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Archival Report

Structural Brain Connectivity in Childhood Disruptive Behavior Problems: A Multidimensional Approach

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ABSTRACT

BACKGROUND: Studies of white matter connectivity in children with disruptive behavior have yielded inconsistent results, possibly owing to the trait's heterogeneity, which comprises diverse symptoms like physical aggression, irritability, and delinquency. This study examined associations of global and specific white matter connectivity with childhood disruptive behavior problems, while accounting for their complex multidimensionality.

METHODS: In a large cross-sectional population-based study of 10-year-old preadolescents ($n = 2567$), we assessed four previously described empirically derived dimensions of disruptive behavior problems using the Child Behavior Checklist: physical aggression, irritability, disobedient behavior, and delinquent behavior. Global and specific white matter microstructure was assessed by diffusion tensor imaging.

RESULTS: Global fractional anisotropy and mean diffusivity were not associated with broad measures of disruptive behavior, e.g., Child Behavior Checklist externalizing problems scale. Global fractional anisotropy was negatively associated with delinquent behavior ($\beta = -.123$, $p_{\text{false discovery rate adjusted}} = .028$) and global mean diffusivity was positively associated with delinquent behavior ($\beta = .205$, $p_{\text{false discovery rate adjusted}} < 0.001$), suggesting reduced white matter microstructure in preadolescents with higher levels of delinquent behavior. Lower white matter microstructure in the inferior longitudinal fasciculus, superior longitudinal fasciculus, cingulum, and uncinate underlie these associations. Global white matter microstructure was not associated with physical aggression, irritability, or disobedient behavior.

CONCLUSIONS: Delinquent behavior, a severe manifestation of childhood disruptive behavior, was associated with lower white matter microstructure in tracts connecting frontal and temporal lobes. These brain regions are involved in decision making, reward processing, and emotion regulation. This study demonstrated that incorporating the multidimensional nature of childhood disruptive behavior traits shows promise in advancing the search for elucidating neurobiological correlates of disruptive behavior.

Keywords: Cerebral white matter, Conduct problems, Delinquency, Diffusion tensor imaging, Disruptive behavior disorder, Irritability

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Disruptive behavior problems, including aggression, irritability, and delinquency, are among the commonest reasons for referral to child and adolescent psychiatric services, and they greatly impact society in terms of costs, criminal convictions, and service utilization (1–3). Several studies have addressed risk factors for childhood disruptive behaviors, and some progress has been made with regard to their neurobiological background (4). Heterogeneity among childhood disruptive behavior disorders has been thought to play a role in inconclusive findings regarding their neurobiological background, particularly with respect to white matter connectivity (4,5). Surprisingly, few studies have disentangled the neurobiological underpinnings of childhood disruptive behavior problems by considering their well-known heterogeneous presentation (4,6–8).

Etiological studies of childhood disruptive behavior problems have not often investigated structural white matter networks. White matter tracts provide high-speed communication of neuronal signals between gray matter regions in the brain. White matter microstructure, which is thought to reflect white matter integrity, can be measured via diffusion tensor imaging (DTI). The few existing studies using DTI to assess the white matter networks associated with childhood disruptive behavior have yielded inconsistent results (5). Some studies observed no differences in white matter microstructure between youths with disruptive behavior and control subjects (9–11), whereas others showed that disruptive behavior was associated with both decreases (12–14) and increases (15–21) in connectivity. Findings have been observed across various white matter tracts in the brain, e.g., association tracts (including tracts connecting frontal and limbic regions), commissural tracts, and projection tracts in both hemispheres (5). It has been proposed that the small clinically referred samples and the large age range of the young people included in these studies might explain the seemingly conflicting mixed findings (5). Moreover, the presence of varying levels of distinct disruptive behaviors (e.g., physical aggression, disobedient behavior, irritability) and comorbid conditions (e.g., lower intelligence) may have contributed to the contradictory results (12). Further, comprehensive assessments of disruptive behavior problems, tailored to developmental stage of the child, are required (4,7,8).

