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Cerebellar activation caused by silent backward repeat of words

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SUMMARY

To investigate the cerebellar contribution to verbal function, we examined regional cerebral activities during a silent backward repeat task using three-syllable words with functional magnetic resonance imaging (fMRI). We found that this task activated the right cerebellar hemisphere (Crus I, Schmahmann's 3D MRI atlas) which had previously been reported by using a word generation task. This suggests that the cerebellum contributes to phonemic manipulation in addition to semantic manipulation of words. Moreover, the activations of perceptual areas during a silent backward repeat task were stronger than those of a silent forward repeat task. This suggests more complicated manipulation after perception activates the perceptual areas more, indicating a limitation of the cognitive subtraction paradigm.

Key words : functional MRI, SPM, cognitive function, cerebellum

Abbreviations : fMRI : functional magnetic resonance imaging
SPM : statistical parametric mapping

I. Introduction

Recently, the cerebellum has been considered to participate in cognitive function as well as motor function through a strong reciprocal connection to the frontal lobe[1-4]. This situation is apparently true for verbal function as well. At an early stage, Pawlik et al[5] at Max-Plank-Institute reported a 27 % increase of glucose metabolism in the right cerebellar hemisphere in voluntary speech which was weak in aphasics. An epoch making research by Petersen and colleagues [6,7] at Washington University adopted the cognitive subtraction method. By making a series of PET scans during the progressive tasks as 1) look at a word 2) read the word 3) answer a verb related to the word, then they made subtraction images to reveal areas related to different mental processes between two tasks. They found that the 3)-2) showed differences of the left inferior prefrontal area and the right cerebellar hemisphere. They considered these areas to be related to generate use,

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and explained that the cerebellum contributes to unknown roles in semantic manipulation which is more than just merely motor function.

To clarify more clearly about the cerebellar contribution to cognitive function, we examined regional cerebral activations during a backward repeat task of words using functional magnetic resonance imaging (fMRI) with the statistical parametric mapping (SPM 96). Our strategy was to examine the manipulation of phoneme, contrary to that of Petersen and colleagues which related to only manipulation of semantics. Both phoneme and semantics are two major aspects of verbal function.

II. Subjects and Methods

Subjects

Seven healthy right-handed male volunteers (mean age±SD, 26.6±2.8 years old), all of whom were native Japanese participated in this study. They were assessed using the Edinburgh Handedness Inventory[8]. All subjects gave informed consent, after a full explanation of the purpose and method of this study.

fMRI

FMRI was performed using a standard clinical 1.5Tesla whole body MRI system (Signa Horizon ver. 5.6, GE Medical Systems, Milwaukee, Wis), with a conventional QD head coil. For fMRI volume, T2* weighted axial images were acquired with gradient-echo EPI sequence (TR/TE: 3980 ms/60ms, flip angle: 90degrees, excitation: 1 NEX, FOV: 24×24cm, Matrix: 64×64, in-plane resolution: 3.75×3.75mm, slice thickness/interslice gap: 6mm/2mm, number of slice: 13 slices, number of phase: 38 phases). Each session (one scanning series) lasted 152sec, that is 38 phases, and a time series of 38 volumes was collected during one session. Each volume consisted of 13 axial slices, basically covering approximately the whole brain.

The subjects laid in the scanner with eyes closed using special headphones for the MRI system (Resonance Technology Inc., Van Nuys, CA), and they underwent two series of fMRI with above parameters. During the scanning, they performed the following tasks.

Experimental paradigm

We used two boxcar designed paradigms for each subject, as illustrated in Fig. 1. During every paradigm (152 seconds), a series of functional MR imaging volumes were collected. In both paradigms, auditory stimulus heard from the headphones was used, with a female voice reciting common three-syllable Japanese nouns. These words were repeated every four seconds and the duration of the each word was adjusted to be approximately 0.5 seconds.

The subjects were required to listen to a three-syllable word and simultaneously repeat the syllables non-verbally in reverse ("silent backward repeat" task), during the "on" period in paradigm #1. For example, when "ha-sa-mi (scissors)" was heard from the headphones, the subject must repeat to himself "mi-sa-ha", without moving his mouth, tongue, or throat. During each "on" period, that lasted 20 seconds, the subjects were required to follow the same procedure with five different three-syllable nouns. A paradigm contains two "on" periods with different sets of words. During the "off" period with no auditory stimulation, that is the "rest" state, subjects were required to silently listen to the sound of the MR scanner which was a "phon phon...", and think of nothing. Three "off" periods were alternated with two "on" periods in each paradigm, with the first "off" period being 40 seconds while the other "off" periods were 36 seconds.

