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Dynamic mapping of hippocampal development in childhood onset schizophrenia

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Abstract

Prior cross-sectional anatomic brain imaging studies of the hippocampus in schizophrenia have generally shown loss in total hippocampal volume although the progressive course of these changes remains unknown. We report the first prospective sub-regional maps of hippocampal development in childhood onset schizophrenia (COS), reconstructed from serial brain MRI scans of 29 children with COS scanned every 2 years (87 scans) and compared to 31 controls matched for age, sex, and scan interval (94 scans). As expected, the COS subjects showed significant bilateral deficits (9–10%) in total hippocampal volume which remained consistent between age 9 and 26. However sub-regional maps showed heterogeneous changes with loss of hippocampal volume in both anterior as well as posterior ends while the body of the hippocampus gained in volume suggesting that hippocampal subunits are differentially affected in schizophrenia.
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Keywords: Childhood onset schizophrenia; MRI; Mapping; Hippocampus; Longitudinal

1. Introduction

The hippocampal involvement in the pathophysiology of schizophrenia has been described in neuroanatomical (Harrison, 1999), neuropsychological (Saykin et al., 1991) and clinical studies (Sachdev et al., 1997). Postmortem studies suggest loss of hippocampal tissue in schizophrenia compared to controls (Jeste and Lohr, 1989; Bogerts et al., 1990a,b) which has been also been seen in many anatomic brain MRI studies (Nelson et al., 1998; McCarley et al., 1999; Velakoulis et al., 1999; Altshuler et al., 2000; Wright et al., 2000; Heckers, 2001; Velakoulis et al., 2001; Heckers and Konradi, 2002; Weiss et al., 2004). Two recent meta-analyses of structural magnetic resonance imaging (MRI) studies showed a consistent, bilateral, approximately 4% loss of total hippocampal volume in patients with adult onset schizophrenia (Nelson et al., 1998; Wright et al., 2000).

Recent functional and anatomic studies suggest that hippocampal sub-regions are structurally and functionally separate with distinct cortical connections and individual developmental trajectories(Gogtay et al., 2006b). It is likely that overall volume reduction seen in schizophrenia is sub-regionally heterogeneous. Studies in adult schizophrenia

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have shown volume deficits specific either to the posterior (Bogerts et al., 1990a,b, 1993; Becker et al., 1996; Hirayasu et al., 1998; Velakoulis et al., 2001) or anterior (Suddath et al., 1990; Shenton et al., 1992; Pegues et al., 2003; Szeszko et al., 2003) region of the hippocampus, although these findings have been inconsistent(Laakso et al., 2001; Levitt et al., 2001; Rajarethinam et al., 2001; Heckers et al., 2004). These inconsistencies could partially be explained by a lack of standard methodology for hippocampal measurement, variable guidelines for defining hippocampal boundaries (Jack et al., 1995; Pantel et al., 2000; Pruessner et al., 2000), and sample heterogeneity; but another important reason is that most studies to-date are cross-sectional which makes them vulnerable to cohort effects. Thus, the temporal relationship of hippocampal changes to the disease course remains unknown due to the lack of prospective studies.

Childhood onset schizophrenia (COS), defined with onset of psychotic symptoms before the 13th birthday and unmodified DSM IIIR/IV criteria, is a rare and severe form of the illness that is continuous with its adult counterpart (Nicolson and Rapoport, 1999). Structural MRI studies of COS show progressive cortical gray matter loss which is most striking during the adolescent years (Rapoport et al., 1999; Thompson et al., 2001; Sporn et al., 2003; Gogtay et al., 2004a,b) and our prior small study measuring total hippocampal volumes suggested non-progressive loss of hippocampal volume in COS (Giedd et al., 1999a,b).

