論’の障害だけでなく，その前段階としてのミラーシステムの障害が関与しているとの仮説を立てた。その根拠としては 1)ミラーニューロンは，’心の理論‘の前駆段階である。 2) 自閉症では運動を始めとする模倣の障害を示すが，ミラーニューロンは模倣に関与する。3)運動学習に模倣は重要な役割を持つが，自閉症では運動の不器用な者が多い。4)常同行動もミラーニューロンのうち運動表出を抑制する抑制系の破綻により説明できるかもしれない。以上の 4 点である。計測の結果、予想通りアスペルガー症候群にではミラーシステム全体での機能低下を認め、特に STS での活動低下が著しかった。この結果は我々の自閉症スペクトラムでのミラーシステム障害仮説を支持するものと考えられる。STS posterior junction はミラーシステムと「心の理論」、両者の神経機構に共通する領域であり、アスペルガー症候群において健常者との違いが最も有意な部位であった。この領域は生物的動き(biological motion)に反応する領域として知られているが(4)、Blake らは自閉症患者において biological motion の認知が悪いことを報告しており(５)、我々の fMRI の結果(アスペルガー症候群での STS の活動低下)と一致する。我々は他者の動きを観察することにより、相手の意図(こちらに用事がある、けんかを仕掛けている、攻撃してくる）更には心的状況（怒っている、楽しそうに、悲しげに）まで読み取る事が可能であるが(４)、自閉症では biological motion に対する認知が悪いために、その後の情報処理が情報不足の状態で行われ、最終的に相手の心的状況を上手く把握できない可能が考えられる。この仮説では視覚情報末梢から中枢向きの(フィードフォワード)の障害、所謂ボトムアップの情報処理障害を想定している。しかし STS は扁桃等の中枢側からのフィードバックを受けることが知られており、中枢側から STS へのフィードバック信号の障害(トップダウン情報処理の障害)によっても STS の活動低下は説明可能である。Castelli ら(６)は単純な図形のアニメーションによる心の理論課題 (http://www.icn.ucl.ac.uk/groups/UF/Research/animations.html にてサンプルが閲覧可能)を用いてアスペルガー症候群を対象に fMRI を行い STS での活動低下と視覚情報処理領域と STS の機能的な結びつきの低下を報告している。Casrelli らは前述したトップダウンの情報処理を想定しているが、今後の検討が必要であると考えられる。最近の研究では STS は Biological motion 以外にも共同注意に関与することが分かっている。マカクサルを用いた研究では人が見るもの、指差すものをサルが見たり、触れたりするという注意の共有（共同注意）の能力が備わっており、共同注意に関する神経活動がサルの STS で観察されている(７)。共同注意は他個体と社会関係を築くコミュニケーション能力の基盤となるものであり、自閉症においてコミュニケーションの目的での

指差し、視線の共有を上手く用いることができないことはよく知られている。ヒトの脳賦活試験においても STS 周囲が視線の向きなど社会的行動の刺激に対して賦活される事が報告されており、STS の機能障害は自閉症スペクトラムの社会性、コミュニケーションの障害に深く関わっていることが推測される。

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The neural network for the mirror system and the `theory of mind' in normally developed children: An fMRI study

Running title: Mirror system and theory of mind in children

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Abstract

We preformed fMRI measurements in normal children to clarify following issues; which cortical areas are commonly involved in the mirror system and the 'theory of mind' (ToM), which areas are specific for ToM, and whether children have the same neural networks for MS and ToM as those adults have. Normal children had the same neural networks for the MS and ToM as those adults have. The common activations were found in the superior temporal sulcus and the fusiform gyri, whereas the ToM specific activation was found in the medial prefrontal, temporal pole and the inferior parietal cortices. We suggest that ToM might evolve from capacity to detect the motion of agents and to infer intentions, further, Tom might require self-perspectives.

