Meta-Analysis of fMRI Studies of Disruptive Behavior Disorders

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Objective: Functional magnetic resonance imaging (fMRI) studies in conduct disorder and in oppositional defiant disorder have shown inconsistencies. The aim of this meta-analysis of fMRI studies in disruptive behavior disorders was to establish the most consistent brain dysfunctions and to address task- and subtype-related heterogeneity.

Method: Web-based publication databases were searched to conduct a meta-analysis of all whole-brain fMRI studies of youths with disruptive behavior disorder or conduct problems up to August 2015. Sub-meta-analyses were conducted in functional subdomains of emotion processing; in cool and hot executive functions, which refer to goal-directed higher cognitive functions with and without motivational and affective significance; and in a subgroup of youths with additional psychopathic traits. The authors performed a meta-analysis of voxel-based group differences in functional activation using the anisotropic effect-size version of seed-based *d* mapping.

Results: Across 24 studies, 338 youths with disruptive behavior disorder or conduct problems relative to 298 typically developing youths had consistent underactivation in the rostral and dorsal anterior cingulate and in the medial prefrontal cortex and ventral caudate. Sub-meta-analyses of fMRI studies showed that medial fronto-cingulate dysfunction was driven by hot executive function. The sub-meta-analysis of emotion processing fMRI studies showed the most consistent underactivation in the dorsolateral prefrontal cortex and temporal pole, while cool executive functions were associated with temporal abnormalities. Youths with disruptive behavior disorder with psychopathic traits showed reduced ventromedial prefrontal-hypothalamic-limbic activation, but they also showed hyperactivation in cognitive control mediating dorsolateral prefrontal-dorsal and striatal regions.

Conclusions: The findings show that the most consistent dysfunction in youths with disruptive behavior disorder is in the rostro-dorsomedial, fronto-cingulate, and ventral-striatal regions that mediate reward-based decision making, which is typically compromised in the disorder. Youths with psychopathic traits, on the other hand, have dysfunctions associated with the ventromedial prefrontal cortex and limbic system, together with dorsal and fronto-striatal hyperfunctioning, which may reflect poor affect reactivity and empathy in the presence of hyperactive executive control. These findings provide potential targets for neurotherapeutic and pharmacological interventions.

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Disruptive behavior disorder comprises conduct disorder, defined as frequent violation of the rights of others and of age-appropriate social rules, and oppositional defiant disorder, characterized by low frustration tolerance and persistently hostile and defiant behavior. It is one of the most prevalent childhood psychiatric disorders and is associated with substantial societal economic burden and increased risk of antisocial personality disorder in adulthood (1).

Youths with disruptive behavior disorder have consistent deficits in emotion processing (2) and executive functions, particularly in response inhibition and attention allocation (3–5). Executive functions refer to higher cognitive control of thought, action, and emotions (6). A further distinction has been made between "hot" executive functions, which refer to motivationally and emotionally significant tasks, and "cool" executive functions, which refer to more abstract tasks (6). Youths with disruptive behaviors are most prominently impaired in hot executive functions, such as in decision making related to punishment or reward measured in tasks of temporal discounting, gambling, reward reversal, and others, suggesting that motivation control is key to the disorder (4, 7, 8).

Structural MRI studies have found abnormalities in youths with disruptive behavior disorder relative to control subjects in the ventral and dorsal medial prefrontal cortex, anterior cingulate, and temporo-limbic regions (9–15).

Functional MRI (fMRI) studies have examined most prominently hot and cool executive functions and emotion processing. fMRI studies of hot executive functions have found underactivation in youths with disruptive disorder compared with control subjects in predominantly paralimbic regions,

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including the orbitofrontal cortex, ventromedial prefrontal cortex, anterior cingulate (16, 17), dorsolateral prefrontal cortex (18), parahippocampal gyrus, caudate, thalamus, and temporal (18–20) and inferior parietal cortices (19) (see Table S1A and Figure S1 in the data supplement that accompanies the online edition of this article). Few fMRI studies have tested cool executive functions, but such studies have shown underactivation in the dorsolateral prefrontal (21), temporoparietal (16, 22, 23), dorsal anterior cingulate, and limbic regions (16) (see Table S1B in the online data supplement).

Studies investigating emotion processing have shown reduced activation relative to control subjects in regions of the affect-controlling paralimbic system, including the anterior cingulate (24, 25); the orbitofrontal, ventromedial, and dorsolateral prefrontal cortices; the temporal lobe; the amygdala (24, 26–29); and the insula (30); however, some studies found enhanced activation in the amygdala (31), anterior cingulate, and orbitofrontal cortex (32) (see Table S1C in the data supplement).

Given the heterogeneity of disruptive behavior disorder, some studies have attempted to disaggregate brain abnormalities associated with the disorder from those linked to the DSM-5 "limited prosocial emotions" specifier, characterized by psychopathic traits of callousness, remorselessness, lack of empathy, and shallow affect (33), or from those linked to the commonly associated attention deficit hyperactivity disorder (ADHD) comorbidity. Severity of psychopathic traits in disruptive behavior disorder has been associated with decreased activation during pain processing and with affective and hot executive functions in the dorsal anterior cingulate, ventromedial prefrontal, and striato-limbic regions (20, 28, 34–40), while ADHD symptoms have been associated with increased insula (30) and decreased frontal activation during emotion processing (41). Direct comparisons showed that youths with noncomorbid conduct disorder, relative to youths with ADHD, had disorder-specific underactivation in the ventromedial orbitofrontal cortex during hot executive functions (16) as well as in the limbic areas of the anterior cingulate, insula, and hippocampus during cool executive functions. Conversely, youths with ADHD had disorder-specific underactivation in the inferior prefrontal and dorsolateral prefrontal cortices (4, 16, 22, 23).

