

ARCHIVAL REPORT

Progressive Deformation of Deep Brain Nuclei and Hippocampal-Amygdala Formation in Schizophrenia

Lei Wang, Daniel Mamah, Michael P. Harms, Meghana Karnik, Joseph L. Price, Mokhtar H. Gado, Paul A. Thompson, Deanna M. Barch, Michael I. Miller, and John G. Csernansky

Background: Progressive decreases in cortical gray matter volume have been reported in schizophrenia. However, studies of progressive change in deep brain nuclei and hippocampal-amygdala formation have not yielded consistent findings.

Methods: Two high-resolution, T1-weighted magnetic resonance images were collected 2 years apart in 56 schizophrenia and 62 control subjects. Large-deformation high-dimensional brain mapping was used to generate surfaces for deep brain nuclei and hippocampal-amygdala formation at baseline and follow-up. Repeated-measures analysis of variance was used to test for longitudinal changes in volume and shape.

Results: The pattern of progressive changes in the deep brain nuclei and hippocampal-amygdala formation in schizophrenia and control subjects was variable. Of the structures that receive direct projections from the cortex, the thalamus, caudate nucleus, nucleus accumbens, and hippocampus showed changes specific to subjects with schizophrenia, and changes in the amygdala and putamen were similar in both groups. Although different at baseline, no progressive change was observed in the globus pallidus, which does not receive direct projections from the cortex.

Conclusions: These findings suggest that the disease process of schizophrenia is associated with progressive effects on brain structure and that brain structures that receive direct, excitatory connections from the cortex may be more likely to show progressive changes, compared with brain structures that receive indirect, inhibitory connections from the cortex. These findings are also somewhat consistent with the hypothesis that overactivity of excitatory pathways in the brain may contribute to the neural degeneration that occurs in at least a subgroup of individuals with schizophrenia.

Key Words: Amygdala, basal ganglia, brain mapping, hippocampus, longitudinal change, thalamus

Postmortem studies of individuals with schizophrenia suggest gray matter volume loss across a range of brain structures (1–3). Similarly, in vivo magnetic resonance (MR) imaging studies provide evidence of widespread gray matter change in individuals with schizophrenia (4–9), including some who are early in their course of illness (10–12).

Recent longitudinal MR studies offer evidence of progressive gray matter loss (12–14) in the cortex. However, the observed pattern of time-dependent changes in deep brain nuclei and hippocampal-amygdala formation has not been consistent (14–16), and this inconsistency may be because the same method of image acquisition and analysis has not been used to survey a variety of relevant structures within the same subjects. The presence or absence of time-dependent changes in these structures may depend on the nature of their connections with the cerebral cortex. The thalamus and striatum all have direct, excitatory connections with the cortex, whereas the globus pallidus receives inhibitory signals from the striatum and limbic structures and, in turn, passes inhibitory signals to the thalamus. Information from different cortical areas, including the prefrontal,

frontal, motor, and sensory areas, is received first by the striatum via excitatory projections and then passed on to the thalamus via inhibitory projections from the globus pallidus. Finally, the thalamus projects to the cortex, completing a cortico-basal ganglia-thalamo-cortical loop (17). The hippocampus and the amygdala also have reciprocal excitatory connections with the medial prefrontal cortex (18,19) and project to the mediodorsal nucleus of the thalamus.

In this study, we characterized the patterns of change in shape and volume in the deep brain nuclei and hippocampal-amygdala formation in schizophrenia. On the basis of the potential for overactive excitatory projections to damage neurons and their processes (i.e., excitotoxicity) (20,21), we hypothesized that structures with direct, excitatory connections with the cortex (thalamus, striatum, hippocampus, and amygdala) would show time-dependent changes, whereas structures with indirect, inhibitory connections with the cortex (globus pallidus) would not. Because brain structural changes may be accompanied by changes in the cognitive functions supported by these structures, we also examined the correlation between these changes.

Methods and Materials

Participants

The subjects in the present study were selected from groups of schizophrenia ($n = 139$, male/female = 90/49, age = 35.0 ± 13.0 years) and healthy comparison subjects ($n = 136$, male/female = 73/63, age = 33.3 ± 14.1 years) that were enrolled into an ongoing study of brain structure and schizophrenia. From these subjects, 56 schizophrenia and 62 healthy comparison subjects returned for follow-up and were included in the present study. All individuals gave written informed consent for participation after the risks and benefits were explained. Subject characteristics are summarized in Table 1.

Individual diagnosis was determined by consensus between a research psychiatrist who conducted a semistructured interview

From the Department of Psychiatry and Behavioral Sciences (LW, JGC), Northwestern University Feinberg School of Medicine, Chicago Illinois; Departments of Psychiatry (DM, MPH, MK), Psychology (DMB), Anatomy and Neurobiology (JLP), Radiology (MHG), and Division of Biostatistics (PAT), Washington University School of Medicine, St. Louis, Missouri; and Center for Imaging Science (MIM), Institute for Computational Medicine (MIM), Johns Hopkins University, Baltimore, Maryland.

Address reprint requests to Lei Wang, Ph.D., Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, 303 E. Chicago Avenue, Abbott Hall 1312, Chicago, IL 60611; E-mail: leiwang1@northwestern.edu.

Received January 17, 2008; revised August 6, 2008; accepted August 7, 2008.

Table 1. Subject Characteristics

Variables	Schizophrenia Subjects	Comparison Subjects	Difference
N	56	62	—
Age at Baseline (yr)	36.6 (12.9 [19.1–60.4])	36.2 (14.5 [14.1–65.7])	$p = .89$
Gender (Male/Female)	37/19	34/28	$p = .21$
Race (Caucasian/African-American/Other)	27/28/1	43/17/2	$p = .041$
Parental SES	3.4 (1.2 [1–5])	2.7 (.8 [1–4])	$p = .046$
Age of Illness Onset (yr)	23.3 (7.1 [5.8–40.2])	N/A	—
Duration of Illness (yr)	15.7 (13.8 [1–44.9])	N/A	—
Global SAPS Score	4.4 (3.0 [0–10])	N/A	—
Global SANS Score	9.0 (4.3 [1–20])	N/A	—
Scan Interval (years)	2.20 (0.76 [.77–5.28])	2.24 (.58 [1.18–5.25])	$p = .73$

Mean (SD [range]), *t* test, or chi-square statistics are shown where appropriate.

SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SES, socioeconomic class.

and a research assistant who conducted the Structured Clinical Interview for the DSM-IV (SCID-IV) (22), using criteria from the DSM-IV (23). The research assistant had a master's-level degree in a mental health discipline and considerable clinical experience. No individual had an unstable medical or neurological disorder or head injury with loss of consciousness, nor did any meet DSM-IV criteria for substance abuse or dependence for 1 month before participation. The symptoms of the individuals with schizophrenia had remained unchanged for at least 2 weeks (24) before the baseline and follow-up assessments.

During the 2-year study period, 39 subjects with schizophrenia were treated with atypical antipsychotic drugs alone, 13 with typical antipsychotic drugs alone or a combination of both, and 7 did not provide treatment information. Treatment with adjunctive medications, including mood stabilizers and antidepressants, was common.

