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Agrammatic comprehension caused by a glioma in the left frontal cortex

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ABSTRACT

It has been known that lesions in the left inferior frontal gyrus (L. IFG) do not always cause Broca's aphasia, casting doubt upon the specificity of this region. We have previously devised a picture–sentence matching task for a functional magnetic resonance imaging (fMRI) study, and observed that both pars triangularis (L. F3t) of L. IFG (extending to pars opercularis (L. F3op)) and the left lateral premotor cortex (L. LPMC) are selectively involved in syntactic processing. The present study with lesion-symptoms mapping was conducted to examine whether the function of these regions is indeed critical for syntactic comprehension. Using the same picture–sentence matching task, we examined 21 patients with a glioma in the left frontal cortex but with no apparent disability in verbal/written communication or intelligence quotient. This task included three main conditions of sentence types: canonical/subject-initial active sentences, non-canonical/subject-initial passive sentences, and non-canonical/object-initial scrambled sentences. The patients preoperatively underwent a high-resolution 3D-MRI, and voxel-based lesion-symptom mapping was employed for the error rates data. We found that the patients with a lesion in L. F3op/F3t or L. LPMC showed differential patterns of condition-selective deficits in the comprehension of sentences. More specifically, the L. F3op/F3t-damaged patients had more profound deficits in the comprehension of non-canonical sentences, whereas the L. LPMC-damaged patients had more profound deficits in the comprehension of object-initial scrambled sentences. These results establish that a lesion in L. F3op/F3t or L. LPMC is sufficient to cause agrammatic comprehension.

1. Introduction

Since the first report of an aphasic patient by Paul Broca in 1861 (Broca, 1994; Signoret, Castaigne, Lhermitte, Abelanet, & Lavorel, 1984), the localization and lateralization of human language have been major issues in neurology, neuropsychology, and neurolinguistics. Broca's aphasia is characterized by non-fluent spontaneous speech with relative sparing of comprehension (Mesulam, 2000; Ingram, 2007), and is generally associated with damage to the pars opercularis (F3op, Brodmann area (BA) 44) and pars triangularis (F3t, BA 45) of the left inferior frontal gyrus (L. IFG). Some previous studies, however, have indicated that damage to L. IFG does not always cause traditional Broca's aphasia (Mohr et al., 1978; Kertesz, Harlock, & Coates, 1979), and the left insula has been proposed to be a crucial region for articulation deficits (Dronkers, 1996). On the other hand, patients with lesions in L. IFG show relatively good comprehension of single words and simple sentences, but show trouble understanding sentences with more complex syntactic structures, such as passive sentences and sentences with object relative clauses (Schwartz, Saffran, & Marin, 1980; Caplan, Baker, & Dehaut, 1985; Grodzinsky, 2000); this aspect of Broca's aphasia is called agrammatic comprehension (Goodglass & Menn, 1985; Menn & Obler, 1990; Pulvermüller, 1995). However, methodological problems have been raised (Badecker & Caramazza, 1985), and general processes of short-term memory or decision-making have been proposed to be disrupted in agrammatic comprehension (Just & Carpenter, 1992; Cupples & Inglis, 1993; Dick et al., 2001). Thus, specificity or reproducibility for agrammatic comprehension remains unclear and controversial. The present lesion study was motivated to examine and establish the presence of agrammatic comprehension.

Despite accumulating results from functional magnetic resonance imaging (fMRI) studies, it has also been far from conclusive whether L. IFG activation is due to any specific factors: e.g., syntactic processing (Dapretto & Bookheimer, 1999; Embick, Marantz, Miyashita, O'Neil, & Sakai, 2000), articulatory rehearsal (Cohen et al., 1997), and short-term memory demands (Fiebach,

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Schlesewsky, Lohmann, von Cramon, & Friederici, 2005). We have previously reported that both the left dorsal F3op/F3t (L. dF3op/dF3t) and lateral premotor cortex (L. LPMC) are selectively involved in syntactic judgment of sentences, even when compared with high-load verbal short-term memory (Hashimoto & Sakai, 2002), indicating the critical role of these left frontal regions in syntactic processing (Sakai, 2005). In our recent fMRI study with a picture–sentence matching task, we further examined the effect of sentence structures strictly controlling general cognitive demands such as the memory load (Kinno, Kawamura, Shioda, & Sakai, 2008), where a sentence was visually presented with a picture representing an action (Fig. 1; the same task and stimuli were used in the present study). The participants indicated whether or not the meaning of each sentence matched the action depicted by the corresponding picture. There were three main conditions with different sentence types: canonical/subject-initial active sentences (AS) (e.g., "○-*ga* □-*o oshiteru*", "○ *pushes* □"), non-canonical/subject-initial passive sentences (PS) (e.g., "□-*ga* ○-*ni osareru*", "□ *is affected by* ○*'s pushing it*"; see Kinno et al. (2008) for *ni* direct passive form), and non-canonical/object-initial scrambled sentences (SS) (e.g., "□-*o* ○-*ga oshiteru*", "*as for* □, ○ *pushes it*"; this form is allowed not only in Japanese but in German, Finnish, and other languages). Under these conditions, each sentence had a *transitive* verb and two arguments (phrases associated with the predicate) with different grammatical relations, i.e., which the subject (S) of a verb (V) is, and which its indirect object (IO) or direct object (DO) is. Sentence comprehension under each condition also explicitly required analysis of two different thematic roles, i.e., who initiates the action, and who is affected by it. In Japanese syntax, the grammatical relations are first marked by case markers (nominative, dative, or accusative in the present stimuli; Fig. 1), which in turn allow the assignment of thematic roles (*agent*, *experiencer*, or *patient*), whereas passiveness is also marked in the verb morphology (*-areru*). More specifically, the AS, PS, and SS sentences correspond to S–DO–V (*agent* and *patient*), S–IO–V (*experiencer* and *agent*), and DO–S–V (*patient* and *agent*) types, respectively. Therefore, these syntactic analyses for the two-argument relationships were critically required in our paradigm. In the fMRI study, we observed that activations in L. dF3t (extending to L. F3op) and L. LPMC were differentially modulated by these three main conditions. Because it is essential to correlate activation studies with the detailed analysis of lesion symptoms (Rorden & Karnath, 2004), our next goal was to directly clarify the functional roles of these two left frontal regions with a lesion-symptom mapping method. Based on the results from the previous neuroimaging studies, we predicted that the patients with a lesion in L. F3op/F3t or L. LPMC would show agrammatic comprehension.

We examined patients with a glioma especially in the left frontal cortex. The tumor locations covered the most of the left frontal regions and thus included L. F3op/F3t and L. LPMC. To examine the presence of agrammatic comprehension, it is crucial to use a task that is sensitive enough to extract *syntactic* components of linguistic judgment among the tested conditions. If such a task is effective enough, we expected that even the patients without apparent disabilities in verbal communication or intelligence would show condition-selective agrammatic comprehension. Our paradigm with three distinct syntactic conditions of AS, PS, and SS would be ideal for this purpose, because the same set of *actions* depicted by pictures was used under the main conditions, thus controlling *semantic* comprehension per se. Moreover, the contrasts among these three conditions differentially modified the activations of L. F3op/F3t and L. LPMC, with their respective contributions dynamically regulated by linguistic requirements (Kinno et al., 2008). To precisely localize the glioma, all patients underwent a high-resolution 3D-MRI on the same day as the task examination. All of these results were actually utilized for the preoperative evaluation of detailed language function and for planning a resection of glioma, thereby minimizing the risk of postoperative language deficits (Haglund, Ojemann, & Hochman, 1992). Because neurological data about the real roles of the left frontal regions in syntactic comprehension have been limited, the present examination would have both fundamental and clinical implications, which are useful for preserving the quality of life (QOL) for each patient.

