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Research Review: Executive function deficits in fetal alcohol spectrum disorders and attention-deficit/hyperactivity disorder – a meta-analysis

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Abstract

Background—Attention-deficit/hyperactivity disorder (ADHD)-like symptoms are common in fetal alcohol spectrum disorders (FASD). FASD and ADHD groups both display executive function impairments; however, there is ongoing debate whether the pattern and magnitude of executive function deficits differs between these two types of disorders.

Methods—An electronic literature search was conducted (PubMed, PsychInfo; 1972–2013) to identify studies comparing the executive functioning of children with FASD with ADHD or control groups. FASD groups included those with and without dysmorphy (i.e., FAS, pFAS, ARND, and other FASD diagnoses). Effect sizes (Hedges' *g*, standardized mean difference) were calculated. Random effects meta-analytic models were performed using the *metafor* package for R.

Results—Fifty-one studies met inclusion criteria (FASD $N = 2,115$; ADHD $N = 453$; controls $N = 1,990$). Children with FASD showed the strongest and most consistent deficits in planning, fluency, and set-shifting compared to controls (Hedges' $g = -0.94, -0.78$) and children with ADHD (Hedges' $g = -0.72, -0.32$). FASD was associated with moderate to large impairments in working memory, compared to controls (Hedges' $g = -.84, -.58$) and small impairments relative to groups with ADHD (Hedges' $g = -.26$). Smaller and less consistent deficits were found on measures of inhibition and vigilance relative to controls (Hedges' $g = -0.52, -0.31$); FASD and ADHD were not differentiated on these measures. Moderator analyses indicated executive dysfunction was associated with older age, dysmorphy, and larger group differences in IQ. Sex and diagnostic system were not consistently related to effect size.

Conclusions—While FASD is associated with global executive impairments, executive function weaknesses are most consistent for measures of planning, fluency, and set-shifting. Neuropsychological measures assessing these executive function domains may improve differential diagnosis and treatment of FASD.

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Supporting information
Additional Supporting Information may be found in the online version of this article:
Table S1. Executive function measures and evidence for task validity.
Figure S1. Full search strategy for article identification, inclusion, and exclusion in the meta-analysis.

Keywords

Fetal alcohol spectrum disorders; attention-deficit/hyperactivity disorder; meta-analysis; executive function; neuropsychology

Introduction

According to the American Academy of Pediatrics, heavy prenatal alcohol exposure is the leading cause of preventable birth defects, mental retardation, and neurodevelopmental disorder (American Academy of Pediatrics, 2000). Fetal alcohol syndrome (FAS), the most extreme consequence of alcohol exposure during pregnancy, is characterized by symptoms in three areas: (a) prenatal and/or postnatal growth retardation; (b) craniofacial abnormalities (smooth philtrum, thin vermilion border, short palpebral fissures); and (c) central nervous system (CNS) dysfunction, including a complex pattern of cognitive and behavioral abnormalities (Chudley et al., 2005; Hoyme et al., 2005). The term partial FAS (pFAS) has been used to describe children who do not have all the characteristics of FAS, but evidence some facial dysmorphic features as well as one of the following: growth deficiency, microcephaly, or behavioral or cognitive impairment (Hoyme et al., 2005). While the presence of growth deficiencies and craniofacial abnormalities (i.e., dysmorphy) permits the identification of a small percentage of children, up to 90% of alcohol-affected individuals do not exhibit these physical abnormalities, which greatly hinder diagnosis (Bertrand, Floyd, & Weber, 2005; May & Gossage, 2001). Recently, the term fetal alcohol spectrum disorders (FASD) has been widely adopted to encompass both children with traditional FAS and pFAS, as well as the larger group of alcohol-affected patients who present with complex behavioral and neurological dysfunction related to their exposure but lack the full pattern of dysmorphy, such as those diagnosed with alcohol-related neurodevelopmental disorder (ARND; Bertrand et al., 2005; Sokol, Delaney-Black, & Nordstrom, 2003). Children across the FASD spectrum are at increased risk for specific neuropsychological deficits, secondary disabilities, and mental health problems, including learning disabilities, behavioral disorders, and attention-deficit/hyperactivity disorder (ADHD; Fryer, McGee, Matt, Riley, Mattson, 2007; Peadon & Elliott, 2010; Streissguth, Barr, Kogan, & Bookstein, 1997).

The overlap in clinical presentation of FASD with other neurodevelopmental disorders, such as ADHD, limits accurate diagnosis of alcohol-affected children, especially when information about maternal prenatal alcohol consumption is unavailable (Peadon & Elliott, 2010). The rate of ADHD among clinic-referred children with FASD is much higher than in the general pediatric population (49–94% vs. 5%, respectively; Fryer et al., 2007; Peadon & Elliott, 2010; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Rasmussen et al., 2010). Children with ADHD present with behavioral and neuropsychological impairments similar to those apparent among children exposed to alcohol (e.g., executive functioning deficits, attention impairment), which increases the risk that alcohol-affected children are not correctly identified (Coles et al., 1997; Jacobson, Dodge, Burden, Klorman, & Jacobson, 2011; Mattson, Crocker, & Nguyen, 2011). There are important clinical benefits to accurately distinguishing children with FASD from nonexposed children with ADHD. Children with FASD do not respond as well as nonexposed children to stimulant

medications used to treat ADHD (Oesterheld et al., 1998; Peadon & Elliott, 2010). Furthermore, alcohol-affected children who are identified and treated early have better academic and cognitive outcomes (Kalberg & Buckley, 2007; Paley & O'Connor, 2009). Understanding the profile and magnitude of cognitive deficits among children with FASD is critical to facilitating early diagnosis, improving treatment, and ameliorating the effects of secondary disabilities.

Executive function

To better understand the complex pattern of cognitive and behavioral abnormalities specific to FASD, and to facilitate the development of therapeutic interventions, researchers have focused considerable attention on understanding the pattern of executive dysfunction in this population. Executive functioning refers to multiple, interrelated higher order cognitive processes that are responsible for purposeful, goal-directed behavior (Anderson, 2002; Stuss & Knight, 2002; Welsh & Pennington, 1998). Different experts include or exclude different specific functions in specifying the components of executive function. Here, we allowed a relatively broad definition that included the following abilities: planning, set-shifting, working memory, fluency, response inhibition, and attentional vigilance (Pennington & Ozonoff, 1996; Stuss & Knight, 2002). Executive abilities are highly relevant for daily life activities, socially appropriate behavior, and academic functioning (Anderson, 2002).

Executive dysfunction is frequently observed in neurodevelopmental disorders and is considered a hallmark deficit for both children with FASD (Mattson et al., 2011) and nonexposed children with ADHD (Barkley, 1997; Nigg, 2005). Both populations are described clinically for their hyperactivity, impulsivity, inattention, poor judgment, and failure to consider consequences. Common symptoms of behavioral disinhibition and disorganization in ADHD and FASD may be related to executive dysfunction (Barkley, 1997; Nigg, 2001; Rasmussen, 2005). In ADHD, neuropsychological findings suggest that behavioral problems result from underlying deficits in delay aversion and executive deficits in response inhibition (Nigg, 2001; Sonuga-Barke, 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Although clinical and experimental studies on children with FASD have documented marked deficits in executive functioning, researchers have debated which skills are most impaired. For example, some researchers contend higher order executive processes are impaired (Aragón et al., 2008; Kodituwakku, 2009), while others suggest attentional deficits (Lee, Mattson, & Riley, 2004; Nanson & Hiscock, 1990) or memory impairments are central to the disorder (Manji, Pei, Loomes, & Rasmussen, 2009). A theoretical model of executive dysfunction within FASD remains to be established.

Several narrative reviews have summarized the cognitive functioning of children affected by prenatal alcohol exposure in an attempt to define a syndrome-specific neurocognitive profile of FASD (Kodituwakku, 2009; Mattson & Riley, 2010; Mattson et al., 2011). However, due to the broad range of cognitive domains assessed and the varied neuropsychological measures employed, it is difficult to qualitatively summarize the overall results from these studies. No systematic, quantitative review of this literature has been completed to date. Executive functioning may be one domain of cognitive functioning most in need of synthesis, as it is highly related to the central clinical difficulties in this population.

Understanding the pattern and magnitude of executive deficits may facilitate the development of therapeutic interventions specific to FASD. In addition, understanding the ways in which FASD and ADHD groups differ on these measures may shed light on their high comorbidity.

The aim of this meta-analysis was to address three central questions that have eluded the field: (a) Which domains of executive function are most consistently impaired in children with FASD, compared to healthy controls; (b) Whether the pattern and magnitude of deficits in children with dysmorphy is greater than children without dysmorphy, compared to healthy controls; and (c) Whether this neurocognitive profile is more globally impaired relative to the profile of children with ADHD. Moderators of the association between executive functioning and FASD status were also explored to determine how these deficits vary with age, sex, intellectual functioning, dysmorphy, and diagnostic system.

To address these questions, the following hypotheses were proposed: (a) All included neuropsychological measures were expected to result in significant differences between FASD and healthy control groups, reflecting deficits in a wide range of executive abilities for children with FASD. No specific predictions were made regarding the magnitudes of differences between FASD and controls across executive function domains; (b) Both dysmorphic and nondysmorphic FASD groups were expected to significantly differ from healthy controls on all neuropsychological measures. It has been postulated that a continuum exists wherein those with prenatal alcohol exposure, but without FAS or pFAS, demonstrate less severe deficits compared to those with FAS or pFAS. Some research groups have reported greater neurocognitive deficits in dysmorphic vs. nondysmorphic groups with prenatal alcohol exposure (e.g., Ervalahti et al., 2007); however, other groups have failed to demonstrate these differences across a variety of cognitive and neuropsychological measures (e.g., Connor, Sampson, Bookstein, Barr, & Streissguth, 2000; Mattson, Riley, Gramling, Delis, & Jones, 1997). Given these inconsistent results, we did not predict a different magnitude or pattern of executive deficits among the FASD diagnostic subgroups, with and without the facial dysmorphology (i.e., FAS/pFAS vs. ARND and other FASD diagnoses); (c) Executive functioning was expected to significantly differ between FASD and ADHD on all neuropsychological measures except for attentional vigilance, working memory, and response inhibition. These hypotheses are based on previous findings suggesting ADHD is associated with attentional and working memory deficits and difficulties with response inhibition (Barkley, 1997; Nigg, 2005; Sonuga-Barke, 2005; Willcutt et al., 2005), while FASD is associated with global executive impairments (Kodituwakku, 2009; Mattson et al., 2011).

Methods

Literature search strategy

The present meta-analysis was conducted in accordance with PRISMA guidelines (Liberati et al., 2009) for undertaking systematic reviews and meta-analysis. A computerized literature search was conducted in PubMed (Medline) and PsychInfo electronic databases from January 1972 to November 2013. Keyword searches, included ‘fetal’, ‘alcohol’, ‘ADHD’, ‘executive function’, and common neuropsychological measures of executive

function, which are presented in Figure S1 (available online). Ascendancy and descendency approaches were used to identify additional articles. A total of 779 potentially relevant studies were initially identified; the abstracts from these studies were reviewed. Of these, 97 studies were identified for full text review.

