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-Analysis

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

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

Challenges for the investigation of EFs emerge from the fact that executive tests involve different types of EFs, yet it remains difficult to determine which executive process contributes most to task achievement. For example, the Wisconsin Card Sorting Test (WCST), widely used in research and clinical practice as a measure of hypothesis generation and ability to shift response (Goldstein and Green 1995), was initially introduced to explore problem-solving and decision-making abilities (Berg 1948; Grant and Berg 1948). In addition, executive tasks are not pure measures of a single skill, and as a result, an individual's executive performance can be contaminated by non-executive requirements of the task (Burgess 1997). Given evidence for impaired visual-spatial ability in patients with TS (see Hong et al. 2009 for review), which might affect executive tasks requiring visual-spatial processing, it could be interesting to consider the impact of procedural aspects on EF performance. Furthermore, another point to consider is that in some EF tasks participants have to provide a response as quickly as possible. The nature of the relation between processing speed and EFs is controversial and remains to be specified (Lee et al. 2013). As reviewed by Mazzocco (2006), a lower processing speed has been described in girls with TS. Therefore, it remains unclear if poor performances in executive timed tasks reflect specific EFs difficulties or if these results are mediated by deficits in processing speed.

Executive Functions in Turner Syndrome Q2

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

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

Response inhibition, within inhibitory control functions, is the most studied in children with TS using tasks assessing impulsivity. One study (Romans et al. 1998) reported that participants with TS responded faster than controls in the Matching Familiar Figures Test (MFFT). Moreover, the number of commission errors was significantly higher in the TS group in the Test of Variables of Attention (TOVA: Romans et al. 1997, 1998). Yet, these findings are not consistent and other studies reported no significant difference between girls with TS and controls in these same tasks (MFFT: Romans et al. 1997; Ross et al. 1998, 1995 – TOVA: Ross et al. 1995), as well as in a Go-NoGo task (Tamm et al. 2003). Concerning the other aspects of

inhibitory control, these processes have been less often explored. Girls with TS may have cognitive inhibition impairments, highlighted by the Stroop task (Temple et al. 1996; Waber 1979). Finally, selective attention deficits were also reported on a flanker task (Quintero et al. 2014) and on the Auditory Attention and Response Set subtest and Visual Attention subtest from the NEPSY (Green et al. 2015).

Evidence for poorer performance on set-shifting tasks appear to be contingent upon task selection. Hence, the majority of studies assessing cognitive flexibility using verbal fluency tasks indicated deficient performance among TS samples for phonemic (Bender et al. 1989; Romans et al. 1997, 1998; Temple et al. 1996; Temple 2002; Waber 1979) and semantic fluency (Rae et al. 2004; Romans et al. 1998; Temple et al. 1996). Girls with TS had more difficulties than control participants in the TMT (Bender et al. 1993) and in the Same-Opposite world subtest from the Test of Everyday Attention for Children (Skuse et al. 1997). In contrast, some studies using the WCST as an indicator for flexibility revealed no difference between TS and control groups (McGlone 1985; Romans et al. 1997, 1998; Temple et al. 1996), although results are not consistent (Bender et al. 1993; Loesch et al. 2005; Waber 1979). Performance is also heterogeneous with the Contingency Naming Test (CNT), where girls with TS obtained lower results than the control group in the two-attribute trials in two studies (Kirk et al. 2005; Mazzocco and Hanich 2010) but not in another (Murphy and Mazzocco 2008).

Higher-level EFs have been assessed in children with TS with the Rey-Osterrieth Complex Figure (ROCF) and different problem-solving tasks such as the Tower of Hanoi (TOH), the Tower of London (TOL) or the Tower subtest from the NEPSY. In most studies (Bishop et al. 2000; Loesch et al. 2005; Reiss et al. 1995; Romans et al. 1997, 1998, 1995, 1997a; Waber 1979), but not all (McGlone 1985), girls with TS had more difficulties than controls to reproduce the ROCF. Concerning the TOH and its variants, some studies did not find any difference between the TS group and the controls (Temple et al. 1996; Green et al. 2015; Skuse et al. 1997), while in others, girls with TS obtained lower results (Romans et al. 1997, 1998).

In TS, differences between studies assessing EFs may be explained, in part, by methodological choices concerning executive tasks, for example, visual or verbal modality, or limited response time. Yet, participant characteristics (age, IQ, parental socioeconomic status, karyotype, hormonal treatments, and psychological co-morbidities) could also explain discrepancies in results.

Moderator Variables of Executive Functions in Turner Syndrome

The development of EFs occurs during the first year of life and goes on until the beginning of adulthood, each EF has its own developmental calendar (Best and Miller 2010). It is plausible to expect that in TS, developmental changes may not follow the same curve as control children and, as age advances, differences between children with TS and their peers may increase or reduce. Hence, heterogeneity of results could be explained by variability of participants' age between studies assessing EFs in TS (e.g. Skuse et al. 1997: age range from 6 to 25 years). Even if in the vast majority of studies, TS and control groups have been matched by age, in some studies (e.g. Kirk et al. 2005; Murphy and Mazzocco 2008) the two groups were matched by full scale IQ. This IQ-matching criterion could have an impact on the magnitude of the ES on EF tasks.

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

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

Other characteristics, specific to children and adolescents with TS, should be also taken into account in EF assessment. In TS, the anomaly affecting one of the two X chromosomes can be present in all cells or only one part (mosaicism). The hypothesis of cognitive differences between different TS karyotypes has been explored in several studies in which girls with 45,X monosomy were compared to girls with mosaic karyotypes and girls with other TS karyotypes (e.g. X partial deletion or X translocation). Regarding intellectual abilities, girls with a ring X chromosome had more verbal and nonverbal difficulties than girls with 45,X monosomy (Kuntsi et al. 2000). These latter obtained significantly lower scores than girls with mosaicism on the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV)'s perceptual reasoning and WM indexes (Bray et al. 2011). Children with structural abnormalities of X chromosome (translocation, isochromosome, partial deletion) had higher Verbal IQ than ones with X monosomy or mosaicism (Messina et al. 2007). Compared to the other karyotypes, 45,X monosomy has been associated

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

Several hormonal treatments are prescribed to children and adolescents with TS, such as growth hormone (GH) to increase adult height and estrogen therapy (around 12 years of age) to induce puberty (Bondy 2007). Regarding cognitive profile, no difference was highlighted between girls with TS receiving GH and girls receiving placebo (Ross et al. 1997b), yet, another study (Rovet and Holland 1993) highlighted improvement of social abilities in the GH group. Furthermore, oxandrolone, an anabolic steroid, is used with GH in children with extreme short stature or when GH treatment is not commenced before 9 years of age (Bondy 2007). After several years of treatment, compared to placebo group, girls with TS receiving oxandrolone had better WM abilities (Ross et al. 2003) and a lower frequency of severe arithmetic learning disabilities (Ross et al. 2009). Moreover, positive effects of an early estrogen treatment on nonverbal processing time, motor speed (Ross et al. 1998), verbal WM, verbal and nonverbal episodic memory (Ross et al. 2000) were emphasized in young girls with TS receiving low doses of estrogen compared to girls receiving placebo.

