의학 석사 학위논문

Maturation of directed interregional connection in adolescent rat brain

소 동물 대상 방향성을 가진 뇌 연결성 발달에 대한 분석

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Abstract

Maturation of directed interregional connection in adolescent rat brain

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Understanding normal brain maturation is important because it can provide reference when disease-related abnormalities are characterized in neurological or psychiatric disorders. Unlike functional magnetic resonance imaging (fMRI) image which only shows changes of brain activity associated with blood flow, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) image can provide metabolic network of brain activity. Metabolic brain connectivity is the correlation among spatially distinct brain regions. The persistent homology is a novel multi-scale framework that generates all brain networks above all possible threshold compensating for the weakness that the existing

method has no generally accepted criterion. Volume entropy is a new invariant of brain graphs methodology indicating the information processing on brain network with direction.

In this study, a longitudinal FDG PET study of metabolic connectivity using persistent homology and volume entropy were performed in 5, 10, and 15week-old brain images of 28 rats. Persistent homology analysis showed that the metabolic brain connectivity was enhanced brain connectivity in bilateral frontal cortices of 10 week-old rat, especially between anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC) compared with 5 week-old rat brain, that are components of "default mode network". In comparison of 10 and 15week-old, the metabolic connectivity between the right insular cortex and other ROIs was significantly enhanced in 15 week-old rat brain. The anterior insula and ACC form a "salience network" that serves to separate the most relevant parts of internal and external stimuli to induce certain behavior. Volume entropy analysis showed the increasing tendency of brain metabolic volume entropy over rat brain maturation (5-10-15 week). The metabolic volume entropy of 15 week-old rat brain was statistically higher than that of 5week-old. In the concept of 'directed network', node and edge capacity of ACC became larger during maturation.

The result of persistent homology analysis confirmed that the metabolic brain connectivity of the regions controlling wakeful rest state of brain and leading complex and flexible behavior was enhanced during normal maturation. The volume entropy of metabolic brain connectivity tended to increase during normal rat brain maturation reflecting efficiency of directed information processing through brain network.

Keywords: directed brain connectivity, volume entropy, persistent homology, FDG PET

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Introduction

Normal brain maturation

Studies on normal brain maturation have been initiated with motivation to characterize the normal developmental patterns to find the disease-related abnormalities in neurological or psychiatric disorders. For neuroimaging study, the evidence of post-adolescent brain maturation in frontal and striatal regions was reported using voxel-by-voxel statistical analysis on high-resolution magnetic resonance imaging (MRI) (1). Subsequent follow-up studies using MRI had been followed, especially with functional MRI (fMRI) which measures brain activity by detecting changes associated with blood flow. The functional brain connectivity based on fMRI indirectly reflects neuronal activity including the cerebral metabolism rate of glucose/ oxygen, cerebral blood flow, and cerebral blood volume. While fMRI measures temporal fluctuations, FDG PET-based metabolic brain connectivity reflects relatively stable information; accumulative metabolic assumption for several minutes of steady resting state (2-4).

There was a precedent study analyzed maturation-related changes of regional brain metabolism and brain connectivity using longitudinal ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scans in adolescent period (5). To identify maturing patterns of metabolic networks, 4

particular components were selected based on independent component analysis (ICA), which anatomically corresponded to limbic/ anterior default mode network (DMN), posterior DMN, motor, and somatosensory. The connectivity analysis showed efficient connection developed between the components particularly pair of region of interests (ROIs) including DMN during adolescent period (5, 6). The pre-selected ROIs, including some not all anatomical brain limited the evaluation of changes in the entire brain network.

Image-based brain connectivity analysis

Brain connectivity can be displayed in graph or network composed by node and edge. Each ROI of brain is defined as node and the network is constructed based on inter-node activity (7-11). Graph measures are useful tool of global organization of large-scale networks. Previous functional brain connectivity studies have focused on verifying the topological characteristics such as small-worldness, scale-freeness, or modularity using well-known graph metrics (12-14). However, the previous methodology of brain connectivity analysis has limitation of 'arbitrary' in selection of the threshold.