Using factor-mixture analyses in three unreferred samples and one clinical sample of youths, we previously demonstrated four correlated dimensions of disruptive behavior problems, i.e., physical aggression, irritability, disobedient behavior, and delinquency (22). Potentially, disentangling the multidimensionality of disruptive behavior problems would aid the search for their correlates, which is particularly pertinent given that few neuroimaging studies have benefited from considering this multidimensionality (4,5). Therefore, in the current population-based neuroimaging study, we assessed the relationship between white matter microstructure and these dimensions. First, we examined the relationship between global white matter microstructure and observed broadband externalizing problems sum scores. Using structural equation modeling, we then tested the hypothesis that reduced global white matter microstructure was associated with disruptive behavior dimensions, e.g., physical aggression and delinquent behavior. Structural equation modeling allows for examination of both latent dimensions of disruptive behavior problems, which—akin to factor analysis—weighs observed items and allows uncertainty in the model using latent behavioral variables and observed white matter microstructural indices. It is therefore optimal for addressing our aims. Such refinement of behavioral phenotyping can potentially help identify underlying neurobiological mechanisms for childhood disruptive behavior problems. Moreover, simultaneously studying these dimensions in one neuroimaging study could lend neurobiological support for a dimension's validity (23). The specific tracts underlying these associations were expected to include structural connections between frontal, temporal, and subcortical structures (5,24–26), with stronger global effects expected for more severe dimensions (e.g., delinquent behavior) and weaker associations of irritability with frontolimbic connections (27).

METHODS AND MATERIALS

Study Population

This cross-sectional population-based neuroimaging study was embedded in the Generation R Study, a prospective birth cohort, which included pregnant women living in Rotterdam, the Netherlands, between 2002 and 2006 (28). The aim of the Generation R Study is to identify environmental and genetic factors influencing health, disease, and development from prenatal life onward. Study protocols were approved by the local ethics committee, and written informed consent and assent was obtained for all participants.

For the current study, data from the 10-years-of-age data collection wave were used. This examination included a research center visit, questionnaires, and a magnetic resonance imaging (MRI) assessment (28). Participants were included if data on the mother-reported Child Behavior Checklist (CBCL) and a DTI scan were available. Last, one random twin was excluded from each twin pair (n = 33), leaving a final sample of 2567 children (see Supplemental Figure S1 for the inclusion flowchart). In a subsample of 2242 children, data were available on nonverbal intelligence.

Disruptive Behavior Problems

Disruptive behavior problems were assessed with the CBCL school-age version (CBCL/6-18), a reliable and valid instrument to measure child externalizing problems over the previous 6 months (29). Individual items were summed to obtain total scores. The CBCL is generalizable across many different nationalities and societies (30) and has previously been shown to adequately identify and screen for disruptive behavior disorders (31).

To assess disruptive behavior problems, items were selected from the CBCL externalizing problems scale, and the multidimensionality of these disruptive behavior problems scores was modeled along four intercorrelated dimensions, as is described in more detail elsewhere (22). Based on clinical relevance for measuring disruptive behavior problems in preadolescent children, items were excluded following three predefined criteria: 1) did not reflect problem behavior, 2) were more indicative of behavior problems/disorders other than disruptive behavior disorders, or 3) were endorsed infrequently due to the child's young age. The following dimensions of disruptive behavior problems were modeled: 1) physical aggression, which captures problem behaviors such as fighting and physically attacking; 2) irritability, which includes items such as temper tantrums and frequent mood changes; 3) disobedient behavior, which is characterized by disobedience and lying/cheating; and 4) delinquent behavior, which comprises behaviors such as destroying things belonging to others and stealing. An overview of the individual items which loaded on these dimensions is presented in Supplemental Figure S2.

Intelligence

Child intelligence (IQ) was measured using the Snijders-Oomen nonverbal intelligence test when the children were on average 6 years of age (32), as data on IQ were not available at later ages. Considering the developmental stage of the children, this test was selected owing to its demonstrated reliability as a measure for nonverbal IQ in toddlerhood (33). These data were available in a subsample of 2242 children.

Image Acquisition

Before undergoing brain MRI, children were invited to participate in a mock scanning session to familiarize them with the procedure (34). If the child was at any point too anxious about the procedure, he or she did not progress to the actual MRI scanning.