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

Aims

Based on Diamond's (2013) hierarchical model of EFs, the present meta-analysis addresses the following research questions (1) When comparing girls with TS and controls, are there ES differences across tasks depending on EF abilities tested? (2) Did children with TS fail only in visual modality EF tasks? (3) Did participants with TS have lower performance than controls only in EF tasks that require a rapid response? To answer these questions, study results, in which EF abilities of girls with TS were compared to age-matched control girls' EF abilities, will be analyzed.

Methods

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

Study Eligibility Criteria

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

Search Strategy

A systematic literature search was performed in September 2015 and updated in September 2017 without any restriction of publication date. Five electronic databases (*Pubmed*, *PsycARTICLES*, *PsycINFO*, *Web of Science Core Collection*, and *Cochrane Central Register of Controlled Trials*) were examined. The following combination of keywords was used: ("executive" or "cognitive" or "cognition" or "neurocognitive" or "neuropsychological" or "inhibitory control" or "inhibition" or "attention" or "cognitive flexibility" or "working memory" or "planning" or "decision making") and ("child*" or "adolescen*") and ("Turner syndrome" or "X monosomy" or "sex chromosome abnormalities" or "45,X" or "Ullrich-Turner syndrome" or "X chromosome abnormalities" or "X chromosome deletion"). Subsequently, the reference section of publications found through our search was checked to identify additional studies that may have been missed. In addition, when data reported in the article were not sufficient to calculate an ES, the authors were contacted to collect missing data and unpublished results.

Study Selection

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

eligible studies according to the inclusion criteria. Any discrepancies were resolved by consensus. These studies were further assessed for eligibility using the full text. Seven authors were contacted to obtain missing data and unpublished results. Unfortunately, none could respond positively to our request.

Data Extraction

Sample Characteristics For each sample, means and standard deviation (SD) of age, Verbal IQ (VIQ) and Performance IQ (PIQ) were extracted for TS group and its matched controls. In several studies, the number of participants could vary depending on the tasks, thus, sample size was extracted for each task. For TS groups, when data were available, the proportion of patients with 45,X karyotype and information concerning hormonal treatment (estrogen therapy and growth hormone therapy) were also extracted.

Executive Function Tasks Neuropsychological measures of EFs were coded separately when assessing one of the following EF components: WM, inhibitory control, cognitive flexibility, higher-order EFs. For each task, one variable was selected as the most appropriate measure of EF. The chosen variable had to be available in all studies included in the meta-analysis. If data from several variables were present in the retained studies, we have selected the one described as the most pertinent measure to assess the targeted EF. This issue was raised for three tasks, the TOVA, WCST and SOPT. For the TOVA, the variable "commission errors" has been chosen because, according to Greenberg and Waldman (1993), it allows the assessment of impulsivity or response inhibition. Concerning the WCST, the percent of perseverative errors, which "may be a better metric of executive function if a single score form the WCST is to be used" (Rhodes 2004, p.488), has been retained. For the SOPT, used in one study, the variable "number of pages before error" has been chosen because it seemed to be the most adequate in the assessment of WM abilities compared to the two others (total item perseveration, total position perseveration). Whenever possible, a time variable was also extracted. For each TS group and its control group, sample size, mean and SD of each variable (or F-value when such data were not available) were extracted. Two studies (Ross et al. 1998, 2000) have examined the effects of an early estrogen treatment on girls with TS cognitive profile by comparing two subgroups (one group with hormonal treatment and one group without). In these studies, the age ranges were 7 to 9 years (Ross et al. 2000) and 10 to 12 years (Ross et al. 1998). Several other studies retained for the meta-analyses included participants in the same age ranges, yet patients with TS did not receive estrogen treatment. Therefore, only placebo subgroup results were extracted from these two studies.

Data Analysis

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

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

In some studies, several tasks have been used to assess EFs. Therefore, data extracted from a same group of participants would be included several times in the meta-analysis. It was necessary to consider the dependence between these ES. A three-level meta-analysis was conducted using the maximum-likelihood method to estimate heterogeneity. An overall ES was calculated with all the ES. Three different levels of heterogeneity are taken into account in this analysis (1) sampling variance of all the ES at level 1, (2) variance between ES extracted from the same sample at level 2 and (3) variance between ES extracted from different samples at level 3 (Assink and Wibbelink 2016). To test the hypothesis of the homogeneity of ES, the Cochran's Q-test was applied (Cochran 1954). The *p*-value threshold was fixed to 10%. If p-value is less than 0.10, the heterogeneity cannot be considered as exclusively due to within-sample error. The level 2 an level 3 heterogeneity variances were estimated with 췌$^2_{(2)}$ and 췌$^2_{(3)}$, respectively. To quantify the heterogeneity, the I^2 index was calculated. $I^2_{(2)}$ and $I^2_{(3)}$ allow to estimate the proportion of the total heterogeneity of the ES due to the level 2 (within-sample) and level 3 (between-sample) heterogeneity. The effect of moderators (task modality, type of assessed EF) was investigated using a mixed-effects model. In these analyses, $R^2_{(2)}$ and $R^2_{(3)}$ estimate the percentage of variance of the heterogeneity explained by the moderator at level 2 and level 3

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

An overall ES was calculated for each EF task employed in several studies. To assess processing speed in girls with TS, an ES was calculated for the response time variable of EF tasks when data were available. In some of these meta-analyses, only a little number of studies could be included. Hence, the results should be interpreted with caution. As for the three-level meta-analysis, Cochran's *Q*-test was used to assess the presence of heterogeneity among the ES (Cochran 1954). The parameter 쵀^2, using DerSimonian and Laird method, estimates the between-sample heterogeneity variance (Borenstein et al. 2009). The I^2 index was calculated to quantify the proportion of total variation due to true variability between samples rather than chance. The I^2 index estimates what percentage of the observed variance would remain if the sampling error could be eliminated (Borenstein et al. 2017). For each univariate meta-analysis, a funnel plot was produced. The number of studies included in this meta-analysis was too low to statistically test funnel plot asymmetry (Higgins and Green 2011). Therefore, the funnel plots were visually inspected to detect outliers. The leave-one-out method was used to verify the robustness of each univariate meta-analysis' results and to assess the impact of outliers on the overall ES. Hence, each analysis was conducted repeatedly removing one study at a time (Viechtbauer 2010).