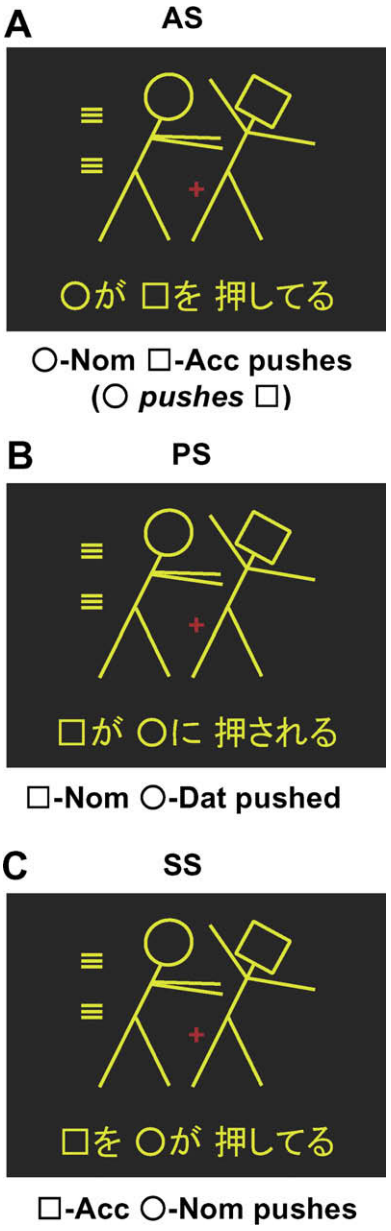

Fig. 1. The three main conditions used in the picture–sentence matching task. Each stimulus consisted of one picture (top) and one sentence (bottom). Pictures depicting actions consisted of two stick figures; each stick figure was distinguished by one of three "head" symbols: a circle (○), square (□), or triangle (Δ). The participants indicated whether or not the meaning of each sentence matched the action depicted in the corresponding picture by pressing one of two buttons. (A) Under the active sentence (AS) condition, canonical/subject-initial active sentences were presented ("○-*ga* □-*o oshiteru*"). Below each example, a word-by-word translation in English is shown. Nom, nominative case; Acc, accusative case; Dat, dative case. (B) Under the passive sentence (PS) condition, non-canonical/subject-initial passive sentences were presented ("□-*ga* ○-*ni osareru*"). (C) Under the scrambled sentence (SS) condition, non-canonical/object-initial scrambled sentences were presented ("□-*o* ○-*ga oshiteru*"). An identical picture set was used under these three conditions. The sentence stimuli were all grammatical and commonly used in Japanese.

2. Subjects and methods

2.1. Participants

All patients were native Japanese speakers newly diagnosed as having a glioma in the left frontal region, who were scheduled for surgery at the Department of Neurosurgery of Tokyo Women's Medical University. The following conditions comprised the criteria for inclusion of patients in the present study: (i) right-handedness, (ii) no deficits in verbal/written communication or other cognitive abilities reported by the patients or physicians, (iii) no history of neurological or psychiatric disorders other than glioma and seizures, (iv) freedom from seizures with or without antiepileptic drug, and (v) no medical problems for MRI acquisition. Twenty-one patients (Table 1) preoperatively underwent a high-resolution MRI scan and performed the picture–sentence matching task at the University of Tokyo, Komaba. The laterality quotient (LQ) was also determined by the Edinburgh handedness inventory (Oldfield, 1971). The verbal/non-verbal intelligence quotient (IQ) was assessed with the Japanese version of the WAIS-III (1997, 2006; Harcourt Assessment, Inc., San Antonio, TX, USA), including more general and demanding tests than the aphasic tests. All but one patient underwent amytal testing. Following injection of amytal, the patient counted numbers with both hands raised. As soon as the contralateral hemiplegia occurred, a picture naming task was used to determine hemispheric dominance, which was either left or bilateral. The tumor type and grade were postoperatively and pathologically diagnosed by the WHO Classification of Tumors of the Nervous System (2000). Using the same paradigm and parameters, we also tested 21 right-handed participants with no history of neurological or psychiatric disorders. These age-matched normal controls included 12 males and 9 females (age: 20–58; mean: 37 years). Informed consent was obtained from each participant after the nature and possible consequences of the studies were explained. Approval for the experiments was obtained from the institutional review board of the University of Tokyo, Komaba.

2.2. Stimuli

Each visual stimulus consisted of a picture at the top and a Japanese sentence at the bottom (Fig. 1). The pictures used for AS, PS, and SS were identical (the number of lines used in each picture, mean ± SD: 14 ± 2.4, $n = 6$). There was one sentence control (SC) condition with *intransitive* verbs (e.g., "□-*to* Δ-*ga hashitteru*", "□ *and* Δ *run*") and equally complex pictures (14 ± 2.5, $n = 6$), which were all different from those used under the three main conditions. Half of the pictures depicted action occurring from left to right, and the other half depicted action from right to left. In the pictures, the use of symbols was also counterbalanced for both sides within each condition.

The sentences describing actions were written in a combination of the "hiragana" and "kanji" writing systems, and all sentence stimuli were grammatical in Japanese. Each sentence included two noun phrases and one verb; for example, a noun phrase (□-*ga*) consisted of a symbol (□) and a hiragana (*ga*). Two sets of Japanese verbs (six transitive verbs: *pull*, *push*, *scold*, *kick*, *hit*, and *call*; and six intransitive verbs: *lie*, *stand*, *walk*, *run*, *tumble*, and *cry*) were used, each of which, including the passive forms, had either four or five syllables. Note that the verb "*call*" is used only as a transitive verb in Japanese. There was no significant difference in frequency between the two sets of verbs (t (10) = .7, $p = .5$), according to the Japanese lexical database ("Nihongo-no Goitokusei" (Lexical Properties of Japanese), Nippon Telegraph and Telephone Corporation Communication Science Laboratories, Tokyo, Japan, 2003). We prepared eight stimuli for each verb; there were 48 stimuli for each condition.

All stimuli were presented visually in yellow against a dark background. Each stimulus was presented for 5800 ms followed by a 200 ms blank interval, which was ample time for the patients (see Table 2). For fixation, a red cross was also shown at the center of the screen. Stimulus presentation and behavioral data collection were controlled using the LabVIEW software and interface (National Instruments, Austin, TX, USA).

Table 1
Characteristics of patients in the present study.

Patient	Gender	Age	LQ	Verbal/non-verbal IQ	Hemispheric dominance	Tumor location	Tumor volume	Tumor type	Tumor grade
L. F3op/F3t-damaged patients									
PT1	F	42	90	95/109	Left	L. F2/F3op/F3t/F3O/insula	74,524	OA	II
PT2	M	29	100	94/100	Left	L. F2/F3op/F3t/insula/striatum	122,535	AOA	III
PT3	F	38	87	111/116	Left	L. F3op/F3t/F3O/insula/striatum	48,901	OD	II
PT4	F	34	75	101/96	–	L. F3op/F3t/F3O/insula/striatum	32,353	OD	II
PT5	M	47	73	93/100	Left	L. F3op/F3t/insula/striatum	18,107	DA	II
L. LPMC-damaged patients									
PT6	M	47	81	105/102	Left	L. F1/F2/SMA/LPMC/F3op	33,139	AOA	III
PT7	M	36	88	102/92	Left	L. F1/SMA/F2/LPMC/F3op	89,172	AA	III
PT8	M	35	89	97/94	Left	L. F1/SMA/F2/LPMC/F3op	87,331	PNET	IV
PT9	F	27	45	101/95	Left	L. F2/LPMC/F3op	22,497	DA	II
PT10	M	36	89	109/98	Left	L. F2/LPMC/F3op	17,948	AOA	III
PT11	M	36	100	84/92	Left	L. LPMC/F3op/insula	31,055	DA	II
Other patients									
PT12	M	25	100	99/101	Left	L. F1/SMA	30,863	OA	II
PT13	F	62	89	98/101	Left	L. F1/F2/SMA	49,285	AOD	III
PT14	M	24	89	115/97	Left	L. F1/F2/SMA/striatum	143,361	OA	II
PT15	F	38	100	106/113	Left	L. F1/F2/striatum	151,819	AOA	III
PT16	F	29	100	86/88	Left	L. F1/F2/F3t/F3O/striatum	48,901	AOD	III
PT17	F	31	100	106/100	Left	L. F1/F2/F3t	45,381	DA	II
PT18	M	31	100	97/98	Left	L. F1/F2	24,920	AOA	III
PT19	M	49	100	105/100	Left	L. F3t/F3O/insula/striatum	15,255	AOA	III
PT20	M	32	100	90/99	Left	L. F3O/insula/striatum	27,358	OA	II
PT21	F	36	100	84/88	Bilateral	L. F3O/striatum	17,710	OA	II
Mean		36	90	99/99			53,925		

Normalized images were used for determination of tumor location and volume (mm^3). IQ, intelligence quotient; LQ, laterality quotient. The determination of tumor types and grades (I–IV, IV as severest) was based on the WHO Classification of Tumors of the Nervous System (2000). *Abbreviations used:* AA, anaplastic astrocytoma; AOA, anaplastic oligoastrocytoma; AOD, anaplastic oligodendroglioma; DA, diffuse astrocytoma; OA, oligoastrocytoma; OD, oligodendroglioma; PNET, primitive neuroectodermal tumor.