Although the majority of studies in disruptive behavior disorder point toward underrecruitment of paralimbic regions that mediate motivation and affect control, such as the ventromedial prefrontal, anterior cingulate, striatal, and temporolimbic areas, inconsistencies in findings likely resulted from small sample sizes, heterogeneity, and comorbidity (e.g., gender, ADHD, psychopathic traits); differences in analytical methodology (e.g., whole-brain or region-of-interest analyses); and/or cognitive domains tested.

The aim of this meta-analysis was to establish the most consistent brain function abnormalities of disruptive behavior disorder using all published whole-brain fMRI studies, which do not bias findings to a priori hypothesized regions (42). To reduce heterogeneity, sub-meta-analyses were conducted of functional subdomains of emotion processing, of hot and cool executive functions, and of patients with psychopathic traits. Furthermore, meta-regression analyses assessed effects of gender, medication, and ADHD comorbidity. Based on whole-brain fMRI findings (Table 1; see also Table S1 in the online data supplement), we hypothesized that youths with disruptive behavior disorder relative to control subjects would show the most consistent underactivation in paralimbic regions of motivation and affect control, such as the medial prefrontal cortex, anterior cingulate, and temporo-striato-limbic areas. Furthermore, we hypothesized that those with psychopathic traits would show more prominent deficits in striato-limbic regions (15, 20, 28, 34–38), while ADHD comorbidity would be associated with inferior prefrontal dysfunction (4).

METHOD

Study Selection

A literature search was conducted of whole-brain fMRI studies in children with disruptive behavior disorder or conduct problems up to August 2015 using the PubMed, ScienceDirect, Google Scholar, Web of Knowledge, and Scopus databases and combinations of the following keywords: "conduct disorder," "oppositional defiant disorder," "conduct problems," "callous-unemotional," "psychopathic traits," "psychopathy," "disruptive behavior," "aggression," "antisocial behavior," plus "fMRI" and "neuroimaging." Paper references were examined to identify additional studies, and additional details from authors were obtained wherever necessary. High-quality criteria for study inclusion were whole-brain analyses, matching for age and gender, inclusion of more than 10 subjects, use of standardized categorical or dimensional measures to assess disruptive behavior disorder or conduct problems, definition of inclusion and exclusion criteria, and report of software and statistical tests used. Studies were excluded if they included region-of-interest analysis only, had no statistical case-control comparison, had no report of peak coordinates, and had different significance or extent thresholds. MOOSE guidelines for meta-analysis of observational studies were followed (45). To avoid duplication, conjunctive group differences across tasks and task conditions, or main group effects across task conditions, were excluded. Peak coordinate and effect size of significant activation differences between case and control subjects were extracted from each contrast of interest for each study.

Comparison of Brain Activation

Regional differences in activation during fMRI tasks were analyzed using the anisotropic effect-size version of seed-based *d* mapping software (http://www.sdmproject.com), a voxel-based meta-analytic approach (46–48). First, the software re-creates the study maps of the effect size of differences in blood-oxygen-level-dependent (BOLD) response between patients and control subjects by converting the t value of each peak to Hedges' effect size and then applying an anisotropic nonnormalized Gaussian kernel so that voxels more correlated with the peak have higher effect sizes.

TABLE 1. Summary of Whole-Brain fMRI Studies of Youths With Disruptive Behavior Disorder or Severe Conduct Problems (DBD/CP) Relative to Healthy Control Subjects Included in the Main Meta-Analyses[a]

Study	DBD/CP Group		Healthy Controls Group		Reduced Activation (relative to healthy controls)	Enhanced Activation
	N	Males (%)	N	Males (%)		
A. Studies using hot executive function tasks						
Rubia et al. (16)	14	100	16	100	R OFC/vMOFC	—
Crowley et al. (18)	20[b]	100	20	100	L/R r/vMPFC, L OFC, L/R r/dACC, L/R insula, L/R precentral, L postcentral g, R pre-SMA, L claustrum, R caudate/putamen, R amygdala, R MTG/STG, L hippocampus, L precuneus, L PCC, R IPL, R lingual g, L and R Cb, L/R rACC, L/R STG/R MTG/ITG, R precuneus, R fusiform g, L/R Cb	L/R dMPFC, L OFC, L/R MTG; L ITG, L brainstem/pons, L culmen, R paracentral g, R PCC, L/R MTG, L precuneus
Kalnin et al. (43)[c]	22	59	22	59	—	—
Cohn et al. (39)[d]	22[e]	73	236	87	—	—
White et al. (19)[c]	15	73.3	15	66.7	L MPFC, L SFG, L DLPFC, R IFG/precentral g, R MPFC, R MTG, L middle occipital g	—
Marsh et al. (40)[f]	14	57	14	79	Amygdala	—
Finger et al. (20)[f]	14	64	14	64	—	L/R MFC, R caudate
Finger et al. (17)[f]	15	60	15	60	R OFC, L MFC, L SFC, L/R IFG, L IPL, L/R MTG, L caudate, L Cb, OFC, L DLPFC, R parahippocampal g	—
White et al. (41)[f]	17	76.5	19	47	L/R SPL, L/R IPL, L cuneus	—
White et al. (41)[f]	17	76.5	19	47	—	—
White et al. (35)[f]	15	80	17	52.9	L MTG	—
B. Studies using cool executive function tasks						
Rubia et al. (22)	13	100	20	100	R PCC/precuneus, L IPL, R postcentral/STG/IPL	—
Rubia et al. (16)	14	100	16	100	R insula/hippocampus/premotor, L dACC, L/R Cb/TL/ thalamus/occipital/hippocampus/L PCC/precuneus	—
Rubia et al. (21)	13	100	20	100	R STG/MTG, R precuneus, R DLPFC	—
Rubia (23)	14	100	20	100	R IPL/precentral g, L STL/IPL, L precuneus, cuneus	—
Marsh et al. (40)[f]	14	57	14	79	—	—
White et al. (41)[f]	17	76.5	19	47	—	—
White et al. (41)[f]	17	76.5	19	47	R MTG, R thalamus	—
White et al. (35)[f]	15	80	17	52.9	—	—
C. Studies using emotion processing tasks						
Herpertz et al. (31)	22	100	22	100	—	—
Passamonti et al. (30)[c]	40	100	20	100	R DLPFC, L MTG, L anterior insula	—
Fairchild et al. (29)	20	0	20	0	—	—
Sebastian et al. (32)	17	100	17	100	—	rACC/OFC
Sebastian et al. (44)	31	100	16	100	—	—
Cohn et al. (38)	25[e]	72	26	89	—	—
O'Nions et al. (26)[f]	16	100	16	100	R r/vMPFC	—
Marsh et al. (28)[c,f]	12	58.3	12	50	R STG	—
Marsh et al. (40)[f]	14	57	14	79	R STG, R PCC, precuneus	—
Jones et al. (27)[f]	17	100	13	100	—	—
White et al. (41)[f]	17	76	19	47	—	L SFC, R MFC
D. Studies using empathic pain tasks						
Lockwood et al. (37)	37	100	18	100	L STG/posterior insula, R Cb, R MTG, R caudate, GP, substantia nigra, L thalamus, L SMA, L and R IFG/insula, L DLPFC/IFG, R Cb, R SFC, L ACC, L precuneus	L parahippocampal g, L Cb
Marsh et al. (36)[f]	14	57	21	71	L SFC, R insula, L amygdala/uncus	—