Study inclusion criteria and selection

Each study selected for inclusion examined the neuropsychological executive function performance of children aged 5–18 years diagnosed with FASD compared to healthy controls and/or children with ADHD. Additional inclusion criteria were: human studies, English-language studies, FASD diagnosis made/confirmed by specialty clinic/team, ADHD diagnosis made/confirmed by physician or specialty clinic, and results not published in another included study. Exclusion criteria were: known prenatal exposure to alcohol and illicit drugs in healthy control and ADHD groups (greater than minimal levels) and no neuropsychological measure of executive function. Since prenatal alcohol exposure is highly correlated with smoking and drug use (e.g., marijuana and cocaine; Jacobson, Chiodo, Sokol, & Jacobson, 2002) we did not exclude studies where FASD participants had reported prenatal exposure to nicotine and illicit drugs. Fifty-one studies met inclusion criteria.

Data extraction

Data were extracted by a single rater (DK) who coded all studies in consultation with a second rater (CC). Both coders have a background in neuropsychological assessment. Sample size, demographic information, and moderator variables were extracted from each study. Thirty coding decisions were made per study. Effect sizes for 20% of studies were blindly recoded after a period of 5 months, with excellent intrarater agreement ($r = .99$).

Measures

Diagnosis of FASD—Four diagnostic systems were used to diagnose FASD: 4-Digit Diagnostic Code (Astley, 2004), 2005 Revised Institute of Medicine criteria (Hoyme et al., 2005), Canadian Guidelines for Diagnosis of FASD (Chudley et al., 2005), and identification of dysmorphology and heavy prenatal alcohol exposure based on standardized procedures used by the Collaborative Initiative (CIFASD; Mattson, Foroud, et al., 2010). We purposively allowed for a broad definition of FASD to ensure breadth and scope of our review of the existing literature. FASD diagnoses included alcohol-affected children with dysmorphy (i.e., FAS and pFAS) and those without clinically discernable dysmorphy (i.e., ARND and other FASDs, such as static encephalopathy alcohol-exposed, neurobehavioral disorder alcohol-exposed, and conditions previously referred to as fetal alcohol effects; Sokol et al., 2003).

Executive function outcomes—Executive functioning measures included: (a) fluency; (b) inhibition; (c) planning; (d) set-shifting; (e) vigilance; and (f) working memory (Anderson, 2002; Kelly, 2000; Pennington & Ozonoff, 1996; Stuss & Knight, 2002; Zelazo & Müller, 2002). Table S1 (available online) outlines the executive function domains included in the meta-analysis, with descriptions of each executive function domain, test measures allocated to each domain, and evidence for the validity of the measure in assessing executive function, based on results of neuropsychological theory, factor analytic, lesion,

neuroimaging studies, and expert consensus. The coding hierarchy for the primary dependent measure within each domain, as well secondary measures (when the primary measure was not reported) is also detailed. Selected measures were deemed to best characterize a single domain of executive function.

Statistical analysis

Effect size calculation—Hedges' *g* standardized mean difference effect sizes were calculated using pooled standard deviation (Rosenthal, 1994). Hedges' *g* is a variation in Cohen's *d* that corrects for biases due to small sample sizes (Hedges & Olkin, 1985). The magnitude of Hedges' *g* may be interpreted using Cohen's (1988) convention as small (0.2), medium (0.5), and large (0.8). Effect sizes were calculated from reported means and standard deviations when available. One-way *t* and *F* statistics were converted to Hedges' *g* using the *compute.es* package for R, which utilizes formulas found in Cooper, Hedges, and Valentine (2009). When no test statistic data were reported, effect sizes were derived from reported *p* values; results described as nonsignificant were assigned an effect size of zero (Rosenberg, Adams, & Gurevitch, 2000). The direction of effect sizes was coded such that greater executive dysfunction in FASD groups was represented by negative effect sizes.

Selection of effect sizes—Effect sizes were coded for every relevant executive function measure reported as defined in Table S1, thus yielding multiple effect sizes per study. When multiple neuropsychological measures were reported, the following coding hierarchy was applied: (a) for neuropsychological measures assessing different domains of executive function or results based on separate groups of participants, each effect size was treated as nonredundant because a unique FASD-executive function relation was examined (Demakis, 2006); and (b) when different neuropsychological measures assessed the same domain of executive function, we employed a conservative approach wherein effect sizes within each FASD-executive function domain were aggregated. This procedure produced a maximum of one effect size per domain of executive function per study. This hierarchy was applied rather than analyzing each neuropsychological measure independently as we were primarily interested in performance on fundamental executive function constructs, not particular neuropsychological measures.

Data analyses

Effect sizes were calculated using the *metafor* package for R using random effects models (Viechtbauer, 2010). Random effects models assume samples are drawn from populations with different effect sizes and allow for both random variation and variation due to true differences between populations (Raudenbush, 1994). The Q_t statistic was computed to test the heterogeneity across included effect sizes; the I^2 index was calculated to identify the variance explained by this heterogeneity. Significant heterogeneity statistics (Q_t) or I^2 index values greater than 50% indicate a heterogeneous distribution not derived from a single population, and may warrant additional moderator analyses (Lipsey & Wilson, 2001). Outlier screening yielded one outlier effect size; this effect size value was replaced with the next-highest (nonoutlier) value within that study.

Three analyses were conducted to test the study hypotheses. First, we compared the executive functioning of FASD groups versus healthy controls. Mixed diagnostic FASD groups (i.e., FAS/pFAS and alcohol-affected children without dysmorphy) were included in this analysis. In the second analysis, we limited the comparison of executive functioning to FASD groups without dysmorphy (i.e., excluded FAS/pFAS) versus healthy controls. Third, we compared the executive functioning of mixed diagnostic FASD groups versus ADHD groups.

Moderator analyses were conducted to examine potential sources of heterogeneity. Moderator variables included executive function domain, age, sex, dysmorphy, intelligence, and diagnostic system. Continuous summary analyses (regression) were used to test the association between sample characteristics (mean age of sample, male proportion of sample, proportion of sample identified as dysmorphic [FAS or pFAS], full-scale intellectual functioning difference between groups [FSIQ or FSIQ estimations based on Verbal or Performance IQ]) and effect size. We tested for differences between groups for categorical moderators (diagnostic system utilized). Prenatal exposures to nicotine or illicit drugs are not commonly reported or statistically controlled for in FASD samples, thus we were not able to compute covariate-adjusted effect sizes to determine how other teratogenic exposures impact the FASD-executive function relation. When available, information regarding prenatal alcohol, nicotine, and illicit drug exposure within FASD groups was coded and exploratory categorical moderation analyses were conducted (see Limitations and Directions for Future Research for a brief discussion of these results).

Finally, to address concerns about the file-drawer problem and possible publication bias we calculated Rosenthal's (1979) fail-safe numbers to determine the number of effect sizes averaging null results that would have to be added to reduce the combined effect size to nonsignificance. We also generated funnel plots and calculated Egger's regression test (Egger, Smith, Schneider, & Minder, 1997) to inspect publication bias in this area.

Results

Sample characteristics

A total of 51 studies including 4,558 participants (FASD $N = 2,115$; ADHD $N = 453$; healthy controls $N = 1,990$) met inclusion criteria. As described above, we coded the FASD studies into two groups: studies including mixed FASD diagnostic groups (FASD: $N = 1,450$) and studies including FASD groups without dysmorphy (FASD nondysmorphic: $N = 665$). Study and sample characteristics are presented in Table 1.

FASD versus controls

To test the hypothesis that children with FASD would be impaired on all domains of executive functioning relative to healthy controls (Hypothesis 1), we analyzed 46 studies that provided relevant data (99 effect sizes, $N = 8,095$, $M = 2.15$ effects per study). The overall effect size revealed moderate executive function impairments for FASD groups versus healthy controls (Hedges' $g = -0.73$, 95% CI [−0.82, −0.65]). To examine the profile of executive strengths and weaknesses, effect sizes were grouped according to executive

function domain using categorical summary analyses (see Table 2; Figure 1A, B). Dysmorphic FASD groups exhibited consistently large deficits in planning (g = −0.94), fluency (g = −0.87), set-shifting (g = −0.87), and working memory (g = −0.84), compared to controls. Moderate deficits in vigilance (g = −0.52) and inhibition (g = −0.50) among FASD groups were also observed, compared to controls.

Nondysmorphic FASD versus controls

To test the hypothesis that nondysmorphic children with FASD would also show significant deficits on all measures of executive functioning relative to healthy controls (Hypothesis 2), we analyzed data from 19 studies that compared the executive functioning of nondysmorphic FASD groups to controls (37 effect sizes, N = 3,564, M = 1.95 effects per study). The overall effect size estimate showed moderate executive impairments in nondsymorphic FASD groups versus healthy controls (g = −0.59, 95% CI[−0.75, −0.43]). This effect size estimate did not statistically differ from the estimate produced by the analysis of dysmorphic FASD groups versus healthy controls (Hedges' g = −0.73, 95% CI[−0.82, −0.65]). Categorical summary analyses revealed large deficits in planning (g = −0.78), fluency (g = −0.86), and set-shifting (g = −0.78) in the nondysmorphic FASD groups, as well as moderate deficits in working memory (g = −0.58), compared to healthy controls. Small and nonstatistically significant deficits on measures of inhibition (g = −0.36) and attentional vigilance (g = −0.31) were observed for the nondysmorphic FASD groups compared to healthy controls (see Table 2, Figure 2).

FASD versus ADHD

To examine whether the executive functioning profile in FASD is more globally impaired relative to the profile of children with ADHD (Hypothesis 3), we examined data from 11 studies comparing the executive functioning of FASD groups to nonexposed groups with ADHD (28 effect sizes, N = 2,814, M = 2.55 effects per study). The overall effect size estimate revealed small, statistically significant deficits for FASD groups compared to ADHD groups (g = −0.28, 95% CI[−0.42, −0.14]). Categorical summary analyses revealed that compared to ADHD groups, FASD was associated with moderate to small deficits in fluency (g = −0.72), planning (g = −0.51), and set-shifting (g = −0.32). Small deficits were found on measures of working memory (g = −0.26) in FASD groups relative to ADHD groups, while no between-group differences were found on measures of attentional vigilance (g = 0.04), or response inhibition (g = −0.08), and these effects were not statistically significant (see Table 2, Figure 3). For each analysis, examination of effect sizes by executive function domain significantly reduced the heterogeneity among most effect sizes, suggesting the categorization of measures was valid.

