



Anterior insular cortex stimulation and its effects on emotion recognition

Kazuya Motomura¹ · Yuri Terasawa² · Atsushi Natsume¹ · Kentaro Iijima¹ · Lushun Chalise¹ · Junko Sugiura³ · Hiroyasu Yamamoto³ · Kyohei Koyama³ · Toshihiko Wakabayashi¹ · Satoshi Umeda²

Received: 8 January 2019 / Accepted: 24 May 2019 / Published online: 5 June 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

With the objective to investigate the role of the insula in recognizing emotion, we performed direct electrical stimulation over the anterior insular cortex during awake surgery while simultaneously delivering an emotional sensitivity task. We registered 18 consecutive patients with brain tumors associated with the insular lobe, who were undergoing tumor resection. An emotional sensitivity task was employed to measure the patients' ability to recognize emotions from facial expressions before, during, and after awake surgery. Furthermore, we performed voxel-based lesion symptom mapping (VLSM) to identify the association between relevant brain lesions and emotion recognition. When we performed direct electrical stimulation over the anterior insular cortex during awake surgery, the results showed that the ability to recognize anger was significantly enhanced with the presence of anterior insular stimulation ($p < 0.05$). Comparing the performance in the emotional sensitivity task before and after surgery, the performance in the anger condition became worse ($p < 0.01$), but became better in the sadness condition after surgery ($p < 0.01$). In the case of anger recognition, lower scores in the correct response index were associated with lesions involving the left insula in the VLSM study. Direct electrical stimulation over the anterior insular cortex enhanced anger recognition in patients with insular tumors. In contrast, accuracy of anger recognition was significantly reduced, and sadness was improved, when the performance of emotional sensitivity was compared pre- and post-surgery. Our findings suggest that the insular cortex is involved in changes in emotion recognition, including anger and sadness recognition by modulating arousal level that is closely connected with interoception.

Keywords Anterior insular cortex · Emotion recognition · Anger recognition · Awake surgery · Brain tumor

Introduction

Neoplasms in the insular lobe, especially intrinsic tumors, are challenging to surgeons because they occur alongside white matter tracts that govern language function, such as the inferior fronto-occipital fasciculus and superior longitudinal fasciculus, as well as to critical vascular structures, including some branches of the middle cerebral artery, the lenticulostriate artery, and the long insular artery. To preserve these brain functions, the gold standard treatment for infiltrative insular tumors is awake surgery with functional brain mapping using direct electrocortical stimulation (Duffau et al. 2008; Sanai et al. 2008; Duffau et al. 2009; Sanai et al. 2010; Hervey-Jumper et al. 2016). However, even when such a procedure is performed, patients sometimes show emotional and behavioral deficits after removal of the insula (D'Angelo et al. 2008; Herbet et al. 2015), although their language and/or motor functions may

Kazuya Motomura and Yuri Terasawa contributed equally to this study.

✉ Kazuya Motomura
kmotomura@med.nagoya-u.ac.jp

✉ Satoshi Umeda
umeda@flet.keio.ac.jp

¹ Department of Neurosurgery, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

² Department of Psychology, Keio University, 2-15-45 Mita, Minato-ku, Tokyo 108-8345, Japan

³ Department of Rehabilitation, Nagoya University Hospital, Nagoya, Japan

be preserved (Motomura et al. 2017; Eseonu et al. 2017; Bello et al. 2007; Ilmberger et al. 2008). Specifically, some patients present with affective disorders such as flat affect, depression, and decreased activity after removal of the insula. However, few studies have examined how insular lobe removal causes changes to brain functions involved in emotion and behavior (Vilasboas et al. 2017; Duffau 2010, 2018), which are essential to the daily personal life of a human being.

