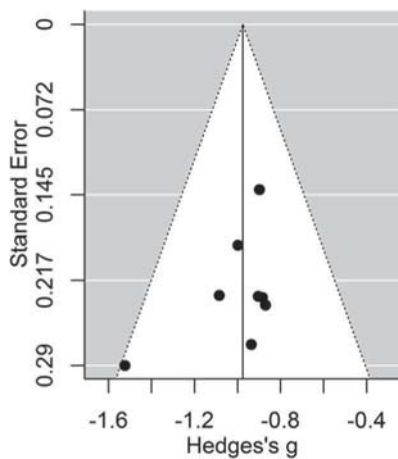
	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau <sup>2</sup>	I <sup>2</sup>
Romans et al. 1997 (7 to 9.9)	-1.00	[-1.29; -0.72]	-6.94	0.000	1.46	0.482	0.00	0.00
Romans et al. 1997 (10 to 12.5)	-0.99	[-1.32; -0.65]	-5.80	0.000	2.36	0.307	0.01	15.29
Romans et al. 1997 (12.5 to 16.9)	-0.84	[-1.16; -0.53]	-5.25	0.000	1.23	0.542	0.00	0.00
Romans et al. 1998	-0.90	[-1.33; -0.47]	-4.10	0.000	2.84	0.242	0.04	29.47

1371

1372 *Rey-Osterrieth Complex Figure*

1373

1374 Funnel Plot of the Rey-Osterrieth Complex Figure



1375

1376 Leave-One-Out Method's Results

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau <sup>2</sup>	I <sup>2</sup>
Reiss et al. 1995	-0.98	[-1.13; -0.83]	-12.57	0.000	4.56	0.601	0.00	0.00
Romans et al. 1997 (7 to 9.9)	-0.99	[-1.14; -0.83]	-12.51	0.000	4.37	0.627	0.00	0.00
Romans et al. 1997 (10 to 12.5)	-0.99	[-1.14; -0.83]	-12.46	0.000	4.41	0.621	0.00	0.00
Romans et al. 1997 (12.5 to 16.9)	-0.96	[-1.12; -0.81]	-12.16	0.000	4.33	0.632	0.00	0.00
Romans et al. 1998	-0.97	[-1.13; -0.81]	-11.89	0.000	4.57	0.601	0.00	0.00
Ross et al. 1995 (younger)	-0.98	[-1.14; -0.83]	-12.43	0.000	4.48	0.612	0.00	0.00
Ross et al. 1995 (older)	-0.94	[-1.09; -0.78]	-12.08	0.000	0.74	0.993	0.00	0.00
Ross et al. 1997a, b	-1.01	[-1.18; -0.83]	-11.36	0.000	4.17	0.653	0.00	0.00

Q6

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