2.3. Tasks

In the picture–sentence matching task (Fig. 1), the participants read a sentence silently and indicated whether or not the meaning of each sentence matched the action of the corresponding picture by pressing one of two buttons. For AS, PS, and SS, all mismatched sentences were made by exchanging two symbols in the original sentences, e.g., "□ *pushes* ○" instead of "○ *pushes* □". For SC, symbol-mismatched and action-mismatched sentences were presented equally often, requiring the sentences to be read completely in order for the participants to arrive at a correct judgment.

In addition to the picture–sentence matching task, we used a visual control task (VC), which required neither word nor sentence processing, as a baseline condition (Kinno et al., 2008). For VC, the same sets of pictures used in the picture–sentence matching task were presented, together with a string of jumbled letters taken from a single sentence in which the symbols (○, □, or Δ) and "kanji" appeared at the same positions in the string as in the picture–sentence matching task. The participants were asked to judge whether or not all the symbols in a letter string were the same as those in the picture, irrespective of the order of the symbols. The participants underwent practice sessions before testing to become fully familiarized with the tasks.

A single run of the testing sessions contained 24 "trial events" of the picture–sentence matching task (six times each for AS, PS, SS, and SC), with variable inter-trial intervals of 6 and 12 s (one and two VC, respectively), pseudorandomized within a run. Since meaningless letter strings were presented throughout VC while sentences were presented only in the trial events, the participants could switch from VC to the trial events according to the stimulus type. The order of AS, PS, SS, and SC was pseudorandomized in each run to prevent any condition-specific strategy. Eight runs were tested in a day per one participant. Half of the stimuli consisted of matched picture–sentence pairs (24 trials for each condition), and the other half consisted of mismatched pairs (24 trials for each condition). All patients underwent the testing sessions inside the scanner while they received three to six fMRI runs, and then they completed the rest of the eight runs outside the scanner. Because the number of fMRI runs was limited by the patients' medical conditions, here we focused on the behavioral data and the anatomical MRI scans alone. All of the behavioral data from normal controls were acquired outside the scanner.

2.4. MRI data acquisition and analyses

The MRI scans were conducted on a 1.5 T scanner (Stratis II, Premium; Hitachi Medical Corporation, Tokyo, Japan), and a high-resolution T1-weighted 3D image (repetition time: 30 ms, acquisition time: 8 ms, flip angle: 60°, field of view: 192 × 192 mm^2, resolution: .75 × .75 × 1 mm^3) was acquired for each patient. The location of the glioma was first identified on this MR image, and the glioma boundary was semi-automatically determined using MRIcro software (http://www.mricro.com/) (Rorden & Brett, 2000). T2-weighted MR images (Department of Neurosurgery of Tokyo Women's Medical University) and positron-emission tomography (PET) data (Chubu Medical Center for Prolonged Traumatic Brain Dysfunction, Mino-Kamo-shi, Japan) were also used to assist the precise determination of the boundary. The circumscribed region of the glioma was then used as a blank mask to restrict the estimation of the normalization parameters to the healthy tissue (cost-function masking; http://www.sph.sc.edu/comd/rorden/mritut.html) (Brett, Leff, Rorden, & Ashburner, 2001). Individual brain images were then spatially normalized to the standard brain space as defined by the Montreal Neurological Institute, which was resampled to 1 × 1 × 1 mm^3 voxel size using

Table 2
Behavioral data under each condition.

Participant	Error rates (%)				RTs (ms)			
	AS	PS	SS	SC	AS	PS	SS	SC
L. F3op/F3t-damaged patients								
PT1	8.3 (4.2)	16.7 (25.0)	16.7 (25.0)	4.2 (4.2)	3512	3227	3657	2011
PT2	27.1 (25.0)	39.6 (33.3)	54.2 (58.3)	6.3 (4.2)	2138	2203	2799	1831
PT3	27.1 (29.2)	39.6 (29.2)	50.0 (54.2)	8.3 (12.5)	3269	3331	3073	2243
PT4	0 (0)	27.1 (25)	39.6 (45.8)	4.2 (4.2)	3325	2439	2268	2305
PT5	0 (0)	8.3 (8.3)	8.3 (8.3)	4.2 (4.2)	3673	3620	3642	3394
L. LPMC-damaged patients								
PT6	12.5 (20.8)	12.5 (12.5)	66.7 (70.8)	6.3 (4.2)	4334	4436	4549	2739
PT7	16.7 (20.8)	6.3 (8.3)	54.2 (58.3)	6.3 (8.3)	2971	3030	3093	2486
PT8	14.6 (12.5)	16.7 (12.5)	54.2 (58.3)	4.2 (4.2)	2764	3163	3063	2646
PT9	0 (0)	0 (0)	20.8 (16.7)	2.1 (0)	4048	4154	4248	2945
PT10	27.1 (29.2)	31.3 (29.2)	81.3 (79.1)	8.3 (8.3)	2488	2573	2621	1746
PT11	8.3 (12.5)	8.3 (8.3)	54.2 (54.2)	0 (0)	2944	2420	2647	2043
Other patients								
PT12	0 (0)	0 (0)	0 (0)	0 (0)	3436	3567	3420	2047
PT13	8.3 (8.3)	6.3 (8.3)	6.3 (8.3)	6.3 (8.3)	3867	4085	3619	3159
PT14	0 (0)	0 (0)	0 (0)	0 (0)	1759	1848	1749	1322
PT15	0 (0)	0 (0)	0 (0)	0 (0)	2609	2881	2669	2111
PT16	0 (0)	0 (0)	0 (0)	0 (0)	3867	4085	3619	3159
PT17	2.1 (4.2)	2.1 (0)	6.3 (4.2)	4.2 (0)	3860	3753	4062	2716
PT18	0 (0)	4.2 (4.2)	14.6 (4.2)	8.3 (12.5)	2702	3128	3326	2153
PT19	14.6 (16.7)	14.6 (16.7)	16.7 (12.5)	4.2 (0)	3856	4223	4432	2954
PT20	0 (0)	0 (0)	0 (0)	0 (0)	3410	3263	3312	2642
PT21	6.3 (8.3)	6.3 (12.5)	6.3 (8.3)	8.3 (8.3)	2795	2921	2969	2063
Mean	*8.2 ± 9.7	*11.4 ± 12.9	*26.2 ± 26.3	4.1 ± 3.1	3220 ± 670	3255 ± 716	3278 ± 708	2415 ± 533
Controls	3.4 ± 4.2	3.5 ± 3.8	3.3 ± 4.4	3.2 ± 3.7	2958 ± 727	2998 ± 648	3123 ± 583	2114 ± 608

Error rates and RTs (for correct trials only) are shown as mean ± SD. The consistency between the error rates (%) of all trials (in 48 trials for each condition) and those of matched trials in brackets (in 24 trials for each condition) indicates similar errors in both matched and mismatched trials. Asterisks denote significant differences between the performances of the patients and normal controls at $p < .05$.

statistical parametric mapping SPM2 software (Wellcome Department of Cognitive Neurology, London, UK) (Friston et al., 1995) on MATLAB (Math Works, Natick, MA, USA).

