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Title: Localized differences in caudate and hippocampal shape are associated with schizophrenia but not antipsychotic type

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Abstract: Background: Differences in the volume of the caudate and hippocampus in patients with schizophrenia are associated with disease and antipsychotic treatment. The relationship between alterations in caudate and hippocampal shape with disease and antipsychotic treatment has not been thoroughly examined.

Methods: Schizophrenia patients, randomly assigned to haloperidol and olanzapine treatment, underwent longitudinal MRI scans at 3, 6, and 9 months. The caudate and the hippocampus were, bilaterally, segmented from high-resolution brain MRI with an automated technique. The shape of the caudate and the hippocampus were represented as a medial representation (M-rep), a mesh structure derived from these segmentations. The shape of the caudate and hippocampus were derived from the M-repusing two quantitative measures: local width and local deformation. A novel nonparametric statistical method, called adjusted exponentially tilted (ET) likelihood, was used to compare the measures of caudate and hippocampus shape across the three groups, while controlling for covariates of interest.

Results: Contrary to our a priori hypothesese, longitudinal shape change was not observed in the hippocampus or caudate when the haloperidol-treated, olanzapine-treated, and healthy controls were examined in a global analysis. Contrary to our a priori hypothesese, no longitudinal shape change was observed when the three groups were examined individually. Consistent with our a priori hypothesise, both baseline and repeated measures analysis showed differences in local caudate and hippocampal size between haloperidol-treated and olanzapine treated patients and controls. Also consistent with our a priori hypothesise, baseline and repeated-measures cross-sectional analysis, showed no consistent differences in hippocampal or caudate shape between the haloperidol-treated and olanzapine-treated patients.

Conclusions: Regionally specific differences in local hippocampal and caudate shape are present in schizophrenic patients. Longitudinal shape change was not observed haloperidol- and olanzapine-treated patients within the observed time frame in our sample. Regionally specific shape differences between in schizophrenia patients and controls: suggests that the M-reps method is valid and reliable, and; provides additional evidence for the presence of disrupted cortico-basal ganglia-thalamo-cortical

circuits in schizophrenia. These results should be confirmed with replication in a different sample, using a study design that controls for confounding factors.

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- lack of knowledge in schizophrenia

Cover Letter

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Editorial Office of Biological Psychiatry

Please accept the submission of our manuscript titled “Localized differences in caudate and hippocampal shape are associated with schizophrenia but not antipsychotic type ” to Biological Psychiatry. In this manuscript, we present interesting and novel results of hippocampus and caudate shape differences in a longitudinal treatment study of first episode schizophrenics.

Thank you, Sincerely,

Martin Styner

Submission to Biological Psychiatry

Localized differences in caudate and hippocampal shape are associated with schizophrenia but not antipsychotic type

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Abstract:

Background: Differences in the volume of the caudate and hippocampus in patients with schizophrenia are associated with disease and antipsychotic treatment. The relationship between alterations in caudate and hippocampal shape with disease and antipsychotic treatment has not been thoroughly examined.

Methods: Schizophrenia patients, randomly assigned to haloperidol and olanzapine treatment, underwent longitudinal MRI scans at 3, 6, and 9 months. The caudate and the hippocampus were, bilaterally, segmented from high-resolution brain MRI with an automated technique. The shape of the caudate and the hippocampus were represented as a medial representation (M-rep), a mesh structure derived from these segmentations. The shape of the caudate and hippocampus were derived from the M-repusing two quantitative measures: local width and local deformation. A novel nonparametric statistical method, called adjusted exponentially tilted (ET) likelihood, was used to compare the measures of caudate and hippocampus shape across the three groups, while controlling for covariates of interest.

Results: Contrary to our *a priori* hypothesese, longitudinal shape change was not observed in the hippocampus or caudate when the haloperidol-treated, olanzapine-treated, and healthy controls were examined in a global analysis. Contrary to our *a priori* hypothesese, no longitudinal shape change was observed when the three groups were examined individually. Consistent with our *a priori* hypothesise, both baseline and repeated measures analysis showed differences in local caudate and hippocampal size between haloperidol-treated and olanzapine treated patients and controls. Also consistent with our *a priori* hypothesise, baseline and repeated-measures cross-sectional analysis, showed no consistent differences in hippocampal or caudate shape between the haloperidol-treated and olanzapine-treated patients.

Conclusions: Regionally specific differences in local hippocampal and caudate shape are present in schizophrenic patients. Longitudinal shape change was not observed haloperidol- and olanzapine-treated patients within the observed time frame in our sample. Regionally specific shape differences between in schizophrenia patients and controls: suggests that the M-reps method is valid and reliable, and; provides additional evidence for the presence of disrupted cortico-basal ganglia-thalamo-cortical circuits in schizophrenia. These results should be confirmed with replication in a different sample, using a study design that controls for confounding factors.

Introduction:

Converging trends in the neuroimaging of schizophrenia have led to the research conducted in this study. The first trend is the association of altered caudate volume in schizophrenia with antipsychotic treatment. Although reduction in caudate volume has been reported in MRI studies of anti psychotic-naïve, first-episode schizophrenia patients [2-4], before effects associated with treatment and disease chronicity should be observed, there are also negative reports [5, 6]. Cross-sectional MRI studies suggest that treatment with typical antipsychotic medications, at higher doses, can be–but are not always–associated with enlarged caudate in schizophrenia. Dose [6] and treatment findings [7-10] have been observed over periods of twelve to twenty-four months in longitudinal MRI studies. Treatment of schizophrenia with atypical antipsychotics for extended periods is associated with decreases in caudate volume [8], although studies in rodents are not entirely consistent with the human data [11][12].

The second trend is the reduction of hippocampal volume demonstrated in cross-sectional MRI studies in schizophrenia [13]. The size of the hippocampus is reduced at onset of the first episode of psychosis, before the effects associated with treatment and disease chronicity should occur [14, 15]. Longitudinal MRI studies in schizophrenia over treatment periods of two to two and one half years have shown hippocampal and temporal lobe volumes decrease [16, 17], although some studies do not show such changes [15]. The negative findings should be viewed in the context of the common [10, 16, 18-24], but not ubiquitous [15, 25] observation that regional grey matter and white matter volumes can decrease, as well as cerebrospinal fluid volumes increase in longitudinal MRI studies in schizophrenia. Although there have been reports of an association between hippocampal volume and antipsychotic type, the finding are inconsistent. In a cross-sectional MRI study, treatment with atypical antipsychotics, compared to haloperidol treatment, was associated with larger hippocampal volumes, but the relationship was observed only in male patients, early in the course of their illness, rather than

chronically ill patients [26]. In a longitudinal MRI study of first-episode schizophrenic subjects treated with haloperidol, compared to those treated with olanzapine, demonstrated more decreases in gray matter volume after 24, 52 and 104 weeks of treatment. Although it is possible that typical versus atypical antipsychotic treatment is associated with differences in hippocampal volume change, as has been observed in the caudate, there is no conclusive evidence yet.

The third trend is the emergence of medial representations or m-reps [28-30], a shape analysis method providing information on a rich set of features not accessible by conventional volume-based morphometry. Quantitative measures of regional volume are highly variable and method dependent; do not indicate the exact location of the pathology or which sub region of the tissue or region of interest is specifically affected, and thus cannot indicate what specific populations of cells or cytoarchitectural fields may be involved. Shape analysis offers an opportunity to address the weaknesses of conventional volumetric methods. MRI studies performed at the UNC Neuro Image Research and Analysis Laboratory using these high-dimensional statistical descriptions of shape in lateral ventricles [31, 32] and hippocampi [33], have demonstrated effects of genetic relatedness and schizophrenia. An effect of antipsychotic type was observed in hippocampal shape of male patients with schizophrenia that underwent atypical- compared to typical antipsychotic treatment [26]

This investigation examined caudate and hippocampal shape in schizophrenia patients randomly assigned to treatment with haloperidol or olanzapine. The specific purpose of the study was to determine if shape differences in the caudate and hippocampus of schizophrenia patients emerge following haloperidol and olanzapine treatment. The specific outcome measures were two quantitative shape measurements: radius and position. These two quantitative measurements of shape for the caudate and hippocampus were defined through medial representation (M-reps). The ***radius*** measurement quantifies the ***local width*** at M-reps node, and is represented in Figure 1 by length of a

thin rod projecting from a sphere. The l ***position*** measurement quantifies ***local deformation*** at a M-reps node, and is represented in Figure 1 by the location of a sphere. ***Local width*** and ***local deformation*** are the shape measures reported in this study. The following questions were addressed: do haloperidol-, olanzapine-treated patients, and healthy control groups—globally or individually—differ at baseline; do the haloperidol-, olanzapine-treated patients and healthy control groups—globally or individually—differ in a repeated measures analysis; does shape change emerge—globally—among the three groups over time, and; do differences in shape change emerge—individually—over time between the three groups? According to the *a priori* hypotheses, the following results were expected for shape measures in the hippocampus and caudate: (1) at baseline, an effect of diagnosis between schizophrenia patients and controls; (2) in the repeated measures analysis, an effect of diagnosis between schizophrenia patients and controls; (3) at baseline as well as in the repeated-measures analysis, no effect of antipsychotic type between schizophrenia patients in the two treatment groups, and; (4) in the global comparison among, as well as in the group comparisons between, olanzapine-treated patients, haloperidol-treated patients and healthy controls, differences will emerge over time12q d.

