Epilepsy & Behavior Reports 14 (2020) 100378

Contents lists available at ScienceDirect

Epilepsy & Behavior Reports

journal homepage: www.elsevier.com/locate/ebcr

Case report

Retained absolute pitch after selective amygdalohippocampectomy

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ARTICLE INFO

Article history:
Received 2 April 2020
Received in revised form 13 June 2020
Accepted 19 June 2020
Available online 3 July 2020

Keywords:
Epilepsy surgery
Absolute pitch
Neuropsychological tests
fMRI
Brain organization

ABSTRACT

This study assessed the pre-operative chronic condition and effect of epilepsy surgery in a 21-year-old Japanese woman with drug-resistant right temporal lobe epilepsy (TLE). For this patient, it was crucially important to preserve language and her music capabilities, including absolute pitch (AP), which is found in the general population at less than 0.1%. The patient became seizure free, and her AP capability was preserved after selective amygdalohippocampectomy in the non-dominant right hemisphere. Most of the neuropsychological test (WAIS-III and WMS-R) scores remained in the normal range, except for low scores in verbal memory and markedly improved attention/concentration index. The patient's pre- and postoperative brain function related to language and music capabilities were investigated using functional magnetic resonance imaging (fMRI) based on two language tasks and a music task (listening to melodies). While task performance was similar in pre- and postoperative examinations, her brain activation patterns markedly differed. The most striking difference was during the music task: areas with significant activation existed in the bilateral frontal and temporal lobes before surgery, whereas postoperative activation was confined to a very limited region in the left angular gyrus. The authors speculate that the surgery triggered some change in functional organization in the brain, which contributed to preserving her capabilities.

1. Introduction

Temporal lobe epilepsy (TLE) is a chronic neurological disorder that often affects cognitive function [1] such as memory [2], and language [3]. Good seizure control, therefore, is one of the important factors required to prevent progressive cognitive deterioration caused by TLE [4]. It is well established that surgical treatment is highly effective for drug-resistant TLE in terms of seizure control when complete removal of the epileptogenic zone is accomplished [5]. In the planning of surgical treatment, the margin of resection is decided based on the policy to preserve the eloquent area. For musicians, preserving music capabilities is of crucial importance. The majority of studies to date, however, have focused on the structural organization or network associated with the functions of language and memory. There has been relatively little investigation into other domains of cognitive function.

How we perceive music depends on the workings of the auditory system, which encodes and retains acoustic information [6]. Absolute pitch (AP) is a rare ability to recognize or produce the pitch of a given tone without any external references [7–9]. The prevalence of AP in professional musicians has been estimated to be 10% to 15% or more [10,11], while in the general population, the number of people with AP is less than 0.1% [12]. Any, because the number of musicians with AP capability who also have epilepsy is very few, there is relatively little literature on the pre- and postsurgical assessment of musical ability and cognitive functions, and reports tend to be case studies. Zatorre reported a 17-year-old pianist who underwent a left anterior temporal lobectomy [13]. Suriadi et al. reported a pianist with TLE who underwent right-side selective amygdalohippocampectomy [14]. A report by Wilson et al. [15] is exceptionally rare in that they used functional magnetic resonance imaging (fMRI) to investigate a professional singer who underwent epilepsy surgery in the right temporal lobe. There was no mention, however, of AP in the singer.

In the present study, we conducted a pre- and postsurgical assessment of both cognitive function and music capability (AP) in a woman with drug-resistant TLE by using behavioral and functional imaging investigations. Our focus regarding music-related functions was not the rhythmic but the melodic structure of music, that is, not the time-based but the pitch-based aspect of music. As for language-related functions, we investigated both language production and listening comprehension. The language production tasks required the phonemic or syllabic handling of words. The listening comprehension tasks examined the auditory understanding of discourse.