Key words: Theory of mind, mirror neuron, fMRI, autism

Introduction

Human beings have an inherent ability to attribute independent mental states, such as beliefs, prides, and desires, to self and others in order to explain and predict behaviors of others. This is referred to as a "theory of mind' (ToM) (1). Several neuroimaging studies have identified the neural network for ToM in the paracingulate medial prefrontal cortex (MPFC), superior temporal sulcus (STS) and the temporal pole in normal adult individuals (2,3,4). Furthermore, some of them demonstrated abnormal neural activities in these areas in autistic disorders having lack of ToM (2, 4).

In 1996, Rizzolatti et al. firstly reported neurons in the monkey ventral premotor cortex (area F5, the homologue of human Broca's area), named the `Mirror neuron', that discharge both when monkey performed a specific action and when it observed another monkey performing a similar action (5, 6, 7). Their data indicated that monkey brain contains an action observation / execution matching system and suggested that even monkey has the lower-level ToM (5,6,7). Following their first report, several monkey studies demonstrated that neurons in the STS (Superior temporal sulcus) and intraparietal sulcus (IPS) also discharge during an observation of goal-directed action (5, 6, 7). As well as monkey, neuroimaging studies also found the mirror system (MS) in the human brain, such as Broca's area, premotor area, STS and the posterior parietal cortices (PPC) (8, 9). Furthermore, animal and human studies revealed that the MS should be involved in not only observation of hand action but also observation of other body parts such as mouth and foot in a somatotopic manner, simulation and imitation of other's actions and action-related sounds (7, 9). Now, several investigators considered that the MS could have an important role in action recognition, motor learning, imitation and understanding the meaning of the observed action, and be a prerequisite for the higher-level of ToM (6,7).

However, direct comparison of cortical activity patterns associated with the MS and ToM in the same subjects has not been done. Furthermore, there are no neuroimaging studies of the MS or ToM in children. Because deficits or delayed development of the MS and ToM have been considered to be associated with disorders of socialization and communication in autistic spectrum disorders (1,2), the data of neural networks for the MS and ToM in children is important and interesting. To clarify following issues, we performed fMRI measurements during objects-related action

observation and ToM task in normal children; 1) which brain areas are common neural substrates for the MS and ToM and which brain areas are specific for ToM 2) whether normally developed children have the same neural substrates for the MS and ToM as those observed in previous studies in adults.

Methods

Eleven right-handed normal children (6 boys and 5 girls, mean age 10 y.o., range 7-13 y.o.) participated in this study. Written informed consent was obtained from all subjects and/or their guardians in accord with ethical guidelines in place at local ethical committee. We performed two sessions of fMRI (the experiment 1 (exp 1) for detecting the MS and the experiment 2 (exp2) for detecting the neural network for ToM) in each subject. The order of each experiment was counterbalanced across subjects with a 20 minutes interval.

Cerebral activation was measured with fMRI using blood oxygen level-dependent contrast (10). After automatic shimming, a time course series of 125 volumes was obtained using single-shot gradient-refocused echo-planar imaging (TR = 4000 msec, TE = 60 msec, flip angle = 90 degree, inter-scan interval 4 sec, in-plane resolution 3.44 x 3.44 mm, FOV = 22 cm, contiguous 4-mm slices to cover the entire brain) with a 1.5T MAGNETOM Vision plus MR scanner (Siemens, Erlangen, Germany) using the standard head coil. Head motion was minimized by placing tight but comfortable foam padding around the subject's head. The fMRI protocol was a block design with two epochs of task condition and control condition. Each fMRI session (the exp 1 and the exp2) was performed in the same timing of epochs and measurement parameters. Each epoch lasted 20 s (equivalent to 5 whole-brain fMRI volume acquisitions). The first five volumes of each fMRI scan were discarded because of non-steady magnetization, with the remaining 120 volumes used for the analysis. In the exp1, subjects were asked to carefully observe videotaped object-related hand actions (e.g. grasping a cup, picking up a hammer, manipulating a telephone) performed by another individual. The observation of object-related hand actions was contrasted with the static hand, arm and the same objects used in the task period as a control condition. The stimuli used in the exp 1 were similar to previous fMRI study of the MS (9). In the exp 2, subjects were asked to watch ToM animations consisted of two triangles. This task was contrasted