[a] Only whole-brain results are reported for the studies. In addition, the results of the studies are summarized in this table for the benefit of the reader; the meta-analysis is not based on these labels but on numerical voxel data. ACC=anterior cingulate cortex; Cb=cerebellum; dACC=dorsal anterior cingulate cortex; DLPFC=dorsolateral prefrontal cortex; dMPFC=dorsomedial prefrontal cortex; g=gyrus; GP=globus pallidus; IFG=inferior frontal gyrus; IPL=inferior parietal lobe; ITG=inferior temporal gyrus; L=left; MFC=middle frontal cortex; MTG=middle temporal gyrus; OFC=orbitofrontal cortex; PCC=posterior cingulate cortex; R=right; rACC=rostral anterior cingulate cortex; rMPFC=rostral medial prefrontal cortex; SFC=superior frontal cortex; SFG=superior frontal gyrus; SMA=supplementary motor area; STG=superior temporal gyrus; SPL=superior parietal lobe; TL=temporal lobe; vMOFC=ventromedial orbitofrontal cortex; vMPFC=ventromedial prefrontal cortex.

[b] Nineteen of 20 subjects met DSM-IV conduct disorder diagnostic criteria, and all met diagnostic criteria of substance use disorder.

[c] Results reported here were obtained through a personal communication with the author or through a data supplement.

[d] Results reported in the article were not statistically significant at the whole-brain level and thus were excluded from the meta-analysis.

[e] Sample recruited from a cohort of adolescents who were first arrested by the police before age 12.

[f] Study included only youths showing a high score for psychopathic traits or callous unemotional traits; hence, this was included in the subgroup meta-analysis of youths with DBD/CP with psychopathic traits.

The software was modified to allow inclusion of a single, combined map with reduced variance for studies sharing subjects (see the online data supplement). This resulted, for example, in a single map for all seven data sets published by Rubia et al. (16, 21–23). Maps were combined with a standard random-effects model, taking into account sample size, intrastudy variability, and between-study heterogeneity (49). Statistical significance was determined using standard permutation tests and default thresholds (49–52).

Additional sub-meta-analyses gauging hot executive functions, cool executive functions, and emotion processing were conducted on these cognitive subdomains. Insufficient fMRI studies were available for a sub-meta-analysis on pain empathic processing. Furthermore, a sub-meta-analysis was conducted on fMRI studies of disruptive behavior disorder with psychopathic traits. To examine effects of gender, age, medication, and ADHD comorbidity, meta-regression analyses were conducted. Jackknife sensitivity analyses, consisting of repeating the same analysis excluding one data set at a time, were conducted on all main and subgroup meta-analyses to establish replicability of findings. Finally, funnel plots were created to detect abnormalities, such as studies reporting opposite results, or publication bias.

RESULTS

Characteristics of Included Studies

Fifty-three high-quality functional task contrasts from 16 independent samples from 24 fMRI studies were included in the main meta-analysis. The main meta-analysis comprised 338 youths with disruptive behavior disorder or conduct problems (the disruptive/conduct problems group) (mean age, 15.2 years; mean age range, 11.9–17.7 years; 80% male) and 298 control subjects (mean age, 15.0 years; mean age range, 11.3–17.9 years; 80% male), taking overlaps into account (Table 1; see also Table S1 in the online data supplement). Five studies (four testing emotion processing and one testing pain empathic processing) assessed conduct problems dimensionally without providing a clinical diagnosis (26, 27, 32, 37, 44). Across nine studies, there were 108 participants with disruptive behavior or conduct problems and psychopathic traits and 115 healthy control subjects. Most (N=11) but not all studies (18, 26, 27, 32, 37, 43, 44) reported ADHD comorbidity rates (0%−88%; most were greater than 50%). Twenty-two hot executive function task contrasts were used to create 10 independent brain maps (171 cases, 177 controls), 10 cool executive function task contrasts created four independent brain maps (60 cases, 70 controls), and 17 emotion processing contrasts created eight independent brain maps (169 cases, 130 controls).

