Published in final edited form as:

Epilepsy Res. 2014 May ; 108(4): 692–700. doi:10.1016/j.epilepsyres.2014.02.003.

Regional brain volumes and cognition in childhood epilepsy: Does size really matter?

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Abstract

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Disclosures

Dr. Berg has received travel funding and honoraria from Eisai, the British Pediatric Neurological Association, and the Epilepsy Research Center (Melbourne); travel funding from UCB, the American Epilepsy Society and the International League Against Epilepsy; awards from the American Epilepsy Society and British Pediatric Neurological Association; and consulting fees from Dow Agro Science. She serves on the Editorial Boards of *Epileptic Disorders* and *Epilepsy & Behavior*. She is past Chair of the ILAE's Commission on Classification and Terminology, Current Chair of the ILAE's Task Force on Classification-Diagnostic Manual, Member of the ILAE's Pediatric Commission's Task Force on Autism, Member of the AES's Commission on Nonepileptic Seizures, Member ad hoc Task Force of the ILAE Commission on Therapeutic Strategies, member of the AES Suicidality Task Force, and Steward for the NINDS Benchmarks in Epilepsy Research.

Dr. Jackson serves on a scientific advisory board for Neurosciences Victoria and receives royalties from the publication of "Magnetic Resonance in Medicine, 2nd ed." (Elsevier 2005).

The remaining authors have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Contributors

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Purpose—Recent studies have correlated neurocognitive function and regional brain volumes in children with epilepsy. We tested whether brain volume differences between children with and without epilepsy explained differences in neurocognitive function.

Methods—The study sample included 108 individuals with uncomplicated nonsyndromic epilepsy (NSE) and 36 healthy age- and gender-matched controls. Participants received a standardized cognitive battery. Whole brain T1-weighted MRI was obtained and volumes analyzed with FreeSurfer (TM).

Key Findings—Total brain volume (TBV) was significantly smaller in cases. After adjustment for TBV, cases had significantly larger regional grey matter volumes for total, frontal, parietal, and precentral cortex. Cases had poorer performance on neurocognitive indices of intelligence and variability of sustained attention. In cases, TBV showed small associations with intellectual indices of verbal and perceptual ability, working memory, and overall IQ. In controls, TBV showed medium associations with working memory and variability of sustained attention. In both groups, small associations were seen between some TBV-adjusted regional brain volumes and neurocognitive indices, but not in a consistent pattern. Brain volume differences did not account for cognitive differences between the groups.

Significance—Patients with uncomplicated NSE have smaller brains than controls but areas of relative grey matter enlargement. That this relative regional enlargement occurs in the context of poorer overall neurocognitive functioning suggests that it is not adaptive. However, the lack of consistent associations between case-control differences in brain volumes and cognitive functioning suggests that brain volumes have limited explanatory value for cognitive functioning in childhood epilepsy.

Keywords

Cognitive function; Case-control Study; Epilepsy; Children; MRI volumetrics

Introduction

Though most childhood-onset epilepsies have no obvious structural lesion and occur in children who are otherwise neurotypical (normal exam and intelligence) (Arts et al., 1999; Berg et al., 1999; Camfield et al., 1996), they exhibit deficits of cognitive function relative to neurotypical children without epilepsy (Fastenau et al., 2009; Hermann et al., 2006; Ostrom et al., 2003; Taylor et al., 2010). Variations of brain structure have been studied using volumetric techniques to quantify differences that are not appreciable with visual interpretation of clinical imaging. Recent studies of normal brain development are providing a context within which to consider volumetric findings (Giedd et al., 1999; Shaw, 2007).