Methods:

Subjects were enrolled in a longitudinal, randomized, , multisite, double-blind study [27]. In this study, 238 first-episode schizophrenia patients were enrolled. After random allocation at baseline, 123 patients were selected to receive the conventional antipsychotic haloperidol (2-20 mg/d), and 115 were selected to receive the atypical antipsychotic olanzapine (5-20 mg/d). Patients were treated and followed for up to 47 months. 56 psychiatrically healthy subjects matched to the patients' demographic characteristics were enrolled as control subject (see Table 1 and Table 2). High resolution MRI (multisite SPGR T1 weighted imaging on 1.5 Tesla scanners at 0.9375 x 0.9375 x 1.5mm resolution) was performed at baseline, months 3, 6, 13, 24, 36 and 47 (approximately, with different subjects having different

visiting times, and some subjects dropped out during the course of the study [27]). Covariates of interest were WBV (whole brain volume = cumulative volume of brain CSF, white matter and gray matter), race (Caucasian, African American and others), age (in years), gender, group (the two schizophrenia groups and the healthy control group) and time (visiting times in months). The dependent variables of interest were the two aforementioned shape measures determined at 24 hippocampal nodes and at 21 caudate nucleus nodes of the medial representations: local width, and; local deformation (see Figure 1).

Prior to structural segmentation, the baseline MRI scans was rigidly aligned to a standard coordinate space and follow up MRI scans were globally, affinely aligned to their baseline data. This setup eliminates inherent effects due to changes over time in MR field-of-view size or MR field inhomogeneity. These effects can result in erroneous longitudinal findings if left uncorrected. Caudate and hippocampus structures were then segmented from the aligned MRI scans with an automated atlas based segmentation tool developed in-house called AutoSeg [34]. Caudate and hippocampus shape were next represented as a medial mesh of sampled nodes via a constrained fit into the binary segmentations [29, 31]. Figure 1 illustrates the medial mesh for both structures with the associated medial node labeling used in the result section. Shape was captured as local size (medial width/radius) and local deformation (medial deformation) as proposed in [35]. While local size is independent of pose, appropriate local deformation analysis necessitates a prior alignment. Alignment was performed for caudate and hippocampus independently via an extension of the standard rigid Procrustes alignment to medial structures [44].

The aim of our study was to investigate the difference of the hippocampal medial width and deformation of hippocampi and caudate nucleus across the three groups (haloperidol-treated, olanzapine-treated, and controls) while controlling for other covariates of interest. We utilized a novel nonparametric method, called adjusted exponentially tilted (ET) likelihood, along with a likelihood ratio

test for hypotheses testing [36]. Assuming only a set of estimating equations, the adjusted ET likelihood is a nonparametric extension of general linear mixed models and generalized estimating equations. This extension of the ET method as a nonparametric method is particularly desirable for the analysis of brain morphometry, because the distribution of the morphometric measures often deviates from the Gaussian distribution. For this study, the Shapiro-Wilk normality test was applied to check this parametric assumption at each atom for both the left and right hippocampi and caudate using the residuals. It turned out that the Shapiro-Wilk test rejected the normality assumption at many atoms of both left and right hippocampus hippocampi and caudate structures; therefore our nonparametric adjusted ET method is preferred for the analysis of this data. We first tested the a priori hypothesis at baseline. We used the adjusted ET likelihood to calculate regression parameter estimates and then conducted hypotheses testing to test group differences [36]. The false discovery rate approach was used to correct for multiple comparisons in all atoms for each structure [37]. Secondly, we performed longitudinal data analyses [38]. The advantage of a longitudinal study over a baseline study is that it allows us to determine whether the change pattern of the response is similar across the three groups and whether there is difference in the response across the three groups on average over time. Again, we used the adjusted ET likelihood coupled with the generalized estimating equations for longitudinal data to estimate the regression parameters and then conducted hypotheses testing to examine the specific group differences.

Results

Hippocampal Shape: Local Width and Local Deformation (See Fig 3)**:**

Contrary to our *a priori* hypotheses, the longitudinal analysis did not reveal significant changes in either local width or deformation in the hippocampus (see Tables 7 and 8). The longitudinal global three-group comparison demonstrated a Group x Time interaction of width at nodes M8 (M = Medial),

C2 (C = Central), C3, and L6 (L = Lateral), in the left hippocampus (increasing numeric value = Posterior to Anterior), but only marginally reached statistical significance (Table 7). Longitudinal analysis of the individual haloperidol-treated, olanzapine-treated and control groups demonstrated no effect of time in deformation or width at these four nodes, nor in any other region of left hippocampus (Table 7). Neither longitudinal global three group comparisons, nor longitudinal analysis of the individual haloperidol-treated, olanzapine-treated, or control groups, demonstrated an interaction of Group x Time, or an effect of Time, with respect to local deformation in the in the left hippocampus (see Table 8). Longitudinal analysis also failed to show any Group x Time interaction, or effect of Time with respect to either width or local deformation in right hippocampus (see Tables 7 and 8).

Consistent with our *a priori* hypotheses, the cross-sectional analysis (using measurements at baseline only), as well as the repeated measures analysis (using shape measurements from all the time points) demonstrated significant effects in width (see Tables 3, 4, 5, and 6). Significant cross-sectional differences in width at baseline were observed in comparison of the haloperidol-treated patients and controls, localized to an antero-medial (node M8) and several mid-central nodes in the left hippocampus (nodes C3, C4 and C5). The repeated measures analysis of haloperidol-treated patients compared to controls revealed significant differences in width, also localized to antero-medial (node M8), and mid-central (nodes C3 and C4) nodes in the left hippocampus. Significant differences in width were observed in the baseline analysis comparison of olanzapine-treated patients to controls, also localized to the mid-central nodes of the left hippocampus (nodes C4 and C5). The repeated-measures analysis did not show significant differences in width, in the comparison of olanzapine-treated patients compared to control in any left or right hippocampal region. As expected, neither the baseline nor the repeated-measures analysis showed any significant differences in width between haloperidol-treated or olanzapine-treated patients in width in the left hippocampus.

In both the baseline and the repeated-measures analysis, both patient groups compared to controls showed differences local hippocampal deformation at the medial nodes (see Tables 5 and 6). Haloperidol-treated patients compared to controls showed differences in the local deformation throughout medial, central and lateral regions nodes of the left hippocampus (nodes M1, M3, M4, M7, M8, C1, C3, C4, C5, C7, C8, L1, L2, L4, L5, and L8) with both the baseline and the repeated-measures analysis. In the baseline analysis only, the olanzapine-treated patients compared to controls showed differences in local deformation in medial, central and lateral nodes the left hippocampus, overlapping with the nodes showing shape differences in the comparison of haloperidol-treated patients compared to controls. However, in the repeated-measures analysis, olanzapine-treated patients compared to controls showed differences in local deformation in only a few of these s, in the repeated measures analysis (left hippocampal nodes M8, C1, L4).