Since Penfield et al. reported that stimulation on the insular cortex elicits nausea or visceral pain, this area has been defined as the “viscerosensory cortex”. The insular cortex is also known to be essential for taste perception and regulation of pain (Feinstein et al. 2016). In the last two decades, neuroimaging studies have consistently reported its enhancement when participants recognized or felt their own emotional states. In this regard, psychological theories of emotion are key concepts for understanding why the insular cortex, also known as the visceral cortex, underlies emotion recognition. Recent studies of the psychology of emotion have suggested that the perception of internal bodily changes (interoception), as well as the interpretation of environmental information, is fundamental to recognizing emotion, and that the insular cortex is critical to these mechanisms. Our previous functional magnetic resonance imaging (fMRI) studies supported this hypothesis, revealing that the right anterior insular cortex was commonly activated when participants were aware of their own emotional and bodily states (Terasawa et al. 2013a, b). From another perspective, neuropsychological studies have indicated that lesions on the insular cortex impair the recognition of emotion from facial expressions (Adolphs et al. 2000; Dal Monte et al. 2013). In particular, its impact on disgust recognition is widely accepted because one influential study reported that a lesion on the left posterior insular cortex impaired the recognition of disgust (Calder et al. 2000). However, our previous study involving three patients with damage to their right insular cortex indicated that such lesions impair patients’ ability to notice their own and others’ emotions, regardless of category (Terasawa et al. 2015). In the same study, participants performed an experimental task using morphed photos with neutral or emotional facial expressions (i.e., anger, sadness, disgust, or happiness). The patients incorrectly identified emotions with high arousal (e.g., anger) as less aroused emotions (e.g., sadness) and one patient showed remarkably low interoceptive accuracy. We concluded that results showed that insular lesions led to attenuated emotional sensitivity across various emotions, rather than to impairments specific to a certain category, such as disgust. These findings may have arisen because the patients had an attenuated ability to perceive emotional arousal through interoception. However, there is limited evidence to suggest that insular lesions impair emotional perception through such a mechanism.

To identify the role of the insula in emotion processing, we performed direct electrical stimulation over the exposed anterior insular cortex during awake surgery. We used an emotional sensitivity task to measure the patients’ ability to recognize emotions from facial expressions. This task was performed both before and after removal of the insula to assess the functional role of selected insular regions. In addition, we sought to correlate behavioral performance with regional distributions of brain damage using voxel-based, lesion–symptom mapping (Bates et al. 2003).

Materials and methods

Patient selection

We registered 18 consecutive patients with glial tumors or brain metastases associated with the insular lobe who underwent tumor resection at Nagoya University Hospital from January 2014 through January 2016. Participants were selected according to the following criteria: (1) location of brain tumor in and/or close to the insular cortex; (2) consent to electrical stimulation of the insula during awake brain mapping; (3) the possibility of removing the tumor under general anesthesia if awake surgery could not be performed; (4) availability of clinical and follow-up data in the neuro-oncology database, and (5) written informed consent from all individual participants included in the study. Conversely, patients were excluded from the study when they could not undergo a detailed preoperative neuropsychological evaluation that included the Standard Language Test of Aphasia (SLTA), the third edition of the Wechsler Adult Intelligence Scale (WAIS-III), and the Wechsler Memory Scale–Revised (WMS-R). The study was approved by the institutional review board at Nagoya University Hospital (2014-0002) and complied with all tenets of the Declaration of Helsinki. The clinical characteristics of the study are summarized in Table 1. Histologically, this study included one WHO grade I glioma (1 pilocytic astrocytoma), ten WHO grade II gliomas (eight diffuse astrocytomas, one oligodendroglioma, one pleomorphic xanthoastrocytoma), two WHO grade III gliomas (one anaplastic astrocytoma, one anaplastic oligodendroglioma), and four WHO grade IV gliomas (four glioblastomas).

Of these patients with intracerebral tumors associated with insular lobe, 16 of the 18 patients (88.9%) underwent awake surgery, while the other two patients underwent tumor resection under general anesthesia. The 18 patients comprised 10 men (55.6%) and 8 women (44.4%) ranging in age from 14 to 72 years (median age 37.5 years). All patients were right-handed. The first clinical symptom was seizure in 9/18 patients (50%). Four patients (22.2%) had preoperative motor or language deficits, while another three (5.6%)

