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Patterns of Cortical Thickness and the Child Behavior Checklist in Childhood Epilepsy

Kevin Dabbs, MS¹, Jana E. Jones, PhD¹, Daren C. Jackson, PhD¹, Michael Seidenberg, PhD², and Bruce P. Hermann, PhD¹

¹Department of Neurology, University of Wisconsin School of Medicine and Public Health, Madison WI

²Department of Psychology, Rosalind Franklin School of Medicine and Science, North Chicago IL

Abstract

The purpose of this investigation was to characterize the neuroanatomical correlates (cortical thickness) of variations in parent reported Child Behavior Checklist (CBCL) scores. 90 children with epilepsy (age 8–18) underwent brain MRI and their parents completed the CBCL. Freesurfer-derived measures of cortical thickness were examined in relation to the CBCL broad and narrow band competence and behavioral problem scales, as well as the newer DSM-oriented scales. Parent reports of higher (better) social competence skills were associated with increased cortical thickness, especially in frontal regions. Parent reports of behavioral problems were associated with patterns of decreased cortical thickness that varied as a function of the specific behavioral issue under investigation. Congruence of patterns of cortical thinning between the DSM-oriented scales and conceptually related specific problem scales (e.g., ADHD Problems with Attention Problems) was generally weak. The parent report version of the CBCL is associated with variations in cortical thickness among children with epilepsy. Anatomic abnormalities specific to selected competence and behavioral problem scales can be identified, with more reliable and robust patterns of thinning across scales assessing externalizing behaviors, with generally less prominent findings on scales assessing internalizing behaviors.

Keywords

epilepsy; children; behavior; CBCL; Freesurfer; cortical thickness

Introduction

The Child Behavior Checklist (CBCL)[1, 2] is a standardized behavioral inventory that has been used extensively to characterize diverse behavioral problems and aspects of social competence in youth with epilepsy. A large body of research has appeared during the past 30 years using the CBCL to address the risk of behavioral problems in childhood epilepsy compared to healthy controls and other illness groups [3], the natural history of behavioral problems in youth with epilepsy including their status at or before the time of recurrent

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Correspondence to: Kevin Dabbs, MS, Department of Neurology, UW Medical Foundation Centennial Building, University of Wisconsin School of Medicine and Public Health, 1685 Highland Avenue, Madison WI 53705-2281.

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seizure onset [2, 4], the course of behavioral problems over time [5–7], and the relative behavioral risk across diverse pediatric epilepsy syndromes [8–10]. The CBCL has also been used to examine the effect of treatments including AEDs [11] and epilepsy surgery [12, 13], the impact of epilepsy on the affected child's siblings [14], and the impact of diverse epilepsy-related comorbidities such as sleep disruption on daytime behavior [15, 16]. Other research has focused on psychometric issues such as potential item invalidity when used with illness groups such as epilepsy [17, 18] and the validity of the CBCL to "gold standard" diagnostic instruments such as the K-SADS [19]. An independent but related line of research has focused on the CBCL total competence scales and the predictors of intact or problematic social skills, activities and school performance [20–22]. The CBCL continues to be translated into different languages [23] which adds to an already extensive international literature, facilitating scientific and clinical communication.

To date only a small number of papers have examined the relationship between measures of cortical anatomy (cortical thickness) and behavior problems and competence measures defined by the CBCL in pediatric populations in general [24–27], and we know of no such investigation in children with epilepsy. This is somewhat unexpected given the extensive literature addressing the underlying neuroanatomical correlates of neuropsychiatric disorders in adults and children [28].

In the current study, we performed a broad analysis of CBCL behavioral problem and competence scales, examining patterns of gray matter thickness across the cortical mantle. By examining diverse CBCL scales in the same cohort of research participants and using identical image processing techniques across all scales, a unique opportunity existed to characterize the neuroanatomical significance of the CBCL for childhood epilepsy.

Because we used the parent completed version of the CBCL, we hypothesized that patterns of cortical abnormality would be more reliably evident for externalizing problems (e.g., oppositional defiant, rule breaking, attention) which tend to be associated with more observable behaviors compared to internalizing problems which are linked more to the child's internal affective experiences (e.g., anxiety) that may be more difficult for parents to reliably assess [29]. Furthermore, by including the DSM-oriented scales we were able to examine the reproducibility of findings for those scales compared to closely related specific problem scales (e.g., DSM-oriented ADHD Problems compared to Attention Problems).

