

Doctoral Dissertation

**Tool-use and language functions in
Language area : fMRI studies**

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言語野内における

道具使用機能と言語機能：fMRI 研究

樋口さとみ

内容梗概

道具使用という複雑な高次認知機能は、人間およびその他の類人猿などに限られた動物の能力である。人間の言語機能も高次認知機能で、チンパンジーなどは訓練により簡単な手話を覚えることができるが、一般に人間以外の動物は言語機能が劣っている。本研究は、fMRIを用いて道具使用時に関する脳活動と言語使用時に関する脳活動を調べることを目的とした。はじめに、道具使用に関わる脳活動部位を調べた。その結果、脳損傷により道具を使用する事が困難になる失行症状とその損傷部位の関係から、道具使用と関係があるとされてきた頭頂間溝だけでなく、前頭葉の一部 (BA44, BA45) や小脳に脳活動がみられた。さらに、小脳の脳活動は道具ごとに異なる分布していた。前頭葉の領域にみられた脳活動の領域は、サルが他者の行動観察を行った際に発火するニューロン (ミラーニューロン) が発見された部位であり、BA44, BA45はブローカ野の一部として知られている領域である。これらの事象から行動観察などで相手の状態を察する事は、コミュニケーションの基本として、ミラーシステムと言語の起源との関係がRizzolattiらより示唆されている。Greenfieldらは道具使用などの運動企画をすることから、言語が進化したと主張しており、Rizzolatti同様、言語は他の機能から発達したという見解である。一方、Chomskyらの言語機能は突然進化した機能で、サルなど他の動物に、この機能は存在しないものであると主張している。そこで道具使用課題と言語課題を行った際の脳活動を調べることで、道具使用などから言語機能が進化した場合、脳活動部位の重複があれば、これらの機能の起源は同じであると考えることができ、重複部位がなければまったく新しい機能として進化したものと仮定し実験を行った。その結果、ブローカ野内で共通の脳活動が見られたため、これらの機能は道具使用などから、言語は進化したという説が支持された。一方、教育心理学の知見から、道具使用と言語活動

の能力の発達の男女差が、女兒が早い時期から話し始め、一方で男児は道具のおもちゃへより興味を示すことが報告されている。そこで、被験者数をそれぞれ14名になるよう増やし、道具使用課題と言語課題を行った際の、男女差があるかどうか調べた。その結果、前の実験から示されたブローカ野の脳活動の位置が前後方向で男女で異なっていることがわかり、さらにその差と被験者のテストステロン量との相関が示された。そこで、ブローカ野に続いて、ウェルニッケ野についてもその脳活動量を調べたところ、Kimuraらと同様の、タスクと寄与する領域の男女差がみられた。これらのことから、道具と言語は機能的に似た種類の脳機能であり、これらの脳機能には様々な男女差があることが示す。

キーワード

fMRI、道具使用、言語、ミラーニューロン、コミュニケーション、言語の起源、ブローカ野、ウェルニッケ野

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Tool-use and language functions in Language area : fMRI studies

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Abstract

Higher cognitive brain functions such as use of complex tools is an ability limited to humans and limited kinds of nonhuman primates. Human language ability is also dominant over any other animal even compared with sign language by extensive training in the chimpanzee. The purpose of this study was to investigate the brain activity related to tool-use and language processing using functional MRI. Firstly, the brain areas related to tool-use were investigated. We found brain activities not only in the intra parietal sulcus areas associated with apraxia, but also in part of the frontal area (BA44 and BA45) and in the cerebellum. Furthermore, the distribution of the brain activities in the cerebellum was different for each tool. The activity in the frontal cortex was that where mirror neurons have been found during observation of others' behavior in monkeys, a region known to be a part of Broca's area. The relation between the mirror system and evolution of language has been suggested by Rizzolatti because the role for mirror neurons is considered a basis function for communication by understanding states of observed behavior of others. It is also suggested that the language evolution has occurred as a result of complex motor planning for tool-use. On the other hand, others believe that language is a saltationally evolved function that is unique to the human (Hauser 2002). We experimented with these contradictory hypotheses. In particular, if there is no common brain activity for tool-use task and language

task then language may be assumed to have evolved saltationally, but if there is common activity then gradual evolution from other function is more probable. Our results show common activity in Broca's area, supporting the latter view. Current literature from educational psychology fields show developmental gender differences; girls start talking earlier, but boys have more preference to play with tools/ toys. Therefore we investigated if there are gender differences during tool-use task and language task in 28 subjects. We found the anterior-posterior positional difference for male and female subject in Broca's area. Furthermore, position differences correlated well with testosterone level differences across subject pairs. Related to tool-use and language, apraxia and aphasia are associated with symptoms which show different disability patterns depending on the brain regions (Broca and Wernicke). Male subjects have more risk of those symptoms with lesion in Wernicke area. On the other hand, female subjects have more risk with the lesion in Broca's area (Kimura D., 1983). Therefore, we investigated the brain activity in Wernicke area as well as Broca's area to test gender difference in those areas. The amount of activity in tool-use and language showed similar gender difference tendencies as the clinical study. We therefore suggest that tool-use and language are functions which have similar structure but have several gender differences.

Keywords:

Reinforcement learning theory, discounting factor, serotonin, fMRI

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Chapter 1

General Introduction

Humans have several higher cognitive brain functions that other animals do not possess. For some of these brain functions, other animals such as apes can acquire simple abilities like tool-use, but more complex tool-use and language communications are human-specific abilities. Greenfield suggested that human-specific functions such as language evolved from the simpler functions that other animals could also perform (Greenfield 1991). On the other hand, Chomsky argued that human language is a saltationally evolved function that does not share an origin with a basic language function of other animals.

Neuron firing has been observed by single-cell recording as monkeys observed meaningful actions (e.g. breaking nuts shell) by other monkeys or humans. These neuron firings suggest that monkeys can understand other agents' actions and that they can interpret the observed action as their own action by inner imitation (mirror neuron theory) (Rizzolatti and Arbib 1998). Accordingly, we can assume that having this ability plays a very important role in understanding other agents in social behavior. Furthermore, for language communication this is an essential function in understanding or inferring an agent's mental state.

Among the higher brain functions, autistic patients are usually good at systemizing skills such as tool-use but poor at empathizing skills, which are required to infer the intention of other agents in verbal communication (Baron-Cohen, Knickmeyer et al. 2005). Empathizing is the capacity to predict and to respond to the behavior of agents (usually people) by inferring their mental states and responding to these with an appropriate emotion. Systemizing is the capacity to predict and to respond to the behavior of non-agentive deterministic systems by analyzing input-operation-output relations and inferring the rules that govern such systems. At a population level, females

are stronger empathizers and males are stronger systemizers. The “extreme male brain” theory posits that autism represents an extreme of the male pattern (impaired empathizing and enhanced systemizing) (Baron-Cohen, Knickmeyer et al. 2005).

Testosterone is one of the sex hormones, and the intensity of this hormone affects the muscularity of the body and behavior. It is known that the level of testosterone intensity differs between genders. Autistic patients appear to have experienced a high testosterone level during the prenatal period, suggesting that empathizing skill and systemizing skill can be correlated with testosterone level. In general, as testosterone levels differ between genders, it has been shown that testosterone-related functional and behavioral traits are more correlated in males than in females. Based on the correlation between anatomical volume in the frontal cortex and genders, it is suggested that higher-testosterone subjects have larger volume (Blanton, Levitt et al. 2004). Furthermore, the left posterior Sylvian fissure is locationally different between genders. These hormones act on specific cells throughout the body and brain and cause them to develop in a masculine (male-typical) fashion. For example, testosterone enters the brain during the early critical periods of development and causes the formation of neuronal cell groups and synaptic connections that control functional and behavioral traits that are more correlated in males than in females. Furthermore, testosterone is the hormone which can go through the blood brain barrier which other hormones can not through. Thus, male who produce more testosterone than female has more direct effect in the brain.

The condition of patients who cannot perform tool-use is called apraxia, and that of patients who cannot use language is called aphasia. These neurological symptoms are known to be correlated with damage in Broca’s area in the inferior frontal cortex (BA44, BA45; BA, Brodmann’s area). The region of neurological damage related to apraxia and aphasia includes Broca’s area and Wernicke’s area. The occurrences of apraxia and aphasia differ between genders. Females have a higher proportion of these conditions in Broca’s area, whereas for males they occur more frequently in Wernicke’s area (Kimura and Mehgel 2002). Passive language comprehension is assumed to be correlated with Wernicke’s area, while executive language action such as speech is known to be correlated with Broca’s area. This gender difference suggests that language and tool-use differ between genders since those functions’ areas are different in how they form passive and active behaviors.

The characteristics of apraxia and aphasia suggest that their related functions have similar components, but autistic patients are able to use tools while they are poor in language communications. Wolpert suggested that the framework of motor control for

object manipulation, which requires short-term inference of a next step, can be considered equivalent to a system for social communication that requires inference of the state of an opponent. How an object moves in reaction to tool-use action is comparatively easy to systemize and understand as patterns, but language communication has so much variability that it is difficult to systemize all of the possibilities. Consequently, language communication could be a more developed function of syntactic processes, in which Broca's area plays a role. If tool-use requiring simple syntax and language use requiring complex syntax have the same source, then these two tasks imply shared brain activity in Broca's area.

A relation between social communication function and Broca's area has been suggested by the finding of mirror neurons in monkey's area F5. Originally, social communication had been considered a function related to the superior temporal sulcus (STS), which partially includes Wernicke's area (Boddaert 2004). Therefore, it is possible that Broca's area and Wernicke's area have similar functions, where Broca's area mainly has a role in systemizing skills while Wernicke's area has a role in empathizing skills for successive tool-use and language functions. Furthermore, since gender differences are known to exist for systemizing and empathizing skills, tool-use and language tasks also involve some gender differences.

In this thesis, we measured which brain region related to tool-use skill.

Chapter 2

Tool-use related activity and its different distribution for each tool

1. Tool related brain area

Such intelligent animals as humans and chimpanzees can use tools. To acquire the ability to use particular tools, for example, scissors or chopsticks, humans and chimpanzees require much practice; however, once such ability is acquired, it cannot be forgotten. According to computational neuroscience, such abilities are carried out by inverse models that calculate the motor command to achieve task goals and forward internal models that predict the sensory feed back from the efference copy of the motor command. Based on these models humans predict or simulate the input-output properties of tool-use (Kawato, Furukawa et al. 1987). By internally representing the relationship between tool manipulation and the outcome of tool-use behavior, the predictive control of tools becomes possible, enabling us to use them quickly and smoothly.

Computational neuroscience fields have proposed that internal models exist in the cerebellum (Kawato 1999). Recent functional neuroimaging studies (Imamizu, Miyauchi et al. 2000) have found cerebellar activity that reflects an internal model of a novel tool, indicating that internal models of novel tools are modularly organized (Imamizu, Kuroda et al. 2003). We investigated whether the internal models of such common tools as chopsticks and scissors are also modularly organized in the cerebellum.

On the other hand, in neurological fields numerous works have suggested that the

parietal cortex is one location candidate that stores internal models (Blakemore and Sirigu 2003; Sirigu, Daprati et al. 2004). Furthermore, many studies have indicated that the parietal cortex is the most important part of a tool-use network. A neuropsychological investigation demonstrated that apraxic patients with a left parietal lesion without paralysis or aphasia make spatial and temporal errors in tool-use as well as when pantomiming such gestures (Heilman, Rothi et al. 1986). Pantomime has been considered an effective test for apraxia since some reports have shown a strong correlation between pantomime and actual tool-use (De Renzi and Lucchelli 1988; Goldenberg and Hagmann 1998). In fMRI experiments on healthy subjects, Moll and Oliveira-Souza et al. (Moll, de Oliveira-Souza et al. 2000) and Choi and Na et al. (Choi, Na et al. 2001) compared activity evoked by tool-use pantomimes to that evoked by a hand movement task devoid of any tool-use connotation by matching the intrinsic properties of the movements employed in the tool-use pantomime task. The involvement of the intra parietal sulcus (IPS) was shown in tool-use skill as well as cognitive knowledge of tool-use. In Positron Emission Tomography (PET) experiments on healthy subjects, Rumiati and Weiss et al. (Rumiati, Weiss et al. 2004) compared activity evoked by imitating observed pantomimed action and pantomiming the use of an observed object, finding activity in the dorso-lateral prefrontal cortex and the dorsal and ventral parietal lobules. We know that pantomime is a useful test for apraxia. An apraxic patient with Alzheimer's disease had more difficulties in a pantomime task than in an actual tool-use task (Kato, Meguro et al. 2001). Some patients showed the opposite case; they could pantomime but had difficulty in actual tool-use (Watson, Fleet et al. 1986; Motomura and Yamadori 1994).

As an example of a non-common tool-use experiment using PET, Inoue and Kawashima et al. asked subjects to manipulate a small graspable object with a pair of tongs and found activity in the posterior parietal cortex ipsilateral to the hand used (Inoue, Kawashima et al. 2001). Their study excluded the cerebellum from analysis because it was outside of the transaxial field of view. An activation study using PET in monkeys (Obayashi, Suhara et al. 2001) with an actual tool-use task revealed IPS, the supplementary motor area (SMA), the ventral part of the premotor, the cerebellum, and some other areas of the brain. However, no actual and common tool-use studies with human subjects have been conducted.

Therefore, to understand the mechanisms of actual tool-use we must determine the brain activity involved when subjects actually use tools. The aim of the present study is to investigate brain activity related to the actual use of various common tools and to infer the underlying neuronal mechanisms. The task for actual tool-use not only evokes

brain activity related to the cognitive knowledge of tool-use and skills for tool-use but also to muscle activity. Therefore, we investigated and compared brain activity related to actual tool-use tasks with activity related to tool-use motor imagery to isolate the cognitive components of common tool-use.

1.1. Method for 16 tool-use study

Eight neurologically normal subjects (23-39 years old; three females and five males) participated in the experiment. Each subject received explanation of the experiment and signed an agreement. The protocol was approved by the Ethics Committee of ATR. All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield 1971) and had normal or corrected-to-normal vision.

There were three conditions in this experiment. In the execution condition, subjects were asked to use one of sixteen common tools along with an appropriate object with visual feedback (e.g., using scissors to cut a sheet of paper). All tools and target objects for the tools are given in Table 1. Subjects were instructed to use all tools with the right hand and taught the operation of each tools; then they practiced with each tool a few times before fMRI scanning. In the imagery condition, subjects were asked to imagine using a tool the same way it was used in the tool-use execution condition. In this condition, the subjects did not actually manipulate the tools but held them and looked at the target (e.g., paper) in the same manner as in the execution condition. In the third condition, a control condition, subjects were asked to hold the tool without imagining its use while keeping their eyes open and maintaining the same hand and arm posture.

Table 1 Tool and manipulation for tools

Tool	Manipulation
brush	brushing something hair-like
chopsticks	Picking up a bead using chopsticks
paper clip	clipping papers together with a clip
comb	combing out something hair-like
screwdriver	turning a screw
fork	threading beads using a fork like rolling up spaghetti
hammer	hammering a nail

knife	cutting clay with a knife
monkey	
wrench	adjusting a nut and turning it
pencil	drawing something on a piece of paper
pliers	turning a nut with pliers
saw	mimicking the sawing of a board by making a little cut
scissors	cutting a sheet of paper
spoon	catching beads using a spoon
toothbrush	cleaning a small hole
wrench	turning a nut with a wrench

Figure 1 shows an instance of tool-use in an execution task. Subjects lied on the bed of the fMRI scanner and looked at their own hand and the tool through two mirrors that were combined to remove all reversal or inversion of the visual image.