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https://doi.org/10.1016/j.ebr.2020.100378

2. Materials and methods

2.1. Subject

The subject was a right-handed 21-year-old Japanese woman who was a college student. She started piano lessons at the age of 4 and continued performing on piano since then. She was aware of her AP capability by the time she entered elementary school at the age of 6, although no scientific or objective evaluation of AP was conducted at that time. She had her first seizure with an aura of palpitation followed by loss of consciousness and oral automatism at the age of 9. She had similar focal impaired awareness seizures weekly and was diagnosed with epilepsy in a local hospital. She was treated with carbamazepine but still had monthly seizures. Her seizures became drug-resistant at the age of 19. At the age of 20, she was referred to the National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders. Prolonged video-electroencephalogram (EEG) captured clinical seizures with the aforementioned semiology. Ictal EEG showed rhythmic theta activity maximal in amplitude in the right sphenoidal electrode. In the interictal period, spikes and sharp waves were seen every 3 to 5 min in stages NI and NII sleep, in the right anterior temporal area with the maximal amplitude in the right sphenoidal electrode. Structural MRIs showed fluid-attenuated inversion recovery (FLAIR)-high signal in the right medial temporal structures including the hippocampus (Fig. 1, panel (A)). The patient was diagnosed with drug-resistant mesial temporal lobe epilepsy and underwent right-sided selective amygdalohippocampectomy (Fig. 1, panel (B)).

The present study was approved by the Ethics Committee of the National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological disorders, and written informed consent was obtained from the subject.

2.2. Pre-operative chronic condition: neuropsychological assessment

One month before the surgical treatment of epilepsy, the subject underwent cognitive evaluation including an Intracarotid Propofol Test and a series of neuropsychological tests. The details of the Intracarotid Propofol Test are mentioned elsewhere [16]. The right hemisphere was first anesthetized with 7 mg of Propofol for assessment of language and memory; and after a 30-minute interval, the left side was tested with the same dose of Propofol

Neuropsychological testing was conducted on another day. We used index scores of the Wechsler Adult Intelligence Scale, third edition (WAIS-III, Japanese version) [17], and the Wechsler Memory Scale-Revised (WMS-R, Japanese version) [18]. The index scores of WAIS-III and WMS-R were evaluated in terms of the normal mean (100) and one standard deviation (SD; 15). Verbal fluency was evaluated by the Japanese version of the Controlled Oral Word Association Test [19]. The total number of words named by the subject was compared with a published norm [n = 24, mean age (SD) = 48.5 (2.9)] [20].

2.3. Evaluation of absolute pitch

A pitch naming test was performed at a later date in a quiet room in the ward. The details of the stimuli and procedures are mentioned elsewhere [14]. Briefly, the subject took a session of a piano-tone test and a pure sinewave tone test, four sessions in total. In each test, 10 sounds were given to the subject with the inter-stimulus interval (ISI) of 6 s by a set of stereo sound speakers located 1 m away from the subject. The pitch of the sounds had a difference of more than nine semitones from the adjacent sounds. The subject wrote the name of each tone on a sheet of paper as soon as possible. No practice run was given to the subject.

Forty piano tones (bases of A4 = 440 Hz, range from C2 to B7) were digitally recorded with a sampling rate of 44.1 kHz. Half of these tones were chosen from the white keys (i.e., the C major scale), and the other half were from the black keys. Forty pure tones chosen from the same criteria were synthesized at 16 bits with a sampling rate of 44.1 kHz using computer software (DigiOn Sound, DigiOn, Japan). Both piano and pure tones had a uniform duration of 1000 ms with onset and offset ramps of 100 ms. We applied the minimal point for AP from the original test by Baharloo et al. [10]. One would be considered to have AP if the score for pure sinewave tones was more than 24.49 out of the full score of 40.

2.4. Evaluation of music and language capabilities

Three sessions of block-design fMRI paradigm were recorded on another day. Each session was designed with six blocks (three 'on' and three 'off'). The 'on' and 'off' blocks were alternately set. The subject performed tasks during the 'on' blocks and paused during the 'off' blocks. During the 'on' block, auditory stimuli from MP3 files were played on a computer system (Windows 7, CF-B10, Panasonic, Japan), and the patient listened with special headphones designed for MRI (NordicNeuroLab, Norway).