The severity of psychopathology in the individuals with schizophrenia was assessed at both time points using the Scale for the Assessment of Positive Symptoms (SAPS) (25) and Scale for the Assessment of Negative Symptoms (SANS) (26). Baseline psychopathology data was used as reference to compute *Z* scores for each psychopathology item. Selected clusters of psychopathological item *Z* scores were averaged to form composite scores for three clinical domains: positive symptoms, negative symptoms, and thought disorganization (27).

The subject assessment also included neuropsychological tests on tasks relevant to cognition in schizophrenia (28–33). *Z* scores were first computed using data from a larger population of research subjects (164 schizophrenia, 161 comparison subjects). The *Z* scores were then grouped to form composite scores for four cognitive domains (27):

1. *Working Memory*: Wechsler Adult Intelligence Scale—Third Edition (WAIS-III) (34) digit span (total forward and backward), WAIS-III spatial span (total forward and backwards), WAIS-III letter-number sequencing, and the CPT-IP (overall d-prime) (35).
2. *Episodic Memory*: Wechsler Memory Scale—Third Edition (WMS-III) logical memory and WMS-III family pictures.
3. *Executive Function*: Verbal fluency (phonological for letter “S” plus categorical for animals), Trails B (scored time to completion), WAIS-III matrix reasoning, and Wisconsin Card Sorting Test perseverative errors.
4. *Crystallized Intelligence*. Standard scores from the vocabulary subtest of WAIS-III.

Image Collection

All MR scans were collected on a Magnetom 1.5-Tesla Siemens (Erlangen, Germany) scanner with a standard head coil using a turbo-FLASH sequence (repetition time = 20 msec, echo time = 5.4 msec, flip angle = 30°, 180 slices, field of vision = 256 mm, matrix = 256 × 256, time = 13.5 min) that acquired 1 mm³ isotropic whole-head images (36). Signed 16-bit images were compressed to unsigned 8-bit images by linear interpolation of voxel intensities.

To control for varying brain sizes, we computed an atlas scaling factor (ASF) for each individual at baseline (37). The ASF is the reciprocal of the determinant of the alignment matrix to Talairach atlas space, and it represents the degree of volume expansion or contraction required for alignment. The ASF approximated brain plus ventricular volume and exhibited group difference at baseline ($F = 4.3$, $df = 1,111$, $p = .04$); therefore, it was used as a covariate in statistical analyses.

Surface Mapping

At baseline, the surfaces of the deep brain nuclei and hippocampal-amygdala formation were transferred from a template scan (from a subject otherwise not included in this study) by applying Large-Deformation High-Dimensional Brain Mapping (HDBM-LD) to each scan (9,38). We have previously established the validity and reliability of HDBM-LD for mapping the hippocampus (39), thalamus (40), and basal ganglia (41). For the amygdala, we compared HDBM-LD-generated segmentations to expert manual segmentations in scans of 10 randomly selected subjects. The average (SD) overlap of voxels was 74.3% (11.3%), volume interclass correlation coefficient was .82, L_1 -error was .29 (.06), and mean surface-to-surface distance was .33 (.07) voxels. These error measures were comparable to the accuracy measures we obtained in other structures; for detailed explanations of these measures see Wang *et al.* (41).

To map the surfaces at follow-up, baseline and follow-up scans were first registered using a nine-parameter affine transformation (42) to adjust for changes in head position and scanner-drift (43). Next, HDBM-LD was used in neuroanatomic regions immediately surrounding the structures of interest, at twice the native-scan resolution. In the literature, whole-brain mapping has been used to characterize whole-brain changes over time (44,45), whereas mapping of subregions has been used for serial mapping of specific structures (46) (Supplement 1).

Note that during the mapping procedure, the only manual interaction occurred during the mapping at baseline: before

diffeomorphic transformations, anatomic landmarks were placed by expert raters who were blinded to the group status of the scan being landmarked. Detailed landmarking procedures can be found in our previous publications (9,38,39,41).

Statistical Analysis

The left and right volumes of each structure at baseline and follow-up were computed as the volumes enclosed by the transformation-derived surfaces. There were no missing values in the data. These volumes were entered into a repeated-measures analysis of variance (RM-ANOVA) model, with diagnostic group as the main effect, and hemisphere and time as repeated factors. The main group and time effects and group-by-time interaction were examined. Baseline group effect was also examined in a similar RM-ANOVA.

To quantitate surface shape, we first applied principal components analysis (PCA) to the baseline right-hand-side surfaces for dimensionality reduction. The first 15 principal components (PC) accounted for more than 80% of total variance in the right hemisphere surface in all structures (range: 82.9%–97.7%). There were no missing values in the data. For each structure, the 15 PC scores were entered into a RM-ANOVA with diagnostic group as the main effect, and hemisphere and time as repeated factors. The 15 PCs were modeled in a general linear model (GLM) as repeated factors of identity type. The PC-by-group term was then reported as the main group effect across all PCs. Modeling the PCs in this doubly repeated-measures analysis was equivalent to an RM-MANOVA with a customized transformation matrix in which within each PC, the follow-up score was subtracted from the baseline score. Main effects of group and time and group-by-time interaction were examined. Baseline group effect was also examined in a similar RM-ANOVA. Finally, for each subject and structure at each time point, a canonical score (8) was computed based on the left-right average PC scores and was used to correlate with other measures (discussed later).

Correlation with Cognition and Psychopathology

We calculated the residualized change for all cognition and psychopathology variables by regressing the baseline variables onto the follow-up variables, and then subtracting the predicted follow-up value from the observed follow-up value. The relationship between changes in measures of cognition, psychopa-

thology and measures of change in brain structure were then examined by calculating the correlations between the residualized measures (47) using Spearman's rho. Significance was not adjusted for multiple comparisons because these relationships were examined on an exploratory basis.

Results

Participants

Compared with the subjects who returned for follow-up, subjects who did not return were younger (30.8 ± 13.5 years, $p = .027$) and had a shorter duration of illness (10.5 ± 9.9 years, $p = .013$) at baseline, but they did not differ in psychopathology as assessed using the total scores from SAPS ($p = .23$) and SANS ($p = .65$).

For the schizophrenia subjects, a repeated-measures general linear model with time as a repeated factor on clinical symptom domain scores showed no time effect for positive symptoms ($F = .67$, $df = 1,54$, $p = .42$) or thought disorganization ($F = 1.8$, $df = 1,54$, $p = .18$). However, there was a time effect for negative symptoms ($F = 5.2$, $df = 1,54$, $p = .027$). Over the period of study, negative symptoms improved from .35 at baseline to .11 at follow-up.

As expected, there were significant group effects at baseline for all four cognitive domain scores ($p < .0001$, see Table 2). Further, a repeated-measures general linear model with time as a repeated factor showed no time effect for working memory ($F = .08$, $df = 1,51$, $p = .77$), episodic memory ($F = .14$, $df = 1,51$, $p = .70$), or crystallized IQ ($F = .14$, $df = 1,51$, $p = .70$). However, there was a significant time effect for executive function ($F = 5.0$, $df = 1,51$, $p = .029$), that is, the domain scores changed from $-.56$ at baseline to $-.40$ at follow-up, reflecting mild improvement.