Figure 1 Example of task situation (chopsticks)

Each condition lasted 30 seconds. The transitions and type of conditions were indicated by a sound stimulus of different frequency presented using Presentation Version 0.42 from Neurobehavioral System. Execution and imagery conditions were always followed by the control condition. Each condition was repeated nine times per session (eighteen minutes). The order of the execution and imagery conditions was randomized. At the beginning of the session the subject was handed a tool that did not change during the session. Thus, the subjects underwent 16 sessions for the 16 tools.

The sessions were conducted over a few days, and the order of tools was randomized.

1.2. MRI acquisition

We used SPM99 software (SPM99 1999) for image processing and statistical analysis. The first two volumes of images were discarded to allow for T1 equilibration, while the remaining 180 image volumes were realigned to the first volume. T2 and T1 structural images were coregistered to the average realigned EPI image and then spatially normalized to the Montreal Neurological Institute (MNI; Montreal, Canada) reference brain. The typical structural image of one of the eight subjects was used in Figure 2. The structural images used in Figure 3 were constructed from the normalized T1 averaged over all subjects. The normalized EPI images were spatially smoothed with a Gaussian kernel with a 6 mm full width at half maximum (FWHM). To remove the drift component of the signal change carried with time, high-pass filtering was applied. The voxel time series was temporally smoothed with a Gaussian filter (FWHM of 4 seconds). Parameter estimates for the imaging and execution trials were determined by fixed effect analysis for each subject using a boxcar function convolved with the HRF. The model was designed to estimate the main effects of each condition (16 tools of execution and imagery).

2. Analysis for 16 tool-use experiment

2.1. Analysis of execution and imagery conditions

Using fixed effect analysis, we investigated activity related to the execution and imagery conditions for each subject across the sixteen tools. Then the main effect of the imagery and execution condition data were independently used for a random effect analysis to investigate activities common to all subjects (random effect analysis $p < 0.001$ uncorrected).

2.2. Analysis of activity position in right upper cerebellum

To investigate activity specific to each tool, we conducted subtraction analysis (imagery minus control and execution minus control) across the subjects separately for each tool (fixed effect model $p < 0.05$ corrected). Because we did not detect any significant activity,

we excluded the SAW tool from this analysis. We limited the region of interest to the right cerebellum superior to the horizontal fissure, since we consistently found activities in this area over all tool conditions. Based on these results, we calculated a t-value-weighted centroid of activation for each tool and investigated the centroid distributions.

3. Results for 16 tool-use experiment

3.1. Activation differences between imagery and execution conditions

Figure 2 shows significant activation ($t > 4.79$, $p < 0.001$) related to the execution condition (blue regions) and the imagery condition (yellow regions). Pink circles indicate a blue and yellow mosaic, i.e., overlap between the imagery and execution conditions.

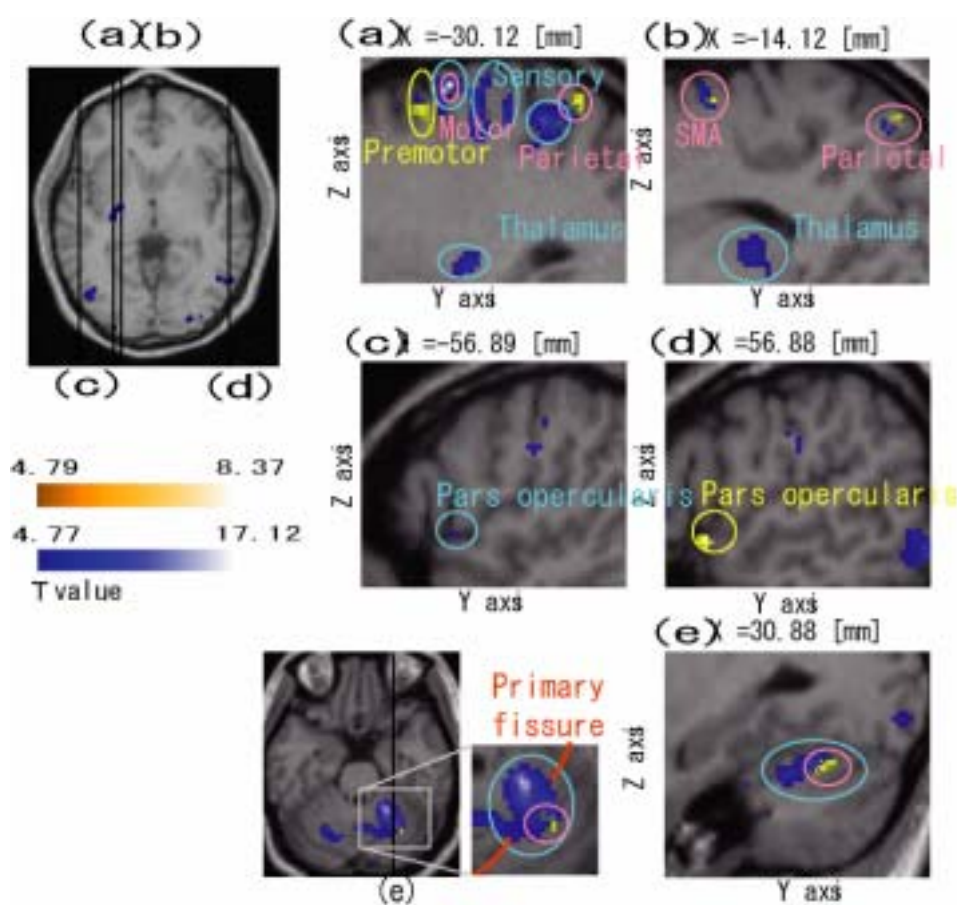


Figure 2 Comparison of brain activity between tool-use motor imagery (yellow) and actual use

(blue). Images a, b, c, and d show sagittal sections at the black lines in left panels. X, Y, and Z in the figure indicate MNI coordinates. The typical structural image of one of the eight subjects was used.

Regions activated only in the imagery condition were found in the left premotor area and right pars opercularis, while regions activated only in the execution condition were found in the primary motor area, the left sensory area, the thalamus, the pars opercularis, and bilaterally in the cerebellum. Overlap between the imagery and execution conditions was found in regions of the left motor area, the SMA, the parietal area, prominently in the posterior IPS, and in the right cerebellum (Figure 2e)).

In the left panel of Figure 2(e), the red line indicates the primary fissure in the cerebellum. Activation related to the execution condition was only located anteriorly to the primary fissure, whereas the overlap was located posteriorly to the fissure. All coordinates are listed in Table 2.

Table 2 Coordinates and t-values of activation peaks for imagery and execution condition as revealed by random effect analysis ($p < 0.001$ uncorrected). Regions of ten highest t-value peaks are listed.

Anatomical description		Lateralit y	x	y	z	T value
IMAGERY						
Central region	Precentral	L	-38	0	50	8.37
	Precentral	R	48	10	48	6.18
	Postcentral	L	-46	-28	52	7.17
Frontal lobe	Supplementary motor area (SMA)	L	-12	4	66	7.55
	Supplementary motor area	L	-8	-6	74	5.99

		(SMA)					
	Pars opercularis	R	56	12	-6	7.6	
Parietal lobe	Posterior part of IPS	L	-26	-72	54	8.37	
	Posterior part of IPS	L	-26	-58	52	6.07	
	Angular gyrus	L	-50	-64	42	7.96	
Cerebellum	Lobule VI	R	32	-62	-28	6.18	
<hr/>							
EXECUTION							
<hr/>							
Central region	Precentral	L	-30	-12	66	17.1	
							2
Parietal lobe	Posterior part of IPS	R	26	-66	52	8.63	
	Inferior parietal	R	40	-48	54	12.7	
							4
	Supramarginal	R	58	-22	26	9	
Occipital lobe	Middle occipital	L	-46	-76	-2	9.7	
	Inferior occipital	R	36	-92	-10	8.36	
Temporal lobe	Inferior temporal	R	52	-64	-4	14.1	
							2
Subcortical area	Putamen	L	-30	-20	0	9.03	
Cerebellum	Lobule IV, V	R	18	-48	-24	14.8	
							7
	Lobule VI	L	-20	-60	-32	10.3	
<hr/>							

3.1.1. Positional relationship between imagery and execution conditions.

For all tools and subjects, control condition activation was subtracted from the activation of the tool-use imagery and execution conditions to assess the brain activity of imagery and execution, respectively ($p < 0.001$ uncorrected). Figure 3 shows the t-value-weighted centroid of activation for each tool projected to horizontal and coronal planes.

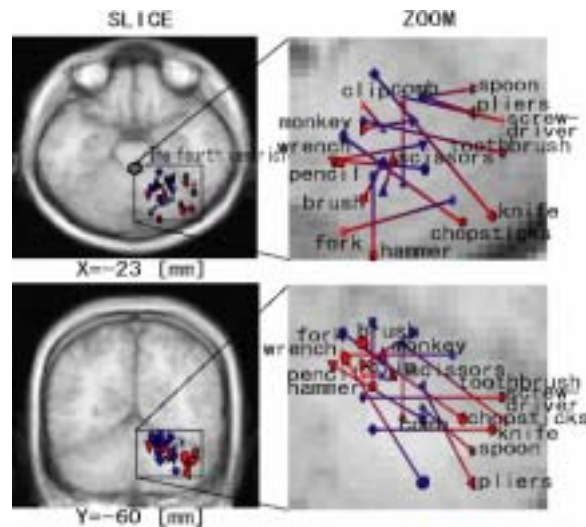


Figure 3 Distribution of t-value-weighted centroid of activation coordinates in tool-use (blue) and imagery (red) conditions. Right figure shows expansion of square area in left figure and coordinates.

Red and blue markers indicate the centers for the imagery and execution conditions, respectively. Corresponding markers are connected by a gradation line that is colored red and blue on the imagery and execution sides, respectively. As shown in Figure 3, imagery activation is located more laterally and posterior relative to the execution activation, which is located more medially and anterior.

3.1.2. Coordinate distribution of the upper right part of cerebellar activity

First, we calculated the coordinates of the t-value-weighted centroid of activation. Then, we calculated the distance between these coordinates and the fourth ventricle, located in the middle of the cerebellum, and averaged these distances over all tools separately for each subject. Finally, we used a signed rank test to examine for significant difference in the distances averaged across subjects

between the imagery and the execution conditions.

Figure 4 shows the distance of the imagery condition (left) and the execution condition (right) from the fourth ventricle located in the center of the cerebellum. According to the signed rank test, the distance in the imagery condition was significantly larger than in the execution condition ($p < 0.05$), which is consistent with observations that, on average, imagery activation is located more laterally and posteriorly.

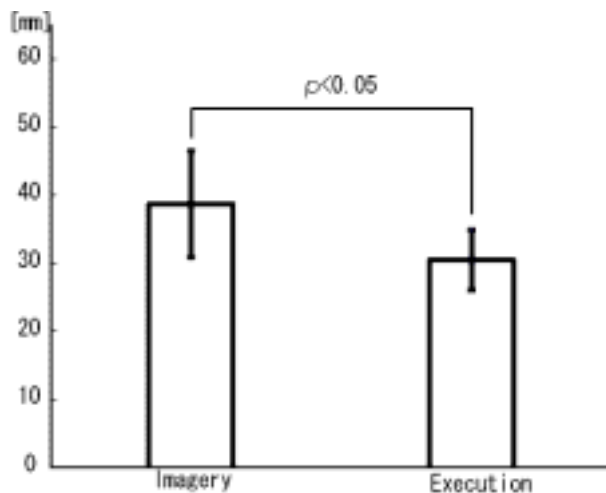


Figure 4 Distance from fourth ventricle to coordinates of t-value-weighted centroid of activation coordinates in tool-use execution and imagery tasks.

Activation for each tool across subjects was investigated in the right upper part of the cerebellum using the same method as in section, “Analysis of activity position in the right upper cerebellum.” In this limited area, the first principal component of all coordinates from both tasks for each tool was calculated. Then all coordinates were projected to the first principal component, and the distances between a given point and projected coordinates were calculated. These distance data were categorized into the execution and the imagery conditions. The coordinates in the execution condition group and in the imagery condition are plotted on the X and Y axes of Figure 5, respectively. If each pair of tool coordinates is located along the primary fissure boundary line, the first principle component for these coordinates will be located near the primary fissure. If execution and imagery condition coordinates are located at a similar location, they will be projected to a closer position and plotted on a 45° sloped line.

Figure 5 shows the plots of the projected coordinates of the t-value-weighted centroid of activation in the tool-use imagery task as a value of the X axis and those in the tool-use execution task as the value of the Y axis. The dotted line in the figure

indicates a 45° slope, and the solid line indicates the principal component vector. The correlation coefficient was 0.5497, which is significantly larger than zero ($p < 0.05$). The coordinates of the t-weighted centroid of activation in the imagery and execution conditions were thus located spatially close to each other.

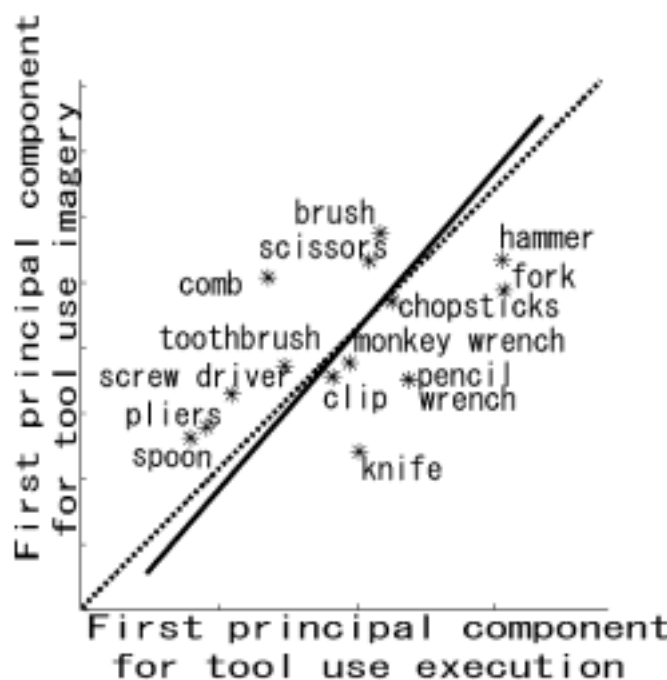


Figure 5 Relationship between t-values-weighted centroid of activation coordinates in tool-use execution and imagery conditions.

3.1.3. Positional relationship of tools in the right upper cerebellum

In this section, we show the analysis results of the distribution of activities by tool in the right upper cerebellum when subjects imagined tool-use. First, we examined brain activity separately for all tools and subjects (fixed effect model $p < 0.001$ uncorrected). The distances of t-value-weighted centroid of activation were calculated from the fourth ventricle to these coordinates. Second, we investigated the order of distance in each subject and compared it to the order obtained from the group-analysis activation map, as shown in Figure 4. In this case, since there was no significant activation evoked by the "SAW" tool, it was excluded from the analysis. Correlation between individual and group order was examined by Spearman rank correlation coefficient. Four of the eight subjects showed marginally significant correlation between the order of the distance

from the fourth ventricle for each tool ($p < 0.10$), suggesting similarity in the spatial distribution of the tools.