Persistent homology

The brain network using graph measure is constructed by estimating the connectivity matrix and setting the threshold at an arbitrary level. The

weakness of this method is that there is no generally accepted criterion for determining a proper threshold (15). Lee, et al. proposed 'persistent homology' as a novel multi-scale framework that models all brain networks generated above all possible threshold (15). The graph filtration traces evolution of network changes over different thresholds. This novel approach has been successfully used in various imaging modality and diseases (16-18). Applying persistent homology, abnormal metabolic connectivity in the drug-induced epilepsy rat model was confirmed. Nodes in epilepsy rats were clustered to single component with larger filtration values than controls, suggesting weak brain connections in epilepsy models (17). Alterations in brain metabolic connectivity in the cortico-striatal-thalamic loop in Parkinson's disease mouse model also reported by applying persistent homology (18).

Volume entropy

Volume entropy is a new invariant of brain graphs suggested by Lee, et al (19-23). The volume entropy assumes that the information flows through the links on a brain graph with direction. The volume entropy level is an indicator of the efficiency of information processing on a brain network. The volume entropy of attention deficit hyperactivity disorder (ADHD) and control rat groups were calculated. The result revealed higher volume entropy was observed in the control rats compared to the ADHD (21). By applying volume entropy, it is possible to validate information processing efficiency through

directed brain networks. Capacity of node or edge can be a parameter of efficiency of directed brain network.

Purpose

The purpose of this study was to analyze ‘directed’ brain connectivity during normal maturation using a newly suggested parameter, volume entropy. The node/ edge capacity can explain the enhanced information processing through directed brain connectivity. As a post-hoc analysis of the previous work by Choi, et al., I additionally adopted persistent homology for undirected brain network analysis and compared the result of persistent homology and that of volume entropy in rat model.

Materials and methods

Original data

As declared in introduction, the present study was a post-hoc analysis of Choi, et al.'s (5). I analyzed the pre-processed FDG PET image data of Choi, et al.'s. Among the total of 86 images, I included 84 images of 28 rats who underwent full longitudinal images of 5, 10, 15 week-old. I state here that material and methods for pre-processed data were done by Choi, et al.

Animal models

Twenty-eight male Sprague-Dawley rats (Koatech, Seoul, Korea) underwent three times of FDG PET/computed tomography scans for brain imaging. They were kept in standard laboratory condition (22–24°C, 12 hour light and dark cycle) and allowed to freely access to standard feeding and water drinking. The Institutional Animal Care and Use Committee at Seoul National University Hospital (IACUC Number 13–0224) approved all the experimental procedures.

FDG PET imaging for animal brain

FDG PET images of rat brain were acquired at the age of 5, 10, and 15 weeks matched with childhood, adolescent and early adulthood, respectively. A dedicated small animal PET (eXplore VISTA, GE Healthcare, WI) was used

for rat brain imaging. For imaging preparation at least 8 hour fasting was required before FDG PET scan. After an intravenous bolus injection (0.3–0.5 mL/rat) of FDG (100–150 MBq/kg), rats were awake and took rest in a dark room for 35 minutes. Anesthetization (2% isoflurane at 1–1.5 L/min oxygen flow for 5–10 min) was performed 10 minutes before PET imaging. Each rat had 45 minute period of FDG uptake. Static PET scan was acquired for 20 minute with the energy window 400–700 keV. A three-dimensional ordered-subsets expectation maximum algorithm with attenuation, random and scatter correction was used for image reconstruction. The voxel size was 0.3875 x 0.3875 x 0.775 mm^3. I acquired 84 PET images considering voxel-wise statistical difference after multiple comparison correction, 28 images for each age (5, 10, and 15 week-old).

Image Preprocessing

Voxels were evenly scaled in factor of 10 for each dimension. All the acquired FDG PET images were spatially normalized to a FDG rat brain template served by PMOD 3.4 (PMOD group, Zurich, Switzerland). For spatial alignment, non-linear registration on Statistical Parametric Mapping (SPM12, University College of London, UK) was performed using rat brain PET template and binary brain mask was applied. In order to adjust image qualities, smoothing with a Gaussian filter of 12 mm full width at half maximum was applied to all PET images. The voxel counts were normalized to the global brain uptake in each PET image to scale voxel intensities.

Voxel-wise regional analysis

A paired t-test was used to compare the change of regional metabolic activity of rat brain during maturation (5 and 10, 10 and 15, 5 and 15 week-old). For multiple comparison correction, the family-wise error (FWE) which is a corrected P-value was applied to determine significance. Minimum of 50 voxels were regarded as a statistically different region.