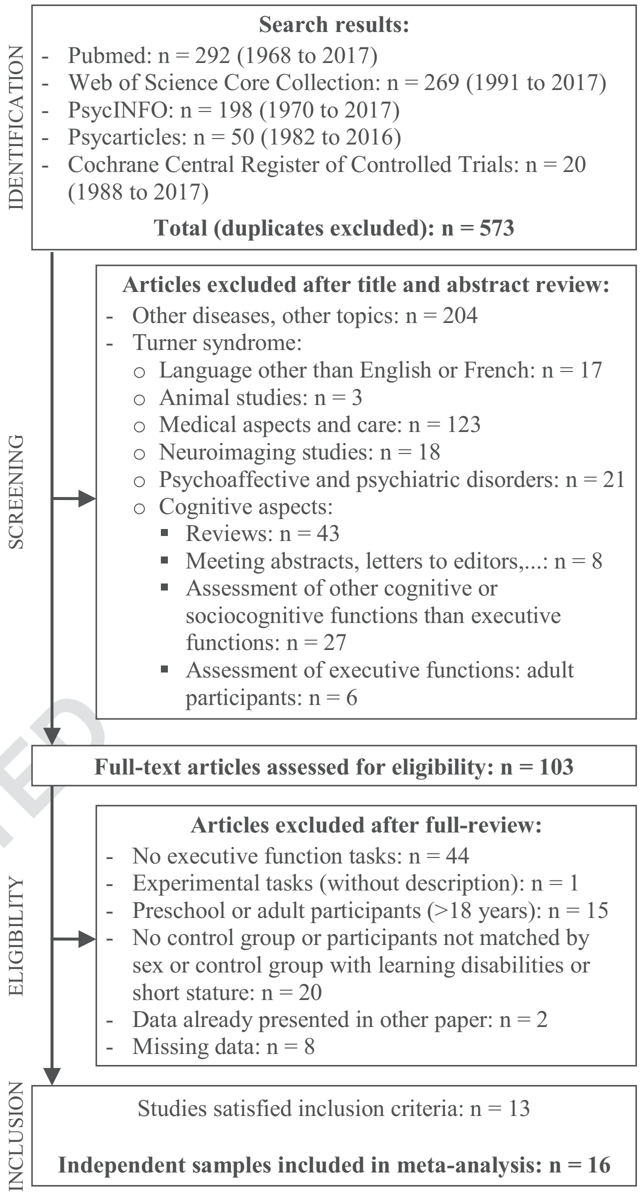

Fig. 1 Flow diagram of selection of studies

Results

Characteristics of the Samples

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

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

t1.1 **Table 1** Summary of samples characteristics

	Studies	Turner syndrome group						Control group			Number of EF tasks
t1.3		Patients with 45,X karyotype	Patients with Estrogen therapy	Patients with GH therapy	Mean age (SD)	Mean VIQ (SD)	Mean PIQ (SD)	Mean age (SD)	Mean VIQ (SD)	Mean PIQ (SD)	
t1.4	Bray et al. 2011	10/14	–	–	10.6 (1.6)	–	–	10.6 (1.5)	–	–	2
t1.5	Quintero et al. 2014	31/31	–	–	10.7 (2.31)	—[a]	—[a]	10.2 (2.27)	—[a]	—[a]	2
t1.6	Rae et al. 2004	9/9	0/9	–	9.92 (1.5)	–	–	9.92 (1.25)	–	–	2
t1.7	Reiss et al. 1995	27/30	3/23 [b]	6/23 [b]	10.5 (3.42)	99 (15.4)	87.7 (13.7)	10.75 (2.83)	115.3 (16.4)	110.3 (15.5)	1
t1.8	Romans et al. 1997 7.0 to 9.9	3 samples confounded: 65/105	0/30	3 samples confounded: 42/105	8.4 (0.8)	107 (15)	94 (13)	8.5 (0.8)	102 (10)	102 (12)	7
t1.9	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
t1.10	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
t1.11	Romans et al. 1998	2 samples confounded: 63/99 [c]	2 samples confounded: 99/99[c]	2 samples confounded: 59/99 [c]	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
t1.12	Ross et al. 1995 younger	2 samples confounded: 36/56	0/35	2 samples confounded: 28/56	8.8 (1.3)	103 (14)	92 (14)	8.7 (0.9)	107 (11)	107 (11)	4
t1.13	Ross et al. 1995 older		0/21		12.3 (0.5)	103 (10)	93 (11)	12.2 (0.8)	104 (10)	106 (14)	4
t1.14	Ross et al. 1997a	83/83	0/83	33/83	11.1 (2.7)	102 (12)	–	11.3 (2.6)	102 (9)	–	1
	Ross et al. 1998	18/23	0/23	0/23	11.9 (0.5)	102 (13)	93 (14)	11.9 (0.7)	104 (11)	105 (16)	1
	Ross et al. 2000	36/54[d]	0/30	0/30	8.1 (0.6)	104 (16)	95 (14)	8.4 (0.6)	104 (9)	105 (14)	2
	Rovet et al. 1994	25/45	–	–	11.5[e]	97.6 (12)	91.7 (14.8)	11.9[e]	106.6 (12)	113 (14.4)	1
	Temple et al. 1996	8/16	–	–	10.42 (1.2)	96 (—)	92 (—)	10.58 (0.87)	–	–	7
	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

[a] The WISC-IV, in which subtests are not any more organized into VIQ and PIQ, was used in this study

[b] Information was not known for 7 participants

[c] 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

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

[e] 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

provide information about treatment received by participants (Bray et al. 2011; Quintero et al. 2014; Rovet et al. 1994; Temple et al. 1996; Temple 2002) and these data were unknown for several girls in another study (Reiss et al. 1995). In several samples, none of the girls with TS received this treatment (Rae et al. 2004; Ross et al. 1995, 1997a, 1998, 2000, 1997), whereas, in other studies, all participants were treated with estrogen (12.5 to 16.9 years old group in Romans et al. 1997, 1998). For GH therapy, information was available in six studies (Romans et al. 1997, 1998, 1995, 1997a, 1998, 2000). The proportion of participants receiving GH was between 0% and 59%. Concerning EF assessment, the number of tasks used varied from one to eight among studies. The executive tasks, and related variables, used in samples included in the current meta-analysis are presented on Table 2.

Three-Level Meta-Analysis

Overall Score Fifty-six variables assessing performances on EF tasks were extracted from fifteen samples. The overall ES was medium and significant ($g = -0.67$, 95% C.I. [−0.77, −0.56], $Z = -12.19$, $p < 0.001$). The Q statistic indicated significant heterogeneity among the ES ($Q(55) = 124.97$, $p < 0.001$). The estimated within-sample heterogeneity variance ($T^2_{(2)}$) was 0.077 and the estimated between-sample heterogeneity variance ($\tau^2_{(3)}$) was 0.002. According to $I^2_{(2)}$ and $I^2_{(3)}$ values, 54.04% and only 1.34% of the total heterogeneity were explained by level 2 and level 3, respectively. See Fig. 2 for the forest plot.