Images were acquired on a 3T GE MR750W Discovery scanner (GE Healthcare, Milwaukee, WI) using an eight-channel head coil. The DTI scan was acquired using an axial spin echo, echo-planar imaging sequence with three b = 0 scans and 35 diffusion directions (repetition time = 12,500 ms, echo time = 72.8 ms, field of view = 240 mm × 240 mm, acquisition matrix = 120 × 120, slice thickness = 2 mm, voxel size = 2 mm × 2 mm × 2 mm, number of slices = 65, asset acceleration = 2).

Image Preprocessing

DTI image preprocessing was conducted using the FMRIB Software Library (FSL), version 5.0.9 (35), as described in more detail elsewhere (36). In short, nonbrain tissue was removed and diffusion images were corrected for eddy current–induced artifacts and translations/rotations resulting from head motion. The diffusion tensor was fitted at each voxel using the RESTORE method from the Camino diffusion MRI toolkit (37), and scalar metrics (e.g., fractional anisotropy [FA], mean diffusivity [MD]) were computed.

White Matter Probabilistic Tractography

Probabilistic white matter fiber tractography was conducted on each child's diffusion-weighted images in native space using the automated FSL plugin AutoPtx (38), to identify connectivity distributions for a number of large, commonly reported fiber bundles. Connectivity distributions were then normalized based on the number of successful seed-to-target attempts, and thresholded to remove voxels that were unlikely to be part of the true distribution. Average FA and MD values were computed for each white matter tract by weighting voxels based on the connectivity distribution (i.e., FA in voxels with higher probabilities received higher weight). For the tract-specific analyses, left and right white matter tract FA and MD values were averaged and weighted for their respective volumes, as we had no a priori hypotheses regarding the laterality of white matter tracts associated with disruptive behavior problems.

Image Quality Assurance

Diffusion image processing was conducted using DTIPrep tool (https://www.nitrc.org/projects/dtiprep/) by inspecting a combination of manual and automated checks, including examining slicewise variation in the diffusion signal, examining the sum-of-squares error of the tensor calculation, and inspecting intersubject registration accuracy.

Covariates

Statistical models were adjusted for a number of potential confounding factors. First, child age at MRI (date of birth) and sex were obtained from medical records. Child ethnicity was classified based on parental birth place and dichotomized into European (mostly Dutch, European, and North American) or non-European descent. Last, maternal education was defined by the highest attained educational level and classified into low/medium (lower and intermediate vocational training, primary school and lower) or high (higher vocational education, and university). Covariates were dichotomized because of the low percentages in separate categories as this facilitated the structural equation modeling.

Statistical Analysis

All analyses were conducted in R statistical software, version 3.3.2 (39) using the Lavaan package for structural equation modeling (40). The structural equation model was constructed as follows (Figure 1). Separately for FA and MD, multiple white matter tracts were set to load on a single latent factor that represents the global DTI measure (green dashed arrows in Figure 1). Left and right hemisphere DTI metrics (e.g., left and right uncinate FA) were allowed to covary (not shown in Figure 1), as this significantly improved model fit, in line with