with the random movements of two triangles used as a control condition. Animations used in exp 2 were modified for fMRI measurement but were essentially the same as stimuli used in previous PET studies (3, 4). The stimuli were presented using Windows Media player running on a PC and back projected onto a screen, approximately 50-cm from the subject's head, using a 65536 -color liquid crystal display and an overhead projector. The subjects viewed the screen through a mirror attached to the head coil. After the exp 2, subjects were presented each animation used the in exp 2 and asked to tell the experimenter what they thought the triangles were doing. This procedure was performed outside the MR scanner. The verbal descriptions given after each animation were corded along four different dimensions, the intentionality, appropriateness, certainty and the length of each answer. Detail of the procedure and scoring for evaluation of behavioral data was identical to the previous PET study (3).

Data analysis

Data were analyzed with Statistical Parametric Mapping software (SPM99, http//:www.fil.ion.ucl.ac.uk/spm). Scans were realigned and EPI BOLD images were summed and co-registered to the subject's T1-weighted MR images. Then T1-weighted MR images were transformed to the standard stereotactic space of Talairach using a T1-weighted MR template (11). The parameter for affine and quadratic transformation to the T1-weighted MR template that was already fit for Talairach space was estimated by least-squares means. This transformation was applied to co-registered EPI BOLD images. Data were then smoothed in a spatial domain (full width at half-maxim = 8 x 8 x 8 mm) to improve the signal to noise ratio. After specifying the appropriate design matrix, delayed box-car function as a reference waveform, the condition, slow hemodynamic fluctuation unrelated to the task and subject effects were estimated according to a general linear model taking temporal smoothness into account. Global normalization was performed using proportional scaling. To test hypotheses about regionally specific condition effects, the estimates were compared by means of linear contrasts of each control and task period. The resulting set of voxel values for each contrast constituted a statistical parametric map of the t statistic SPM {t}. Common activation pattern in the mirror system and ToM was estimated by using a conjunction analysis. The specific activation associated with ToM was estimated by using an exclusive mask with the MS associated activations threshold at $p < 0.05$. To account

for interindividual variance, all group analyses were computed using a random-effects model (12). Group analysis across subjects involved a one-sample *t*-test on the images generated by pooling over the session the individual contrasts of activation versus control, conjunction with activations of the MS and ToM, and ToM related activations exclusively masked by the MS related activations for each subject. The voxels and clusters of significant voxels were given a threshold of $p < 0.001$ without corrections for multiple comparisons.

Results

Table 1 shows the ratings of the descriptions of each type of animation. Subjects attributed more intentionality to the characters' behavior during ToM animations than during random movements (paired t test, $p < 0.001$). The length of descriptions for ToM animations was longer than those for random movements (paired t test, $p < 0.001$). There was no difference in the appropriateness or certainty.

In comparison with the observation of object and static hands (control condition), the observation of object-related hand actions activated the left dorsal premotor cortex (PMdr), Broca's area (left Brodmann's area 44:BA44), right parietal operculum, bilateral intraparietal sulci (IPS), bilateral superior temporal sulci (STS), bilateral fusiform gyri and the bilateral visual association areas (BA18, BA19) (Fig.1a, table 2).

Fig. 2 shows activations associated with ToM. As compared to random movements, significant activations were noted in the right medial prefrontal cortex (MPFC) (BA9), right dorsolateral prefrontal cortex (DLPFC), bilateral STS (right dominant), right inferior parietal cortex (BA40, BA39), right temporal pole, bilateral fusiform gyri (BA37), bilateral visual association areas (BA18) and the left cerebellum (fig.1b, Table1).