4. Discussion

4.1. Comparison with previous tool-use studies

Action or grasping related brain circuits have been studied in macaque monkeys. The connectivity between the parietal cortex and inferior frontal areas has been well-studied (Matelli and Luppino 2000). We also found activity in the parietal cortex especially in the posterior IPS and in the inferior frontal region in the case of tool-use. Activity in the inferior frontal region was found in the left hemisphere only during execution condition and in the right hemisphere only during imagery condition (Figure 2 (c) and (d)). However, with a lower threshold ($p < 0.005$ uncorrected), bilateral activities can be found in both imagery and execution conditions. While (Johnson-Frey, Maloof et al. 2003) have shown the importance of this region for grasping, our experiments showed that this region was more activated during test conditions than the control condition of grasping. Therefore, we believe this region is involved in tool-use functions and not just grasping. Tamada et al. (Tamada, Miyauchi et al. 1999) investigated the learning of a new tool (a rotated computer mouse) and found activity in the inferior frontal region when a rotated computer mouse condition was contrasted with a normal computer mouse condition. In Tamada's and our experiments, both the test and control conditions had a grasping component, so that inferior frontal region activity needs to be interpreted as a cognitive function, such as knowledge of how the tool works. This cognitive function cooperates with tool-use in the absence of motor components; simply imaging the use of a tool is sufficient to activate the inferior frontal region. Moreover, cortical activity in the left inferior frontal region found during the execution condition in the present study was localized laterally in comparison to the activities reported by Tamada et al. (Tamada, Miyauchi et al. 1999), suggesting that spatial localization may be different for novel and common tools.

As shown in Figure 2 (a) and (b), activation near the left intra parietal sulcus (IPS) of the parietal lobule is consistent with fMRI studies that showed left IPS activation in a pantomiming task (Moll, de Oliveira-Souza et al. 2000). Similarly in another study, the left IPS was activated both in left-hand and right-hand tool-use pantomime (Choi, Na et al. 2001). As in a PET study, the dorsal lateral parietal cortex was activated during the pantomiming of object use (Rumiati, Weiss et al. 2004). The present result is consistent

with studies conducted on nonhuman primates (macaque monkeys) using complex tools (Obayashi, Suhara et al. 2002) and intermanual transfer of tool-use (Obayashi, Suhara et al. 2003), which reported significant activities in the left IPS and cerebellum. As shown in Figure 2 (e), we found activity in the cerebellum. The cerebellum has not been studied as much as the cerebral cortex because of such technical problems as the limited transaxial field of view of PET and the impossibility of bringing metallic objects close to the fMRI scanner. In addition, it is difficult to control muscle activity and sensory input. To differentiate activity from muscle and sensory input and activity from tool-use, our imagery condition had no changes of muscle movement during the task. Recent studies have shown that the cerebellum is also important for tool-use (Imamizu, Miyauchi et al. 2000; Obayashi, Suhara et al. 2001; Imamizu, Kuroda et al. 2003), and other experimental data and the clinical studies have shown that the lateral part of the cerebellum has various cognitive functions (Grafman, Litvan et al. 1992; Parsons, Fox et al. 1995).

Activity reported from a PET experiment on using new tools was found in the right IPS area (Inoue, Kawashima et al. 2001), which is inconsistent with other pantomime and novel tool-use experiments as well as this experiment. We believe that the left IPS is an important region for tool-use, and his finding of right IPS activity might be caused by different experimental conditions, such as a non-common tool-use experiment.

In our tasks, the control condition was tool-holding, which might have implicitly activated the same brain regions as tool-use imagery, a possibility we cannot reject. But even if the intended and implicit imagery of the control condition share the same brain functions, as Grezes et al. (Grezes, Tucker et al. 2003) have shown, we found significantly larger activity in tool-use imagery tasks compared with tool-holding tasks. Furthermore, the subjects were asked to simply hold the object and no imagery was required during the tool-holding condition, so tool-holding was a suitable control for tool-use imagery. Therefore, most of the difference between the imagery and control conditions was imagined or not imagined tool-use.

Pantomime is a traditional test for Ideomotor Apraxia. The left posterior parietal lesions, including the intra parietal sulcus, often lead Ideomotor Apraxia (Heilman, Rothi et al. 1986; Heilman, Maher et al. 1997; Goldenberg 2003). However, left parietal stroke patients showed improvements in actual tool performances compared to pantomiming use (Wada, Nakagawa et al. 1999). In apraxia patients, the dissociation of automatic and voluntary tool-use is known as automatic voluntary dissociation. The result that a subject who has damage to the left parietal cortex can still use the actual tool indicates that the left parietal cortex is not always involved in the actual tool-use process. Pantomime and actual tool-use appear to involve different mechanisms. Pantomime

requires a more intentional process while actual tool-use can also be carried out at least partly by an automatic process.

Consciously accessing knowledge about tool-use might be distinct from the automatic skills related to tool-use, as suggested by a hypothesis of the automatic-voluntary dissociation first described as Baillarger-Jackson principle (Alajouanine 1960). He showed a patient who could not make the sign of the cross at the clinic but did so automatically when entering a church. In this case, the patient had an internal model for signing the cross, but could not voluntarily retrieve it in an arbitrary situation and could only automatically retrieve it. Sirigu, Daprati et al. (Sirigu, Daprati et al. 2004) proposed that internal models for voluntary (self-initiated) actions exist in the parietal cortex. Signing the cross at the clinic is an intentional and voluntary action, and thus this function might be located in the parietal cortex. Hanakawa, Immisch et al. (Hanakawa, Immisch et al. 2003) reported the relationship between the accuracy of motor imagery and activity in the left IPS and superior precentral regions. Since such accuracy may relate to how much the subject intentionally concentrates on doing so, it could be strongly related to intensity of intentional efforts. Accordingly, Sirigu's internal model could be closely related to conscious actions, which at least partially necessitates intentional processes. In general, this intentional process might also increase the intentional visual (imagery) process more than the automatic processes. Recent vision research revealed IPS activity when a voluntary saccades task was contrasted with a reflexive (automatic) saccades task using fMRI (Mort, Perry et al. 2003). When contrasting reflexive with voluntary tasks, IPS was not activated. So, we speculate that the parietal cortex could be more related to internal models of intentional processing than to those of automatic processing.

4.2. Distribution of t-value-weighted centroid of activation coordinates

Figure 3 suggests that tool-use execution activation is processed in the superior part of the cerebellum and that tool-use imagery tends to be located in the more inferior and lateral parts. The distance from the fourth ventricle in the imagery condition was larger than the execution condition (Figure 4). Furthermore, we found significant correlation in the distances of the projected point on the principle vector of the t-value weighed centroid coordinates between imagery and execution conditions (Figure 5). These results support the hypothesis that the cerebellum is involved in non-motor functions. Relative to the cerebellum study, the brain activity in both movement and imagery processing were located in the posterolateral part of the cerebellum (Naito,

Kochiyama et al. 2002). This study also suggests that a positional correlation exists between the imagery and execution activation sites. Regarding the distance from the fourth ventricle for each tool, similarity was found in the order of tools among the subjects, as revealed by Spearman rank correlation coefficient. This similarity of distances was prominent in near and far coordinates for half of the subjects. These results suggest that tool-use skills and/or cognitive knowledge of tool-use are acquired in similar distribution, even though there is a large difference between subjects who have different familiarity of tool-use or different skill acquisition.

We used an extended tied mixture model to represent the spatial distribution of the brain activity that showed that cerebellar activity can be explained with six clusters (Furukawa, Ueda et al. 2002). In Grodd, Hulsman et al. (Grodd, Hulsman et al. 2001), most of the clusters showed similar somatotopic topography of hand and wrist muscle control while two other clusters were located in the bilateral region near the posterior superior fissure, which are not included in Grodd's topography map. Therefore, these two clusters were considered to be related to the internal model of tool-use rather than simple muscle control. One cluster related to the internal model in the right cerebellum was located more posterior and more lateral to the cluster for the hand muscle control area. In Figure 5, "chopsticks" and "scissors," which require complex finger controls, were projected in a closer region. At the same time, "screwdriver" and "pliers," which require wrist controls, were projected in a closer region. In the horizontal section shown in Figure 3, "screwdriver" and "pliers" were located more anterior than "chopsticks" and "scissors." These position relationships are compatible with Grodd's topography map that showed that the wrist is located more anterior than the finger control center. So we speculate that internal models are engaged for the related muscle control areas of the hand, the fingers, and the wrist, and they will be shifted near the location of the hand muscle control center in the cerebellum. This could be one reason why activity related to the internal model was similar among subjects: the muscles used should be identical between subjects for each tool.

On the other hand, the organization of internal models in the cerebellum seems also related to familiarity because cerebellar activity was associated with novel tool-use manipulation (rotated computer mouse manipulation) by hand (Imamizu, Miyauchi et al. 2000). This novel tool internal model activates more lateral area than activity associated with common tool-use in the present experiment. Therefore, a newer internal model might be acquired in more lateral parts of the cerebellum and then gradually move to the more medial and anterior area where the action- or movement-related muscle control centres exist.

As mentioned above, some studies exist which examine cerebellum function related to

tool-use, but generally the cerebellum has not been considered an important site for tool-use especially in clinical studies. Clinical studies of tool-use have often examined apraxic patients, where apraxia is defined by tool-use difficulty without paralysis. However, most apraxic patients have damage to the left parietal cortex, while cerebellar-associated apraxia is rare or non-existent. Because the internal models for tool-use are located close to the muscle control center in the cerebellum, it would be highly unlikely to have selective damage to the tool-use internal models in the cerebellum without also damage to the general motor control areas. This would result in more severe motor deficits and no longer considered apraxia. Thus, it is really difficult to find an apraxia patient with cerebellum damage. Another reason for the lack of clinical studies relating the cerebellum to tool-use, is that if the cerebellum has a particular role in automatic tool-use (see discussion section), then patients may still be able to use tools intentionally via the parietal pathway. Therefore, because the behavior at the clinic is mostly intentional action for patients, previous patient studies may have ignored any deficit in automatic tool-use.

4.3. Network related to tool-use in brains

Tamada, Miyauchi et al. (Tamada, Miyauchi et al. 1999) reported functional connectivity between the cerebellum and pars opercularis or pars triangularis in tasks that require the acquisition of internal models. We also found activity in the pars opercularis or pars triangularis and the cerebellum, so these activities may also be functionally connected, as in Tamada's study.

It seems that both parietal and cerebellum networks exist for tool-use. Parietal activity confirms the neuropsychological findings from apraxia, and cerebellum activity confirms other experiments related to tool-use. Perhaps the existence of parallel networks could explain automatic-voluntary dissociation in apraxia (i.e., parietal automatic and cerebellar intentional networks). During tool-use, even when a subject automatically controls the tool, at some point he/she begins to control that tool intentionally, making slight adaptations to the surrounding environment. We don't know if the parietal and cerebellum actually work cooperatively or simply in parallel but at least it seems there are two ways for tool-use. Interestingly, the existence of a brain network connection between the cerebellum and parietal regions was reported in neurophysiological and anatomical studies (Clower, West et al. 2001; Clower, Dum et al. 2004). These input-output relationships could be used in tool-use mechanisms.

Chapter 3

A shared mechanism for language and tool-use: implications for the evolution of language

1. Introduction for evolutionary theory of language

The question of the origin and evolution of language is controversial. A gradual approach of evolution supposes the adaptation of existing primate features. The hypothesis that tool-use and tool-making are precursors for or co-evolved with language has a long history (e.g. (Greenfield 1991)), and has recently been revived by the finding of mirror neurons in monkeys' inferior premotor cortex (Rizzolatti and Arbib 1998). In contrast, it was recently proposed, in agreement with a saltatory approach of evolution that a unique novelty, namely recursive computation, was responsible for the apparition of human language.

Saltational evolution theory claims that a child acquires any natural languages within a few years, without the aid of analytical thinking and without explicit "grammar" instructions. The origin of grammatical rules should thus be ascribed to an innate system in the human brain which is nonexistent in monkey (Chomsky 2000). It was claimed that this evolutionary leap, dedicated to and specific of language, could be the recursive computations supporting syntax (Hauser, Chomsky et al. 2002). Neuroimaging studies indicate that the human Broca's area is uniquely specialized to process these syntactic aspects of sentence comprehension, and it was proposed that it can be regarded as the "grammatical center" (see (Sakai 2005) for a recent review).

Controversially, the role of tool-use and tool-making as a precursor for or as co-evolving with language has been extensively discussed (Greenfield 1991). In this view, the neural substrate for manual action would provide a foundation for the evolution of language before the divergence of hominids and great apes. Several mirror systems have been described in the ventral premotor and frontal portion of it of monkeys, and fMRI (functional Magnetic Resonance Imagin) and PET (Positron Emission Tomography) showed that both tool-use (Obayashi, Suhara et al. 2002) and action observation (Nelissen, Luppino et al. 2005) activate the depth of the arcuate sulcus in the inferior frontal cortex. A putative link was proposed between mirror systems and the apparition of the language ability (Rizzolatti and Arbib 1998). If human language exapted computational resources from primates' tool-related mirror system (Ferrari, Rozzi et al. 2005), then neural resources involved in both language tasks and tool-use should overlap in Broca's area.

2. Methods

Seven females and nine males were studied (age range, 18-35 years). Each subject received an explanation of the experiment in writing and signed an agreement to participate in the experiment. The protocol was approved by the ethics committees of Advanced Telecommunications Research Institute. All volunteers were right-handed according to the Edinburgh Inventory (Oldfield 1971).

The fMRI experiment comprised 5 conditions. During tool-use EXECUTION volunteers were asked to use one of three common tools (to cut a sheet of paper using scissors, to connect lines on the peace of paper using pencil and to move beads using chopstick) with their right hand placed on an elbow chair to prevent head movement. Two mirrors were combined to provide subjects with a visual feed-back of their hand and tool without reversal of the image. During tool-use IMAGERY, subjects were asked to imagine using a tool the same way it is used in the tool-use execution condition. They hold the tool and looked at the target (e.g., paper) as in the execution condition. During HOLD, volunteers were asked to hold the tool and look at the target object without imagining tool-use. To investigate language, subjects listened to a fairy story narrated by professional story teller (STORY). A control condition consisted in playing the same story backward (REVERSE). Transitions and type of conditions were indicated by different pitch of sound stimuli.

One tool was used per session, and one session was acquired for each tool, so that

subjects underwent three sessions, with the order of tool randomized between subjects. Conditions were repeated three times within session (except HOLD, six times). Each condition lasted forty seconds (except HOLD, twenty seconds) and the order was randomized within each repetition (except HOLD, second and fifth position in each repetition).

2.1. MRI data acquisition

The 1.5T MRI scanner (Shimadzu-Marconi Magnex ECLIPSE 1.5T) of the Advanced Telecommunications Research Institute brain imaging center was used to obtain blood oxygen level dependent (BOLD) contrast functional images. Images weighted with the apparent transverse relaxation time (T^*_2) were obtained with an echo-planar imaging sequence (repetition time = 5 s, echo time = 50 ms, flip angle = 90°). Voxel size was 3 x 3 x 3 mm (64 x 64 x 64 pixels), which gave a total field of view 192 x 192 mm². A total of 369 image volumes were acquired in this experiment over 30 min. In a separate session, high-resolution whole-brain images were acquired from each subjects to improve the localization of activation foci using a T1-weighted three dimensional (3D) segmented radio frequency-spoiled Fourier acquired steady state technique covering the whole brain.