Main Meta-Analysis

The disruptive/conduct problems group, compared with the control group, showed significantly decreased activation in a cluster comprising the dorsal and rostral anterior cingulate and medial prefrontal cortex, extending into the supplementary motor area and ventral caudate. Case subjects, compared with control subjects, showed no significantly increased activations (Table 2A, Figure 1A, and Figure 2A).

Cognitive Subdomain Meta-Analyses

The subgroup meta-analyses showed that, compared with control subjects, youths with disruptive behavior and conduct problems across all hot executive function fMRI data sets had decreased activation in the dorsal anterior cingulate and dorso-medial prefrontal cortex extending into the supplementary motor area, along with increased right dorsal caudate activation (Table 2B, Figure 2B). Across all cool executive function fMRI data sets, they had decreased activation in the right superior and middle temporal gyrus, posterior insula, and putamen (Table 2C, Figure 2C). Across all emotion processing fMRI data sets, they had decreased activation in the right dorsolateral prefrontal cortex and left temporal pole (Table 2D, Figure 2D).

Subgroup Meta-Analysis in the Disruptive/Conduct Problems Group With Psychopathic Traits

The subgroup meta-analysis including only youths with disruptive/conduct problems with psychopathic traits showed decreased activation relative to control subjects in a cluster comprising the hypothalamus and thalamus extending into the ventral striatum and ventromedial prefrontal cortex, in addition to increased activation in the rostral dorsolateral prefrontal cortex and right dorsal caudate (Table 2E, Figure 1B, and Figure 2E).

Findings remained significant when studies with non-diagnosed youths with conduct problems were excluded.

Meta-Regression Analyses of Effects of Age, Medication, Gender, and ADHD

The meta-regression analyses showed that increasing age was associated with progressive hypoactivation in the right dorsolateral prefrontal cortex (Montreal Neurological Institute coordinates: x=50, y=28, z=36; 16 voxels), which overlapped with the reduced cluster during emotion processing; that medication was associated with increased activation in the temporal and medial frontal regions bilaterally, the cerebellar vermis, and the posterior cingulate/precuneus and with decreased activation in the cerebellar vermis, right insula, and left hippocampus (see Figure S1 in the online data supplement), none of which overlapped with any group difference clusters; that male gender was associated with lower activation (i.e., more severe dysfunction than females) in the left anterior cingulate in the disruptive/conduct problems group relative to the control group; and that ADHD comorbidity across the 11 available studies with this information was not significantly correlated with neural underactivation relative to control subjects.

Reliability Analyses

Whole-brain jackknife sensitivity analyses showed that the main meta-analysis finding in the dorso-rostral anterior cingulate, medial prefrontal cortex, and ventral caudate was robust and replicable (Table 3), as it was preserved in all but two brain map combinations. For the subgroup meta-analyses, the brain difference findings were preserved in

TABLE 2. Results of the Meta-Analysis of Whole-Brain fMRI Studies in Youths With Disruptive Behavior Disorder or Severe Conduct Problems (DBD/CP) Compared With Healthy Control Subjects Including All Tasks, by Cognitive Subdomain and Presence of Psychopathic Traits[a]

Contrast	MNI Coordinates (x, y, z)	Effect Size	95% CI[b]	Seed-Based *d* Mapping Z Score	p	Number of Voxels	Cluster Breakdown (number of voxels)
A. Main meta-analysis for all tasks							
DBD/CP < healthy controls							
Rostro-dorsal ACC/ MPFC/SMA	0, 20, 24	−0.08	−0.12, −0.04	−1.345	<0.00005	1,445	dACC: BA24/BA32 (850), rACC: BA24/BA32 (52), dMPFC: BA8/BA9 (100), rMPFC: BA9/10 (33), SMA: BA6 (12)
Ventral caudate	14, 18, 12	−0.07	−0.11, −0.03	−1.087	<0.0005	307	R caudate head ventral (152)
B. Hot executive functions							
DBD/CP < healthy controls							
dACC/dMPFC/ SMA	0, 12, 38	−0.09	−0.16, −0.03	−1.034	<0.005	335	dACC: BA24/32 (264), dMPFC: BA9/32 (58), SMA: BA6 (13)
DBD/CP > healthy controls							
Dorsal striatum (caudate)	18, 0, 26	0.11	0.06, 0.16	1.075	<0.00005	32	R caudate body dorsal (32)
C. Cool executive functions							
DBD/CP < healthy controls							
Right superior/middle temporal/insula/putamen	40, −12, −8	−0.16	−0.24, −0.16	−1.133	<0.00005	1,131	R STG: BA22 (363), R MTG: BA21 (75), R putamen (331), insula (330)
D. Emotion processing							
DBD/CP < healthy controls							
Left middle/inferior temporal/fusiform	−48, −8, −26	−0.10	−0.15, −0.05	−1.126	<0.00005	637	L ITG: BA20/BA21 (464), L MTG: BA20/BA21 (167), FG (6)
Right middle frontal	48, 26, 34	−0.11	−0.17, −0.06	−1.222	<0.00005	522	R DLPFC: BA9 (502), BA46 (20)
E. DBD/CP+PT subgroup meta-analysis for all tasks							
DBD/CP+PT < healthy controls							
Hypothalamus/thalamus/ vMPFC/ventral striatum	0, 0, 0	−0.11	−0.16, −0.05	−1.027	<0.00005	555	Hypothalamus (244), thalamus (150), VS (50), vMPFC: BA 25 (40)
DBD/CP+PT > healthy controls							
Rostral dorsolateral PFC	24, 48, 12	0.15	0.09–0.21	1.189	<0.000001	276	Rostral DLPFC (260)
Right striatum (caudate)	18, 0, 26	0.17	0.10–0.24	1.182	<0.000001	46	R caudate body (46)

[a] BA=Brodmann's area; dACC=dorsal anterior cingulate cortex; DLPFC=dorsolateral prefrontal cortex; dMPFC=dorsomedial prefrontal cortex; FG=fusiform gyrus; ITG=inferior temporal gyrus; L=left; MNI=Montreal Neurological Institute; MTG=middle temporal gyrus; PT=psychopathic traits/callous unemotional traits; R=right; rACC=rostral anterior cingulate cortex; rMPFC=rostral medial prefrontal cortex; SMA=supplementary motor area; STG=superior temporal gyrus; vMPFC=ventromedial prefrontal cortex; VS=ventral striatum.