No significant differences in local deformation left hippocampal position in the left hippocampus were observed between haloperidol-treated or olanzapine-treated patients in the left hippocampus in either cross-sectional analysis (Tables 5 and 6). In the right hippocampus, differences in local deformation were observed in the repeated measures analysis between haloperidol-treated patients and controls localized to medial, central and lateral nodes (right hippocampal nodes M1, M7, M8, C1, C3, C6, C7, L2, and L7), but no differences in local deformation were noted in the right hippocampus between either the olanzapine-treated patients compared to healthy controls or the olanzapine-treated compared to and haloperidol -treated patients.

Caudate Shape: Local Width and Local Deformation (See Fig 3)**:**

Contrary to our *a priori* hypotheses, there was little evidence for significant longitudinal caudate shape change, in either width or local deformation (see Tables 13 and 14). Global comparison of the three groups in the longitudinal analysis demonstrated a Group x Time interaction in local width

localized to the left caudate at superior and inferior nodes (nodes S5 and I1, Node location: S = Superior, C = Central, I = Inferior; 1 ... 7 = Posterior to Anterior), but these findings only marginally reached statistical significance No effect of Time was observed in local width at nodes S5 and I1 in the individual group longitudinal analysis the haloperidol-, olanzapine-treated patients or controls. In the right caudate, global comparison of the three groups in the longitudinal analysis demonstrated a Group x Time interaction in local width at superior and inferior nodes (nodes S1, S4 and I2), but no effect of Time was observed in the individual longitudinal analysis of the haloperidol-, olanzapine-treated patients or the controls. Longitudinal analysis of deformation did not show significant effects in either left or right caudate. Specifically, global analysis of the three groups did not show any Group x Time interaction in the left or right caudate.

The baseline and repeated measures cross-sectional analysis performed for left and right caudate width, showed highly similar results, with respect to regional specificity (Tables 9, 10). The treatment group comparisons showed no left caudate width differences between the haloperidol-treated, or olanzapine-treated patients and controls. In the baseline analysis, haloperidol-treated patients compared to controls, showed significant differences in right caudate width, localized to superior and inferior nodes (nodes S4 and I7). The cross-sectional analysis also showed right caudate width differences at node I7. Olanzapine-treated patients compared to normal controls also had significant right caudate width differences localized to a superior node (node S4) in the baseline, but not the cross-sectional analysis. No significant differences were observed between haloperidol-treated or olanzapine-treated patients in the right caudate in the cross-sectional analysis.

Cross-sectional analysis of local deformation in both patient groups compared to controls showed widespread differences in the caudate (Tables 11 and 12). In the baseline analysis, haloperidol-treated patients compared to controls showed differences in deformation in the left caudate localized

to superior, central and inferior nodes (nodes S2-8, C1, C3, C4, I1-I6), which was also reflected in the repeated measures analysis, since haloperidol-treated patients compared to controls also showed significant differences in deformation in superior, central and inferior nodes (S2, S5, S6, C3, I1, I2 and I6). Olanzapine-treated patients compared to controls showed differences in deformation in superior, central and inferior nodes of the left caudate (nodes S2-5, C1, C4, I1-4, and I6 and I7). One superior node in the left caudate (S2) showed differences in deformation when the haloperidol-treated and the olanzapine-treated patients were compared (Table 12), but this finding was not regionally widespread or observed in width. Cross-sectional analysis of right caudate deformation demonstrated similar differences between both treatment groups and controls: in haloperidol-treated patients, differences in local deformation were observed at nodes S2-6, C1, C5, I1-6; in olanzapine-treated patients differences in local deformation were observed at nodes S1-5, C1 and C2, C5, I1-I4, I6 and I7. No differences in deformation were noted in right caudate between olanzapine- and haloperidol -treated patients (Table 12).

Discussion:

Contrary to our *a priori* hypotheses, longitudinal changes in local width or deformation were not observed globally in haloperidol-, olanzapine-treated patients or controls. Differences in longitudinal change in local width or local deformation were not observed when the three groups themselves were examined individually. Consistent with our *a priori hypotheses*, both cross-sectional analyses, one including only the baseline measures and the repeated-measures including data from all time points, demonstrated differences in left hippocampal width that were localized to medial-posterior and central-mid left hippocampal areas. Differences in local deformation and width between patients and controls in left hippocampal local width were observed in medial-, central- and lateral-anterior, middle and posterior nodes. Furthermore, patients and controls also showed differences in local deformation in medial, central, and lateral anterior-/ posterior- nodes of the right hippocampus. Consistent with our *a*

priori hypotheses, cross-sectional analysis demonstrated differences in caudate local width and deformation between patients and controls that were localized to: superior-middle and inferior-posterior right caudate nodes, as well as; superior-anterior/middle, central-anterior/middle, and inferior-anterior/middle/posterior nodes. Cross-sectional analysis of the haloperidol-treated and olanzapine-treated schizophrenic treatment groups and controls showed a considerable degree of regional overlap of in differences in local deformation and width. Consistent with our *a priori* hypotheses, there were no consistent differences in local width or deformation between the haloperidol and olanzapine-treated patients, which suggest that the M-reps method accurately detected shape differences between patients and controls.

Contrary to our *a priori hypothesis*, and surprising to our team of investigators, significant differences in shape change were not observed over time between haloperidol- and olanzapine-treated patients. There are several potential explanations for why our primary hypothesis was not supported. First, it is possible that the results are false-negative, and that significant shape differences do emerge between the treatment groups, but our methods did not detect these differences emerging over time. This is possible, but unlikely, given that shape differences were observed at baseline between controls and schizophrenic subjects, and that considerable regional overlap existed between the caudate and hippocampal shape differences at baseline between the two treatment groups and controls. Second, it is possible it is possibility our results are true negative. This seems a likely possibility, given that the structural changes in the caudate nucleus associated with typical and atypical antipsychotic treatment are small in size, and not always seen in every study. Third, although shape measures are thought to be more sensitive measures than volume measures, the shape change associated with antipsychotic treatment may be smaller than volume changes, and are not detectable using the M-reps method. Fourth, unidentified confounding factors may have had an effect of shape measures, an effect that was greater than the effects than antipsychotic treatment. It is certainly possible that confounding factors

masked actual shape change, since it is not possible to match subjects on every factor than may alter brain structure. Several factor are attributed to the alteration of brain structures measured with MRI in this population : disease progression [39], whether an altered neurodevelopmental trajectory or a chronic active disease process; external environmental events associated with schizophrenia, that alter the physiology of brain tissue, including : changes in tissue perfusion; changes in fat content, and changes in water content, as well as; changes in the neuronal and non-neuronal tissue compartments in the brain [40]. Several potential confounding factors were not controlled for in this study, including hydration status, body weight, illness severity, and previous antipsychotic medication treatment before entering the study to undergo randomization to typical or antipsychotic medications.

Differences in the shape of the hippocampus and caudate between schizophrenic patients and controls using these methods is a novel finding, though not unexpected. There is extensive evidence of anatomical specificity of connections between the basal ganglia, hippocampus and cerebral cortex[43]. There is also evidence from functional neuroimaging studies suggesting the presence of dysfunctional prefrontal cortical-hippocampal [41] and prefrontal-basal ganglia[42] circuits in schizophrenia. . Demonstrating a direct relationship between altered caudate and hippocampal morphometry with dysfunction of specific circuits, would provide additional evidence for the dysfunction of prefrontal cortical-hippocampal and prefrontal-basal ganglia circuits in schizophrenia.

This study is the first large-scale analysis that specifically examines longitudinal changes in local width and deformation in schizophrenia patients treated with typical and atypical antipsychotics using the M-reps method. The one previous study, performed in our laboratory, had very limited generalizability to the schizophrenic patient population, because it examined a small sample, of exclusively male patients, in a cross-sectional design [26]. The absence of shape differences at baseline

between schizophrenia patients randomized to haloperidol or olanzapine treatment indicates that our execution of the M-reps method was stable and reliable.