Moderator analysis

Given the significant heterogeneity observed among effect sizes, moderators of the FASD-executive function relation were analyzed for each of the three sets of analyses, which corresponded to our three hypotheses. These analyses produced very similar results. For parsimony, only moderators of the larger dysmorphic FASD-executive function analysis and in-consistencies across the three sets of moderation analyses are presented in text (see Table 3 for the complete set of moderation results). Studies with older mean age (g = −0.07 per

year, 95% CI[−0.11, −0.03]), greater proportion of participants identified as dysmorphic (g = −0.33, 95% CI[−0.59, −0.06]), and greater IQ differences between groups (g = −0.03 per IQ point, 95% CI[−0.03, −0.02]) had larger effect sizes, indicating greater executive dysfunction in the FASD group compared to healthy controls. In contrast, proportion male (g = −0.08, 95% CI[−0.17, 0.00]) was not consistently related to effect size. Categorical summary analyses revealed that all diagnostic systems produced similarly large and statistically significant effects. Although dysmorphy and IQ differences among groups were related to effect size in comparisons of FASD versus control groups, these variables did not account for executive function weaknesses observed in FASD groups relative to ADHD groups (dysmorphy: g = −0.27, 95% CI[−0.65, 0.11]; IQ: g = 0.00 per IQ point, 95% CI[−0.02, 0.02]).

As a post hoc analysis, we investigated the nature of age, dysmorphy, and IQ moderation effects. Linear and quadratic effects were simultaneously modeled to examine curvilinear relations between age and effect size. This analysis revealed that the relation between age and executive function deficits in the dysmorphic FASD-executive function analysis was curvilinear, such that deficits increased sharply from age 5 to age 12, and stabilized at age 12 (Age [linear)]: g = −0.41, 95% CI[−0.79, −0.03], p < .05; Age^2 [quadratic] g = 0.02, 95% CI[−0.00, 0.03], p = .08). Follow-up analyses showed that studies with an average sample age between 5 and 11 years produced effect sizes which were moderate in magnitude (K = 31; 76 effect sizes; g = −0.57, 95% CI[−0.67, −0.46]), while studies with an average sample age between 12 and 15 years produced effect sizes which were large in magnitude (K = 20; 62 effect sizes; g = −0.92, 95% CI [−1.03, −0.81]).

Next, we examined whether dysmorphy was associated with impairments in specific executive function domains. There was a moderate association between dysmorphy and planning (g = −0.59, 95% CI[−1.27, 0.09]), however, this effect did not reach statistical significance, and dysmorphy was not associated with deficits for any other executive function domain.

A subset of studies included IQ matched samples (within 10 FSIQ points). Among IQ matched samples, FASD groups demonstrated small to moderate executive function deficits compared to healthy controls (K = 9; 20 effect sizes; g = −0.45, 95% CI[−0.62, −0.28]) and ADHD groups (K = 6; 18 effect sizes; g = −0.32, 95% CI[−0.51, −0.14]). Among nondysmorphic FASD groups, IQ matched samples produced small, but nonstatistically significant effect sizes compared to healthy controls (K = 4; 10 effect sizes; g = −0.15, 95% CI[−0.38, 0.08]).

IQ meta-analysis

To better understand the level of intellectual functioning impairment of FASD participants among the included studies, we conducted a post hoc metaanalysis on IQ outcomes. Results revealed large IQ impairments for children with FASD versus healthy controls (K = 36, g = −1.42, 95% CI[−1.69, −1.16]), nondysmorphic children with FASD versus healthy controls (K = 15, g = −1.45, 95% CI[−2.01, −0.90]), and children with FASD versus children with ADHD (K = 10; g = −1.02, 95% CI[−1.32, −0.73]). Significant heterogeneity was detected for each of these effect sizes.

Publication bias

Visual inspection of funnel plots and Egger's regression test for asymmetry of the funnel plot did not indicate any significant evidence of publication bias for each of our three meta-analyses (Egger's regression test: FASD versus controls: $Z = -1.286$, $p = 0.198$; nondysmorphic FASD versus controls: $Z = -1.719$, $p = 0.086$; FASD versus ADHD: $Z = 1.569$, $p = 0.117$). In addition, the fail-safe numbers were substantially larger than the minimum required when applying Rosenthal (1979) formula ($5k + 10$; where k indicates the number of effect sizes) to our meta-analyses to demonstrate the robustness of our findings (see Table 2). Taken together, this evidence suggests no substantive publication bias in this research area.

Discussion

As predicted, the meta-analysis revealed a pattern of global executive function impairment for children with FASD compared to control children. Specifically, FASD groups both with and without dysmorphy exhibited executive deficits that were similarly moderate in magnitude (Hedges' $g = -0.73$ and -0.59, respectively), which significantly differed from healthy controls. Moderator analyses indicated that studies with a greater proportion of FASD participants identified as dysmorphic had larger effect sizes compared with healthy controls; yet, this effect size was small and only explained a small portion (~5%) of the variability among effect sizes. Together, these results indicate that while FAS and pFAS represent the most severely affected individuals on the FASD spectrum, both dysmorphic and nondysmorphic individuals display significant executive deficits relative to healthy controls. These findings are important because despite the intuitive link between dysmorphy and neurocognitive functioning, results from the current study and others (Mattson et al., 1997; Riley & McGee, 2005) reveal that deficits in neurocognitive functioning are observed across the entire FASD spectrum. The association between dysmorphy and neurocognitive capacity is small, which suggests that a diagnosis of FASD should focus more on CNS deficits, rather than on the presence of craniofacial dysmorphy (Chudley et al., 2005). These results also highlight the need for increased screening of alcohol-affected children without clinically discernable dysmorphy, as most are currently undiagnosed and untreated (May & Gossage, 2001).

What is the pattern of executive deficits?

Although executive functioning is considered a hallmark deficit in FASD, there is little agreement among researchers regarding which domains are most impaired and whether these deficits are specific to FASD (Aragón et al., 2008; Kodituwakku, 2009; Rasmussen, 2005). Executive deficits for the dysmorphic FASD group ranged from about one half to one full standard deviation greater than healthy controls, with variability in effect sizes across executive function domains. Specifically, when comparing the executive performance of dysmorphic FASD groups versus healthy controls, the strongest and most consistent deficits were obtained on neuropsychological measures of planning, set-shifting, fluency, and working memory, which were large in magnitude. Moderate impairments in attentional vigilance and response inhibition were also observed, relative to controls. Examination of the executive function profile for the nondysmorphic FASD group indicated a similar pattern

of executive deficits. Compared to controls, nondysmorphic FASD groups exhibited moderate to large deficits on neuropsychological measures of planning, set-shifting, fluency, and working memory. Attentional vigilance and response inhibition were associated with small effect sizes that did not differentiate nondysmorphic FASD groups from controls. Previous researchers have hypothesized that deficits in attentional vigilance and inhibition are central to FASD (Lee et al., 2004; Manji et al., 2009; Nanson & Hiscock, 1990). However, attentional vigilance and response inhibition are more weakly related to FASD than many other domains of executive function. Given the broad executive deficits experienced by children across the FASD spectrum, planning, fluency, and set-shifting tasks may be particularly vulnerable since they include multiple executive demands.

We were interested in examining executive function outcomes for children with an FASD diagnosis, rather than problems associated with prenatal alcohol exposure more generally. While our results show a strong FASD-executive function relation, previous studies have not shown consistent impairments for children exposed prenatally to alcohol at mild-to-moderate levels on measures of attention, inhibition, or cognition (Dolan, Stone, & Briggs, 2010; Flak et al., 2014; Streissguth et al., 1994). Studies in this area generally find more consistent impairments on more ‘complex’ neurocognitive tasks (e.g., planning tasks, IQ measures) and for patterns of heavier prenatal exposure or binge drinking (Dolan et al., 2010; Flak et al., 2014; Streissguth et al., 1994). Collectively, these findings indicate that FASD outcomes are affected by the dose and pattern of alcohol consumption. In addition, although prenatal alcohol exposure exerts global and widespread teratogenic effects on the human brain, specific brain regions may be particularly sensitive to the effects of prenatal alcohol exposure (Riley & McGee, 2005).

Potential moderators of the relation between executive function and FASD

While effect sizes reveal broad impairment for FASD groups versus healthy controls on neuropsychological measures of executive function, there was considerable variability in effect sizes across studies as indicated by the significant heterogeneity statistics (Q_t). Several participant demographic factors appear to be robust moderators of the FASD-executive function relationship. Moderation analysis revealed that the magnitude of the executive function-FASD association increased with sample age, with group differences peaking at age 12 and stabilizing in the teenage years. All included studies used age-standardized scaled scores with age-matched samples; thus, the observed association of increasing deficits across childhood likely reflects developmental changes. Results support the general consensus among researchers that interventions initiated in early or mid-childhood may produce maximal benefit to children with FASD, by assisting them to adapt to cognitive, behavioral, and functional difficulties, and by reducing secondary disabilities (Streissguth et al., 1997).

Full-scale intelligence scores for FASD groups included in the current meta-analysis ranged from 64 to 99, with an average of 84 for both dysmorphic and nondysmorphic groups. Meta-analytic results revealed that FASD groups showed large intellectual functioning deficits relative to healthy controls ($g = -1.42$; equivalent to 20 IQ points) and children with ADHD ($g = -1.02$; equivalent to 16 IQ points). Interestingly, children with FASD evidenced greater executive functioning impairments than healthy controls and ADHD groups, even among

studies where groups were matched on intellectual functioning ($g = -0.45$, $g = -0.32$, respectively). Traditionally, researchers have theorized that intellectual deficits underpin executive function weaknesses and have proposed that IQ should always be statistically controlled to ensure that executive function impairments cannot be explained by deficits in general intelligence. However, components of executive function have been shown to exert a critical influence on IQ and some theorists view IQ as a component of executive function (Borkowski & Burke, 1996; Conway, Kane, & Engle, 2003). Additional research is needed to understand the complex relationship between intellectual deficits and executive dysfunction and whether the discriminability of executive measures changes with varying levels of IQ.

Finally, sex, based on study proportion, was not consistently related to effect size. When comparing functioning of children with FASD versus healthy controls, no differences emerged across the four diagnostic systems. Although there are several standardized diagnostic systems with nuanced distinctions in diagnostic criteria, each system appears to capture the underlying, fundamental distinguishing characteristics of FASD.

ADHD and FASD: clinical implications

ADHD is the most frequent comorbid diagnosis among children with FASD (Fryer et al., 2007; Streissguth et al., 1997); however, the literature is unclear about whether the pattern and magnitude of executive function deficits differs between these two populations. Consistent with our hypotheses, overall executive dysfunction was greater among FASD groups when compared to children with ADHD ($g = -0.28$). As predicted, children with FASD showed small to moderate deficits on measures of planning, set-shifting, fluency, and working memory compared to nonexposed children with ADHD, although this latter effect was not statistically significant. No group level differences were found on measures of attentional vigilance or inhibition.

