学位論文内容の要旨

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学 位 論 文 題 名

Noninvasive evaluation of the brain by using recent magnetic resonance imaging techniques
（最新 MRI 法を用いた脳の非侵襲的評価）

Chapter 1. The usefulness of diffusion kurtosis imaging in the detection of subtle brain abnormalities in mood disorders

Background and Objectives: Identifying the abnormalities of the brain in bipolar (BD) and major depressive disorders (MDD) is essential for understanding the underlying biological processes. This prospective study evaluated the microstructural alterations of the brain in BD and MDD by using whole-brain voxel-based diffusion kurtosis imaging (DKI).

Materials and Methods: Seventeen BD patients, 19 MDD patients, and 20 age-, gender-, and years of education-matched healthy volunteers underwent DKI of the brain. Group differences in the major DKI indices were compared voxel-by-voxel by using one-way analysis of variance (ANOVA), and significantly different voxels were tested for correlation with clinical variables {i.e., Young Mania Rating Scale (YMRS), 17-item Hamilton Depression Rating Scale (17-HDRS), Montgomery-Åsberg Depression Rating Scale, total disease duration, duration of current episode, and the number of past manic/depressive episodes} by using Pearson's product-moment correlation analyses. The performance of DKI indices in detecting the brain alterations was determined by using receiver operating characteristic (ROC) analysis.

Results: There were 65 significant clusters ($P < 0.001$, ≥ 50 voxels), of which nine showed differences among the three groups. Mean kurtosis (MK) in the gray matter of right inferior parietal lobule declined in the order of MDD patients, healthy volunteers, and BD patients. MK of this region also had the largest area under the curve, which is 0.906. A significant correlation was observed between the MK of this region and YMRS in BD patients ($r = -0.641$, corrected $P = 0.042$) or 17-HDRS in MDD patients ($r = -0.613$, corrected $P = 0.030$). Significant correlations were also observed between the kurtosis fractional anisotropy (KFA) of right inferior frontal operculum ($r = -0.676$, corrected $P = 0.012$) or mean diffusivity (MD) in the white matter of right orbital gyrus ($r = 0.626$, corrected $P = 0.024$) of the MDD patients and total disease duration, and between MD in the white matter of the left orbital gyrus of the BD patients and the duration of the current disease episode ($r = 0.696$, corrected $P = 0.018$).

Discussion: MK is an MRI indicator of tissue structural complexity. From the documentation of decreased gray matter volume in the right inferior parietal lobule in BD and hypergyrification and increased cortical thickness of this region in MDD, the observation of altered MK in this region is thought as due to a decreased number of neurons or dendritic arborization in BD and delayed or failed dendritic pruning associated with hypergyrification or increased cortical thickness.

Conclusions: DKI detected differences in water diffusion across the brain -- suggestive of microstructural alterations, in BD and MDD. Its indices may be useful to distinguish BD and MDD or to reflect disease severity and duration.

Chapter 2. Establishment of a cognitive training program to improve cognitive function

Background and Objectives: Little is known about how combined computerized cognitive training (CCT) modulated cognitive functions such as cognitive control functions, i.e., spatial attention and working memory. Cognitive control functions are the fundamental building blocks of general cognitive function, and are essential for the improvement of several other cognitive functions. In this study, a combined CCT program designed to improve cognitive control functions was developed, and its effect on cognitive performance was examined.

Materials and Methods: Thirty-four healthy adults were included. A combined CCT targeting cognitive control functions was developed. The program consisted of dual n-back training (DBT) and attention network training (ANT). Each CCT session lasted an hour, which is 30 minutes for each training. Twenty CCT sessions were conducted in 4 weeks, equivalent to five times per week. All participants underwent a set of neuropsychological tests twice, separated by an interval of 4 to 6 weeks. The neuropsychological tests consisted of 13 tasks designed to reflect task-specific (2 tests), near-transfer (6 tests), and far-transfer (5 tests) effects of the assigned tasks. Two different test versions to prevent the learning effect on repeated testing were prepared. Whether this action