[b] Confidence intervals estimated using the inverse of the normal distribution of the p values.

all but one or two combinations of brain maps (see Tables S2–S5 in the online data supplement).

Publication Bias

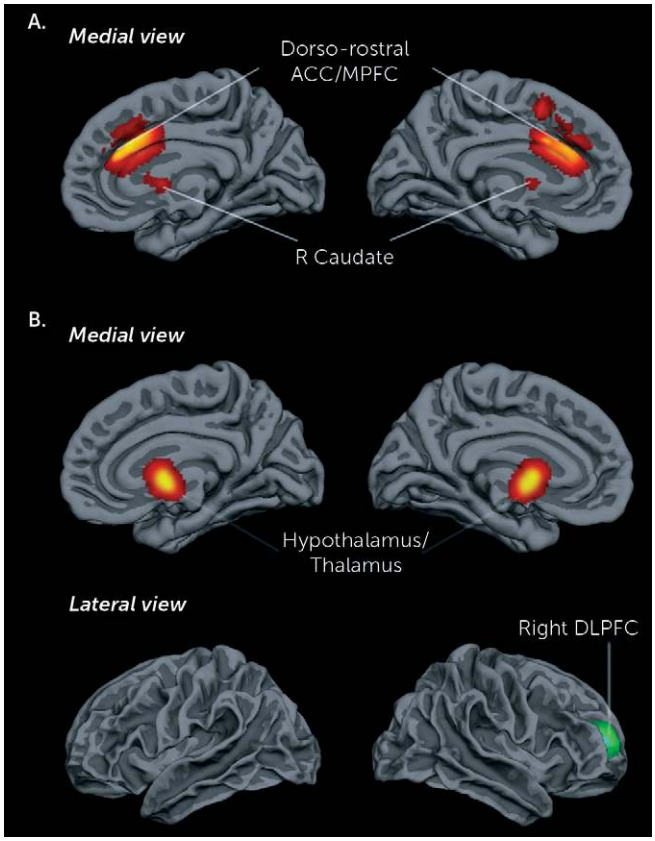
Funnel plots showed that studies with smaller sample sizes were associated with smaller effect sizes, which is opposite to the association observed in publication bias.

DISCUSSION

The meta-analysis across 53 whole-brain fMRI task contrasts showed that youths with disruptive behavior or conduct problems have the most consistent deficits in the closely interconnected dorsal and rostral anterior cingulate and medial prefrontal cortex involved in top-down regulation of motivation and affect, and in the ventral striatum, which is part of the same affect control network. The dysfunction in the dorsal and ventral medial prefrontal cortex largely arose from studies of hot executive function subdomains, suggesting that this dysfunction is associated with reward-related decision making.

The dorso-rostral anterior cingulate and medial prefrontal cortex, together with their close connections to the ventral striatum and limbic regions, lie at the interface between emotion and cognition and form part of the mesolimbic fronto-striatal dopamine pathway modulating reward processing (53), reward-based decision making, and motivation control (54). Recent meta-analyses and fMRI reviews of decision making show that both structures are crucial for

FIGURE 1. Results of the Main Meta-Analysis and of the Subgroup Meta-Analysis of Youths With Disruptive Behavior Disorder or Severe Conduct Problems With Psychopathic Traits[a]



[a] In panel A, decreased activation in youths with disruptive behavior disorder or conduct problems compared with healthy control subjects is shown in red in the dorsal and rostral anterior cingulate cortex (ACC), in the dorsal and rostral medial prefrontal cortex (MPFC), and in the supplementary motor area and ventral caudate. In panel B, decreased activation in youths with disruptive behavior disorder or conduct problems with psychopathic traits compared with healthy controls is shown in red in the hypothalamus and thalamus extending into the ventral medial prefrontal cortex and ventral striatum. Increased activation is shown in green in the dorsolateral prefrontal cortex (DLPFC). The increased dorsal caudate activation finding is not shown in Figure 1 but in Figure 2.