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

The impact of the type of assessed EF on the ES was also explored (see Fig. 2). Overall ES varied from small for inhibitory control ($g = -0.44$, 95% C.I. [−0.60, −0.28], $Z = -5.52$, $p < 0.001$) to medium for cognitive flexibility ($g = -0.57$, 95% C.I. [−0.75, −0.40], $Z = -6.17$, $p < 0.001$) and large for working memory ($g = -0.89$, 95% C.I. [−1.07, −0.70], $Z = -9.42$, $p < 0.001$) and higher-order EFs ($g = -0.87$, 95% C.I. [−1.04, −0.70], $Z = -10.05$, $p < 0.001$). With this moderator, the estimated heterogeneity variance τ^2 at level 2 and level 3 were 0.026 and 0.007, respectively. The type of assessed EF explained almost 66% of the heterogeneity at the level-2 ($R^2_{(2)} = 65.85\%$), whereas this variable did not explain between-sample heterogeneity ($R^2_{(3)} = 0.00\%$).

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

Working Memory Tasks

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

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

t2.1 **Table 2** Tasks used to assess executive functions

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

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

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

[b] The sign of effect size was reversed

[c] There were seven samples for response time variable

[d] This composite score takes into account accuracy, completion time and problem difficulty

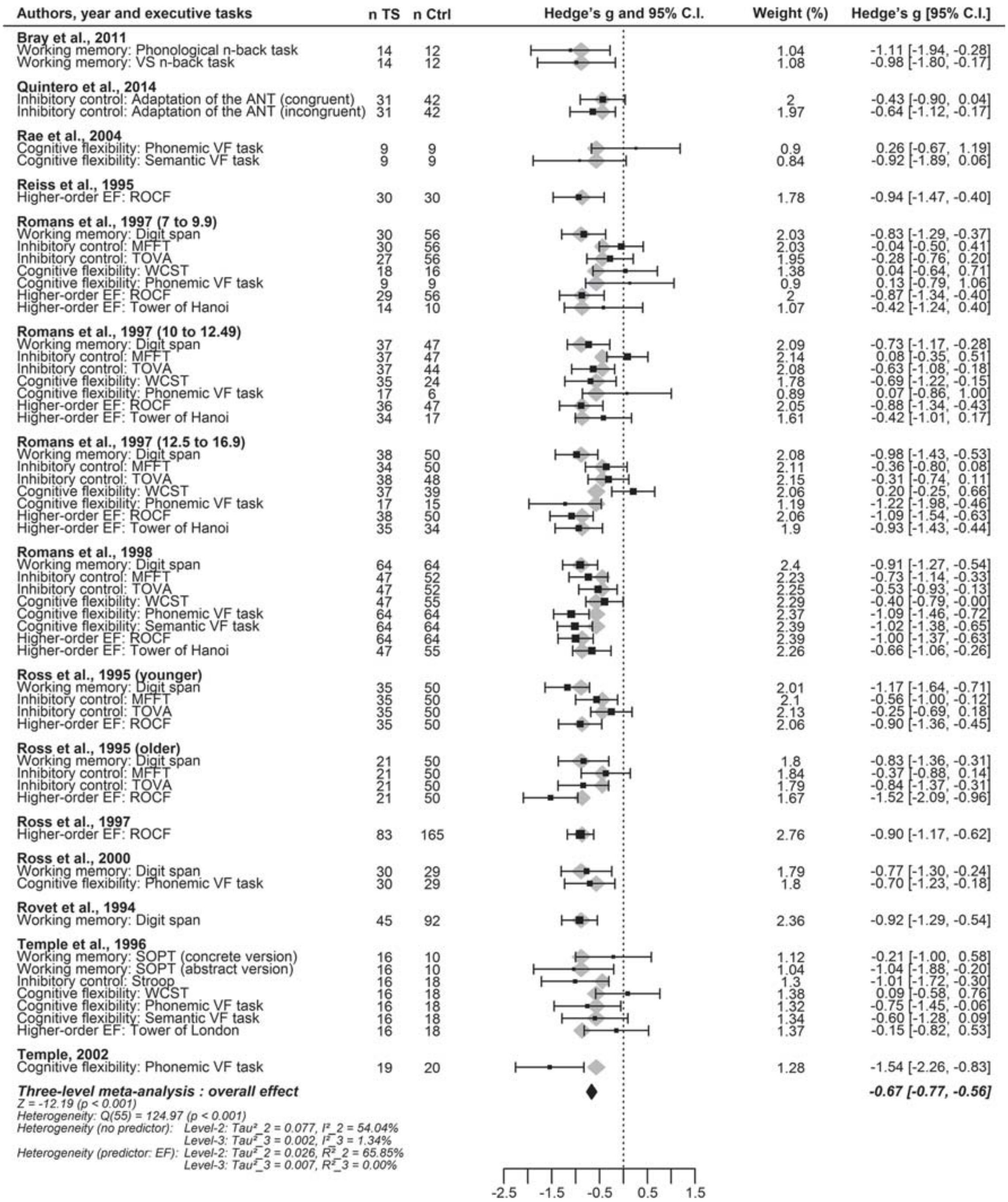

Fig. 2 Forest plot of individual effect sizes and overall effect size estimate. *n TS* number of participants with Turner syndrome, *n Ctrl* number of control participants, *C.I.* Confidence Interval, VS visual-spatial, *ANT* Attention Network Test, *VF* verbal fluency, *ROCF* Rey-Osterrieth Complex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

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

Inhibitory Control Tasks

Different aspects of inhibitory control were assessed with the MFFT ($k = 6$), the TOVA ($k = 6$), an adaptation of the children's ANT ($k = 1$), and the Stroop task ($k = 1$). In the Stroop task used only by Temple et al. (1996), the difference in time between the interference condition and the baseline condition was more important in the TS group than in the control group. The ES was large for this task ($g = -1.01$). In the adaptation of the ANT used in Quintero et al.'s study (Quintero et al.