Thalamus

For volume, baseline group effect trended toward significance, with schizophrenia subjects having smaller left and right volumes (see Tables 3 and 4). Longitudinal analysis showed a trend toward significant main group effect, a significant time effect, and a trend toward significant group-by-time interaction, with the schizophrenia subjects showing a more rapid 2-year reduction as compared to the comparison subjects (see Tables 3 and 4). The hemisphere effect was significant in both the baseline ($R > L$, $F = 18.2$, $df = 1,116$, $p < .0001$) and longitudinal

Table 2. Means (SD) Z Scores of Psychopathology and Cognitive Measures at Baseline and Follow-Up

	Schizophrenia			Comparison		
	Baseline	Follow-up	Change (%)	Baseline	Follow-up	Change (%)
Psychopathology						
Positive symptoms	.27 (.91)	.39 (1.07)	46.0	—	—	—
Negative symptoms	.35 (.71)	.11 (.72)	-69.4 ^a	—	—	—
Disorganized thought	.24 (.70)	.42 (.84)	74.7	—	—	—
Global SAPS	4.43 (3.02)	5.24 (4.19)	18.2	—	—	—
Global SANS	8.96 (4.30)	7.67 (4.64)	-14.5	—	—	—
Cognition						
Working memory	-.47 (.73) ^b	-.49 (.65)	-4.7 ^c	.41 (.71)	.58 (.69)	39.7 ^a
Episodic memory	-.66 (.67) ^b	-.71 (.68)	-7.7	.59 (.68)	.52 (.71)	-12.1
Executive function	-.55 (.67) ^b	-.38 (.78)	30.5 ^a	.48 (.52)	.63 (.57)	32.9 ^a
Crystallized IQ	-.51 (.96) ^b	-.55 (.91)	-6.6	.45 (.81)	.52 (.79)	15.2

The percentage change was calculated as $100 * (\text{follow-up} - \text{baseline}) / \text{abs}(\text{baseline})$. The effects of group (at baseline), time, and group-by-time interaction were computed via a repeated-measures mixed model.

^aTime effect $p < .05$.

^bBaseline group difference $p < .0001$.

^cGroup-by-time interaction $p < .05$.

Table 3. Mean (SD) of Volumes at Baseline and Follow-Up: Thalamus, Hippocampus, Amygdala, Nucleus Accumbens, Caudate Nucleus, Globus Pallidus, and Putamen

	Schizophrenia			Comparison		
	Baseline	Follow-up	Change (%)	Baseline	Follow-up	Change (%)
Thalamus						
L	7241 (851)	7122 (891)	-1.64	7573 (687)	7536 (729)	-.49
R	7380 (934)	7296 (991)	-1.14	7722 (704)	7702 (737)	-.25
Hippocampus						
L	2312 (306)	2271 (306)	-1.75	2402 (350)	2388 (347)	-.58
R	2735 (424)	2698 (414)	-1.35	2808 (400)	2809 (427)	.06
Amygdala						
L	1512 (248)	1466 (243)	-3.04	1519 (194)	1489 (197)	-2.00
R	1579 (266)	1531 (260)	-3.01	1700 (254)	1667 (251)	-1.92
Caudate Nucleus						
L	3354 (391)	3301 (429)	-1.58	3418 (414)	3437 (385)	.54
R	3289 (381)	3229 (424)	-1.82	3391 (424)	3394 (411)	.09
Nucleus Accumbens						
L	402 (69)	396 (75)	-1.49	414 (55)	417 (60)	.80
R	410 (65)	405 (71)	-1.12	407 (56)	410 (62)	.68
Putamen						
L	5039 (706)	5058 (707)	.38	5026 (672)	5064 (682)	.76
R	4921 (750)	4911 (765)	-.20	4914 (645)	4937 (676)	.48
Globus Pallidus						
L	1669 (227)	1663 (249)	-.33	1671 (184)	1655 (200)	-.96
R	1672 (237)	1672 (251)	-.04	1679 (204)	1671 (213)	-.45

In addition to Mean (SD), also listed are percent changes of each structural volume across time for each group. Results of statistical comparison of volume differences and volume changes can be found in Table 4 and Table 5.

models ($F = 21.6$, $df = 1,115$, $p < .0001$). Further analysis showed no hemisphere-by-group interaction at baseline ($F = 0$, $df = 1,115$, $p = .95$), or hemisphere-by-group-by-time interaction ($F = .11$, $df = 1,115$, $p = .74$).

For surface shape, baseline group effect was significant. Longitudinal analysis showed significant group effect, time effect, and group-by-time interaction. The hemisphere effect was significant in both the baseline ($F = 12.8$, $df = 15,102$, $p < .0001$) and longitudinal models ($F = 12.5$, $df = 15,101$, $p < .0001$). Further analysis showed no hemisphere-by-group interaction at baseline ($F = 1.2$, $df = 15,102$, $p = .30$) or hemisphere-by-group-by-time interaction ($F = 1.3$, $df = 15,101$, $p = .21$).

Hippocampus

For volume, baseline group effect was not significant. Longitudinal analysis showed a significant time effect without a significant group effect and group-by-time interaction. The hemisphere effect was significant in both the baseline ($R > L$, $F = 519$, $df = 1,114$, $p < .0001$) and longitudinal models ($F = 476$, $df = 1,113$, $p < .0001$). Further analysis showed no hemisphere-by-group interaction at baseline ($F = .24$, $df = 1,114$, $p = .62$), or hemisphere-by-group-by-time interaction ($F = .51$, $df = 1,113$, $p = .47$).

For surface shape, baseline group effect not significant. Longitudinal analysis showed significant time effect and group-by-time interaction without significant group effect. The hemisphere effect was significant in both the baseline ($F = 417$, $df = 15,100$, $p < .0001$) and longitudinal models ($F = 411$, $df = 15,99$, $p < .0001$). Further analysis showed no hemisphere-by-group interaction at baseline ($F = 1.0$, $df = 15,100$, $p = .42$), or hemisphere-by-group-by-time interaction ($F = .46$, $df = 15,99$, $p = .95$).

Amygdala

For volume, baseline group effect was significant, with schizophrenia subjects having smaller volumes on both the left and right sides. Longitudinal analysis showed a significant group effect and time effect with no group-by-time interaction. The hemisphere effect was significant in both the baseline ($R > L$, $F = 33$, $df = 1,114$, $p < .0001$) and longitudinal models ($F = 32$, $df = 1,113$, $p < .0001$). Further analysis showed significant hemisphere-by-group interaction at baseline reduced asymmetry for schizophrenia ($F = 7.1$, $df = 1,114$, $p = .009$) but no hemisphere-by-group-by-time interaction ($F = 1.12$, $df = 1,113$, $p = .29$).