We found that bilateral STS, fusiform gyri and visual association areas (BA18) were commonly activated by both action observation and ToM (fig2a, table 2). On the other hand, the right MPFC, right inferior parietal cortex, and left cerebellum were recruited in only ToM (fig.2b, table 2).

Discussion

Our experiments were designed to identify the cortical areas associated with

the MS and/or ToM in normally developed children. We found activations in the PMdr, Broca's area, parietal operculum, IPS and the STS during objects-related hand actions. The significant activation in the visual association areas, particularly in the motion related area (V5), probably due to moving stimuli will not be discussed here. The results well correspond with those of previous studies of human MS in adult subjects (8,9). Our study also replicated activations in the MPFC, temporal pole, STS and the T-P junction that have been considered to be crucial neural components for ToM (2,3,4). The behavioral data indicated that all subjects well understand the meaning of ToM animations. These results indicate that normally developed children have fully developed neural substrates for the MS and ToM. Additionally, significant activations associated with ToM were noted in the bilateral fusiform gyri (right dominant) and left cerebellum. Although previous PET studies using essentially the same stimuli for ToM did not demonstrate cerebellar activation (3,4), we suggest that cerebellum also has an important role in mentalizing. Similar cerebellar activation associated with ToM was reported by Brunet et al. (13) and Calarge et al. (14) (Calarge reported right cerebellar activation). Recent neuroimaging studies have revealed that the cerebellum should be involved in higher cognitive functions, such as language and memory (15). Furthermore, pathological and morphological studies of autism have demonstrated cerebellar abnormalities (16). Since impairments of socialization and communication in autism may be explained by lack or delayed development of ToM, it is plausible that the cerebellum also contributes to ToM.

One of aims of this study was to identify common cortical regions for the MS and ToM and to identify specific areas for ToM. Because the MS is considered to be a neural network for the lower-level of ToM and a prerequisite for the higher-level of ToM, we assumed that several regions should be common for both levels of ToM. On the other hand, even primates have the lower-level of ToM, however, the higher-level of ToM seems to be unique to our spices (17). If so, there may be different neural components for the higher-level of ToM from those for the lower-level one. As expected, common activations in two systems were found in the posterior part of the STS in the temporal lobe and the fusiform gyri. Single-cell recordings in macaque and human neuroimaging studies have demonstrated that the STS region receives inputs from both the ventral and dorsal visual streams and processes perception of biological motion (18). Because

biological motion is important information to understand intention of others', it is not surprising that the STS is a common neural substrate for the MS and ToM. The fusiform gyrus has been considered to selectively process perception of faces (so called the fusiform face area), however, a recent fMRI study using similar stimuli to ours suggested that the fusiform gyrus should have a general role in social perception including the perception of intentional behaviors as well as the STS (19). We suggest that the higher-level of ToM might have evolved from capacity to detect the motion of animate agents and, subsequently, to infer intentions from actions which could be processed in the STS and fusiform gyrus.

Although the STS in the temporal lobe may be a common neural substrate for the MS and ToM, the most posterior part of the right STS, the inferior parietal cortex was recruited by only ToM. Previous studies of ToM suggested that activation in this region should be related to biological motion and/or a general role of detecting agency from visual cue rather than biological motion itself (2,3,4). However, our study indicated that the STS in temporal lobe might be more involved in such processes than the parietal cortex. We speculate that the right inferior parietal activation in ToM may be associated with 'self-perspective', taking ones own perspective. Recently, Ruby and Decety (20) reported that the right inferior parietal cortex was recruited in distinguishing the perspective of the self and those of others. They suggested that the right parietal lobe have a determinant role in self-representation. Vogeley et al. (21) also reported the importance of the right inferior parietal area in the metarepresentation of ones own mental states. The ToM capacity is based on taking someone else's perspective, and projecting ones own attributes on someone else. During such mentalizing, one has to be aware of who the self is, in order to be able to imagine another person with the same neural resources as the self. In this context, the higher-level of ToM, such as understanding false belief and deception should require self-perspective. We assume that the right STS in the temporal lobe may be recruited in detecting agency of others, whereas the right STS in the parietal lobe may be recruited in detecting agency of one's own.