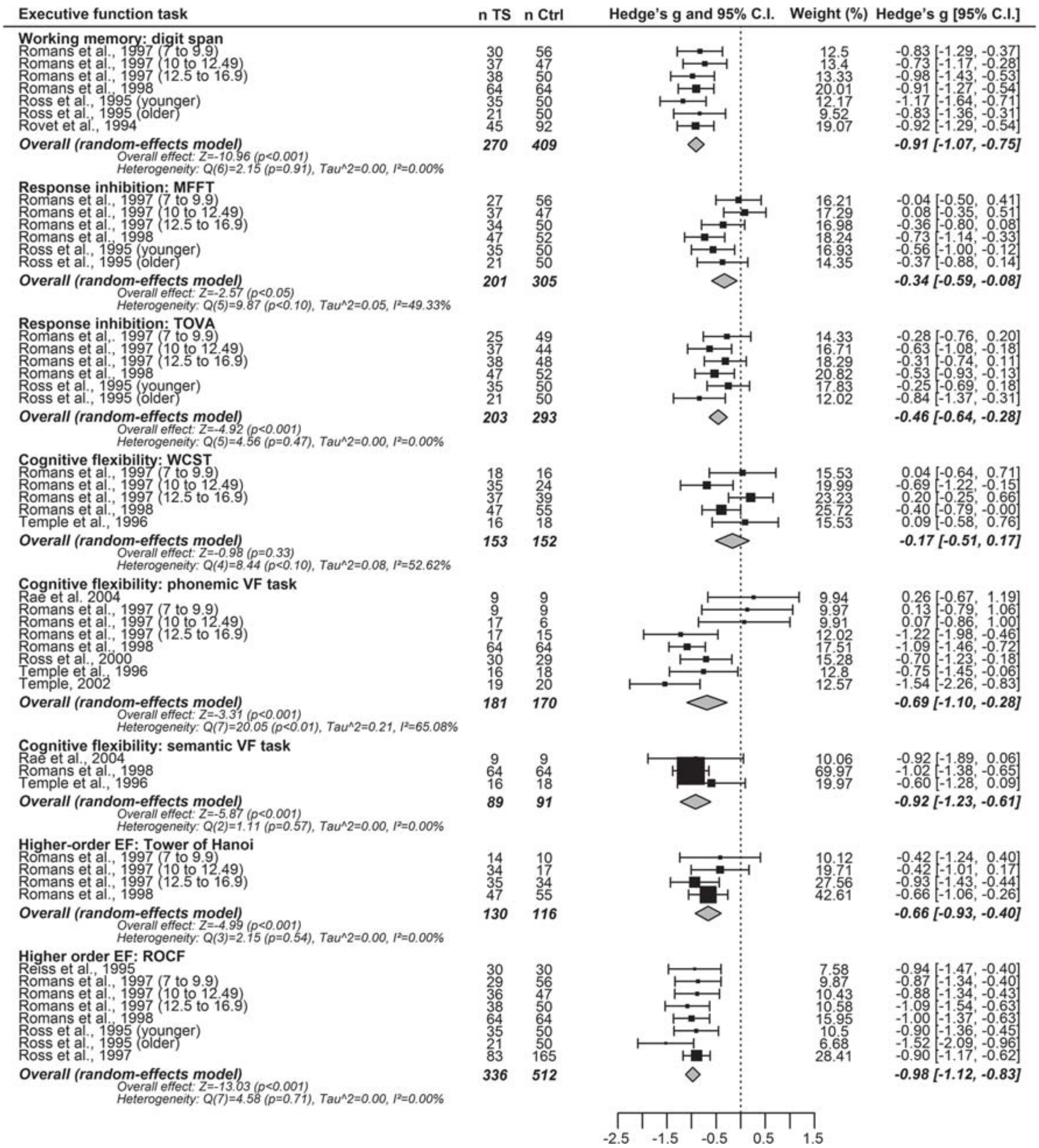

Fig. 3 Forest plots of overall effect size estimate for executive function tasks. *n TS* number of participants with Turner syndrome, *n Ctrl* number of control participants, *C.I.* Confidence Interval, *MFFT* Matching Familiar Figures Test, *TOVA* Test of Variables of Attention, *WCST* Wisconsin Card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

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

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

Concerning the ANT, reaction time was higher in the TS group for both incongruent and congruent conditions (see previous part Analysis by task). In the same way, participants with TS were slower than controls in the other conditions for this attentional task (neutral cue: $g = -0.45$; no cue: $g = -0.55$; valid cue: $g = -0.49$; invalid cue: $g = -0.45$). For each condition, response time differences between the TS group and its control group were small or, for the no cue condition and the congruent condition, medium. The difference between the TS group and the control group slightly increased with task difficulty (neutral cue vs no cue, congruent vs incongruent).

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

In the TOVA, response time variable may assess information processing speed and motor response speed (Greenberg and Waldman 1993). Girls with TS were faster than control participants and the difference between TS and control groups was small and significant. ($g = 0.32$, 95% CI [0.11; 0.54], $Z = 2.96$, $p < 0.01$). The results were not significantly different across the six samples ($Q(5) = 6.90$, $p = 0.23$, $I^2 = 27.50\%$). One outlier (youngest group from Ross et al. 1995) was observed in the funnel plot (see Appendix). When this sample was removed, overall ES value increased but remained small ($g = 0.42$, 95% CI [0.22; 0.62], $Z = 4.08$, $p < 0.001$). The meta-analysis results seemed to be robust. The range of overall ES obtained with the leave-one-out method was from 0.27 to 0.42.

Cognitive Flexibility Tasks

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

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

Time Variables There was no time variable in the WCST. For the verbal fluency tasks, response time limit is 60 s. Thus, the number of correct responses may reflect processing speed. In a same period, the girls with TS produced significantly less words than controls (see previous section Analysis by task).

Higher-Order Executive Functions Tasks

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

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

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

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

Discussion

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

Executive Functions Impairments in Turner Syndrome

In the three-level meta-analysis, the overall ES was negative and medium, corroborating the argument that girls with TS have executive impairments. However, this result should be interpreted in light of the within- and between-sample variability. Indeed, between-sample heterogeneity was surprisingly lower than the within-sample heterogeneity. Only fifteen studies have been included in this meta-analysis and, among them, the number of outcome variables ranged from one to eight. A negative and large ES was obtained for each of the studies in which only one variable was extracted (Reiss et al. 1995: ROCF: g = −0.94; Ross et al. 1997a, b: ROCF: g = −0.90; Rovet et al. 1994: Digit span subtest: g = −0.92; Temple 2002: phonemic verbal fluency task: g = −1.54). Between-sample heterogeneity would have been higher if, in some of these studies, the authors had used a task in which small differences between girls with TS and controls have been observed (e.g. MFFT). Moreover, four studies, in which seven or eight variables were extracted, were conducted by the same research team (Ross et al. 1997a, b; Romans et al. 1998). The authors investigated different EFs, used the same tasks and obtained heterogeneous results in the four studies. Within-sample heterogeneity would have been lower if, in some studies, the authors had explored only one EF with several tasks (such as Bray et al. 2011). Indeed, according to moderator analysis, the type of assessed EF might explain a large part of within-sample heterogeneity.