For surface shape, baseline group effect was significant. Longitudinal analysis showed significant group effect and time effect with no group-by-time interaction. The hemisphere effect was significant in both the baseline ($F = 295$, $df = 15,100$, $p < .0001$) and longitudinal models ($F = 285$, $df = 15,99$, $p < .0001$). Further analysis showed trend toward significant hemisphere-by-group interaction at baseline ($F = 1.7$, $df = 15,100$, $p = .067$) but no hemisphere-by-group-by-time interaction ($F = .79$, $df = 15,99$, $p = .68$).

Caudate Nucleus

For volume, baseline group effect was not significant. Longitudinal analysis showed a trend toward a significant main group effect, no significant time effect, and a significant group-by-time interaction, with the schizophrenia subjects showing a more rapid 2-year reduction compared with the comparison subjects. The hemisphere effect was significant in both the baseline ($R < L$, $F = 9.2$, $df = 1,116$, $p = .003$) and longitudinal models ($F = 11$, $df = 1,115$, $p = .0015$). Further analysis showed no hemisphere-by-group interaction at baseline ($F = 1.5$, $df = 1,116$, $p = .21$) nor

Table 4. Statistical Comparisons of Thalamus, Hippocampus, Amygdala, Nucleus Accumbens, Caudate Nucleus, Globus Pallidus, and Putamen, with No Covariates

	Measure	Baseline	Longitudinal		
		<i>F</i> (<i>df</i> ₁ , <i>df</i> ₂) <i>p</i>	Group Effect	Time Effect	Group-by-Time Interaction
Thalamus	Volume	2.79 (2,115) .066	2.2 (4,112) .074	14.55 (1,115) .0002	3.86 (1,115) .052
	Shape	2.54 (15,102) .0031	2.97 (15,101) .0006	5.27 (15,101) <.0001	1.91 (15,101) .031
Hippocampus	Volume	1.35 (2,113) .26	1.15 (4,110) .34	8.04 (1,113) .0054	1.25 (1,113) .27
	Shape	.95 (15,100) .52	.93 (15,99) .53	4.71 (15,99) <.0001	2.22 (15,99) .010
Amygdala	Volume	4.15 (2,113) .018	2.67 (4,110) .036	32.2 (1,113) <.0001	.18 (1,113) .68
	Shape	2.54 (15,100) .0031	2.49 (15,99) .0037	3.77 (15,99) <.0001	.47 (15,99) .95
Caudate Nucleus	Volume	1.39 (2,115) .25	2.1 (4,112) .086	2.14 (1,115) .15	5.23 (1,115) .024
	Shape	2 (15,102) .022	2.04 (15,101) .019	2.8 (15,101) .0011	1.78 (15,101) .047
Putamen	Volume	.01 (2,115) .99	.36 (4,112) .83	1.21 (1,115) .27	1.1 (1,115) .30
	Shape	2.14 (15,102) .013	2.16 (15,101) .013	4.09 (15,101) <.0001	1.09 (15,101) .38
Nucleus Accumbens	Volume	1.67 (2,115) .19	1.55 (4,112) .19	.1 (1,115) .76	2.74 (1,115) .10
	Shape	1.68 (15,102) .066	1.48 (15,101) .13	2.53 (15,101) .0032	2.23 (15,101) .0096
Globus Pallidus	Volume	.02 (2,115) .98	.23 (4,112) .92	2.3 (1,115) .13	.79 (1,115) .37
	Shape	1.82 (15,102) .042	1.85 (15,101) .037	1.5 (15,101) .12	.71 (15,101) .77

Significant ($p < .05$) effects are shown in bold.

hemisphere-by-group-by-time interaction ($F = .2$, $df = 1,115$, $p = .66$).

For surface shape, baseline group effect was significant. Longitudinal analysis showed significant group effect, time effect, and group-by-time interaction. The hemisphere effect was significant in both the baseline ($F = 14$, $df = 15,102$, $p < .0001$) and longitudinal models ($F = 14$, $df = 15,101$, $p < .0001$). Further analysis showed no hemisphere-by-group interaction at baseline ($F = 1.2$, $df = 15,102$, $p = .29$), nor hemisphere-by-group-by-time interaction ($F = .62$, $df = 15,101$, $p = .85$).

Putamen

For volume, baseline group effect was not significant. Longitudinal analysis showed no significant group effect, time effect, or group-by-time interaction. The hemisphere effect was significant in both the baseline ($R < L$, $F = 21$, $df = 1,116$, $p < .0001$) and longitudinal models ($F = 22$, $df = 1,115$, $p < .0001$). Further analysis showed no hemisphere-by-group interaction at baseline ($F = .01$, $df = 1,116$, $p = .92$), nor hemisphere-by-group-by-time interaction ($F = .52$, $df = 1,115$, $p = .47$).

For surface shape, baseline group effect was. Longitudinal analysis showed significant group effect and time effect, without group-by-time interaction. The hemisphere effect was significant in both the baseline ($F = 6.0$, $df = 15,102$, $p < .0001$) and longitudinal models ($F = 6.0$, $df = 15,101$, $p < .0001$). Further analysis showed no hemisphere-by-group interaction at baseline ($F = 1.5$, $df = 15,102$, $p = .11$), nor hemisphere-by-group-by-time interaction ($F = .84$, $df = 15,101$, $p = .63$).

Nucleus Accumbens

For volume, baseline group effect was not significant. Longitudinal analysis showed no significant group effect, time effect or group-by-time interaction. The hemisphere effect was not significant in either the baseline ($F = .02$, $df = 1,116$, $p = .89$) or longitudinal model ($F = .02$, $df = 1,115$, $p = .89$).

For surface shape, baseline group effect trended toward significance. Longitudinal analysis showed significant time effect and group-by-time interaction without significant group effect. The hemisphere effect was significant in both the baseline ($F = 12$, $df = 15,102$, $p < .0001$) and longitudinal models ($F = 12$, $df = 15,101$, $p < .0001$). Further analysis showed a significant hemisphere-by-group interaction at baseline ($F = 1.9$, $df = 15,102$, $p = .033$) but no hemisphere-by-group-by-time interaction ($F = .81$, $df = 15,101$, $p = .67$).

Globus Pallidus

For volume, baseline group effect was not significant. Longitudinal analysis showed no significant main group effect, time effect, or group-by-time interaction. The hemisphere effect was not significant in either the baseline or longitudinal models. Further analysis showed no hemisphere-by-group interaction at baseline nor hemisphere-by-group-by-time interaction.