Using the resulting individually normalized images, we next employed voxel-based lesion-symptom mapping (VLSM; http://crl.ucsd.edu/vlsm) to analyse the relationship between glioma location and the error rates on a voxel-by-voxel basis (Bates et al., 2003). The patients were divided into two groups according to whether they did or did not have a glioma including that voxel. The error rates for each condition or the difference in error rates between two conditions (e.g., PS – AS) were then compared for these two groups by a *t*-test, in which the statistical threshold was set to $p = .05$ after correction for multiple comparisons using the false discovery rate (FDR). To minimize the effects of outlier observations, the voxels used in the VLSM analysis were within the gliomas of at least two patients. Finally, the result of VLSM was projected onto a standard brain using MRIcro software.

3. Results

In our paradigm with three main conditions of AS, PS, and SS, under which two-argument relationships were critically required (see the Introduction), the same set of actions depicted by pictures was used, thus controlling semantic comprehension per se. In contrast, a different set of pictures were used under the SC condition (e.g., "□ *and* Δ *run*"), which basically required matching between words (symbols and verbs) and pictures alone, *without* syntactic analyses for the two-argument relationships. Thus, the SC condition was syntactically less complex and easier to comprehend than other conditions. It was therefore mandatory to analyse the three main conditions and SC separately. Moreover, the analyses also match with our fMRI study (Kinno et al., 2008), in which SC was used as a separate control. In Sections 3.1–3.4, we focus on the main conditions of AS, PS, and SS, and the results of SC are presented in Section 3.5.

3.1. Behavioral analyses

The error rates for the patients and the normal controls are shown in Table 2. A repeated-measures analysis of variance (rANOVA) with two factors (group [patients and normal controls] × condition [AS, PS, and SS]) revealed significant main effects of group ($F(1, 40) = 12$, $p = .0011$) and condition ($F(2, 80) = 13$, $p < .0001$), as well as a significant interaction of group by condition ($F(2, 80) = 14$, $p < .0001$). The patients showed significantly higher error rates than the normal controls for each of AS, PS, and SS (*t*-test; AS: $t\ (40) = 2.1$, $p = .046$; PS: $t\ (40) = 2.7$, $p = .011$; SS: $t\ (40) = 3.9$, $p = .0003$). According to paired *t*-tests on the three main conditions, the patients' error rates were significantly higher for SS than for AS and PS (AS: $t\ (20) = 4.2$, $p = .0005$; PS: $t\ (20) = 3.4$, $p = .0026$), whereas there was no significant difference between AS and PS ($t\ (20) = 1.9$, $p = .07$). However, there was no significant difference among the normal controls' error rates under the main conditions ($p > .7$).

The reaction times (RTs) for the patients and the normal controls are also shown in Table 2. An rANOVA with two factors (group [patients and normal controls] × condition [AS, PS, and SS]) showed that neither a main effect of group ($F(1, 40) = 1.3$, $p = .3$) nor that of condition was significant ($F(2, 80) = 2.3$, $p = .1$), with no significant interaction of group by condition ($F(2, 80) = .66$, $p = .5$). There was no significant difference in RTs between these groups for each condition ($p > .1$). According to paired *t*-tests on the three main conditions, there was no significant difference in RTs of the patients ($p > .4$). The normal controls showed significantly longer RTs for SS than for AS ($t\ (20) = 2.2$, $p = .044$), whereas there was no significant difference between AS and PS, as well as between PS and SS ($p > .1$). Because there was a significant main effect of condition regarding the error rates, the error rates were better indicators than RTs for estimating condition-selective effects.

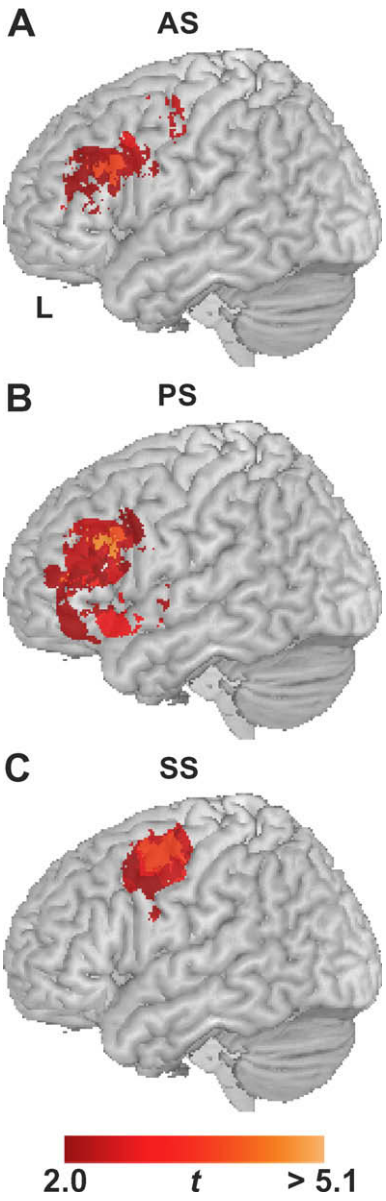

Fig. 2. Results from VLSM analyses for the three main conditions. (A–C) Brain regions identified by the VLSM analysis among the left frontal-damaged patients ($n = 21$) for AS, PS, and SS, respectively. The resultant *t*-map is projected on the left (L) lateral surface; the threshold was established at $t > 2.0$ (FDR corrected $p < .05$).

The error rates of the patients for the three main conditions (Table 2) were not significantly affected by the picture–sentence consistency, as indicated by the comparison (paired *t*-test, $p > .1$) between matched (AS: 9.1 ± 10.5%; PS: 11.1 ± 11.2%; SS: 27.0 ± 27.8%) and mismatched trials (AS: 7.3 ± 9.6%; PS: 11.7 ± 15.4%; SS: 25.4 ± 25.4%). It should be noted that these significant errors were observed in spite of the patient's normal verbal and non-verbal IQs (Table 1; range: 84–116 within about 1 SD of ± 15; one sample *t*-test for the difference from 100: verbal, $t\ (20) = .56$, $p = .6$ and non-verbal, $t\ (20) = .65$, $p = .5$). According to correlation analyses, the large individual differences for the three main conditions (Table 2; note the larger SDs for the three main conditions than for SC) could not be attributed to their ages,

verbal/non-verbal IQs, or tumor volumes ($p > .1$). It is thus likely that the tumor locations affected the actual performance of the three main conditions.

3.2. VLSM analyses for each sentence condition

To identify any critical regions for the main conditions of AS, PS, and SS, we first conducted VLSM analyses, in which error rates for each condition were evaluated among the left frontal-damaged patients ($n = 21$). We found that significantly higher error rates for AS were associated with lesions in L. IFG, including L. dorsal F3op/F3t, as well as isolated lesions in L. LPMC (Fig. 2A). Moreover, significantly higher error rates for PS were associated with lesions in L. dorsal F3op/F3t, further extending to ventral F3op/F3t (Fig. 2B). In contrast, significantly higher error rates for SS were associated with lesions in L. LPMC alone (Fig. 2C). These results indicate that both of L. F3op/F3t and L. LPMC are the critical regions for AS, PS, and SS.

3.3. VLSM analyses for non-canonical sentence conditions

Next we examined which regions were critically involved in the comprehension of syntactically complex sentences. For this purpose, we conducted VLSM analyses, in which the *difference* in error rates between the conditions of non-canonical vs. canonical sentences, i.e., PS – AS or SS – AS, was evaluated among the left frontal-damaged patients. We found that the significantly larger difference in PS – AS was associated with lesions in L. ventral F3op/F3t (Fig. 3A). Moreover, it is striking to note that L. ventral F3op/F3t identified by the present study spatially overlapped with L. dorsal F3t (extending to ventral F3op) reported by our fMRI study in PS – AS (Kinno et al., 2008). In contrast, we found that the significantly larger difference in SS – AS was associated with lesions in L. LPMC (Fig. 3B), which spatially overlapped with L. LPMC reported previously by our fMRI study in SS – AS (Kinno et al., 2008). These results indicate that both of L. F3op/F3t and L. LPMC are critically involved in the comprehension of syntactically complex sentences.