In the first session of the music task, the patient listened to excerpts from an unfamiliar melody played by a clarinet and was told to name each musical note in the melody. In the second session, which was language production, the patient performed a last-syllable word-chain

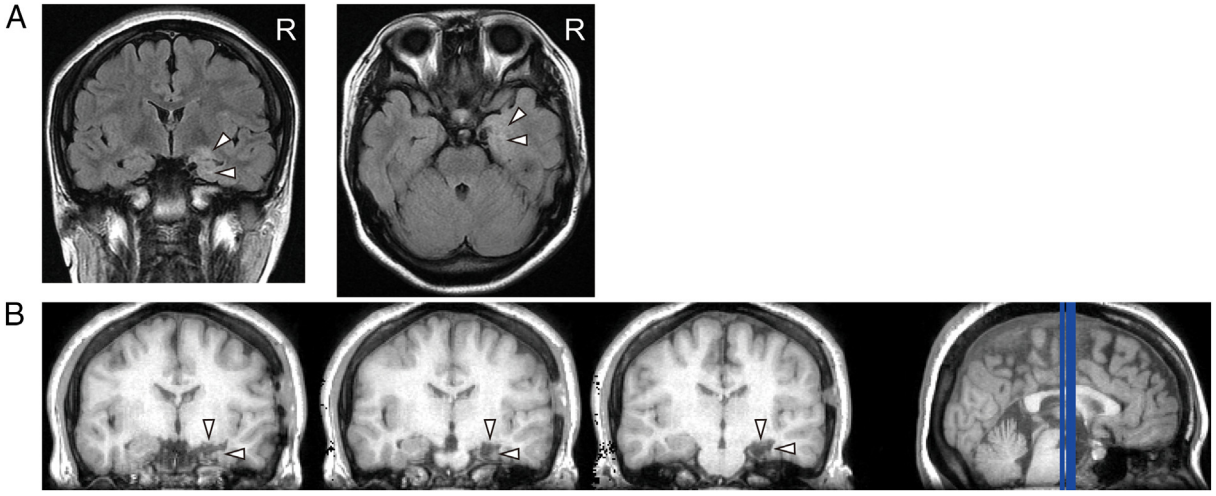

Fig. 1. Pre- and postoperative MRI evaluation performed on a 1.5-T system. (A) Pre-operative coronal (left) and axial (right) FLAIR images showing the lesion in the right medial temporal structures (white arrowheads). (B) One-year postoperative coronal fast spoiled gradient echo (FSPGR) T1-weighted images showing the extent of resection (white arrowheads). The images are presented by using MRIcron software (copyright Chris Rorden).

game, which is called Shiritori in Japanese. The first word for starting the word-chain game was given to the subject by the examiner through the headphones at the beginning of each 'on' block. The third session of listening comprehension required the subject to listen to excerpts of narratives from a Japanese scientific radio program designed for general audiences and to remember the content. The patient's performance was tested by post-scan questionnaires.

2.5. fMRI protocol and analyses

Whole-brain MRIs were taken by a 1.5-Tesla Signa HDxt Optima Edition Twin Speed system (GE Healthcare Corporate), with pulse sequence of 2D gradient echo, echo-planar image (EPI) (TE = 40 ms, TR = 3000 ms), with 90 degree FAs. Blood-oxygenation-level-dependent (BOLD) contrast was used to evaluate cerebral activation. Anatomical T1-weighted MRIs were taken with a 3D fast spoiled gradient-recall (FSPGR) sequence (TR = 7.856 ms, TE = 2.996 ms, FOV = 24.0 cm, 1.3 mm slice thickness, 122 slices).

We analyzed the data using parametric mapping software SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), operating on MATLAB R2016a. The data were spatially realigned and co-registered with the subject's anatomical 3D T1-images. Both EPI and anatomical T1-images were normalized to a standard Montreal Neurological Institute (MNI) space with the voxel size of 2.0 × 2.0 × 2.0 mm, and smoothed with an 8-mm Gaussian kernel. For each session, T contrast was estimated and statistical parametric maps were created. Voxel-wise significance corrected in the whole brain for family-wise error (FWE) was applied. Voxels with a p value less than 0.05 were regarded as significant. The anatomical location of the areas with significant activation was labeled using the Neuromorphometrics atlas in the SPM12.