prevented the learning effect was tested on seven participants. A 2 × 2 mixed-design ANOVA with group (training or control) and time (initial or re-assessment) was used to identify the effects of combined CCT. The effect size (Cohen's d) was also calculated.
Results: Test of learning effect revealed no learning effect between the two test versions in all eight tests {Digit span test (forward): P= 1.00, Digit span test (backward): P= 0.604, Tapping span test (forward): P= 0.356, Tapping span test (backward): P= 0.689, Trail making test part A: P= 0.699, Trail making test part B: P= 0.440, Paced auditory serial addition test (2.0 second paced presentation): P= 0.348, and Paced auditory serial addition test (1.0 second paced presentation): P= 0.812, paired t-tests}. Neuropsychological performance improved significantly after the CCT in the training group, which was evident in 10 of 13 tasks evaluated. The effect sizes for the performance of neuropsychological tests which evaluated the near-transfer effect was larger in the training group (Cohen's d= |0.327 – 1.586|) than in the control group (Cohen's d= |0.000 – 0.308|) at initial vs. re-assessment condition. The effect sizes for the performance of neuropsychological tests which evaluated the far-transfer effect was also larger in the training group (Cohen's d= |0.591 – 0.989|) than in the control group (Cohen's d= |0.041 – 0.144|) at initial vs. re-assessment condition.
Discussion: The results may suggest CCT focusing on cognitive control function can improve the general cognitive function via near- and far-transfer effects. The observation of larger effect sizes for tests which evaluate the transfer effects with near- and far-transfer, compared to CCT targeted only at working memory or spatial attention (Cohen's d= |0.21-0.89|) and multi-domain cognitive training that did not include the cognitive control functions (Cohen's d= |0.28-1.04|) , is thought to imply the augmentation of transfer effect with combined CCT.
Conclusions: The 4-week combined CCT focusing on the cognitive control function can improve the cognitive performance in healthy adults, not only through task-specific and near-transfer but also via far-transfer.

Chapter 3. Noninvasive assessment of cognitive training-related changes of the brain
Background and Objectives: Some previous studies have reported the evidence the short-term training modulate the brain structure and function, but very few reports have shown relationship between changes of these neuroimaging indices and cognitive performance. This prospective study aimed to elucidate the neural mechanism of far-transfer effect of cognitive training, through the structural and functional brain changes and the relationship between these changes and cognitive performance.
Materials and Methods: Twenty-three healthy adults were recruited in this study. Two of the participants failed to complete the training. Thus, 21 participants were evaluated. Eight age, gender, and education level-matched healthy volunteers were also recruited to serve as the control group. Training group underwent the 4-week combined CCT. Control group received no training. All participants underwent neuropsychological tests and brain MRI twice, separated by an interval of 4 to 6 weeks by the same procedure described in Chapter 2. Generalized fractional anisotropy (GFA), fractional anisotropy (FA) maps were generated from diffusion spectrum imaging (DSI) data, and resting-state functional connectivity (rsFC) was calculated from resting-state functional MRI (rsfMRI) data. GFA and FA maps and rsFC were used to detect the CCT-induced changes of water diffusion and temporal correlation of blood-oxygen-level-dependent (BOLD) signals across the brain. A 2 × 2 mixed-design ANOVA with group (training or control) and time (initial or re-assessment) was used to identify the effects of combined CCT in neuropsychological tests, and the DSI and rsfMRI data. Pearson's product-moment correlation analyses were used to test the correlations of the changes in DSI indices and the changes in rsFC with the changes in neuropsychological tests.
Results: Neuropsychological performance improved significantly after CCT in the training group. GFA and FA in the right inferior parietal lobule significantly decreased and rsFC between this region and the left inferior frontal gyrus increased, after the combined CCT. There were significant negative correlation between the GFA changes in the right inferior parietal lobule and the changes in percent correctness of PASAT-2.0s (r= 0.561, uncorrected P= 0.008) and significant positive correlation between the FA changes in the right cerebellar vermis and the changes in the number of the correctness S-PA (unrelated) (r= 0.561, uncorrected P= 0.008).
Discussion: The right inferior parietal lobule is known to be a core region in the fronto-parieto-occipital network and is involved in motor learning, execution, inhibition, and spatial attention, and the right cerebellar vermis is known to involve in language processing. The right inferior parietal lobule and its neural connections as well as the right cerebellar vermis may play in modulating cognitive functions such as provoking the far-transfer effect.
Conclusions: The effect of combined CCT on cognitive performance and the brain structure and function was evaluated. The right inferior parietal lobule and its neural connections and the right cerebellar vermis are thought to involve in cognitive improvement by CCT.