2.2. Data processing and statistics

We used SPM2 software (SPM2 2003) for image processing and analysis. The first three volumes of each session were discarded to allow for T1 equilibration, while the remaining 120 image volumes were realigned to the first volume and unwarped. The estimated movement did not exceed 3 mm. A mean image was created using realigned volumes. T2 and T1 structural images were aligned to the mean EPI image and then spatially normalized to the Montreal Neurological Institute (MNI; Montreal, Canada) reference brain. The normalized images of 2 X 2 X 2 mm³ were spatially smoothed by a Gaussian kernel of full width half maximum 6 mm only for the group analysis. A cytoarchitectonic investigation of Brodmann areas 44 and 45 led to the development of probabilistic maps (Amunts, Schleicher et al. 1999). Firstly, we analysed the activated area related with tool-use and language task using whole brain those activated peaks of the Z score identified in Table 3 and confirmed both tasks activates Broca's area. To focus on Broca's area activity, we restricted all EPI images to the brain region defined in this probabilistic map in the left hemisphere. We didn't apply smoothing to EPI images

in order to identify task-related activity voxel-wise for individual subject analysis.

Parameter estimates for the EXECUTION, IMAGERY, HOLD, STORY and REVERSE trials were determined by fixed effect analysis for each subject using a box-car function convolved with a hemodynamic response function and high-pass filtering (cut-off frequency = 400 ms) was applied. We tested for significant effects by using voxelwise t statistics assembled into a statistical parametric map.

Three contrasts of interest were computed (EXECUTION-HOLD, IMAGERY-HOLD and STORY-REVERSE). The resulting contrast images for each subject were used for a random effect analysis of variance (see **Table 4**) to identify voxels activated in language (STORY-REVERSE), tool-use (conjunction between EXECUTION-HOLD and IMAGERY-HOLD), and both language and tool-use (conjunction between EXECUTION-HOLD, IMAGERY-HOLD and STORY-REVERSE). Conjunction was computed as the minimum statistical value of the two contrasts images (Nichols, Brett et al. 2005) and that with a null hypothesis of three contrasts images do not have an effect in each voxel (Nichols, Brett et al. 2005). We located the activity according to the probabilistic map of BA44, BA45 and BA6 (Geyer, Ledberg et al. 1996; Amunts, Schleicher et al. 1999) using the Anatomy toolbox (Eickhoff, Stephan et al. 2005). Figures indicate the parameter estimates for the three contrasts of interest in the peaks of Z-scores indicated in **Table 4**, with activated voxels rendered on the average over subjects of normalized T1 structural image (Figure 7) or on the normalized T1 structural image of a typical subject (Figure 8).

2.3. Results for shared activity between language and tool-use tasks

The main effect of STORY-REVERSE reveals voxels in Broca's area, both BA 44 and BA 45, which activity is related to language processing in both group analysis (random effect analysis; results in Figure 7) and single subjects analysis. BA 45 activity (-52, 24, 18) was not associated with the use of tools in subsequent analyses, implying that this area's contribution to language (Hashimoto and Sakai 2002) is specific.

The conjunction analysis between EXECUTION-HOLD and IMAGERY-HOLD used to investigate tool-use revealed regions involved in both the execution and the imagery of tool-use, but not regions whose activity is related to holding the tool, and is suited to investigate high level skills about tool-use without the motor components. Two clusters of significant activity were found in BA44. Finally, a conjunction between LANGUAGE-REVERSE, EXECUTION-HOLD and IMAGERY-HOLD revealed overlapping activity in the dorsal part of BA 44 with 60% probability to this area by

Amunts's cytoarchitectonic map. In contrast, no activity related to language was found in the tool-use cluster found in the ventral part of BA 44.

Table 3 Brain regions showing increased activity in the contrasts of interests investigating tool-use (top) and language processing (bottom). SPM were height thresholded at Z-value > 4 (all activities are $p < 0.05$ corrected for False Discovery Rate), extent threshold > 10 voxels, and sub-clusters separated by at least 25 mm.

Region	BA*	Coordinates (MNI)	Z-value
<i>Imagery AND execution of tool-use VERSUS tool holding</i>			
Left	Inferior Frontal Gyrus44	-52 4 36	5.38
Left	Middle Frontal Gyrus 6	-24 2 54	4.66
Right	Middle Frontal Gyrus 6	28 -6 50	4.25
Left	Pre-SMA 6	-6 4 56	4.67
Left	Superior Parietal Lobule 7	-28 -54 64	4.19
Left	Postcentral Gyrus 2	-46 -28 42	4.47
<i>Story listening VERSUS reversed story listening</i>			
Left	Inferior Frontal Gyrus44	-46 14 24	4.25
Left	Inferior Frontal Gyrus45	-56 24 10	4.28
Left	Inferior Frontal Gyrus47	-44 26 -8	4.38
Left	Middle Frontal Gyrus 6	-42 2 46	4.31
Left	Superior Temporal Gyrus 22	-56 -52 12	4.48
Left	Middle Temporal Gyrus 21	-54 -24 -12	5.14
Left	Middle Temporal Gyrus 21	-54 8 -20	5.35
Right	Middle Temporal Gyrus 21	54 -24 -10	4.48
Right	Middle Temporal Gyrus 21	58 4 -20	5.11
Right	Superior Temporal Pole 38	48 18 -22	4.68
Right	Fusiform Gyrus 19	22 -80 -24	4.25
Right	Cerebellar Crus 1	18 -88 -34	4.47

BA: Brodmann area, when applicable.

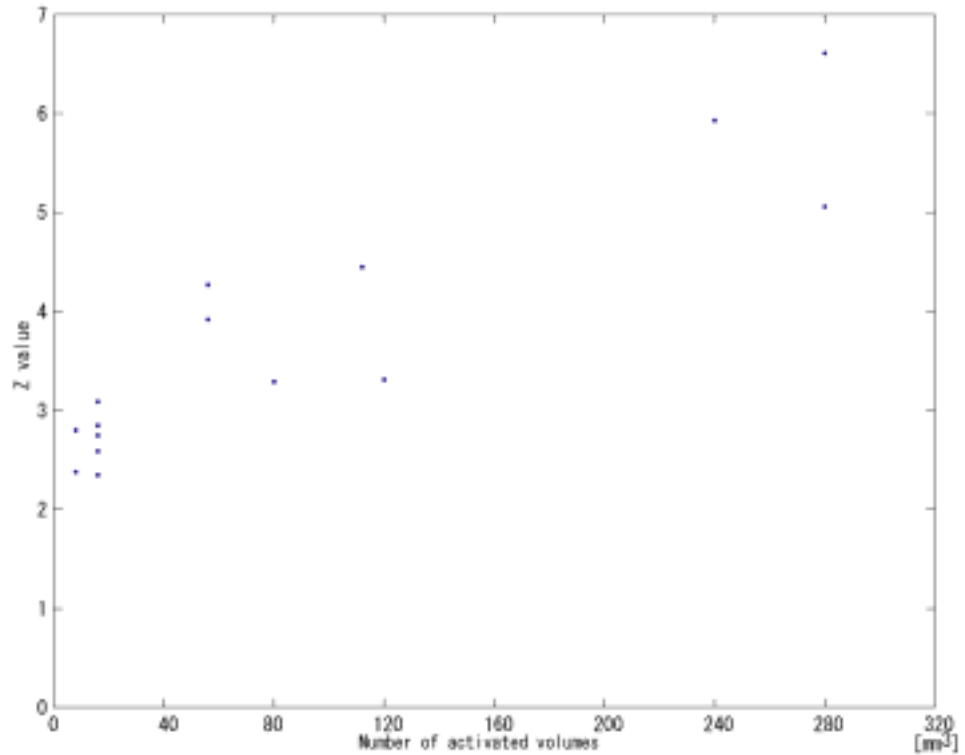


Figure 6 Number of activated volumes and Z-value for each subject by conjunction analysis between IMAGEY-HOLD, EXECUTION-HOLD and STORY-REVERSE. Each plot indicate the number of activated volumes and Z value of the peak cluster in the Broca's area threshold at $p < 0.01$ uncorrected

Table 4 Results of random effect analysis. Language: STORY-REVERSED; Tool-use: conjunction between EXECUTION and IMAGERY; Language and Tool-use: conjunction between STORY-REVERSED, EXECUTION and IMAGERY. ($p < 0.001$)

Cluster	Z-m	Coordinates(MNI)			Brodman
		x	y	z	n's
Ext	ax				Area
<u>Tool-use</u>					
32	3.43	-5 0	2	2 0	44

	1	3.09	-5	6	3	44
	2	3.13	0	1	4	44
			8	0	4	
<u>Language</u>						
<u>ge</u>						
	9	3.33	-4	1	2	44
			0	4	8	
	521	4.53	-5	2	1	44/45
			2	4	8	
<u>Language and Tool-use</u>						
	44	4.69	-5	8	3	44
			0	6		

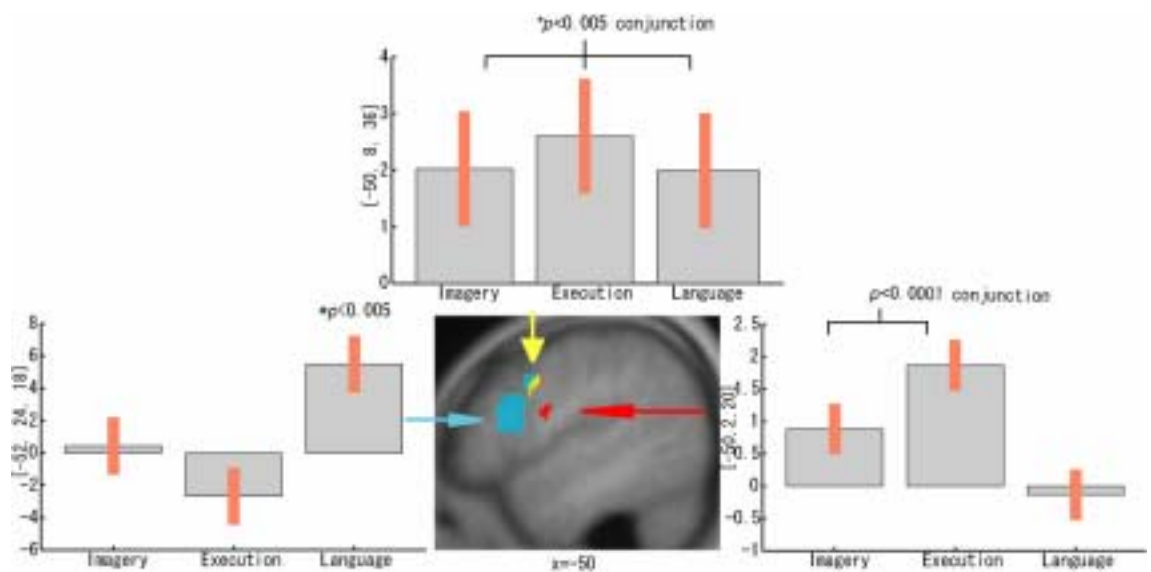


Figure 7 Results of random effect analysis superimposed on sagittal sections of the average of subjects' normalised T1 image (Cyan: STORY-REVERSE ; Red: conjunction of EXECUTION and IMAGEYR; Yellow: conjunction of STORY-REVERSE, EXECUTION and IMAGERY). Histograms show contrasts estimates at the local maximum in each cluster. *contrast significant with family wise error correction $p < 0.05$.

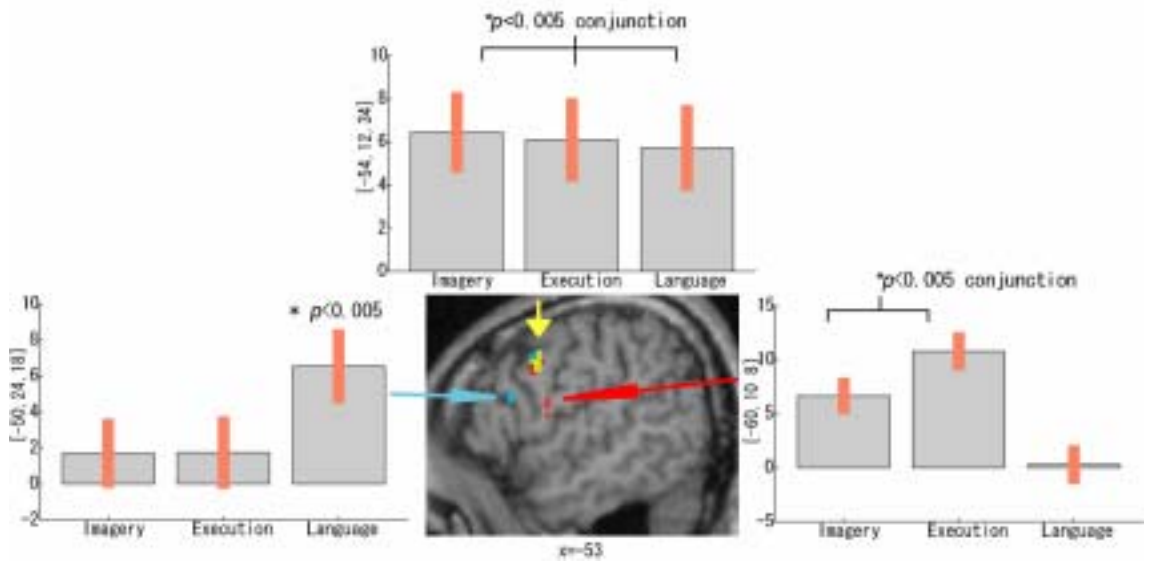


Figure 8 Activity by typical subject superimposed on sagittal sections of the normalised T1 image. Details as in Figure 7.

To measure the position relationship between tool related and language activities, all activated voxels were projected to the Y axis to define the distribution of activity along the Y axis. The activated volume sizes along with Y axis were applied for all subjects individually. The activated peak coordinates were very much different for tool-use and language task.

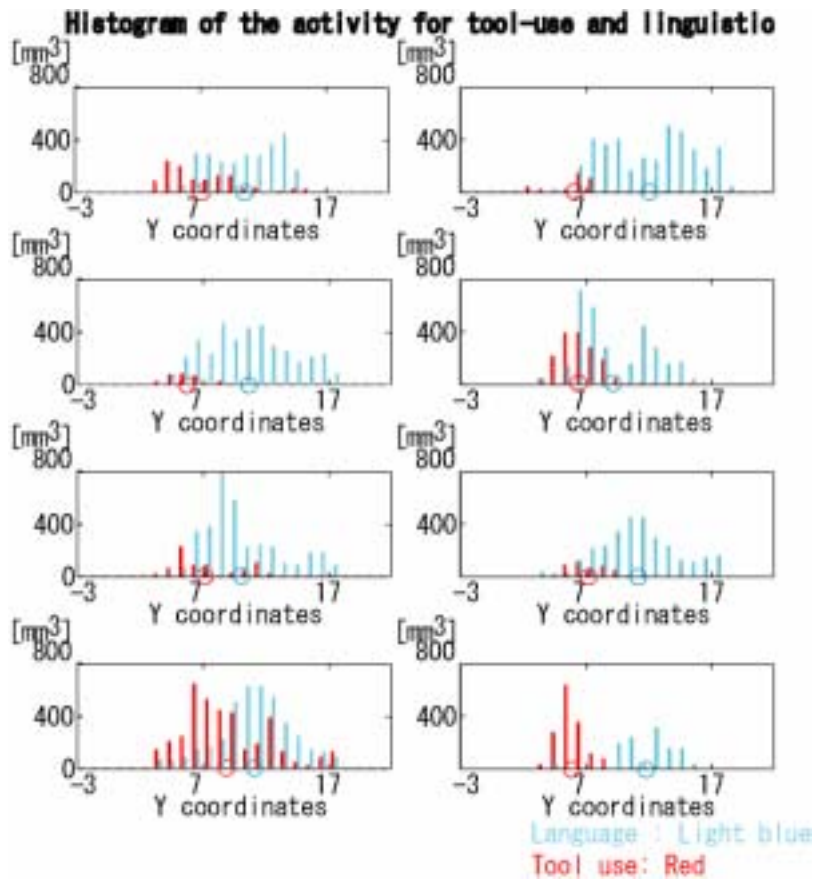


Figure 9 Histogram of the activated volume along to Y axis. The centre of gravity coordinates point were shown with circle mark.