Here we present first longitudinal sub-region specific maps of hippocampal development in children and adolescents diagnosed with COS using a prospectively acquired sample of anatomic brain MRI scans for 29 COS children rescanned every two years for 6–10 years (age 9–26 years; 87 total scans) and compared with 31 age, and sex-matched controls (94 total scans). Scanning a pediatric sample during a period of considerable brain reorganization would also seem an age range more likely to show progressive changes. We hypothesized that the hippocampal development in COS would show bilateral reduction in total hippocampal volumes, and as seen in the cortical GM development for COS, that it would show relatively greater loss in the anterior hippocampal regions (Thompson et al., 2001; Gogtay et al., 2006b).

2. Materials and methods

2.1. Subjects

Since 1991, through review of more than 2000 case records and in-person screenings of more than 250 subjects, 84 patients met DSM IIIR/IV criteria for schizophrenia with the onset of psychosis before the 13th birthday(McKenna et al., 1994). Patients with a history of substantial medical problems, substance abuse, or an IQ score lower than 70 prior to the onset of psychotic symptoms were excluded. Further details of patient selection are described elsewhere (Kumra et al., 1996). All COS subjects participated in a prospective brain MRI developmental study (Giedd et al., 1996a,b) and from this population, 29 subjects, with 2 or more usable MRI scans were chosen for this study (average number of scans 3 (SD 0.83); range 2 to 5 scans). The study was approved by the NIMH institutional review board and an informed consent was obtained at each scan from subjects over 18 or from parents of minor subjects. Additional written assent was obtained from each minor subject.

Thirty-one healthy subjects were randomly selected as controls from a larger prospective study of normal brain development, which matched for age, sex and scan interval to the COS subjects. Control subjects were free of lifetime medical or psychiatric disorders as determined by means of clinical examination and standardized interview. Psychiatric illness in a first-degree relative was also exclusionary. Further details are described elsewhere (Giedd et al., 1999a,b).

2.2. Image processing and analysis

MRI images were acquired at the NIMH on the same 1.5 Tesla GE scanner and the sequence was consistent throughout the study. T1-weighted images with contiguous 1.5-mm slices in the axial plane and 2.0-mm slices in the coronal plane were obtained using three-dimensional spoiled gradient recalled echo in the steady state (SPGR). Coronal images were used for hippocampal mapping. Imaging parameters were echo time 5 ms, repetition time 24 ms, flip angle 45°, acquisition matrix 256×192, number of excitations = 1, and 24 cm field of view. With each major software/hardware upgrade, the reliability of the data before and after the upgrade was tested by scanning a set of subjects before and after the upgrade (Giedd et al., 1996a,b). Briefly, for each scan, a radio-frequency bias field correction algorithm was applied. Details have been previously addressed here. (Giedd et al., 1996a,b; Narr et al., 2001; Gogtay et al., 2004a,b, 2006a; Thompson et al., 2004).

2.3. Hippocampal mapping

The hippocampi were manually traced bilaterally by a single individual blind to gender, demographics, and scan order. Anatomical segmentation was performed

using a standard neuroanatomical atlas of the hippocampus (Duvernoy, 1998), according to previously described criteria, whose inter- and intra-rater errors have been established (Narr et al., 2001). Hippocampal models were delineated in contiguous coronal brain sections including the hippocampus proper, dentate gyrus, and subiculum using all 3 orthogonal viewing planes as has been described in detail in earlier studies (Thompson et al., 2004; Lin et al., 2005; Frisoni et al., 2006). Volumes obtained from these tracings were retained for statistical analyses. Anatomical mesh modeling methods were then used to match equivalent hippocampal surface points, obtained from manual tracings, across subjects as described before, which can detect localized changes over time (Thompson et al., 2004). The radial size of each hippocampus at each boundary point was also assessed by measuring the radial distances from homologous hippocampal surface points to the central 3D curve threading down the hippocampal axis. This approach can detect localized GM volume change in the hippocampus (Thompson et al., 2004). Briefly, the 3D parametric mesh models of each individual's hippocampi were analyzed to estimate the regional specificity of hippocampal growth and regression during development, and localized changes over time. To assess patterns of regional hippocampal change, a "medial curve" was