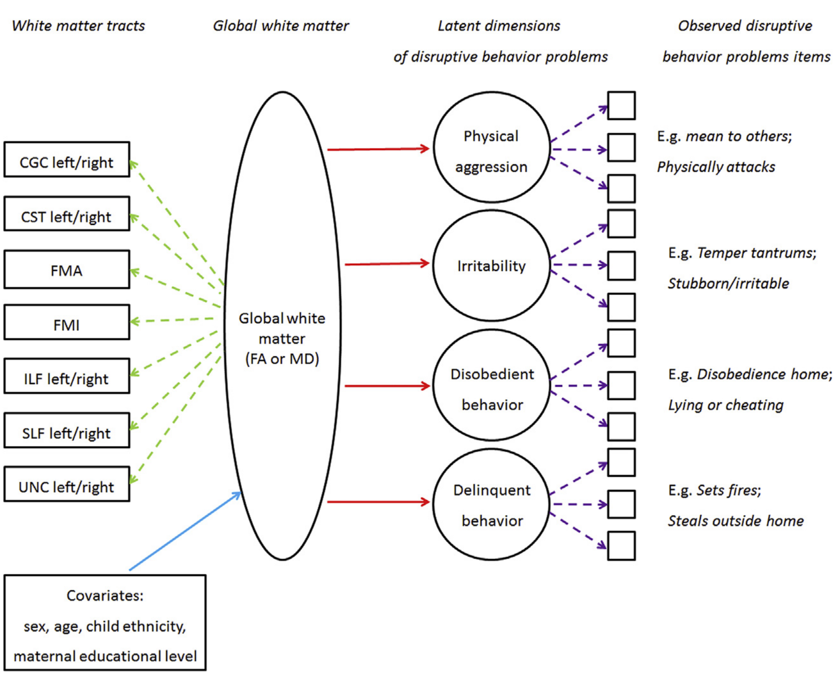

Figure 1. Outline of the structural equation model. Factor loading paths are depicted with dashed lines and structural equation regression paths are depicted with solid lines. For the sake of simplicity of the figure, the interhemispheric correlations between white matter tracts (e.g., left and right uncinate) are not shown. In addition, all four dimensions of disruptive behavior problems were allowed to correlate with one another, which is also not shown in the figure. CGC, cingulate gyrus part of cingulum bundle; CST, corticospinal tract; FA, fractional anisotropy; FMA, forceps major; FMI, forceps minor; ILF, inferior longitudinal fasciculus; MD, mean diffusivity; SLF, superior longitudinal fasciculus; UNC, uncinate fasciculus.

previous work using a similar approach (36). All CBCL items loaded on separate dimensions (latent factors) of disruptive behavior problems (purple dashed arrows in Figure 1). All CBCL raw item scores were dichotomized (i.e., scores of 1 or 2 were collapsed) to reduce the number of empty cells in bivariate frequency tables and, hence, to facilitate polychoric correlations. First, we examined the relationship between global FA and MD and each dimension of disruptive behavior problems separately (red solid arrows in Figure 1). Next, all four dimensions of disruptive behavior problems were allowed to correlate with one another to accommodate the multidimensional nature of disruptive behavior problems (not shown in Figure 1).

Initial analyses of the relationship between white matter connectivity and behavior examined whether latent constructs of global FA and MD were associated with the observed (i.e., not latent) raw scores of the CBCL externalizing problems scale, and its syndrome scales aggressive behavior and rule-breaking behavior. Next, we examined the association between global FA and MD and the dimensions of disruptive behavior problems, e.g., physical aggression and delinquent behavior. As the dimensions of disruptive behavior problems were allowed to correlate with one another, the estimates reflect the effect of global DTI indices on each distinct dimension over and above general effects on disruptive behavior problems, i.e., estimates were mutually adjusted for each distinct dimension of disruptive behavior problems. Subsequently, separate association analyses were performed between specific white matter tracts (e.g., uncinate) and dimensions of disruptive behavior problems. Finally, structural equation regression paths were adjusted for confounders (blue solid arrow in Figure 1).

In sensitivity analyses, the association between global white matter connectivity and dimensions of disruptive behavior problems were additionally adjusted for nonverbal IQ scores. Also, we repeated our analyses with the additional irritability item "sulks a lot" to tap into irritability's more tonic, persistent elements. Furthermore, the main analyses on the association between global FA and MD and dimensions of disruptive behavior problems were repeated in those children who scored in the highest decile of externalizing problems.

All structural equation models were estimated using the weighted least squares means and variances estimator because of the binary nature of the CBCL items and to account for missingness on covariates (41). Model fit was judged to be good when the following three fit metrics were satisfied: root mean square of approximation <0.05, comparative fit index >0.95, and Tucker-Lewis index >0.95. In the primary analysis, a false discovery rate (FDR) correction was applied to control for the number of dimensions of disruptive behavior in each statistical model performed in R, as this might increase type I error due to multiple testing (42).

RESULTS

Attrition Analysis

Within the group of children with CBCL data ($N = 4920$), we compared demographic covariates between the study population ($n = 2567$) and participants who did not have usable DTI data available ($n = 2353$). An overview of the flowchart and how many participants were excluded at different steps is presented in Supplemental Figure S1. The children did not differ in age (9.71 years of age vs. 9.72 years of age; $t = 1.43$, $p = .152$), sex (50.68% vs. 50.23% girls; $\chi^2_1 = 0.08$, $p = .775$), and proportion of participants of non-European ethnicity (25.04% vs. 26.60%; $\chi^2_1 = 1.45$, $p = .228$). Children who had DTI data available were more likely to have mothers with higher educational levels (65.11% vs. 59.27%; $\chi^2_1 = 16.90$, $p < .001$) and had lower CBCL externalizing problems scores (3.66 points vs. 4.17 points; $t = 3.62$, $p < .001$).