Table 1 Clinical characteristics

Patient no.	Age (years)	Sex	Handedness	Pathology	WHO grade	First symptom	Tumor side (R/L)	Tumor location	Awake surgery	Initial tumor volume (cm ³)	Postoperative tumor volume (cm ³)	Final EOR (%)	Preoperative EST	Intraoperative EST	Postoperative EST
1	72	M	R	Diffuse astrocytoma	II	Memory disturbance	L	Insula	+	24.9	3.4	86.2	+	+	+
2	28	M	R	Pleomorphic xanthoastrocytoma	II	Seizure	L	Insula	+	0.6	0	100	+	+	+
3	37	F	R	Glioblastoma	IV	Memory disturbance	L	Insula	+	118.7	18.4	84.5	+	+	+
4	31	M	R	Diffuse astrocytoma	II	Seizure	R	Insula	-	34.7	5.5	84.2	+	-	+
5	35	F	R	Diffuse astrocytoma	II	Hemiparesis Paraphasia	L	Insula	+	61.6	16.5	73.3	+	-	+
6	39	M	R	Diffuse astrocytoma	II	Numbness	L	Insula	+	61.7	33.1	46.3	+	+	+
7	67	F	R	Diffuse astrocytoma	II	Seizure	L	Insula	+	32.0	0.8	97.6	+	+	-
8	21	F	R	Piloeytic astrocytoma	I	Incidental	L	Temporal	+	14.0	0	100	+	+	+
9	38	F	R	Glioblastoma	IV	Memory disturbance	L	Insula	+	43.2	13.5	68.8	+	+	-
10	33	F	R	Metastasis of adenocarcinoma	-	Hemiparesis Aphasia	L	Insula	-	55.6	0	100	+	-	-
11	38	F	R	Diffuse astrocytoma	II	Hemiparesis Aphasia	L	Insula	+	85.5	0.9	98.8	+	-	+
12	14	M	R	Glioblastoma	IV	Hemiparesis Aphasia	L	Insula	+	109.4	22.9	79.1	+	-	-

Table 1 (continued)

Patient no.	Age (years)	Sex	Handedness	Pathology	WHO grade	First symptom	Tumor side (R/L)	Tumor location	Awake surgery	Initial tumor volume (cm ³)	Postoperative volume (cm ³)	Final EOR (%)	Preoperative EST	Intraoperative EST	Postoperative EST
13	29	M	R	Diffuse astrocytoma	II	Seizure	L	Insula	+	45.3	0	100	+	+	+
14	42	F	R	Anaplastic astrocytoma	III	Seizure	L	Insula	+	71.0	18.8	73.5	+	-	+
15	54	M	R	Glioblastoma	IV	Seizure	R	Temporal-insula	+	89.2	8.4	90.6	+	+	+
16	58	M	R	Anaplastic oligodendroglioma	III	Seizure	L	Temporal-insula	+	91.8	5.6	93.9	+	-	+
17	32	M	R	Oligodendroglioma	II	Seizure	L	Insula	+	12.2	0	100	+	+	+
18	48	M	R	Diffuse astrocytoma	II	Seizure	R	Insula	+	33.8	5.5	83.9	+	+	+

EOR extent of resection, *EST* the emotional sensitivity task

showed memory disturbances. In one patient, the tumor was incidentally discovered on MR images. With regard to the final histopathological diagnosis, the present study included patients with gliomas or brain metastases, as shown in Table 1. The 18 cases comprised the following: 15 (83.3%) insular tumors, two (11.1%) temporal-insular tumors, and one (5.6%) temporal tumor. These tumors were located in the left hemisphere in 15 patients (83.3%) and in the right hemisphere in three patients (16.7%). The median tumor volume, measured on MRI images at preoperative diagnosis, was 50.5 cm³ (range 0.6–118.7 cm³). A final extent of resection (EOR) of > 90% was achieved in nine patients (50%).

Neuroimaging data acquisition

A 3.0-Tesla scanner (Siemens MAGNETOM Verio with a 32-channel head coil) was used to acquire a high-resolution anatomical image from each participant at the Nagoya University Hospital. The imaging parameters were as follows: whole-brain, high-resolution, T1-weighted, phase encoding direction: anterior to posterior, matrix size—256 × 256, repetition time (TR)—2.5 s, echo time (TE)—2.48 ms, 192 slices, slice thickness—1 mm with no gaps, flip angle—15°, voxel size—1 × 1 × 1 mm³, field of view (FOV) 256 mm.

Preoperative neurocognitive evaluation

All patients underwent neuropsychological testing upon admission and both before and after surgery. Handedness was examined using a standardized questionnaire from the Edinburgh inventory (Oldfield 1971). Hemispheric dominance was determined according to a comprehensive interpretation of the fMRI results. We performed all fMRI studies using the same scanner. The patients' neurocognitive functions, including language function, were evaluated by both speech therapists and occupational therapists using a neuropsychological battery that comprised the SLTA, WAIS-III, and WMS-R.

Emotional sensitivity task

The emotional sensitivity task was employed to measure the participants' ability to recognize emotions from facial expressions. The task was developed on the basis of our previous studies (Terasawa et al. 2014, 2015). It was used during the awake surgery, as well as in the preoperative phase (1 week before the operation) and in the postoperative phase (from 4 months to 18 months after the operation). In this way, we were able to analyze changes in the patients' abilities.