For surface shape, baseline group effect was significant. Longitudinal analysis showed significant group effect with a significant time effect or group-by-time interaction. The hemisphere effect was significant in both the baseline ($F = 8.1$, $df = 15,102$, $p < .0001$) and longitudinal models ($F = 9.1$, $df = 15,101$,

Table 5. Statistical Comparisons of Thalamus, Hippocampus, Amygdala, Nucleus Accumbens, Caudate Nucleus, Globus Pallidus, and putamen, with Atlas Scaling Factor at Baseline as a Covariate

<i>F</i> (<i>df</i> ₁ , <i>df</i> ₂) <i>p</i>	Measure	Baseline		Longitudinal	
		Group Effect	Group Effect	Time Effect	Group-by-Time Interaction
Thalamus	Volume	1.5 (2,109) .23	1.22 (4,106) .31	.05 (1,109) .83	2.7 (1,109) .10
	Shape	2.58 (15,96) .0027	3.07 (15,95) .0005	.89 (15,95) .58	2.03 (15,95) .021
Hippocampus	Volume	.41 (2,107) .67	.46 (4,104) .76	.46 (4,104) .76	.96 (1,107) .33
	Shape	.66 (15,94) .82	.63 (15,93) .85	1.06 (15,93) .41	2.2 (15,93) .011
Amygdala	Volume	3.79 (2,107) .026	2.75 (4,104) .032	0 (1,107) .96	.06 (1,107) .81
	Shape	2.26 (15,94) .009	2.24 (15,93) .0099	1.18 (15,93) .30	.51 (15,93) .93
Caudate Nucleus	Volume	.56 (2,109) .57	1.47 (4,106) .22	2.2 (1,109) .14	5.48 (1,109) .021
	Shape	1.65 (15,96) .074	1.67 (15,95) .070	.51 (15,95) .93	1.79 (15,95) .046
Putamen	Volume	.82 (2,109) .44	.78 (4,106) .54	.35 (1,109) .56	.84 (1,109) .36
	Shape	1.72 (15,96) .060	1.72 (15,95) .060	1.1 (15,95) .36	1.05 (15,95) .42
Nucleus Accumbens	Volume	.78 (2,109) .46	1.16 (4,106) .33	.85 (1,109) .36	3.08 (1,109) .082
	Shape	1.26 (15,96) .24	1.07 (15,95) .40	1.26 (15,95) .24	1.73 (15,95) .059
Globus Pallidus	Volume	.63 (2,109) .54	.61 (4,106) .65	1.49 (1,109) .23	1.44 (1,109) .23
	Shape	1.41 (15,96) .16	1.38 (15,95) .17	1.94 (15,95) .028	.56 (15,95) .90

Significant ($p < .05$) effects are in bold.

$p < .0001$). Further analysis showed no hemisphere-by-group interaction at baseline ($F = .78$, $df = 15,102$, $p = .70$) nor hemisphere-by-group-by-time interaction ($F = .36$, $df = 15,101$, $p = .99$).

Covariate

Statistical comparisons using baseline ASF as a covariate are reported in Table 5. Group and time effects for the thalamus volume and time effect for the thalamus surface shape became nonsignificant. Time effect for the hippocampus volume and surface shape became nonsignificant. Time effect for the amygdala volume and surface shape became nonsignificant. Time effect for the caudate nucleus surface shape became nonsignificant. Time effect for the putamen surface shape became nonsignificant. Baseline group effect and time effect for the nucleus accumbens surface shape became nonsignificant. Group effect for the globus pallidus surface shape became nonsignificant; however, the time effect for its shape became significant. All other effects remained unchanged.

Correlation with Changes in Psychopathology and Cognition in Schizophrenia Subjects

There was a correlation between the residualized change in positive symptoms and the residualized change in thalamus shape (canonical score: $r = .32$, $p = .019$). As the shape of the thalamic surface became progressively more abnormal (i.e., more disparate from the surface shape of the healthy comparison subjects), positive symptoms became more severe. A similar inverse correlation at the trend level was found between the residualized change in positive symptoms and thalamic volume ($r = -.25$, $p = .066$).

As the thalamic volume became progressively smaller, positive symptoms became more severe. These correlations remained significant after partialling out baseline ASF (canonical score: $r = .34$, $p = .017$; volume: $r = -.28$, $p = .051$). No other correlations between changes in psychopathology and brain structure were significant.

There was a correlation between the residualized change in episodic memory and the residualized change in caudate nucleus shape ($r = .39$, $p = .0039$). Worsened episodic memory performance was associated with progressively more abnormal shape of the caudate nucleus surface (i.e., more disparate from the surface shape of the healthy comparison subjects). This correlation remained significant after partialling out baseline ASF ($r = .38$, $p = .0084$). There was a correlation between the residualized change in crystallized IQ and the residualized change in nucleus accumbens shape ($r = -.45$, $p = .0008$) and globus pallidus shape ($r = -.30$, $p = .030$). Lowered crystallized IQ was associated with progressively more abnormal shape of the nucleus accumbens and globus pallidus surfaces (i.e., more disparate from the surface shape of the healthy comparison subjects). These correlations remained significant after partialling out baseline ASF (Na: $r = -.49$, $p = .0004$; Pl: $r = -.26$, $p = .078$). There were no other correlations between changes in cognition and brain structure.

Effect of Antipsychotic Treatment During the Study Period

Because some evidence suggest that antipsychotic medications may affect cortical gray matter (48,49), we assessed the impact of the type of antipsychotic drug treatment on changes in brain structure in

the schizophrenia subjects by examining the effects of time and time-by-drug treatment type (atypical vs. typical antipsychotics) interaction on measures of structure volume and shape. We found that the thalamic shape showed a significant time-by-treatment type interaction ($F = 2.01$, $df = 15,36$, $p = .043$). In individuals with schizophrenia treated with atypical antipsychotics during the 2-year follow-up period, the inward deviation of the thalamic surface in the superior and lateral regions was deeper relative to subjects treated with typical antipsychotics during that same time period (not shown). There were no other time effects or time-by-treatment interactions for other brain structures.

Discussion

In this study, we found that progressive change in the deep brain nuclei and hippocampal-amygdala formation in subjects with schizophrenia was of modest magnitude and extent: As predicted, the structure of the thalamus, caudate, hippocampus, and nucleus accumbens showed disease-specific progressive (shape) changes, whereas the globus pallidus did not. However, putamen and amygdala showed progressive changes that were similar in the groups of schizophrenia and comparison subjects. When adjusted for ASF, only thalamus, caudate, and hippocampus showed group differences in the rate of shape change.

In several structures, we found that changes in brain structural shape showed more substantial group differences, whereas volume changes were small and not widespread. That abnormality of shape change could be revealed without significant volume reductions was consistent with our previous studies of brain structure in schizophrenia (7,50,51). This pattern of findings suggests that schizophrenia is associated with progressive changes in particular subregions rather than the entire extent of a given structure. However, because the observed progressive change is not a widespread phenomenon in subjects with schizophrenia but of modest magnitude and limited to only a few structures, interpretation of finding should be made with caution. Figure 1 depicts the differential pattern of progressive change in the thalamus and caudate surfaces for the schizophrenia and comparison subjects. The tha-

lamic surface regions approximating the ventrolateral nucleus and the central part of the caudate nucleus are marked in red and white circles, respectively. Regions where the most clear group differences occurred included the ventrolateral (as well as ventroanterior) nuclei of the thalamus, which receive their inputs from the dorsolateral striatum via the direct and indirect pathways through the globus pallidus and interact with motor and premotor areas of the brain (52–56). Even before the advent of antipsychotic medications, individuals with schizophrenia have been observed to develop abnormal involuntary movements (e.g., tardive dyskinesia). Moreover, the ventrolateral and ventroanterior nuclei of the thalamus also interact with the association, sensory, and dorsolateral prefrontal cortices (57–59). Notably, other groups have reported progressive dysfunction in these regions of the cerebral cortex in subjects with schizophrenia (5,13,60–64).