2.6. Post-operative evaluation

The seizure outcome and prolonged video-EEG were evaluated twice after the surgery. The subject underwent the first evaluation 1 year after the surgery and the second 2 years after the surgery. At the first evaluation, she also took the pitch naming test and underwent an fMRI study. At the second evaluation, she underwent a postoperative neuropsychological evaluation.

2.7. Medication

Before the surgical treatment the patient took carbamazepine (1000 mg/day) and clobazam (15 mg/day). The medication remained unchanged for 2 years after surgery.

3. Results

3.1. Surgical outcome

The histopathological examination of the resected specimens confirmed focal cortical dysplasia (FCD type IIIa) [21]: the specimen from the mediobasal temporal cortex showed abnormalities in cortical lamination with severe gliosis; the hippocampus showed severe gliosis and neuronal cell loss in the CA1, CA4, and the dentate granular cell layers and moderate neuronal cell loss in the CA3 layer, which was typical hippocampal sclerosis. The patient became seizure-free after the surgery.

3.2. Pre- and postoperative cognitive functions: neuropsychological assessment

The left intracarotid injection of Propofol induced transient aphasic responses. In the right-side examination, the subject showed delayed responses (~20 s) in picture naming, with a mildly low ratio of correctly recognized items in the memory test. The results showed that the left hemisphere was dominant for language and that the right hemisphere might be involved in language-related function.

The results of pre- and postoperative neuropsychological testing are summarized in Table 1. In the postoperative assessment, the WAIS-III indices were improved by 2 to 7 points. In the WMS-R, the Attention/Concentration Index showed an improvement of 27 points, which surpassed one SD. The other three index scores were lower than those of the pre-operative evaluation by 4 to 7 points. The score of the verbal fluency test was improved by 4 points and came within one SD of the mean score of the published norm.

3.3. Evaluation of absolute pitch

In the pre-operative evaluation, the patient's AP test score for pure sinewave tone was 33.50 and for piano tone was 35.75. In the postoperative evaluation, her AP test score for pure sinewave tone was 32.25 and for piano tone was 32.25. The pre- and postoperative scores for pure sinewave tone surpassed the cutoff score of possessors of people who have AP (24.49).

3.4. Pre- and postoperative fMRI

The cortical areas with statistically significant activation ($p < 0.05$, FWE corrected) during music, language production, and listening comprehension tasks are shown in Table 2. Fig. 2 is a projection of the sites with significant activation ($p < 0.0001$, uncorrected) on the inflated standardized brain in SPM12 (peak coordinates are listed in Table 2). In the pre-operative evaluation, the music task activated both the left and the right frontal and temporal cortical areas. The left and the right cerebellum also showed portions with significant activation. Two language tasks showed different patterns of activation. The language production task activated two cortical areas in the left frontal lobe, one in the precentral gyrus and the other in the medial frontal gyrus (i.e., supplementary motor cortex). In the listening comprehension task, an area in the left superior temporal gyrus showed significant activation. Partial overlap of the activated area for the music and language tasks was observed in the left precentral gyrus and the left superior temporal gyrus.

Fig. 3 shows the patient's postoperative 3D MRIs. Panel (A) shows T1-weighted images that had no deformed signal. The EPI for the fMRI study (Panel B) showed distorted images with artifacts caused by titanium plates and screws used for the scalp fixation. In the postoperative fMRI study, we therefore evaluated the activation only in the left hemisphere. After surgery (Table 2; Fig. 2, panel B), the music task activated a very limited area in the left angular gyrus. Although nonsignificant if FWE

Table 1
Pre- and postoperative indices/scores in neuropsychological tests.

Test	Type of index	Pre-op	Post-op
WAIS-III	Verbal comprehension	92	99
	Perceptual organization	91	97
	Working memory	96	98
	Processing speed	102	105
WMS-R	Verbal memory	81	77
	Visual memory	108	102
	Attention/concentration	87	114
	Delayed recall	82	75
Verbal fluency		20	24

WAIS-III: Wechsler Adult Intelligence Scale, third edition, Japanese version [17].
WMS-R: Wechsler Memory Scale, Revised, Japanese version [18].
Mean index score (1SD) = 100 (15).
Mean Verbal-fluency test score (1SD) in published norms = 25.4 (1.8) [20].