Demographic Characteristics

Descriptive characteristics of the study population are shown in Table 1. Supplemental Figure S2 demonstrates the endorsement of the CBCL items pertaining to the dimensions of disruptive behavior problems. Symptoms of the irritability dimension and disobedient behavior dimension were most commonly endorsed. Physical aggression symptoms were less frequently reported, and delinquent behavior symptoms were relatively rarely endorsed.

Associations Between Global White Matter Measures and Disruptive Behavior Problems

Global FA and MD were not associated with the CBCL broadband externalizing problems scores, or aggressive behavior or rule-breaking behavior syndrome scale scores (Table 2).

In contrast, global FA was negatively associated with delinquent behavior (Table 3) ($\beta = -.123$; $p_{\text{FDR adjusted}} = .028$), but not with other dimensions of disruptive behavior problems. Similarly, delinquent behavior was associated with global MD, in a consistent direction as reflected by a positive association ($\beta = .205$, $p_{\text{FDR adjusted}} < .001$). No other dimensions of disruptive behavior problems were associated with global MD. Model fit of the structural equation models on the association between global DTI measures and multidimensional disruptive behavior problems were good (Table 3, footnote). Sensitivity analyses with the additional irritability item "sulks a lot" led to similar results (Supplemental Table S1).

Considering the low endorsement of delinquent behavior items (range, 0.4–3.4% of the sample had high delinquent behavior items scores) (Supplemental Figure S2), we considered the possibility of outliers driving this association. Hence, a

Table 1. Descriptive Sociodemographic Characteristics of the Study Sample ($n = 2567$)

Child Characteristics	Mean ± SD or %
Age at MRI, years	10.12 ± 0.58
Female	50.68
Ethnicity	
European descent	74.96
Non-European descent	25.03
Nonverbal IQ	104.29 ± 14.53
Maternal Educational Level	
High	65.11
Medium and low	34.89

MRI, magnetic resonance imaging.

Table 2. Associations Between Global White Matter Measures and CBCL Scales

White Matter Metric	Outcome	B	95% CI	β	p	RMSEA	CFI	TLI
FA	Externalizing problems	−0.115	−0.536 to 0.306	−.012	.593	0.055	0.936	0.923
	Aggressive behavior	−0.035	−0.358 to 0.288	−.005	.830	0.055	0.937	0.924
	Rule-breaking behavior	−0.073	−0.204 to 0.058	−.024	.272	0.056	0.934	0.921
MD	Externalizing problems	0.000	−0.261 to 0.261	.000	1.000	0.072	0.916	0.899
	Aggressive behavior	−0.017	−0.217 to 0.183	−.003	.871	0.072	0.917	0.900
	Rule-breaking behavior	0.019	−0.061 to 0.099	.010	.640	0.073	0.914	0.897

Analyses are corrected for child age, child sex, child ethnicity, and maternal educational level.

CBCL, Child Behavior Checklist; CFI, comparative fit index; CI, confidence interval; FA, fractional anisotropy; MD, mean diffusivity; RMSEA, root mean square error of approximation; TLI, Tucker-Lewis index.

scatterplot of the latent global FA/MD score and the latent score of delinquent behavior is presented in Supplemental Figure S3. No outliers were observed that would give disproportionate weight to certain values in the associations between delinquent behavior latent score and global FA/MD latent scores.

Associations Between Individual White Matter Tracts and Disruptive Behavior Problems

Supplemental Table S2 shows the results of the secondary analyses between FA metrics of white matter tracts and dimensions of disruptive behavior problems, and Supplemental Table S3 shows the post hoc results of the models involving MD. Several DTI tracts were associated with delinquent behavior. In terms of FA metrics, negative associations were observed with the inferior longitudinal fasciculus (β = −.111, p = .007), superior longitudinal fasciculus (β = −.102, p = .011), and uncinate (β = −.093, p = .021). In terms of MD metrics, positive associations were observed with the cingulum (β = .118, p = .006), forceps minor (β = .094, p = .046), inferior longitudinal fasciculus (β = .148, p = .001), superior longitudinal fasciculus (β = .174, $p < .001$), and uncinate (β = .180, $p < .001$). Physical aggression was only associated with higher cingulum FA (β = .056, p = .045) and lower inferior longitudinal fasciculus FA (β = −.065, p = .023). Disobedient behavior was negatively associated with inferior longitudinal fasciculus FA (β = −.073, p = .006). Irritability was not associated with any DTI tract FA or MD score. The latter findings should be interpreted cautiously as no association was observed between global FA or MD and physical aggression, disobedient behavior, or irritability. The strengths of the associations between each individual tract FA and dimensions of disruptive behavior problems are depicted in Figure 2.