In paradigm #2 however, the "silent forward repeat" task was used for activation. This "silent forward repeat" task consisted of listening to three-syllable words, and then repeat forward the syllables non-verbally. During each "on" period, the subjects continued the same procedure with five different three-syllable nouns. In paradigm #2, the stimulus word sets were different from that of paradigm #1.

The stimulus words used in both studies were common Japanese words selected from the word groups of approximately the same level of familiarities [9]. Just after the two paradigms, all subjects were required to choose the stimulus word, which they could recall, from the previously made word list. This word list was composed of 65 various common nouns however only 20 words were used in our examination. They were also required to explain how they had reversed the words mentally during the "silent backward repeat" task of paradigm #1.

Data Analysis

The fMRI data was analyzed with SPM96 (the Wellcome Department of Cognitive Neurology, London, UK) [10] implemented in MATLAB (Mathworks, Inc, Natiek, MA), on Ultra2 workstation (Fujitsu).

The first three volumes of all series of functional MR imaging were discarded because of unsteady magnetization. The remaining 35 volumes were used for analysis.

The 35 volumes in each session were realigned to the first volume as a reference for motion correction. Subsequently, spatial normalization was performed by transforming those volumes into a standard stereotaxic space corresponding closely to the atlas of

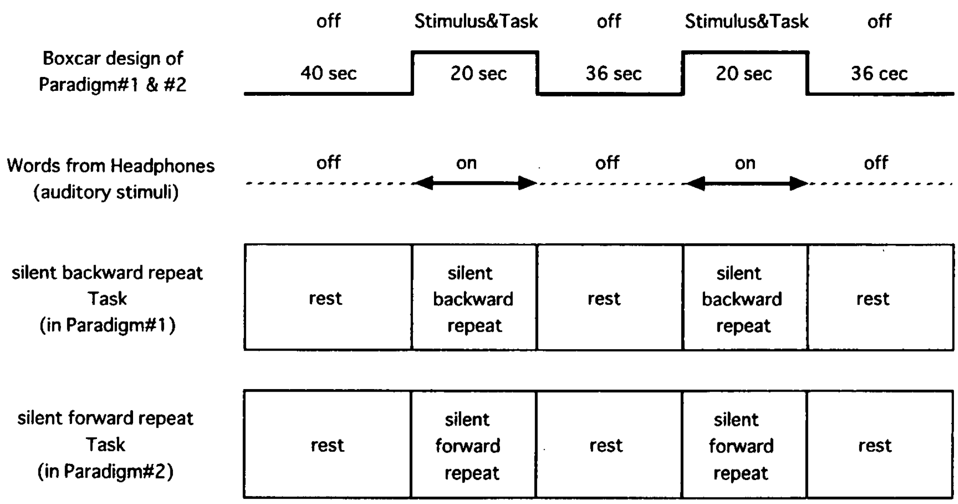

Fig. 1
Boxcar designs of the two paradigms. In paradigm #1 and #2, a similar stimulus pattern was used, but with a different task. Task in paradigm #1 was a "silent backward repeat", and task in paradigm #2 was a "silent forward repeat". During the "silent backward repeat" condition, subjects listened to three-syllable words from headphones and then repeated the syllables non-verbally in reverse. In the "silent forward repeat" condition, subjects did a similar procedure to that of the "silent backward repeat" condition except subjects did a forward repeat. In the "rest" condition, subjects listened to the sound of the MR scanner.

Talairach and Tournoux[11]using MNI template (Montreal Neurological Institute). This spatial normalization involved linear and nonlinear transformations. These normalized volumes were spatially smoothed with an 8mm FWHM (the Full Width at Half Maximum) isotropic Gaussian kernel, and the data series were temporally smoothed with a 2.8sec FWHM Gaussian kernel to increase signal-to-noise ratio.

The hemodynamic response function was modeled after a simple delayed boxcar waveform (6sec. delayed). The effect of differences in global activity (whole brain activity) across scans was removed using proportional scaling. Low frequency physiological noises and baseline drifts were eliminated by using a high-pass filter (0.5 cycle／min) at each voxel.

Statistical parametric maps were generated for the group of seven subjects (14sessions) using the ANCOVA model implemented through the General Linear Model formulation of SPM96. Three contrasts were used, "silent backward repeat vs rest", "silent forward repeat vs rest", and "silent backward repeat vs silent forward repeat". For all contrasts, the SPM{Z} were thresholded at $p=0.01$ (uncorrected) for voxel height, and spatial extent threshold was $n=15$voxels.