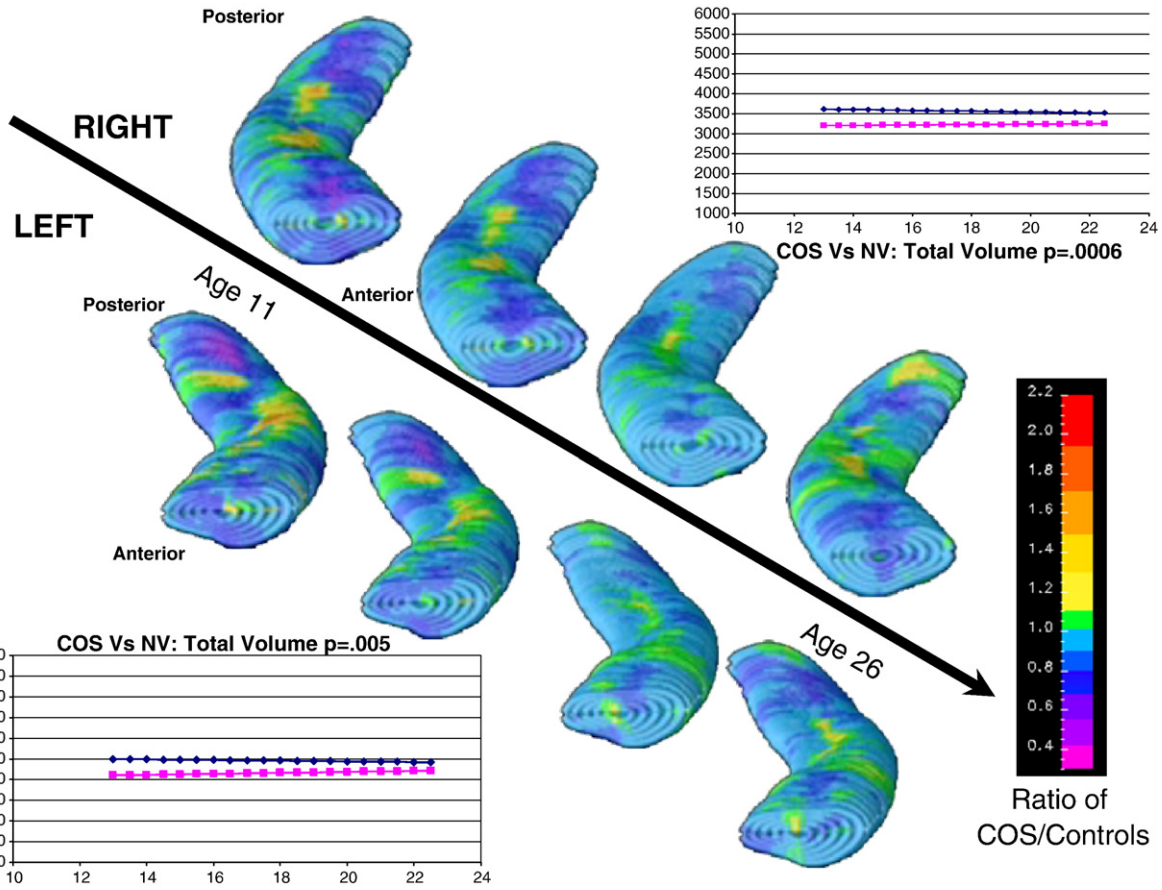

Fig. 1. Dynamic sequence of hippocampal development between age 9 through 26 years in patients diagnosed with childhood onset schizophrenia: the images are ratio maps at each age obtained by dividing the average hippocampal size of the COS subset at given age, at each hippocampal point by the size at the corresponding hippocampal point of the control group at the matched age. The images represent sequential progression in both brain hemispheres for the middle 90% of the data range (top panel—right hippocampus; bottom panel—left hippocampus) starting at age 11 (first pair of images) through age 26 years (last pair of images). The side bar shows a color representation of ratios where ratios >1 indicate that there is gain in hippocampal volume at the point while ratios <1 indicate smaller (reduced) volumes in later scans (later age). Graphs show mixed model regression plots for total hippocampal volume in the right and left hemispheres, which were not significant for either linear, quadratic or cubic terms. The *X*-axis represents age in years and *Y*-axis represents total hippocampal volume. The COS sample is indicated with pink, and the matched controls with blue. Data used for regression plots included only the middle 80% of the age range.