Table 2
MNI coordinates for voxels associated with activation for music and language tasks in pre- and postoperative examinations (whole-brain family-wise error corrected, $p < 0.05$).

Pre/post	Tasks	L/R	Brain region (probability)	Coordinates (MNI)			t-Value	k
				x	y	z		
Pre-op	Music	L	Precentral gyrus (57.2%)	−54	0	38	8.64	142
		L	Planum temporale (14.3%) Parietal operculum (12.2%)	−50	−44	20	7.88	197
		L	Superior temporal gyrus (31.2%) Middle temporal gyrus (18.4%)	−68	−22	−2	6.58	85
		L	Supplementary motor cortex (44.4%)	−2	0	62	6.47	87
		R	Precentral gyrus (44.8%)	58	0	38	8.75	157
		R	Superior temporal gyrus (54.1%)	64	−30	8	6.48	49
		L	Cerebellum (84.1%)	−26	−70	−30	6.61	45
		R	Cerebellum (84.6%)	28	−66	−28	5.59	10
	Language production	L	Precentral gyrus (35.0%)	−58	−4	42	7.72	60
		L	Supplementary motor cortex (47.7%)	−4	18	46	6.13	15
	LC	L	Superior temporal gyrus (30.4%) Middle temporal gyrus (19.1%)	−54	−26	0	6.25	48
Post-op	Music	L	Angular gyrus (39.8%)	−44	−58	54	5.42	2
	Language production	L	Precentral gyrus (49.4%)	−56	−2	38	12.45	488
		L	Supplementary motor cortex (48.1%)	−4	4	60	12.43	1299
		L	Parietal operculum (12.8%)	−46	−42	28	6.79	47
		L	Anterior insula (43.4%)/orbital part of inferior frontal gyrus (4.3%)	−32	18	−10	5.92	15
	LC	L	Superior temporal gyrus (35.8%) Planum polare (23.3%)	−56	−8	−2	8.57	823

LC: listening comprehension; L: left; k: number of voxels; R: right.

correction was made, a region in the left posterior superior temporal gyrus also showed activation. In the language production task, four regions showed significant activation: two in the left frontal lobe, one in the parietal lobe, and one in the anterior insula cortex and/or orbital part of the inferior frontal gyrus. In the listening comprehension task, a region in the superior temporal gyrus showed significant activation.

4. Discussion

4.1. Successful surgery: preserved AP

Although surgical treatment is highly effective for drug-resistant TLE, surgery may also affect the cognitive outcome with a risk of additional