Methods

Participants

Research participants consisted of children with recent-onset epilepsy (n=90). All participants were aged 8–18 years and attended regular schools. They were recruited from pediatric neurology clinics at three Midwestern medical centers (University of Wisconsin-Madison, Marshfield Clinic, Dean Clinic). Initial inclusion criteria were a diagnosis of epilepsy within the past 12 months, no other developmental disabilities or neurological disorders, normal neurological examination and normal neuroimaging (MRI or CT). The medical records for all potential participants were first reviewed by the study coordinator to screen for inclusion and exclusion criteria. Those potential participants who appeared to meet all study criteria then underwent another round of review by the research pediatric epileptologist to confirm that potential participants had idiopathic epilepsies, provide independent confirmation of syndrome diagnosis, and ensure that other clinical criteria (e.g., normal neuroimaging, absence of other neurological or neurodevelopmental disorders) were met. Neuroimaging for the epilepsy participants was performed as part of routine clinical care. The reports, and when needed the actual scans, were reviewed by the research pediatric epileptologist who assessed study inclusion and exclusion criteria. Potential epilepsy

participants with lesions were excluded at that point. In addition, all research MRIs were read by an independent neuroradiologist as mandated by the IRB process and any incidental findings were brought to our attention. 44 females and 46 males participated in the study, with a mean age of 12.69 years ($SD = 3.38$), mean grade level of 6.57 ($SD = 3.40$), and mean full-scale IQ of 101.06 ($SD = 13.52$). 46 participants had localization-related epilepsy vs. 44 with idiopathic generalized epilepsy; mean age of disease onset was 11.86 ($SD = 3.44$). Two participants were taking 2 anti-epileptic drugs (AED's) at the time of testing, while 76 were taking one AED, and 12 were not currently taking an anti-epileptic medication. This study was reviewed and approved by the Institutional Review Boards of all collaborating institutions. On the day of study participation families and children gave informed consent and assent and all procedures were consistent with the Declaration of Helsinki [30].

Procedures

As part of their research visit, children with epilepsy underwent a standard protocol involving neuropsychological and behavioral testing and neuroimaging including structural MRI. Parents underwent a clinical interview and completed questionnaires to characterize their child's neurodevelopmental, behavioral, medical, familial, educational and seizure history. All pertinent medical records were obtained after signed release of information was obtained from the parent. The parent accompanying the child to the research visit completed the Child Behavior Checklist for children age 6–18 (CBCL/6–18) from the Achenbach System of Empirically Based Assessment (ASEBA) [2]. The dependent variables of interest included: a) overall CBCL/6–18 years summary scales and their components including Total Competence and the Activities, Social, and School scales; Total Problems and its Total Internalizing and Total Externalizing scales, b) the CBCL/6–18 syndrome scales including Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule Breaking Behavior, and Aggressive Behavior, and c) the CBCL DSM oriented scales including Affective Problems, Anxiety Problems, Somatic Problems, ADHD Problems, Oppositional Defiant Problems, and Conduct Problems.

Regarding the DSM oriented scales, Achenbach & Rescorla (2001) constructed scales for scoring the CBCL forms using items that experienced psychiatrists and psychologists judged to be very consistent with several DSM categories. Procedurally, forms were constructed for rating the consistency of each behavior problem item of the CBCL with 8 DSM-IV diagnostic categories. A total of 22 highly experienced child psychiatrists and psychologists from 16 cultures rated each item as *not consistent*, *somewhat consistent*, and *very consistent* with target DSM-IV diagnostic category. Items that were rated as *very consistent* by at least 14 of the 22 raters (64%) were deemed to be sufficiently consistent with DSM categories, resulting in the DSM-oriented scales titled Affective Problems, Anxiety Problems, ADHD Problems, Conduct Problems, Oppositional Defiant Disorder, and Somatic Problems. The DSM-oriented scales were normed on the same national sample as the empirically-based scales (Achenbach & Rescorla, 2001) scales.