defined as the 3D curve traced out by the centroid (center of mass) of the hippocampal boundary in each section. This medial curve, computed separately for each individual and each time-point, threads down the center of each individual's hippocampus. The radial size of each hippocampus at each boundary point was assessed by measuring the radial distances from homologous hippocampal surface points to the central core of the individual's hippocampal surface model. These distances can be thought of as a map of radial extent or thickness (Thompson et al., 2004), assigning numbers to each hippocampal boundary point that record how far it is from the medial curve of the hippocampus. Changes in these numbers over time can therefore measure localized growth or reduction in the GM volume as has been successfully validated in several studies (Narr et al., 2002; Carmichael et al., 2005; Becker et al., 2006). Note that each subject has a medial curve of unique length, curvature, and direction, all of which also change over time. The reference curves in each individual scan are distinct, and the distances of each hippocampal surface point to its respective medial curve are represented on the hippocampal surface, in the form of a map. Since all hippocampal surfaces are represented using the same parametric mesh structure, corresponding surface traces can be matched across time and across subjects, and averaged across a group, together with their associated distance measures. Distance fields indexing local expansions or contractions in hippocampal surface morphology were compared statistically between groups and across time, at equivalent hippocampal surface points in 3D space.

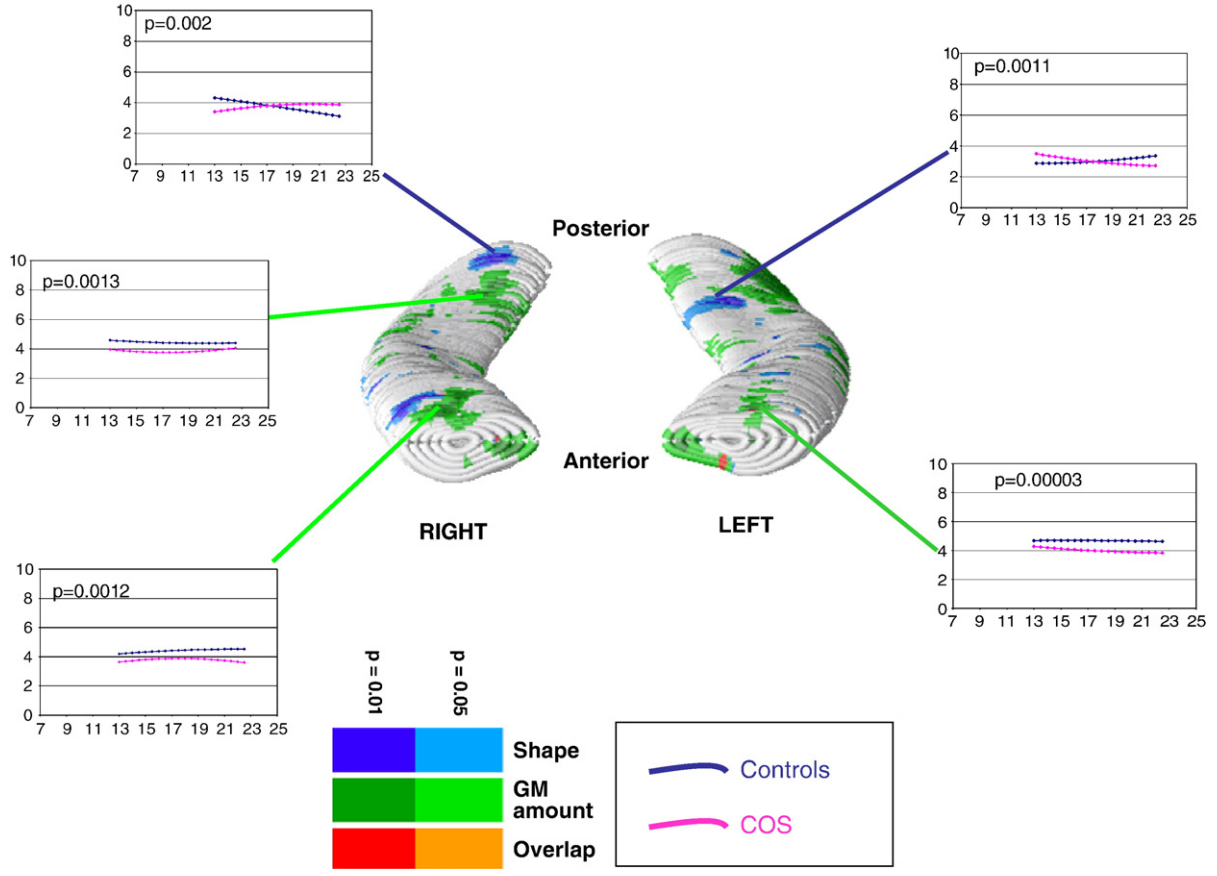

Fig. 2. Significance maps for differences in longitudinal hippocampal development in COS patients compared to healthy controls using mixed model regression analyses at each hippocampal point. *P* values were generated at each point for both GM difference and difference in the 'shape' of the trajectories. For difference in GM amount p values at <0.05 are represented by 'aqua', and $p<0.01$ are shown with 'blue' color. For shape differences between the trajectories, p values at <0.05 are shown with 'light green' and $p<0.01$ are shown with 'dark green' color. Points where both the 'GM amount' and 'trajectory' are significantly different are shown as either 'orange' ($p<0.05$) or 'red' ($p<0.01$). Graphs represent individual trajectories at representative points for both groups.