Volumetric variations of brain structure can be seen in children and adults with chronic epilepsy which may be attributable to seizures, underlying pathology, or medication effects (Bernhardt et al., 2009; Betting et al., 2006; Chan et al., 2006; Lawson et al., 2000; Pardoe et al., 2013). Given that neurocognitive differences are present at the onset of childhood epilepsy, some investigators have considered whether subtle structural variations are also present at or near epilepsy onset and whether they explain variations in cognitive function. Most evidence has come from analyses in two cohorts. Studies in one cohort provide limited

evidence of grey matter cortical volumetric differences between children with idiopathic epilepsy and healthy controls (Hermann et al., 2010; Hermann et al., 2006; Hutchinson et al., 2010; Pulsipher et al., 2011; Tosun, Dabbs, et al., 2011). At the same time, academic difficulties and ADHD were found to be associated with grey matter differences (Hermann, Jones, Dabbs, et al., 2007; Hermann et al., 2006), and anomalies of white matter and subcortical structures were identified (Hermann et al., 2010; Lin et al., 2012; Pulsipher et al., 2011; Pulsipher et al., 2009). In a subsample of the same cohort, microstructural white matter differences were indicated by diffusion tensor imaging in the absence of white matter volume anomalies (Hutchinson et al., 2010). In a second cohort, cortical grey matter anomalies were reported in subsamples with childhood onset absence epilepsy (Caplan et al., 2009; Tosun, Siddarth, et al., 2011) and cryptogenic epilepsy characterized by complex partial events (Caplan et al., 2010; Tosun, Caplan, et al., 2011).

Volumetric measurements have been examined in relation to cognitive functioning in the same cohorts (Caplan et al., 2009; Hermann et al., 2006; Pulsipher et al., 2009; Tosun, Dabbs, et al., 2011; Tosun, Siddarth, et al., 2011). The results of those analyses suggest that associations between cognitive variables and brain volumes in childhood epilepsy differ from those in controls, though only one study directly tested interaction effects (Tosun, Siddarth, et al., 2011). A common limitation of prior studies has been heterogeneity of clinical samples combining epilepsy syndromes having specific neurocognitive signatures such as childhood absence epilepsy (CAE), benign epilepsy with central temporal spikes (BECTS), and juvenile myoclonic epilepsy (JME), and samples including both generalized and focal epilepsies.

We studied total and regional brain volumes and neurocognitive functioning in a prospective community-based sample with well-controlled or remitted childhood-onset nonsyndromic epilepsy with focal features, with or without generalization (NSE), approximately nine years after initial diagnosis, and compared them to healthy controls. Our goals were 1) to determine whether case-control brain volume differences were present, 2) to examine case-control differences in neurocognitive functioning, and 3) to see whether case-control differences in regional brain volumes account for differences in cognitive functioning.

Methods

Participants

Participants were recruited when first diagnosed with epilepsy (onset 0–15 years) in the state of Connecticut between 1993 and 1997 (Berg et al., 1999). Approximately 8–9 years following their initial diagnosis, 298 members of the original cohort participated in a follow-up research protocol which included an MRI brain scan conducted on a 1.5T research scanner under a uniform protocol and a standardized neurocognitive test battery (Berg et al., 2008b). Of these, 108 cases having uncomplicated non-syndromic epilepsy with focal features, with or without generalization, (NSE) were identified. Participating cases had no indications of a brain lesion and their research MRI scans were normal to clinical interpretation. They also had a normal neurologic exam, IQ ≥ 70 , and were seizure free at the time of participation. Thirty-six healthy siblings of participants, recruited as matched controls, completed the same imaging and neurocognitive test protocol, with the goal of

collecting identical data from a sibling as close as possible to the case's age. All controls were neurologically normal and without epilepsy or unprovoked seizures.

Neurocognitive testing

Participants completed a neurocognitive test battery administered by a licensed psychologist or trained psychometrician. The battery included an abbreviated adult (Wechsler, 1997) or child (Wechsler, 1991) Wechsler intelligence scale (depending on age), an age-appropriate version of the California Verbal Learning Test (CVLT) (Delis et al., 1994; Kramer et al., 1987) and the Conners' Continuous Performance Test, Second Edition (CPT-II) (Conners, 2000). Abbreviated versions of the Wechsler intelligence scales were based upon a short form estimating Full Scale IQ (FSIQ) which was originally derived for the Wechsler Intelligence Scale for Children, Third Edition (Donders, 1997), composed of the factors Verbal Comprehension (VC, Vocabulary and Similarities subtests), Perceptual Organization (PO, Picture Completion and Block Design subtests), Working Memory (WM, Arithmetic and Digit Span subtests), and Processing Speed (PS, Coding and Symbol Search subtests). The CVLT parameter of interest was the Total T-Score, which represents total recall over the task's five learning trials. Two variables from the CPT-II were studied: the mean reaction time to correct target stimuli (mean hit reaction time), and the standard error of mean hit reaction time, which measures variability of response speed. These CPT-II parameters were selected based on their sensitivity to neurocognitive dysfunction in childhood epilepsy (Fastenau et al., 2009) and evidence supporting the importance of intra-individual reaction time variability as an indicator of neurocognitive integrity in a number of clinical populations (MacDonald et al., 2006; Simmonds et al., 2007). Age-adjusted standardized scores were used in all analyses.