The center of gravity from tool use data (tool use point) and language data (language point) were calculated by using histogram of activated volume for each Y coordinates. The difference between the tool use point and language point were compared with each other by Wilcoxon rank sum test. The language center of gravity points were significantly anterior than the tool-use center of gravity point.

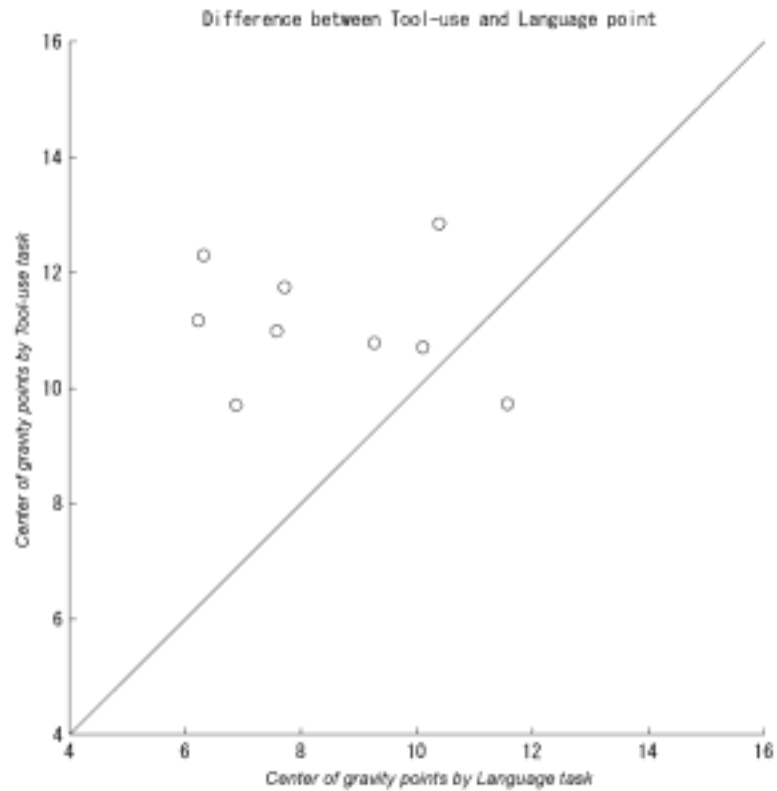


Figure 10 *Relationship between Tool-use and Language distribution*

To clearly show that the language center of gravity points locate anterior than the tool-use center of gravity points, we plotted those points to each axis by subjects who showed the significant activity in both tasks (**Figure 10**). The line in the figure showed 45 degree, if those pair of center of gravity points located above this line, this means the language point was located anterior than tool-use.

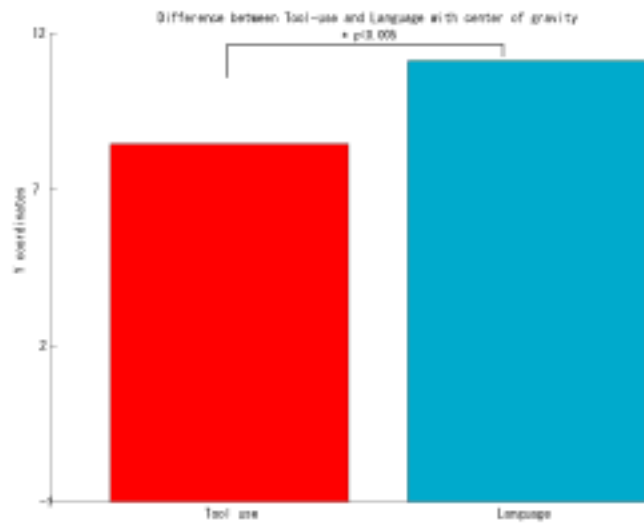


Figure 11 *The center of gravity mean points difference between tool-use and language for all subjects who showed activity in both tasks. Tool-use median points colored with red (left) and language points colored with cyan (right) Those coordinates showed significant difference at $p < 0.005$*

3. Discussion

As expected from existing literature, contrasts investigating the brain correlates of language perception and tool-use yielded clusters of increased activity in Broca's area. Historically this region was defined as the center for the production of language (Broca 1861). This role has been confirmed by subsequent neuropsychology and more recently, the advent of neuroimaging techniques (Sakai 2005). Though the exact location of Broca's area cannot be resolved, it is agreed that it includes the dysgranular Brodmann area (BA) 44 and granular BA 45, as well as, for some authors, the ventral part of the agranular BA 6 and the lateral orbital BA 47. Considering the consensus on the core location of language skills, the availability of probabilistic maps based on cytoarchitectonics (Amunts, Schleicher et al. 1999) and our interest in higher-order aspects of the task, we restricted our analysis to BA 44 and 45 and excluded premotor BA 6.

Though the neurophysiology of monkey's rudiments of language skills (e.g. grammar skills of cotton-tap tamarin (Fitch, Hauser et al. 2005)) have not been investigated yet, much is known about the observation/execution matching system. "Mirror neurons", activated when monkeys perform goal-directed actions or observe the

same action performed by another agent facing them, provide the observer with an internal representation of that action. It was proposed that these representations could be used to “understand” other people’s actions, and that language could derive from this system (Rizzolatti and Arbib 1998). Originally described in region F5 of premotor BA 6, a recent monkey fMRI experiment demonstrated that more rostral BA 44 and 45 have context-independent responses to the observation of action (Nelissen, Luppino et al. 2005). The abstract level of action representation encoded in BA44 and 45. “mirror systems” is pertinent to understand the role of these regions in language but also in tool-use skills investigated in the present experiment.

In the wild, apes have demonstrated rudiments of tool-use (Breuer, Ndoundou-Hockemba et al. 2005) can be developed with training (Iriki, Tanaka et al. 1996), which has been shown to modify neural networks in the anterior parietal cortex (Ishibashi, Hihara et al. 2002). Activity in macaques’ inferior prefrontal cortex has also been related to tool-use, using both electrophysiology (Ferrari, Rozzi et al. 2005) and PET (Obayashi, Suhara et al. 2001). Authors proposed that their findings pertain to premotor area F5, but recent findings (Petrides, Cadoret et al. 2005) suggest that the location of activated clusters ((Obayashi, Suhara et al. 2001), fig. 2 and 3) and of a subset of recorded neurons ((Ferrari, Rozzi et al. 2005), fig. 7) in the depth of the arcuate sulcus could actually be in the brain regions homologous to human BA 44 and 45. In humans, pantomime of everyday objects use activates a similar network of inferior parietal and prefrontal cortex with activity in the cerebellum and the putamen (Rumiati, Weiss et al. 2004). A recent fMRI study of 16 common tools use (Higuchi et al., in press) reported activity in the ventral BA44 for execution but not imagery of tool-use, similar to the cluster only found in tool-use in the present experiment. Reciprocal connections between the parietal and prefrontal cortices (Rizzolatti and Arbib 1998) could form, together with cerebellar and subcortical centers, the essential network for tool-use (Maravita and Iriki 2004).

Both the tool-use and language require the processing of hierarchical structures. Tool-use involves knowledge about the target on which the tool is used, the specific motor controllers to hold and manipulate the tool correctly, and on-line control of tool-target interactions. Great apes imitative behaviors demonstrate rudimentary hierarchically organized planning system for action planning (Byrne and Russon 1998). Similarly language consists in the combination of a finite number of symbols according to existing rules, usually collectively referred to as a grammar, in order to form an infinite number of meaningful sentences. Producing an action (language or tool-use) or making sense of a perceived action (another person’s verbalization or action) requires

that both the meanings of any single objects (semantics) and of the rules to structure objects together (grammar) are shared between individuals. The fact that both language and tool-use rely on hierarchically organized sequential behavior led some researchers (i.e., (Greenfield 1991)) to speculate on a common origin to both functions.

The overlap of brain activity in the dorsal aspect of BA44 suggests that similar neural processes are being used for both language perception and skills related to the use of tools. Note that the use of a conjunction between contrasts describing actual use of tool and tool-use imagery precludes any conclusion based solely on the motor aspects of the task, and was designed to investigate higher-order skills related to the use of tools. In humans, arguments in favor of a role of this region in grammatical or syntactic aspects of language have recently accumulated (Hagoort 2005; Sakai 2005). The overlap with tool-use skills revealed here suggests that this aspect is not specific to language but generalizes to at least one other cognitive function, tool-use, that includes a hierarchical and sequential organization of behavior similar to grammar in language. Thus, in contrast to the claim that recursion, the main aspect of grammar, is specific to humans and to language (Hauser, Chomsky et al. 2002), the present overlap suggests that the same mechanisms related to the organization of behavior were developed from both language and tool-use-related skills. In addition, monkeys have rudiments of sequential organization of behaviors exemplified by their use of tools, which neural correlates include the depth of the arcuate sulcus, putatively homologous to humans' Broca's area, suggesting that the recursive computation performed in this brain region is present, in a more rudimentary form, in monkeys and is therefore not specific to humans.

Interestingly, (Hamzei, Rijntjes et al. 2003) reported a cluster of overlap between language production and action observation in Broca's area. However the main activity was not found in dorsal part of BA44, speculatively because the verb generation task didn't require rules in recursive computation and the activity in this area was just by automatic verb-tool association. In addition, (Grabowski, Damasio et al. 1998) reported a peak different activities in Broca's area by tool, animal and person naming tasks and also a common activity to those tasks with strongest activity by tool task in the junction for the inferior frontal sulcus and the precentral sulcus (x,y,z=-53 10 32 in MNI). Thus, tool activates automatically connection to the dorsal part of BA44 and not so much for other categories which don't have sequenced organization.

Previous investigation reported an overlap between the execution and perception of monosyllables in the more caudal premotor Brodmann area 6, suggesting low-level mirror processes are involved in phonological perception. The present findings extend

this original finding showing that in the higher order ventral prefrontal regions BA 44, mirroring takes place at a higher level of cognitive processing, putatively the sequential organization of behavior, and in effector-independent manner. The involvement of such a mirror system to produce and understand different sequentially and hierarchically organized behaviors offers a unified framework to explain the different functions attributed to Broca's area, that has been described as a "multi-purpose action-perception matching interface" (Schubotz and von Cramon 2004). Furthermore, Wolpert et al. (Wolpert, Doya et al. 2003) described that syntactically organized language and sequentially ruled action (current case in tool-use) can be treated in the similar computational architecture because of similarity of those hierarchical structure. Thus, it is more plausible that same neural systems are used both in language and tool-use since those structures can compute in the similar way.

4. Conclusion

The finding of an overlap between brain activity in contrasts designed to investigate tool-use and language is meaningful in the light of current theories about the evolution of the language. It suggests that, in contrast to a recent proposal that recursive computation is specific to both human and language, brain mechanisms for grammar in BA44 are also involved in tool-use and present, in a rudimentary form, in monkeys. We proposed that these mechanisms correspond to a higher order mirror system for sequentially and hierarchically organized behaviors. Altogether, inferior frontal cortex mirror systems of increased abstraction (BA6, BA44 and BA45) could represent increased complexity in both language (phonology, syntax and semantics) and action (goal-directed, tool-use and social interaction).

Chapter 4

Gender difference in Broca's area

1. Background

Several gender differences in human and animals are known from a variety of research works. These differences have been reported as males being better in motor or spatial skills rather than in language skills. For example, male rats perform significantly better than female rats do on a radial arm and the Morris water maze (Roof 1993). This gender difference can be eliminated by castrating males or by treating females with testosterone neonatally (De Vries, Rissman et al. 2002). These findings suggest that the differences are caused by a hormonal effect such as testosterone level. In humans, the tendency was shown to be the same as that found in other animals' studies, since male subjects commit fewer errors and require less time to complete a "virtual" maze than do female subjects (Moffat, Hampson et al. 1998). Gender differences other than motor and spatial skills have also been reported; for example, young male vervet monkeys preferred to play with toy trucks, whereas young female vervets preferred dolls (Alexander and Hines 2002). This finding suggests that gender differences in toy preferences in human children are not caused by education or culture but come from innate biological preferences. Other differences in gender-related preferences in social interests have been suggested by studies of human infants. When one-day-old babies are presented with either a live face or a mechanical mobile, girls spend more time looking at the face, whereas boys prefer the mechanical object (Connellan, Baron-Cohen et al. 2001). One of the major gender differences is in verbal ability. These differences have been reported in

children as young as five years. When given the California Verbal Learning Test, girls were reported to use more semantic clustering than boys (Kramer, Delis et al. 1997). They recalled and recognized more items than did boys and more often related words together as a recall aid. This language-related gender effect remains throughout childhood and adolescence. Additionally, Maccoby and Jacklyn (Maccoby and Jacklyn 1966) reported that girls outperform boys during preschool and early school years in articulation, use of longer sentences, verbal fluency, and tests of grammar and spelling. In summary, previous behavioral studies have shown the relevancy of testosterone's role in motor and special skills, toy preferences between mechanical objects and dolls, and language-skills differences based on gender.

Not only behavioural differences but also anatomical gender differences have been reported. Gender difference has been reported for the left inferior frontal gyrus, including Broca's area, in normal children (Blanton, Levitt et al. 2004), as has been shown in vervet monkeys (Alexander and Hines 2002). Autistic patients who have difficulty in communicating with other people have shown anatomical developmental delay in the inferior frontal cortex compared to healthy subjects (Just, Cherkassky et al. 2004). The relation between autism and testosterone level indicates that the severity of autistic disorders correlates with the amount of testosterone present in the amniotic fluid. A series of examinations of autistic children has shown that plasma testosterone levels were significantly elevated in comparison with those of neurotypical control children (Geier, Tenikoff et al. 2005). Accordingly, the relationship between anatomical structure and testosterone level differences in Broca's area is assumed to correlate with behavioural differences or preferences.

Therefore, we hypothesized that tool-use tasks, in which boys show a higher preference, and language tasks, in which girls show better performance in early ages, will also reveal brain activity differences in adult subjects related to Broca's area.

2. Methods

Fourteen females and fourteen males were studied (age range, 18-35 years). Each subject received an explanation of the experiment in writing and signed an agreement to participate in the experiment. The protocol was approved by the Ethics Committees of the Advanced Telecommunications Research Institute. All

volunteers were right-handed according to the Edinburgh Inventory (Oldfield 1971).