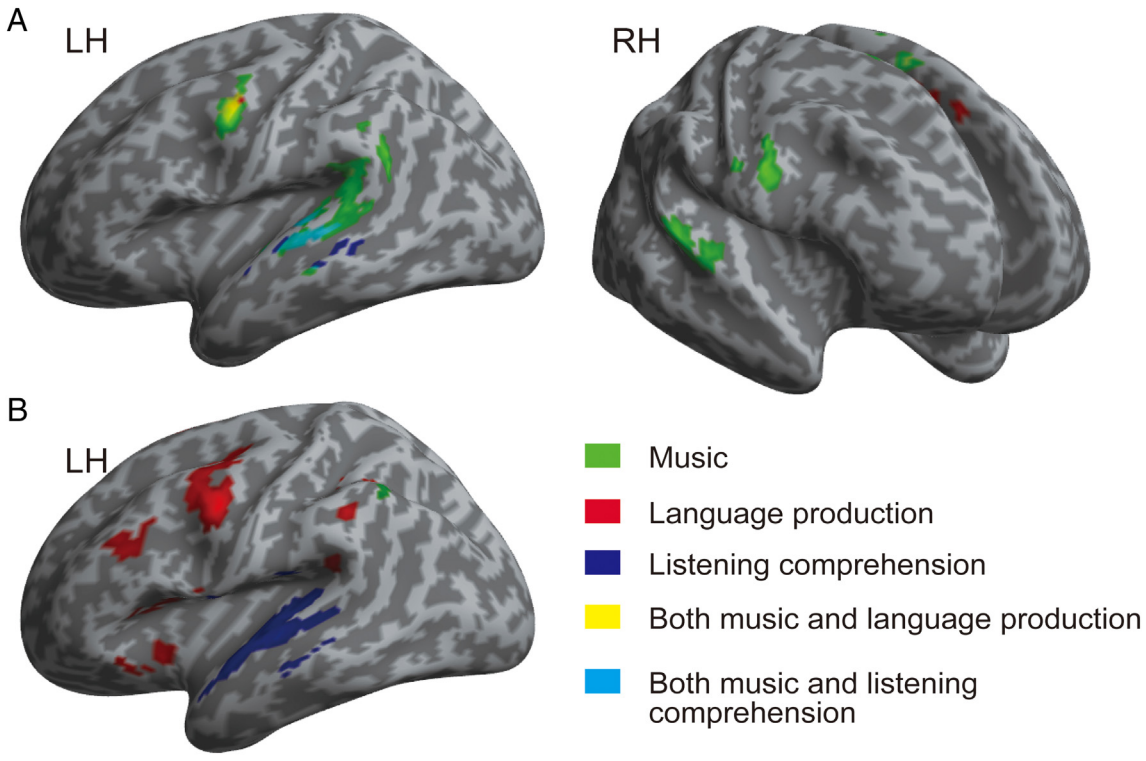

Fig. 2. Pre- and postoperative fMRI activation for music and language tasks. Activation for music (green), language production (red) and listening comprehension (blue) are rendered onto the standardized and inflated cerebrum ($p < 0.0001$, family-wise error uncorrected). (A) Activated areas before surgery. Lateral view of the left hemisphere and oblique view of the right hemisphere are shown. The music task activated multiple areas, including the left precentral gyrus, supplementary motor cortex, superior temporal gyrus, and their right homologous areas. The language production task activated the left precentral gyrus. Since this area overlapped with the activated area for music, the overlap is displayed in yellow. The language production task also activated the left supplementary motor cortex, which is shown in the oblique view from the side of the right hemisphere. The listening comprehension task activated areas mainly in the left superior temporal gyrus. The overlap of activated areas between the music and listening comprehension tasks are shown in light blue. (B) Activated areas after surgery. Because of the influence of the metallic surgical apparatus on the MRI, only the left hemisphere was studied after surgery. LH: left hemisphere; RH: right hemisphere.