Image acquisition and volumetric processing

Participants were imaged with a 1.5 T MRI scanner using a previously described protocol (Berg, Pardoe, et al., 2011). The acquired MRI scans were processed using Freesurfer 5.0 with default processing parameters (Dale et al., 1999). Total Brain Volume (TBV), white and grey matter volume, and subcortical grey matter volume were measured by segmenting brain regions using the subcortical processing routines in Freesurfer (Fischl et al., 2002). Cortical grey matter was further subdivided into frontal, parietal, occipital, temporal, and pre- and post-central regions as well as the insula, cingulate, and hippocampus using the PALS-B12 lobar atlas (Van Essen, 2005) provided with the Freesurfer 5.0 software package. The volumes of these lobar segments (Supporting information Figure S1) (Desikan et al., 2006) were measured. Because specific hypotheses regarding laterality were not proposed for this study, all volumetric indices were bilateral. Regional brain volumes were adjusted for TBV by applying a previously described covariance method that is commonly used for this purpose (Berg, Pardoe, et al., 2011).

Statistical analysis

T-tests were used to compare the case and control groups on neurocognitive and volumetric indices. Subsequent analyses included only the neurocognitive variables and volumetric indices that differed significantly between cases and controls. Pearson correlations were

used to examine associations between neurocognitive scores and brain volumes separately in the case and control groups. Multiple linear regression was then employed to examine associations between brain volumes and neurocognitive variables after adjustment for case-control status, and to test whether regional brain volumes interacted with case-control status in predicting neurocognitive indices. Associations are designated as small ($r = 0.10 - 0.29$), medium ($r = 0.30 - 0.49$) and large ($r > 0.50$), based on commonly-accepted criteria (Cohen, 1988). Analyses were performed using SAS (SAS 9.2, SAS Institute Inc, Cary, NC, USA).

All procedures used in this study were approved by the Institutional Review Boards of the participating institutions. Written informed consent and assent were obtained as appropriate for all subjects.

Results

Demographic features of the sample are presented in Table 1. Cases and controls were similar with respect to gender and age at the time of assessment. Two-thirds of cases were taking no antiepileptic drugs at the time of testing and were seizure-free, indicating that their epilepsy was in remission. 62 (57%) cases had experienced, lifelong, one or more generalized tonic clonic events. 25 cases (23%) had experienced one or more seizures in the year prior to participation in the study. 66 cases (61%) had been seizure free for five or more years prior to participation.

Case-control differences in neurocognitive function

Comparisons of neurocognitive test indices (Table 2) indicate that cases scored significantly lower than controls on all five Wechsler intelligence indices: FSIQ, VC, PO, WM, and PS. Case-control differences were not found for the CVLT Total T-Score or for the mean hit reaction time of the CPT-II. However, the standard error of hit reaction time on the CPT-II (CPTSE) was significantly higher in cases than controls, indicating greater variability of response speed (i.e., worse performance) in cases. The standard deviation of the CPTSE index was also significantly larger in the case group than in the control group, indicating greater variability among members of the case group than among controls.

Case-control differences in total and regional brain volumes

TBV was significantly smaller in cases ($M = 1483406 \text{ mm}^3$, $SD = 155018$) than in controls ($M = 1547669 \text{ mm}^3$, $SD = 139421$), $p = 0.03$. Adjusted for TBV, cases had significantly larger cortical grey matter volumes than controls overall, specifically in frontal, parietal, and precentral cortex (Table 3).