MRI acquisition

Images were obtained on a 1.5T GE Signa MRI scanner (GE Healthcare, Waukesha, WI, U.S.A.). Sequences acquired for each participant were T1-weighted, three-dimensional (3D) spoiled gradients recall (SPGR) using the following parameters: TE = 5ms, TR = 24ms, flip angle = 40 degrees, NEX = 1, slice thickness = 1.5mm, slices = 124, plane = coronal, field of view (FOV) = 200mm, matrix = 256×256 . All MR images were inspected before image processing. Image quality was rated from 0 – 4 (with 4 being the highest quality images) scale and we required a minimum quality score of 3 for the scan to be included in the analysis.

MRI processing

Images were transferred to a Mac OSX (Apple Inc., Cupertino, CA, U.S.A.) computer for processing with the FreeSurfer image analysis suite, which is documented and freely available for download online (<http://surfer.nmr.mgh.harvard.edu/>). FreeSurfer is a set of software tools for the study of cortical and subcortical anatomy. The T1 volumetric MRI scans were used for cortical reconstruction and volumetric segmentation. The technical details of these procedures are described in prior publications [27, 31–37]. Briefly, this processing includes removal of nonbrain tissue using a hybrid watershed/surface deformation procedure [35], automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) [38, 39], intensity normalization [40], tessellation of the gray matter-white matter boundary, automated topology correction [32, 41], and surface deformation following intensity gradients to optimally place the grey-white and gray-cerebrospinal fluid (CSF) borders at the location where the greatest shift in intensity defines the transition to the other tissue class [27, 31, 33].

After establishment of the white matter and pial surfaces, voxel-wise measurements of cortical thickness, area, volume and curvature are generated. Thickness is calculated as the closest distance from the gray-white boundary to the grey-CSF boundary at each vertex on the tessellated surface [33]. Gyrus and sulcal features are then used to delineate surface curvature. Comparison of surface measures across subjects is possible after surface inflation [42], and registration to a spherical atlas, which uses individual cortical folding patterns to match cortical geometry across subjects [43]. The spherical atlas naturally forms a coordinate system in which point-to-point correspondence between subjects can be achieved. Mean thickness differences between groups can then be displayed on the pial surface of the standard atlas.

The reported data were produced using the FreeSurfer 5.1 default processing stream (recon-all -all). Data were visually inspected, and manual interventions were performed when the automated steps reported errors. These included manual alignment to the Talairach template in cases where automated registration was poor, and adjustments to the watershed threshold to restore areas of the brain that were erroneously removed during skull stripping. Occasional editing of the gray matter and white matter segmentation image was completed when defects were evident.

Data Analyses

Analyses focus on the relationship between the behavioral variables and cortical thickness in the participants with epilepsy. For cortical measurements, we performed a surface based group analysis using FreeSurfer's statistical tool Qdec. The participants' surface data were smoothed to improve intersubject averaging with a 15 mm full width half maximum (FWHM) Gaussian kernel. Age and gender were modeled as covariates for all measures. To correct for multiple comparisons, a Monte-Carlo simulation was implemented with an initial cluster-forming threshold set to a $p < 0.05$. Clusters were then tested against an empirical null distribution of maximum cluster size built using synthesized Z distributed data across 10,000 permutations, producing cluster wise p-values (CWP) fully corrected for multiple comparisons.

Results

Figures 1–3 provide cortical thickness maps for those CBCL scales where significant age- and genderadjusted cluster-corrected findings were obtained. Table 1 summarizes the

significant cortical clusters that were identified for each of the scales depicted in Figures 1–3.

Total Competence

Figure 1 shows that higher scores (indicating better competence ratings) were associated with increased cortical thickness for the Total Competence, Activities and Social scales. As shown in Table 1, increased thickness in the left superior frontal lobe was associated with higher (better) scores across all scales; increased thickness in the left postcentral gyrus was associated with higher Total Competence and Activities scores; and increased thickness in the left insula and left lateral occipital regions, as well as left superior frontal region and right pars triangularis (inferior frontal gyrus) were associated with higher ratings on the Social scale. There were no significant relationships between cortical thickness and the School scale.

Summary Behavior Problem and Syndrome Scales

Figure 2 shows that higher scores (more problematic behavioral ratings) were associated with decreased cortical thickness across summary scales including Total Problems and Total Internalizing. As shown in Table 1, decreased cortical thickness in the left inferior parietal region was associated with higher scores for both scales, with additional decreased cortical thickness in the left pars operularis (inferior frontal gyrus) and right supramarginal gyrus for Total Problems, and right lateral occipital lobe for Total Internalizing. As these are composite scores summed across specific behavior problem scales, we hypothesized that more specific structure—function relationships might be observed when examining the specific behavior problem scales which are reported below. There were no significant relationships between cortical thickness and Total Externalizing.