Sensitivity Analysis With Intelligence

The correlation between the delinquent behavior latent score and nonverbal IQ was low but statistically significant (r = −.078, $p < .001$). Thus, the main analyses involving global FA and MD were repeated with additional adjustment for nonverbal intelligence, and comparable results were obtained (Supplemental Table S4). Specifically, global white matter FA and MD were associated with delinquent behavior (global FA [β = −.140, p = .002], global MD [β = .244, $p < .001$]), but not with any other dimension of disruptive behavior problems.

Sensitivity Analysis in a Subset of Children at Increased Clinical Risk

We repeated our main analyses in a group of children who scored in the highest decile of the CBCL externalizing problems scale (n = 478) (Supplemental Table S5). Results in this subsample were similar to those in the full sample, where lower FA and higher MD were associated with delinquent behavior (global FA [β = −.287, $p_{FDR\ adjusted}$ = .056], global MD

Table 3. Associations Between Global White Matter Measures and Dimensions of Disruptive Behavior Problems

		Model 1 (Unidimensional)					Model 2 (Multidimensional)				
White Matter Metric	Outcome	B	95% CI	β	p	p_{adj}	B	95% CI	β	p	p_{adj}
FA	Physical aggression	−0.027	−0.132 to 0.079	−.016	.626	.889	−0.023	−0.139 to 0.089	−.013	.693	.924
	Irritability	−0.003	−0.105 to 0.099	−.002	.960	.960	−0.004	−0.114 to 0.106	−.002	.945	.945
	Disobedient behavior	−0.073	−0.193 to 0.047	−.037	.231	.616	−0.075	−0.190 to 0.050	−.038	.215	.573
	Delinquent behavior	−0.309	−0.458 to −0.160	−.174	<.001	<.001	−0.221	−0.382 to −0.060	−.123	.007	.028
MD	Physical aggression	−0.014	−0.067 to 0.039	−.014	.604	.889	−0.020	−0.078 to 0.039	−.019	.498	.924
	Irritability	−0.012	−0.069 to 0.045	−.012	.667	.889	−0.013	−0.074 to 0.048	−.012	.673	.924
	Disobedient behavior	0.003	−0.064 to 0.070	.002	.932	.960	0.003	−0.064 to 0.070	.003	.924	.945
	Delinquent behavior	0.224	0.140 to 0.308	−.211	<.001	<.001	0.219	0.129 to 0.309	.205	<.001	<.001

All analyses are corrected for child age, child sex, child ethnicity, and maternal educational level. Model 1 includes separate structural regression analyses for each dimension. In model 2 all dimensions are correlated in a multidimensional fashion. Fit indices for global fractional anisotropy (FA) are the following: root mean square error of approximation (RMSEA) = 0.023; comparative fit index (CFI) = 0.954; Tucker-Lewis index (TLI) = 0.950. Fit indices for global mean diffusivity (MD) are the following: RMSEA = 0.029; CFI = 0.979; TLI = 0.977.

CI, confidence interval; p_{adj}, false discovery rate–adjusted p value.

