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Putamen Development in Children 12 to 21 Months Old

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Abstract

We studied the developmental trajectory of the putamen in 13–21 months old children using multivariate surface tensor-based morphometry. Our results indicate surface changes between 12 and 15 months' age groups in the middle superior part the left putamen. The growth of the left putamen at earlier ages slows down after 15 months. The most important surface changes were detected in the right putamen between 18 and 21 months and were located in the anterior part of the structure. Our results demonstrate the heterochronic growth of the right and left putamen related to different functional subregions within putamen. Our results are compatible with previous studies devoted to total putamen volume changes during normal development.

Keywords

Putamen; brain development; heterochrony; surface-based morphometry; tensor-based morphometry; MRI

I. INTRODUCTION

The putamen is a part of the striatum and is the largest basal ganglia structure in the brain. Different alterations within putamen were found in children with ADHD^{22, 7}, in children with autistic spectrum disorder (related to repetitive and stereotyped behavior⁶) and in premature newborns^{17,11}.

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While there are some reports about the putamen's involvement in abnormal development, there are few studies about normal putamen changes during childhood. In a morphometric developmental analysis in human fetuses, Nakae, Goto and Nara (1990) revealed that total number of putaminal neurons increase gradually from 21 to 33 gestation weeks, and the migration of putaminal neurons continues at least up to the 33rd gestation week. Neuronal numbers increase markedly after 33 gestation weeks, and no neuronal death was observed from 21 to 34 gestation weeks¹⁴. In their MRI-based morphometric analysis, Choe and colleagues (2013) revealed that the putamen shows logarithmic growth without any gender differences from 3 to 13 months-old. They also found a shift in putamen asymmetry during the first year of life: at 3–4 months there was a leftward asymmetry in the putamen, no asymmetry was detected at 6–7 months, and rightward asymmetry in putamen volume was observed at 12–13 months. From the age of four years old onward, a slow, significant decrease in putamen volume was observed^{20, 15}.

All the studies devoted to normal putamen development focus on the total volume of the putamen, yet the putamen has well-established anatomical and functional segregation^{16, 18}. According to the most recent unbiased data-driven metanalytic study on resting-state connectivity data by Pauli, W. M., O'Reilly, R. C., Yarkoni, T., & Wager, T. D. (2016), the putamen can be segregated into anterior and posterior parts. The anterior putamen is associated with the lateral sensorimotor cortex, supplementary/presupplementary motor areas and the intraparietal sulcus, while the posterior putamen is connected with the medial sensorimotor cortex, posterior and mid-insulae and the operculum and medial temporal lobes. The posterior putamen is involved in sensorimotor functions, including aspects of their affective qualities like pain and pleasure, while the anterior putamen is implicated in language processes and social functions like empathy¹⁶. In light of these results, it is reasonable to expect that different parts of the putamen increase/decrease during different time periods (heterochronically).

Here we aim to detect these patterns of heterochronical regional putamen growth using surface tensor-based morphometry. While this family of methods has successfully been used to reveal regional brain differences between groups of subjects with different disorders and controls^{3, 10, 11, 17, 8} only a few attempts have been made to apply surface based morphometry to study normal developmental changes, mostly focusing on the cortex^{13, 9}.

Our study aims to report the developmental trajectory of the putamen's growth between 13 and 21 months of age, and to verify the hypothesis that putamen volume increases non-uniformly in correspondence to its functional and anatomical segregation.

II. METHOD

We used T1 MRI data of 53 children from Advanced Baby Imaging Lab's healthy children database (12 months old - 13 subjects; 15 months old - 14 subjects; 18 months old - 16 subjects; 21 months old - 14 subjects). Additional details on the data acquisition can be found in previous publications^{4,5}. Each subject or their guardian was informed of the goals of the study and signed a formal consent. The studies were approved by the Institutional Review

Board of Brown University. All data was de-identified. Before the anatomic segmentation of the putamen, all T1 images from each group were registered to a randomly selected image from the corresponding age group using FSL's rigid body registration algorithm¹⁹. Bias field correction and denoising were then performed using ANTs¹.

Segmentation

The putamen was segmented in the right and left hemisphere manually using ITK-SNAP²³. The quality of segmentation was approved by an experienced pediatric neuroradiologist. Segmentation of the putamen was performed according to established segmentation guidelines. The inter-rater average percent volume overlap for the putamen segmented twice in a two weeks' interval is 80%.

Analysis

We applied an in-house pipeline for surface based analysis of subcortical structures which has already been used in our previous studies, and the whole procedure is well-described^{17, 11}. We used a deformation-based method - multivariate tensor-based morphometry (TBM), which computes the spatial derivatives of the deformation fields after warping individual reconstructed meshes to the template. The applied deformation fields represent the differences between each subject and the template, and then can be used for detecting regional morphological differences between groups^{12, 21}. For group statistical analysis we used four metrics:

1. the radial distance (medial axis distance, **MAD**) - represents the thickness of the shape at each vertex.
2. the determinant of the Jacobian matrix (**DetJ**). this metrics represents the difference in surface area without directional information.
3. The logged deformation tensors (**mTBM**) - describes the directional differences in regional surface area between each subject and template.
4. Combined **mTBM & MAD** metric. While these two metrics are complementary to each other (MAD represents the changes in thickness, mTBM detects changes in surface), we combined these metrics into one multivariate vector for the analysis we were using in our previous works^{21, 11, 17}.