Metabolic brain network analysis

ROIs of rat brain

Schiffer template in PMOD 3.4 (PMOD group, Zurich, Switzerland) was adopted for ROIs of rat brain. Among the 58 ROIs of Schiffer template, 32 ROIs were selected for analysis. The 32 ROIs included frontal, parietal, occipital, temporal, and insular cortices and limbic structures. The cerebellar ROIs were excluded in this analysis.

Persistent homology using graph filtration

Each ROI was regarded as a node in constructing a weighted brain metabolic network. An edge was defined as a connection between two nodes, which was determined when the correlation between nodes exceeds a predetermined correlation threshold. Short edge reflects strong correlation between the nodes.

Persistent homology considered every possible threshold to construct network, in the effort of avoiding bias caused by arbitrary threshold. Graph filtration was used over changing thresholds. The filtration value which determines a connection between two nodes was defined as single linkage distant (SLD) of connected two nodes. The single linkage distance matrix (SLM) displayed all the SLDs between all nodes.

Permutation for SLM comparison

SLMs underwent a permutation procedure that generated random samples under the null hypothesis; permuted 10,000 times and $P \leq 0.0001$ was applied.

Efficiency of information processing on directed brain network

Volume entropy calculation

Universal covering tree was used in volume entropy, which is an infinite connected network without terminal node (figure 1). Without backward processing, all possible paths with radius r on universal covering tree of a base node v_0 were indicated by $(v_{0,} r)$. Volume entropy (h_{vol}) is sum of all edge-weights when r comes to infinite and following formula came out (22):

$$h_{vol} = \lim_{r \to \infty} \frac{\log l(B(v_0,r))}{r}$$

To calculate volume entropy the degree of all nodes should be equal or larger than 3. The number of nodes and edges were fixed by using sub-graph with a one nearest neighbor. That is because the value of volume entropy was highly dependent on the number of nodes and edges (21).

Application of volume entropy

Volume entropy was calculated with varying threshold in 5, 10, and 15 week-old rat groups. Comparisons between 5-10week-old, 10-15 week-old, and 5-15 week-old were performed with 10000 times of permutation and $P < 0.05$ was applied.

Node and edge capacity

The capacity considers not only the efficiency but also the direction of information through brain network. Every possible pair of directed capacity of edges and nodes (ROIs) is demonstrated in matrix. The difference between 5 and 10week-old, 10 and 15 week-old, and 5 and 15 week-old were performed with 10000 times of permutation with corrected P-value (FWE) of 0.05.

A. Weighted network B. Universal covering tree

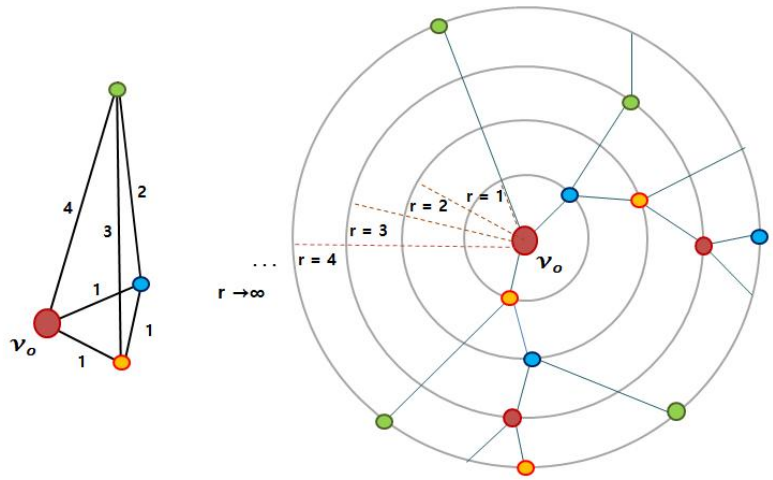


Figure 1. Volume entropy calculated on universal covering tree

An example of closed weighted network composed of 4 nodes and 6 edges and is converted to universal covering tree (A). The universal covering tree starts on a base node of v_0 and extending with all possible networks without terminal node or radius (B).