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Tables (all in one word doc)

	Age (years)		Baseline Whole Brain Volume (liters)	
	Mean	**SS.D.**	**Mean**	**SS.D.**
Haloperidol	24.14	4.89	1.335	0.129
Olanzapine	23.56	4.63	1.330	0.143
Controls	25.28	3.97	1.368	0.127

Table 1. Demographic Characteristics of Patients and Controls at Baseline

	Gender		Race			
Haloperidol	102	21	65	48	10	123
Olanzapine	89	26	57	45	13	115
Controls	37	19	34	15	7	56

Table 2. Demographic Characteristics of Patients and Controls at Baseline

	left				right		
	HC	OC	HO		HC	OC	HO
M1	0.4396	0.9694	0.6242	M1	0.7874	0.7883	0.5023
M2	0.7946	0.9391	0.6242	M2	0.9893	0.7269	0.5023
M3	0.3858	0.7747	0.9212	M3	0.8162	0.7269	0.5023
M4	0.3858	0.7426	0.9951	M4	0.9893	0.9091	0.9064
M5	0.4820	0.9868	0.6242	M5	0.8138	0.8626	0.5561
M6	0.7946	0.7426	0.8928	M6	0.5340	0.7279	0.5023
M7	0.7946	0.9694	0.9212	M7	0.5340	0.7269	0.9064
M8	0.2057	0.9391	0.1944	M8	0.8162	0.8964	0.9064
C1	0.2057	0.7426	0.9212	C1	0.7744	0.8964	0.5023
C2	0.5291	0.7747	0.8928	C2	0.5340	0.8426	0.5023
C3	**0.0214**	0.7426	0.3256	C3	0.8162	0.8626	0.5023
C4	**0.0214**	0.5760	0.6242	C4	0.9893	0.7269	0.5023
C5	0.1689	0.7426	0.9368	C5	0.7744	0.8626	0.5023
C6	0.2057	0.7438	0.6242	C6	0.8138	0.9091	0.5023
C7	0.5291	0.7426	0.8928	C7	0.9893	0.7269	0.5561
C8	0.3858	0.5760	0.6242	C8	0.7744	0.7269	0.9064
L1	0.3858	0.7438	0.9368	L1	0.7874	0.8250	0.9064
L2	0.6177	0.7747	0.9368	L2	0.7744	0.8426	0.9064
L3	0.7946	0.7426	0.9368	L3	0.5340	0.7269	0.5561
L4	0.7946	0.9391	0.9368	L4	0.7744	0.8426	0.5023
L5	0.6177	0.7438	0.6242	L5	0.8162	0.7279	0.5023
L6	0.5291	0.7426	0.9368	L6	0.8162	0.8626	0.5561
L7	0.2057	0.7747	0.3256	L7	0.8138	0.7269	0.5561
L8	0.6284	0.7747	0.8398	L8	0.7874	0.8627	0.5023

Table 3. Hippocampal Width Full Group Effects

Cross-sectional with repeated measures component
Nodes: M = medial, C =Central, L = Lateral
Node number: 1 = Posterior, 8 = Anterior
Groups: H = Haloperidol; O = Olanzapine; C = Control

	left				right		
	HC	OC	HO		HC	OC	HO
M1	0.7451	0.6138	0.6006	M1	0.6323	0.8251	0.6629
M2	0.6875	0.5964	0.6681	M2	0.7573	0.8251	0.8227
M3	0.3579	0.4833	0.8010	M3	0.5906	0.9691	0.8227
M4	0.2657	0.4833	0.8010	M4	0.8135	0.9691	0.8227
M5	0.6490	0.7403	0.6681	M5	0.6200	0.8251	0.6629
M6	0.7694	0.4194	0.6681	M6	0.3984	0.9691	0.5048
M7	0.7451	0.7103	0.6006	M7	0.5906	0.8251	0.8227
M8	**0.0296**	0.4833	0.6006	M8	0.3984	0.9819	0.5048
C1	0.6490	0.4833	0.9947	C1	0.3984	0.8251	0.8227
C2	0.7694	0.9773	0.6681	C2	0.3984	0.8251	0.5382
C3	**0.0068**	0.4194	0.6006	C3	0.3984	0.9819	0.5048
C4	**0.0068**	**0.0406**	0.6681	C4	0.3984	0.9819	0.5048
C5	**0.0189**	**0.0406**	0.8995	C5	0.3984	0.9691	0.5382
C6	0.1118	0.4833	0.6681	C6	0.5725	0.9819	0.5048
C7	0.7694	0.4833	0.9681	C7	0.6153	0.8251	0.9506
C8	0.7694	0.4833	0.6681	C8	0.3984	0.8251	0.8227
L1	0.7178	0.9660	0.6681	L1	0.5725	0.8251	0.8881
L2	0.7694	0.4833	0.6681	L2	0.8135	0.9691	0.8227
L3	0.7178	0.4833	0.8010	L3	0.3984	0.8251	0.8227
L4	0.7178	0.4833	0.8010	L4	0.5659	0.9691	0.5048
L5	0.5496	0.9773	0.6681	L5	0.5906	0.9691	0.8227
L6	0.7694	0.4833	0.6681	L6	0.5725	0.9691	0.8227
L7	0.2657	0.4833	0.8010	L7	0.8135	0.9691	0.8227
L8	0.2805	0.4833	0.6681	L8	0.6323	0.9691	0.7785

Table 4. Hippocampal Width Baseline Group Effects

Cross-sectional without repeated measures component
Nodes: M = medial, C =Central, L = Lateral
Node number: 1 = Posterior, 8 = Anterior
Groups: H = Haloperidol; O = Olanzapine; C = Control

	left				right		
	HC	OC	HO		HC	OC	HO
M1	**0.0079**	0.0752	0.7655	M1	0.1833	0.6100	0.3733
M2	0.1197	0.5293	0.7655	M2	0.5543	0.6707	0.3680
M3	**0.0271**	0.2168	0.7655	M3	0.3076	0.6100	0.4154
M4	**0.0079**	0.3169	0.7655	M4	0.6575	0.6100	0.3680
M5	0.4365	0.6990	0.7655	M5	0.6150	0.6100	0.5107
M6	**0.0271**	0.2174	0.7655	M6	0.6150	0.6100	0.3680
M7	**0.0018**	0.0997	0.7655	M7	0.1267	0.7488	0.3680
M8	**0.0012**	**0.0354**	0.7655	M8	0.0896	0.6100	0.3680
C1	**0.0012**	**0.0354**	0.7655	C1	0.1984	0.7863	0.6735
C2	0.0620	0.2174	0.7655	C2	0.9746	0.7488	0.3680
C3	**0.0271**	0.2168	0.7655	C3	0.1833	0.7588	0.5107
C4	**0.0044**	0.1582	0.7655	C4	0.6150	0.6100	0.4542
C5	**0.0151**	0.3274	0.7655	C5	0.3076	0.8371	0.5399
C6	0.5531	0.5293	0.7655	C6	0.1521	0.9357	0.3680
C7	**0.0043**	0.0831	0.7655	C7	0.0696	0.8371	0.3680
C8	**0.0014**	0.1582	0.7655	C8	0.1502	0.8371	0.3680
L1	**0.0271**	0.1434	0.7655	L1	0.1709	0.8371	0.3680
L2	**0.0392**	0.3274	0.7655	L2	0.0696	0.6100	0.3680
L3	0.0867	0.3274	0.7655	L3	0.1344	0.6100	0.4154
L4	**0.0000**	**0.0354**	0.7655	L4	0.1267	0.6100	0.7010
L5	**0.0029**	0.0831	0.7655	L5	0.4503	0.6100	0.6872
L6	0.0012	0.0354	0.7655	L6	0.1833	0.6100	0.4154
L7	0.0000	0.1157	0.7655	L7	0.1836	0.6707	0.6735
L8	**0.0000**	0.0662	0.7655	L8	0.1833	0.6100	0.3680