3.4. Condition-selectivity in error rates for L. F3op/F3t- or L. LPMC-damaged patients

We further examined the condition-selectivity in error rates for the patients, who were divided into three groups based on tumor locations (Table 1): L. F3op/F3t-damaged patients ($n = 5$; Fig. 4A), L. LPMC-damaged patients ($n = 6$; Fig. 4C), and other patients ($n = 10$; Fig. 4E). Its criterion was whether or not a glioma of each patient overlapped, at least partially on a voxel-by-voxel basis, with the region identified by the VLSM analyses in PS – AS or SS – AS (red to orange region in Fig. 3A or B). The other patients had a glioma in either L. F1 or L. F3O, but sparing L. F3op and L. LPMC (Table 1). One patient of this group (PT19 in Table 2) showed non-selective deficits for all of AS, PS, and SS. When the fMRI results in PS – AS or SS – AS (blue region in Fig. 3A or B) were used to assign the patient groups, the three patient groups of all but one patient (PT10) were identical to those determined by the VLSM results; the glioma of this patient overlapped with functionally determined L. F3op/F3t and L. LPMC. It is notable that this patient showed the severest deficits under the three main conditions (Table 2).

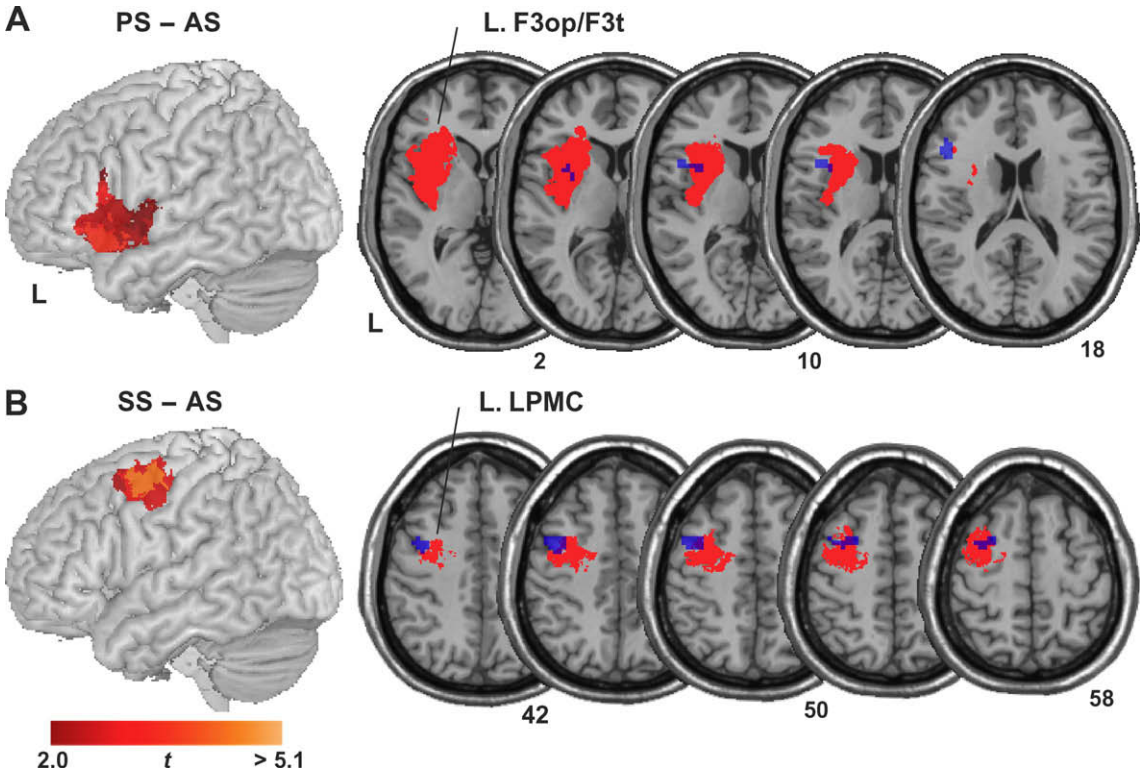

Fig. 3. Results from VLSM analyses for non-canonical sentence conditions. (A) Brain regions identified by the VLSM analysis among the left frontal-damaged patients ($n = 21$) in PS – AS. The resultant t-map is projected on the left (L) lateral surface. The axial slices demonstrate the spatial overlap between L. F3op/F3t identified by the present study (red to orange) and that reported by our fMRI study in PS – AS (blue) (Kinno et al., 2008). (B) Brain regions identified by the VLSM analysis in SS – AS. The axial slices demonstrate the spatial overlap between L. LPMC identified by the present study (red to orange) and that reported by our fMRI study in SS – AS (blue) (Kinno et al., 2008).

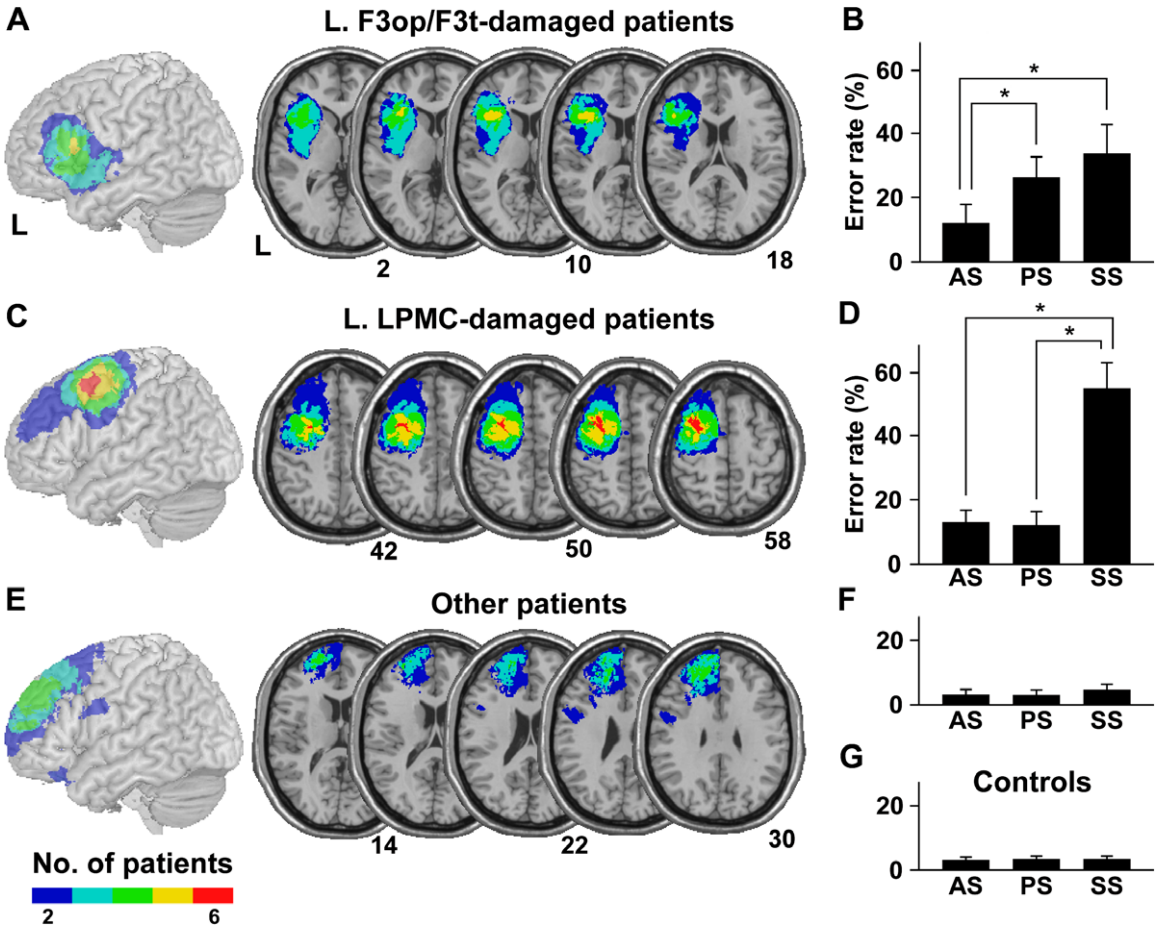

Fig. 4. Condition-selectivity in error rates for L. F3op/F3t- or L. LPMC-damaged patients. (A, C, and E) The lesion overlap map in the L. F3op/F3t-damaged patients ($n = 5$), the L. LPMC-damaged patients ($n = 6$), and the other patients ($n = 10$), respectively (Table 1). The color scale denotes the number of patients. (B, D, F, and G) Histograms for the error rates of the L. F3op/F3t-damaged patient, the L. LPMC-damaged patients, the other patients, and the normal controls ($n = 21$), respectively. Error bars indicate the SEM, and asterisks denote $p < .05$.