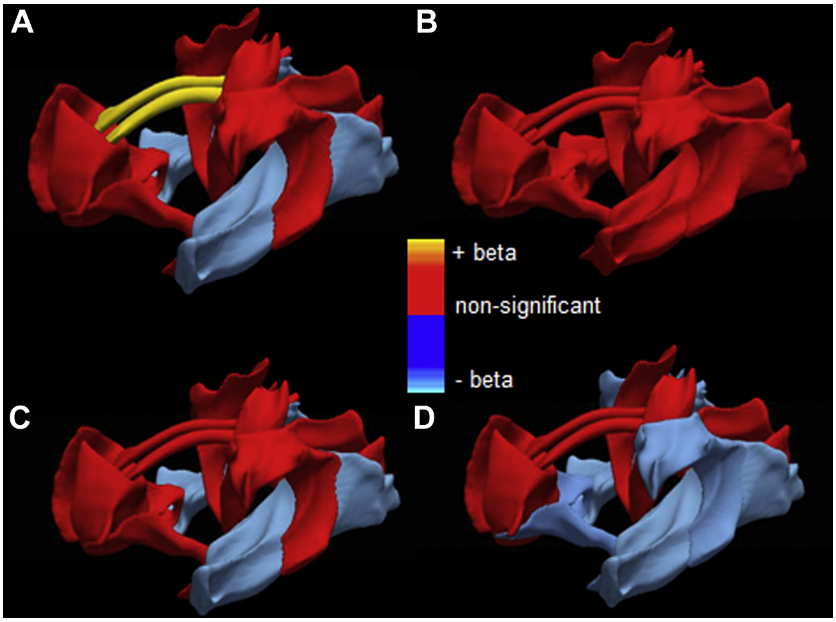

Figure 2. Associations between individual white matter tracts fractional anisotropy and dimensions of disruptive behavior problems: **(A)** physical aggression, **(B)** irritability, **(C)** disobedient behavior, **(D)** delinquent behavior. Nonsignificant associations are depicted in red, positive associations are depicted in yellow, and negative associations are depicted in blue.

[$\beta_{FDR\ adjusted}$ = .359, $p < .001$]), but not with any other dimension.

DISCUSSION

In this population-based neuroimaging study, we demonstrated that lower global FA and higher global MD, indicators of less developed white matter integrity, were uniquely associated with delinquent behavior, and not with other dimensions of childhood disruptive behavior problems, including physical aggression, irritability, and disobedient behavior. The individual white matter tracts underlying the association between reduced global white matter integrity and delinquent behavior comprised the inferior longitudinal fasciculus, superior longitudinal fasciculus, cingulum, and uncinate. These observations are in line with some previous DTI studies (12–14), but not with others (15–21). The current results should be evaluated in the context of mixed findings of prior studies (5). Against this background, these results provide empirical neurodevelopmental support for the multidimensional approach of childhood disruptive behavior problems, and underscore the importance of acknowledging the heterogeneity of child psychiatric phenotypes in the search for their (neurobiological) characteristics.

To our knowledge, this is the first study that examined whether the well-known heterogeneity of childhood disruptive behavior problems can be explained through differential structural neurobiological correlates. In contrast, we were not able to demonstrate an association between white matter microstructure and established measures of conduct problems, i.e., CBCL broadband externalizing problems, or aggressive behavior and rule-breaking problems syndrome scores. Furthermore, our main findings extended to a subset of children with high externalizing problems scores, representing a group of children at higher risk of clinical disorder. This further supports the dimensional specificity of white matter microstructure correlates associated with delinquent behavior.

Less developed global white matter microstructure was uniquely associated with delinquent behavior in this study, and not with any other dimension of disruptive behavior problems. Delinquent behavior, which consisted of behaviors such as stealing and destroying property, was relatively rarely endorsed in this sample and is indeed quite rare in preadolescent youths (6,43,44). This low prevalence notwithstanding, delinquent behavior was robustly associated with reduced global white matter microstructure, also in analyses additionally adjusted for nonverbal IQ. It could be argued that the presence of delinquent behavior at young ages is indicative of greater psychiatric problems severity, which might affect normal childhood neurodevelopment. For example, severe delinquent behaviors are associated with social learning and behavioral inhibition deficits (6), which might potentially disrupt normative white matter development. In line with this, previous work from our group showed that higher rates of early childhood externalizing symptoms at baseline were associated with smaller increases in subcortical gray matter volume and global FA over time (45). Although the current study is cross-sectional, it might be possible that the severe nature of delinquent behavior in early childhood has significant effects on childhood brain development. Against this background, as children with high scores of delinquent behaviors are at increased risk for continued antisocial behavior, substance use, and more service use in adulthood (3,6,44,46), those children who also exhibit less developed white matter microstructure could be at highest risk for these problems in adulthood. Further neurodevelopmental assessments of these children are necessary to more accurately examine the direction of associations between behavioral and neurodevelopmental trajectories.