The stereotaxic coordinates of Talairach and Tournoux[11]were used to report the observed activation foci, and to determine the anatomical localization of the activated area. In the cerebellar area, Schmahmann's 3D MRI atlas based on Larsell's nomenclature [12]was used.

Ⅲ. Result

Scanning of all subjects was executed with no difficulties. Just after scanning, five subjects reported they had correctly done the task by 100%, one subject 90%, and the others 80%. Two participants imagined the characters of the words when they reversed the words, the others reversed the words directly. No one repeated words before they reversed then. The mean rate of correctly choosing the stimulus words from the word list was 28.6%±16.8% (mean±SD).

The activated areas in both paradigm #1 and #2, that is the contrast of "silent backward repeat condition (SBR condition) vs rest condition" and "silent forward repeat condition (SFR condition) vs rest condition", are summarized in Table 1. In this table, hei ght threshold is $p=0.01$ (uncorrected), and extent threshold is $n=15$voxels. The "SBR condition vs rest condition" contrast has 10 activated clusters, and the "SFR condition vs rest condition" contrast has 7 activated clusters.

The activated areas of the contrast of "SBR condition vs SFR condition" is summarized in Table 2. The maximum intensity projection is described in Fig. 2, and the rendering images are in Fig. 3. Threshold is the same as in Table 1. In this contrast, a similar pattern of activation as to "SBR condition vs rest condition" was revealed. Of all 13 areas, 10 activated areas were in the same location as in Table 1.

There are three largely activated areas. Firstly, bilateral, but left dominant, cingulate gyri and superior frontal gyri (medial part) were largely activated in all contrasts. This area contained a part of the anterior cingulate gyrus and the supplementary motor area. The Z-score and size of clusters were largest in the "SBR vs rest" contrast, and smallest in the "SFR vs rest" contrast.

Following the two largely activated areas were the right middle temporal gyrus and the left superior and middle temporal gyrus. These are parts of Brodmann area (BA) 21

Table 1 Activated areas for the contrast of silent backward repeat vs rest and the contrast of silent forward repeat vs rest

anatomical location	left/right	Brodmann area or Schmahmann's nomenclature	silent backward repeat vs rest: Talairach coordinates (mm)					silent forward repeat vs rest: Talairach coordinates (mm)				
			x	y	z	Z-score value	cluster size (voxels)	x	y	z	Z-score value	cluster size (voxels)
cingulate gyrus ~superior frontal gyrus (medial part)	left (>right)	BA32~6~8	− 6	16	52	7.12	789	− 8	− 2	64	5.89	553
middle temporal gyrus	right	BA21~22	62	−10	−12	6.74	296	62	−10	−12	5.85	284
superior temporal gyrus ~middle temporal gyrus	left	BA22~21	−68	−14	−20	6.41	598	−62	−12	0	5.64	550
precentral gyrus ~inferior frontal gyrus ~middle frontal gyrus	left	BA6~ BA9	−52 −58 −50	0 8 14	48 36 32	5.8	54	−54	−2	48	5.3	32
inferior frontal gyrus	left	white matter (~BA44)	−48	10	16	4.74	112	−48	10	16	3.46	23
cerebellar hemisphere	right	Crus I	36	−62	−32	4.25	26	(36	−62	−32	2.57	5)*
superior temporal gyrus ~middle temporal gyrus	right	white matter (~BA22)	46	−28	0	3.98	39	no cluster				
lingual gyrus	left	BA17~18	− 8	−96	− 8	3.87	39	no cluster				
lentiform	left	putamen	−22	2	0	3.86	32	−24	2	0	3.41	20
inferior frontal gyrus	left	white matter (~BA47~11)	−34	22	−12	2.92	24	no cluster				
middle frontal gyrus	left	BA6	no cluster					−32	− 4	64	4.62	62

Talairach coordinates : Talairach coordinates of the voxels with the highest Z score in the regions
Z-score value : value of the highest Z in the region
height threshold : $P = 0.01$ (uncorrected), extent threshold : $n = 15$voxel
* : under extent threshold
BA : Brodmann area

and BA22 corresponding to the association auditory cortex, which were activated in all three contrasts. On the left side, this cluster was so large as to contain a part of the supramarginal gyrus. On the right side, inside the above mentioned area, a small area was activated in the white matter or inner part of the sulcus between the superior and middle frontal gyrus, in only two contrasts of "SBR vs rest" and "SBR vs SFR". Moreover, on the left side, posterior of the above large cluster, a small activated cluster of gray matter of the middle temporal gyrus was observed in only "SBR vs SFR" contrast.

