



Anterior cingulate cortex findings in child disruptive behavior disorders. [☆] A meta-analysis

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ARTICLE INFO

Article history:

Received 7 January 2012
Received in revised form 3 July 2012
Accepted 6 July 2012
Available online 20 July 2012

Keywords:

Child disruptive behavior disorders
Aggressive behavior
Anterior cingulate cortex
Cognitive self-regulation

ABSTRACT

The brain imaging literature suggests that child disruptive behavior disorders (DBD) are associated with structural and functional abnormalities of the anterior cingulate cortex (ACC). However, there is a lot of heterogeneity in findings in terms of direction of modifications identified until this point. The present study used a meta-analytic design to aggregate the empirical findings from the literature on functional and structural abnormalities of the ACC in children with DBD. A total of eight structural and functional brain imaging (sMRI and fMRI) studies were included and results obtained from a sample of 266 children show a large effect size ($D = -.98$ (95% CI $[-1.18, -0.77]$) in terms of reduced activation of the ACC in children presenting with DBD. Effects of ACC abnormality were moderated by: 1) the type of imaging used in the study (i.e., functional vs. structural); 2) the presence or absence of co-morbid attention deficit hyperactivity disorder (ADHD); 3) the mean age of the samples of children presenting with DBD. Overall, findings confirm functional impairments of the ACC in children with DBD and highlight the importance of using such neurological information to design innovative treatments.

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[☆] This work was supported by a grant of the first author from the Romanian National Authority for Scientific Research, CNCS – UEFISCDI, project number PN-II-RU-PD-2011-3-0131. Part of this work was supported by the Foundation Dinu Patriciu through a scholarship for the first author at Harvard Medical School, Laboratories of Cognitive Neurosciences.

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1. Introduction

Child disruptive behavior disorders (DBD) are the reason for nearly half of all referrals to children's mental health agencies (Nock & Kazdin, 2002). According to the DSM-IV-TR (APA, 2000), DBDs include conduct disorder (CD) and oppositional defiant disorder (ODD), both of which are defined by the persistent presence of non-compliant and aggressive behavior in children. Children with DBD lack the ability to regulate their

thoughts, feelings, and emotional impulses during intense, negative emotional states (e.g. anger) and find it difficult to shift their attention away from anger-inducing cues (Blair, Colledge, Murray, & Mitchell, 2001; Boes, McCormick, Coryell, & Nopoulos, 2008; Damasio, 2000; Davidson, Putnam, & Larson, 2000; Huebner et al., 2008; Stadler et al., 2007; Sterzer, Stadler, Krebs, Kleinschmidt, & Poustka, 2005). Such conditions may increase the risk of children developing serious behavioral problems (Huebner et al., 2008) and can have the effect of diminishing the quality of their relationships (e.g., with parents or peers) (Card & Little, 2006; Frick et al., 2003; Rubin, Burgess, Dwyer, & Hastings, 2003). Indeed, there is an association between aggression in childhood and severe psychosocial maladjustment, antisocial behavior, adolescent delinquency, and criminality in adulthood (Nock & Photos, 2006). Thus, it has been suggested that the antisocial and aggressive behaviors of children with DBD actually reflect neurological abnormalities in those regions of the brain that are involved in the voluntary regulation of negative emotions and in emotional restraint (Cappadocia, Desrocher, Pepler, & Schroeder, 2009). In this way, the inability of children with DBD to regulate their emotions and behaviors is considered a reflection of their fundamental lack of executive (or intentional) control (Hoptman, 2003).