This pattern of findings provides limited support for our overall hypothesis that brain structures that receive direct, excitatory connections from the cortex are more likely to show progressive changes, compared with brain structures that receive indirect, inhibitory connections from the cortex. It is also somewhat consistent with the hypothesis that overactivity of excitatory pathways in the brain may contribute to the neural degeneration that occurs in at least a subgroup of patients with schizophrenia (20,21), although our results indicate that all such brain regions are not equally affected. Detailed postmortem studies of these structures, as well as clinical trials of neuroprotective drugs that target the process of excitotoxicity, may be helpful in further testing of this hypothesis.

It should be noted that the relationship between neurotoxicity and gray matter volumetric reductions is unclear, because possibilities other than neuronal loss, including neuropil, water content, and synaptic pruning, may also account for reductions in gray matter volume as detected by imaging studies. Also, many factors could have contributed to the divergent pattern of time-dependent changes as well as the unaccounted variance observed in this study, and these include intrinsic features of these structures (i.e., plasticity), medication related changes,

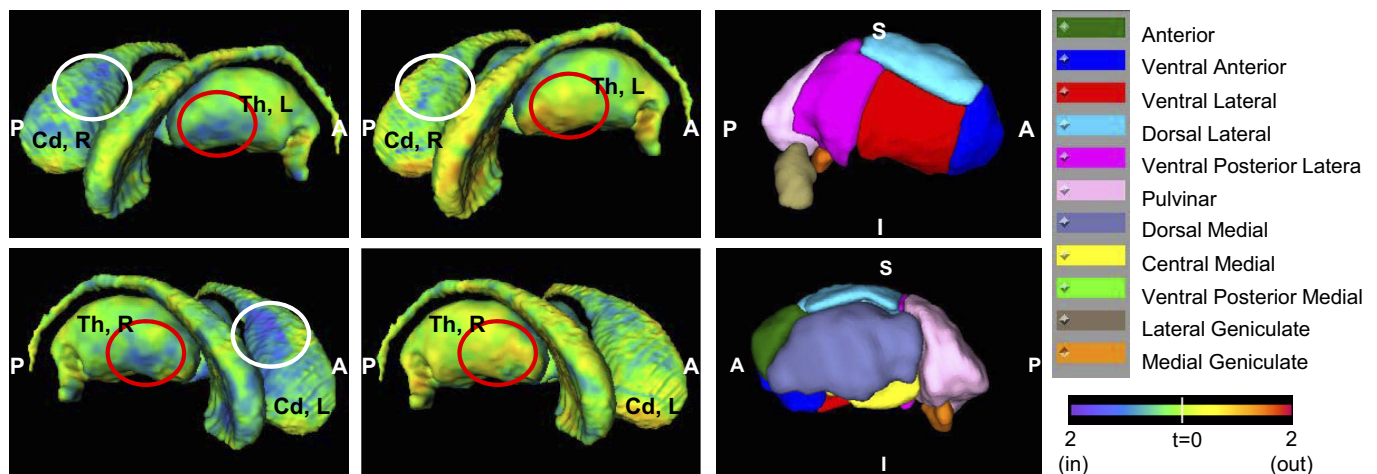


Figure 1. Significant ($p < .05$) effects are in bold. Longitudinal change for the comparison group, lateral views of the left and right caudate and thalamus surfaces. Flame scale reflect t values, and cooler colors ($t < 0$) indicate inward deformation in time of the surface. Circles indicate the location on the surfaces where the longitudinal changes were different between the two subject groups. The red circles mark the thalamic surfaces approximating the dorsolateral nucleus. The white circles mark the central part of the caudate nucleus surface. Right column: Schematic of the major thalamic nuclei as projected onto the template thalamic surface, which was derived according to the images in the atlas text by Mai *et al.* (68). Cd, caudate nucleus; Th, thalamus; L, left; R, right; A, anterior; P, posterior; I, inferior; S, superior.

genetic factors, and sensitivity to stress. For example, caudate nucleus may be more sensitive to D2 blockade than hippocampus (65), and hippocampus may be more vulnerable to stress than the other structures (66,67).

There were several important limitations to this study. First, the sample was one of convenience. The subjects with schizophrenia had a wide variation in duration of illness and were not followed under "controlled" conditions. Those who returned for follow-up may have been more severely affected compared with those who did not return, resulting in the selective retention of schizophrenia subjects with a more progressive component to their illness. However, because of the limited sample size, we were not able to test the hypothesis that neuroanatomic progression may be a feature of a particular subgroup of schizophrenia subjects. Thus, it is possible that larger progressive changes, or progressive changes in a larger number of deep brain nuclei and hippocampal-amygdala formation, might occur as an early feature of the disease process. Second, a significant shape difference could be consistent with either a highly localized volume loss or a change in the conformation of the structure. At present, our methods cannot distinguish between these two possibilities. The changes reported by this study could also be caused by factors other than the underlying disease (schizophrenia), such as antipsychotic medication use and the often marginalized and unhealthy lifestyle of the patient group. Also, the treatment conditions during the time interval were variable between subjects. Thus, similar or different patterns of changes in neuroanatomic structures might be observed in untreated patients or in patients treated with different types of drugs. The presence of a significant time-by-treatment interaction effect on the thalamus shape (but not volume) suggests that progressive changes in particular subregions of the thalamus may also be associated with the type of antipsychotic drug treatment received by the schizophrenia subject. We did not have data on which subject had a history of substance abuse or dependence before the month preceding study enrollment; hence, we cannot address the question of a possible relationship between substance use in schizophrenia and our measures of brain pathology and progression. Another limitation is that the MR images were collected on a relatively low-field (1.5-Tesla) scanner. As with any longitudinal study, the methods used for data collection are often not "cutting edge" by the time the data from all time points have been collected. Higher-field (e.g., 3-Tesla) scanners may produce better contrast-to-noise ratio, which may better reveal changes and differences in the changes.

To our knowledge, this study would be the first to apply the same methods for assessing progressive changes in structure across a wide variety of deep brain nuclei and hippocampal-amygdala formation in subjects with schizophrenia, and thus our results may be particularly valuable for addressing the question of whether progressive changes are characteristic of a particular subset of these structures.

Funding for this study was provided by National Institute of Mental Health Grant No. R01-MH056584, the Conte Center for the Neuroscience of Mental Disorders at Washington University School of Medicine (Grant No. P20-MH071616), and Grant No. P41-RR15241.

The authors reported no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online.

