Amygdala and hippocampal volumes in children with Down syndrome: A high-resolution MRI study

Article abstract—The objective of this study was to use high-resolution MRI techniques to determine whether children with Down syndrome exhibit decreases in hippocampal and amygdala volumes similar to those demonstrated in recent studies of adults with this condition. When corrected for overall brain volumes, amygdala volumes did not differ between groups but hippocampal volumes were significantly smaller in the Down syndrome group. These findings suggest that the hippocampal volume reduction seen in adults with Down syndrome may be primarily due to early developmental differences rather than neurodegenerative changes.

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Down syndrome (DS), the most common genetic cause of mental retardation, results in characteristic physical and neuropsychological findings, including mental retardation and deficits in language and memory.[1,2] The neuroanatomic bases for these cognitive deficits remain poorly understood. Recent volumetric neuroimaging studies of adults with DS have revealed decreased overall brain volumes, with disproportionate reductions of cerebellar, brainstem, frontal lobe, and hippocampal volumes.[3,4] Caution must be exercised in interpreting these prior studies as most have employed small numbers of subjects, and much of the volumetric data were obtained with relatively low-resolution image acquisition techniques (e.g., 5 mm brain slices with between-slice gaps of 2.5 mm). A more recent MRI study of adults with DS, however, using high-resolution MRI techniques, provides compelling evidence for a selective hippocampal volume decrease.[5]

Surprisingly few MRI studies of affected children have been published. One volumetric MRI study of six children with DS suggested a reduction in amygdala and hippocampal volumes.[6] However, because this study used lower resolution MRI techniques than currently available, and measured a "temporal limbic" region including uncus and parahippocampal gyrus, it is unclear whether the hippocampus or amygdala were specifically or separately affected. The goal of the current study was to obtain more precise quantitative neuroimaging data in children and young adults with DS, and to determine whether the findings of smaller volumes of amygdala and hippocampus in previous imaging studies of the aging DS brain also are observed in children with this genetic condition.

Methods. *Subjects.* Sixteen individuals with DS (11 male, 5 female; mean age 11.3 years, SD = 5.2) and 15 normal controls matched for sex and age (mean age 11.9, SD = 4.7) were studied. All subjects with DS were recruited through the Down Syndrome Clinic at the Kennedy Krieger Institute between 1991 and 1997. Written informed consent was obtained from the parents of all subjects, with oral assent given by subjects when feasible, before participation. The diagnosis of DS was confirmed both by clinical examination by one of the authors (G.T.C.) and by karyotype. All DS subjects were found to have trisomy 21.

Imaging. MRI of all subjects were obtained on a GE-Signa 1.5 T scanner (General Electric, Milwaukee, WI). Coronal images were acquired with a three-dimensional volumetric radio frequency spoiled gradient using the following parameters: repetition time = 35, echo time = 7, flip angle = 45, number of excitations = 1, matrix size = 256 × 128, field of view = 20 to 24 cm, slice thickness = 1.5 mm, 124 slices. Each subject's brain image was imported into the program BrainImage 4.XX[7] for semiautomated brain tissue isolation and volumetric measurement. Manual delineation of the hippocampus and amygdala was carried out according to previously described procedures.[8] Figure 1 shows representative T1-weighted coronal MRI slices demonstrating boundaries of amygdala and hippocampus used to delineate volumes. Interrater reliability for the two raters (W.E.B., J.E.S.) was established from measurements of 25 trials for the hippocampus (intraclass correlation = 0.96) and from measurements of 39 trials for the amygdala (intraclass correlation = 0.89). Each rater measured approximately one-half of the scans in this study.

Statistics. Because the measurements being compared did not meet the requirements for parametric statistical analysis, Mann–Whitney *U* tests with a *p* value of 0.05 set as the significance threshold were used to assess differences in volume of total brain, amygdala, and hippocampus between subjects with DS and controls. To adjust for differences in total brain volumes, amygdala and hippocampal volumes were each assessed as a ratio to total brain volume. Group differences in asymmetry for each of

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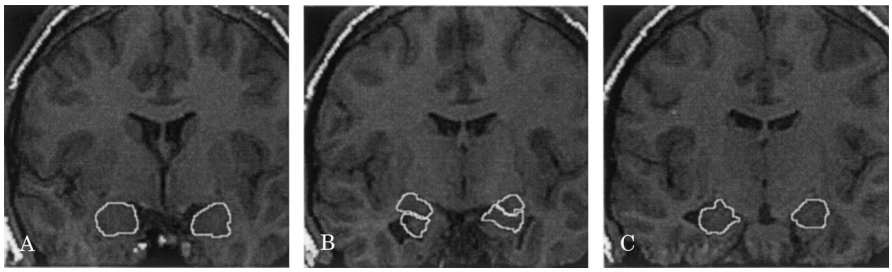

Figure 1. Representative T1-weighted coronal MRI slices demonstrate boundaries of amygdala (A and superior structures in B) and hippocampus (C and inferior structures in B) used to delineate volumes.

these structures were investigated using the formula (R − L)/(R + L), and then analyzed by the same nonparametric statistical methods described above.