Higher scores (indicating more problematic behavioral ratings) were associated with decreased cortical thickness across several CBCL syndrome scales including Withdrawn/Depressed, Thought Problems, Attention Problems, and Rule Breaking. As shown in Table 1, higher Withdrawn/Depressed scale scores were associated with significantly decreased cortical thickness in the left caudal anterior cingulate and the right lateral occipital regions. Higher Thought Problems scale scores were associated with significantly decreased cortical thickness in the right superior temporal gyrus and lateral occipital areas; and the left transverse temporal and lateral occipital regions. Higher Attention Problems scale scores were associated with significantly decreased cortical thickness in the left and right superior frontal regions; right rostral middle frontal gyrus, caudal middle frontal gyrus, posterior cingulate, and fusiform gyrus; and the left inferior parietal lobule. Higher Rule Breaking scale scores were associated with significantly decreased cortical thickness in areas of the left and right caudal middle frontal gyri; left and right inferior parietal lobules; and right posterior cingulate. There were no significant areas of significantly decreased or increased cortical thickness for the Anxious/Depressed, Somatic Complaints, or Aggressive Behavior scales.

DSM scales

As shown in Figure 3 and specified in Table 1, increasing Affective Problem scores were associated with significantly decreased cortical thickness in the left precuneus. Increasing Anxiety Problems were associated with decreased cortical thickness in the left superior parietal gyrus. Increasing Somatic Problems scores were associated with decreased cortical thickness in the right lateral occipital region. A greater range of decreased cortical thickness was observed in relation to ADHD Problems, including the left superior frontal and lateral occipital regions in addition to right fusiform gyrus. Higher Oppositional Defiant Problems scale scores were associated with significantly decreased cortical thickness in the left caudal

middle frontal and superior frontal lobe regions and right postcentral gyrus. Increasing Conduct Problems scale scores were associated with significantly decreased cortical thickness in the left superior frontal region, left inferior frontal gyrus [pars triangularis], right inferior parietal lobule, right posterior cingulate and right caudal middle frontal regions.

Discussion

This study addressed the neuroanatomical correlates (cortical thickness) of parent-rated CBCL social competence and behavioral problem scales for their children with epilepsy. The CBCL has been used for 30+ years to assess behavioral problems and dimensions of social competence in children with epilepsy, but the degree to which it is associated with and reflects variations in neuroanatomy has remained underexplored. A modest number of investigations have examined the anatomical correlates of specific CBCL behavioral problem scales in healthy controls or other medical conditions [24–27], but to our knowledge this is the first investigation to address the issue comprehensively in youth with epilepsy. We canvassed the Total Competence, Total Problems, and DSM-oriented scales using an identical image processing and analytic approach, characterizing patterns of association (increased and decreased thickness) in a search for localized and lateralized anatomic associations with parent-reported observations. The following represent the core findings.

First, all but four CBCL scales revealed patterns of anatomic variation linked to parent report of their child's behavior. Brain-behavior associations were observed when assessing aspects of social competence, behavioral problems, and several of the DSM oriented scales. Clearly, parent reports of their children's behavior, as structured and assessed by the CBCL, are reflected in variable patterns of cortical thickness.

Second, across the CBCL scales there was a directional trend in that increasing competence ratings were associated with patterns of increased cortical thickness, while higher behavior problem ratings were associated with decreased cortical thickness. There was no instance where increased cortical thickness was linked with behavioral problems or where decreased cortical thickness was associated with better competence.