Table 5. Hippocampal Deformation Full Group Effects

Cross-sectional with repeated measures component
Nodes: M = medial, C =Central, L = Lateral
Node number: 1 = Posterior, 8 = Anterior
Groups: H = Haloperidol; O = Olanzapine; C = Control

	left				right		
	HC	OC	HO		HC	OC	HO
M1	**0.0048**	**0.0393**	0.9244	M1	**0.0321**	0.4092	0.3072
M2	0.2094	0.1619	0.6284	M2	0.0562	0.4092	0.3072
M3	**0.0348**	**0.0232**	0.6284	M3	0.3127	0.3936	0.5867
M4	**0.0018**	**0.0250**	0.6284	M4	0.4924	0.4092	0.8997
M5	0.1774	0.3576	0.7572	M5	0.5309	0.4092	0.3072
M6	0.0608	0.1150	0.7837	M6	0.5960	0.6479	0.5867
M7	**0.0010**	**0.0330**	0.7572	M7	**0.0321**	0.4092	0.6235
M8	**0.0048**	**0.0250**	0.6284	M8	**0.0084**	0.4092	0.2232
C1	**0.0131**	**0.0255**	0.9472	C1	**0.0202**	0.4092	0.5361
C2	0.1774	0.2787	0.7572	C2	0.3399	0.5710	0.3072
C3	**0.0004**	**0.0250**	0.6284	C3	**0.0120**	0.4092	0.3072
C4	**0.0004**	**0.0250**	0.7801	C4	0.9634	0.4092	0.3072
C5	0.1312	0.1397	0.9403	C5	0.6639	0.4092	0.7668
C6	0.0608	0.1021	0.6284	C6	**0.0321**	0.4092	0.3104
C7	**0.0014**	**0.0232**	0.9244	C7	**0.0084**	0.5453	0.3072
C8	**0.0013**	**0.0285**	0.6284	C8	0.0538	0.8802	0.3072
L1	**0.0004**	**0.0250**	0.3304	L1	0.0562	0.5134	0.6864
L2	**0.0019**	**0.0250**	0.0576	L2	**0.0120**	0.4092	0.3072
L3	**0.0199**	0.0569	0.3304	L3	0.0550	0.4092	0.5867
L4	**0.0004**	**0.0144**	0.9244	L4	0.1265	0.4092	0.7902
L5	**0.0018**	**0.0250**	0.8571	L5	0.4924	0.4315	0.7547
L6	**0.0012**	**0.0250**	0.6284	L6	0.0795	0.4092	0.5867
L7	**0.0000**	0.0708	0.6284	L7	**0.0405**	0.4335	0.6235
L8	**0.0000**	**0.0250**	0.6284	L8	0.0550	0.4315	0.3104

Table 6. Hippocampal Deformation Baseline Group Effects

Cross-sectional without repeated measures component
Nodes: M = medial, C =Central, L = Lateral
Node number: 1 = Posterior, 8 = Anterior
Groups: H = Haloperidol; O = Olanzapine; C = Control

	left					right			
	group*time	**H time**	**O time**	**C time**		**group*time**	**H time**	**O time**	**C time**
M1	0.6624	0.8285	0.4288	0.8681	M1	0.5959	0.7149	0.268	0.3993
M2	0.2684	0.496	0.5267	0.5443	M2	0.1286	0.5843	0.6252	0.3771
M3	0.5937	0.848	0.4463	0.9243	M3	0.1035	0.3072	0.7212	0.3106
M4	0.4316	0.7987	0.4198	0.9024	M4	0.6955	0.4687	0.7986	0.4193
M5	0.8541	0.9529	0.8242	0.8233	M5	0.6912	0.5588	0.5296	0.864
M6	0.8278	0.9225	0.9506	0.6766	M6	0.3618	0.391	0.5278	0.8987
M7	0.4551	0.9096	0.3007	0.6498	M7	0.4054	0.7022	0.3046	0.7701
M8	**0.0257**	0.3551	0.4598	0.2977	M8	0.9882	0.6015	0.4582	0.5044
C1	0.4004	0.6636	0.3878	0.7083	C1	0.2015		0.3694	0.6508
C2	**0.0466**	0.5744	0.2765	0.2882	C2	0.3499	0.3752	0.8143	0.4528
C3	**0.0435**	0.605	0.2062	0.6757	C3	0.5941	0.5819	0.3382	0.6679
C4	0.1051	0.7993	0.2043	0.4159	C4	0.3237	0.645	0.7088	0.6142
C5	0.0724	0.9994	0.6881	0.3372	C5	0.5744	0.7552	0.4489	0.6957
C6	0.4827	0.7385	0.7506	0.5152	C6	0.0784	0.3017	0.8724	0.252
C7	0.4642	0.8178	0.38	0.3099	C7	0.1982	0.4319	0.6508	0.6335
C8	0.4102	0.5975	0.2344	0.2369	C8	0.6735	0.9479	0.4208	0.7241
L1	0.5060	0.7148	0.9592	0.4169	L1	0.7856	0.7608	0.7663	0.7836
L2	0.2458	0.3641	0.6154	0.8323	L2	0.3776	0.888	0.9058	0.4855
L3	0.4904	0.8154	0.4549	0.4732	L3	0.0718	0.2442	0.6262	0.812
L4	0.5559	0.6717	0.8233	0.5124	L4	0.8677	0.6307	0.7243	0.4845
L5	0.1429	0.756	0.4538	0.312	L5	0.5803	0.5813	0.2786	0.5243
L6	**0.0307**	0.7912	0.7098	0.2566	L6	0.9751	0.8192	0.7346	0.869
L7	0.1788	0.8045	0.2904	0.2291	L7	0.0882	0.934	0.4112	0.4792
L8	0.5361	0.8394	0.3892	0.5541	L8	0.6895	0.522	0.3051	0.5235

Table 7. Hippocampal Width, longitudinal

Time effect, P-value

Nodes: M = medial, C =Central, L = Lateral

Node number: 1 = Posterior, 8 = Anterior

Groups: H = Haloperidol; O = Olanzapine; C = Control

left

	group*time	H time	O time	C time
M1	0.9611	0.7181	0.3917	0.2954
M2	0.3344	0.7779	0.2206	0.1487
M3	0.2527	0.9388	0.1902	0.2739
M4	0.9031	0.9907	0.4296	0.3921
M5	0.8953	0.7213	0.8323	0.4110
M6	0.7936	0.7033	0.4409	0.4911
M7	0.8448	0.8258	0.4403	0.3140
M8	0.4775	0.9040	0.4379	0.2571
C1	0.7788	0.9402	0.4375	0.3597
C2	0.3819	0.8497	0.2845	0.1683
C3	0.5740	0.7334	0.2720	0.3148
C4	0.8610	0.8586	0.2641	0.3628
C5	0.4137	0.9641	0.2729	0.1901
C6	0.9071	0.7381	0.3376	0.6445
C7	0.8972	0.9592	0.3328	0.3487
C8	0.5955	0.9232	0.3139	0.2707
L1	0.6266	0.9867	0.2847	0.2676
L2	0.6306	0.9978	0.3566	0.3505
L3	0.7160	0.7951	0.5331	0.8824
L4	0.7369	0.9315	0.3388	0.5595
L5	0.5627	0.9309	0.2972	0.2324
L6	0.8191	0.7986	0.4541	0.5012
L7	0.2285	0.5915	0.2726	0.1466
L8	0.3612	0.9487	0.1859	0.1626

right

	group*time	H time	O time	C time
M1	0.8820	0.4043	0.7353	0.3789
M2	0.6712	0.7558	0.1903	0.3469
M3	0.8556	0.9630	0.6183	0.8667
M4	0.8142	0.8220	0.6764	0.9016
M5	0.2397	0.8633	0.4457	0.3838
M6	0.5205	0.5850	0.7657	0.2116
M7	0.7891	0.6915	0.6524	0.5085
M8	0.8512	0.8042	0.8757	0.5350
C1	0.9727	0.9500	0.8748	0.6064
C2	0.8971	0.9609	0.4066	0.5154
C3	0.9896	0.9664	0.5598	0.8666
C4	0.8749	0.6688	0.8196	0.9969
C5	0.5134	0.7396	0.6428	0.5320
C6	0.3541	0.6080	0.3382	0.7786
C7	0.5989	0.6991	0.2768	0.4375
C8	0.9998	0.8317	0.5949	0.5823
L1	0.9300	0.4090	0.5643	0.2999
L2	0.9942	0.5367	0.5631	0.3624
L3	1.0000	0.7182	0.7015	0.5703
L4	0.9986	0.8504	0.8499	0.7315
L5	0.7617	0.8904	0.5871	0.8680
L6	0.6222	0.4962	0.5933	0.3638
L7	0.9691	0.7909	0.4710	0.5614
L8	0.9529	0.8134	0.6068	0.6812