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

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

The association between TS and inhibition impairment varied across inhibitory measures. In the three Stroop conditions, a cognitive inhibition task, girls with TS were slower than controls. The Stroop effect value ($g = -1.01$) may suggest that these girls have significantly more difficulties inhibiting a prepotent response when compared to controls. The other inhibitory processes described by Diamond (2013), focused attention and response inhibition, seem to be more preserved in girls with TS. Thus, they were slower than controls in the ANT (a focused-attention task), but this difference in response time was quite similar among the six conditions of ANT despite different difficulty levels (ES range from −0.64 to −0.45). Therefore, a slower processing speed in girls with TS compared to their matched controls may explain differences observed between the two groups. As for response inhibition, even if children with TS had more difficulties than their healthy peers to inhibit impulsive behaviors, differences with controls were small for the accuracy and response time variables in tasks assessing impulsivity.

Concerning cognitive flexibility, a discrepancy was found between the tasks used to explore this function. Compared to healthy controls, girls with TS had significantly lower performance on verbal fluency tasks with medium to large ES, whereas there was no significant difference between groups in the WCST. Two hypotheses can be advanced to explain these differences. First, maybe these tasks do not assess the same aspects of cognitive flexibility. Eslinger and Grattan (1993) distinguished spontaneous flexibility, assessed by fluency tasks that require generation of diverse answers, versus reactive flexibility, assessed by the WCST where participants need to adapt their answers to the examiner's demands or to stimuli. In TS, spontaneous flexibility may be impaired whereas reactive flexibility may be more preserved. The second explanation is that the impairment observed in verbal fluency tasks could be due to the fact that participants have a limited period of time to generate as many words as possible. In the present meta-analysis, this time constraint was absent in the WCST in which the chosen variable was the number of perseverative errors. Differences observed across cognitive flexibility tasks may be attributed, at least in part, to a slowdown in information processing speed.

According to Diamond's model (2013), the three core EFs contribute to higher-order EFs. However, conflicting results have been reported under the type of planning task used. Hence, children with TS took more time to complete the TOH and could not reach the same level as that of controls (a medium ES was found). In contrast, in the case of TOL a small difference was found between the TS group and the control group concerning both the accuracy score and response time. While these two tasks appear to be very similar, they may involve different cognitive processes. For instance, it has been suggested that WM and inhibition may be related to TOL results, whereas only inhibition may contribute to TOH performance (Welsh et al. 1999). In contrast, Zook et al. (2004) have proposed that only fluid intelligence measure was related to scores of the TOL, whereas WM, inhibitory response, fluid intelligence, and TOH performances were correlated. The current meta-analysis results are congruent with those obtained by Zook et al. (2004). Planning abilities have also been assessed with the ROCF. Large differences between girls with TS and healthy controls were observed, yet, this could be explained by impairments observed in patients with TS in visual constructional abilities which are necessary in succeeding this task.

Visual-Spatial Impairment and EFs in Girls with Turner Syndrome

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

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

Links between visual-spatial impairments and EFs have been explored in other studies, which did not meet the inclusion criteria for this meta-analysis. In Lepage et al. (2011), girls with TS had significantly lower scores than controls on the Attention-Executive Domain of the NEPSY. Performances of patients with TS on Tower and Visual Attention subtests were significantly and positively correlated to subtests from Perceptual Reasoning Index score of the WISC-IV. This association was not observed in the control group. These results are interesting but it is unclear if the TS results on EF tasks were due exclusively to EF impairment or if the visual nature of stimuli accentuated impairments. In another study (Green et al. 2015), girls with TS were divided in two sub-groups according to the severity of ADHD-associated behaviors and were compared to neurotypical children as well as to children with idiopathic ADHD. All girls with TS had lower results than neurotypical controls in all the NEPSY domains. The two TS groups had the same profile compared to children with idiopathic ADHD, except for visual-spatial tasks in which girls with TS had poorest results. There was no difference between the two TS groups in visual-spatial EF tasks but girls with TS with ADHD-associated behaviors had lower results on auditory EF tasks than the other ones without ADHD. Therefore, an EF deficit, at least partially independent of visual-spatial impairments, could be observed in girls with TS and may be associated with the ADHD profile, a variable, among others, that should be considered when performances in EF tasks are analyzed.

Moderator Variables of Executive Functions in Children with Turner Syndrome

In the current meta-analysis, heterogeneous results across samples were observed for three EF tasks, the MFFT, the phonemic fluency verbal task, and the WCST. Several variables could explain these ES differences between 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 differences 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 hypothesis 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 included 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 effect 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 patients 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 significant 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 various karyotypes (mosaic patterns, partial deletions, translocations). Significant differences were mentioned between 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 solid statistical analysis) to create different sub-groups under 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

(absence of control group; Ross et al. 1997b), participants who received GH and those who received placebo obtained similar performances on all cognitive tasks including EF tasks (MFFT, TOVA, ROCF, digit span subtest). Concerning the potential impact of estrogen treatment on EF abilities, only two samples among the sixteen included in the present analysis (Ross et al. 1998, 2000) detailed results regarding estrogen status. Three EF tasks were used – a digit span subtest, a phonemic verbal fluency task (Ross et al. 2000), and the MFFT (Ross et al. 1998) – and a difference was observed across the participants with TS only on the digit span backward. There was no difference between healthy controls and estrogen-treated TS group whereas placebo-treated TS group had significantly lower results than controls (Ross et al. 2000). However, the lack of information in the other included samples ($k = 14$) is a barrier when further exploring the impact of this treatment upon EFs in girls with TS. The role played by estrogen in brain development and neuroplasticity, as well as its neuroprotective effects (Crider and Pillai 2016), strengthens the argument that estrogen therapy could improve cognition in TS. Therefore, compliance regarding this therapy, prescribed in most patients with TS (Bondy 2007), must be taken into account when cognitive processes are assessed. Some cognitive differences across adolescents with TS may be partially explained by the variation in compliance behaviors. These hormonal treatments may also have positive effects on psychological well-being in girls with TS (Ross et al. 1996; Rovet and Holland 1993), another moderator variable that may have an impact on EF abilities.

The prevalence of psychiatric disorders, such as anxiety, depression, or ADHD, is higher in patients with TS (Kiliç et al. 2005; McCauley et al. 2001; Russell et al. 2006; Saad et al. 2015). Among the studies retained, depression, anxiety, and ADHD symptoms were assessed in only one study (Reiss et al. 1995). There was no significant difference between the TS group and the control group on depression or anxiety items of the Child Behavior Checklist but the children with TS had significant higher scores than the control group on the attention and social problem scales. Authors did not analyze the association between these scores and performances on EF tasks. To our knowledge, the impact of depression or anxious symptoms upon cognitive skills has never been explored in children and adolescents with TS. Considering negative effects observed in populations presenting these symptoms (Han et al. 2016; Ursache and Raver 2014; Wagner et al. 2015), these aspects should also be considered in TS to improve the understanding of these girls' cognitive profileS and to adapt their psychological care and rehabilitation.