Third Figures 1–3 and Table 1 provides specifics regarding the localization and lateralization of cortical thickness findings with CBCL competence and behavioral rating scales. Regarding the Total Competence scales (Total Competence, Activities, Social), increased thickness especially in the left superior frontal lobe was associated with higher (better) scores across all scales; increased thickness in the left postcentral gyrus was associated with higher Total Competence and Activities scores; and increased thickness in left insula and left lateral occipital regions, as well as left superior frontal region, was associated with higher ratings on the Social scale. While Table 1 and Figures 1–3 characterize the patterns of decreased cortical thickness for individual CBCL behavior problem scales, interesting trends emerge when examining *patterns* of decreased cortical thickness across types of behavior problems. Specifically, *disruptive behaviors* (i.e., attention problems, rule breaking, oppositional defiant problems, conduct problems) were, as a group, associated with decreased cortical thickness in *bilateral* superior frontal, caudal middle frontal, and inferior parietal regions; with lateralized findings in the left superior frontal and right posterior cingulate and fusiform gyri. The prominence of broad frontal lobe decreased cortical thickness in these behavioral issues is noteworthy given the important role of the frontal lobes in attention and development of behavior/cognitive control via top-down regulation of subcortical brain structures in childhood and adolescence (for a review., [44]). In contrast, we found that *internalizing behaviors* (i.e., total internalizing and affective

anxiety, and somatic problems) were associated with a different set of anatomical findings with much less frontal involvement with few bilateral findings. The one exception to this trend was the association between decreased cortical thickness of the left caudal anterior cingulate cortex, a region known to be involved in self-regulation [45] with connections to several rostral anterior cingulate and frontal regions associated with depression, and scores on the Withdrawn/Depressed scale (e.g., [46]). More generally, the specific internalizing behavior scales as a group tended to yield limited effects (e.g., affective problems, anxiety problems) which could be due to the possibility that parents may not be especially informed about their child's internal feelings and thoughts [29].

Fourth, there were instances where patterns of cortical thickness were unanticipated (e.g., decreased lateral occipital thickness with increasing Internalizing Problems scores). Because this is the first systematic characterization of patterns of cortical thickness associated with the CBCL, a firmer grasp of anatomic signal from noise will come from similar attempts in the future. That said, our approach was rigorous in terms of patient selection, image quality, and analytic procedures.

Finally, the DSM oriented scales are newer additions to the CBCL and how they relate and compare to established scales remains to be clarified. We found that there were instances where notably different anatomic patterns existed when scales assessing similar behavioral problems were examined (e.g., ADHD Problems versus Attention Problems). Here the patterns of cortical thinning were more limited for the former.

Limitations and future directions

It should be remembered that we used only the parent report form of the CBCL in this investigation. It would be optimal to use behavioral ratings from several sources including not only parents but also teachers and perhaps the self-report of the children themselves. But use of the parent form has been a very frequent and traditional style of investigation in this literature and our examination here informs that approach. It remains to be determined whether anatomic findings would vary with other raters or sources of information (e.g., parent versus teachers), the degree of consistency across multiple raters, and how these patterns would compare to youth self-report.

The results presented here were obtained through examination of children with new/recent onset epilepsy. A limited number of studies have used the CBCL in the study of youth with new onset epilepsy [2, 4, 5, 47, 48]. Across those studies the results have consistently indicated more problems in youth with epilepsy compared to controls, even prior to AED initiation [2, 4, 48]. It remains to be determined whether the presence of behavioral problems or their associated anatomic patterns have implications for prospective neurodevelopmental processes or behavioral course.

Lastly, we examined a moderately sized but mixed epilepsy group. In the future, with larger numbers of children within distinct syndrome groups, we will be in a better position to determine the generalizability of findings across specific epilepsy syndromes. We have purposely limited the focus of this investigation to the anatomic correlates of CBCL performance. Many interesting issues remain to be investigated including patterns of cortical thickness and volume across epilepsy syndromes, the effects of clinical seizure factors (e.g., duration of epilepsy, AEDs) on anatomy, and other important clinical and theoretical concerns in the childhood epilepsies.

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Highlights

- The anatomical correlates (cortical thickness) of the CBCL were examined.
- Total Competence scales are associated with increased cortical thickness.
- Behavior problems are associated with decreased cortical thickness.