Results

Regional glucose metabolism

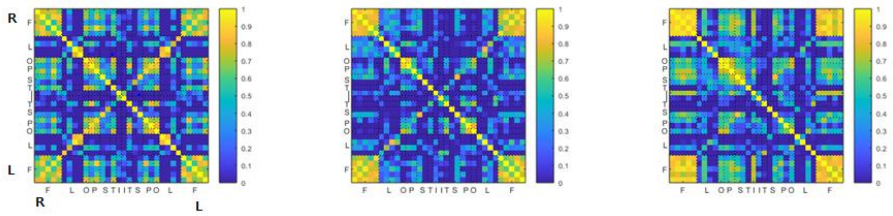
Regional glucose metabolic changes in rat brain maturation were analyzed by voxel-wise comparisons. The comparisons were performed among FDG PET brain images of rats aged 5, 10, and 15 week-old using SPM. Applying a corrected P-value (FWE) of 0.05, the glucose metabolism significantly increased in bilateral anterior cingulate cortex (ACC) of 10 and 15 week-old rat brain, compared with 5 week-old rat brain. That is, the results show that as the brain matures the glucose uptake in the ACC region increases. However, in the comparison between 10 and 15 week-old rat brain metabolism, there was no statistical difference in paired t-test (FWE >0.05). The regional glucose metabolism in bilateral hippocampus and thalamus (mainly in the right) was decreased in 10 and 15 week-old rat, respectively compared with 5 week-old rat brain.

Persistent homology-based metabolic network in brain maturation

The 32 ROIs of each FDG PET brain images of 5, 10, and 15 week-old rats were analyzed by persistent homology. The distance matrices and correlation matrices were displayed in Figure 2. SLM was constructed under graph

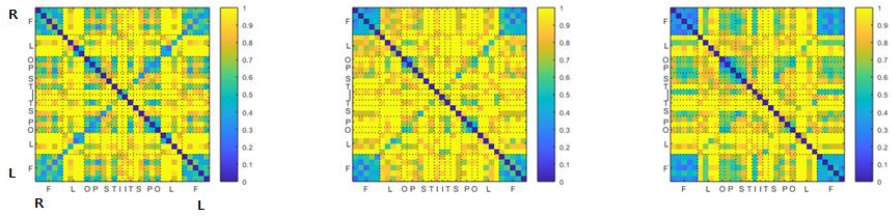
filtration procedure, which applied all available thresholds on the distance (Figure 2C).

A. Correlation Matrix



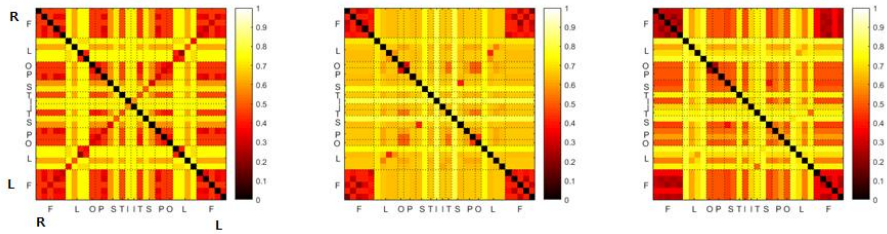
5wk 10wk 15wk

B. Distance Matrix



5wk 10wk 15wk

C. Single Linkage Matrix



5wk 10wk 15wk

Figure 2. Correlation, distance, and single-linkage matrices of normal rats at 5, 10, and 15 week-old

The positive correlation matrix (A), distance matrix (B), and single-linkage matrix (C) applied 32 ROIs were constructed.

Comparison between 5 and 10 week-old rat brains

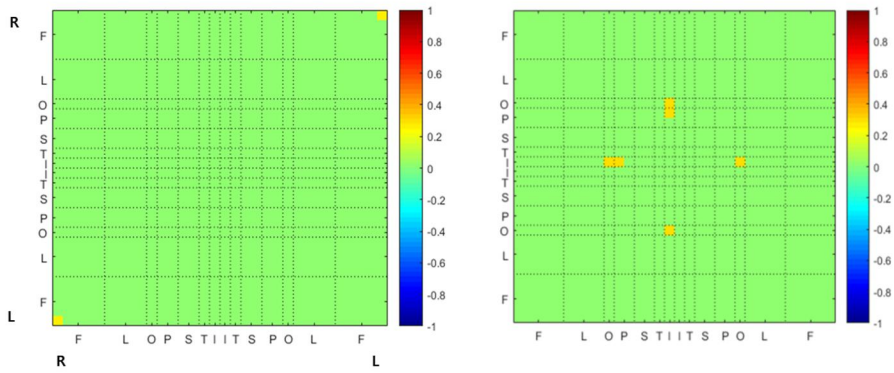
In comparison of metabolic connectivity applying unadjusted 10000-times permutation test, the connectivity between bilateral ACC was significantly enhanced in 10 week-old rat compared with 5 week-old rat (figure 3A, unadjusted 10000-permuted test, $P \leq 0.0001$). There was no significantly weakened connectivity during aging, from 5 to 10week.