Associations between brain volumes and cognitive scores

Among cases, bivariate correlations between TBV and neurocognitive test scores (Table 4) indicated small but significant associations with FSIQ, VC, PO, and WM indices. In controls, medium correlations were found between TBV and WM and CPTSE, with other correlations being non-significant. As a formal test of whether there were differences in brain volume-cognitive score correlations in cases versus controls, we constructed interaction terms ($G*V$) and tested them in a multivariable linear regression model ($S = \beta_0 +$

$\beta_1G + \beta_2V + \beta_3G*V$), where S = cognitive test score, G = case/control group status, and V = brain volume. None of the interactions was significant.

Bivariate correlations between adjusted regional brain volumes found to differ between cases and controls and neurocognitive test scores (Table 5) indicate, for cases, small associations between WM scores and total cortical grey matter and precentral grey matter, and a medium association between WM scores and parietal grey matter. VC scores showed small associations with total cortical grey matter and parietal grey matter, and FSIQ was similarly associated with parietal grey matter. There was only one significant finding in controls, that of a medium association between PO and parietal grey matter, although many correlation coefficients were similar in magnitude to those seen in cases. As with total brain volume, no tests of interaction effects upon these correlations by case-control status were significant.

To determine the relative importance of case status versus brain volumes on cognitive scores, we created a series of multivariable models in which each neurocognitive test was modeled as a function of brain volume and case-control status (Table 6). Within the multivariable model, all cognition-brain volume associations were found to be either small or non-significant. Of the significant effects, working memory (WM) was predicted by TBV and total cortical grey, parietal grey, and precentral grey matter volumes, after adjustment for case-control differences. TBV and parietal grey matter were also significant predictors of FSIQ, VC, and PO scores, and total cortical grey matter significantly predicted VC. In contrast, moderate to strong associations were found between case-control status and neurocognitive test scores, with the exception of relationships between VC, PO, and WM scores and TBV.

Discussion

Consistent with the findings of others, we obtained evidence of neurocognitive compromise in neurotypical young people with nonsyndromic epilepsy relative to controls. We also identified significant differences between cases and controls at the level of total and adjusted regional brain volumes. While TBV was smaller in cases, we found cases to have regions of relative cortical grey matter enlargement. However, associations between regional brain volumes and cognitive indices were small and inconsistent. In cases and controls separately, we found a few small positive correlations between cortical grey matter volumes and cognitive scores, but a consistent pattern of association did not emerge. Most importantly, we found no indication that differences in brain volumes between cases and controls explained differences in their cognitive functioning. Put simply, case-control status clearly made a difference with respect to several aspects of cognitive functioning, and with respect to selected regional cortical grey matter volumes, but the latter differences did not explain the former.

Our findings of cognitive deficits in NSE are consistent with a large literature indicating that children with epilepsy are at significant risk for adverse neurocognitive outcomes. Previous studies have identified cognitive deficits as well as academic difficulties at the time of initial diagnosis (Berg et al., 2008a, 2008b; Hermann et al., 2006; Oostrom et al., 2003; Oostrom et

al., 2005). Our neurocognitive results therefore reflect previous findings in a sample with well-controlled NSE, several years after initial diagnosis.

The relationship between epilepsy and brain morphology in childhood has been studied primarily in two cohorts, one from Wisconsin (Hermann et al., 2010; Hermann, Jones, Dabbs, et al., 2007; Hermann et al., 2006; Hermann, Jones, Sheth, et al., 2007; Hutchinson et al., 2010; Lin et al., 2012; Pulsipher et al., 2011; Pulsipher et al., 2009) and one from the Los Angeles area (Caplan et al., 2009; Caplan et al., 2010; Tosun, Caplan, et al., 2011; Tosun, Siddarth, et al., 2011). Our finding of smaller TBV in cases diverges from analyses of subsets of those cohorts which have failed to identify differences (Caplan et al., 2009; Caplan et al., 2010; Hermann, Jones, Dabbs, et al., 2007; Pulsipher et al., 2009). However, larger TBV was recently reported in a subsample of 13 children with BECTS from the Wisconsin cohort (Lin et al., 2012). While various differences in epilepsy diagnosis and treatment could potentially be related to these divergent results, the fact that our sample had substantially earlier age of onset than the other cohorts is particularly noteworthy.