The task stimuli were prepared using photos selected from the ATR Facial Expression Database (DB99 of the Advanced Telecommunications Research Institute

International). The database comprises several sets of photos of Japanese men and women categorized by facial expression. We selected photos of the following facial expressions: anger, sadness, disgust, happiness, and neutral. We also created morphed continua photos that combined the same person's neutral facial expression with each of the other above-mentioned expressions to form happy–neutral, sad–neutral, disgusted–neutral, and angry–neutral expressions. Each morphed photo had two variations—40% and 60% of each emotion. The morphed images were created using Photomorph software. The slideshow function of Microsoft PowerPoint was used to present the stimuli. Each stimulus was presented twice, although the neutral stimulus was presented five times. Thus, there were 29 trials in a session: four emotions × three variations × two repetitions, plus five neutral stimuli.

The following components constructed a trial: (1) a fixation was presented for 2 s, (2) a face stimulus associated with response alternatives (name of emotions: anger/sadness/disgust/happiness/neutral) was presented for 4 s. During the second phase, participants were asked to choose one of the alternatives regarding what was expressed by the face stimulus. During the surgical operation, participants completed one session when the anterior insular cortex was stimulated and another session when the stimulation was not applied. We changed the order of stimulation from a session-based to a trial-based schedule after case 12. Subsequently, stimulation of the anterior insular cortex was alternated. The orders of the sessions and trials were counterbalanced among the subjects. The same task was used during the preoperative and postoperative phases.

Response types and the correct response index

We classified the participants' responses into three categories: a "hit" was a correct response, which indicates that the participants reported the target emotion—for example, a response of "anger" with an anger stimulus. A "recognition error" was defined as any response other than the target emotion—for example, a response of "anger" with a disgust stimulus. A "miss" was defined as a failure to detect emotion in a stimulus—in other words, the responses "neutral" with emotion-laden stimuli were classified as a missed response. After each test, the numbers for each of the three response types were counted in each emotional category. The "correct response index" was then calculated for each emotional category using the following formula: (number of hits – number of recognition errors – number of misses)/(number of hits + number of recognition errors + number of misses).

The index ranged from –1 to 1. If a participant was able to appropriately recognize a certain emotion, the index was 1 assigned. However, if the participant totally misunderstood a certain emotion, the index –1 was assigned. This indexing

system was selected because the number of recognition errors and misses exceeded the number of hits.

We used this index to evaluate the sensitivity to emotions of the participants because the index accounted for both correct and incorrect responses and represented the accuracy of their responses regarding emotional recognition on a scale.

Surgical procedure

In 16 of the 18 patients, awake surgery with direct electrical stimulation for the brain tumor was performed using an asleep–awake–asleep technique, as previously reported (Motomura et al. 2014; Fujii et al. 2015; Iijima et al. 2017; Motomura et al. 2017). In brief, we performed a wide craniotomy under the guidance of a neuro-navigation system (BrainLAB; Vector Vision Compact) (Nimsky et al. 2007). Firstly, we placed letter tags along the tumor margins before any brain shifts could occur. Subsequently, with the patient under general anesthesia, we opened the Sylvian fissure using the sharp dissection method to expose the insular cortex.

After then, in first stage, we then performed cortical mapping using counting tasks and picture naming tasks, presented on a monitor, to detect the cortical language regions. After language disorders had been evaluated, number tags were placed on the brain surface to identify motor and language functions. Next, the exposed anterior insular cortex was stimulated while the emotional sensitivity tasks were presented in number order (one set of emotional sensitivity tasks). We applied direct electrocortical stimulation to the middle short gyrus and/or posterior short gyrus in the anterior insular cortex (Fig. 1a, b). Finally, the tasks were repeated in the same order and no stimulation was given. We used a bipolar stimulator (Unique Medical, Osaka, Japan) to deliver a biphasic current (pulse width: 0.2 ms, pulse frequency: 60 Hz, single pulse phase duration: 0.5 ms, amplitude: 2–8 mA). Cortical mapping was performed by stimulating the primary motor cortex. This mapping was begun at 1 mA and increased in steps of 0.5 mA until a reproducible functional response was obtained. In this way, we ascertained the optimal threshold of stimulation and used it to stimulate the anterior insular cortex (Motomura et al. 2017). The maximum individual current intensity ranged from 2 to 8 mA. We performed the emotional sensitivity task during awake surgery.