Researchers have begun to investigate the structural and functional brain abnormalities associated with emotion regulation and neuropsychiatric disorders using several brain imaging procedures, such as magnetic resonance imaging (MRI). In this way, it has been possible to explore the neurobiological bases of externalizing behavior disorders in children, with particular respect to DBD and attention deficit/hyperactivity disorder (ADHD) (Herpertz et al., 2005; Herpertz et al., 2007; Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006; Stadler et al., 2007). While many studies have used imaging procedures to investigate ADHD (Nigg & Casey, 2005; Seidman, Valera, & Makris, 2005), considerably fewer have used such procedures to investigate DBD despite the fact that there are data available on the neural mechanisms of aggressive behavior. Certain regions of the brain—particularly the ventromedial prefrontal cortex (vmPFC), anterior cingulate cortex (ACC), and amygdala—have been implicated in emotional control and decision-making (Berlin, Rolls, & Kischka, 2004). Neuroimaging and lesion studies have focused primarily on prefrontal regions that mediate appraisal, inhibitory control, and self-monitoring, all considered to be critical components of emotion regulation (Bechara & Van Der Linden, 2005). Other research highlights the important roles of the ACC in emotional processing (Blair, 1999; Bush, Luu, & Posner, 2000; Drevets & Raichle, 1998; Lane et al., 1998; Morris, Frith, Perrett, Rowland, & Young, 1996). The dorsal ACC is involved in various higher cognitive processes, including response conflict and error monitoring (“cognitive division”), whereas the ventral and anterior ACCs are primarily involved in the regulation of emotional behavior (“affective division”) (Bush et al., 2000).

The present study used a meta-analytic design to aggregate the empirical findings from the literature on functional and structural abnormalities of the ACC in children with DBD. Since this is the first meta-analysis on this topic, we chose to discuss both theoretical and practical implications that could influence future research and the development of rehabilitation procedures for children diagnosed with DBD.

2. Method

2.1. Study selection

Studies included in the present meta-analysis were identified using a keyword search of the PubMed and PsychInfo databases as of December 2010. Keywords were chosen based on their relevance to aggressive behavior and brain imaging (i.e., disruptive, externalizing, aggression, aggressive, defiant, behavior, antisocial, violent, oppositional

defiant disorder, conduct disorder, neural, neuroimaging, structural imaging/sMRI, functional magnetic resonance imaging/fMRI, functional imaging, anterior cingulate cortex/ACC). Additional studies were identified by reviewing the reference lists of eligible studies and by reviewing relevant review articles on the relationship between brain imaging and aggressive behavior in children (e.g., see Sterzer & Stadler, 2009).

Eligibility criteria were: 1) a study using group comparison had to include at least one group of children with disruptive behavior (defined as a group that contains children with CD, ODD, or DBD (not otherwise specified), or antisocial children) and one control group of either appropriate psychiatric controls or healthy normal subjects; 2) studies had to include one or both of the structural and/or functional brain imaging methods (sMRI and/or fMRI). In other words, the imaging method had to assess either the structure (e.g., volume, neural connectivity) or function (e.g., hemodynamic response, regional cerebral blood flow) of the ACC. The ACC was defined as the Brodmann Areas (BA) 24 and 32. Findings that used a different nomenclature for anatomical regions were classified into regions of interest (ROIs) and examined using the information provided by the authors (i.e., BA locations, anatomical landmarks); and 3) studies had to be published in peer-reviewed journals to ensure both quality of the study and sufficient statistical information to allow for the calculation of effect size and the conduction of moderator analyses. Animal studies and case reports/observations were excluded. If a particular group was used in more than one publication, the one with the largest sample size was included for analysis.

Following this systematic search, a total of 46 publications were retrieved, 8 of which met all of the inclusion criteria.

The demographic information and antisocial characteristics of the samples in the eight eligible studies are presented in Table 1.

A total of 266 children participated across these eight studies, with 135 children in the DBD group and 131 children in the control group. All participants were male (see Table 1). Studies used well established instruments based on the DSM-IV-TR (APA, 2000) in order to diagnose child DBDs (e.g., Child Behavior Checklist, CBCL; Achenbach, 1991; see Table 1).