The error rates of each of the three groups are shown in Fig. 4B, D, and F; those of the normal controls are shown in Fig. 4G. An rANOVA with two factors (group [L. F3op/F3t-damaged patients, L. LPMC-damaged patients, and other patients] × condition [AS, PS, and SS]) revealed significant main effects of group ($F(2, 18) = 11$, $p = .0006$) and condition ($F(2, 36) = 88$, $p < .0001$), as well as a significant interaction of group by condition ($F(4, 36) = 39$, $p < .0001$). These results suggest that these three groups can be characterized by condition-selectivity in error rates.

For the L. F3op/F3t-damaged patients, paired t-tests among the three main conditions showed that these patients' error rates were significantly higher for PS and SS than AS (PS vs. AS: $t(4) = 4.1$, $p = .015$; SS vs. AS: $t(4) = 3.6$, $p = .023$), whereas there was no significant difference between PS and SS ($t(4) = 2.4$, $p = .08$) (Fig. 4B). These results suggest that the L. F3op/F3t-damaged patients had more profound deficits in the comprehension of non-canonical sentences. For the L. LPMC-damaged patients, on the other hand, paired t-tests showed that these patients' error rates were significantly higher for SS than AS and PS (SS vs. AS: $t(5) = 8.1$, $p = .0005$; SS vs. PS: $t(5) = 8.6$, $p = .0004$), whereas there was no significant difference between AS and PS ($t(5) = .039$, $p = .7$) (Fig. 4D). These results suggest that the L. LPMC-damaged patients had more profound deficits in the comprehension of object-initial scrambled sentences. In contrast, for the other patients, there was no significant difference among the three main conditions regarding these patients' error rates ($p > .2$) (Fig. 4F).

When compared with the normal controls, significantly higher error rates for AS, PS, and SS were observed for the L. F3op/F3t-damaged patients (AS: $t(24) = 2.6$, $p = .014$; PS: $t(24) = 6.8$, $p < .0001$; SS: $t(24) = 6.6$, $p < .0001$), as well as for the L. LPMC-damaged patients (AS: $t(25) = 3.8$, $p = .0009$; PS: $t(25) = 3.2$, $p = .0036$; SS: $t(25) = 12$, $p < .0001$). These results suggest that both of these patient groups had deficits in syntactic analyses for the two-argument relationships. In contrast, the other patients showed no significant difference in error rates under the main conditions when compared with the normal controls ($p > .4$). The other patients' normal performances indicate that neither medical condition nor the difference in testing condition (inside or outside the scanner) affected the performance. This result is thus complementary with the agrammatic comprehension caused by a glioma in L. F3op/F3t or L. LPMC, in that the patients with intact L. F3op/F3t and L. LPMC had normal syntactic comprehension of sentences.

3.5. The analyses of the SC condition

We compared the performance data for SC between all patients and the normal controls to examine whether or not such basic comprehension of sentences was affected for the patients. The patients showed no significant difference in error rates for SC when compared with the normal controls ($t(40) = .64$, $p = .5$) (Table 2). Regarding RTs for SC, there was no significant difference between the patients and normal controls ($t(40) = 1.3$, $p = .2$). Moreover, paired t-tests showed that the patients' error rates were

significantly lower for SC than for AS, PS, and SS (AS: t (20) = 2.4, p = .028; PS: t (20) = 3.0, p = .0076; SS: t (20) = 4.1, p = .0006), whereas the normal controls' error rates for SC were not significantly different from those for the three main conditions (p > .7). For both the patients and normal controls, RTs were significantly shorter for SC than for the three main conditions (all, p < .0001).

Some patients' error rates were about 10% for SC, but VLSM analyses showed that error rates for SC were not significantly associated with any lesions in the left frontal regions. An ANOVA with one factor of group [L. F3op/F3t-damaged patients, L. LPMC-damaged patients, and other patients] showed no significant main effect of group (F(2, 18) = 1.0, p = .4). Moreover, each of these three groups showed no significant difference in error rates for SC when compared with the normal controls (p > .3). These results indicate that basic comprehension of sentences under the SC condition was preserved among the patients.

4. Discussion

The present study with the picture–sentence matching task successfully clarified that both of L. F3op/F3t and L. LPMC are the critical regions for AS, PS, and SS (Fig. 2), and that both regions are indeed critically involved in the comprehension of syntactically complex sentences (Fig. 3). It is striking to note that these brain regions identified by the present study spatially overlapped with those reported by our fMRI study (Kinno et al., 2008). The patients with a lesion in either L. F3op/F3t or L. LPMC had significant deficits in syntactic analyses for the two-argument relationships required for the three main conditions, but without deficits in any factors required for SC. When the patients were divided into groups based on tumor locations, the L. F3op/F3t-damaged patients had more profound deficits in the comprehension of non-canonical sentences for both PS and SS (Fig. 4B), whereas the L. LPMC-damaged patients had more profound deficits in the comprehension of object-initial scrambled sentences for SS (Fig. 4D). These differential patterns of condition-selective deficits are indeed consistent with the distinct activation patterns in L. F3op/F3t or L. LPMC shown by our fMRI study (Kinno et al., 2008). These results provide direct evidence that L. F3op/F3t and L. LPMC subserve syntactic comprehension.

The condition-selectivity in error rates for the patients with a lesion in either L. F3op/F3t or L. LPMC cannot be explained by general disorders of the patients, including visual/memory/motor impairment, attention disturbance due to drowsiness or dizziness, and perseveration for a particular sentence type. It is natural to assume that the patients with normal verbal IQ would not otherwise experience or exhibit difficulty in language comprehension with such simple sentences; however the patients indeed exhibited clear deficits even for canonical sentences for AS in the present study. In daily conversation, pragmatic information about word use resolves syntactic difficulty (e.g., "*The officer chased the thief*" is more acceptable than "*The thief chased the officer*."). The use of appropriate syntactic judgment tests is thus necessary for a proper assessment of syntactic comprehension. The present results are also consistent with another recent fMRI study, in which both L. dF3t and L. LPMC were selectively activated for the syntactic comprehension of honorification, in which two-argument relationships of either subject honorifics or object honorifics were critically involved (Momo, Sakai, & Sakai, 2008). Further research is required for understanding both anatomical and functional bases for the differential roles of these two critical regions.

In the present study, the L. F3op/F3t-damaged patients showed deficits in syntactic analyses for the two-argument relationships including active, passive, and scrambled sentences. More specifically, these patients showed more profound deficits in the comprehension of non-canonical sentences for PS and SS than that of canonical sentences for AS (Fig. 4B). It is widely assumed in theoretical as well as in experimental linguistics that not only scrambling but also passivization is a purely syntactic operation. It is true that different grammatical theories include different ways of implementing the distinctions between these two types of syntactic operations: e.g., syntactic movement in Government and Binding Theory/Minimalist Program (Chomsky, 1995), type of linking in Lexical-Functional Grammar (Bresnan, 2001), and structure to meaning mapping in Role and Reference Grammar (Van Valin, Jr. & LaPolla, 1997). However, these theories commonly assume a direct relation between the syntactic operations and the underlying syntactic structures. Our present findings agree well with the account of sentence processing proposed in contemporary linguistics, and thus we conclude that the deficits of the L. F3op/F3t-damaged patients are purely syntactic in nature, i.e., agrammatic comprehension. Therefore, the critical role of the L. F3op/F3t, such that a lesion in this region alone sufficiently causes selective deficits in syntactic comprehension, is now established.