1. Benes FM (2000): Emerging principles of altered neural circuitry in schizophrenia. *Brain Res Brain Res Rev* 31:251–269.
2. Byne W, Buchsbaum MS, Mattiace LA, Hazlett EA, Kemether E, Elhakem SL, *et al.* (2002): Postmortem assessment of thalamic nuclear volumes in subjects with schizophrenia. *Am J Psychiatry* 159:59–65.
3. Altshuler LL, Casanova MF, Goldberg TE, Kleinman JE (1990): The hippocampus and parahippocampus in schizophrenia, suicide, and control brains. *Arch Gen Psychiatry* 47:1029–1034.
4. Andreasen N, Nasrallah HA, Dunn V, Olson SC, Grove WM, Ehrhardt JC, *et al.* (1986): Structural abnormalities in the frontal system in schizophrenia. A magnetic resonance imaging study. *Arch Gen Psychiatry* 43:136–144.
5. Zipursky RB, Lim KO, Sullivan EV, Brown BW, Pfefferbaum A (1992): Widespread cerebral gray matter volume deficits in schizophrenia. *Arch Gen Psychiatry* 49:195–205.
6. Ananth H, Popescu I, Critchley HD, Good CD, Frackowiak RS, Dolan RJ (2002): Cortical and subcortical gray matter abnormalities in schizophrenia determined through structural magnetic resonance imaging with optimized volumetric voxel-based morphometry. *Am J Psychiatry* 159:1497–1505.
7. Csernansky JG, Wang L, Jones D, Rastogi-Cruz D, Posener JA, Heydebrand G, *et al.* (2002): Hippocampal deformities in schizophrenia characterized by high dimensional brain mapping. *Am J Psychiatry* 159:2000–2006.
8. Harms MP, Wang L, Mamah D, Barch DM, Thompson PA, Csernansky JG (2007): Thalamic shape abnormalities in individuals with schizophrenia and their nonpsychotic siblings. *J Neurosci* 27:13835–13842.
9. Mamah D, Wang L, Barch D, de Erausquin GA, Gado M, Csernansky JG (2007): Structural analysis of the basal ganglia in schizophrenia. *Schizophr Res* 89:59–71.
10. Ettinger U, Chitnis XA, Kumari V, Fannon DG, Sumich AL, O'Ceallaigh S, *et al.* (2001): Magnetic resonance imaging of the thalamus in first-episode psychosis. *Am J Psychiatry* 158:116–118.
11. Nakamura M, Salisbury DF, Hirayasu Y, Bouix S, Pohl KM, Yoshida T, *et al.* (2007): Neocortical gray matter volume in first-episode schizophrenia and first-episode affective psychosis: A cross-sectional and longitudinal MRI study. *Biol Psychiatry* 62:773–783.
12. Ho BC, Andreasen NC, Nopoulos P, Arndt S, Magnotta V, Flaum M (2003): Progressive structural brain abnormalities and their relationship to clinical outcome: A longitudinal magnetic resonance imaging study early in schizophrenia. *Arch Gen Psychiatry* 60:585–594.
13. Vidal CN, Rapoport JL, Hayashi KM, Geaga JA, Sui Y, McLemore LE, *et al.* (2006): Dynamically spreading frontal and cingulate deficits mapped in adolescents with schizophrenia. *Arch Gen Psychiatry* 63:25–34.
14. van Haren NE, Hulshoff Pol HE, Schnack HG, Cahn W, Mandl RC, Collins DL, *et al.* (2007): Focal gray matter changes in schizophrenia across the course of the illness: A 5-year follow-up study. *Neuropsychopharmacology*. 32:2057–2066.
15. Lieberman J, Chakos M, Wu H, Alvir J, Hoffman E, Robinson D, *et al.* (2001): Longitudinal study of brain morphology in first episode schizophrenia. *Biol Psychiatry* 49:487–499.
16. Sim K, Cullen T, Ongur D, Heckers S (2006): Testing models of thalamic dysfunction in schizophrenia using neuroimaging. *J Neural Transm* 113: 907–928.
17. Kandel ER, Schwartz JH, Jessell TM (1991): *Principles of Neural Science*, 3rd ed. Norwalk, CT: Appleton & Lange.
18. Carmichael ST, Price JL (1995): Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. *J Comp Neurol* 363:615–641.
19. Barbas H, Blatt GJ (1995): Topographically specific hippocampal projections target functionally distinct prefrontal areas in the rhesus monkey. *Hippocampus* 5:511–533.
20. Olney JW, Newcomer JW, Farber NB (1999): NMDA receptor hypofunction model of schizophrenia. *J Psychiatr Res* 33:523–533.
21. Humphrey WM, Dong H, Csernansky CA, Csernansky JG (2002): Immediate and delayed hippocampal neuronal loss induced by kainic acid during early postnatal development in the rat. *Brain Res Dev Brain Res* 137:1–12.
22. First M, Spitzer R, Gibbon M, Williams J (1995): *Structured Clinical Interview for DSM-IV Axis I Disorders—Patient Edition* (SCID-I/P, Version 2.0). New York: Biometrics Research Department, New York State Psychiatric Institute.
23. American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: American Psychiatric Association.
24. Rastogi-Cruz D, Csernansky J (1997): Clinical rating scales. In: Guze S, editor. *Adult Psychiatry*. St. Louis: Mosby.