Comparison between 10 and 15 week-old rat brains

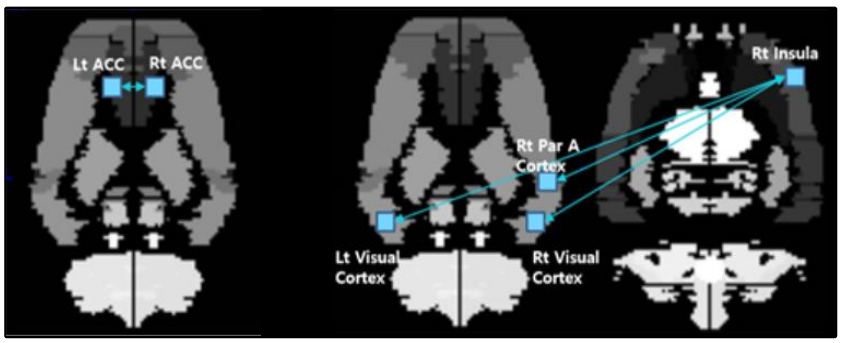
From 10 week to 15 week-old, the brain network between right insula and bilateral parieto-occipital cortices were significantly strengthened. Figure 3B represents the results of comparison in SLMs between 10 and 15 week-old rats. In comparison between 5 and 15 week-old, there was no statistically significant result.

A. $SLM_{5wk} - SLM_{10wk}$

B. $SLM_{10wk} - SLM_{15wk}$



C. Enhanced brain network during aging



From 5wk to 10wk

From 10wk to 15wk

Figure 3. SLM difference and enhanced edges during brain maturation with unadjusted 10000-permuted test (P≤0.0001)

Statistically differed interregional connections between the 32 ROIs were colored between 5 and 10 week (A), 10 and 15 week (B) using the 10000-

permuted test. The cold color means shorter SLD and the warm color represents longer SLD, which means the distance between two edges was shortened during aging. Significantly enhanced edges connecting brain ROIs during maturation are demonstrated in C.

Maturation of metabolic network based on volume entropy

Volume entropy was calculated for each rat group with 5, 10 and 15 week-old using the distance matrices with every available threshold. There was a trend of increasing volume entropy during maturation from 5 to 15 week-old. The permuted comparison revealed the metabolic volume entropy of 15 week-old rat brain was significantly higher than that of 5 week-old (Figure 4).

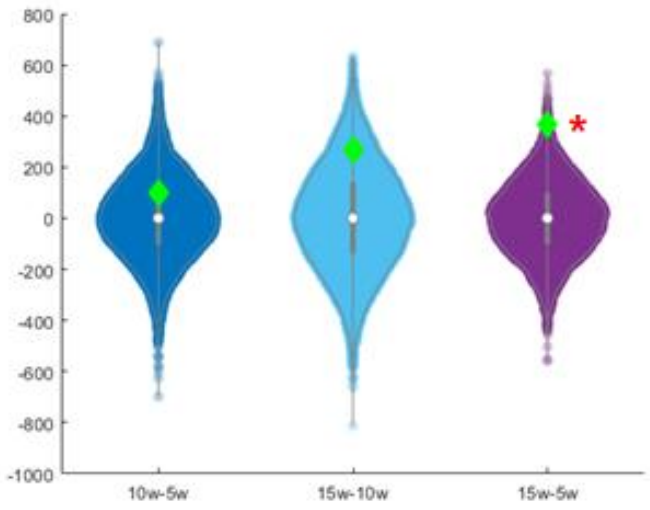


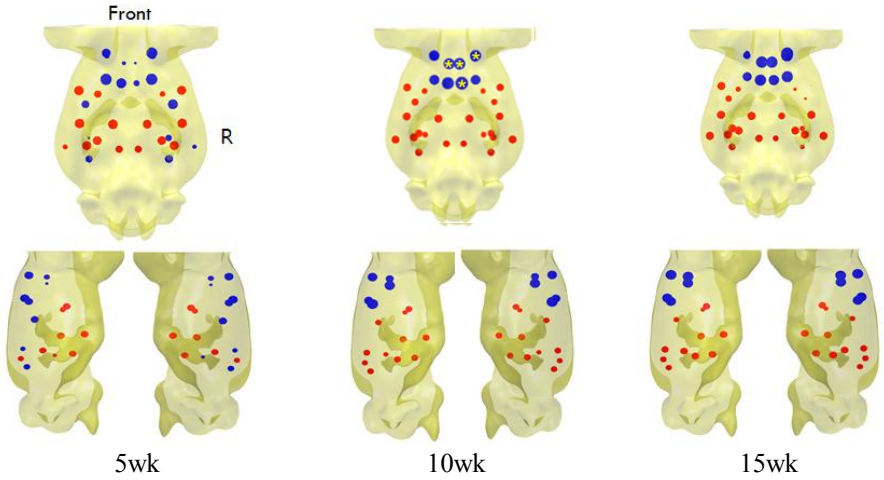
Figure 4. Volume entropy difference during aging and difference with 10000-permuted test