Finally, the tumor was removed using the subpial resection technique, and subcortical mapping was performed to determine the functional boundary. After tumor resection during awake craniotomy, patients then underwent intraoperative MRI (iMRI) using a 0.4-T vertical field MR scanner (Aperto Inspire; Hitachi, Tokyo, Japan) installed in the operating room of the Brain Theater of Nagoya University Hospital to confirm the extent of tumor resection.

Lesion symptom mapping

To examine whether lesion location could be a reliable predictor of behavioral performance, we selected the voxel-based lesion symptom mapping (VLSM) method, which estimates the statistics on a voxel-by-voxel basis, allowing higher spatial precision (Bates et al. 2003; Rorden and Karnath 2004; Rorden et al. 2007). We used the non-parametric lesion mapping function in MRICron (<http://www.mccauslandcenter.sc.edu/mricron/mricron/>) to correlate a binary categorical measure of lesion in the whole brain with a continuous measure of behavioral performance in the tasks (Barbey et al. 2014; McDonald et al. 2017; Campanella et al. 2014; Reilly et al. 2014). We derived the lesion volumes in the native space using the original lesion tracings from the postoperative (follow-up period) T1- and T2-weighted structural MRI images in each patient. The area of the lesions in the “volume of interest” format was then co-registered with the T1 and T2-weighted images on transverse planes, and spatial normalization was performed using Statistical Parametric Mapping (SPM8; Wellcome Trust Centre for Neuroimaging, <http://www.fil.ion.ucl.ac.uk/spm/>). Voxel-by-voxel statistical analysis, specifically the Brunner–Munzel test, was then performed using NPM software in MRICron (Rorden et al. 2007). A separate VLSM analysis was then performed using the correct response index of the emotional sensitivity task as the predictor in the NPM analysis.

Results

Emotion recognition during anterior insular stimulation

Figure 2 shows the average and individual scores of the correct response index of the emotional sensitivity task during on and off stimulation of the anterior insular cortex. Although some participants could not complete the task during the operation because of their arousal state or whole bodily condition, 11 participants did complete the task (Table 1). We conducted *t* tests at each emotional condition to examine the effects of insula stimulation on task performance. Like the results of the *t* test, the effect of insular stimulation was statistically significant only in the anger condition [$t(10) = 2.88, p = 0.02$]. As Fig. 2 shows, the participants’ performance improved in anger recognition when they received insular stimulation. Statistically significant differences in the other emotional conditions were not obtained [happiness: $t(10) = -0.48, p = 0.64$, sadness: $t(10) = 0.14, p = 0.90$, disgust: $t(10) = 0.94, p = 0.37$, neutral: $t(10) = 1.23, p = 0.25$].