Table 1
Demographics of the study sample

	COS (N=29)	Healthy controls (N=31)	Statistic (df)	p value
Sex	12 F; 17 M	12 F; 19 M	χ^2=0.04 (1)	p=.83
Handedness	20 R; 5 L; 4 M	28 R; 0 L; 3 M	χ^2=6.4 (2)	p=.04
IQ (M, SD)[a]	82.1(19.0)	120.1(13.4)	t=−8.9 (50)	p<.001
Mean age at scan 1	14.6(2.4) [N=29]	14.6(2.2) [N=31]	t=−.11 (58)	p=.91
Mean age at scan 2	17.3(2.8) [N=29]	17.3(2.7) [N=31]	t=−.06 (58)	p=.96
Mean age at scan 3	20.2(2.7) [N=19]	19.7(2.3) [N=26]	t=.61 (43)	p=.54
Mean age at scan 4	21.3(1.2) [N=6]	23.4(1.6) [N=5]	t=−2.6 (9)	p=.03
Mean age at scan 5	24.4 [N=4]	24.2 [N=1]	–	–
Mean age over all scans	17.6(3.7) [N=87]	17.5(3.5) [N=94]	t=.224 (179)	p=.82

[a] Unequal variances.

2.4. Ratio maps (dynamic sequence)

To compare cortical change between the COS hippocampi with the age- and sex-matched control hippocampi, ratio maps were generated by dividing the GM density regression curves at each of the 30,000 points. These ratios, which estimate the percent difference in GM at each age between patients and controls, were then color coded to visualize a 3-dimensional map and animated into a dynamic sequence.

This method has been successfully used in several previous studies of hippocampal measurements in Alzheimer's disease and anterior lobe epilepsy(Thompson et al., 2004; Carmichael et al., 2005; Lin et al., 2005).

2.5. Statistical analyses

To examine the group differences between the total left and right hippocampal volume measures, we used mixed effect polynomial regression models. The dependent measures were scaled volumes (which control for total brain volume), fixed effects included age, diagnosis, and diagnosis × age interaction terms, and subject intercept was the random effect (Gogtay et al., 2004a,b). Age was centered at the sample average age (mean age=17.54 years) so group differences were determined at the average age instead of the intercept (where age=0).