Our findings of relative enlargement in TBV-adjusted parietal and frontal association cortices as well as motor cortex in cases relative to controls are of particular interest, as EEG fMRI studies have shown that these areas are involved in networks underlying a number of forms of epilepsy. For example, frontal and parietal association areas are specifically involved in the network implicated in absence seizures of childhood (Carney et al., 2012). In Lennox Gastaut syndrome (LGS), interictal discharges of paroxysmal fast activity are associated with pathological activation of a network involving frontal and parietal cortex which has been termed, 'diffuse association network activation', or DANA (Pillay et al., 2013). It has been proposed that this abnormal network interferes with cognition in LGS by disrupting attention and cognitive functions.

Analyses of the Wisconsin and Los Angeles cohorts have generally not found case-control grey matter differences (Daley et al., 2007; Hermann et al., 2006; Hutchinson et al., 2010), although one study using an alternate volumetric method reported complex regional grey and white matter discrepancies (Tosun, Dabbs, et al., 2011). Our negative findings for white matter differences are consistent with the majority of previous analyses (Hermann, Jones, Dabbs, et al., 2007; Hermann et al., 2006; Hutchinson et al., 2010).

In healthy adults, most studies have indicated a positive correlation between TBV and IQ (McDaniel, 2005). In children, the NIH MRI Study of Normal Brain Development also identified positive associations overall between TBV and intelligence (Lange et al., 2010). Overall, these data seem to suggest a nonspecific positive association between TBV and IQ, and our data are therefore generally consistent with findings in healthy children and adults.

Initial analyses of the Wisconsin and Los Angeles cohorts did not find associations between intellectual indices and regional brain volumes in childhood epilepsy (Caplan et al., 2009; Daley et al., 2007; Hermann et al., 2006). However, more recent investigations of the Wisconsin cohort, in relatively modest samples, have reported positive associations involving executive task performance and thalamic and frontal volumes in juvenile myoclonic epilepsy (N = 20) (Pulsipher et al., 2009), regional cortical thickening and

intelligence in children with absence epilepsy (N = 24) (Tosun, Siddarth, et al., 2011), and executive task performance and putamen volume in BECTS (N = 13) (Lin et al., 2012).

Our overall finding of regional cortical grey matter enlargement in the context of poorer neurocognitive functioning in cases suggests that this enlargement is not adaptive, raising the possibility that such enlargement may be an indicator of a pathological neural substrate. As our sample was comprised of individuals whose epilepsy was either remitted or well-controlled, we suspect that our grey matter findings are related to the underlying cause of the epilepsy at its outset and not a consequence of refractory seizures. One simple interpretation would be that increased grey matter represents a developmental abnormality of the cortex (along the lines of occult or very subtle dysplasia) which may give rise to both epilepsy and volumetric findings. A possible mechanism for this enlargement could be disruption of subtractive neurodevelopmental processes such as synaptic pruning (Huttenlocher & Dabholkar, 1997) which normally result in regional neocortical volume reductions with age. The presence of such disruptions has not yet been directly demonstrated in epilepsy, and would be an appropriate focus of future research.

Our failure to identify a consistent pattern of associations between case-control differences in adjusted grey matter volumes and case control differences in cognitive functioning suggests that standard clinical MRI has limited value for investigating finer cognitive deficits associated with childhood onset epilepsy. Advanced imaging methods such as diffusion weighted imaging or fMRI techniques may be more sensitive to brain changes associated with cognitive dysfunction in these disorders. Recent findings of abnormal white matter connectivity in children with epilepsy, despite normal regional white matter volumes (Hutchinson et al., 2010), altered resting state functional connectivity in childhood absence epilepsy, also without obvious macrostructural brain changes (Masterton et al., 2012), and significant associations between cognitive impairment and white matter fractional anisotropy in childhood onset localization-related epilepsy (Widjaja et al., 2013), support this point, suggesting that gross structural features such as brain volumes tell only part of the story of abnormal brain development, and that the most critical differences in childhood epilepsy must be understood at a microstructural level.