25. Andreasen NC (1984): *The Scale for Assessment of Positive Symptoms* (SAPS). Iowa City: University of Iowa.
26. Andreasen NC (1983): *The Scale for Assessment of Negative Symptoms* (SANS). Iowa City: The University of Iowa.
27. Delawalla Z, Barch DM, Fisher Eastep JL, Thomason ES, Hanewinkel MJ, Thompson PA, *et al.* (2006): Factors mediating cognitive deficits and psychopathology among siblings of individuals with schizophrenia. *Schizophr Bull* 32:525–537.
28. Sugiura M, Shah NJ, Zilles K, Fink GR (2005): Cortical representations of personally familiar objects and places: Functional organization of the human posterior cingulate cortex. *J Cogn Neurosci* 17:183–198.
29. Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD (2001): Conflict monitoring and cognitive control. *Psychol Rev* 108:624–652.
30. Carlson S, Martinkauppi S, Rama P, Salli E, Korvenoja A, Aronen HJ (1998): Distribution of cortical activation during visuospatial n-back tasks as revealed by functional magnetic resonance imaging. *Cereb Cortex* 8:743–752.
31. Hirono N, Mori E, Ishii K, Ikejiri Y, Imamura T, Shimomura T, *et al.* (1998): Hypofunction in the posterior cingulate gyrus correlates with disorientation for time and place in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 64:552–554.
32. Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JC (2001): Conflict monitoring and cognitive control. *Psychol Rev* 108:624–652.
33. Brown JW, Braver TS (2005): Learned predictions of error likelihood in the anterior cingulate cortex. *Science* 307:1118–1121.
34. Wechsler D (1997): *Wechsler Adult Intelligence Scale, 3rd ed.* San Antonio, TX: Psychological Corporation.
35. Cornblatt BA, Risch NJ, Faris G, Friedman D, Erlenmeyer-Kimling L (1988): The Continuous Performance Test, identical pairs version (CPT-IP): I. New findings about sustained attention in normal families. *Psychiatry Res* 26:223–238.
36. Venkatesan R, Haacke E (1997): Role of high resolution in magnetic resonance (MR) imaging: Applications for MR angiography, intracranial T1-weighted imaging, and image interpolation. *Int J Imaging Syst Technol* 8:529–543.
37. Buckner RL, Head D, Parker J, Fotenos AF, Marcus D, Morris JC, *et al.* (2004): A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: Reliability and validation against manual measurement of total intracranial volume. *Neuroimage* 23:724–738.
38. Csernansky JG, Wang L, Joshi SC, Ratnanather JT, Miller MI (2004): Computational anatomy and neuropsychiatric disease: Probabilistic assessment of variation and statistical inference of group difference, hemispheric asymmetry, and time-dependent change. *Neuroimage* 23:556–68.
39. Haller JW, Banerjee A, Christensen GE, Gado M, Joshi S, Miller MI, *et al.* (1997): Three-dimensional hippocampal MR morphometry with high-dimensional transformation of a neuroanatomic atlas. *Radiology* 202:504–510.
40. Csernansky JG, Schindler MK, Splinter NR, Wang L, Gado M, Selemon LD, *et al.* (2004): Abnormalities of thalamic volume and shape in schizophrenia. *Am J Psychiatry* 161:896–902.
41. Wang L, Lee DY, Bailey E, Hartlein JM, Gado MH, Miller MI, *et al.* (2007): Validity of large-deformation high dimensional brain mapping of the basal ganglia in adults with Tourette syndrome. *Psychiatry Res* 154:181–190.
42. Freeborough PA, Woods RP, Fox NC (1996): Accurate registration of serial 3D MR brain images and its application to visualizing change in neurodegenerative disorders. *J Comput Assist Tomogr* 20:1012–1022.
43. Buckner RL, Snyder AZ, Shannon BJ, LaRossa G, Sachs R, Fotenos AF, *et al.* (2005): Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *J Neurosci* 25:7709–7717.
44. Freeborough PA, Fox NC (1998): Modeling brain deformations in Alzheimer disease by fluid registration of serial 3D MR images. *J Comput Assist Tomogr* 22:838–843.
45. Fox NC, Crum WR, Scahill RI, Stevens JM, Janssen JC, Rossor MN (2001): Imaging of onset and progression of Alzheimer's disease with voxel-compression mapping of serial magnetic resonance images. *Lancet* 358:201–205.
46. Chan D, Fox NC, Jenkins R, Scahill RI, Crum WR, Rossor MN (2001): Rates of global and regional cerebral atrophy in AD and frontotemporal dementia. *Neurology* 57:1756–1763.
47. Llabre MM, Spitzer SB, Saab PG, Ironson GH, Schneiderman N (1991): The reliability and specificity of delta versus residualized change as measures of cardiovascular reactivity to behavioral challenges. *Psychophysiology* 28:701–711.
48. Lieberman JA, Tollefson GD, Charles C, Zipursky R, Sharma T, Kahn RS, *et al.* (2005): Antipsychotic drug effects on brain morphology in first-episode psychosis. *Arch Gen Psychiatry* 62:361–370.
49. Moore GJ, Bebchuk JM, Wilds IB, Chen G, Manji HK (2000): Lithium-induced increase in human brain grey matter. *Lancet* 356:1241–1242.
50. Csernansky JG, Joshi S, Wang L, Haller JW, Gado M, Miller JP, *et al.* (1998): Hippocampal morphometry in schizophrenia by high dimensional brain mapping. *Proc Natl Acad Sci U S A* 95:11406–11411.
51. Wang L, Joshi SC, Miller MI, Csernansky JG (2001): Quantifying hippocampal asymmetry in schizophrenia. *Schizophr Res* 49:170.
52. Mink JW, Thach WT (1991): Basal ganglia motor control. III. Pallidal ablation: Normal reaction time, muscle cocontraction, and slow movement. *J Neurophysiol* 65:330–351.
53. Mink JW, Thach WT (1991): Basal ganglia motor control. II. Late pallidal timing relative to movement onset and inconsistent pallidal coding of movement parameters. *J Neurophysiol* 65:301–329.
54. Mink JW, Thach WT (1991): Basal ganglia motor control. I. Nonexclusive relation of pallidal discharge to five movement modes. *J Neurophysiol* 65:273–300.
55. Mink JW, Thach WT (1987): Preferential relation of pallidal neurons to ballistic movements. *Brain Res* 417:393–398.
56. McFarland NR, Haber SN (2001): Organization of thalamostriatal terminals from the ventral motor nuclei in the macaque. *J Comp Neurol* 429:321–336.
57. Haber SN, Kim KS, Maily P, Calzavara R (2006): Reward-related cortical inputs define a large striatal region in primates that interface with associative cortical connections, providing a substrate for incentive-based learning. *J Neurosci* 26:8368–8376.
58. Calzavara R, Maily P, Haber SN (2007): Relationship between the corticostriatal terminals from areas 9 and 46, and those from area 8A, dorsal and rostral premotor cortex and area 24c: An anatomical substrate for cognition to action. *Eur J Neurosci* 26:2005–2024.
59. McFarland NR, Haber SN (2000): Convergent inputs from thalamic motor nuclei and frontal cortical areas to the dorsal striatum in the primate. *J Neurosci* 20:3798–3813.
60. Berman KF, Illowsky BP, Weinberger DR (1988): Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. IV. Further evidence for regional and behavioral specificity. *Arch Gen Psychiatry* 45:616–622.
61. Pantelis C, Harvey CA, Plant G, Fosse E, Maruff P, Stuart GW, *et al.* (2004): Relationship of behavioural and symptomatic syndromes in schizophrenia to spatial working memory and attentional set-shifting ability. *Psychol Med* 34:693–703.
62. Ohrmann P, Siegmund A, Suslow T, Spitzberg K, Kersting A, Arolt V, *et al.* (2005): Evidence for glutamatergic neuronal dysfunction in the prefrontal cortex in chronic but not in first-episode patients with schizophrenia: A proton magnetic resonance spectroscopy study. *Schizophr Res* 73:153–157.
63. Selemon LD, Kleinman JE, Herman MM, Goldman-Rakic PS (2002): Smaller frontal gray matter volume in postmortem schizophrenic brains. *Am J Psychiatry* 159:1983–1991.
64. Mendrek A, Kiehl KA, Smith AM, Irwin D, Forster BB, Liddle PF (2005): Dysfunction of a distributed neural circuitry in schizophrenia patients during a working-memory performance. *Psychol Med* 35:187–196.
65. Kohler C, Karlsson-Boethius G (1988): In vivo labelling of rat brain dopamine D-2 receptors. Stereoselective blockade by the D-2 antagonist raclopride and its enantiomer of 3H-spiperone, 3H-N, N-propylnorapomorphine and 3H-raclopride binding in the rat brain. *J Neural Transm* 73:87–100.
66. Patel PD, Lopez JF, Lyons DM, Burke S, Wallace M, Schatzberg AF (2000): Glucocorticoid and mineralocorticoid receptor mRNA expression in squirrel monkey brain. *J Psychiatr Res* 34:383–392.
67. Pryce CR, Feldon J, Fuchs E, Knuesel I, Oertle T, Sengstag C, *et al.* (2005): Postnatal ontogeny of hippocampal expression of the mineralocorticoid and glucocorticoid receptors in the common marmoset monkey. *Eur J Neurosci* 21:1521–1535.
68. Mai JK, Assheuer J, Paxinos G (1997): *Atlas of the Human Brain*. San Diego, CA: Academic Press.