The L. LPMC-damaged patients also exhibited deficits in syntactic analyses for the two-argument relationships. More specifically, these patients showed more profound deficits in the comprehension of object-initial scrambled sentences for SS than that of subject-initial sentences for AS and PS (Fig. 4D). The ignorance of case markers or the persistent semantic analysis regarding the first noun as an agent, irrespective of sentence type, cannot explain the less impaired performance of these patients for AS and PS. One explanation for this SS-selective impairment is that the building of syntactic structures might be unimpaired but that the derivation of the corresponding meaning, i.e., its interpretation, is affected by a glioma in L. LPMC. Along with this line, a linguistic operation at the syntax-semantic interface has been proposed, such that the feature of animacy (Grewe et al., 2006) or an argument hierarchy (Bornkessel, Zysset, Friederici, von Cramon, & Schlesewsky, 2005) is related to this operation. However, the L. LPMC-damaged patients showed significantly higher error rates not only for SS but for AS and PS than the normal controls (Fig. 4D and G), even under the conditions without scrambling and thus with little load of such a linguistic operation. Alternatively, we propose that the SS-selectivity is due to difficulty in the basic syntactic analysis of structurally more complex sentences (Saito & Fukui, 1998), and that AS and PS are also under the control of such a general syntactic analysis. This possibility provides further support for agrammatic comprehension associated with a lesion in L. LPMC.

It has been long believed that not only the left frontal cortex but the left temporal cortex is also involved in sentence comprehension. In our fMRI study with the same paradigm, we have reported that a localized activation in the left posterior superior/middle temporal gyrus (L. pSTG/MTG) was also enhanced for SS when compared with AS and PS (Kinno et al., 2008). Other fMRI studies have also reported that this region was activated by contrasting object-initial vs. subject-initial sentences (Bornkessel et al., 2005), as well as by contrasting sentences with syntactic/semantic anomaly and normal sentences (Suzuki & Sakai, 2003). It is thus possible that a lesion in L. pSTG/MTG also results in the SS-selective deficit. A recent intraoperative electrocorticography study in humans showed bidirectional connectivity between L. IFG and L. pSTG/MTG (Matsumoto et al., 2004), and additional evidence for this connectivity has been reported in studies using MRI to investigate structural connectivity (Catani, Jones, & Ffytche, 2005; Friederici, Bahlmann, Heim, Schubotz, & Anwander, 2006). Therefore, it is possible that this network subserves syntactic integration, thereby combining multiple linguistic information. Further lesion studies are required to examine whether or not a lesion in the left temporal region is sufficient to cause deficits in such a linguistic process.

Compared with a cerebrovascular disease such as an infarct or a hemorrhage, a glioma has both advantages and disadvantages in neuropsychological and neurolinguistic research. First, it is advantageous that the location of a glioma is basically random in the cerebrum and not restricted by the cerebrovascular distribution. Indeed, damage to the middle cerebral artery affects the perisylvian cortex including F3op/F3t, but it spares more dorsal regions including LPMC. Using the lesion data with a glioma, we successfully showed the functional roles of L. F3op/F3t and L. LPMC. Second, the precise determination of the location and extent of a glioma is often difficult, because a glioma may induce edemas, abnormalities by compressing its peripheral region, and infiltration. In the present study, we used both T2-weighted MR images and PET data, which enabled us to determine precise boundary of lesions including brain edemas and abnormalities of perfusion. Third, some neural functions may be still preserved within a glioma, as indicated by cortical stimulation and fMRI studies (Ojemann, Miller, & Silbergeld, 1996; Krainik et al., 2003). It has been also reported that patients with tumors in the left hemisphere showed less language impairment than their counterparts with stroke (Anderson, Damasio, & Tranel, 1990). In the present study, however, we regarded an entire glioma as a lesion, and clear language deficits were observed despite such residual functions. Fourth, the onset and time course of a glioma is difficult to determine; a glioma develops gradually without apparent symptoms such as hemiplegia or dysarthria. In the present study, the patients were at least 24 years old at their start of medication (Table 1), and had no prior history of benign or malignant brain tumors, indicating an adult-onset glioma. For evaluating the real function of a cortical region, it is thus important to correlate the lesion symptom data with the functional neuroimaging data from normal controls.

It has been recently demonstrated that slow-growing lesions like WHO grade II gliomas, but not high-grade gliomas, may induce cortical reorganization even before operation (Desmurget, Bonnetblanc, & Duffau, 2007). Moreover, the grade II gliomas undergo anaplastic transformation over the years, i.e., the progression into grade III gliomas (Behin, Hoang-Xuan, Carpentier, & Delattre, 2003), which may be enough time for cortical reorganization. Such a functional reshaping might affect the observation of the present study, because the tumor types of the patients (Table 1) were heterogeneous including WHO grade II ($n = 11$), III ($n = 9$), and IV ($n = 1$) gliomas, with different biological processes for each tumor. However, it should be noted that the patients with a glioma in either L. F3op/F3t or L. LPMC showed marked deficits in syntactic comprehension, which had not been rescued by any functional reshaping. It is possible that the reorganization of other cortical regions due to a lesion in L. F3op/F3t or L. LPMC is entirely different each other, thus leading to the differential patterns of condition-selective deficits. This possibility also explains some deviations between the error rate patterns in the present study (Fig. 4B and D) and the activation patterns in our previous fMRI study (Fig. 5A and C of Kinno et al., 2008). Further functional neuroimaging studies for brain-damaged patients are required to clarify real mechanisms of cortical reorganization.

While a glioma in the cerebral cortex causes a deficit in cognitive function, the severity and course of such a dysfunction need to be thoroughly assessed (Wefel, Kayl, & Meyers, 2004). An extensive study of tumors with multiple neuropsychological tests have confirmed that patients with left hemispheric tumors exhibited poorer verbal fluency and verbal learning than those with right hemispheric tumors (Hahn et al., 2003). The present study demonstrated the severity of dysfunction, such that a glioma in L. F3op/F3t and/or L. LPMC can cause deficits in syntactic comprehension almost at a chance level. Our language task would be thus sensitive enough and useful for a general assessment of linguistic knowledge. Our findings further indicate that brain surgery for a glioma in the left frontal cortex requires careful assessment for maintaining syntactic abilities, which are indeed the source of the creative faculty for producing infinite expressions (Hauser, Chomsky, & Fitch, 2002), and thus for ensuring the best possible QOL for individual patients.

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References

Anderson, S. W., Damasio, H., & Tranel, D. (1990). Neuropsychological impairments associated with lesions caused by tumor or stroke. *Archives of Neurology, 47*, 397–405.

Badecker, W., & Caramazza, A. (1985). On considerations of method and theory governing the use of clinical categories in neurolinguistics and cognitive neuropsychology: The case against agrammatism. *Cognition, 20*, 97–125.

Bates, E., Wilson, S. M., Saygin, A. P., Dick, F., Sereno, M. I., Knight, R. T., et al. (2003). Voxel-based lesion-symptom mapping. *Nature Neuroscience, 6*, 448–450.

Behin, A., Hoang-Xuan, K., Carpentier, A. F., & Delattre, J.-Y. (2003). Primary brain tumours in adults. *Lancet, 361*, 323–331.

Bornkessel, I., Zysset, S., Friederici, A. D., von Cramon, D. Y., & Schlesewsky, M. (2005). Who did what to whom? The neural basis of argument hierarchies during language comprehension. *Neuroimage, 26*, 221–233.

Bresnan, J. (2001). *Lexical-functional syntax*. Malden, MA: Blackwell Publishers.

Brett, M., Leff, A. P., Rorden, C., & Ashburner, J. (2001). Spatial normalization of brain images with focal lesions using cost function masking. *Neuroimage, 14*, 486–500.