There was a trend of increasing volume entropy during maturation, the permuted comparison revealed the metabolic volume entropy of 15 week-old was statistically higher than 5 week-old rat brain ($P<0.05$, marked with red star).

Directed network analysis: node and edge capacity

Volume entropy considered direction in brain network. The capacity analysis of node and edge was performed. If the incoming information of a node is more than the outgoing, the capacity of the node is considered high. Compared with 5week-old, the input information in ACC and mPFC was larger than output in 10wk-old rat rain with 10000-permuted test, FWE<0.05 (Figure 5). Figure 6 shows the difference of edge capacity between 5wk-10wk-old. The cold color in matrix represents the enhanced capacity during aging, whereas the warm color means lessen capacity. The edge capacity of edges directed from bilateral frontal, parietal and occipital cortices to right ACC were enhanced from 5week-old to 10week-old age rat brain.

A. Node capacity



B. Node capacity difference

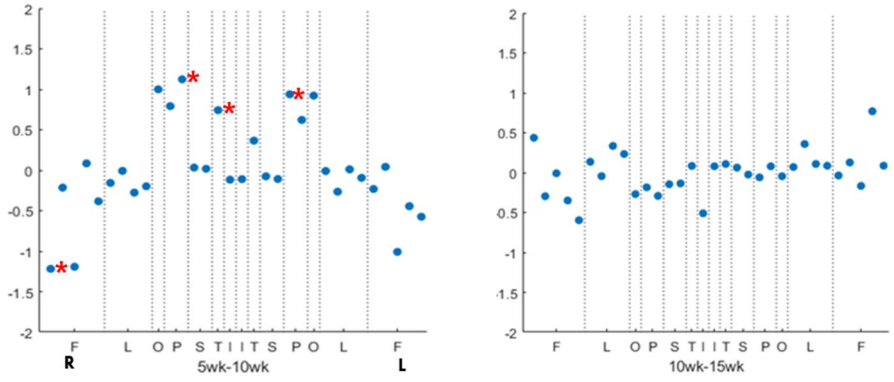
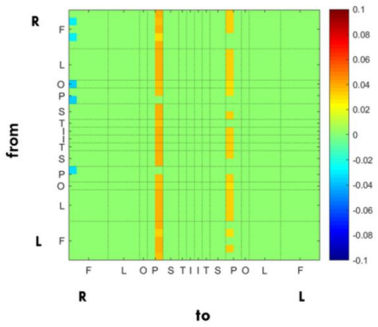


Figure 5. Node capacity and node capacity difference

Node capacity illustrated as blue or red dots on rat brain (A). The blue dot represents high node capacity and the red dot means more than input information is leaving from the node. The size of dot reflects of the amount of information. In comparison between 5-10wk-old, increased node capacity during maturation was found in right ACC and mPFC, statistically

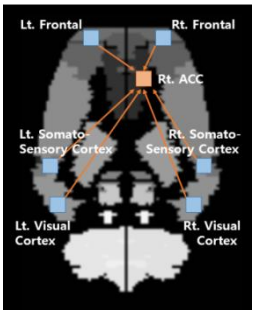
significant;10000-permutated with FWE <0.05 (yellow star in A and red star in B).

A. Edge capacity difference matrix



5wk – 10wk

B. Enhanced edge capacity



from 5wk to 10wk

Figure 6. Edge capacity difference with 10000-permuted test (FWE <0.05)

The edge capacity of edges directed from bilateral frontal, parietal and occipital cortices to right ACC were significantly enhanced from 5week-old to 10week-old age rat brain.