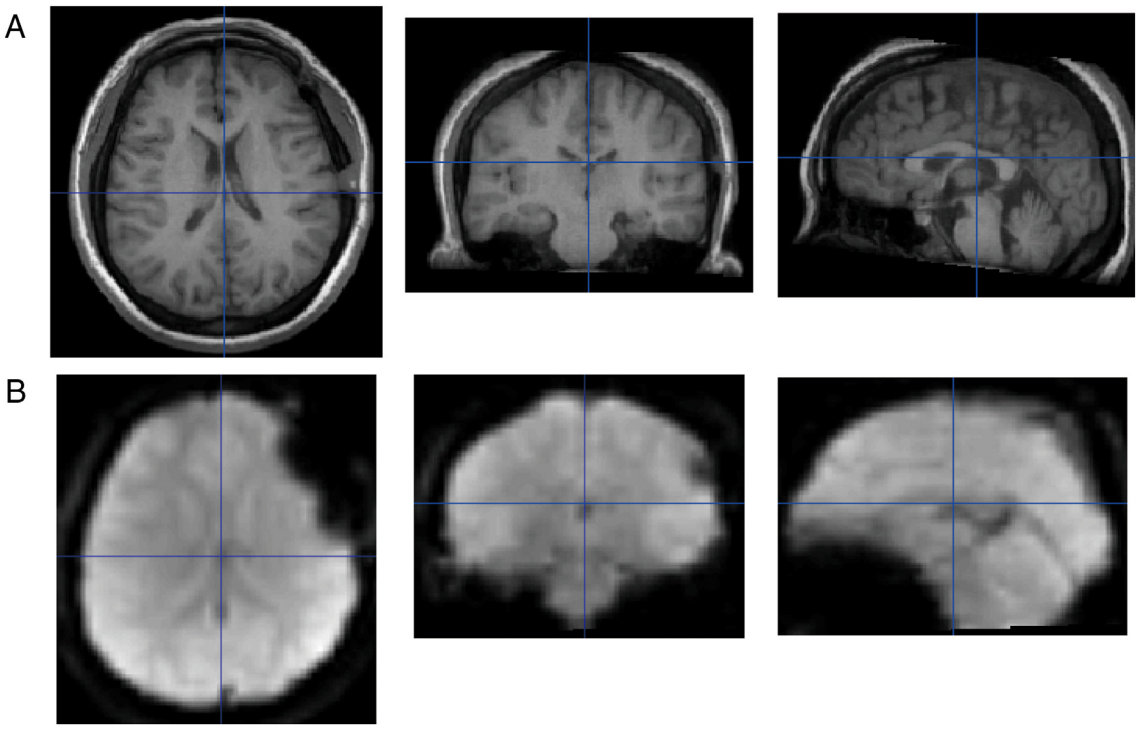

Fig. 3. (A) Postoperative three-dimensional FSPGR axial (left), coronal (middle) and sagittal (right) T1-weighted structural images. (B) Echo-planar images (EPI) of the same slices as in (A). In EPI, images were distorted in the right hemisphere due to titanium plates and screws used for the scalp fixation.

impairment or no functional recovery. Our patient underwent resection of the right mediobasal and medial temporal structures including hippocampus and amygdala (FCD type IIIa). The surgical outcome was almost ideal for a music student: seizure freedom and a mostly preserved AP ability and cognitive functions. The only exceptions were verbal and delayed memory: these two indices were pre-operatively lower compared with other indices and they decreased postoperatively.

As for the mechanism of AP, albeit not fully understood, Levitin suggested that those people with AP have internalized stable pitch references and are able to spontaneously transfer musical tones to linguistic labels [22,23]. In healthy people with AP, music- and language-processing networks would function separately without entanglement. With lesions, however, the ability of AP and/or language ability may be affected in proportion to the lesion within the crucial network.

4.2. Influence of right amygdalohippocampectomy on music capability and language-related functions

The anatomical structure of our patient had no change in the left hemisphere because she underwent resection in the right hemisphere. Our functional imaging studies, however, demonstrated that activation patterns before and after surgery for both music and language tasks clearly differed; changes were observed both in the right and the left hemisphere.

In the music task of naming the pitch of an unfamiliar melody, several cortical areas in the left and right frontal and temporal lobes, as well as the cerebellum, were activated before surgery. After surgery, however, the only area that showed statistically significant activation was in the left angular gyrus, which showed no significant activation before surgery.

In the literature, a variety of brain areas were associated with music pitch processing in people without AP [24]; the posterior portion of the right and left superior temporal gyrus [25,26], right Heschl's gyrus [27], left and right superior temporal gyrus and planum polare [28], and the anterior portion of the right superior temporal gyrus [29]. The processing of the harmonic aspect of music is related to bilateral frontal regions, such as the inferior frontal gyrus, frontal operculum, and insula [30,31]. In a study of neurologically normal people with AP, Zatorre et al. reported increased cerebral blood flow in the left dorsolateral prefrontal cortex in addition to the aforementioned auditory cortical areas [32]. Our pre-operative finding was in agreement with these reports, although there was some difference in anatomical sites.

The angular gyrus has been assumed to be one of the high level cortical hubs for multimodal abstraction [33]. Although no reliable data of postoperative activation in the right hemisphere were available due to the technical limitation of fMRI, preserved AP capability with greatly varied postoperative activation observed in the left also illustrated that the left hemisphere was essential for music processing for reorganization in this particular subject.

Noticeable changes in activation during language-related tasks also appeared after surgery. The language production task activated two new regions in the anterior insula and/or inferior frontal gyrus and parietal operculum in addition to the pre-operative activation areas in the frontal lobe. The listening comprehension task activated the left superior temporal lobe both before and after surgery. The postoperative study, however, exhibited some increase in number of voxels. The overall postoperative activation pattern obtained from both language tasks was similar to so-called 'typical' activation to language tasks, with significant activations in the left frontal and temporal lobes [34].