For group comparisons, we used a Student t-test for univariate metrics (MAD, DetJ) and a Hotelling's T^2 test for the two multivariate metrics (mTBM, mTBM&MAD). We run a permutation test on two levels: 1) at the vertex level, we used a permutation test in order to avoid the assumption of normal distribution and 2) over the whole structure, to correct the results for multiple comparisons.

To show the direction of changes, we computed the vertex-wise ratio of the determinants and of the radial distances (MAD) of younger/older age groups.

To make the results comparable with previous studies, we additionally computed the volume of the putamen in mm³ using ITK-SNAP (Figure 3).

III. RESULTS

Surface changes

The surface p-value maps for group comparisons between 12 vs. 15, 15 vs. 18 and 18 vs. 21-months age groups are shown in Figure 1.

Significant surface changes in the **right putamen** are revealed for all time periods. 12 vs. 15 months' clusters are small and mostly located in the posterior part of the right putamen, and differences are significant only for combined multivariate metric (MAD & mTBM).

Significant differences in the right putamen between 15 and 18 months are diffusively located along the structure; these differences are significant for the mTBM and MAD & mTBM metrics. Consistent significant differences for all four metrics were obtained only for the anterior part of the right putamen when comparing 18 and 21 months old subjects (Table 2).

For the **left putamen**, significant differences between 12 and 15 months' age groups were found with the combined multivariate metric (MAD & mTBM). Significant clusters are detected mostly in the medial superior part of the left putamen (Table 2, Figure 1). Other results of the group analysis did not pass the control for multiple comparisons errors.

Volume changes

Significant increase of the putamen volume was detected only between 12 and 15 months' groups for the left putamen ($t = -2.4228$, $df = 24.953$, $p = 0.023$). Additionally, significant differences in volume between left and right putamen were seen only in the 15 months old group ($t = -2.9331$, $df = 25.972$, $p\text{-value} = 0.007$, see Figure 2).

IV. DISCUSSION

In agreement with previous works, we found out that multivariate metrics for surface-based morphometry were more sensitive than univariate ones^{21, 12, 17, 11}.

We detected surface changes in the left putamen only in the beginning of the second year of life (12 vs. 15 month groups), and continuous increases of surface metrics in the right putamen through all three time periods. These results reflect the heterochronic growth patterns of the brain²⁴. Our data covers a period of changes in the left putamen between 12 and 15 months, and a period of changes in the right putamen between 12 and 21 months, with its peak at the end of second year of life. To determine the full extent of these periods of changes, our sample will be expanded to include ages from 3 months to 36 months.

From our results, significant changes during the second year of life occur mostly in the right putamen. During the first two time periods (12 vs. 15, 15 vs. 18 months) these changes are diffusive but during the last period, these changes are located in the anterior part of the right putamen. This finding partially supports our hypothesis that putamen volume increases non-uniformly with correspondence to its functional and anatomical segregation. The last several months of the second year of life are associated with language development, using words as a tool for social interaction and increasing of social relationships²⁵. The anterior part of the

putamen is known to contribute to language processes and social functions¹⁶. According to our data, we can hypothesize the particular role of the right putamen in these behavioral changes. However, the relative and total contributions of the right and left hemispheres to language development change during childhood², so we expect these results to vary with age.

According to Choe and colleagues (2013), we should expect a rightward asymmetry in the putamen in our sample, but significant differences were observed only in 15 months' age group, with the left putamen being bigger than the right. Contradictory results are also reported in the literature: leftward asymmetry in children and adolescents²² and rightward asymmetry in children²⁶. One of the reasons for this discrepancy could be small sample sizes, which is common for children studies.

IV. CONCLUSIONS

As a result of this study we revealed preliminary evidence for

1. the nonuniform increase of the right putamen related to its functional and anatomical segregation;
2. the heterochronic growth patterns for the right and left putamen during two first years of life;

In order to make this evidence stronger, the sample should be expanded from 3 to 36 months. Moreover, gender differences and correlation between surface-based metrics and behavioral scores should be examined.

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Figure 1. Surface-based p-value maps for each of the metrics: vertex-wise p-values for the comparison of four age groups, using four different metrics. Global p-values for each metric are Tables 1 and 2.

Figure 2.
Vertex-wise ratio of determinants (DetJ) and the radial distances (MAD) of younger/older age groups.

Figure 3.
Volume changes of the right and left putamen with age.

Table 1

Global p-values for the left putamen: results of permutation test over the whole structure to correct for multiple comparisons.

Left Putamen	12 vs. 15	15 vs. 18	18 vs. 21
MAD	0.188	0.303	0.258
DetJ	0.122	0.467	0.521
mTBM	0.072	0.193	0.286
MAD & mTBM	0.035*	0.093	0.108

Table 2

Global p-values for the right putamen: results of permutation test over the whole structure to correct for multiple comparisons.

Right Putamen	12 vs. 15	15 vs. 18	18 vs. 21
MAD	0.279	0.068	0.028*
DetJ	0.195	0.054	0.003*
mTBM	0.071	0.026*	0.010*
MAD & mTBM	0.046*	0.015*	0.007*