2.2. Procedure

This meta-analysis was performed using Comprehensive Meta-Analysis, Version 2, Biostat (Borenstein et al., 2005). The effect size for each paper was calculated using Cohen's method (the difference between means divided by the pooled standard deviation) and expressed as Cohen's *d* (Cohen, 1988; Hedges & Olkin, 1985). Functional and structural MRI data were coded using the same procedure that Yang and Raine (2009) used in their meta-analysis of the prefrontal structural and functional brain abnormalities in antisocial, violent, and psychopathic adults. If more than one probability (*P*) was presented for a sub-region, results were combined following the method proposed by Rosenthal (1978). If multiple groups in one study were reported independently (e.g., aggressive behavior in children with and without co-morbid ADHD), these groups were treated separately. Small, medium, and large effect sizes were defined by Cohen's *d* values of 0.2, 0.5, and 0.8, respectively (Cohen, 1988). Negative effect sizes in the present study reflect smaller ACC volume and reduced ACC activation, both of which are associated with increased aggressive behavior in children. The 95% confidence interval for the effect size was also calculated.

The homogeneity (*Q*) test was performed to determine whether the studies could reasonably be described as sharing a common effect size (Hedges & Olkin, 1985). We obtained a $\chi^2 = 119.49$, $p < 0.05$ for the *Q* test. Consequently, this meta-analysis was based on the more conservative random effects model. According to this model, we considered both the within study variances (e.g., sample size of each group) and the between-study variances (e.g., the number of studies, the weight of each study). Studies were weighted according

Table 1
Demographic information and sample characteristics of the eight studies.

Study	Imaging procedure	Aggressive children/ control sample		Subjects	Mean age experimental group (years)	Characteristics					Effect size (Cohen's <i>d</i>)
		Number of subjects				Clinical diagnosis method	Task (stimuli/ cues used in study)	Callous– unemotional traits (CUT sample)	ADHD comorbidity (sample)	Variable of interest	
		Aggressive children	Control								
1. Boes, Tranel, Anderson, and Nopoulos (2008)	sMRI	20	20	40	12.08	CBCL	No	No	Right ACC	– 1.22	
2. De Brito et al. (2009)	sMRI	23	25	48	11.8	The Conduct Problem sub-scale of Strengths and Difficulties Questionnaire	No	CUT (23)	The Callous– Unemotional trait scale of the Antisocial Process Screening Device	Dorsal right ACC Rostral left ACC Dorsal left ACC	1.05 0.79 0.79
3. Decety, Michalska, Akitsuki, and Lahey (2009)	fMRI	8	8	16	16–18	The Diagnostic Interview Schedule for Children	Cognitive			Left ACC Right ACC	– 1.78 – 1.80
4. Gatzke-Kopp et al. (2009)	fMRI	19	11	30	13.6	Adolescent Symptom Inventory, Child Behavior Checklist (CBCL)	Cognitive	ADHD (10)		Left ACC Right ACC	– 1.44 – 1.44
5. Herpertz et al. (2008)	fMRI	22	22	44	14.7	Kiddie Sads – Semistructured interview, CBCL	Emotional (International Affective Picture System)	ADHD (16)		Left ACC	– 1.10
6. Rubia et al. (2009)	fMRI	14	16	30	13.10	Clinical diagnostic based on Maudsley Standardized Interview The Hyperactivity sub-scale of the Strengths and Difficulties Questionnaire	Cognitive (The Rewarded Continuous Performance Test)	No		Postgenual left ACC Posterior left ACC	– 1.04 – 1.40
7. Stadler et al. (2007)	fMRI	16	15	31	12.85	Clinical Structured Interview, CBCL	Emotional (International Affective Picture System) in leg. Cu novelty seeking	ADHD (8)		ACC	– 1.30
8. Sterzer et al. (2005)	fMRI	13	14	27	12.85	Diagnostic System for Psychiatric Disorders in Childhood and Adolescence, CBCL	Emotional (International Affective Picture System)	ADHD (8)		Dorsal right ACC	– 2.16

to the precision of their d estimate, which was proportional to the study sample size. For the overall weighted effect size (D) of the ACC, a meta-analysis was performed combining all sub-regions in all of the studies.