Hypothesis tests for model building were based on F statistics with α=0.05. Specifically, F tests were used to determine if the order of a developmental growth model was cubic or quadratic. If a cubic model was not significant, (i.e., the cubic terms for both groups combined did not significantly contribute to the model df=2 p>0.05) a quadratic model was tested, and if that was not significant a linear model was tested. The final model was linear and group differences in slope were statistically compared using t tests.

2.6. Significance maps (P maps)

The developmental trajectories (obtained using quadratic mixed model regression analyses) between the COS and healthy control subjects were also compared statistically at each hippocampal point. The regression model was fit at every hippocampal point regressing gray matter volume against diagnosis, age, age-squared, and age and age-squared by diagnosis. A quadratic model was chosen because oru prior findings indicate a curvilinear pattern for this age span (Gogtay et al., 2006b). A random intercept was included to model within subject dependence. Age was centered at the average age and group differences at the average age were determined using t tests, and the significance of the group trajectory difference at each point was determined using an F test. The generated $p$values for both the difference in GM amount (height of the curve at average age) and for difference in the shape of the trajectories were differentially color coded for two alpha levels (alpha=0.05 and alpha=0.01) and re-plotted on the cortical surfaces (Fig. 2). Representative fitted trajectories (graphs) were also generated for individual points of interest over both lateral and medial cortical surfaces (Fig. 2). All mixed effect regression models were conducted using SAS PROC MIXED.

Table 2
Hippocampal volumes

	COS mean (SE)	NV mean (SE)	Average difference: mean (SD)	95% CI	% Difference	p
Left scaled	3158 (75.34)	3460.28 (72.41)	302.28 (104.5)	93.21–511.35	9%	p=0.005
Right scaled	3227.46 (68.20)	3570 (65.50)	343.22 (94.56)	154.00–532.45	10%	p=0.001

Volumes at average age and are adjusted for total brain volume (scaled).

All data were used to estimate regression coefficients. We then graphed the fitted regression lines for the middle 80% of the age range of our data set, where we have the greatest density of data points and the most confidence in the fitted values.

2.7. Reliability

We examined inter- and intra-rater variability and reliability and possible rater drift. For reliability measures, we mapped a "gold standard" set of 6 hippocampi. At the beginning of the study, individual raters' tracings were mathematically compared to this "gold standard" until they achieve high reliability, and then periodically, approximately every six months, to assess any rater drift over time. The regional errors and intraclass correlations can also be color coded and visualized 3-dimensionally across the hippocampus. Longitudinal reliability was measured by identifying 5 individuals with 3 time-point scans, and measuring their scans twice in random order, the reliability for the error term at each time-point was measured.

In the present study all the hippocampi were mapped by a single rater. Intra-rater reliability (cross-sectional) both with the gold standard set at the beginning of the study and for rater drift at the end of the study was 0.9.

3. Results

Sample demographics are shown in Table 1.

COS subjects showed bilateral 9–10% deficit in total hippocampal volume (after adjusting for the total brain volume) compared to the matched controls (Table 2). These differences remained statistically constant between ages 9 through 26. Total Right and Left hippocampal volumes did not significantly change over time and developmental trajectories remained flat.

At sub-regional level, the changes in hippocampal GM in COS were heterogeneous showing bilateral loss in both anterior and posterior regions, while the body of the hippocampus and posterior end of the right hippocampus showed minimal gain.

Significance maps (from quadratic mixed effect regression models) of group differences at individual hippocampal points showed significant GM loss in COS in anterior as well as posterior regional bilaterally, whereas in other regions(e.g. right posterior end) longitudinal trajectory (shape) was significantly different (Fig. 2).

When the group was divided by gender (males: $n=17$, 55 scans; females: $n=15$, 32 scans), no statistically significant differences emerged for either GM amount or the slopes (shapes) of the trajectories and there was no gender by age interaction.

4. Discussion

COS patients showed bilateral reduction in total hippocampus volume which remained consistent between age 9 and 26, but the changes were sub-regionally heterogeneous with anterior and posterior portions showing progressive loss while the body showed modest gain.