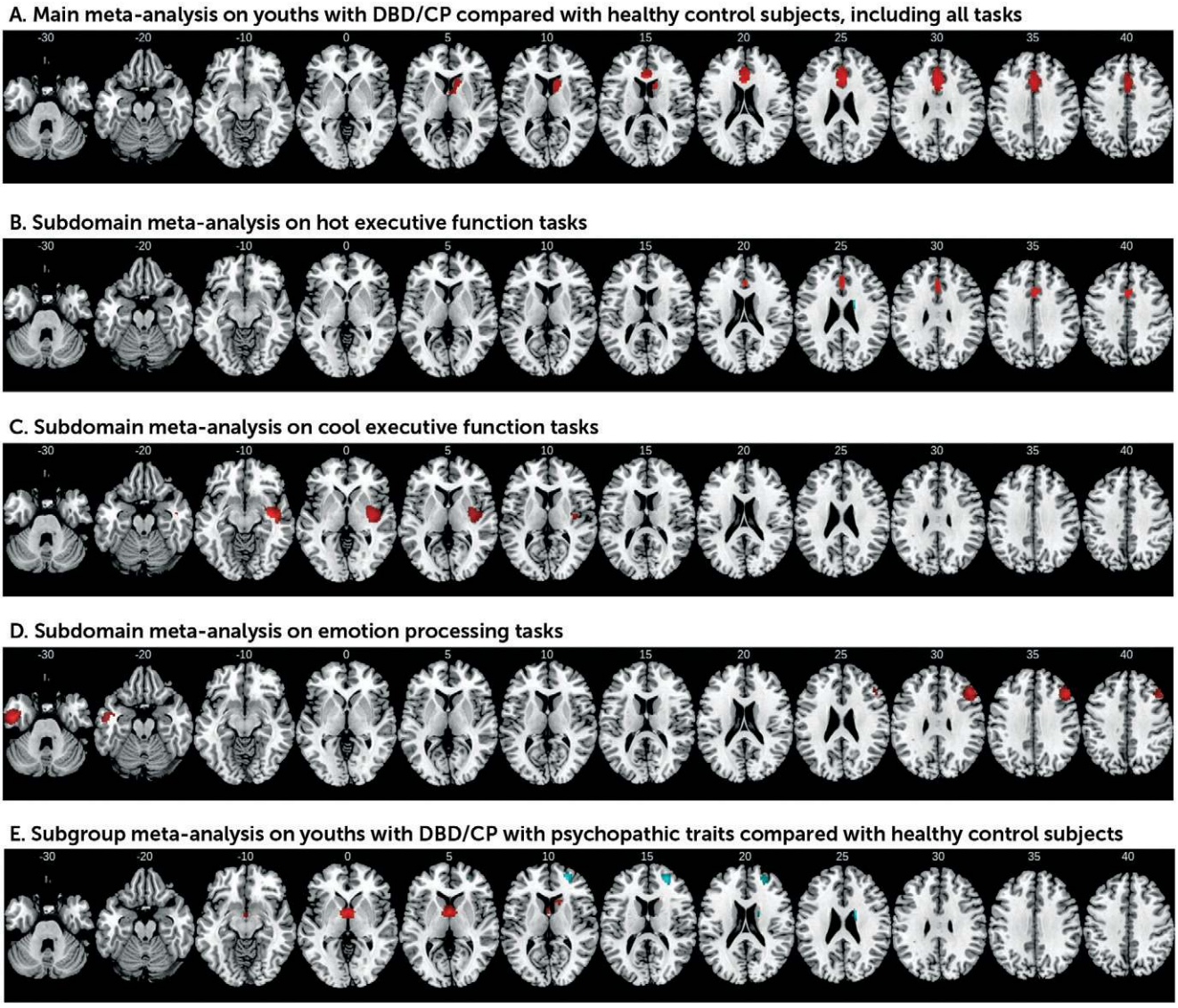
the integration of affective and reward information into cognitive processes governing decision making (55, 56), such as reappraisal (56, 57), reward-based decision making (54, 58, 59), reward processing (60), reinforcement learning (61, 62), and intertemporal choice (54, 55, 63). The dysfunction finding is parallel to two recent whole-brain structural MRI meta-analysis findings of reduced gray matter in the anterior cingulate in youths with conduct problems, and in the dorsomedial and frontopolar prefrontal cortices in youths with antisocial behavior (15, 64). This abnormality in decision making mediated by the dorsomedial and prefrontal cortices and in the reward-processing region of the ventral caudate may represent the neural underpinning for evidence that perturbed reward-based decision making is key to conduct disorder with and without psychopathic traits and is more common than perturbed empathy or threat sensitivity (65). This abnormality may contribute to the maladaptive impulsive-aggressive, norm-violating behaviors observed in this population (5), possibly due to increased frustration resulting from poor decisions that lead to reactive aggression (66). Male gender was associated with more severely decreased function of the dorsal anterior cingulate. However, this finding must be interpreted with caution because males made up more than 50% of most study populations. A caveat is that the majority of fMRI studies included in this meta-analysis tested hot executive functions, given consistent neurocognitive impairments (4, 5, 8, 65), which likely biased the findings. Future meta-analyses of a larger number of fMRI studies of emotion processing may reveal more abnormalities in the orbitofrontal and limbic regions.

The sub-meta-analysis of cool executive function revealed right superior and middle temporal dysfunction in the disruptive/conduct problems group. The temporal lobes have been suggested to be dysfunctional in neurobiological theories of conduct disorder and psychopathy (12, 67) because they are among the most consistently observed structural deficit regions (9, 14, 15, 64, 68). The temporal lobes form part of the paralimbic motivation system, and together with the amygdala, they mediate stimulus-reinforcement learning (69); hence, temporal lobe hypoactivity may reflect insufficient motivation (4). Alternatively, superior temporal regions have also been associated with attention functions (70, 71) that are affected in the disorder (3, 4).

The decreased activation of the right dorsolateral prefrontal region during emotion processing also suggests poor frontal top-down cognitive control over emotion processing, a key functional role of this region (57, 72), while reduced function of the left temporal pole may reflect impaired socio-emotional processes (73). Interestingly, older patients had more dorsolateral prefrontal dysfunction, which may suggest progressive age-related impairments. However, the reliability analysis showed that the temporal dysfunction was found only in two fMRI studies (20, 30), while dorsolateral prefrontal dysfunction was found only in the largest study (30). Unexpectedly, we did not observe abnormalities in limbic regions, such as the amygdala, during emotion processing. The amygdala is a relatively small region and is rarely observed in whole-brain studies (e.g., 36, 40); it is examined mostly in region-of-interest fMRI studies (24, 27–29, 32). Furthermore, during negative emotions, amygdala activation has been found to be decreased in conduct disorder with psychopathic traits but increased in conduct disorder without psychopathic traits (66), which may have resulted in negative findings because most included studies did not screen out individuals with psychopathic traits.