Impact of Executive Functions Impairments in Children with Turner Syndrome

Children and adolescents with TS present mathematical impairments (Baker and Reiss 2016; Mazzocco 1998; Mazzocco and Hanich 2010; Murphy and Mazzocco 2008). Many studies highlighted significant associations between EFs, most particularly WM abilities, and mathematics (e.g. De Smedt et al. 2009; Gathercole et al. 2004). In children with TS, there was no correlation between Calculations score from Woodcock-Johnson Psychoeducational Battery-Revised and executive tasks such as a digit span backward subtest (Murphy and Mazzocco 2008). Another study explored the impact of increasing WM demand on tasks which assess automaticity and accuracy of participants to compose and decompose numbers. It appeared that, in girls with TS, WM abilities may be involved in numerical tasks which, in contrast, are supposedly effortless in control children (Mazzocco and Hanich 2010). Furthermore, a positive correlation between visual-spatial results and those obtained in a symbolic numerical magnitude comparison task has been also described in girls with TS but not in control participants (Brankaer et al. 2016). Associations between WM, or other EFs, and mathematic disabilities in TS are not yet clear and need to be further explored in future researches.

Many studies highlighted social disabilities in girls with TS (Hong et al. 2011; Lepage et al. 2013b; Lesniak-Karpiak et al. 2003; McCauley et al. 1995, 2001; Reiss et al. 1995). A deficit in emotion recognition has been described (McCauley et al. 1987; Romans et al. 1998; Hong et al. 2014), yet theory of mind abilities have been assessed in only two studies and the results were conflicting (Hong et al. 2011; Yamagata et al. 2012). Theory of mind abilities play a crucial role to adopt behaviors appropriate to social situations and several EFs, such as inhibition and WM could be involved in theory of mind abilities (e.g. Austin et al. 2014; Carlson et al. 2002). Thus, WM and cognitive inhibition impairments observed in girls with TS might be associated with theory of mind weaknesses and social difficulties in these young girls.

Limitations and Future Directions

Even if this meta-analysis improves knowledge of EF profile of children and adolescents with TS, these results should be interpreted in light of some limitations. This syndrome is a heterogeneous rare disorder and, unfortunately, few research teams have been interested in EF abilities of patients with TS. The number of studies respecting all inclusion criteria was small and the methodology varied. It was not possible to explore the potential effects of

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

Another limitation comes from the nature of EF tasks. The different tasks retained in the current analysis could reflect different cognitive abilities. It was the case for example in the Tower tasks, as previously indicated, this task may target different cognitive processes depending on the version. Some tasks using different type of stimuli (e.g. the SOPT) would be more discriminant than simpler EF tasks. In addition, in the current analysis, planning and inhibitory control have been assessed exclusively with tasks in which visual-spatial abilities operate. Therefore, the role played by the visual-spatial deficit on executive impairments must be considered. It is plausible to suggest that EF assessment in this population includes both verbal and visual tasks for each EF. Another possibility to differentiate the visual-spatial deficit and EFs impairments would be to decompose EF tasks, as Roy et al. (2010) have done to assess planning abilities in children with neurofibromatosis type 1. These authors used two conditions of the ROCF copy, namely, the "Formulation" condition (similar to the classic task) and the "Execution" condition. In this last condition, planning abilities play a less important role. Five sheets are successively presented to children. In each sheet, different elements of the ROCF are progressively added. Therefore, the children reproduce the figure by including progressively in their drawings the elements that appear in each new sheet presented. A significantly higher score in the "Execution" condition when compared to the "Formulation" condition provides arguments in favor of planning impairments.

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

Conclusion

This systematic review and meta-analysis confirms the presence of EF impairments in girls with TS. Difficulties seem to affect particularly WM and higher-order EFs. Self-regulation and reactive flexibility abilities appear to be less impaired. Girls with TS were slower than controls in several EF tasks yet this slower processing speed did not totally explain poor performances observed in cognitive inhibition and problem-solving timed tasks. Given visual-spatial impairments described in TS, in order to improve our understanding of these patients' EF profile, each EF should be assessed through tasks in visual-spatial modality and tasks in verbal modality. Moreover, the use of decomposed EF tasks could help distinguish the different processes involved. Several moderator variables should be controlled, such as SES, IQ, karyotype, presence of psychological comorbidities, or compliance to the hormonal treatment. A better understanding of EF impairments could help to explore difficulties encountered by girls living with TS, such as mathematical difficulties or social disabilities.

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Compliance with Ethical Standards

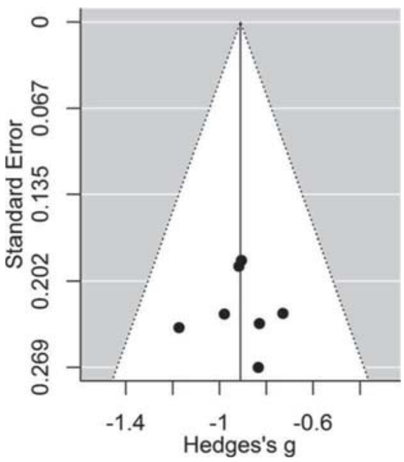
Conflict of Interest The authors declare that they have no conflict of interest.

Appendix

Working Memory Task

Digit Span Subtest

Funnel Plot of the Digit Span Subtest



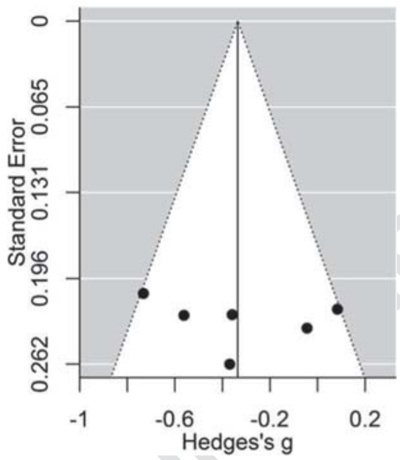
Leave-One-Out Method's Results

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau^2	I^2
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

Inhibitory Control Tasks

Matching Familiar Figures Test

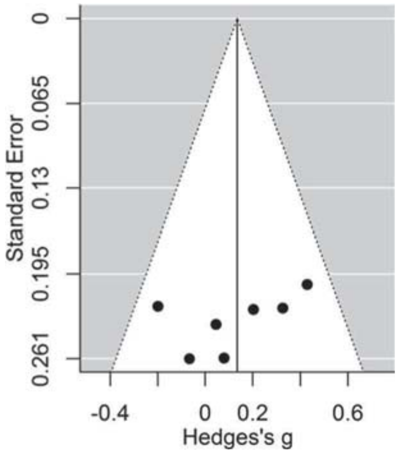
Funnel Plot of the Matching Familiar Figures Test (Correct Answers)