**Total
Competence**

Activities

Social

Figure 1.
Competence Scales

Total Problems

**Internalizing
Problems**

**Withdrawn/
Depressed**

**Thought
Problems**

**Attention
Problems**

Rule Breaking

Figure 2.
Syndrome Scales

Affective Problems

Anxiety Problems

Somatic Problems

ADHD Problems

**Oppositional Defiant
Problems**

Conduct Problems

Figure 3.
DSM Oriented Scales

Table 1

Regions of Cortical Thickness Associated with Behavioral Ratings

CBCL Scale	Anatomical regions	Cluster size(mm ²)	P corrected	Tal. Coord.(x,y,z)
Total Competence	Left post central	3684.43	0.00010	-51.9 -15.7 38.5
	Left superior frontal	7155.06	0.0001	-10.8 8.4 60.0
	Right precentral	2046.85	0.0042	55.2 -0.6 11.2
Activities	Left post central	2068.31	0.0022	-50.4 -17.3 39.9
	Left superior frontal	3599.26	0.0001	-8.7 8.3 60.9
	Right inferior parietal	1500.85	0.0356	43.3 -64.7 9.7
Social	Left insula	4178.02	0.0001	-35.7 -13.1 18.9
	Left superior frontal	2326.24	0.0007	-13.6 1.0 62.6
	Left lateral occipital	1435.10	0.0290	-46.6 -76.0 10.2
	Right pars triangularis	1464.94	0.0403	54.0 24.5 7.7
Total Problems	Left inferior parietal	3089.26	0.0001	-33.9 -80.6 18.5
	Left pars opercularis	1430.39	0.0295	-34.8 9.1 22.0
	Right fusiform	1426.55	0.0463	30.8 -70.3 -7.5
	Right supramarginal	1476.13	0.0389	54.3 -18.7 16.6
Internalizing Problems	Left inferior parietal	2996.57	0.0002	-36.0 -81.9 20.3
	Right lateral occipital	1406.76	0.0499	32.6 -88.8 -6.9
Withdrawn/Depressed	Left caudal anterior cingulate	2231.93	0.0013	-10.2 6.3 34.0
	Right lateral occipital	2037.41	0.0043	42.2 -76.6 -7.0
Thought Problems	Left transverse temporal	1311.45	0.0471	-45.7 -18.9 5.5
	Left lateral occipital	1935.54	0.0047	42.8 -76.0 -7.0
	Right superior temporal	1822.43	0.0095	39.1 -31.5 12.3
	Right lateral occipital	1611.3	0.0234	42.8 -76.0 -7.0
Attention Problems	Left superior frontal	2117.27	0.0018	-16.4 49.3 27.9
	Left inferior parietal	1742.06	0.0086	-32.3 -78.6 17.5
	Right fusiform	2135.08	0.003	33.3 -66.0 -9.1
	Right posterior cingulate	1981.06	0.0053	7.4 2.7 36.7
	Right caudal middle frontal	1646.59	0.0203	29.9 9.6 46.3
	Right superior frontal	1510.48	0.0343	14.3 22.4 49.6
	Right rostral middle frontal	1941.94	0.006	38.4 40.2 15.1
Rule Breaking	Left caudal middle frontal	1742.36	0.0086	-33.4 14.0 25.3
	Left inferior parietal	3941.74	0.0001	-41.5 -63.5 26.5
	Right caudal middle frontal	1732.81	0.0141	31.2 20.2 41.4
	Right inferior parietal	2689.91	0.0003	48.7 -43.8 36.5
	Right posterior cingulate	1637.17	0.0213	7.4 -0.3 37.9
Affective Problems	Left precuneus	1666.16	0.0172	-12.6 -51.6 32.9
Anxiety Problems	Left superior parietal	2104.39	0.0037	-16.3 -48.4 58.2

CBCL Scale	Anatomical regions	Cluster size(mm ²)	P corrected	Tal. Coord.(x,y,z)
Somatic Problems	Right lateral occipital	1662.42	0.0192	30.1 -90.5 -7.2
ADHD Problems	Left superior frontal	1884.56	0.0054	-16.4 48.9 28.6
	Left lateral occipital	1854.81	0.0061	37.9 -85.3 -3.2
	Right fusiform	2151.92	0.0028	35.4 -63.3 -10.0
Oppositional Defiant Problems	Left caudal middle frontal	1802.65	0.0111	-36.5 18.6 26.8
	Left superior frontal	1429.2	0.0404	-10.3 38.7 20.8
	Right postcentral	1442.51	0.0439	57.9 -13.6 18.6
Conduct Problems	Left superior frontal	1686.45	0.0108	-9.7 35.7 23.5
	Left pars triangularis	1641.95	0.0127	-51.8 27.4 4.9
	Right inferior parietal	1848.01	0.0088	44.5 -61.0 30.9
	Right posterior cingulate	1954.63	0.0059	6.7 -0.3 37.8
	Right caudal middle frontal	1634.29	0.0213	40.7 15.0 42.8