The white matter tracts associated with delinquent behavior included frontolimbic connections involving the anterior cingulate cortex and orbitofrontal cortex, structures that have previously been implicated in reward processing and affect regulation (24). These observations are compatible with results from meta-analyses of functional and structural MRI studies (24,25), and extend observations from DTI studies using smaller samples of clinically referred youths (5,12,13), by demonstrating the involvement of various white matter tracts in delinquent behavior in preadolescents from the general population. It is surprising that in the current study irritability was not associated with variation in any white matter tract. This might be due to the population-based as opposed to clinically referred sample of this study, possibly reflecting less severe phenotypic presentations of irritability. It is has become increasingly clear that childhood irritability co-occurs with both internalizing and externalizing problems (26,47). In this study, irritability was modeled in the context of disruptive behavior problems, and potentially the neural correlates of irritability are best studied in conjunction with internalizing problems such as depression and anxiety (48,49). However, several developmental and genetic studies support the substantial association of irritability with disruptive behavior problems (22,50–52). Alternatively, the neurobiological correlates of irritability might not lie with structural white matter. Recent reviews of functional neuroimaging studies suggest that irritability is characterized by heightened external threat orientation as well as deficits in reward processing and affect regulation networks (23,26 27), but to our knowledge no study has yet examined structural white matter connectivity in association with childhood irritability. Our group and others have previously described the correlation between irritability and other dimensions of disruptive behaviors (22,23,50–53). It is possible that the observed associations between delinquent behavior and frontolimbic tracts, e.g., the uncinate and cingulum, reflect a combination of dysfunctions in affect regulation and reward processing (54), salience processing, and associative learning deficits (55). These interrelated processes have similarly been associated with other dimensions of disruptive behavior, including, but not limited to, delinquent behavior and irritability (4–6,24–26,45,56).

This study's strengths included its large population-based sample, advanced structural equation modeling strategy to accommodate the multidimensional characteristics of disruptive behavior, and prospective assessments of behavior problems and intelligence. However, several limitations should be noted. First, this was a cross-sectional study, and it is therefore not possible to infer causality from the associations found between white matter microstructure and dimensions of disruptive behavior problems. Although it is generally assumed that neurobiological abnormalities underlie psychiatric problems or disorders, recent research shows that the relationship between these might actually be bidirectional (45). Second, children with higher scores on CBCL externalizing problems were less likely to have useable DTI data, which might have affected the current findings. However, although attrition influences prevalence, it seems that attrition typically only marginally affects the validity of association analyses in population-based studies (57). Furthermore, our results extended to a subsample of children with high scores of disruptive behavior problems. Third, it would have been optimal to have concurrent assessments of IQ, disruptive behavior, and DTI, but IQ was only examined at 6 years of age in this study population. However, intelligence is moderately stable during childhood (58), supporting our analyses with additional adjustment for IQ at 6 years. Last, relying on the CBCL to generate an irritability domain might not have adequately captured both irritability's tonic and episodic elements. However, sensitivity analyses with additional irritability items led to similar results, and these items are comparable to those used previously (52,59–61) and to those included in more detailed assessments such as the Affective Reactivity Index (62,63).

These limitations notwithstanding, our findings demonstrate that employing a multidimensional approach is advantageous in the search for neurobiological correlates of childhood disruptive behavior problems. We observed a negative association between global white matter microstructure and delinquent behavior, a relatively severe presentation of disruptive behavior at this developmental stage. The individual white matter tracts underlying this association included structural connections between frontal and limbic brain regions, which reciprocally connect the amygdala to prefrontal cortices. These findings provide novel clues on behavior-specific neurobiological characteristics of childhood disruptive behavior problems in the general population. These findings might aid the development of future etiologic research of early life disruptive behavior. This is needed considering the relatively strong associations between white matter microstructure and delinquent behavior observed at such a young age. This also suggest that early screening for delinquent behavior in high-risk populations might be necessary to prevent the development of severe antisocial behavior later in adolescence. Investigations of strategies that have shown increases in daily life functioning and brain structure, such as daily physical training (64), music training (65), mindfulness meditation (66), and other related interventions, should all be further investigated as candidate therapies for improving neurodevelopmental outcomes in at-risk children.

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