Orwin's fail safe-analysis N (Orwin, 1983) was conducted in order to check the stability of our meta-analytic results and to evaluate whether the available literature was biased toward excluding non-significant studies. Orwin's fail-safe N addresses the "file drawer problem" (Rosenthal, 1979, 1991) by calculating the number of studies (with an effect size of 0) needed to make the mean effect size non-significant ($p < 0.05$).

2.3. Coding for potential moderators

Studies were coded for several moderators, as there are several genetic polymorphisms that impact aggression (Kreek, Nielsen, Butelman, & LaForge, 2005), and emerging data suggest that these genetic variations may correspond to differences in the structure and function of the vmPFC-ACC-amygdala circuit (Pezawas et al., 2005; Shaw, Gornick, & Lerch, 2007). For example, it has been suggested that a common neurobiological circuit may predispose individuals to develop CD and ADHD, and the difference in externalizing symptoms may depend on the risk factors that children are exposed to (Beauchaine, Gatzke-Kopp, & Mead, 2007) (Fig. 1).

Studies were coded for each of the following potential moderators: (1) functional vs. structural imaging procedure, (2) children with DBD with vs. without ADHD co-morbidity, (3) cognitive vs. emotional stimulus tasks, and (4) presence vs. absence of callous unemotional traits

(CU). The co-morbidity code was assigned to those studies reporting on children with DBD and co-morbid ADHD, whereas those studies that did not report co-morbid ADHD were coded as without ADHD co-morbidity. The code for healthy control was assigned to studies that used a healthy comparison group, presenting without any neurological and psychological illness. All moderators are listed in Table 1. The influence of each moderator was individually tested using analysis of variance (ANOVA) for categorical moderators and fixed effect regression for continuous moderators. To determine moderator effects, the minimum level of significance was set to $p < 0.05$.

3. Results

3.1. Meta-analysis

Our findings are detailed in Table 2, together with a funnel plot (Fig. 2) and a forest plot (Fig. 3).

A meta-analysis including all ACC and sub-regional ACC findings indicated that boys presenting DBD show, overall, reduced function and structure in the ACC, compared with control subjects, $D = -0.98$, 95% CI $[-1.18, -0.77]$. We also calculated the magnitude of the functional abnormalities in the ACC of the boys presenting DBD and we obtained a $D = -0.92$, 95% CI $[-0.92, -0.91]$. Based on the four effect sizes derived from two studies, we obtained a $D = -0.07$, 95% $[-0.28, 0.20]$ showing no significant structural abnormalities of ACC in DBD boys. Analyses on the ROIs showed the ACC abnormality to be localized in the right ACC ($D = -1.06$, $[-1.21, -0.90]$), left ACC ($D = -0.34$, $[-0.63, -0.05]$), right ventral ACC ($D = -1.4$, $[-1.58, -1.22]$) and left