Our sample of 108 children with NSE is the largest pediatric epilepsy cohort to date subjected to quantitative volumetric analyses. The largest previously reported sample consisted of 75 subjects, 35 with idiopathic generalized epilepsies and 40 with localization-related epilepsies (Hermann, Jones, Dabbs, et al., 2007), and, as noted above, many previous volumetric analyses have been based upon samples of 50 or fewer children with epilepsy. Although we examined our cohort members several years after their initial diagnosis of epilepsy, the subjects were mostly well controlled and many were off medications when studied, thus we are reasonably confident that we are not observing a volumetric phenomenon caused by refractory seizures over time. In all, our findings are representative of a relatively healthy subpopulation of children with epilepsy, albeit a segment that is also quite common (Berg, Testa, et al., 2011). Unlike the Wisconsin cohort, we did not have neurocognitive testing or research brain imaging for the purpose of volumetric analysis for participants when they entered our cohort; some would have been too young to be tested. As a result, we were unable to examine differences in brain structure or cognitive function, or

their associations, within a longitudinal framework. We also had a limited control group (N=36); however, its size is not inconsistent with control groups used in many analyses from the Wisconsin and Los Angeles groups, and in fact it is larger than the epilepsy samples analyzed in several of those studies.

From previous literature, it was unclear whether, in analyses of brain volumes such as those conducted for this study, regional brain volumes should be adjusted for TBV or another measure of cranial capacity. The central argument against adjustment for TBV would be that the absolute size of a brain region should be related to its functionality, independent of TBV or its size relative to other brain regions. The argument for adjustment is that functionality of a brain region depends upon its relationship to other brain regions. All studies of regional brain volumes in childhood epilepsy conducted to date have adjusted for overall brain size. When we conducted analyses upon regional brain volumes without adjusting for TBV, all significant relationships were lost. This finding supports a regional relativity approach to volumetric analyses in childhood epilepsy.

While it would be attractive to relate increased regional brain volumes to case-control differences in cognitive functioning, our results do not support a straightforward relationship at this level of analysis. They instead emphasize the importance of studying the neural substrate of childhood epilepsy at microstructural and functional levels. Prospective longitudinal studies with large and diagnostically homogeneous clinical samples hold particular promise to advance our understanding of neurodevelopmental changes in childhood-onset epilepsy and their relationship to functional cognitive outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was funded by a grant from the National Institutes of Health, NINDS-NS-R37-31146, to Anne T. Berg, Ph.D.

We wish to thank the physicians in Connecticut who allowed us to recruit and follow their patients and the many families who have participated in this project over the years.

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Table 1

Demographic features of cases and controls.

	Cases (<i>N</i> = 108)	Controls (<i>N</i> = 36)
Male	52 (49%)	19 (53%)
Age at scan (years)	14.6 (SD = 4.2, 8–24)	14.9 (SD = 3.2, 10–21)
Age at first seizure (years)	5.7 (SD = 4.2, 0.08–15.5)	-
Number of AEDs at time of testing		
0	71 (66%)	-
1	24 (22%)	-
2 or more	12 (11%)	-

AEDs, antiepileptic drugs.

Except as indicated, values shown are mean (standard deviation, range)

Table 2

Comparisons of cases and controls on neuropsychological test indices.

	Cases (N = 108)	Controls (N = 36)	<i>p</i> -value ^a
Wechsler Full Scale IQ^b	98.5 (17.9)	108.4 (12.7)	0.0005
Wechsler Verbal Comprehension^b	103.2 (17.6)	109.7 (12.5)	0.02
Wechsler Perceptual Organization^b	100.6 (18.7)	108.5 (15.1)	0.02
Wechsler Working Memory^b	97.9 (17.2)	105.4 (13.6)	0.02
Wechsler Processing Speed^b	95.1 (16.3)	103.0 (12.6)	0.009
CVLT Total T-Score^c	50.8 (13.4)	54.4 (13.9)	0.17
CPT-II hit reaction time^c	48.4 (12.7)	46.8 (10.7)	0.50
CPT-II standard error of hit reaction time^c	50.8 (13.1)	44.0 (8.8)	0.0007 ^d

CVLT, California Verbal Learning Test; CPT-II, Conners' Continuous Performance Test, Second Edition.