The left precentral gyrus (BA6) corresponding to the premotor cortex was also activated in all contrasts. Only in the contrast of "SBR vs rest", did it extend to the middle and inferior frontal gyrus, which is the prefrontal cortex (BA9). These clusters are not large. Slightly inside and posterior of this cluster, in gray or white matter between BA4 and BA6 of the left precentral gyrus, a small activation is observed only in the "SBR vs SFR" contrast.

Activation of the left inferior frontal

Table 2 Activated areas for the contrast of silent backward repeat vs the silent forward repeat

anatomical location	left/right	Brodmann area or Schmahmann's nomenclature	Talairach coordinates (mm) x	y	z	Z-score value	cluster size (voxels)
cingulate gyrus ~superior frontal gyrus (medial part)	left (>right)	BA32~6~8	− 6	16	48	6.62	786
superior temporal gyrus ~middle temporal gyrus	left	BA22~21	−66	−20	4	5.65	594
middle temporal gyrus	right	BA21~22	62	−10	−12	5.51	241
precentral gyrus	left	BA6	−52	0	48	4.78	32
inferior frontal gyrus	left	white matter (~BA44)	−46	10	16	4.01	88
lingual gyrus	left	BA17~18	− 8	−96	− 8	3.89	36
lentiform	left	putamen	−22	4	0	3.74	32
superior tenporal gyrus ~middle tenporal gyrus	right	white matter (~BA22)	48	−28	4	3.46	27
precentral gyrus	left	white matter (~BA4)	−46	− 6	48	3.16	16
middle temporal gyrus	left	BA21	−54	−54	−12	3.11	15
cerebellar hemisphere	right	Crus I	36	−62	−32	2.97	16
middle frontal gyrus	right	white matter (~BA6)	32	− 8	44	2.92	17
inferior frontal gyrus	left	white matter (~BA47~11)	−34	24	−16	2.83	20

Talairach coordinates : Talairach coordinates of the voxels with the highest Z score in the regions
Z-score value : value of the highest Z in the region
height threshold : $P=0.01$ (uncorrected), extent threshold : $n=15$voxel
BA : Brodmann area

gyrus was observed in all contrasts. This peak point was in the white matter but this cluster contains gray matter of Broca's area (BA44). In "SBR vs rest" contrast, a relatively large activation of 112 voxels was observed. In "SFR vs rest", the activation cluster is less than a quarter of the other contrasts.

In the white matter of the right middle frontal gyrus, a small activation was observed. This was observed in the "SBR vs SFR" contrast.

The left lingual gyrus (BA17, 18), corresponding to V1 and V2 of the visual cortex, was activated in the "SBR vs rest" and the "SBR vs SFR" contrast, but not in the "SFR vs rest" contrast.

The left putamen was activated in all contrasts.

In "SBR vs rest" and "SBR vs SFR" con

trasts, a small activation area was observed in the right cerebellar hemisphere. In "SFR vs rest", the cluster was too small to reach a significant level under this extent threshold. Anatomical location was "lobulus semilunaris superior" in conventional nomenclature. According to Schmahmann's 3D MRI atlas based on Larsell's nomenclature[12], anatomical location is determined "crus I" ("crus I of HVIIA／lobuli ansiformis" in Larsell's nomenclature).

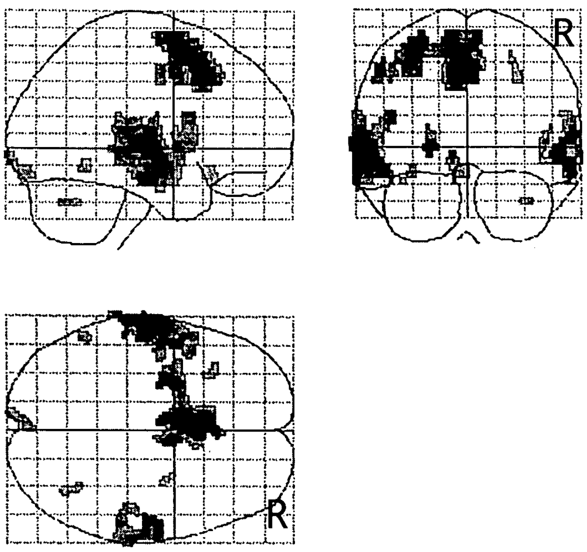

Fig. 2
Statistical parametric maps (glass brain views of maximum intensity projection) with the Z-score of the contrast, "silent backward repeat" vs "silent forward repeat" (height threshold : p=0.01, extent threshold : n=15 voxels). Maximum Z-scores and coordinates of each region are summarized in Table 2.