The subgroup meta-analysis findings in youths with disruptive/conduct problems and psychopathic traits differed from those in the whole group, in line with evidence for different neurological etiological mechanisms in conduct disorder with and without psychopathic traits (44, 65, 66, 74). Thus, the functional deficits in this subgroup were in the ventromedial prefrontal-limbic regions known to be involved in reward and decision making and in areas of affective reactivity, especially to negative emotions, such as the hypothalamus and thalamus (75, 76). Hypothalamus hypoactivity

FIGURE 2. Axial Sections Showing Regions That Were Significantly Reduced (Red) and Increased (Green) in Youths With Disruptive Behavior Disorder or Conduct Problems (DBD/CP) Relative to Healthy Control Subjects[a]



[a] Montreal Neurological Institute z coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.

is consistent with evidence for abnormal reactivity in the hypothalamic-pituitary-adrenal neuroendocrine system and with reduced levels of cortisol in this group (77, 78), and these levels furthermore are correlated with psychopathic traits (79, 80). The underfunctioning in the ventromedial prefrontal-hypothalamic regions, both closely interconnected with the amygdala, may play a role in the psychopathic symptoms of reduced affect, such as reduced responsiveness to threat and distress cues, lack of empathy, low anxiety levels, and guilt (65, 66, 81, 82). The ventral striatum is a key region of reward and loss processing and is thought to be at the core of psychopathic traits (83–85). The deficit findings are in line with Blair's psychopathy model (65, 66) of ventromedial prefrontal, amygdala, hypothalamus, and striatal abnormalities, with the exception that we found no amygdala underactivation. As discussed above, this may be due to the use of whole-brain fMRI analyses and a prevalence of fMRI studies of reward-based decision making. Overactivation of the rostral dorsolateral prefrontal cortex and the dorsal caudate in the disruptive/conduct problems group with psychopathic traits is in line with findings of abnormally increased caudate volumes in psychopathic adults and violent offenders (86, 87); with higher structural connectivity in cingulo-fronto-striatal tracts in adolescent arrestees, correlated with grandiose-manipulative traits (88); and with correlations between dorsolateral prefrontal hyperactivity and psychopathic traits (89). The rostral dorsolateral prefrontal cortex and caudate are involved in planning (90, 91), and enhanced activity in these regions is in line with neurocognitive studies showing no deficits in executive functions,

TABLE 3. Results of the Jackknife Reliability Analyses of the Main Meta-Analysis Findings Based on 52 Different Task Contrast Results From 16 Independent Samples[a]

Study	Contrast Included in Brain Maps	R/D ACC/PFC/SMA (MNI coordinates: 0, 20, 24)	Right Caudate (MNI coordinates: 14, 18, 12)
Herpertz et al. (31)	Negative/positive > neutral valence images	Yes	Yes
Passamonti et al. (30)	Angry/sad > neutral expression	Yes	Yes
Fairchild et al. (29)	Angry/sad > neutral expression	Yes	Yes
Marsh et al. (28)	Fearful/angry > neutral expression	Yes	Yes
Marsh et al. (40)	Positive > negative valenced objects; categorizing illegal > legal words; incongruent > congruent trials	Yes	Yes
Marsh et al. (36)	One's pain > other's pain; other's pain > one's pain	Yes	Yes
Jones et al. (27)	Fearful > neutral expression	Yes	Yes
White et al. (41)	Eye gaze task: neutral > anger expression; fear > neutral expression; fear congruent > fear incongruent; incongruent > congruent (interference effect)	Yes	Yes
Sebastian et al. (32)	Fearful eyes: (fear/eyes > calm/eyes) > (fear/face > calm/face)	Yes	Yes
Sebastian et al. (44)	Affective theory of mind > cognitive theory of mind /physical causation	Yes	Yes
O'Nions et al. (26)	Theory of mind > physical causation	Yes	Yes
Cohn et al. (38)	Fear conditioning: conditioned > unconditioned	Yes	Yes
Cohn et al. (39)	Monetary incentive delay task: reward > neutral trial anticipation; loss > neutral trial anticipation; reward hit > reward miss; loss miss > loss hit	Yes	Yes
Lockwood et al. (37)	Pain > no pain	No	No
Rubia et al. (16)	Rewarded CPT: rewarded > nonrewarded targets; nonrewarded target > nontargets	Yes	Yes
Rubia et al. (22)	Stop task: failed stop > go; successful stop > failed stop	Yes	Yes
Rubia et al. (23)	Switching task: switch trials > repeat trials	Yes	Yes
Rubia et al. (21)	Simon task: incongruent > oddball trials; oddball > congruent trial	Yes	Yes
Crowley et al. (18)	Colorado balloon game: risky decision making > instructions; winnings > no outcome; losing > no outcome	No	No
Kalnin et al. (43)	Emotional stroop: violent > nonviolent words	Yes	Yes
White et al. (19)	Choose not to open appetitive door > choose to open appetitive door; appetitive choice > physical threat choice; appetitive choice > contamination choice; physical threat > appetitive stimuli feedback; appetitive stimuli > contamination threat feedback	Yes	Yes
Finger et al. (20)	Reversal learning: punished reversal errors > rewarded correct responses	Yes	Yes
Finger et al. (17)	Passive avoidance task: early > nonearly trials; rewarded correct hits > punished commission errors; punished commission errors > rewarded correct hits	Yes	No
White et al. (35)	Emotion-attention bars task: fear > neutral expressions; high > low attentional load	Yes	Yes
Total		14/16	13/16