The fMRI experiment studied five conditions, as did a previous experiment. During tool-use EXECUTION volunteers were asked to use one of three common tools (to cut a sheet of paper using scissors, to connect lines on a piece of paper using a pencil, and to move beads using chopsticks) with their right hand placed on an arm chair to prevent head movement. Two mirrors were combined to provide subjects with visual feedback of their hand and the tool without reversal of the image. During tool-use IMAGERY, subjects were asked to imagine using a tool the same way it is used in the tool-use execution condition. They were instructed to hold the tool and look at the target (e.g. paper) as in the execution condition. During HOLD, volunteers were asked to hold the tool and look at the target object without imagining tool-use. To investigate language, subjects listened to a fairy tale narrated by a professional storyteller (STORY). A control condition consisted of playing the same story backward (REVERSE). Transitions and types of conditions were indicated by sound stimuli.

One tool was used in each session and one session was performed for each tool, so subjects underwent three sessions, with the order of tool were randomised between subjects. Conditions were repeated three times within a session (except HOLD, repeated six times). Each condition lasted forty seconds (except HOLD, twenty seconds) and the order was randomised within each repetition (except HOLD, second and fifth position in each repetition).

2.1. MRI Data acquisition

The 1.5T MRI scanner (Shimadzu-Marconi Magnex ECLIPSE 1.5T) of the Advanced Telecommunications Research Institute's Brain Imaging Center was used to obtain blood oxygen level dependent (BOLD) contrastive functional images. Images weighted with the apparent transverse relaxation time (T^*_2) were obtained with an echo-planar imaging sequence (repetition time = 5 s, echo time = 50 ms, flip angle = 90°). Voxel size was 3 x 3 x 3 mm (64 x 64 x 64 pixels), which gave a total field of view of 192 x 192 mm². A total of 369 image volumes were acquired in this experiment over 30 min. In a separate session, high-resolution whole-brain images were acquired from each subject to improve the localization of activation foci using a T1-weighted three-dimensional (3D)

segmented radio-frequency-spoiled Fourier-acquired steady-state technique covering the whole brain.

2.2. Data processing and statistics

We used SPM2 software (SPM2 2003) for image processing and analysis. The first three volumes of each session were discarded to allow for T1 equilibration, while the remaining 120 image volumes were realigned to the first volume and unwarped. The estimated movement did not exceed 3 mm. A mean image was created using realigned volumes. T2 and T1 structural images were aligned to the mean EPI image and then spatially normalized to the Montreal Neurological Institute (MNI; Montreal, Canada) reference brain. The normalized images of $2 \times 2 \times 2 \text{ mm}^3$ were spatially smoothed by a Gaussian kernel of full-width half-maximum 6 mm only for the group analysis. A cytoarchitectonic investigation of Brodmann areas 44 and 45 led to the development of probabilistic maps (Amunts, Schleicher et al. 1999). To focus on Broca's area activity, we restricted all EPI images to the brain region defined in this probabilistic map in the left hemisphere. We did not apply smoothing to EPI images in order to identify task-related activity voxelwise for individual subject analysis.

Parameter estimates for the EXECUTION, IMAGERY, HOLD, STORY and REVERSE trials were determined by fixed effect analysis for each subject using a box-car function convolved with a hemodynamic response function, and high-pass filtering (cut-off frequency = 400 ms) was applied. We tested for significant effects by using voxelwise t statistics assembled into a statistical parametric map.

A conjunction was computed as the minimum statistical value of the two contrasts or three images in each voxel (Nichols, Brett et al. 2005). We located the activity according to the probabilistic map of the BA44, BA45, BA6 (Amunts, Schleicher et al. 1999) (Geyer, Ledberg et al. 1996) using the Anatomy Toolbox (Eickhoff, Stephan et al. 2005).

The testosterone level of each subject was measured by his or her saliva. Saliva measurement was conducted once a week (four times), following the procedure of the Fukui Lab at Nara Educational University (Fukui 2001).

3. Results

3.1. Activated region in Broca's area

A conjunction between STORY-REVERSE, EXECUTION-HOLD and IMAGERY-HOLD revealed overlapping activity in the dorsal part of BA 44, as was reported in a previous study. This time male subject and female subject data were modeled independently in the random effect analysis with EPI images restricted to Broca's area.

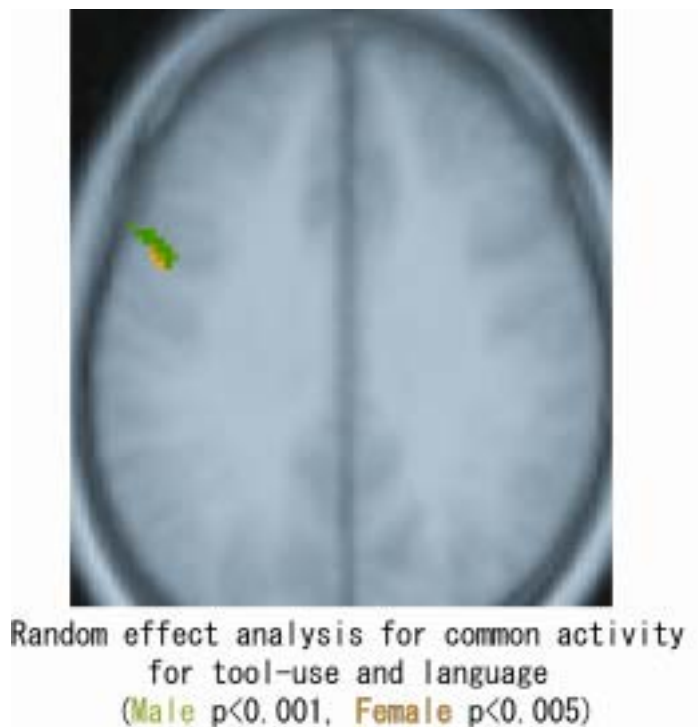


Figure 12 Results of random effect analysis of 14 female subjects (coloured yellow $p < 0.001$ uncorrected) and 14 male subjects (coloured green $p < 0.05$ with false discovery rate of multiple comparison) were superimposed on a standard brain. Conjunction among EXECUTION-HOLD, IMAGERY-HOLD and STORY-REVERSED was applied for this contrast image.

The result showed that conjunct activity for three contrasts by male subjects were located anterior to that by female subjects (**Error! Reference source not found.**). We also measured the distribution difference along the Y axis, so we projected activity to the Y axis and tested the positional difference at the

centre-of-gravity points by individual subject. The middle points were calculated by taking the mean value of the language points and tool-use points ((tool-use points + language points) /2). These middle points are considered equivalent to the dividing point of tool-use and language tasks. We found significant difference between the median middle points of male and female subjects at $p < 0.05$ with the Wilcoxon rank sum test.

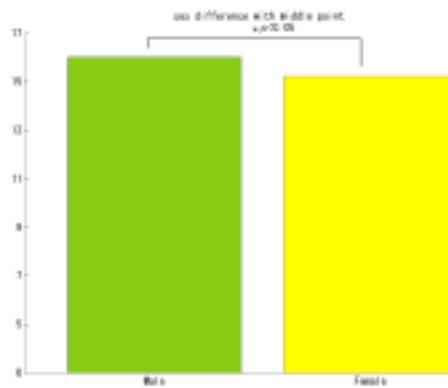


Figure 13 *Middle point difference between males (colored green) and females (colored yellow).*

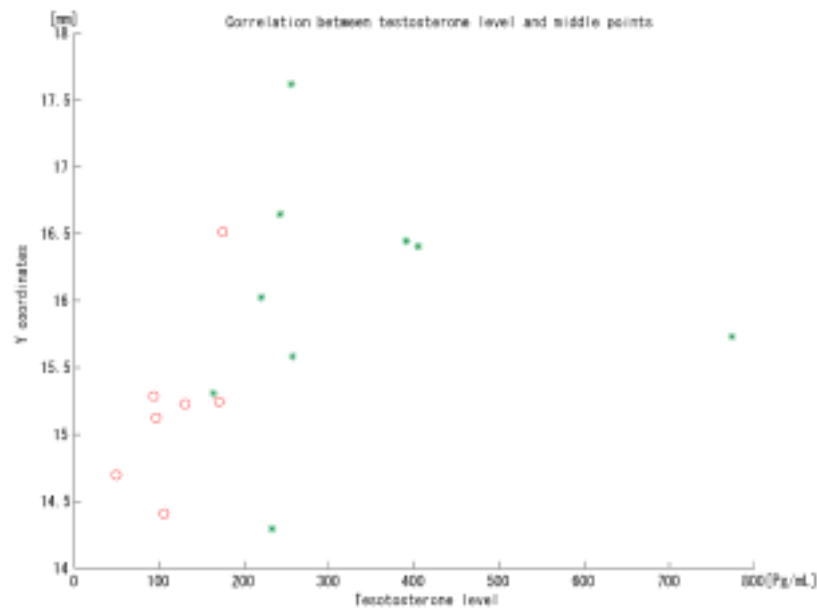


Figure 14 Correlation between testosterone level and middle points of the Y coordinates of tool-use and language points. (*: male, o: female)

Activated volume size was larger for language use in male (ns¹) and female (p<0.02 with two-sample T test) subjects (**Error! Reference source not found.**). Volume size of the defined regions of interest for Broca's area and Wernicke's area are different, so we normalized the activities by tasks (Language / (Language + tool-use) and Tool-use / (Language + tool-use)). Normalized tool-use activity in male subjects was larger than in female subjects, while normalized language activity in female subjects was larger than in male subjects (**Error! Reference source not found.**, ns).

We tested the correlation between the middle points and testosterone level within the subject with the hypothesis that the cognitive bias is correlated with testosterone level. The middle point and the mean testosterone level for each

subject were correlated by a rank correlation coefficient ($N= 16$, $r=0.63$, $z=2.42$, $p<0.02$) (**Error! Reference source not found.**).

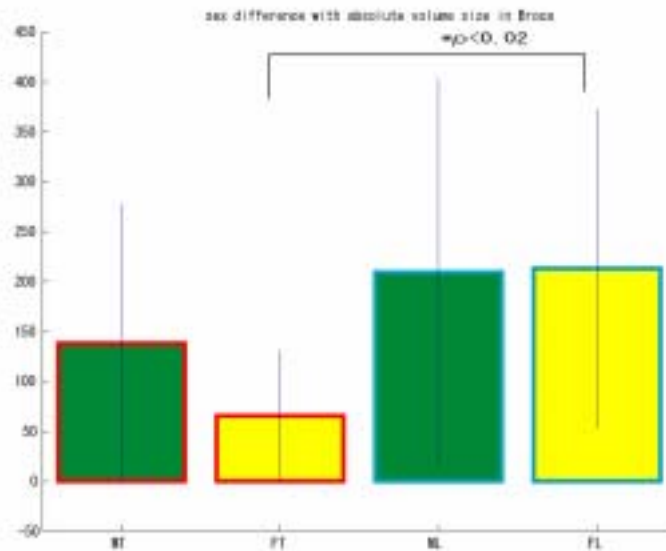


Figure 15 Activated volume size difference between language and tool-use task. (MT: male tool-use, FT: female tool-use, ML: male language, FL: female language; colored red: tool-use, colored cyan: language, colored green: male, colored yellow: female)

re 16 Activated percentage tendency difference between male and female subjects. (Colour and mark details as in **Error! Reference source not found.**)

4. Discussion

In the previous chapter, we showed the common activity between tool-use and language processing in Broca's area. In this chapter, the separating boundary position between the tool-use activity cluster and the language activity cluster was calculated. Moreover, gender differences with those points were tested. The separating points for tool-use and language in Broca's area were significantly ($p<0.05$) different between male and female subjects.

Gender differences in Broca's area could explain some aspects of gender-related cognitive skills. Female subjects showed larger activity for language processing than tool-use processing, which suggests that a part of the

tool-use region may be used by the language region in the limited Broca's area. Therefore, the boundary may have shifted to the posterior side. On the other hand, male subjects showed a larger activated region for tool-use processing than for language processing, suggesting that a part of the language region may be used by the tool-use region, therefore pushing the boundary to the anterior side.

Further study on Broca's area has been conducted by Nelissen et al. (Nelissen, Luppino et al. 2005). Their activation study with different combinations of object, hand and action suggested a transition, in the monkey frontal lobe, from context-dependent descriptions in F5c (BA6) to more abstract descriptions in F5a (BA44) and 45B (BA45). This suggests that inferior frontal cortex mirror systems of increased abstraction (BA6, BA44 and BA45) could represent increased complexity in both language and action. Along the lines of this idea, tool-use involves more context-dependent description because the relationship between tool and object usually does not differ so much in similar situations. Conversely, language could be said to involve more abstract description, due to the character of language itself as symbolising the abstracted situations in nature. Female subjects revealed more activity in the anterior side specifically, so they may process the task in a more abstractive way than male subjects do in language. In contrast, male subjects revealed more activity in the posterior side, so they may process the task in a more context-dependent way than female subjects do in tool-use. This hypothesis is consistent with the cognitive preference known in behavioral study, e.g. boys prefer play with mechanical toys, which has more importance in a context such as turning on a switch to make a model train move. Moreover, girls prefer more abstractive playing styles such as role play using dolls to guess the doll's mind.

Several works in the literature have shown the relationship of hormones with the brain and/or behaviour, and one of the most intriguing findings in adults is that cognitive patterns may remain sensitive to hormonal fluctuations throughout life. As a relation between behaviour and hormonal level, Hampson et al. showed that women's performances at certain tasks changed throughout the menstrual cycle as levels of estrogen varied (Hampson 1995). In addition, high levels of the hormone were associated not only with relatively depressed spatial ability but also with enhanced speech and manual skill tasks (*review in* (Kimura 2002)).

We defined ascending sulcus activity on the normalized brain for each

subject, where there could be a dividing point of BA44 and BA45. However, location of the ascending sulcus did not show a significant correlation with testosterone level or dividing point defined by functional activity. Therefore, testosterone level affects the activation of the functional dividing position rather than anatomical gender differences. However, higher testosterone concentrations were associated with larger hemispheric, frontal, and parietal regional brain volumes and with smaller left occipital brain volume. The mechanism for those anatomical changes is assumed to be as follows: Testosterone affects the anatomy in the frontal cortex, since the hypothalamus projects the nerves to the frontal cortex. Testosterone is the main hormone that can go directly to the brain through the blood/brain barrier. Therefore, it's highly possible that testosterone affects the higher cognitive skills. In addition, the correlation with brain maturation and hormonal level was shown in the left and right Broca's area and the left superior temporal sulcus (STS) (Blanton, Levitt et al. 2001; Blanton, Levitt et al. 2004). Therefore, the existence of testosterone's affect on Broca's area is plausible and its correlation to tasks that involve the gender effect is probable.

Correlations can thus be proposed between the hormonal level, which is directly correlated to gender difference, and behaviour pattern differences that demonstrate several gender differences. Recent literature has shown that the hormone level affects the anatomical difference between the Broca's and STS (posterior STS overlap with Wernicke's area) regions (Blanton, Levitt et al. 2001). The Broca's and STS regions are where anatomical gender differences have been found, and they are considered language-related areas. Since Broca's area has functions not only for language but also for general ruled action such as tool-use, then STS may have some other function as well.