The cerebellar activation areas in the three contrasts were summarized in Table 3 to consider the function of the cerebellum in our task. The coordinates of the voxels with the highest Z-score of the activated areas were the same, but the Z-score and cluster size were largest in the "SBR vs rest contrast", and smallest in the "SFR vs rest contrast".

The left inferior frontal gyrus, corresponding to the prefrontal cortex (BA47 and 11, orbitofrontal area), was also activated. However, it is necessary to be cautious when interpreting this activation because the susceptibility artifact may occur strongly here.

IV. Discussion

In the SBR vs SFR contrast, activation was observed in the left superior to middle temporal gyrus, the right middle temporal gyrus, the left supramarginal gyrus, the anterior cingulate gyrus, the supplementary motor area, the Broca's area, the left premotor cortex area and the right cerebellar hemisphere. This indicates that these areas play some roles in the inversion of phoneme of

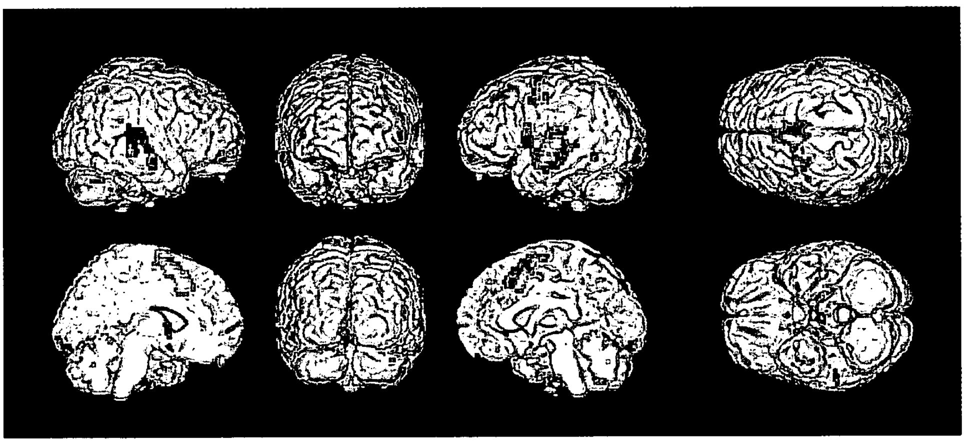

Fig. 3
The same data presented in Fig. 2, but here, statistical parametric maps with the Z-score was rendered on surface images.

Table 3 Comparisons of cerebellar activation between three contrasts

contrasts	activated area in the cerebellum					Z-score value	cluster size (voxels)
	left/right	anatomical location (Schmahmann's nomenclature)	Talairach coordinates (mm)				
			x	y	z		
silent backward repeat vs silent forward repeat	right	loblus semilunalis superior (Crus I)	32	−62	−32	2.97	16
silent backward repeat vs rest	right	loblus semilunalis superior (Crus I)	32	−62	−32	4.25	26
silent forward repeat vs rest	right	loblus semilunalis superior (Crus I)	32	−62	−32	2.57	5

Talairach coordinates : Talairach coordinates of the voxels with the highest Z score in the regions
Z-score value : value of the highest Z in the region
height threshold : $P=0.01$ (uncorrected)

words, if the cognitive subtraction paradigm is correct.

We will discuss the roles of each area, according to previous reports. The bilateral temporal areas are the auditory association cortex which are related to perception of auditory input. The supramarginal gyrus has been considered to relate to storage of phoneme[13,14], and transformation of orthography into a phonological representation[15] through the activation studies. Also, this area has been found to be more sensitive to change in syllables than in tone[16]. A direct electrical stimulation of this area has caused semantic and phonemic error in speech, so it has been considered to bare binding functions of semantics and phoneme[17]. Considering these findings, we suggest this area relates to the investigation of the phonemic component of words. However, its contribution to inversion of the order of phoneme has not been fully denied.