As well as the right inferior parietal cortex, the right MPFC and right TP were also recruited in only ToM. The activations in these regions are consistent findings amongst previous neuroimaging studies of the ToM. We have no additional interpretation for

these activities. However, we finally discuss the right dominancy in our results. Most studies demonstrated the left MPFC activation regardless of modalities of stimuli (2,3,4), whereas our study demonstrated the right MPFC activation. A similar result was reported by Brunet et al. (13). They suggested that the discrepancy in laterality reflects different nature of tasks (e.g. verbal or non-verbal) used in each study. However, our stimuli and the experimental design were essentially the same as those of previous PET studies demonstrating the left MPFC activation (3,4). One possible explanation is that different laterality may be caused by the differences in spatial resolution of PET and fMRI studies, as PET data were smoothed with larger filters such as 12 mm. The precise assignment of an activation of a midline structure to either hemisphere should be more difficult with PET than fMRI. Indeed, using fMRI measurement, Vogeley et al. (21) reported the right MPFC activation related to ToM task with verbal material. Furthermore, our finding of right hemispheric dominance for ToM is well concordant with results of neuropsychological studies in patients with right hemispheric lesions. According to lesion studies, patients with right hemispheric lesions demonstrate difficulties with communication, such as the understanding of metaphors, indirect meaning, the emotional-prosodic quality of expressions, and ToM (22). The results support the right hemispheric dominancy in the ToM.

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Fig.1 Activations associated with the action observation and a 'Theory of mind' (ToM)

Fig.1a: The observation of object-related hand actions activated the left dorsal premotor cortex, Broca's area, right parietal operculum, bilateral intraparietal sulcus (IPS), bilateral superior temporal sulcus (STS), bilateral fusiform gyri and bilateral visual association areas.

Fig. 1b Activations associated with ToM. As compared to random movement, significant activations were noted in the right medial prefrontal cortex, right dorsolateral prefrontal cortex, bilateral STS, right inferior parietal cortex, right

temporal pole, bilateral fusiform gyri , bilateral visual association areas and the left cerebellum.

Fig.2 The common activity for the mirror system and ToM, and specific activity for ToM.

Fig.2a The bilateral STS, fusiform gyri and visual association areas were commonly activated by both action observation and mentalizing.

Fig. 2b Activations in the MPFC, right temporal pole and right inferior parietal cortex and left cerebellum were observed in only ToM.

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Table 1 Verbal descriptions given by subjects for ToM and random movement animations rated on four dimensions

Total score maximum	ToM mean (s.d.)	Random movement mean (s.d.)
20	14.7 (2.4)	0.8 (1.6)
12	9.8 (2.8)	10.5 (1.2)
12	8.7 (1.6)	9.8 (1.9)
16	10.4 (4.5)	6.1 (2.7)

Table 2 Brain activity of the whole group during maze task

Anatomical region	BA	Talairach coordinate			t value
Mirror					
Frontal					
L Premotor area	6	-36	-5	54	4.46
L Precentral gyrus	44	-48	1	11	4.16
Parietal					
R Parietal operclum	40	55	-24	18	4.53
R Intraparietal sulcus	7 / 40	40	-45	55	5.43
L Inferior parietal lobule	40	-42	-40	54	5.01
STS					
R Superior temporal gyrus	21/22	64	-40	9	7.03
L Middle temporal gyrus	21	-63	-38	6	7.51
Visual Association Areas					
R Middle oppcipital gyrus	18 / 19	50	-71	-4	10.67
L Middle occopital gyrus	18 / 19	-48	-75	0	8.65
ToM					
Frontal					
R Medial preforntal area	9	4	56	25	4.8
R Middle frontal gyrus	9	36	17	25	5.55
Temporal-Parietal					
R Superior temporal gyrus	22/42	59	-38	9	8.65
R Supramarginal gyrus	40	48	-42	19	7.74
R Superior temporal gyrus	39	57	-48	19	7.33
R Middle temporal gyrus	21	51	-22	-9	10.67
R temporal pole	38	45	4	-20	9.22
R Fusiform gyrus	37	48	-51	-16	5.67