Although a universal profile of executive dysfunction for ADHD, as measured by standardized neuropsychological assessment, has proven elusive, recent meta-analyses reveal that children with ADHD show the most consistent deficits on measures of vigilance and inhibition (omission and commission errors on the CPT and Stop-Signal RT tasks; Frazier, Demaree, & Youngstrom, 2004; Van Mourik, Oosterlaan, & Sergeant, 2005; Willcutt et al., 2005). Statistically significant deficits on working memory and some measures of planning have also been reported for ADHD children when compared to healthy controls (Frazier et al., 2004; Van Mourik et al., 2005; Willcutt et al., 2005). In contrast, measures assessing set-shifting (e.g., trail making, Wisconsin Card Sort) and fluency are more weakly related to ADHD than other executive function tasks (Frazier et al., 2004; Willcutt et al., 2005). This literature also demonstrates that there is a great deal of neuropsychological variability within ADHD groups, with fewer than half of children with ADHD exhibiting significant impairment on any specific executive function task (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). Taken together, these data provide evidence that on a group level, FASD does not produce an identical cognitive profile to ADHD. Specifically, FASD is associated with a larger magnitude of executive deficits than ADHD on a group level, and more consistent impairments in planning, set-shifting, fluency, and possibly

working memory. Thus, attention and executive function deficits in FASD may represent a different underlying etiological pathway than those observed in ADHD, which may mandate a different approach to treatment (O'Malley & Nanson, 2002).

There is a limited amount of intervention research for alcohol-affected children (Kodituwakku, 2010). However, a series of recent randomized controlled trials provides emerging evidence that early interventions targeting self-regulation and executive functions among children with FASD produce more effective and generalizable improvements than domain-specific interventions (e.g., literacy or math training; Bertrand, 2009; Kodituwakku, 2010; although these programs have been shown to be highly effective for improving the specific skills being targeted). One possible reason for the limited progress in FASD intervention research concerns the failure of the neurobehavioral research to be synthesized such that key intervention targets are identified. We hope that the present meta-analysis can aid in this regard.

Limitations and directions for future research

Several methodological limitations, related to the complexity of conducting research on prenatal alcohol exposure, should be considered when interpreting the results of this meta-analysis. The included samples generally comprised retrospectively recruited children of women who drank heavily or abused alcohol during pregnancy (e.g., consumption of four or more drinks per occasion at least once per week, or greater than 14 drinks per week throughout pregnancy). Information regarding dose effects is often difficult to obtain in retrospectively recruited samples, and the majority of included studies (approximately 90%) did not report any information about the extent or timing of prenatal alcohol, nicotine, or drug exposures. Preliminary analyses showed that studies reporting heavy prenatal alcohol exposure produced similarly large effect sizes compared to studies that confirmed prenatal alcohol exposure, but did not specify the amount of exposure. Similarly, studies reporting prenatal nicotine or drug exposure did not produce significantly different results than studies that did not screen for these exposures. These results likely reflect the fact that among FASD clinic-referred samples, most children are heavily exposed to alcohol prenatally, and also have some prenatal exposure to nicotine and illicit drugs. Studies in this area should control for nicotine and drug exposures going forward to help differentiate between the effects of prenatal alcohol exposure and other determinants of neuropsychological outcomes. In addition, although control groups did not have any known exposure to alcohol or illicit drugs above minimal levels, ADHD samples are rarely well screened for prenatal alcohol exposure and ARND may not have been appropriately ruled out in these samples.

We could not obtain sufficiently detailed information to analyze other moderators, including FASD subtype diagnosis, parental characteristics, socioeconomic status, and intervention services received. Future work should better define how these demographic characteristics moderate the FASD-executive function relation. Finally, the question of whether neuropsychological tests of executive functioning can serve as diagnostic tools cannot be definitively answered by this meta-analysis, as there was no way to compute sensitivity and specificity analyses. This important question is beginning to be addressed by researchers in the field (e.g., Mattson, Roesch, et al. 2010; Mattson et al., 2013), although additional

research is needed to test the sensitivity and specificity of these neuropsychological tools with clinical comparison groups.

Conclusion

The findings of the present meta-analysis suggest that FASD is associated with weaknesses in several key executive function domains, including planning, fluency, set-shifting, and working memory. Effect sizes for these executive function measures generally fell in the medium range and executive deficits for FASD groups were greater compared to both healthy controls and children with ADHD. Smaller and less consistent deficits were found on measures of inhibition and attentional vigilance. FASD groups with and without clinically discernable dysmorphy exhibited significant executive impairment, highlighting the need for increased efforts to delineate the diagnostic criteria for alcohol-affected children across the FASD spectrum. Current evidence for the diagnostic value of neuropsychological tests is lacking; yet, tests of planning, set-shifting, fluency, and working memory may be instrumental to precisely define the clinical phenotype of FASD. These executive domains may help differentiate FASD from ADHD, however, more research on this question is warranted. Although FASD is associated with specific weaknesses in executive function, these impairments are likely to be only one important component of the complex neuropsychology of FASD. FAS and other FASD diagnoses are being refined as researchers further clarify the pattern of neurocognitive and behavioral effects resulting from prenatal alcohol exposure. Data from this study may inform these efforts, which are vital to strengthening the diagnostic methods and specialized therapeutic interventions for FASD.

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References

References marked with an asterisk indicate studies included in the meta-analysis

American Academy of Pediatrics; Committee on Substance Abuse and Committee on Children With Disabilities. Fetal alcohol syndrome and alcohol-related neurodevelopmental disorders. Pediatrics. 2000; 106:358–361. [PubMed: 10920168]

Anderson P. Assessment and development of executive function (EF) during childhood. Child Neuropsychology. 2002; 8:71–82. [PubMed: 12638061]

*. Aragón AS, Kalberg WO, Buckley D, Barela-Scott LM, Tabachnick BG, May PA. Neuropsychological study of FASD in a sample of American Indian children: Processing simple versus complex information. Alcoholism: Clinical and Experimental Research. 2008; 32:2136–2148.

Astley, SJ. Diagnostic guide for fetal alcohol spectrum disorders: The 4-digit diagnostic code. 3. Seattle, WA: University of Washington Publication Services; 2004.

*. Astley SJ, Aylward EH, Olson HC, Kerns K, Brooks A, Coggins TE, … Richards T. Functional magnetic resonance imaging outcomes from a comprehensive magnetic resonance study of children with fetal alcohol spectrum disorders. Journal of Neurodevelopmental Disorders. 2009; 1:61–80. [PubMed: 21547622]

*. Astley SJ, Olson HC, Kerns K, Brooks A, Aylward EH, Coggins TE, … Richards T. Neuropsychological and behavioral outcomes from a comprehensive magnetic resonance study of children with fetal alcohol spectrum disorders. Canadian Journal of Clinical Pharmacology. 2009; 16:e178–e201. [PubMed: 19329824]

Barkley RA. Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. Psychological Bulletin. 1997; 121:65–94. [PubMed: 9000892]

Bertrand J. for Children with Fetal Alcohol Spectrum Disorders Research Consortium Interventions. Interventions for children with fetal alcohol spectrum disorders (FASDs): Overview of findings for five innovative research projects. Research in Developmental Disabilities. 2009; 30:986–1006. [PubMed: 19327965]

Bertrand J, Floyd RL, Weber MK. Guidelines for identifying and referring persons with fetal alcohol syndrome. Morbidity and Mortality Weekly Report. 2005; 54:1–14. [PubMed: 15647722]

Borkowski, JG., Burke, JE. Theories, models and measurements of executive functioning: An information processing perspective. In: Lyon, GR., Krasnegor, NA., editors. Attention, memory and executive function. Baltimore: Brookes; 1996. p. 235-261.

*. Burden MJ, Andrew C, Saint-Amour D, Meintjes EM, Molteno CD, Hoyme HE, … Jacobson SW. The effects of fetal alcohol syndrome on response execution and inhibition: An event-related potential study. Alcoholism: Clinical and Experimental Research. 2009; 33:1994–2004.

Chudley AE, Conry J, Cook JL, Loock C, Rosales T, LeBlanc N. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. Canadian Medical Association Journal. 2005; 172:1–21.

Cohen, J. Statistical power analysis for the behavioral sciences. 2. New Jersey: Lawrence Erlbaum; 1988.

*. Coles CD, Platzman KA, Lynch ME, Freides D. Auditory and visual sustained attention in adolescents prenatally exposed to alcohol. Alcoholism: Clinical and Experimental Research. 2002; 26:263–271.

*. Coles CD, Platzman KA, Raskind-Hood CL, Brown RT, Falek A, Smith IE. A comparison of children affected by prenatal alcohol exposure and attention deficit, hyperactivity disorder. Alcoholism: Clinical and Experimental Research. 1997; 21:150–161.

Connor PD, Sampson PD, Bookstein FL, Barr HM, Streissguth AP. Direct and indirect effects of prenatal alcohol damage on executive function. Developmental Neuropsychology. 2000; 18:331–354. [PubMed: 11385829]

Conway AR, Kane MJ, Engle RW. Working memory capacity and its relation to general intelligence. Trends in Cognitive Sciences. 2003; 7:547–552. [PubMed: 14643371]

Cooper, H., Hedges, LV., Valentine, JC. The handbook of research synthesis and meta-analysis. New York: Sage; 2009.

Demakis GJ. Meta-analysis in neuropsychology: Basic approaches, findings, and applications. The Clinical Neuropsychologist. 2006; 20:10–26. [PubMed: 16393918]

*. Diwadkar VA, Meintjes EM, Goradia D, Dodge NC, Warton C, Molteno CD, … Jacobson JL. Differences in cortico-striatal-cerebellar activation during working memory in syndromal and nonsyndromal children with prenatal alcohol exposure. Human Brain Mapping. 2013; 34:1931–1945. [PubMed: 22451272]

Dolan GP, Stone DH, Briggs AH. A systematic review of continuous performance task research in children prenatally exposed to alcohol. Alcohol and Alcoholism. 2010; 45:30–38. [PubMed: 19995853]

Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315:629–634. [PubMed: 9310563]

Ervalahti N, Korkman M, Fagerlund Å, Autti-Rämäo I, Loimu L, Hoyme HE. Relationship between dysmorphic features and general cognitive function in children with fetal alcohol spectrum disorders. American Journal of Medical Genetics Part A. 2007; 143:2916–2923.

Flak AL, Su S, Bertrand J, Denny CH, Kesmodel US, Cogswell ME. The association of mild, moderate, and binge prenatal alcohol exposure and child neuropsychological outcomes: A meta-analysis. Alcoholism: Clinical and Experimental Research. 2014; 38:214–226.

Frazier TW, Demaree HA, Youngstrom EA. Meta-analysis of intellectual and neuropsychological test performance in attention-deficit/hyperactivity disorder. Neuropsychology. 2004; 18:543–555. [PubMed: 15291732]

*. Fryer SL, Mattson SN, Jernigan TL, Archibald SL, Jones KL, Riley EP. Caudate volume predicts neurocognitive performance in youth with heavy prenatal alcohol exposure. Alcoholism: Clinical and Experimental Research. 2012; 36:1932–1941.

Fryer SL, McGee CL, Matt GE, Riley EP, Mattson SN. Evaluation of psychopathological conditions in children with heavy prenatal alcohol exposure. Pediatrics. 2007; 119:733–741.