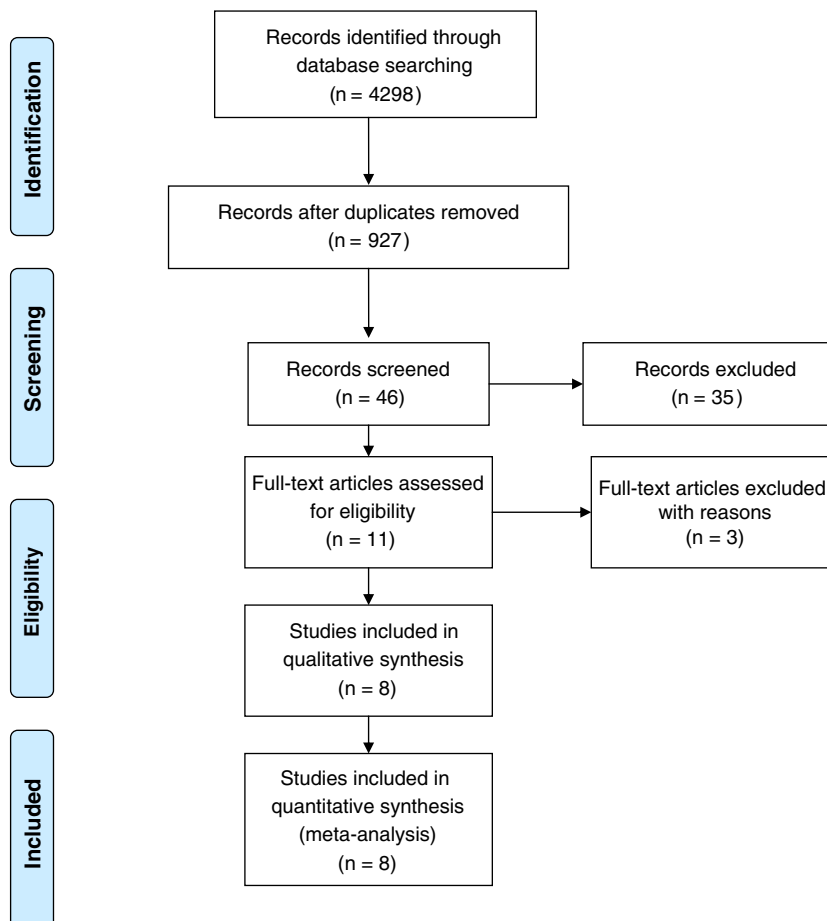


Fig. 1. Study flow diagram, Prisma model (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009).

Table 2

Mean effect sizes for the regions of interest across the eight structural and functional imaging studies.

ROI	Cohen's <i>d</i>	95% confidence interval
ACC (combined)	−0.98	[−1.18, −0.77]
Left ACC	−0.34	[−0.63, −0.05]
Right ACC	−1.06	[−1.21, −0.90]
Dorsal ACC	−0.007	[−19.32, 19.31]
Ventral right ACC	−1.4	[−1.58, −1.22]
Ventral left ACC	−1.33	[−1.51, −1.15]

ventral ACC ($D = -1.33$, $[-1.51, -1.15]$). In contrast, no abnormality was found in the dorsal ACC across studies ($D = -0.007$; $[-19.32, 19.31]$).

The assessments of publication bias confirmed that there was no publication bias for the ACC (Fail-safe $N = 66.6$), showing that a number of 66 studies showing no effect would be needed in order to invalidate the findings.

3.2. Moderator analysis

ANOVA comparisons revealed a stronger association between DBD and ACC abnormalities in the functional imaging studies than for the structural imaging studies ($F(1,12) = 21.13$, $p < 0.001$). Comparisons also indicated significantly greater functional impairments of the ACC in children presenting with DBD and co-morbid ADHD when compared to those children presenting with DBD alone ($F(1,12) = 13.98$, $p = 0.004$). Fixed-effect regression revealed that effects were moderated by the mean age of the sample of children, with larger effect sizes being recorded for older children ($b = -0.36$, $p = 0.01$). We did not conduct a moderator analysis for co-morbid DBD and CUs, as only one study reported on this co-morbidity. Moderating effects for emotional vs. cognitive stimulus tasks were found to be statistically insignificant.

4. Discussion

This is the first quantitative meta-analysis assessing the relationship between ACC anomalies and child DBD. Interestingly, while all studies in this meta-analysis investigated brain abnormalities in children with DBD, each study only included male participants, which may be due to the fact that DBD is more prevalent in the male population. Consequently, our results indicate that DBD in boys, in particular, is significantly associated with reduced ACC activity, more specifically of the right ACC, left ACC, and ventral ACC. While effects were not moderated by the type of task stimulus used in each study (i.e., cognitive vs. emotional stimulus), moderating effects were found for type of imaging methodology used (i.e., functional vs. structural) and for co-morbid ADHD. Overall, these findings provide fairly robust and significant support for functional abnormalities in the ACC in boys with DBD.