[a] ACC=anterior cingulate cortex; D=dorsal; MNI=Montreal Neurological Institute; PFC=prefrontal cortex; R=rostral; SMA=supplementary motor area; yes=brain region remains significantly decreased in the jackknife analysis when the independent sample in question is excluded from the meta-analysis; no=brain region is no longer significantly decreased when the independent sample in question is excluded.

or even superior executive functions, such as in planning, set-shifting, and language abilities (92–95), and it matches the defining features of proactive, planned, and goal-directed aggression (as opposed to frustration- or threat-induced reactive aggression in those without psychopathic traits) (96), as well as the ability to manipulate, cheat, and con. A dysfunctional affect and a hyperfunctional executive control system in disruptive groups with psychopathic traits provide neurofunctional support for behavioral theories of good executive functioning in the presence of dampened affect. Thus, it has been suggested that a hypoactive bottom-up affective system (reflecting reduced affective reactivity and lower anxiety), together with good top-down executive control over emotions, may lead to less emotional interference with cognitive functions, explaining superior performance in psychopathy (92–95).

However, the subgroup meta-analysis on disruptive/conduct problems with psychopathic traits should be treated with caution, as studies were heterogeneous in methods, informants, and cutoff scores for psychopathic traits. Future studies need to clearly distinguish groups with disruptive behavior disorder with and without psychopathic traits based on internationally agreed-upon, age-normalized, standardized measures from multiple informants to establish the neurofunctional underpinnings of both subtypes (97–99).

The meta-regression analyses showed that ADHD comorbidity, age, or medication had no effect on dysfunctions, suggesting that they are specific to disruptive behavior disorder. Despite evidence of dorsal anterior cingulate underfunctioning in ADHD during executive functions (4, 47), comparison between ADHD comorbid and noncomorbid with conduct disorder showed that dorsal anterior cingulate underactivation was specific to conduct disorder (4, 16). In addition, rostro-dorsal anterior cingulate dysfunction in conduct disorder in fMRI studies of emotion processing remained when ADHD was controlled for (24) and correlated specifically with conduct disorder symptoms and aggressive behavior (24, 36, 100). Structural analyses also found anterior cingulate volume to be associated with disruptive behavior disorder when ADHD was included as a covariate (101). Hence, findings of underactivation in the rostro-dorsal anterior cingulate in ADHD may be associated with commonly co-occurring antisocial features (4). Meta-analytic fMRI evidence in ADHD also suggests more prominently lateral, rather than medial, frontal underactivation during executive functions (46, 47). Alternatively, reward-based decision making, which is also impaired in ADHD (4), even if it is mostly accounted for by antisocial behaviors in dimensional analyses (8), may be a transdiagnostic endophenotype of both ADHD and disruptive behavior disorders, with a common underlying neural substrate in the dorsomedial prefrontal cortex. However, ventral striatum underactivation is also a consistent meta-analytic finding in ADHD during reward anticipation (102), based on region-of-interest studies. This dysfunction has not been observed in whole-brain meta-analyses of ADHD, which could explain the lack of association with ADHD comorbidity. Alternatively, ventral striatum dysfunction in ADHD may be associated with comorbidity with conduct disorder, which is rarely excluded in ADHD fMRI studies.

This study has a number of limitations inherent to all meta-analyses. First, meta-analyses based on peak and effect size use data from published studies rather than raw statistical brain maps, increasing the likelihood of having less accurate results (49). Second, different studies used different statistical thresholds. Third, while the voxel-wise meta-analytic method provided good control of false positive results, false negative results are more difficult to avoid, making results more conservative (49). Fourth, although substance abuse is common among youths with disruptive/conduct problems and has an important effect on brain structure and function (103, 104), many studies including youths with substance use disorder comorbidity did not report case numbers (17, 20, 27, 32, 37, 44, 100), hampering our ability to examine its effect. It is also likely that the neurofunctional substrates of patients with pure oppositional defiant disorder differ from those of patients with pure conduct disorder, and future studies should address this heterogeneity. Fifth, studies have suggested differences between early- and late-onset disruptive behavior disorders (10, 30), but there was insufficient information to conduct subtype meta-analyses. Sixth, mean age ranged only from 11.9 years to 17.7 years, and therefore the age-based meta-regression analysis should be interpreted with caution. Seventh, seed-based *d* mapping software does not directly take into account the reported cluster size, which could improve the re-creation of effect size maps. However, cluster size is indirectly accounted for through the use of cluster local peaks and the fact that cluster size depends on the height of the peaks and the local covariance between neighboring voxels. Lastly, the sub-meta-analysis of cool executive functions was relatively underpowered with only eight data sets, and 50% of the studies came from the same research group using the same 13–14 subjects, which renders the subdomain meta-analysis findings unrepresentative. Further research on cool executive functions in groups with disruptive behavior disorder or conduct problems is needed.

In summary, to our knowledge this is the first meta-analysis of fMRI studies of deficits in youths with disruptive behavior disorder or conduct problems. The meta-analysis shows that the core dysfunction in this population lies in the rostro-dorsal and medial fronto-cingulate regions that exert top-down control over interconnected limbic motivation systems (such as the ventral caudate, which is also underactivated) and that underlie reward-based decision making, which is typically compromised in the disorder. Psychopathic traits in the disorder are more prominently associated with ventromedial frontal-hypothalamic-limbic underfunctioning and dorsolateral prefrontal-striatal hyperfunctioning, which presumably reflect poor empathy and affect reactivity together with and perhaps caused by enhanced dorsolateral prefrontal-striatal top-down control. Finding dissociated neuro-functional correlates in the disruptive-behavior groups with and without psychopathic traits adds to increasing evidence for different underlying neurobiology and supports the utility of the DSM-5 callous-unemotional specifier in the classification of youths with conduct disorder. The meta-analysis findings provide potential targets for neurotherapeutic and pharmacological interventions.

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