Values shown are means (standard deviations).

^a *p*-values are based on *t*-tests.^b Mean = 100, Standard deviation = 15.^c Mean = 50, Standard deviation = 10.^d Test of equality of variances indicated differences.

Table 3

Comparisons of cases and controls on adjusted regional brain volumes.

Region	Cases (<i>N</i> = 108)	Controls (<i>N</i> = 36)	<i>p</i> -value ^a
Total cortical grey	527129 (38074.4)	510009 (37077.7)	0.02
Total cortical white	481488 (35915.7)	487670 (35125.3)	0.37
Frontal grey	170117 (13524.3)	162247 (13540.5)	0.003
Temporal grey	116069 (13457.6)	116355 (9345.6)	0.89
Parietal grey	106806 (10397.5)	99832.7 (10109.9)	0.0006
Occipital grey	50465.8 (5201.1)	50297.7 (5284.2)	0.87
Subcortical grey	200570 (14170.3)	199094 (12388.8)	0.58
Pre-central grey	27048.5 (2652.8)	25514.8 (2523.4)	0.003
Post-central grey	19543.8 (2464)	18833.1 (1878.6)	0.12
Cingulate	22435.7 (2199.9)	22276.1 (2232.2)	0.71
Insula	14656.5 (1552.6)	14653.9 (1365.7)	0.99
Hippocampus	8512.6 (917.7)	8507.8 (629.3)	0.98

All volumes are bilateral, adjusted for total brain volume.

Values shown are means (standard deviations), mm³.

^a *p*-values are based on *t*-tests.

Table 4

Correlations between total brain volume and neuropsychological test indices for cases and controls.

	Cases (<i>N</i> = 108)	Controls (<i>N</i> = 36)
Wechsler Full Scale IQ	0.23 (0.01)	0.25 (0.14)
Wechsler Verbal Comprehension	0.23 (0.02)	0.04 (0.82)
Wechsler Perceptual Organization	0.21 (0.03)	0.30 (0.08)
Wechsler Working Memory	0.26 (0.007)	0.33 (0.05)
Wechsler Processing Speed	0.09 (0.37)	−0.12 (0.49)
CPT-II standard error of hit reaction time	−0.12 (0.24)	0.35 (0.04)

CPT-II, Conners' Continuous Performance Test, Second Edition.

Values are Pearson correlations, *r* (*p*-values)

Table 5
Correlations between adjusted regional brain volumes and neuropsychological test indices for cases and controls.

Region	Full Scale IQ ^a	Verbal Comprehension ^a	Perceptual Organization ^a	Working Memory ^a	Processing Speed ^a	CPTSE
Total cortical grey						
Cases	0.15 (0.13)	0.19 (0.05)	0.04 (0.69)	0.27 (0.005)	0.02 (0.78)	-0.06 (0.52)
Controls	-0.01 (0.97)	-0.11 (0.52)	0.17 (0.32)	0.02 (0.89)	-0.29 (0.08)	0.12 (0.47)
Frontal grey						
Cases	0.03 (0.74)	0.05 (0.62)	-0.06 (0.53)	0.16 (0.09)	0.01 (0.91)	-0.10 (0.32)
Controls	-0.05 (0.79)	-0.11 (0.52)	0.10 (0.56)	0.03 (0.85)	-0.24 (0.16)	0.07 (0.68)
Parietal grey						
Cases	0.21 (0.03)	0.25 (0.01)	0.17 (0.09)	0.31 (0.001)	-0.07 (0.49)	-0.06 (0.55)
Controls	0.20 (0.25)	0.03 (0.85)	0.36 (0.03)	0.08 (0.66)	-0.22 (0.21)	0.27 (0.11)
Pre-central grey						
Cases	0.10 (0.31)	0.11 (0.27)	0.02 (0.81)	0.22 (0.03)	-0.04 (0.68)	-0.01 (0.91)
Controls	0.10 (0.58)	-0.03 (0.84)	0.26 (0.12)	0.05 (0.79)	-0.25 (0.14)	0.14 (0.42)

All regional brain volumes are adjusted for total brain volume.