Broca, P. (1994). Notes on the site of the faculty of articulated language, followed by an observation of aphemia. In P. Eling (Ed.), *Reader in the history of aphasia: From Franz Gall to Norman Geschwind* (pp. 41–49). Amsterdam: John Benjamins Publishing Company.

Caplan, D., Baker, C., & Dehaut, F. (1985). Syntactic determinants of sentence comprehension in aphasia. *Cognition, 21*, 117–175.

Catani, M., Jones, D. K., & Ffytche, D. H. (2005). Perisylvian language networks of the human brain. *Annals of Neurology, 57*, 8–16.

Chomsky, N. (1995). *The minimalist program*. Cambridge, MA: The MIT Press.

Cohen, J. D., Perlstein, W. M., Braver, T. S., Nystrom, L. E., Noll, D. C., Jonides, J., et al. (1997). Temporal dynamics of brain activation during a working memory task. *Nature, 386*, 604–608.

Cupples, L., & Inglis, A. L. (1993). When task demands induce “asyntactic” comprehension: A study of sentence interpretation in aphasia. *Cognitive Neuropsychology, 10*, 201–234.

Dapretto, M., & Bookheimer, S. Y. (1999). Form and content: Dissociating syntax and semantics in sentence comprehension. *Neuron, 24*, 427–432.

Desmurget, M., Bonnetblanc, F., & Duffau, H. (2007). Contrasting acute and slow-growing lesions: A new door to brain plasticity. *Brain, 130*, 898–914.

Dick, F., Bates, E., Wulfeck, B., Utman, J. A., Dronkers, N., & Gernsbacher, M. A. (2001). Language deficits, localization, and grammar: Evidence for a distributive model of language breakdown in aphasic patients and neurologically intact individuals. *Psychological Review, 108*, 759–788.

Dronkers, N. F. (1996). A new brain region for coordinating speech articulation. *Nature, 384*, 159–161.

Embick, D., Marantz, A., Miyashita, Y., O’Neil, W., & Sakai, K. L. (2000). A syntactic specialization for Broca’s area. *Proceedings of the National Academy of Sciences of the United States of America, 97*, 6150–6154.

Fiebach, C. J., Schlesewsky, M., Lohmann, G., von Cramon, D. Y., & Friederici, A. D. (2005). Revisiting the role of Broca’s area in sentence processing: Syntactic integration versus syntactic working memory. *Human Brain Mapping, 24*, 79–91.

Friederici, A. D., Bahlmann, J., Heim, S., Schubotz, R. I., & Anwander, A. (2006). The brain differentiates human and non-human grammars: Functional localization and structural connectivity. *Proceedings of the National Academy of Sciences of the United States of America, 103*, 2458–2463.

Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J.-P., Frith, C. D., & Frackowiak, R. S. J. (1995). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping, 2*, 189–210.

Goodglass, H., & Menn, L. (1985). Is agrammatism a unitary phenomenon? In M.-L. Kean (Ed.), *Agrammatism* (pp. 1–26). Orlando, FL: Academic Press.

Grewe, T., Bornkessel, I., Zysset, S., Wiese, R., von Cramon, D. Y., & Schlesewsky, M. (2006). Linguistic prominence and Broca's area: The influence of animacy as a linearization principle. *Neuroimage, 32*, 1395–1402.

Grodzinsky, Y. (2000). The neurology of syntax: Language use without Broca's area. *Behavioral and Brain Sciences, 23*, 1–71.

Haglund, M. M., Ojemann, G. A., & Hochman, D. W. (1992). Optical imaging of epileptiform and functional activity in human cerebral cortex. *Nature, 358*, 668–671.

Hahn, C. A., Dunn, R. H., Logue, P. E., King, J. H., Edwards, C. L., & Halperin, E. C. (2003). Prospective study of neuropsychologic testing and quality-of-life assessment of adults with primary malignant brain tumors. *International Journal of Radiation Oncology, Biology, and Physics, 55*, 992–999.

Hashimoto, R., & Sakai, K. L. (2002). Specialization in the left prefrontal cortex for sentence comprehension. *Neuron, 35*, 589–597.

Hauser, M. D., Chomsky, N., & Fitch, W. T. (2002). The faculty of language: What is it, who has it, and how did it evolve? *Science, 298*, 1569–1579.

Ingram, J. C. L. (2007). *Neurolinguistics: An introduction to spoken language processing and its disorders*. Cambridge, UK: Cambridge University Press.

Just, M. A., & Carpenter, P. A. (1992). A capacity theory of comprehension: Individual differences in working memory. *Psychological Review, 99*, 122–149.

Kertesz, A., Harlock, W., & Coates, R. (1979). Computer tomographic localization, lesion size, and prognosis in aphasia and nonverbal impairment. *Brain and Language, 8*, 34–50.

Kinno, R., Kawamura, M., Shioda, S., & Sakai, K. L. (2008). Neural correlates of noncanonical syntactic processing revealed by a picture–sentence matching task. *Human Brain Mapping, 29*, 1015–1027.

Krainik, A., Lehéricy, S., Duffau, H., Capelle, L., Chainay, H., Cornu, P., et al. (2003). Postoperative speech disorder after medial frontal surgery: Role of the supplementary motor area. *Neurology, 60*, 587–594.

Matsumoto, R., Nair, D. R., LaPresto, E., Najm, I., Bingaman, W., Shibasaki, H., et al. (2004). Functional connectivity in the human language system: A cortico-cortical evoked potential study. *Brain, 127*, 2316–2330.

Menn, L., & Obler, L. K. (1990). Theoretical motivations for the cross-language study of agrammatism. In L. Menn & L. K. Obler (Eds.), *Agrammatic aphasia: A cross-language narrative sourcebook* (pp. 3–12). Amsterdam: John Benjamins Publishing Company.

Mesulam, M.-M. (2000). *Principles of behavioral and cognitive neurology*. New York, NY: Oxford University Press.

Mohr, J. P., Pessin, M. S., Finkelstein, S., Funkenstein, H. H., Duncan, G. W., & Davis, K. R. (1978). Broca aphasia: Pathologic and clinical. *Neurology, 28*, 311–324.

Momo, K., Sakai, H., & Sakai, K. L. (2008). Syntax in a native language still continues to develop in adults: Honorification judgment in Japanese. *Brain and Language, 107*, 81–89.

Ojemann, J. G., Miller, J. W., & Silbergeld, D. L. (1996). Preserved function in brain invaded by tumor. *Neurosurgery, 39*, 253–259.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9*, 97–113.

Pulvermüller, F. (1995). Agrammatism: Behavioral description and neurobiological explanation. *Journal of Cognitive Neuroscience, 7*, 165–181.

Rorden, C., & Brett, M. (2000). Stereotaxic display of brain lesions. *Behavioural Neurology, 12*, 191–200.

Rorden, C., & Karnath, H. O. (2004). Using human brain lesions to infer function: A relic from a past era in the fMRI age? *Nature Reviews Neuroscience, 5*, 813–819.

Saito, M., & Fukui, N. (1998). Order in phrase Structure and movement. *Linguistic Inquiry, 29*, 439–474.

Sakai, K. L. (2005). Language acquisition and brain development. *Science, 310*, 815–819.

Schwartz, M. F., Saffran, E. M., & Marin, O. S. M. (1980). The word order problem in agrammatism. I. Comprehension. *Brain and Language, 10*, 249–262.

Signoret, J. L., Castaigne, P., Lhermitte, F., Abelanet, R., & Lavorel, P. (1984). Rediscovery of Leborgne's brain: Anatomical description with CT scan. *Brain and Language, 22*, 303–319.

Suzuki, K., & Sakai, K. L. (2003). An event-related fMRI study of explicit syntactic processing of normal/anomalous sentences in contrast to implicit syntactic processing. *Cerebral Cortex, 13*, 517–526.

Van Valin, R. D., Jr., & LaPolla, R. J. (1997). *Syntax: Structure, meaning, and function*. Cambridge, UK: Cambridge University Press.

Wefel, J. S., Kayl, A. E., & Meyers, C. A. (2004). Neuropsychological dysfunction associated with cancer and cancer therapies: A conceptual review of an emerging target. *British Journal of Cancer, 90*, 1691–1696.