4.1. Localization and lateralization of ACC impairments

Our results are consistent with other theoretical models suggesting an involvement of the ACC in antisocial behavior (Bush et al., 2000). When findings for each hemisphere were analyzed separately and compared to non-clinical samples, ACC functional anomalies were found to be localized in both the left and right hemispheres of boys with DBD, with greater functional impairment in the right hemisphere (particularly in the right ventral ACC). No moderation effects were found for the ACC across hemispheres. Overall, as suggested by previous lesion studies (Bechara & Van Der Linden, 2005), our data confirms that boys with DBD exhibit functional abnormalities of the right ACC, which have been associated with cognitive control deficits and poor decision-making (Ochsner & Gross, 2005).

While we obtained large effect sizes for functional anomalies in the ventral ACC, we did not find functional abnormalities of the dorsal ACC. Even so, functional impairments of the ventral ACC have been associated with having difficulty controlling one's cognitive impulses and anticipating negative consequences of one's actions (Boes et al., 2008; Damasio, 2000; Davidson et al., 2000; Huebner et al., 2008). These findings are in line with several biological theories about antisocial behavior and psychopathology (Damasio, 1994; Gorenstein & Newman, 1980) in that they suggest that aggressive behavior in children might be a consequence of inherited or acquired anomalies in the ACC and frontal brain areas.

4.2. Limitations and future directions

As with many meta-analyses, the present study has its limitations. First, while we were able to assess the structural and functional abnormalities in the ACC of children with DBD, only two of the eligible studies used the sMRI procedure, which ultimately prevented us from conducting subsidiary analyses to reveal the relevant structural deficits. Perhaps, this is the reason why we found weaker associations between DBD and ACC abnormalities for the structural imaging studies than we did for the functional imaging studies. A second limitation of the present meta-analysis is that it only included male children, perhaps suggesting that more research should aim to investigate both structural and functional brain anomalies in female children with DBD, as well.

4.3. Implications for treatment strategies

This paper attempts to find a link between neuroscientific and clinical findings on DBD with the goal of highlighting potentially important therapeutic targets for the treatment of DBD. Parenting interventions are presently considered the most effective and suitable clinical solution to the early-onset of antisocial behavior in children (see NICE, 2006). However, the identification of both structural and functional markers of chronic antisocial behavior in children with DBD might increase treatment response and suggest new avenues for the development of targeted therapeutic strategies (Gavita, David, Bujoreanu, Tiba, & Ionutiu, 2012; Gavita & Joyce, 2008; Gavita, Joyce, & David, 2011).

Given that functional anomalies in the ACC have been linked to impaired decision making abilities (Kerns et al., 2004; Rushworth, Buckley, Behrens, Walton, & Bannerman, 2007), and considering that we found significant functional abnormalities in the ACC of boys with DBD, it might be suggested that effective psychotherapeutic strategies should also target decision making and problem solving (Trip, McMahan, Bora, & Chipea, 2010). Additionally, it has been

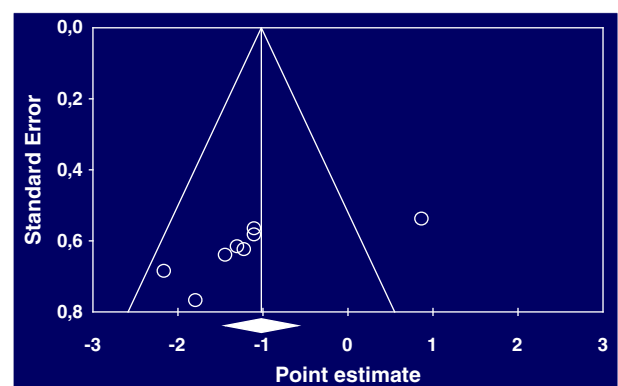


Fig. 2. Funnel plot of standard error by point estimate of effect sizes across studies.