The fact that the music and language capabilities of our patient remained stable and that areas of activation exhibited notable changes suggest that there is no single way for the brain to organize for these functions. Rather, cerebral correlates are flexible and adaptable to changing circumstances.

4.3. Possibility of network reorganization

Epileptic neural activities persistently affect some of the crucial areas, which might shift a specific function from one area to another, or might re-route certain pathways from traditional to non-traditional sites within the hemisphere. There are numerous reports regarding reorganization. Baciu et al. summarized differing patterns of language

reorganization among epilepsy patients in their extensive review [35]. Wilson et al. reported a case in which function of covert vocal singing exhibited reorganization accompanied by improved behavioral performance following resection of an epileptogenic lesion in the right temporal lobe [15]. Pillai suggested post-lesional plasticity as a heterogeneous spectrum of functional cortical reorganization patterns [36]. Pravatà et al. reported the relationship between pre-operative lateralization and functional connectivity of the language network, and postoperative change in language performance in patients with TLE [37]. A variety of ideas regarding interhemispheric shift, or intra-hemispheric re-routing, are also reported in the literature (see reference [3]).

In the case of our patient with AP, the AP test and neuropsychological evaluation exhibited almost stable AP ability and cognitive function after surgery. The medication was the same at the pre- and postoperative evaluations. The interval between the pre- and postoperative fMRI studies was 1 year, which was long enough to eliminate test–retest effects from the pre-operative study. The pre- and postoperative change in pattern of activation identified by fMRI, therefore, possibly indicated that her brain flexibly adapted postoperatively to new circumstances by modifying the pre-operative network.

4.4. Limitations

The Intracarotid Propofol Test indicated that the dominant hemisphere for language was the left, while some of the language-related functions might be supported by the right hemisphere. Although we speculate that improvement in some of the neuropsychological test scores and changes in cortical activation after the right-side surgery were related to these findings, our data were far short of proving these as fact. The distributed network of brain regions might indicate another issue: which of these brain areas is dedicated specifically to language or music? Some of these regions might not only overlap but might also share processing components with other functions. Although we used both expressive and receptive language tasks, it must be noted that the task we used should be interpreted as assessing not all but portions of aspects of language processing. We must note that other types of music and language tasks may evoke differing patterns of neural activity. In other words, the recruitment of neural resources for music and language processing in the human brain depends on the experimental paradigm. Although fMRI is versatile technique, we should be aware that overlap of some functional areas, for example, is actually within the accuracy of the spatial resolution of fMRI.

4.5. Conclusions

This report is a within-subject investigation of a woman with drug-resistant TLE who had AP, which is an extremely rare combination of conditions. We evaluated the patient's music and language capabilities before and after selective amygdalohippocampectomy. The presurgical examination delineated a chronic condition caused by focal epilepsy, and the postsurgical evaluation reflected an overall change in the functional state induced by surgical treatment. She became seizure-free and her AP ability was preserved. Most of the neuropsychological test scores were stable within normal range. The fMRI studies indicated that surgery may have triggered change in functional organization of music processing of AP in the brain.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We are grateful to Yoshinobu Kasai for conducting neuropsychological testing. This research was partly supported by JSPS KAKENHI Grant Number 16K09723 to KU. This work was also supported by MEXT KAKENHI Grant Number 15H05874 Grant-in-Aid for Scientific Research on Innovative Areas “Non-linear Neuro-oscillology: Towards Integrative Understanding of Human Nature” to TN.

CRediT authorship contribution statement

Keiko Usui: Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing, Funding acquisition, **Jun Shinozaki:** Software, Visualization, Writing - review & editing, **Naotaka Usui:** Investigation, Resources, Writing - review & editing, **Kiyohito Terada:** Investigation, Resources, Writing - review & editing, **Kazumi Matsuda:** Investigation, Resources, Visualization, Writing - review & editing, **Akihiko Kondo:** Investigation, Resources, Writing - review & editing, **Takayasu Tottori:** Investigation, Resources, Writing - review & editing, **Takashi Nagamine:** Supervision, Writing - review & editing, Funding acquisition, **Yushi Inoue:** Supervision, Project administration, Writing - review & editing.

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