CPTSE, standard error of hit reaction time for Conners' Continuous Performance Test, Second Edition

Values are Pearson correlations, r (p -levels)

^aWechsler intelligence scales

Table 6

Multivariable analyses modeling neuropsychological test scores as a function of brain volumes and case-control status.

Region	Full Scale IQ ^a	Verbal Comprehension ^a	Perceptual Organization ^a	Working Memory ^a	Processing Speed ^a	CPTSE
Total brain	2.86 <i>p</i> = 8.40	2.34 <i>p</i> = 0.011	2.86 <i>p</i> = 0.004	3.17 <i>p</i> =	0.59 <i>p</i> = 0.487	-0.46 <i>p</i> = -6.79
Control	(3.25) <i>p</i> = 0.011	5.37 (3.22) <i>p</i> = 0.098	6.36 (3.46) <i>p</i> = 0.068	5.74 (3.13) <i>p</i> = 0.068	7.62 (3.04) <i>p</i> = 0.013	(2.42) <i>p</i> = 0.006
Total cortical^b	6.89 <i>p</i> = 0.064	7.41 <i>p</i> = 0.042	4.78 <i>p</i> = 0.228	10.68 <i>p</i> = 0.003	-0.63 <i>p</i> = 0.853	-2.02 <i>p</i> = 0.454
Control	11.42 (3.32) <i>p</i> =	8.12 (3.25) <i>p</i> = 0.014	9.04 (3.55) <i>p</i> = 0.012	9.58 (3.16) <i>p</i> = 0.003	7.92 (3.04) <i>p</i> = 0.010	-7.43 (2.41) <i>p</i> = 0.003
Frontal grey^b	6.34 <i>p</i> = 0.548	6.30 <i>p</i> = 0.543	0.63 <i>p</i> = 0.955	19.84 <i>p</i> = 0.051	-2.56 <i>p</i> = 0.788	-8.36 <i>p</i> = 0.270
Control	10.78 (3.39) <i>p</i> = 0.002	7.40 (3.33) <i>p</i> = 0.028	8.31 (3.61) <i>p</i> = 0.023	9.35 (3.26) <i>p</i> = 0.005	7.82 (3.07) <i>p</i> = 0.012	-7.74 (2.44) <i>p</i> = 0.002
Parietal grey^b	39.68 <i>p</i> = 0.003	38.33 <i>p</i> = 0.004	40.79 <i>p</i> = 0.004	46.24 <i>p</i> = 0.004	-1.08 <i>p</i> = 0.385	-4.21 <i>p</i> = 0.670
Control	12.96 (3.32) <i>p</i> =	9.49 (3.26) <i>p</i> = 0.004	11.00 (3.53) <i>p</i> = 0.002	10.95 (3.18)	7.30 (3.09) <i>p</i> = 0.020	-7.37 (2.46) <i>p</i> = 0.003
Pre-central^b	79.31 <i>p</i> = 0.146	67.31 <i>p</i> = 0.209	65.63 <i>p</i> = 0.257	127.43 <i>p</i> = 0.015	-38.95 <i>p</i> = 0.431	-4.22 <i>p</i> = 0.915
Control	11.48 (3.38) <i>p</i> =	7.92 (3.32) <i>p</i> = 0.018	9.24 (3.59) <i>p</i> = 0.011	9.75 (3.24) <i>p</i> = 0.003	7.44 (3.07) <i>p</i> = 0.017	-7.16 (2.45) <i>p</i> = 0.004

Italicized values $\times 10^{-5}$ represent regression coefficients for brain volume as predictors of 0.004 neuropsychological test scores, after adjustment for case-control differences.

Control values represent mean score advantage (Standard Error) for controls over cases, after adjustment for brain volume listed.

CPTSE, standard error of hit reaction time for Conners' Continuous Performance Test, Second Edition.

^aWechsler intelligence scales.

^bAdjusted for total brain volume.