Discussion

This study confirmed maturation during adolescent by regional metabolic analysis and development of DMN and SN during normal aging using persistent homology in animal model. Volume entropy was enhanced in normal matured brain compared with early stage of maturation. The enhanced volume entropy means abundant information is processed through brain network with direction. This is the first approach using volume entropy analysis on metabolic connectivity of normal brain development from childhood to early adulthood. The understanding of normal brain development has its significance in that it can be a criterion for identifying and clarifying neuropsychiatric disorders.

Majority of previous studies on normal brain maturation were analysis of fMRI images (23, 24). While the fMRI-based functional connectivity measures correlation of fast temporal fluctuations, metabolic connectivity measured by FDG PET reflects accumulative energy consumption in several minutes and provides relatively stable information regarding steady resting state (25-29). Early studies on functional maturation of human brain with FDG PET have found that the brain undergoes extended period in which activity-dependent synaptic stabilization occurs before reaching the adult state. Chugani HT. suggested that ontogeny of local cerebral metabolic rates of glucose utilization in cerebral cortex may provide an indirect measure of synaptogenesis in the brain. In middle childhood, the upward curve of the

glucose metabolism leaded to the plateau, which represented the period of synaptic excess and abundant connectivity associated with increased energy requirement by cortex. The author believed that childhood is the biological 'window of opportunity' when learning is efficient (30).

In the present study, regional brain glucose metabolism of ACC increased in adolescence and early adulthood compared with childhood. ACC is one of the crucial brain regions to play a crucial role in initiation, motivation, and goal-directed behaviors. More specifically, ACC engages in the evaluative processes and inhibiting responses toward less desirable but easily obtainable goals in favor of more desirable goals that may also require more physical or mental effort (31, 32).

The previous study by Choi, et al. confirmed connection efficiency during rat brain maturation by regional metabolic activity analysis with limited ROIs. They focused on metabolic DMN in rat brain, not global brain network (5). The result revealed that efficient connection developed among their ROIs, DMN during adolescent. Regional metabolic analysis of this study underwent further steps from previous study in two aspects, extended ROIs and persistent homology based multi-scale network analysis framework. The persistent homology of the present study analyzed 32 ROIs which included most of cerebrum. The result showed that the functional brain connectivity of adolescence was enhanced in bilateral frontal cortices compared with that of childhood. The result showed enhanced brain connectivity in bilateral frontal lobes of adolescent rat, especially between ACC and mPFC. ACC and mPFC

are frontal midline structure, main part of DMN of rat brain. DMN has been characterized as the basal network of activity since many goal-oriented tasks deactivated this network (33-40). In comparison with adolescence and early-adulthood, the functional connectivity between the right insular cortex and other ROIs are significantly enhanced in early adulthood rat brain. The anterior insula and ACC form a SN that serves to separate the most relevant parts of internal and external stimuli to induce certain behavior (41). The SN is the network responsible for integrating sensory, internal thinking and information about goals and plans to update expectations for internal and external environments. Throughout the life span, the strength of connections within the SN and between the SN and other networks changes in ways that enables more complex and flexible behavior (42-44).

I also performed volume entropy analysis, a new graph entropy-based graph invariant. There was no previous study using volume entropy analysis in longitudinal normal rat brain FDG PET images from childhood to early adulthood. The volume entropy assumes that the information flows through the links on a brain graph with direction. The larger the volume entropy is, the more information flows on the graph. The results showed the increasing tendency of brain metabolic volume entropy during rat brain maturation (5-10-15 week-old) and the metabolic volume entropy of early adulthood rat brain was significantly larger than that of childhood. The volume entropy was more related to global efficiency than local efficiency. Thus, it should be noted that even though the graphs had similar global efficiencies, the volume

entropy could vary depending on the local efficiencies of the graphs.

As mentioned above, the understanding of normal brain development has its significance in that it can be a criterion for identifying and clarifying neuropsychiatric disorders. There has been rare study on normal brain maturation using FDG PET since repeated imaging using radiotracer is not been welcomed ethically and practically. Recently, Turpin, et al. suggested mathematic models of regional relative brain metabolism using 88 pediatric FDG PET data of normal pediatric brains (59 for development group and 29 for validation group), accounting for sex and age. The result revealed the suggested models have the advantage of being able to interpolate results for parameters that may not be well represented in a limited database (45).