The anterior cingulate has been considered to relate to attentional function. The supplementary motor area (SMA) has been suggested to relate to the initiation of action [18], imagery of a skilled action[18], storage of motor programs[19], and preparation of action[20]. Considering these findings, we suggest this area contributes in making the output programs of reversed phoneme. Recently, this area has been considered to have two parts, pre SMA and SMA proper. Lee and colleagues[21] found the former was active at the preparation period of action and the latter was active at the execution of action, and he suggested they have different roles. Buckner and colleagues[22] reported that the auditory word recall task compared to repetition caused more activation of this area. According to these findings, intentional manipulation such as recall or generation of words can activate this area, however not in passive manipulation such as simple repetition.

Activation of the Broca's area has been reported in silent speech[23,24]. The premotor cortex has been reported to be activated in imagery of motion, generation of a motor program, and the revision of motor program according to sensory information[19]. We consider the Broca's area and the premotor cortex, along with the left putamen, participate in making a program of a new series of phoneme.

Next, we need to discuss the roles of the cerebellum. The cerebellum is considered to play some cognitive roles in collaboration with the frontal lobes, because they have a thick reciprocal anatomic connection [1-4,25]. An early study by Petersen reported the repeat of words in itself dose not activate the cerebellum nor the frontal lobe[6,26]. Decety had reported silent count activated the cerebellum [27]. Fiez and colleagues previously reported that short term maintenance of verbal information such as five related words, unrelated words, pseudo words activated both frontal areas (dorsolateral prefrontal cortex) and the cerebellum [28]. Recently, Desmond and colleagues, using a word stem completion task, found that the right cerebellum was activated when the correct answers were few in numbers, the left middle frontal gyrus and the left caudate head were activated when there were more correct answers [29]. They suggested the search for a response caused the former activation, and the selection of a response caused the latter. Allen and colleagues[30] advocate that the cerebellar activation is related to attentional function.

Our results suggest that the cerebellum plays some roles in manipulating the order of phoneme. However, according to the above reports, the exact role(s) of the cerebellum has many possibilities such as storage of phoneme, intentional manipulation, search of response, and attentional function.

We consider it noteworthy that, the auditory perceptual areas were increasingly activated during complicated afterward manipulation (a back ward repeat) than at a simple manipulation (a forward repeat). This indicates a limitation of the cognitive subtraction paradigm in which we hypothesize that a new task containing additional mental processes only activates the areas related to that process. To perform more complicated afterward manipulation, more careful analysis of a stimulation is possibly needed even in the perceptual process.

Also, we found it intriguing that the left lingual gyrus, corresponding to V1 and V2 of the visual cortex, was activated in "SBR vs SFR" and "SBR vs rest" but not in "SFR vs rest" condition. This is possibly due to the fact that two participants imagined the characters when reversing the words. Another possibility is that the activation is unconsciously transmitted to other mental resources which are related to the words, when complicated afterward manipulation is required.

We will discuss the main drawbacks of our study. The task of this study may have merely activated the semantic memory because we used familiar words as stimulation. Also, the activation of semantic memory has been considered to automatically cause a new episodic memory process [31]. However, the recognition rate of words after the scan was almost at chance level which indicates the memory process was not activated in our task. We could have chosen meaningless three syllable words as stimulation because they have only phoneme but no semantics. However, we considered that the distractive noise from the MRI machine may interfere with the perception of the meaningless syllables which would cast a big load on the perceptual process. We therefore chose the task which would cast less load on the perceptual process to investigate the mental manipulation process itself.

Finally, we would like to comment on the significance of this study. This study could possibly contribute to the elucidation of the pathology of autism which has recently been considered to relate to cerebellar dysfunction [32]. Furthermore, it may contribute to the elucidation of schizophrenia. A hypothesis of cerebellar dysfunction[33], and more recently, a prefrontal-thalamic-cerebellar circuit (PTC circuit) dysfunction [32] was advocated for schizophrenia. Moreover, this method may be useful in examining the practice related to changes in human brain functional anatomy during non-motor learning.

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要　旨

小脳の高次機能，特に言語機能への関与を検討する目的で，健常人が三音節単語（日本語）の逆唱を行う際の脳賦活をfunctional MRIを用いて検討した。これまで，語の意味の操作を行う際に右小脳半球が賦活されることが報告されていたが，今回の結果は，右小脳半球（Schmahmann's 3D MRI atlasの命名法でCrus Iの一部）が，語の音韻の操作を中心とする課題でも賦活されることを明らかにした。また，逆唱課題vs順唱課題のコントラストと逆唱課題vs安静時のコントラストの差が量的差であったことから，困難な課題を行う際は，単純な課題と比較して，低次の領域もより強く賦活してくることが示唆された。このことは高次脳機能に関する減算法パラダイムの限界を示していると考えられた。

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