Prior cross-sectional studies in adult schizophrenia patients have shown approximately 4% reduction in total hippocampal volume (Nelson et al., 1998; Velakoulis et al., 2006), however the progressive nature of the hippocampal abnormalities in schizophrenia has not been explored. In this study, we found a more profound (9–10% at average age; left $p=0.005$, right $p<0.001$), but non-progressive (slopes of trajectories not significantly different from zero) reduction in total hippocampal volume for COS compared to controls (Fig. 1). The fact that hippocampal volume reduction for COS is more robust compared to that seen for adult patients is not surprising as the cortical GM loss is also more severe for this population and probably represents a more severe and/or earlier onset phenotype(Rapoport et al., 1999; Gogate et al., 2001; Thompson et al., 2001; Sporn et al., 2003). The non-progressive nature of hippocampal volume loss is consistent with an early and fixed lesion as has been proposed for patients (DeLisi et al., 1997; Weinberger, 1999) and for animal models of schizophrenia (Lipska et al., 1993).

Although the reduction in total hippocampal volume was non-progressive, the changes at sub-regional level were heterogeneous. Both anterior and posterior regions of the hippocampus showed significant progressive bilateral reduction for COS, while the middle portion (body) gained in volume (Figs. 1 and 2). These sub-region specific alterations, which could also explain the hippocampal shape changes reported in some studies on adult onset schizophrenia (Csernansky et al., 2002; Connor et al., 2004), are not surprising given evidence that the hippocampus is made up of distinct structural and functional subunits, and the anterior and posterior regions have different cortical inputs (Strange et al., 1999; Kesner et al., 2004). Thus differential impact of the disease on cortical regions could also result in selective sub-regional alterations in the hippocampus (Csernansky et al., 1998, 2002). In general, the posterior hippocampus is more involved with spatial memory functions and the anterior region (along with amygdala) subserves the anxiety and fear response along with

cognitive functions (Bannerman et al., 2004; Schacter and Wagner, 1999a,b) and cognitive and memory deficits reported in schizophrenia could either be the result of or the cause for these volume alterations.

The cortical GM loss seen in COS appears to be an exaggeration of GM loss during adolescent brain development (Thompson et al.; Gogtay et al.). In our recent mapping of the normal hippocampal development only the anterior hippocampus showed GM loss while the posterior region showed progressive gain in volume (Gogtay et al., 2006b). Consistent with the pattern of 'exaggeration of the normal loss', the anterior hippocampus showed significant loss of volume in COS (Figs. 1 and 2). The posterior hippocampus also showed significant loss probably suggesting a severe impairment as a result of the disease process. However, the gain in the middle portion of the hippocampus (body) is intriguing and difficult to explain although most of it did not reach statistical significance (Fig. 2). This region, which appears to overlap with the CA1 and CA3 cytoarchitechtonic fields, has anatomic connections with the entorhinal and perirhinal cortices through the prefrontal pathways and while it is understood that these regions are critical to informational processing in the hippocampus, their role is not well understood (Mizuno and Giese, 2005). The gain in GM in this region for COS may suggest a restitutive or plastic response of the hippocampus to the disease process, and may also be the reason for the consistent total hippocampal volume.

There are several limitations to the study. First, the effect of chronic medication treatment on the hippocampal volume changes could not be ruled out. Prior studies have shown volume changes in deeper cortical structures with antipsychotic medications (Chakos et al., 1994, 1995, 1998). Although the cortical and hippocampal GM may have different plastic responses to medications, our prior analyses suggest that long term cortical GM changes in COS are not influenced by antipsychotic treatment (Gogtay et al., 2004a,b) and our ongoing analyses on patients with atypical psychosis who had similar initial presentation and are age and treatment matched with the COS cohort supports this. Second, it is not possible to pinpoint the exact anatomic location of GM changes based on a surface map and hence it is difficult to understand which hippocampal layers are affected at the sub-regional level, which may become possible only with higher resolution scans (7 or 9T). Finally, whether these hippocampal changes represent a trait marker or a plastic response to the disease process remains unknown. We are currently mapping longitudinal hippocampal development in healthy COS siblings to address some of these questions.

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