*. Fryer SL, Tapert SF, Mattson SN, Paulus MP, Spadoni AD, Riley EP. Prenatal alcohol exposure affects frontal–striatal BOLD response during inhibitory control. Alcoholism: Clinical and Experimental Research. 2007b; 31:1415–1424.

*. Glass L, Ware AL, Crocker N, Deweese BN, Coles CD, Kable JA, … Mattson SN. Neuropsychological deficits associated with heavy prenatal alcohol exposure are not exacerbated by ADHD. Neuropsychology. 2013; 27:713–724. [PubMed: 24040921]

*. Green CR, Mihic AM, Brien DC, Armstrong IT, Nikkel SM, Stade BC, … Reynolds JN. Oculomotor control in children with fetal alcohol spectrum disorders assessed using a mobile eye-tracking laboratory. European Journal of Neuroscience. 2009; 29:1302–1309. [PubMed: 19302166]

*. Green CR, Mihic AM, Nikkel SM, Stade BC, Rasmussen C, Munoz DP, Reynolds JN. Executive function deficits in children with fetal alcohol spectrum disorders (FASD) measured using the Cambridge Neuropsychological Tests Automated Battery (CANTAB). Journal of Child Psychology and Psychiatry. 2009; 50:688–697. [PubMed: 19175817]

*. Green CR, Munoz DP, Nikkel SM, Reynolds JN. Deficits in eye movement control in children with fetal alcohol spectrum disorders. Alcoholism: Clinical and Experimental Research. 2007; 31:500–511.

Hedges, LV., Olkin, I. Statistical methods for meta-analysis. Orlando, FL: Academic Press; 1985.

Hoyme HE, May PA, Kalberg WO, Kodituwakku P, Gossage JP, Trujillo PM, … Robinson LK. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: Clarification of the 1996 institute of medicine criteria. Pediatrics. 2005; 115:39–47. [PubMed: 15629980]

Jacobson SW, Chiodo LM, Sokol RJ, Jacobson JL. Validity of maternal report of prenatal alcohol, cocaine, and smoking in relation to neurobehavioral outcome. Pediatrics. 2002; 109:815–825. [PubMed: 11986441]

Jacobson JL, Dodge NC, Burden MJ, Klorman R, Jacobson SW. Number processing in adolescents with prenatal alcohol exposure and ADHD: Differences in the neurobehavioral phenotype. Alcoholism: Clinical and Experimental Research. 2011; 35:431–442.

Kalberg WO, Buckley D. FASD: What types of intervention and rehabilitation are useful? Neuroscience & Biobehavioral Reviews. 2007; 31:278–285. [PubMed: 16919732]

Kelly TP. The development of executive function in school-aged children. Clinical Neuropsychological Assessment. 2000; 1:38–55.

Kodituwakku PW. Neurocognitive profile in children with fetal alcohol spectrum disorders. Developmental Disabilities Research Reviews. 2009; 15:218–224. [PubMed: 19731385]

Kodituwakku PW. A neurodevelopmental framework for the development of interventions for children with fetal alcohol spectrum disorders. Alcohol. 2010; 44:717–728. [PubMed: 20036485]

*. Kodituwakku PW, Adnams CM, Hay A, Kitching AE, Burger E, Kalberg WO, … May PA. Letter and category fluency in children with fetal alcohol syndrome from a community in South Africa. Journal of Studies on Alcohol and Drugs. 2006; 67:502–509.

*. Kodituwakku PW, Handmaker NS, Cutler SK, Weathersby EK, Handmaker SD. Specific impairments in self-regulation in children exposed to alcohol prenatally. Alcoholism: Clinical and Experimental Research. 1995; 19:1558–1564.

*. Kodituwakku PW, May PA, Clericuzio CL, Weers D. Emotion-related learning in individuals prenatally exposed to alcohol: An investigation of the relation between set shifting, extinction of responses, and behavior. Neuropsychologia. 2001; 39:699–708. [PubMed: 11311300]

*. Kooistra L, Crawford S, Gibbard B, Kaplan BJ, Fan J. Comparing attentional networks in fetal alcohol spectrum disorder and the inattentive and combined subtypes of attention deficit hyperactivity disorder. Developmental Neuropsychology. 2011; 36:566–577. [PubMed: 21667361]

*. Kooistra L, Crawford S, Gibbard B, Ramage B, Kaplan BJ. Differentiating attention deficits in children with fetal alcohol spectrum disorder or attention-deficit–hyperactivity disorder. Developmental Medicine & Child Neurology. 2010; 52:205–211. [PubMed: 19549201]

*. Korkman M, Autti-Rämö I, Koivulehto H, Granström ML. Neuropsychological effects at early school age of fetal alcohol exposure of varying duration. Child Neuropsychology. 1998; 4:199–212.

*. Laforce R, Hayward S, Cox LV. Impaired skill learning in children with heavy prenatal alcohol exposure. Journal of the International Neuropsychological Society. 2001; 7:112–114. [PubMed: 11253837]

*. Lane, K. Doctoral dissertation. McGill University; Montreal, QC: 2011. Visual filtering in children with fetal alcohol spectrum disorder.

*. Lee KT, Mattson SN, Riley EP. Classifying children with heavy prenatal alcohol exposure using measures of attention. Journal of the International Neuropsychological Society. 2004; 10:271–277. [PubMed: 15012847]

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. BMJ. 2009; 339:b2700. [PubMed: 19622552]

Lipsey, MW., Wilson, DB. Practical meta-analysis. Thousand Oaks, CA: Sage; 2001.

*. Malisza KL, Allman AA, Shiloff D, Jakobson L, Longstaffe S, Chudley AE. Evaluation of spatial working memory function in children and adults with fetal alcohol spectrum disorders: A functional magnetic resonance imaging study. Pediatric Research. 2005; 58:1150–1157. [PubMed: 16306185]

*. Malisza KL, Buss JL, Bolster RB, de Gervai PD, Woods-Frohlich L, Summers R, … Longstaffe S. Comparison of spatial working memory in children with prenatal alcohol exposure and those diagnosed with ADHD; A functional magnetic resonance imaging study. Journal of Neurodevelopmental Disorders. 2012; 4:1–20. [PubMed: 22958445]

Manji S, Pei J, Loomes C, Rasmussen C. A review of the verbal and visual memory impairments in children with foetal alcohol spectrum disorders. Developmental Neurorehabilitation. 2009; 12:239–247. [PubMed: 19842823]

*. Mattson SN, Calarco KE, Lang AR. Focused and shifting attention in children with heavy prenatal alcohol exposure. Neuropsychology. 2006; 20:361–369. [PubMed: 16719629]

Mattson SN, Crocker N, Nguyen TT. Fetal alcohol spectrum disorders: Neuropsychological and behavioral features. Neuropsychology Review. 2011; 21:81–101. [PubMed: 21503685]

Mattson SN, Foroud T, Sowell ER, Jones KL, Coles CD, Fagerlund Å, … Riley EP. Collaborative initiative on fetal alcohol spectrum disorders: Methodology of clinical projects. Alcohol. 2010; 44:635–641. [PubMed: 20036488]

*. Mattson SN, Goodman AM, Caine C, Delis DC, Riley EP. Executive functioning in children with heavy prenatal alcohol exposure. Alcoholism: Clinical and Experimental Research. 1999; 23:1808–1815.

*. Mattson SN, Riley EP. Implicit and explicit memory functioning in children with heavy prenatal alcohol exposure. Journal of the International Neuropsychological Society. 1999; 5:462–471. [PubMed: 10439591]

Mattson SN, Riley EP. The quest for a neurobehavioral profile of heavy prenatal alcohol exposure. Alcohol Research & Health: The Journal of the National Institute on Alcohol Abuse and Alcoholism. 2010; 34:51–55.

*. Mattson SN, Riley EP, Gramling L, Delis DC, Jones KL. Heavy prenatal alcohol exposure with or without physical features of fetal alcohol syndrome leads to IQ deficits. The Journal of Pediatrics. 1997; 131:718–721. [PubMed: 9403652]

*. Mattson SN, Roesch SC, Fagerlund A, Autti-Ramo I, Jones KL, May PA, … Riley EP. Toward a neurobehavioral profile of fetal alcohol spectrum disorders. Alcoholism: Clinical and Experimental Research. 2010; 34:1640–1650.

*. Mattson SN, Roesch SC, Glass L, Deweese BN, Coles CD, Kable JA, … Riley EP. Further development of a neurobehavioral profile of fetal alcohol spectrum disorders. Alcoholism: Clinical and Experimental Research. 2013; 37:517–528.

May PA, Gossage JP. Estimating the prevalence of fetal alcohol syndrome: A summary. Alcohol Research and Health. 2001; 25:159–167. [PubMed: 11810953]

*. McGee CL, Schonfeld AM, Roebuck-Spencer TM, Riley EP, Mattson SN. Children with heavy prenatal alcohol exposure demonstrate deficits on multiple measures of concept formation. Alcoholism: Clinical and Experimental Research. 2008; 32:1388–1397.

*. Mihic, AMT. Doctoral dissertation. Queen's University; Kingston, ON: 2010. Children with alcohol-related neurodevelopmental disorder or attention deficit/hyperactivity disorder differ on neuropsychological tasks and measures of eye movement control.

*. Nanson JL, Hiscock M. Attention deficits in children exposed to alcohol prenatally. Alcoholism: Clinical and Experimental Research. 1990; 14:656–661.

Nigg JT. Is ADHD a disinhibitory disorder? Psychological Bulletin. 2001; 127:571–598. [PubMed: 11548968]

Nigg JT. Neuropsychologic theory and findings in attention-deficit/hyperactivity disorder: The state of the field and salient challenges for the coming decade. Biological Psychiatry. 2005; 57:1424–1435. [PubMed: 15950017]

Nigg JT, Willcutt EG, Doyle AE, Sonuga-Barke EJ. Causal heterogeneity in attention-deficit/hyperactivity disorder: Do we need neuropsychologically impaired subtypes? Biological Psychiatry. 2005; 57:1224–1230. [PubMed: 15949992]

*. O'Brien JW, Norman AL, Fryer SL, Tapert SF, Paulus MP, Jones KL, … Mattson SN. Effect of predictive cuing on response inhibition in children with heavy prenatal alcohol exposure. Alcoholism: Clinical and Experimental Research. 2013; 37:644–654.

Oesterheld JR, Kofoed L, Tervo R, Fogas B, Wilson A, Fiechtner H. Effectiveness of methylphenidate in Native American children with fetal alcohol syndrome and attention deficit/hyperactivity disorder: A controlled pilot study. Journal of Child and Adolescent Psychopharmacology. 1998; 8:39–48. [PubMed: 9639078]

*. O'Hare ED, Lu LH, Houston SM, Bookheimer SY, Mattson SN, O'Connor MJ, Sowell ER. Altered frontal-parietal functioning during verbal working memory in children and adolescents with heavy prenatal alcohol exposure. Human Brain Mapping. 2009; 30:3200–3208. [PubMed: 19263420]

*. Olson HC, Feldman JJ, Streissguth AP, Sampson PD, Bookstein FL. Neuropsychological deficits in adolescents with fetal alcohol syndrome: Clinical findings. Alcoholism: Clinical and Experimental Research. 1998; 22:1998–2012.