L Supeior temporal gyrus	22	-61	-50	14	6.42
L Fusiform gyrus	37	-46	-55	-11	6.14
Visual area					
R Middle oppcipital gyrus	18	32	-91	1	6.62
L Middle occopital gyrus	18	32	-91	0	6.14
Cerebellum					
L Cerebellum		-22	-79	-28	7.6
Common activation					
R Middle temporal gyrus	21	51	-22	-9	10.67
R Supeior temporal gyrus	22	51	-38	7	8.65
L Middle temporal gyrus	22	-51	-44	4	4.99
R Middle oppcipital gyrus	18	32	-91	1	6.62
L Middle occopital gyrus	18	32	-91	0	6.14
R Fusiform gyrus	37	48	-51	-16	5.67
L Fusiform gyrus	37	-46	-55	-11	6.14
ToM only					
Frontal					
R Medial preforntal area	9	4	56	25	4.8
R Middle frontal gyrus	9	36	17	25	5.55
Temporal-Parietal					
R Supramarginal gyrus	40	48	-42	19	7.74
R Superior temporal gyrus	39	57	-48	19	7.33
R temporal pole	38	45	4	-20	9.22
L Supeior temporal gyrus	22	-61	-50	14	6.42
Cerebellum					
L Cerebellum		-22	-79	-28	7.6