Chapter 5

Gender difference related to Broca's area and Wernicke's area

When observing an action by someone else, the same relevant neurons become active as an observer is acting the same behavior by internal representation in Broca's area (mirror neuron study). However, a recent study revealed that when subjects judge the beliefs of actors regarding the weight of a box, the activity was found not only in the posterior part of Broca's area but also in the posterior ascending superior temporal sulcus. In another judging study, subjects were asked to judge "how tiring" they believed observed ballet and capoeira dance to be; interestingly, stronger activity was found in the posterior superior temporal sulcus (STS) than in Broca's area (Calvo-Merino, Glaser et al. 2005). Wernicke's area is known as a comprehension centre for language listening that includes a part of the posterior STS area. Thus, although both tasks were action-observation tasks, when subjects were asked to judge action or create internal representation. As a result, different brain regions were activated.

Patients with apraxia have difficulty using tools, even when they do not have paralysis or linguistic problems. Brain activity differences between the genders have been found for speech and certain manual functions. Women incur aphasia (impairment of the power to produce and understand speech) more often after anterior damage than after posterior damage to the brain. Conversely, in men, posterior damage more often

affects speech. A similar pattern is seen in apraxia (difficulty in selecting appropriate hand movements), such as when a patient shows how to manipulate a particular object or copies the movements of an experimenter. Women seldom experience apraxia after left posterior damage, whereas men often do. Men also incur aphasia from left hemisphere damage more often than women do. One explanation suggests that restricted damage within a hemisphere after a stroke more often affects the posterior region of the left hemisphere. Because men rely more on this region for speech than women do, they are more likely to be affected. We do not yet understand the effects on cognitive patterns of such divergent representation of speech and manual functions (Kimura and Mehgel 2002) (Kimura D, 1983).

We do know that language and tool-use are very closely related tasks in regards to the basic function of language production. Accordingly, we hypothesized that the gender difference patterns of aphasia and apraxia found in lesion studies could also be found in our study on language and tool-use.

1. Methods

1.1. Subjects

Fourteen females and fourteen males participated in our study (age range: 18-35 years). Each subject received an explanation of the experiment in writing and signed an agreement to participate in the experiment. The protocol was approved by the Ethics Committees of the Advanced Telecommunications Research Institute. All volunteers were right-handed according to the Edinburgh Inventory (Oldfield 1971).

1.2. Experimental procedures

The fMRI experiment included five conditions, as was the case in a previous experiment. During tool-use EXECUTION volunteers were asked to use one of three common tools (to cut a sheet of paper using scissors, to connect lines on a piece of paper using a pencil, and to move beads using chopsticks) with their right hand placed on an arm chair to prevent head movement. Two mirrors were combined to provide subjects with visual feedback of their hand and tool without reversal of the image. During tool-use IMAGERY, subjects were asked to imagine using a tool the same way it is used in the tool-use execution condition. They were instructed to hold the tool and look at the target (e.g. paper) as in the execution condition. During HOLD, volunteers

were asked to hold the tool and look at the target object without imagining tool-use. To investigate language, subjects listened to a fairy tale narrated by professional storyteller (STORY). A control condition involved playing the same story backward (REVERSE). Transitions and types of conditions were indicated by sound stimuli. One tool was used in each session and one session was performed for each tool, so subjects underwent three sessions, with the order of tools randomised between subjects. Conditions were repeated three times within a session (except HOLD, repeated six times). Each condition lasted forty seconds (except HOLD, twenty seconds) and the order was randomised within each repetition (except HOLD, second and fifth position in each repetition).

Twelve healthy right-handed males aged 22-25 years gave their informed consent to participate in the experiment, which was conducted with the approval of the Ethics and Safety Committees of the Advanced Telecommunication Research Institute International (ATR) and Hiroshima University. On the screening day, a psychiatrist interviewed each volunteer to screen them for psychiatric problems using the Structured Clinical Interview for DSM-IV, and each volunteer received a health examination including blood and urine tests, a chest X-ray, and an electrocardiogram. We excluded participants who had health and/or psychiatric problems or who disliked the isotonic drink used as the reward in the experiment.

1.3. Data acquisition

The 1.5T MRI scanner (Shimadzu-Marconi Magnex ECLIPSE 1.5T) of the Advanced Telecommunications Research Institute's Brain Imaging Center was used to obtain blood oxygen level dependent (BOLD) contrastive functional images. Images weighted with the apparent transverse relaxation time (T^*_2) were obtained with an echo-planar imaging sequence (repetition time = 5 s, echo time = 50 ms, flip angle = 90°). Voxel size was 3 x 3 x 3 mm (64 x 64 x 64 pixels), which gave a total field of view of 192 x 192 mm². A total of 369 image volumes were acquired in this experiment over 30 min. In a separate session, high-resolution whole-brain images were acquired from each subjects to improve the localization of activation foci using a T1-weighted three-dimensional (3D) segmented radio-frequency-spoiled Fourier-acquired steady-state technique covering the whole brain.

1.4. Data processing and statistics

We used SPM2 software (SPM2 2003) for image processing and analysis. The first three volumes of each session were discarded to allow for T1 equilibration, while the remaining 120 image volumes were realigned to the first volume and unwarped. The estimated movement did not exceed 3 mm. A mean image was created using realigned volumes. T2 and T1 structural images were aligned to the mean EPI image and then spatially normalized to the Montreal Neurological Institute (MNI; Montreal, Canada) reference brain. The normalized images of $2 \times 2 \times 2 \text{ mm}^3$ were spatially smoothed by a Gaussian kernel of full-width half-maximum 6 mm only for the group analysis. A cytoarchitectonic investigation of Brodmann areas 44 and 45 led to the development of probabilistic maps (Amunts, Schleicher et al. 1999). To focus on Broca's area activity, we restricted all EPI images to the brain region defined in this probabilistic map for left hemisphere activity. For Wernicke's area, we used the BrainMap tool to define this region of interest (Fox, Laird et al. 2005) and restricted all EPI images to the brain region defined in BrainMap for left hemisphere activity. The restricted regions for Broca's area and Wernicke's area are drawn in **Error! Reference source not found.** We did not apply smoothing to EPI images in order to identify task-related activity voxelwise for individual subject analysis.

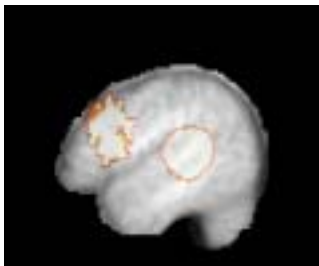


Figure 17 Selected regions of Broca's area (anterior region) and Wernicke's area (posterior region)

ter estimates for the EXECUTION, IMAGERY, HOLD, STORY and REVERSE trials were determined by fixed effect analysis for each subject using a box-car function convolved with a hemodynamic response function, and high-pass filtering (cut-off frequency = 400 ms) was applied. We tested for significant effects by using voxelwise t statistics assembled into a statistical parametric map.

Three contrasts of interest were computed: EXECUTION-HOLD, IMAGERY-HOLD and STORY-REVERSE. The resulting contrast images for each subject were used for a random effect analysis of variance to identify voxels activated in language (STORY-REVERSE), tool-use (conjunction between EXECUTION-HOLD and IMAGERY-HOLD), and both language and tool-use (conjunction among EXECUTION-HOLD, IMAGERY-HOLD and STORY-REVERSE). A conjunction was

computed as the minimum statistical value of the two contrasts or three images in each voxel (Nichols, Brett et al. 2005). We located the activity according to the probabilistic map of the BA44, BA45, BA6 (Geyer, Ledberg et al. 1996; Amunts, Schleicher et al. 1999) using the Anatomy toolbox (Eickhoff, Stephan et al. 2005). For identification of Wernicke's area, we used BrainMap (Laird, Lancaster et al. 2005) to get the most probable area for this region.

First, we analysed the entire brain's EPI image (before EPI restriction), and then we analysed restricted EPI images of Broca's area and Wernicke's area independently. Finally, we conducted analysis while dividing the subjects into male and female groups.

2. Results

2.1. Activated regions during tool-use and language tasks

Random effect analysis of the main effect of STORY-REVERSE reveals that voxels mainly in Wernicke's area are related to heard language processing. A conjunction analysis between EXECUTION and IMAGERY conditions reveals regions involved in both the execution and the imagery of tool-use but not regions whose activity is related to holding the tool and thus suitable for investigating high-level knowledge of tool-use without motor components. Conjunction analysis between STORY-REVERSE, EXECUTION-HOLD and IMAGERY-HOLD revealed Broca's area (BA44) and the border of Wernicke's area (BA21) at $p < 0.001$ uncorrected (*see* **Error! Reference source not found.**). The activated regions were rendered to the standard brain; interestingly, the activated region for conjunction of STORY-REVERSE, EXECUTION-HOLD and IMAGERY-HOLD (right panel in **Error! Reference source not found.**) were mainly in Broca's area and Wernicke's area.

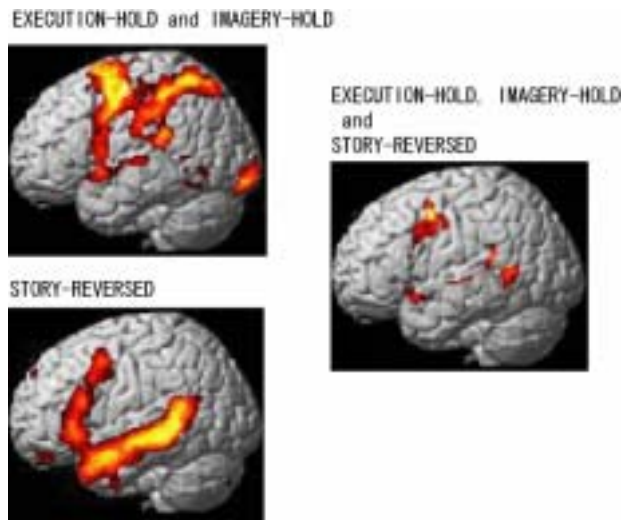


Figure 18 Results of random effect analysis of all 28 subjects rendered on standard brain. Top-left panel: conjunction between EXECUTION-HOLD and IMAGERY-HOLD; bottom-left panel: main effect of STORY-REVERSED; right panel: conjunction between EXECUTION-HOLD, IMAGERY-HOLD and STORY-REVERSED. *threshold at $p < 0.001$ without multiple comparison.

5 Top 10 activated coordinates are listed from whole-brain analysis

	Coordinates	Broadmann			Area*
	Z-max	x	y	z	
<u>Tool-use</u>	5.6	-50	0	46	6
	5.28	-24	4	56	6
	4.81	-12	-64	56	7
	5.11	54	6	42	6
	4.19	30	-4	50	6
	3.17	66	8	14	6
	4.84	-28	-98	-12	18
	4.73	26	-98	-8	18
	4.06	68	-30	22	48
	3.75	-64	-20	2	22
<u>Language</u>					

7.59	-52	6	-24	21
6.98	-54	-44	-2	21
5.84	-48	24	-6	38
7.04	58	4	-20	21
5.72	52	-38	-2	21
4.97	-16	-18	-18	35
4.72	-10	56	40	9
4.27	22	-80	-38	
4.24	26	-18	-16	20
3.89	0	44	-22	11

Language and Tool-use

6.51	-46	2	46	6
3.67	-52	14	24	44
4.9	-56	18	-6	38
4.63	-52	-50	6	46
4.46	-60	-24	0	21
4.46	-4	-24	8	
4.41	-56	-42	16	42
4.14	-20	-2	8	
4.03	48	24	-18	38
3.94	22	-72	-28	

* BA: Brodmann area, when applicable.

To measure the activated volume difference between Broca's area and Wernicke's area, the number of all activated voxels was calculated for all three conditions for each subject. These differences are shown in **Error! Reference source not found.** In Wernicke's area, there was only a marginal difference in activated volume for tool-use and language tasks. A three-way ANOVA on volume

size was performed with factors of task, region and gender. As a result, significant effects of task, region and gender were found for volume size ($p < 0.02$).

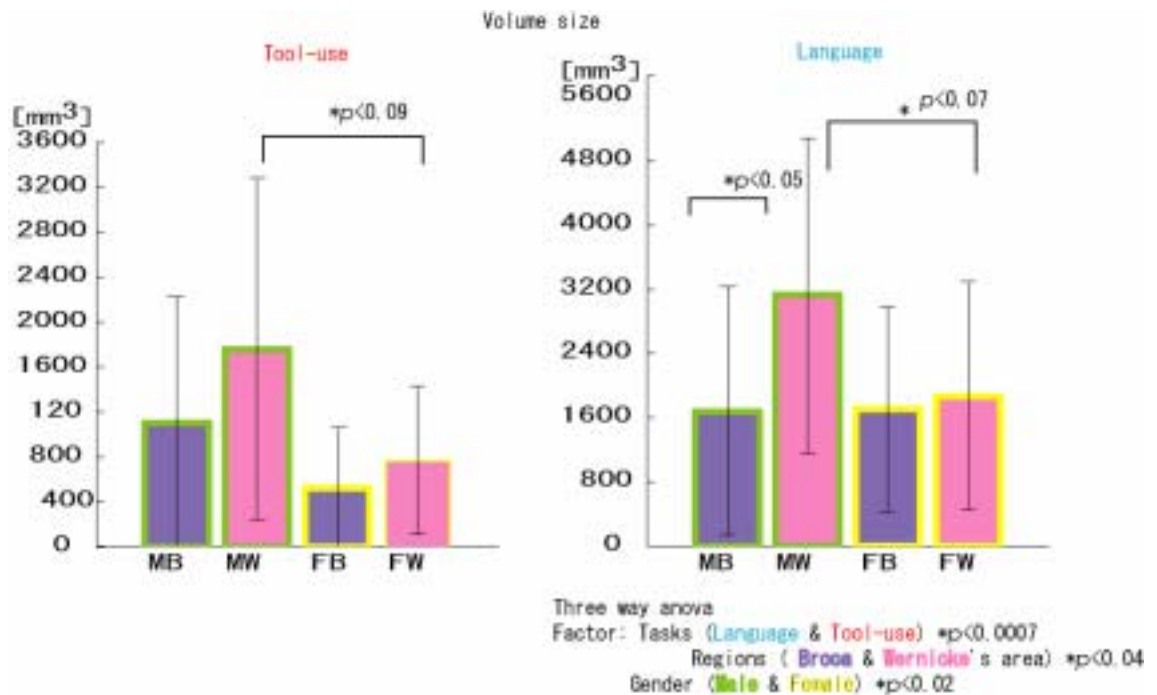


Figure 19 Activated volume size differences in Broca's area and Wernicke's area for tool-use task (left panel) and language task (right panel). (MB: male in Broca's area, MW: male in Wernicke's area, FB: female in Broca's area, FW: female in Wernicke's area; male coloured green, female coloured yellow, Broca's area coloured purple, Wernicke's area coloured pink.)

The defined regions of interest for Broca's area and Wernicke's area (see **Error! Reference source not found.**) were different, so the activated volume sizes were normalized by using the ratio of activities in both regions (e.g. Broca's activity/(Broca's activity and Wernicke's activity). A three-way ANOVA on volume size was performed with factors of task, region and gender. This showed a significant effect of region ($p < 0.002$) and an effect of interaction between regions and genders ($p < 0.005$) on volume size.