This animal study has following limitations. Although metabolic networks have advantages to reveal steady-state connectivity in longer term scale than resting fMRI, it is difficult to perform longitudinally repeated PET in the growing normal children. The study for human brain FDG PET has been constrained by ethical, methodological, and practical considerations. And because metabolic brain network using FDG PET is group-based analysis, there is limitation to distinguish individual-based functional network done by fMRI. Although rat brains have similar features of metabolic network to human brains, there are several technical issues of interest. Unlike human studies, rats should be anesthetized during either FDG injection or image acquisition. Since anesthesia could affect brain metabolism, rats were awake after the injection until imaging to minimize the anesthesia effects. I admit

that it is difficult to draw clinical significance from the present results. Further studies are needed to validate that the results from rat model is compatible with human brain. Additional human fMRI study on normal brain maturation using persistent homology and volume entropy analysis is expected to be complementary.

Conclusions

The regional brain metabolism from childhood to early adulthood was observed as increased in bilateral frontal cortices. The result of persistent homology analysis confirmed that the functional brain connectivity of the default mode network was enhanced during adolescence. In early adulthood, the functional network responsible for more complex and flexible behavior was strengthened compared with adolescence. The volume entropy of functional brain connectivity tended to increase during normal rat brain maturation reflecting more directed information flow. The ‘directed’ information, from somatosensory and visual cortex to ACC was enhanced in adolescent period.

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국 문 초 록

소 동물 대상 방향성을 가진 뇌 연결성 발달에 대한 분석

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정상 뇌 성숙 과정에 대한 이해는 신경·정신학적인 병적 상태를 규정하기 위한 기준이 될 수 있다라는 점에서 그 중요성이 있다. 혈류와 관련된 뇌 활동의 변화를 보여주는 fMRI 영상과 달리 FDG PET 영상은 비교적 안정되게 축적된 대사를 이용한 뇌 활동을 근거로 대사적 네트워크 분석이 가능하다. 퍼시스턴트 호몰로지는 임계 값을 임의로 선택하는 기존의 방법의 한계를 보완하도록 가능한 모든 임계 값을 적용하여 뇌 네트워크를 구성하는 멀티스케일 방법론이

다. 또한 볼륨엔트로피는 뇌 네트워크를 통해 방향성을 가지고 처리되는 정보의 능률성을 확인하는 새롭게 제안된 분석법이다.

본 연구에서는 소동물 28마리의 5, 10, 15 주 3번의 연속된 FDG PET 뇌 영상을 얻어 퍼시스턴트 호몰로지와 볼륨엔트로피를 이용한 정상발달에서의 대사적 네트워크 성숙과 효율성을 분석하였다. 퍼시스턴트 호몰로지 분석 결과는 10주 째 뇌의 전두엽 내, 특히 전측 대상피질과 내측 전두엽 피질, 즉 디폴트모드네트워크의 대사적 연결성이 5주의 것에 비해 유의하게 강화된 것을 보여주었다. 10주 째와 15주 째 뇌 대사연결성 비교에서는 15주 째의 우측 섬피 피질과 다른 뇌 영역간의 대사적 연결성이 강화됨이 확인되었다. 섬피 피질과 전측 대상피질은 내·외적 정보 또는 자극을 적절히 처리하여 복잡하고 유연한 행동이 실행될 수 있도록 하는 중요한 뇌 영역인 '셀리언스 네트워크'를 구성한다. 뇌 네트워크의 볼륨엔트로피는 정상 발달 과정 동안 강화되는 경향을 보였고 15주 째의 볼륨엔트로피는 5주 째의 볼륨 엔트로피에 비해 유의하게 강화되어 있었다.

퍼시스턴트 호몰로지 분석 결과는 정상적 뇌 성숙 과정에서 청소년기에 특정 의도한 사고, 행동이 이루어지지 않는 상태에서 활성화되는 '디폴트모드네트워크'가 발달하며, 내·외적 정보 또는 자극을 적절히 처리하여 복잡하고 유연한 행동이 실행될 수 있도록 하

는 중요한 뇌 영역인 '셀리언스네트워크' 의 연결성 강화가 초기 성인기에 이루어짐을 확인해 주었다. 뇌 네트워크내 정보처리의 효율성을 분석하기 위해 새로이 제안된 볼륨 엔트로피 분석은 정상 뇌 성숙이 뇌 네트워크간의 정보처리 효율성이 높아 지는 방향으로 발전함을 보여주었다. 또한 방향성을 가진 뇌 연결성 분석을 통해 청소년기에 해당하는 시기의 동물모델 뇌에서 체감각과 시각피질에서 우측 전반 대뇌피질로의 정보이동이 강화됨을 확인하였다.