a

b

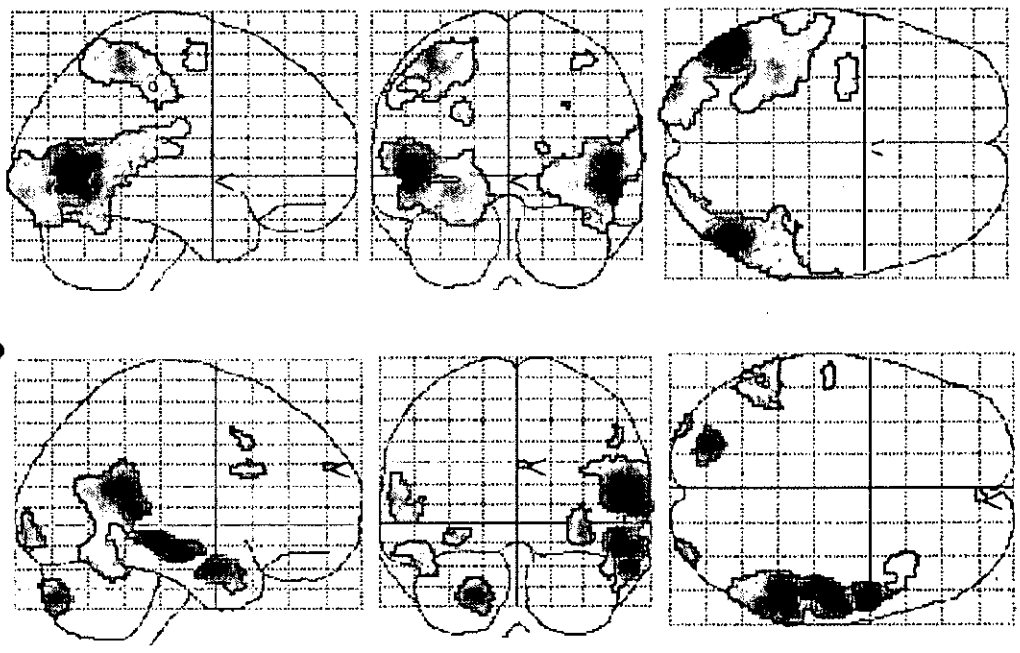

Fig.1

a

b

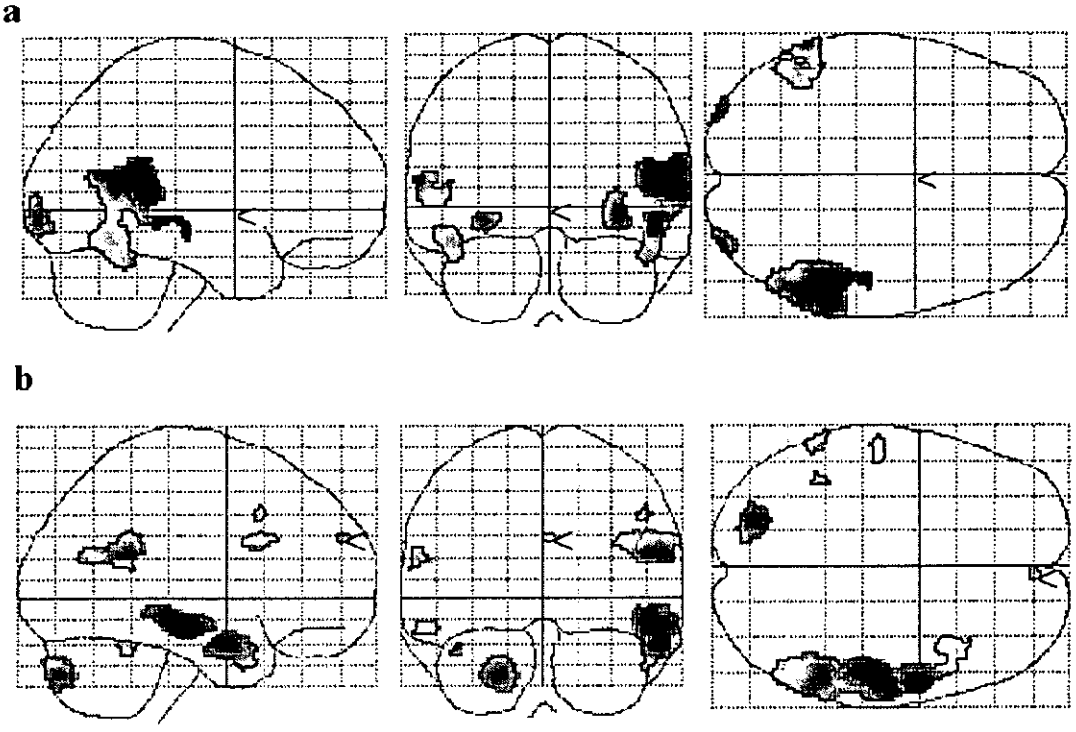

Fig.2

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	頁
Nonaka Y, Hayashi T, Ohnishi T, Okabe S, Teramoto N, Ueno S, Watabe H, Matsuda H, Iida H, Ugawa Y.	A coil for magnetic stimulation of the macaque monkey brain.	Paulus W, Tergau F, Nitsche MA, Rothwell JC, Ziema U, Hallet M.	Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation	Elsevier Science	Amsterdam	2003	75-80

雑誌

発表者氏名	論文タイトル名	発表紙名	巻名	ページ	出版年
Yotsutsuji T, Saitoh O, Suzuki M, Hagino H, Mori K, Takahashi T, Kurokawa K, Matsui M, Seto H, Kurachi M	Quantification of lateral ventricular subdivisions in schizophrenia by high-resolution three-dimensional magnetic resonance imaging	Psychiatry Research: Neuroimaging	122	1-12	2003
Adachi N, Kato M, Sekimoto M, Ichikawa I, Akanuma N, Uesugi H, Matsuda H, Ishida S, Onuma T.	Recurrent postictal psychosis after remission of interictal psychosis: further evidence of bimodal psychosis.	Epilepsia	44	1218-1222	2003
松田博史	新しいSPECTの臨床応用の可能性	分子精神医学	3	287-294	2003

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以降は雑誌/図書等に掲載された論文となりますので、
「研究成果の刊行に関する一覧表」をご参照ください。