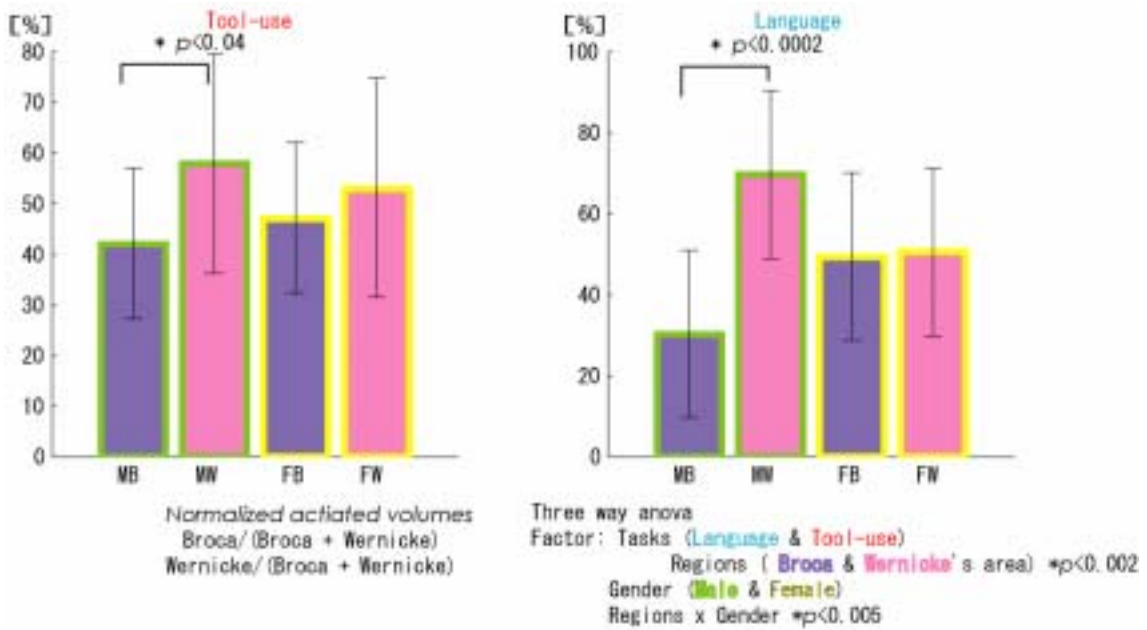


Figure 20 Activated ratios for Broca's area and Wernicke's area. (Details as in *Error! Reference source not found.*)

To show the difference in activity balance between Broca's area and Wernicke's area, the activity in Broca's area was subtracted from that in Wernicke's area. Both the tool-use and language activities in Wernicke's area were larger than those in Broca's area. The stronger activity balance of Wernicke's area was significantly higher in male subjects than in female subjects ($p < 0.02$).

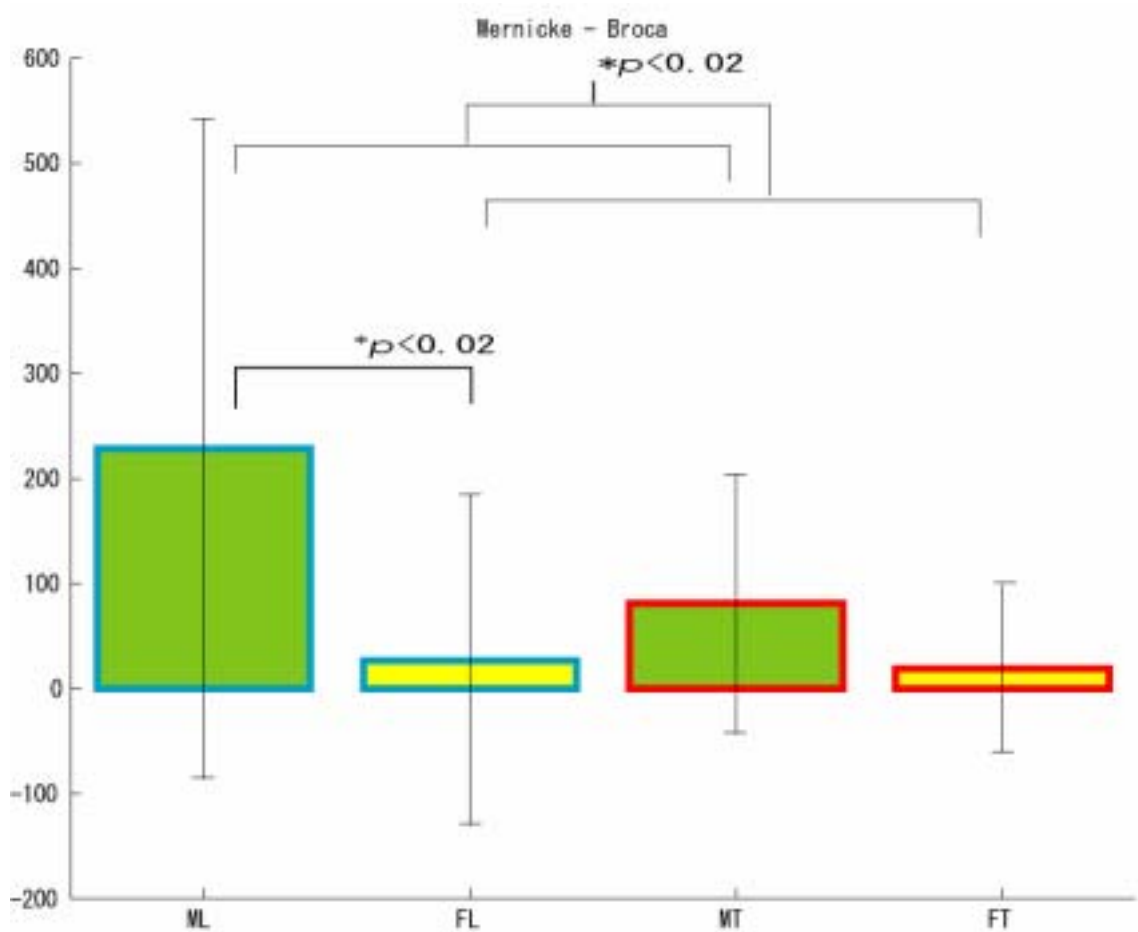


Figure 21 Activity weight differences between Broca's area and Wernicke's area for tool-use and language.
 e and language.
 anguage.

3. Discussion

We found a similar tendency to the results of previous region studies showing a gender difference in apraxia and aphasia relative to Broca's and Wernicke's areas. Mirror neuron studies suggested that Broca's area is related to understanding another's action by internal representation other's action. This internal representation makes the possibility of guessing other person's mind. Trying to understand someone's action requires empathetic processing, so it is possible that Broca's area plays a role in understanding other's action by empathetic processing. On the other hand, action judgment tasks suggested that Wernicke's area is related to judging an action by analyzing the action as a third person. Trying to judge an action requires systemizing

processing, so it is possible that Wernicke's area plays a role in understanding other's action by systemizing processing. From our results, male subjects, who are assumed to be good at systemizing, showed more activity in Wernicke's area. In contrast, female subjects, who are assumed to be good at empathizing, showed more activity in Broca's area. Therefore, although subjects are performing the action at the same level, the preferred strategy in the brain might differ between genders.

4. Conclusion

In our experiment, tool-use and language tasks are well-learned tasks, so the cognitive process may vary according to the subject's preferences. Therefore, our results showed different weights for Broca's area and Wernicke's area. These results indicate that male subjects have a preference to process tasks in a more analytical way, while female subjects have a preference for an inner-simulation way. These styles closely fit Baron-Cohen's theory of females, which states that they are good at empathy while males are good at systemizing (Baron-Cohen, Knickmeyer et al. 2005).

Chapter 6

General Discussion

The occurrences of Broca's aphasia and Wernicke's aphasia are known to have correlation to the inferior frontal cortex and superior temporal gyrus. Patients with damage to Broca's area (left inferior frontal cortex, BA44 and BA45) show no difficulty in understanding the agent speaking, but they do have difficulty in responding by speaking smoothly. On the other hand, patients with damage to Wernicke's area (left posterior superior temporal gyrus, STS, BA22) show no difficulty in speaking, but they do have difficulty in reading and listening comprehension.

STS, which is partially in Wernicke's area, has been suggested as the region related to social communication. This region is activated by making judgments on another person's gaze direction and by observing biological—but not non-biological—motion. On the other hand, observing meaning-intended action by another agent activates the Broca's area and monkey's F5 area, suggesting that people or monkeys perform inner imitation of others to understand and empathize. Thus, not only the STS region but also Broca's area is related to social communication. Therefore, areas related to social communication could also be related to language areas.

The findings on brain activities related to tool-use and story-listening tasks in our experiments indicated that Broca's area is related to active behavior while Wernicke's area is related to passive behavior. Active behavior and passive behavior are very much interacted functions, and thus it is very difficult to differentiate the functions of Broca's

and Wernicke's areas. However, our results suggest these areas could function differently for empathy-oriented and analytically oriented tasks.

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Appendix

文章聴解タスクに使われた刺激文章

1. 各地の方言は暖かく、それぞれの音声には特徴があって変化に満ちています。この多彩で生き生きとした方言音声は、日本語の歴史のなぞときの資料でもありなのです。どうしたら後世にもつたえることができるでしょうか？次に、同じ話者が方言桃太郎を語り、共通語桃太郎を読みます。方言ももたろうでは、どの話者もみごとにその地域の言葉で語ります。一方共通語の読みも、話者によっては別人のように変わります。

2. 濁音になる例が多いせいでしょうか？むがし、むがし、あるところに、と清音が濁音になります。全体が鼻にかかった発音です。また山さのように、共通語の「何処どこへ」、「何々に」、にあたる「さ」が使われ、「いてきたきゃ」のように「と」は「きゃ」となります。ももたろうず何々という、「つけたじ」これは「つけたと」もあり、その他、大きな桃がは、「出たらんだ桃が」となっています。

3. アナウンサーの読みに似ていますね。でもここでは助詞を高く強く言っており、アナウンサーの読みとは違いますが、このような語り東京周辺では普通かもしれません。これも東京方言です。ここでは、おじいさとおばあさがと語っています。気仙沼ではおじんちゃんとおばんちゃんですが、一方南の鹿児島では、おばっさんです。ここ浜松では、おばあさがと「ん」を省き、他では、おばあと音を伸ばす代わりに「ん」をいれ、また、おばっさんのよう「っ」となります。

4. せんだくのように、単語によって濁音になっている場合があります。京都、大阪、奈良など関西では、たとえば「かかと」を「かがと」など東京や九州と違って、単語によっては濁音になることがあるのです。ここも京都大阪と同じアクセントの地域です。おったいのお、いっちゃったといのおなど文末が特徴的です。いっちゃったなどは東京でもいいいますが、いんじゃった、われちゃって、のように、「何々しちゃった」という言い方が多いのでここでは目立ちます。

5. 例えば、かごしまというときは、「かごつま」、のようにいいます。文末にはわい「もうした」これは、申したですが、そういう音が聞かれます。あるとこい、しばかいて、いって、かわかんの、そんなもも、など音が変わっていますが、なにかこう風格がありますね。明治時代の西郷さんの語り方も、こんな様だったのでしょうか。共通語のももたろうの場合にも少し尻上がりで、アクセントにも特徴があります。

6. むかし～、長く伸ばしてやさしい語り口で始まります。文の終わりは、

「いやったとよ」、「いきやったとよ」のように「た」と「よ」という言い方で結んでいます。いかにも子供がそばで聞いているような、いい雰囲気を作っていますね。「やった」という言い方も効果的です。また、な～おつきやったとよ、の、な～と伸ばすのは関西的です。が、関西でも「な」をもっと短くいう場合もあり、様々です。

7. 東北の場合とにしていますね。とんとんむかしがあっただけな。という語り口には物語の世界に引き込むような、なにかそういうムードがありますね。文末のげなというのは名古屋と同じです。あーとこに、しばかーに、ではら行の音がしょうりゃくされています。文末を見ると、おんしゃったげな、いけんしゃったげな、のようにすべて「げな」で結んでいます。また、何々しやったという言い方も多いです。おじいさんな～、おばあさんな～の言い方がやさしく聞こえます。

8. これは男性ですけど、どこか舞妓さんを連想させるような、やわらかく、やさしい話し方ですね。いはりましたよ、は軽い敬語です。京都とそれから他には沖縄の首里だけが敬語を使っていますが、どちらもかつて都でした。うまれたんやでー、なおつけたんや、など終わりの助詞が、また特にアクセントに特徴があります。これも真似してみませんか？このような言い方は大阪などでも聞くことができます。

9. 昔々、あるところに、おじいさんとおばあさんがありました。おじいさんは山へ芝かりに、おばあさんは川へ洗濯に行きました。おばあさんが洗濯をしていると、川上から大きな桃がどんぶらこ、どんぶらこと流れてきました。おばあさんはその桃を拾ってうちへかえりました。おばあさんが桃を切ろうとすると、ももが二つに割れ、中から大きな男の子が生まれました。おじいさんとおばあさんはその子に桃太郎という名をつけました。

List of Publications

Peer-reviewed research articles:

- Higuchi S., Imamizu H., Yoshioka T, Kawato M.
Cerebellar activity evoked by actual tool-use and tool-use imagery task. – *Cortex in press*
- Imamizu H., Higuchi S., Toda A, Yoshioka T, Kawato M.
Reorganization of brain for multiple internal models after short but intensive training.
– Cortex in press
- Higuchi S., Imamizu H., Yoshioka T, Kawato M.
·Cerebellar activity during tool-use motor imagery task: An fMRI study
IEICE (in Japanese) – Vol. J88-A No.3 pp.411-421 (2005)
- Toda A., Imamizu H., Higuchi S., Wada Y., Kawato M.
Reorganization of brain activity for multiple internal models
IEICE (in Japanese) – in press

Technical reports:

- Higuchi S., Imamizu H., Kawato M.
·Correlation in volume of brain activation between tool-use and linguistic processing
IEICE technical report (in Japanese), Vol.103, No.602, p.25-30, 2004
- Higuchi S., Imamizu H., Kawato M.
·Brain activity evoked by tool-use motor imagery: An fMRI study
IEICE technical report (in Japanese), Vol.101, No.615, p.103-110, 2002
- Furukawa T, Ueda N, Higuchi S., Doya K, Kawato M
Brain activity analysis by extended tied mixture models
IEICE technical report (in Japanese), Vol.101, No.615, p.111-118, 2002

International conferences and workshops:

- Higuchi S., Chaminade T., Imamizu H., Kawato M.
·Broca's area during tool use and linguistic processing
Society for Neuroscience 34th Annual Meeting, San Diego, 2004
- Higuchi S., Imamizu H., Kawato M.
·Sex difference in T-value weighted volume of brain activity during tool use and linguistic processing
Mechanisms of Brain and Mind: 4th Winter Workshop, Rusutsu, Japan 2004
- Higuchi S., Imamizu H., Kawato M.
·Correlation in volume of brain activation between tool-use and linguistic processing

3rd International Symposium on Emergent Mechanisms of Communication in the Brain, Japan, 2004

- Higuchi S., Imamizu H., Yoshioka T, Kawato M.

·Composition of acquired internal models for novel sensory-motor environment: An fMRI study

Society for Neuroscience 32nd Annual Meeting, Orlando, 2002

- Higuchi S., Imamizu H., Kawato M.

·Brain activity evoked by tool-use motor imagery: An fMRI study

8th International Conference on Functional Mapping of the Human Brain, Sendai, 2002