O'Malley KD, Nanson JO. Clinical implications of a link between fetal alcohol spectrum disorder and attention-deficit hyperactivity disorder. The Canadian Journal of Psychiatry. 2002; 47:349–354. [PubMed: 12025433]

Paley B, O'Connor MJ. Intervention for individuals with fetal alcohol spectrum disorders: Treatment approaches and case management. Developmental Disabilities Research Reviews. 2009; 15:258–267. [PubMed: 19731383]

*. Paolozza A, Rasmussen C, Pei J, Hanlon-Dearman A, Nikkel SM, Andrew G, … Reynolds JN. Deficits in response inhibition correlate with oculomotor control in children with fetal alcohol spectrum disorder and prenatal alcohol exposure. Behavioural Brain Research. 2013; 259:97–105. [PubMed: 24185031]

*. Paolozza A, Titman R, Brien D, Munoz DP, Reynolds JN. Altered accuracy of saccadic eye movements in children with fetal alcohol spectrum disorder. Alcoholism: Clinical and Experimental Research. 2013; 37:1491–1498.

Peadon E, Elliott EJ. Distinguishing between attention-deficit hyperactivity and fetal alcohol spectrum disorders in children: Clinical guidelines. Neuropsychiatric Disease and Treatment. 2010; 6:509–515. [PubMed: 20856914]

Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. Journal of Child Psychology and Psychiatry. 1996; 37:51–87. [PubMed: 8655658]

Polanczyk G, de Lima M, Horta B, Biederman J, Rohde L. The worldwide prevalence of ADHD: A systematic review and metaregression analysis. American Journal of Psychiatry. 2007; 164:942–948. [PubMed: 17541055]

*. Quattlebaum JL, O'Connor MJ. Higher functioning children with prenatal alcohol exposure: Is there a specific neurocognitive profile? Child Neuropsychology. 2013; 19:561–578. [PubMed: 22905880]

Rasmussen C. Executive functioning and working memory in fetal alcohol spectrum disorder. Alcoholism: Clinical and Experimental Research. 2005; 29:1359–1367.

Rasmussen C, Benz J, Pei J, Andrew G, Schuller G, Abele-Webster L, … Lord L. The impact of an ADHD co-morbidity on the diagnosis of FASD. The Canadian Journal of Clinical Pharmacology. 2010; 17:e165–e176. [PubMed: 20395649]

*. Rasmussen C, Bisanz J. The relation between mathematics and working memory in young children with fetal alcohol spectrum disorders. The Journal of Special Education. 2010; 45:184–191.

*. Rasmussen C, Pei J, Manji S, Loomes C, Andrew G. Memory strategy development in children with foetal alcohol spectrum disorders. Developmental Neurorehabilitation. 2009; 12:207–214. [PubMed: 19842820]

*. Rasmussen C, Soleimani M, Pei J. Executive functioning and working memory deficits on the CANTAB among children with prenatal alcohol exposure. Journal of Population Therapeutics and Clinical Pharmacology. 2011; 18:e44–e53. [PubMed: 21289378]

*. Rasmussen C, Tamana S, Baugh L, Andrew G, Tough S, Zwaigenbaum L. Neuropsychological impairments on the NEPSY-II among children with FASD. Child Neuropsychology. 2013; 19:337–349. [PubMed: 22384972]

*. Rasmussen C, Wyper K, Talwar V. The relation between theory of mind and executive functions in children with fetal alcohol spectrum disorders. Canadian Journal of Clinical Pharmacology. 2009; 16:e370–e380.

Raudenbush, SW. Random effects models. In: Cooper, H., Hedges, LV., editors. Handbook of research synthesis. New York: Sage; 1994. p. 301-321.

*. Regan, MF. Doctoral dissertation. Columbia University; New York, NY: 1997. Evidence for a cerebellar contribution to the neuropsychological performance of children with fetal alcohol syndrome.

Riley EP, McGee CL. Fetal alcohol spectrum disorders: An overview with emphasis on changes in brain and behavior. Experimental Biology and Medicine. 2005; 230:357–365. [PubMed: 15956765]

Rosenberg, MS., Adams, DC., Gurevitch, J. Meta Win. Statistical software for meta-analysis. Sunderland, MA: Sinauer Associates; 2000.

Rosenthal R. The file drawer problem and tolerance for null results. Psychological Bulletin. 1979; 86:638–641.

Rosenthal, R. Parametric measures of effect size. In: Cooper, H., Hedges, LV., editors. The handbook of research synthesis. New York: Sage; 1994. p. 239-244.

*. Schonfeld AM, Mattson SN, Lang AR, Delis DC, Riley EP. Verbal and nonverbal fluency in children with heavy prenatal alcohol exposure. Journal of Studies on Alcohol and Drugs. 2001; 62:239–246.

Sokol RJ, Delaney-Black V, Nordstrom B. Fetal alcohol spectrum disorder. JAMA. 2003; 290:2996–2999. [PubMed: 14665662]

Sonuga-Barke EJ. Causal models of attention-deficit/hyperactivity disorder: From common simple deficits to multiple developmental pathways. Biological Psychiatry. 2005; 57:1231–1238. [PubMed: 15949993]

*. Steinmann, TP., Andrew, CM., Thomsen, CE., Kjar, TW., Meintjes, EM., Molteno, CD., … Sorensen, HB. An auditory Go/No-Go study of event-related potentials in children with fetal

alcohol spectrum disorders. Engineering in Medicine and Biology Society, EMBC, 2011 Annual International Conference of the IEEE; 2011. p. 789-792.

Streissguth, AP., Barr, HM., Kogan, J., Bookstein, FL. Primary and secondary disabilities in fetal alcohol syndrome. In: Streissguth, AP., Kanter, J., editors. The challenge of fetal alcohol syndrome: Overcoming secondary disabilities. Seattle, WA: University of Washington Press; 1997. p. 25-39.

Streissguth AP, Sampson PD, Olson HC, Bookstein FL, Barr HM, Scott M, … Mirsky AF. Maternal drinking during pregnancy: Attention and short-term memory in 14-year-old offspring: A longitudinal prospective study. Alcoholism: Clinical and Experimental Research. 1994; 18:202–218.

Stuss, DT., Knight, RT. Principles of frontal lobe functioning. New York: Oxford University Press; 2002.

Van Mourik R, Oosterlaan J, Sergeant JA. The Stroop revisited: A meta-analysis of interference control in AD/HD. Journal of Child Psychology and Psychiatry. 2005; 46:150–165. [PubMed: 15679524]

*. Vaurio, L. Doctoral dissertation. UC San Diego; San Diego, CA: 2011. Emotion-based decision-making in children with fetal alcohol spectrum disorders.

*. Vaurio L, Riley EP, Mattson SN. Differences in executive functioning in children with heavy prenatal alcohol exposure or attention-deficit/hyperactivity disorder. Journal of the International Neuropsychological Society. 2008; 14:119–129. [PubMed: 18078538]

*. Vaurio L, Riley EP, Mattson SN. Neuropsychological comparison of children with heavy prenatal alcohol exposure and an IQ-matched comparison group. Journal of the International Neuropsychological Society. 2011; 17:463–473. [PubMed: 21349236]

Viechtbauer W. Conducting meta-analyses in R with the metafor package. Journal of Statistical Software. 2010; 36:1–48.

*. Ware AL, Crocker N, O'Brien JW, Deweese BN, Roesch SC, Coles CD, … Mattson SN. Executive function predicts adaptive behavior in children with histories of heavy prenatal alcohol exposure and attentiondeficit/hyperactivity disorder. Alcoholism: Clinical and Experimental Research. 2012; 36:1431–1441.

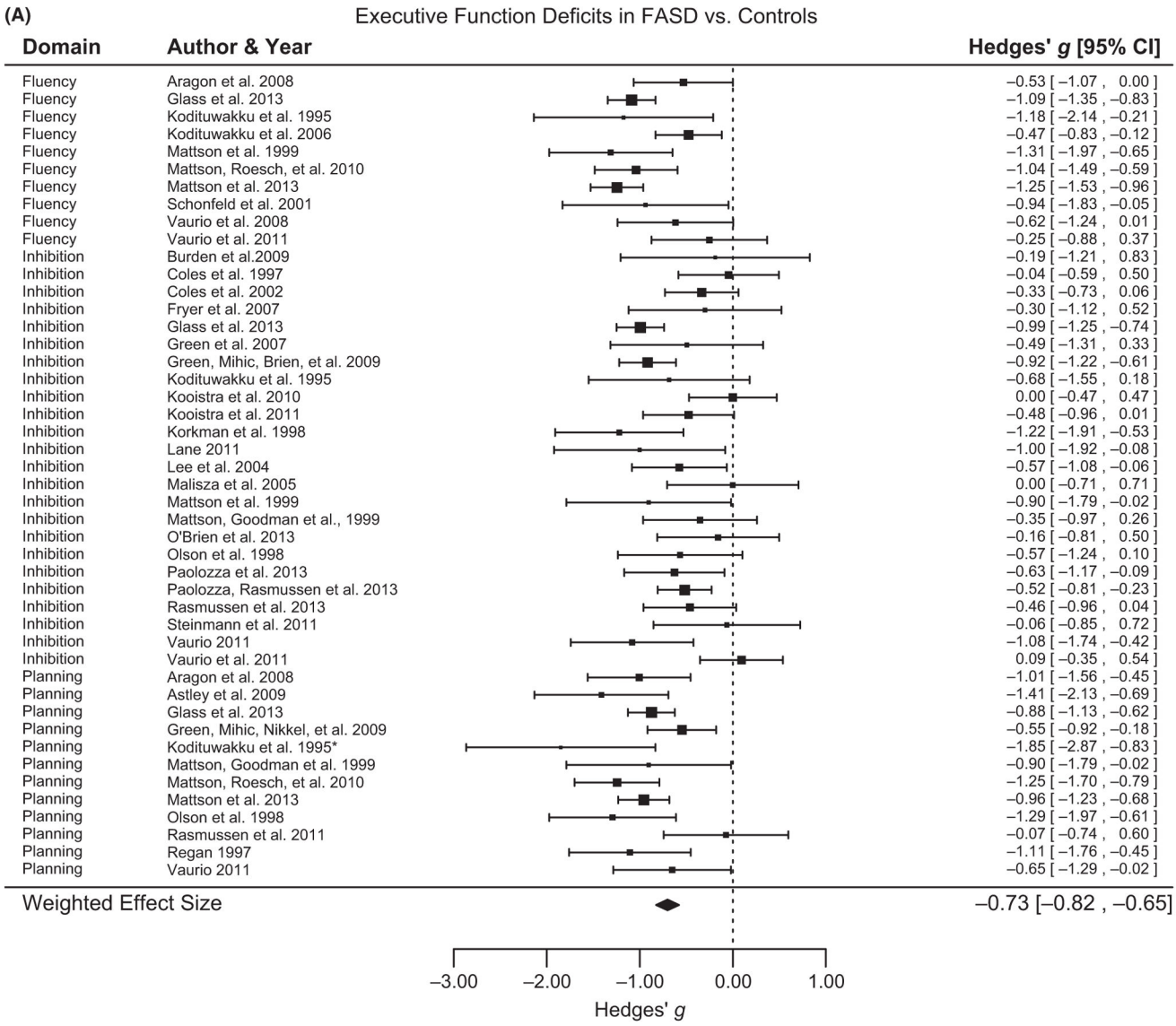
Welsh MC, Pennington BF. Assessing frontal lobe functioning in children: Views from developmental psychology. Developmental Neuropsychology. 1998; 4:199–230.

Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: A meta-analytic review. Biological Psychiatry. 2005; 57:1336–1346. [PubMed: 15950006]

Zelazo, PD., Müller, U. Executive function in typical and atypical development. In: Goswami, U., editor. Handbook of childhood cognitive development. Oxford, England: Blackwell; 2002. p. 445-469.

Key points

- Deficits in executive function are common in both FASD and ADHD. However, it is unclear how the pattern and magnitude of executive dysfunction differs between these clinical groups.
- This article is the first meta-analysis comparing the executive functioning of children with FASD compared to healthy controls and children with ADHD.
- Results reveal that FASD is associated with moderate to large deficits in planning, set-shifting, fluency, and working memory, while attentional vigilance and inhibition are associated with small to moderate deficits.
- Alcohol-affected children with and without dysmorphy show a similar pattern and magnitude of executive deficits.
- Children with FASD are more globally impaired on measures of executive function than children with ADHD.



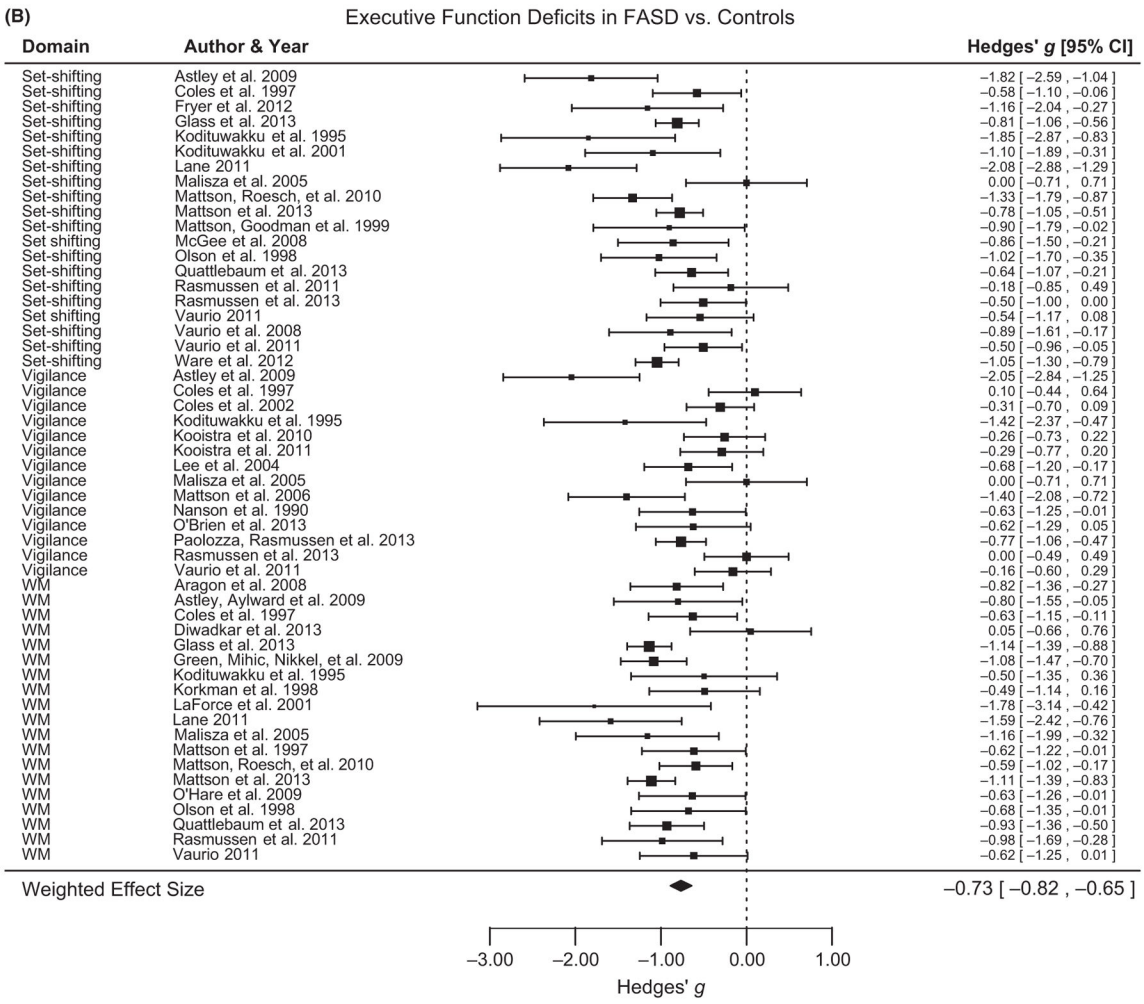


Figure 1.

(A) The figure represents a forest plot for the average effect size (Hedges' *g*) of the effect executive function (fluency, inhibition, and planning) between groups with FASD compared to healthy controls. Studies were weighted by sample size, and larger filled squares for the effect size estimate represent larger samples. Error bars represent the 95% confidence interval. *Outlier effect size. (B) The figure represents a forest plot for the average effect size (Hedges' *g*) of the effect executive function (set-shifting, vigilance, working memory) between groups with FASD compared to healthy controls. Studies were weighted by sample size, and larger filled squares for the effect size estimate represent larger samples. Error bars represent the 95% confidence interval. WM=working memory

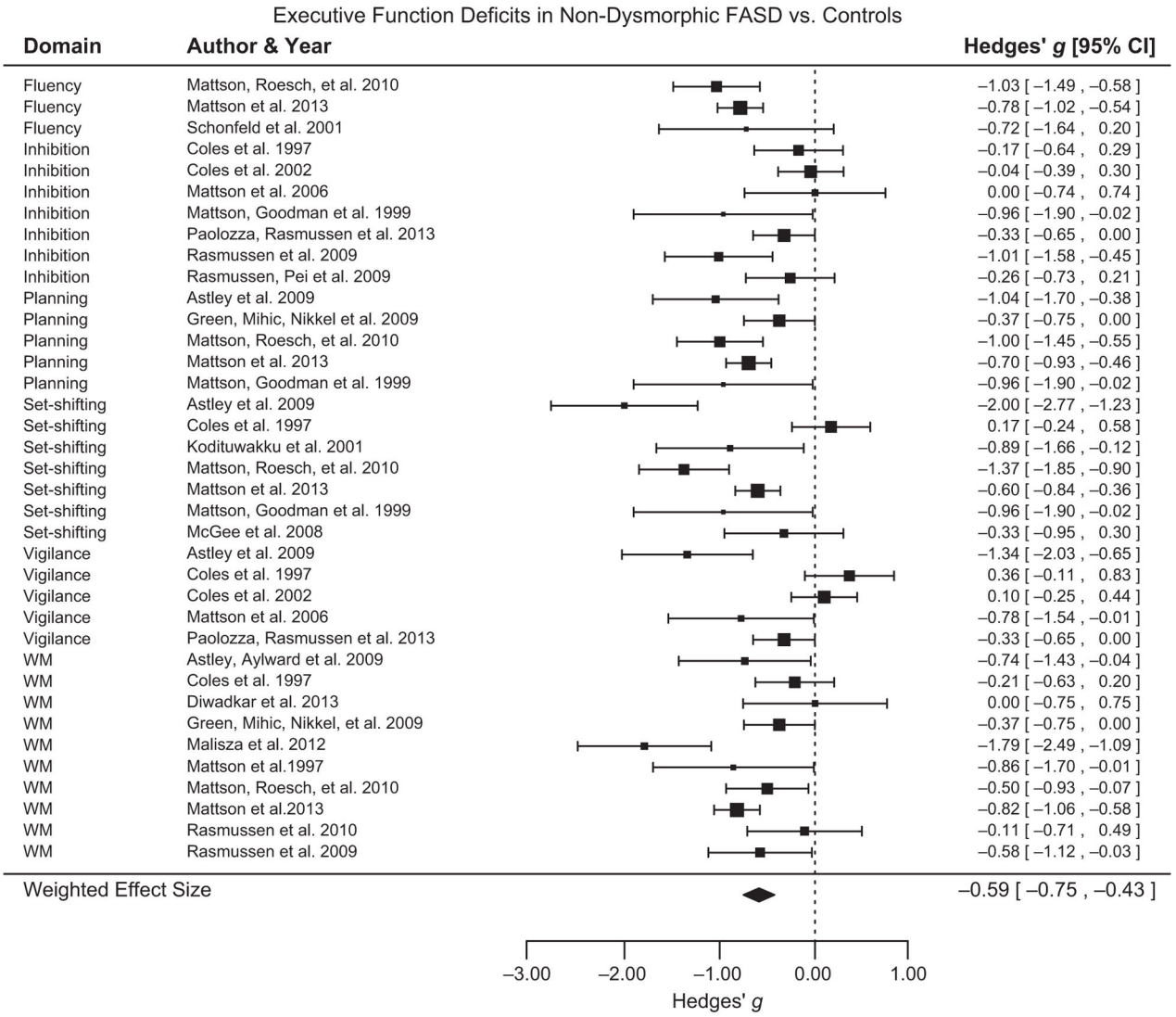


Figure 2.