Results. The table shows mean volumes of total brain, amygdala, and hippocampus of the DS and control groups. The mean total brain volume in DS subjects was 18% smaller than that of controls ($p < 0.0001$). After adjusting for total brain volume, neither right nor left amygdala volumes differed between DS and control groups ($p = 0.323$ for the right amgydala, $p = 0.268$ for the left amygdala). Both left ($p = 0.0016$) and right ($p = 0.033$) adjusted hippocampal volumes in the DS group, however, were smaller than those of the control group. Figure 2 shows a scatterplot of total hippocampal volume (R + L) vs age for both groups. The calculated asymmetry ratios [(R − L)/(R + L)] for amygdala were −0.001 (SD = 0.078) for the DS and 0.006 (SD = 0.084) for the control group. Hippocampal asymmetry ratios were 0.044 (SD = 0.045) for DS and 0.029 (SD = 0.051) for controls. No differences in pattern of asymmetry of amygdala ($p = 0.7820$, $U = 113$) or hippocampus ($p = 0.2204$, $U = 89$) were noted between the DS and control groups.

Discussion. Our results indicate that hippocampal volumes are decreased out of proportion to overall brain volumes in children and young adults with DS, whereas adjusted amygdala volumes do not differ significantly from controls. These results are consistent with a recent study that reported similar hippocampal volume decreases, and no significant differences in amygdala volumes, among nondemented adults with DS.[5] Because that study included no subjects under age 30, it could not be determined whether the smaller hippocampal volume was longstanding or related to adult-onset neurodegenerative changes. Our results suggest that these changes are present from early in development.

Virtually all adults with DS exhibit the characteristic neuropathologic changes of Alzheimer's disease (AD), including prominent involvement and atrophy of both hippocampus and amygdala.[9] MRI volumetric studies of both subjects with AD[10] and DS with dementia[5] have revealed dramatic volume decreases in amygdala and hippocampus. These results raised the possibility that the hippocampal volume decreases seen in studies of nondemented adults with DS might represent a presymptomatic stage of volume loss associated with early AD pathology. However, whereas three recent MRI studies of nondemented adults with DS have shown significantly decreased hippocampal volumes compared to controls,[3-5] the fact that the two most recent studies failed to show any age-related decreases within the DS groups supports instead our hypothesis of a primarily developmental origin for the observed volume differences.[4,5]

Contrary to the decreased hippocampal volumes apparently present from early childhood, after adjustment for total brain volume, amygdala volumes in subjects with DS in our study did not differ significantly from those of controls. Our results differ from the presumed volume decrease in this area noted in a prior childhood DS volumetric MRI study,[6] but are consistent with a recent study reporting preserved amygdala volumes in nondemented adults with DS.[5] These results suggest that the amygdala has a developmental pattern distinct from the hippocampus in DS, and that neurodegenerative changes in the amygdala during adulthood may underlie the observed volume decreases in older subjects with DS and dementia.

Overall, our demonstration of decreased hip-

Table *Mean volumes in Down syndrome and control groups*

Structure	Down syndrome, n = 16	Controls, n = 15	*p* Value, *U* score
Total brain volume	1,068.3 (79.7)	1,297.5 (124.2)	*<0.0001, 12
Right amygdala	1.859 (0.429)	2.093 (0.328)	†0.3230, 95
Left amygdala	1.848 (0.373)	2.088 (0.457)	†0.2684, 92
Right hippocampus	2.875 (0.402)	3.957 (0.685)	†0.0328, 66
Left hippocampus	2.627 (0.320)	3.715 (0.521)	†0.0016, 40

Values are mean volumes (SD), reported as cm^3.
* Mann–Whitney rank.
† Mann–Whitney rank using ratio to total brain volume.

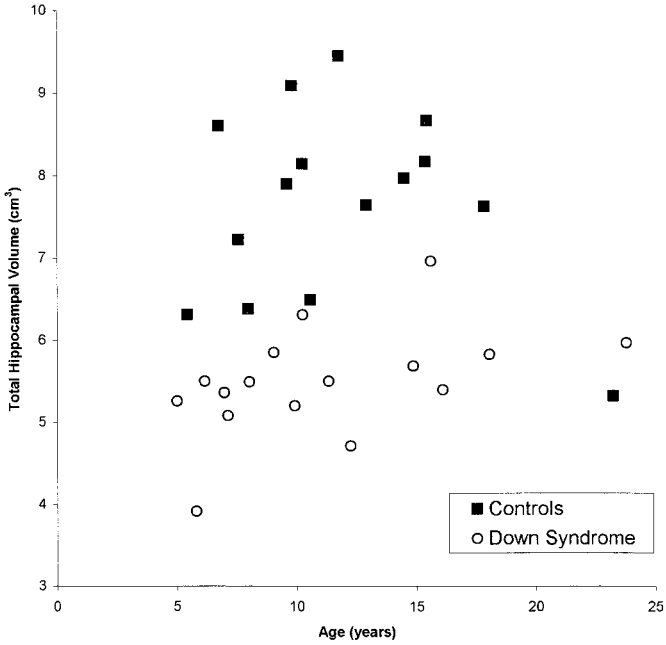

Figure 2. Scatterplot shows total (R + L) hippocampal volumes vs age in Down syndrome and control subjects.

pocampal volumes in children with DS suggests that similar findings in adult studies cannot be attributed only to neurodegenerative changes, but are likely due to highly specific early developmental differences in these temporal lobe structures. An alternative possibility is that neurodegenerative processes leading to hippocampal volume loss begin extremely early in this condition. In either case, this study provides preliminary evidence for quantitative neuroanatomic abnormalities that may contribute to the specific cognitive and developmental deficits seen in children with DS. We found no evidence for abnormal patterns of amygdala or hippocampal asymmetry in individuals with DS.

A limitation of this study is that no children under age 5 were included. Studies including younger children with DS are needed to help pinpoint the period of deviation from normal brain development. Future planned neuropsychological and functional MRI studies will be important to determine if these volume differences are associated with DS-specific language and memory deficits or with abnormal patterns of brain activation.

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