Leave-One-Out Method's Results

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau^2	I^2
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

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

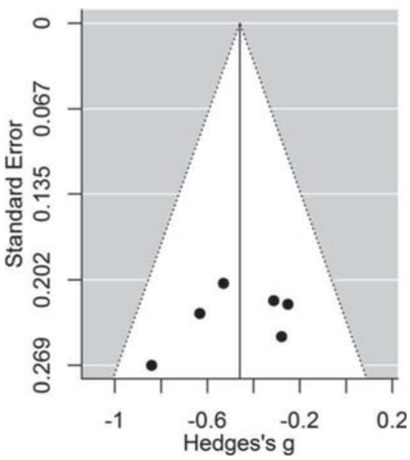


Leave-One-Out Method's Results

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau^2	I^2
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

Test of Variables of Attention

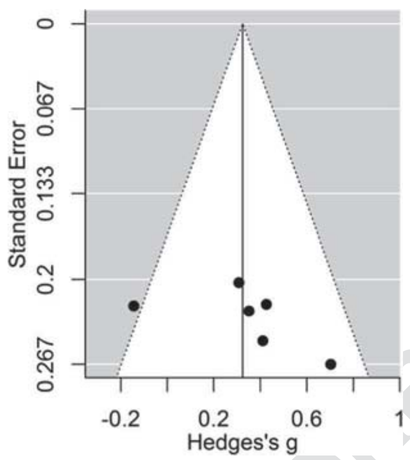
Funnel Plot of the Test of Variables of Attention (Commission Errors)



Leave-One-Out Method's Results

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau^2	I^2
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

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



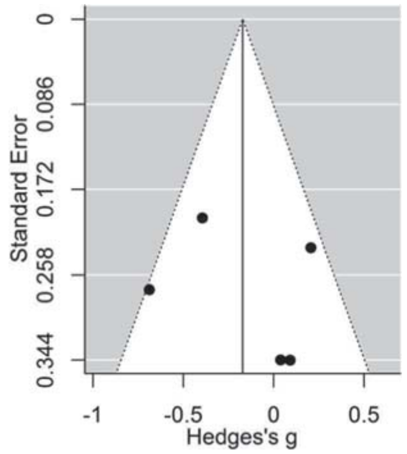
Leave-One-Out Method's Results

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau^2	I^2
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

Cognitive Flexibility Tasks

Wisconsin Card Sorting Test

Funnel Plot of the Wisconsin Card Sorting Test

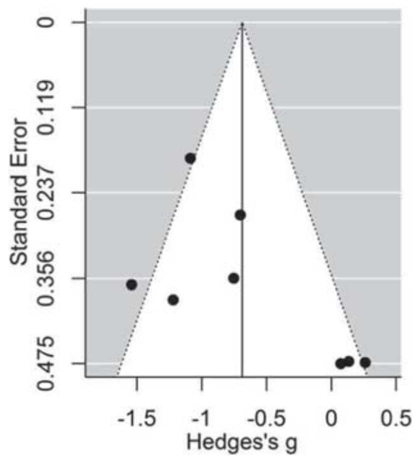


Leave-One-Out Method's Results

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau^2	I^2
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

Phonemic Verbal Fluency Task

Funnel Plot of the Phonemic Verbal Fluency Task

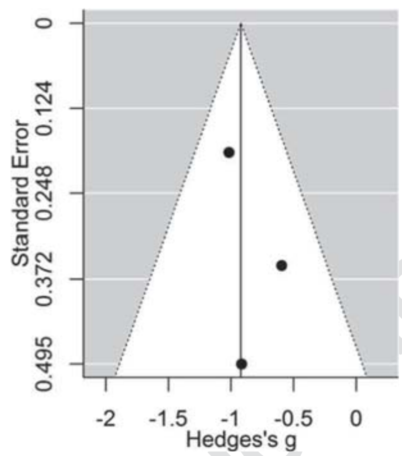


Leave-One-Out Method's Results

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau^2	I^2
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

Semantic Verbal Fluency Task

Funnel Plot of the Semantic Verbal Fluency Task



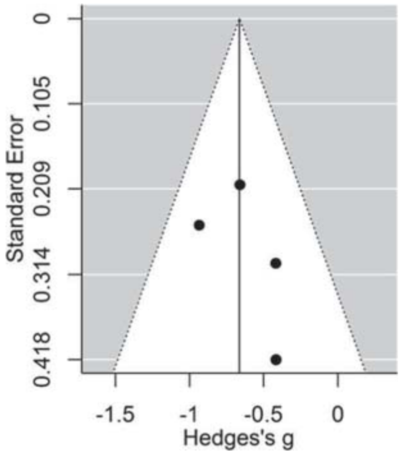
Leave-One-Out Method's Results

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau^2	I^2
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

Higher-Order Executive Function Tasks

Tower of Hanoi

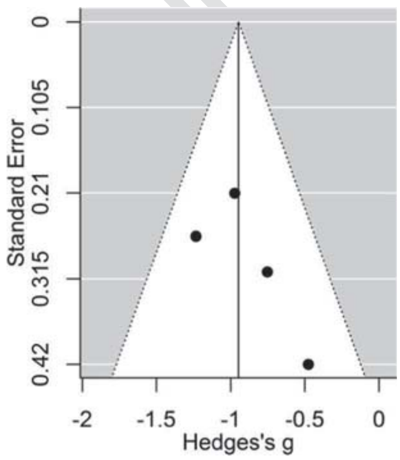
Funnel Plot of the Tower of Hanoi (Score Variable)



Leave-One-Out Method's Results

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau^2	I^2
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

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

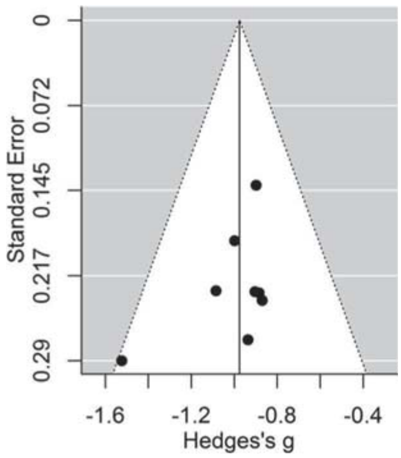


Leave-One-Out Method's Results

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau^2	I^2
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

Rey-Osterrieth Complex Figure

Funnel Plot of the Rey-Osterrieth Complex Figure



Leave-One-Out Method's Results

	Estimate	95% [C.I.]	Z	p-value	Q	p-value	Tau^2	I^2
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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