Table 8. Hippocampal Deformation, longitudinal

Time effect, P-value,
Nodes: M = medial, C =Central, L = Lateral
Node number: 1 = Posterior, 8 = Anterior
Groups: H = Haloperidol; O = Olanzapine; C = Control

	left				right		
	HC	OC	HO		HC	OC	HO
S1	0.9961	0.9999	0.9995	S1	1.0000	0.9999	1.0000
S2	0.9961	0.9999	0.9995	S2	1.0000	0.9999	1.0000
S3	0.9961	0.9999	0.9995	S3	1.0000	0.9999	1.0000
S4	0.1134	0.2961	0.9995	S4	1.0000	0.9999	1.0000
S5	0.9961	0.9999	0.9995	S5	1.0000	0.9999	1.0000
S6	0.9961	0.9999	0.9995	S6	1.0000	0.9999	1.0000
S7	0.9961	0.9999	0.9995	S7	0.9366	0.9999	1.0000
C1	0.9961	0.9999	0.9995	C1	0.9382	0.9999	1.0000
C2	0.9961	0.9999	0.9995	C2	1.0000	0.9999	1.0000
C3	0.9961	0.9999	0.9995	C3	1.0000	0.9999	1.0000
C4	0.9961	0.9999	0.9995	C4	1.0000	0.9999	1.0000
C5	0.9961	0.9999	0.9995	C5	1.0000	0.9999	1.0000
C6	0.9961	0.9999	0.9995	C6	1.0000	0.9999	1.0000
C7	0.9961	0.9999	0.9995	C7	1.0000	0.9999	1.0000
I1	0.9961	0.9999	0.9995	I1	1.0000	0.9999	1.0000
I2	0.9961	0.9999	0.9995	I2	1.0000	0.9999	1.0000
I3	0.9961	0.9999	0.9995	I3	1.0000	0.9999	1.0000
I4	0.9961	0.9999	0.9995	I4	1.0000	0.9999	1.0000
I5	0.9961	0.9999	0.9995	I5	1.0000	0.9999	1.0000
I6	0.4820	0.9999	0.9995	I6	0.1796	0.9999	1.0000
I7	0.4865	0.9999	0.9995	I7	**0.0042***	0.9999	1.0000

Table 9. Caudate Width Full Group Effects

Cross-sectional with repeated measures component
Nodes: S = Superior, C =Central, I = Inferior
Node number: 1 = Posterior, 7 = Anterior
Groups: H = Haloperidol; O = Olanzapine; C = Control

	left				right			
	HC	OC	HO			HC	OC	HO
S1	1.0000	1.0000	0.9999		S1	0.9977	0.9995	0.9998
S2	1.0000	1.0000	0.9999		S2	0.9977	0.9995	0.9998
S3	1.0000	1.0000	0.9999		S3	0.9977	0.9995	0.9998
S4	1.0000	1.0000	0.9999		S4	**0.0252**	**0.0042**	0.9998
S5	1.0000	1.0000	0.9999		S5	0.4704	0.2972	0.9998
S6	1.0000	1.0000	0.9999		S6	0.9977	0.9995	0.9998
S7	1.0000	1.0000	0.9999		S7	0.7069	0.9995	0.9998
C1	1.0000	1.0000	0.9999		C1	0.4919	0.9995	0.9998
C2	1.0000	1.0000	0.9999		C2	0.4930	0.9995	0.9998
C3	1.0000	1.0000	0.9999		C3	0.4704	0.9995	0.9998
C4	1.0000	1.0000	0.9999		C4	0.4704	0.8266	0.9998
C5	1.0000	1.0000	0.9999		C5	0.2153	0.4802	0.9998
C6	1.0000	1.0000	0.9999		C6	0.9977	0.9995	0.9998
C7	1.0000	1.0000	0.9999		C7	0.9977	0.9995	0.9998
I1	1.0000	1.0000	0.9999		I1	0.9977	0.9995	0.9998
I2	1.0000	1.0000	0.9999		I2	0.9977	0.9995	0.9998
I3	1.0000	1.0000	0.9999		I3	0.7069	0.9995	0.9998
I4	1.0000	1.0000	0.9999		I4	0.9977	0.9995	0.9998
I5	1.0000	1.0000	0.9999		I5	0.9977	0.9995	0.9998
I6	1.0000	1.0000	0.9999		I6	0.0938	0.8266	0.9998
I7	1.0000	1.0000	0.9999		I7	**0.0415**	0.9995	0.9998

Table 10. Caudate Width Baseline Group Effects

Cross-sectional without repeated measures component
Nodes: S = Superior, C =Central, I = Inferior
Node number: 1 = Posterior, 7 = Anterior
Groups: H = Haloperidol; O = Olanzapine; C = Control

	left				right		
	HC	OC	HO		HC	OC	HO
S1	0.1664	0.2702	0.8603	S1	0.7576	0.5684	0.9845
S2	**0.0284**	0.2624	0.7428	S2	0.1591	0.2219	0.9845
S3	0.2470	0.1533	0.8603	S3	**0.0200**	**0.0368**	0.9845
S4	0.1470	0.1527	0.9557	S4	**0.0200**	**0.0294**	0.9845
S5	**0.0284**	0.1533	0.8636	S5	0.1591	0.2212	0.9845
S6	**0.0284**	0.3195	0.7428	S6	0.2176	0.3045	0.9845
S7	0.1470	0.7325	0.7428	S7	0.8461	0.7941	0.9929
C1	0.2221	0.2624	0.7428	C1	0.4312	0.5684	0.9845
C2	0.0936	0.3480	0.8603	C2	0.5297	0.5919	0.9845
C3	**0.0466**	0.0525	0.7428	C3	0.8877	0.8217	0.9845
C4	0.2470	**0.0494**	0.7428	C4	0.1591	0.7446	0.9845
C5	0.4138	0.1825	0.8636	C5	0.8290	0.7446	0.9845
C6	0.3860	0.6511	0.7428	C6	0.7576	0.4053	0.9845
C7	0.2562	0.7552	0.7428	C7	0.9838	0.7048	0.9845
I1	**0.0284**	0.0525	0.8603	I1	0.4175	0.4053	0.9845
I2	**0.0462**	0.1621	0.7428	I2	0.1591	0.2219	0.9845
I3	0.0725	0.0525	0.8636	I3	0.1591	0.2835	0.9845
I4	0.3637	0.2624	0.8636	I4	0.1591	0.4053	0.9845
I5	0.4138	0.7048	0.8636	I5	0.5297	0.7672	0.9845
I6	**0.0495**	**0.0494**	0.8509	I6	0.1591	0.2219	0.9845
I7	0.2381	0.0676	0.7428	I7	0.7576	0.5684	0.9845

Table 11. Caudate Deformation Full Group Effects

Cross-sectional with repeated measures component
Nodes: S = Superior, C =Central, I = Inferior
Node number: 1 = Posterior, 7 = Anterior
Groups: H = Haloperidol; O = Olanzapine; C = Control

	left					right		
	HC	OC	HO			HC	OC	HO
S1	0.0743	0.2664	0.8307		S1	0.1673	**0.0037**	0.7606
S2	**0.0050**	**0.0475**	**0.0168**		S2	**0.0298**	**0.0084**	0.9127
S3	**0.0156**	**0.0147**	0.7103		S3	**0.0000**	**0.0005**	0.9127
S4	**0.0000**	**0.0000**	0.7655		S4	**0.0000**	**0.0000**	0.7602
S5	**0.0011**	**0.0011**	0.7103		S5	**0.0007**	**0.0005**	0.9127
S6	**0.0320**	0.2426	0.7103		S6	**0.0320**	0.1998	0.9127
S7	**0.0110**	0.3421	0.7655		S7	0.4242	0.4343	0.9127
C1	**0.0298**	**0.0028**	0.7103		C1	**0.0298**	**0.0017**	0.7606
C2	0.0757	0.3548	0.8420		C2	0.0851	**0.0263**	0.9127
C3	0.5321	0.3770	0.7727		C3	0.5587	0.3206	0.9747
C4	**0.0320**	0.2342	0.7103		C4	0.2261	0.7065	0.9127
C5	0.5321	0.1274	0.7655		C5	**0.0048**	**0.0042**	0.9127
C6	0.5321	0.5157	0.7727		C6	0.5338	0.0888	0.9127
C7	0.0757	0.4582	0.4253		C7	0.5942	0.1708	0.9127
I1	**0.0102**	**0.0114**	0.8307		I1	**0.0011**	**0.0005**	0.9127
I2	**0.0042**	**0.0147**	0.7655		I2	**0.0011**	**0.0036**	0.9127
I3	**0.0042**	**0.0047**	0.8420		I3	**0.0068**	**0.0076**	0.9127
I4	**0.0298**	**0.0114**	0.8466		I4	**0.0011**	**0.0063**	0.9127
I5	0.1560	0.3069	0.8307		I5	**0.0320**	0.2195	0.7606
I6	**0.0108**	**0.0050**	0.7727		I6	**0.0070**	**0.0028**	0.7602
I7	0.1356	**0.0131**	0.7103		I7	0.3164	**0.0202**	0.9127