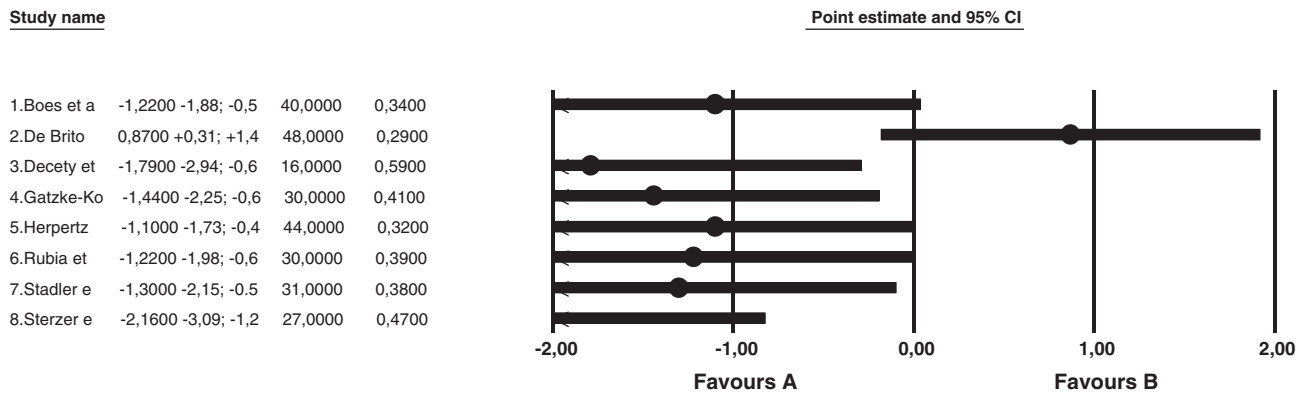


Fig. 3. Forest plot of effect sizes across studies.

suggested that aberrant dorsal ACC activation might have an impact on stimulus appraisal during top-down processing (Ochsner & Gross, 2005). Therefore, new psychosocial treatments for DBD could involve the introduction of cognitive re-appraisal strategies to children exhibiting overly negative appraisals.

Additionally, given that we found a link between treatment response and structural/functional anomalies in the ACC (Bryant et al., 2008) future research should investigate the role of the ACC in DBD. Further, more research might be needed to identify key neural correlates of DBD in children. Our results might also suggest that more insights on both structural and functional anomalies in the brain of children with DBD are also crucial to the development of more targeted psychotherapeutic strategies aimed at alleviating psycho-social consequences. Furthermore, the ACC works closely with several other brain regions. In order to provide a more comprehensive neurological background for the treatment of children with DBD, future meta-analyses should further investigate other brain regions involved in emotion regulation and decision-making.

4.4. Conclusions

The present study provides strong support of functional abnormalities of the ACC in children presenting with DBD. More specifically, results indicate that DBD is significantly associated with reduced ACC function, particularly of the right ACC, left ACC, and ventral ACC, when compared to healthy controls. Furthermore, our results indicate anomalies in the ACC of children with DBD and co-morbid ADHD when compared to those children with DBD alone. In summary, the present meta-analysis stresses the critical need for imaging studies on female children with DBD and also investigating other potential mediating variables (e.g., impulsivity, emotional regulation, and novelty seeking). Multiple regions other than the ACC are likely to be implicated in child DBD. Future research should therefore focus on those areas of the brain that work closely with the ACC (e.g., amygdala, OFC, hippocampus, insula, and angular gyrus). These findings provide fertile ground for further investigation aimed at improving treatment of child DBD. Indeed, future neurobiological research—incorporating neuroimaging, neuropsychological, and behavioral techniques—is needed to further our understanding of the complex mechanisms underlying the externalization of DBD and ultimately provide new grounds for the development of effective treatments.

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