The figure represents a forest plot for the average effect size (Hedges' *g*) of the effect executive function between FASD nondysmorphic groups compared to healthy controls. Studies were weighted by sample size, and larger filled squares for the effect size estimate represent larger samples. Error bars represent the 95% confidence interval. WM=working memory

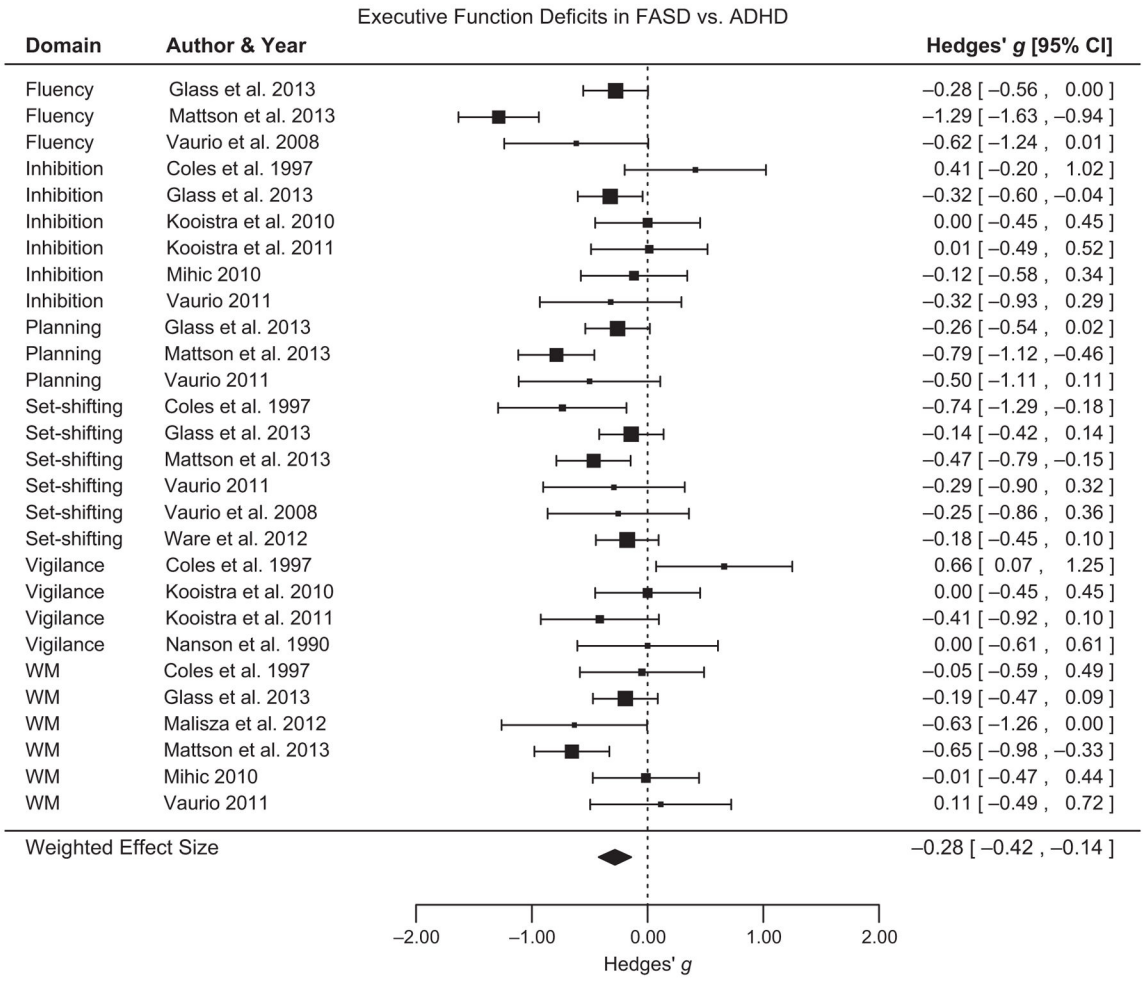


Figure 3.

The figure represents a forest plot for the average effect size (Hedges' *g*) of the effect executive function between FASD nondysmorphic groups compared to healthy controls. Studies were weighted by sample size, and larger filled squares for the effect size estimate represent larger samples. Error bars represent the 95% confidence interval. WM=working memory

Table 1

Study and sample characteristics of the 51 included studies

Characteristic	*K*	*N*	*M* (*SD*)
Sample size	51	4,558	89.37 (92.29)
Age	51	4,558	11.00 (2.21)
Age range	51	4,558	5.27–15.03
Sex (% male)	48	4,479	50.66 (11.74)
FSIQ			
FASD	38	1157	83.50 (12.96)
Nondysmorphic FASD	16	511	84.19 (12.57)
ADHD	10	422	99.96 (14.70)
Controls	38	1339	103.54 (12.09)
FSIQ Range			
FASD	38	1157	64.40–98.04
Nondysmorphic FASD	16	511	72.20–99.46
ADHD	10	422	84.75–111.76
Controls	38	1339	67.20–123.90
% Dysmorphy*			
FASD vs. Controls	44	1342	71.65 (32.17)
Nondysmorphic	19	665	0.00
FASD vs. Controls			
FASD vs. ADHD	10	432	44.48 (40.83)
Diagnostic system	49	4508	–
Traditional	26	2780	–
4 Digit	10	683	–
IOM	3	92	–
Canadian	10	953	–

K, number of studies reporting this information; *N*, total number of participants; *M*, mean; *SD*, standard deviation. Average age and male proportion were calculated for each study by averaging FASD and control group data, which were similarly age- and sex-matched. Effect sizes for group differences in full-scale intellectual functioning (FSIQ; or estimations based on Verbal or Performance IQ) were calculated for each study reporting such data.

* Proportion of FASD participants identified as FAS or pFAS.

Diagnostic system: Traditional = FASD diagnosis made based on presence of heavy prenatal alcohol exposure and dysmorphology exam, based on the CIFASD guidelines. 4-Digit = 4-Digit Diagnostic Code. IOM = 2005 Revised Institute of Medicine criteria. Canadian = Canadian Guidelines for Diagnosis of FASD.

Table 2

Effect sizes by subgroup and executive function domain

Comparison	Effect sizes[a]	*N*	Hedges' *g*	95% CI (UL, LL)	Q_t	I^2	Fail-safe N[b]
All Executive Function Domains							
FASD	99	8,095	**−0.734**	−0.821, −0.648	254.36**	63.52	28,394
Nondysmorphic FASD	37	3,564	**−0.588**	−0.750, −0.426	136.40**	78.19	2,861
ADHD	28	2,814	**−0.282**	−0.422, −0.142	78.93**	67.61	498
Executive Function Domain							
FASD vs. Controls	Q_M = 352.18 (6, 94), p < .001						
Fluency	10	992	**−0.874**	−1.113, −0.634	21.87**	59.42	499
Inhibition	24	1,725	**−0.499**	−0.663, −0.336	49.44**	51.91	715
Planning	12	1,181	**−0.941**	−1.167, −0.716	19.46	40.86	708
Set-shifting	20	1,781	**−0.869**	−1.046, −0.691	43.10**	61.02	1,581
Vigilance	14	894	**−0.519**	−0.727, −0.311	44.25**	75.85	268
Working memory	19	1,522	**−0.835**	−1.020, −0.651	26.16	30.41	1,240
Nondysmorphic FASD vs. Controls	Q_M = 58.18 (6, 31), p < .001						
Fluency	3	404	**−0.860**	−1.411, −0.310	0.97	0.00	55
Inhibition	7	602	−0.356	−0.720, 0.008	11.09	44.17	27
Planning	5	576	**−0.776**	−1.203, −0.350	5.96	39.52	104
Set-shifting	7	660	**−0.782**	−1.158, −0.407	37.93**	86.44	145
Vigilance	5	473	−0.312	−0.736, 0.112	21.68**	86.69	8
Working memory	10	849	**−0.579**	−0.886, −0.272	24.75**	66.48	194
FASD vs. ADHD	Q_M = 31.57 (6, 22), p < .001						
Fluency	3	401	**−0.722**	−1.091, −0.354	19.77**	86.94	43
Inhibition	6	509	−0.084	−0.365, 0.197	5.85	18.53	0
Planning	3	401	**−0.510**	−0.876, −0.145	5.77	62.72	22
Set-shifting	6	717	**−0.321**	−0.588, −0.055	5.44	13.98	28
Vigilance	4	218	0.040	−0.325, 0.406	7.35	60.04	0
Working memory	6	568	−0.257	−0.533, 0.019	10.31	51.42	13

N, total number of participants; Q_t, heterogeneity test statistic; I^2, estimates (in percent) how much of the total variability in the effect size estimates can be attributed to heterogeneity among the true effects; Q_M, test of between-group differences. Statistically significant effect sizes are marked in bold.

[a] Number of effect sizes.

[b] Fail-safe *n* using Rosenthal's method.

** p < .01.

Table 3

Moderation of effect sizes by age, sex, dysmorphy, IQ, and diagnostic system

Moderator	Subgroup analysis	Effect sizes[a]	Hedge's *g*	95% CI (UL, LL)	Q_T	I^2
Age (years)	FASD vs. Controls	99	**−0.071**	−0.113, −0.029	223.68**	58.46
	Nondysmorphic FASD vs. Controls	37	**−0.069**	−0.131, −0.006	124.45**	76.01
	FASD vs. ADHD	28	**−0.097**	−0.173, −0.021	66.14**	61.54
Sex (% male)	FASD vs. Controls	93	−0.081	−0.165, 0.004	220.97**	61.75
	Nondysmorphic FASD vs. Controls	37	**−0.029**	−0.051, −0.007	109.98**	73.83
	FASD vs. ADHD	28	−0.007	−0.040, 0.025	78.37**	69.20
Dysmorphy (proportion FAS or pFAS)*	FASD vs. Controls	93	**−0.325**	−0.587, −0.062	242.96**	63.52
	FASD vs. ADHD	24	−0.270	−0.653, 0.113	60.46**	68.90
IQ difference (FSIQ quotients)	FASD vs. Controls	80	**−0.026**	−0.034, −0.019	121.97**	32.86
	Nondysmorphic FASD vs. Controls	31	**−0.033**	−0.044, −0.023	52.25**	49.69
	FASD vs. ADHD	26	0.003	−0.017, 0.022	71.97**	70.14
Diagnostic system	FASD vs. Controls	97			238.95**	64.02
	Traditional	61	**−0.766**	−0.876, −0.657		
	4-Digit	15	**−0.639**	−0.861, −0.417		
	IOM	5	**−0.595**	−1.007, −0.183		
	Canadian	16	**−0.698**	−0.915, −0.481		
	Nondysmorphic FASD vs. Controls	37			133.32**	78.53
	Traditional	24	**−0.518**	−0.721, −0.314		
	4-Digit	6	**−0.857**	−1.287, −0.428		
	Canadian	7	**−0.620**	−0.979, −0.261		
	FASD vs. ADHD	28			73.99**	68.29
	Traditional	21	**−0.323**	−0.484, −0.162		
	4-Digit	4	−0.095	−0.474, 0.284		
	Canadian	3	−0.220	−0.670, 0.229		

Average age and male proportion were calculated for each study by averaging FASD and control group data, which were similarly age- and sex-matched. Effect sizes for group differences in full-scale intellectual functioning (FSIQ; or estimations based on Verbal or Performance IQ) were calculated for each study reporting such data.

*Proportion of FASD participants identified as FAS or pFAS.

Diagnostic system: Traditional = FASD diagnosis made based on presence of heavy prenatal alcohol exposure and dysmorphology exam, based on the CIFASD guidelines. 4-Digit = 4-Digit Diagnostic Code. IOM = 2005 Revised Institute of Medicine criteria. Canadian = Canadian Guidelines for Diagnosis of FASD. Statistically significant effect sizes are marked in bold.

[a]Number of effect sizes.

**$p < .01$.