Table 12 Caudate Deformation Baseline Group Effects

Cross-sectional without repeated measures component
Nodes: S = Superior, C =Central, I = Inferior
Node number: 1 = Posterior, 7 = Anterior
Groups: H = Haloperidol; O = Olanzapine; C = Control

	left			
	group*time	**H time**	**O time**	**C time**
S1	0.4142	0.5760	0.6267	0.7861
S2	0.3372	0.6921	0.4018	0.8490
S3	0.2076	0.2615	0.9604	0.4140
S4	0.0870	0.3686	0.2562	0.8396
S5	**0.0493**	0.2855	0.4266	0.5134
S6	0.8957	0.8337	0.8484	0.8202
S7	0.9501	0.4663	0.4903	0.5104
C1	0.1553	0.4470	0.3540	0.9169
C2	0.2774	0.4195	0.5831	0.8989
C3	0.5504	0.9066	0.3352	0.3704
C4	0.1975	0.8472	0.6632	0.2907
C5	0.4423	0.4209	0.8739	0.4506
C6	0.1829	0.4146	0.4135	0.9842
C7	0.1673	0.4489	0.3788	0.8205
I1	**0.0192**	0.3365	0.8223	0.4632
I2	0.2834	0.4246	0.5146	0.8606
I3	0.8863	0.4450	0.3442	0.4475
I4	0.1104	0.8690	0.6667	0.3568
I5	0.0575	0.5192	0.4982	0.3361
I6	0.2550	0.4593	0.8483	0.3436
I7	0.8933	0.8006	0.4638	0.5107

	right			
	group*time	**H time**	**O time**	**C time**
S1	**0.0485**	0.3394	0.2699	0.5159
S2	0.3413	0.3453	0.8512	0.6438
S3	0.0614	0.2802	0.5813	0.9255
S4	**0.0290**	0.0952	0.1125	0.1445
S5	0.0510	0.1412	0.1864	0.3177
S6	0.1930	0.6024	0.1608	0.2389
S7	0.3063	0.3672	0.5012	0.8832
C1	0.7192	0.3272	0.3458	0.4155
C2	0.0537	0.4207	0.4060	0.4069
C3	0.1676	0.5459	0.9531	0.2944
C4	0.4134	0.5381	0.5346	0.9188
C5	0.4630	0.5220	0.9278	0.8196
C6	0.7247	0.9491	0.4365	0.4752
C7	0.3614	0.4642	0.7740	0.7944
I1	0.3340	0.5548	0.5658	0.5467
I2	**0.0404**	0.1684	0.3122	0.4200
I3	0.1951	0.9252	0.2216	0.4258
I4	0.7113	0.9724	0.7240	0.5354
I5	0.3246	0.5219	0.4911	0.6820
I6	0.4099	0.2916	0.6604	0.4786
I7	0.4341	0.9785	0.3300	0.8027

Table 13. Caudate Width, longitudinal

Time effect, P-value,
Nodes: S = Superior, C =Central, I = Inferior
Node number: 1 = Posterior, 7 = Anterior
Groups: H = Haloperidol; O = Olanzapine; C = Control

	left					right			
	group*time	H time	O time	C time		group*time	H time	O time	C time
S1	0.9861	0.4929	0.8584	0.5787	S1	0.8925	0.8553	0.3313	0.7306
S2	0.6928	0.4639	0.9544	0.5855	S2	0.9519	0.6819	0.8879	0.9753
S3	0.5208	0.3056	0.9789	0.9699	S3	0.8032	0.2438	0.6067	0.3910
S4	0.6751	0.3526	0.9776	0.5423	S4	0.3285	0.1281	0.0842	0.1062
S5	0.8437	0.4741	0.7944	0.3633	S5	0.8655	0.5915	0.3086	0.5155
S6	0.8784	0.4074	0.9386	0.5248	S6	0.9162	0.7661	0.2761	0.4080
S7	0.8708	0.4453	0.8262	0.3956	S7	0.9947	0.7959	0.3954	0.4315
C1	0.9379	0.4545	0.8982	0.4129	C1	0.6343	0.6203	0.3441	0.6105
C2	0.7516	0.4367	0.6694	0.7032	C2	0.8422	0.9828	0.4074	0.4268
C3	0.8865	0.3926	0.8006	0.5203	C3	0.6645	0.4640	0.5141	0.7548
C4	0.9998	0.8795	0.8355	0.7476	C4	0.3577	0.1494	0.4356	0.2541
C5	0.6249	0.1833	0.9050	0.2799	C5	0.6658	0.5035	0.2570	0.3665
C6	0.8911	0.4805	0.9973	0.6810	C6	0.8733	0.7533	0.7235	0.8158
C7	0.6802	0.4463	0.9634	0.7740	C7	0.7422	0.7542	0.7627	0.9831
I1	0.9190	0.4179	0.9388	0.4874	I1	0.7464	0.5265	0.3664	0.4866
I2	0.6176	0.2985	0.9603	0.4445	I2	0.9680	0.8486	0.6127	0.5951
I3	0.5878	0.4155	0.9058	0.3210	I3	0.9558	0.9135	0.8015	0.7926
I4	0.9378	0.7851	0.8517	0.7458	I4	0.9161	0.6180	0.8890	0.7973
I5	0.4842	0.3357	0.8080	0.5894	I5	0.9077	0.9845	0.7752	0.8804
I6	0.6150	0.5205	0.6709	0.7599	I6	0.8146	0.9435	0.7015	0.8898
I7	0.8343	0.5257	0.6726	0.5882	I7	0.7904	0.7642	0.7922	0.9626

Table 14. Caudate Deformation, longitudinal

Time effect, P-value,
Nodes: S = Superior, C =Central, I = Inferior
Node number: 1 = Posterior, 7 = Anterior
Groups: H = Haloperidol; O = Olanzapine; C = Control

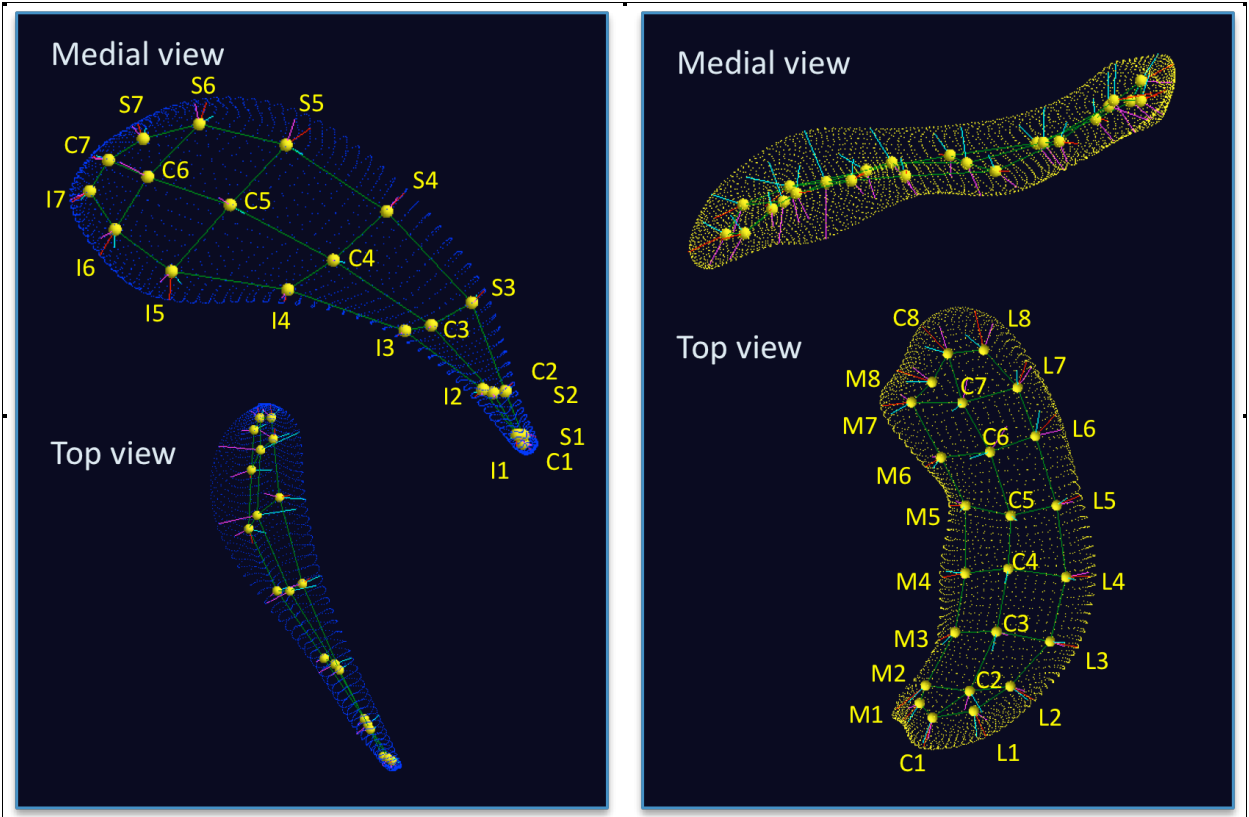
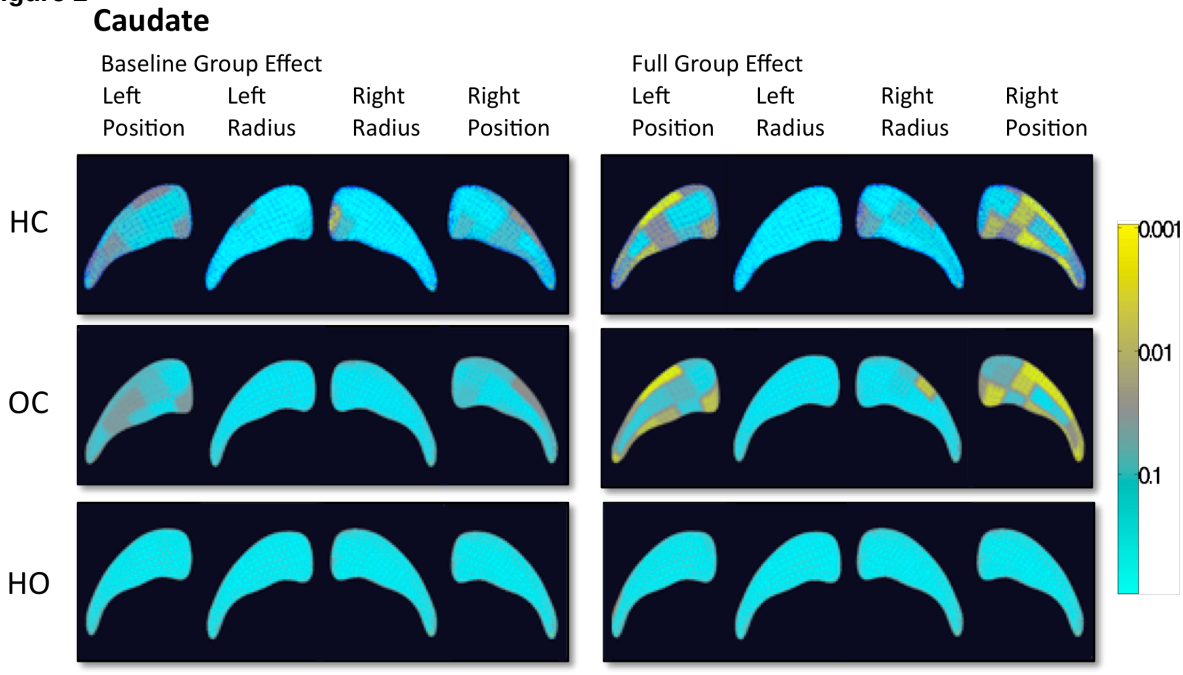


Figure 1: Visualization of the medial representation grid and node labeling for right caudate (left, labeled from a medial view) and hippocampus (right, labeled frrom the top view). Labels: S = Superior, C = Central, I = Inferior, M = Medial, L = Lateral. Increasing numerical value means going from a posterior to an anterior location. Local ***radius*** is represented by the length of the thin rods projecting from the node points, measuring the node **width**. Local ***position*** is represented by the location of the node points, measuring local **deformation**.

Figure 2



H: Haloperidol; O: Olanzapine; C: Control

Figure 2: Visualization of local significance in medial position and radius in the caudate. Left: Baseline group effect only (without repeated measures), Right: Full group effect. P-values are visualized from cyan (p=0.1) to yellow (p=0.001). All maps are corrected for multiple comparisons.

Figure 3

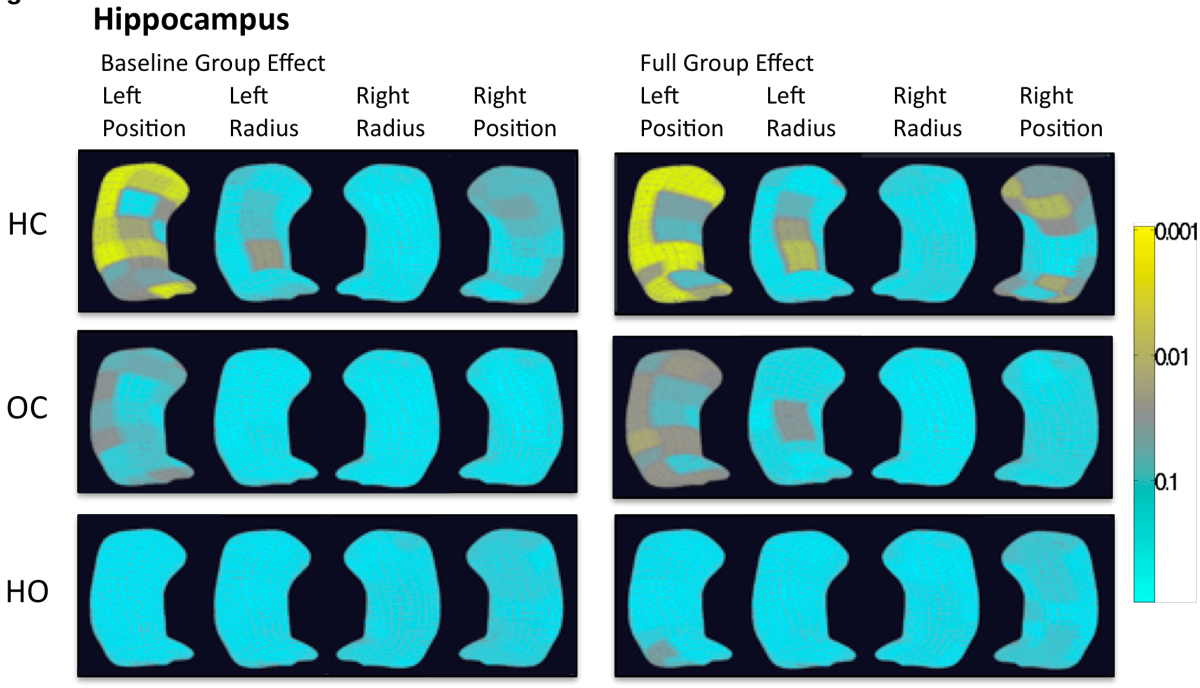


Figure 3: Visualization of local significance in medial position and width in the hippocampus. Left: Baseline group effect only (without repeated measures), Right: Full group effect. P-values are visualized from cyan (p=0.1) to yellow (p=0.001). All maps are corrected for multiple comparisons.

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