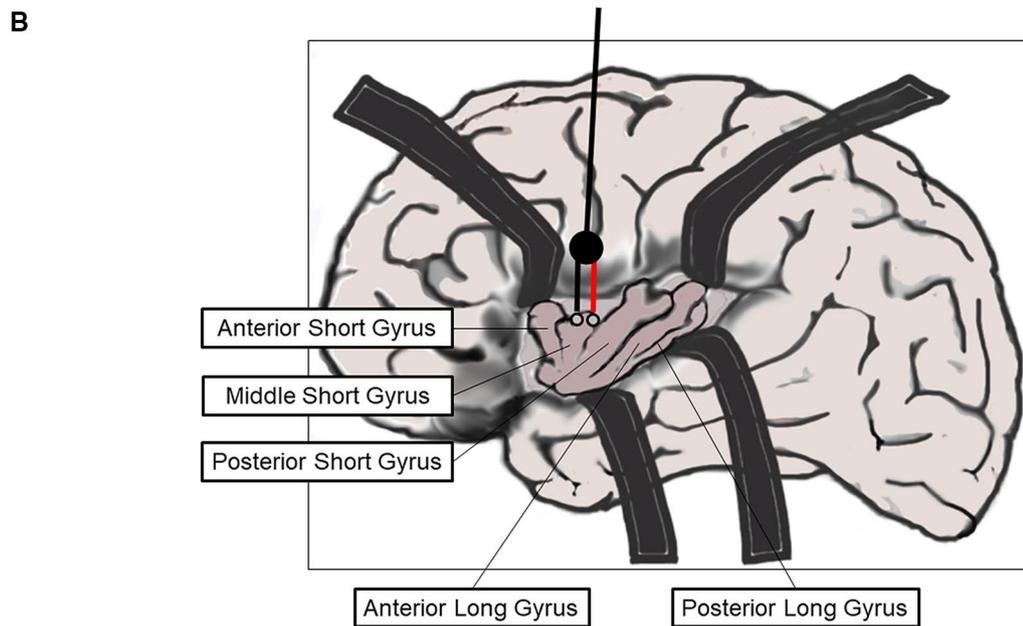
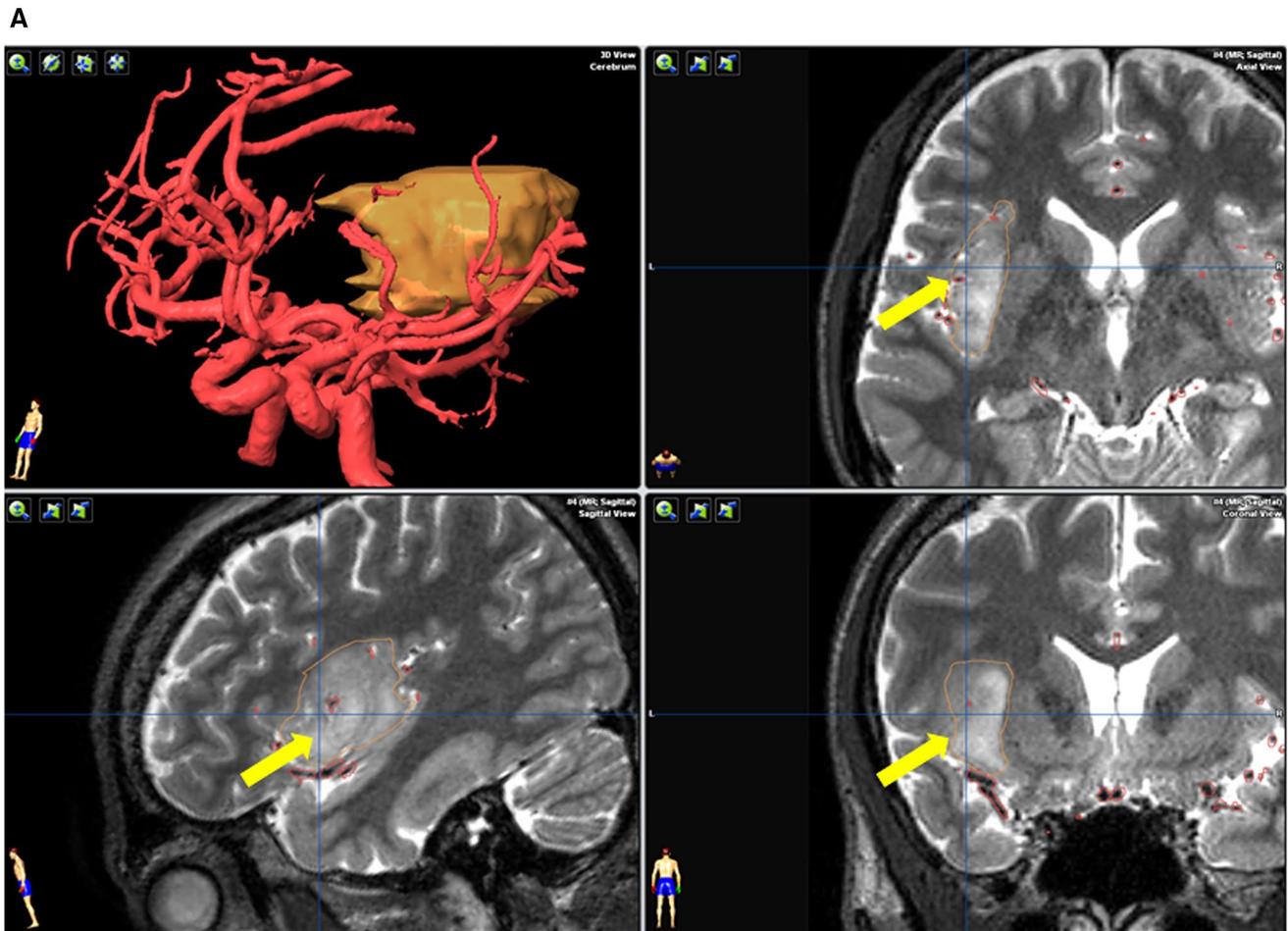
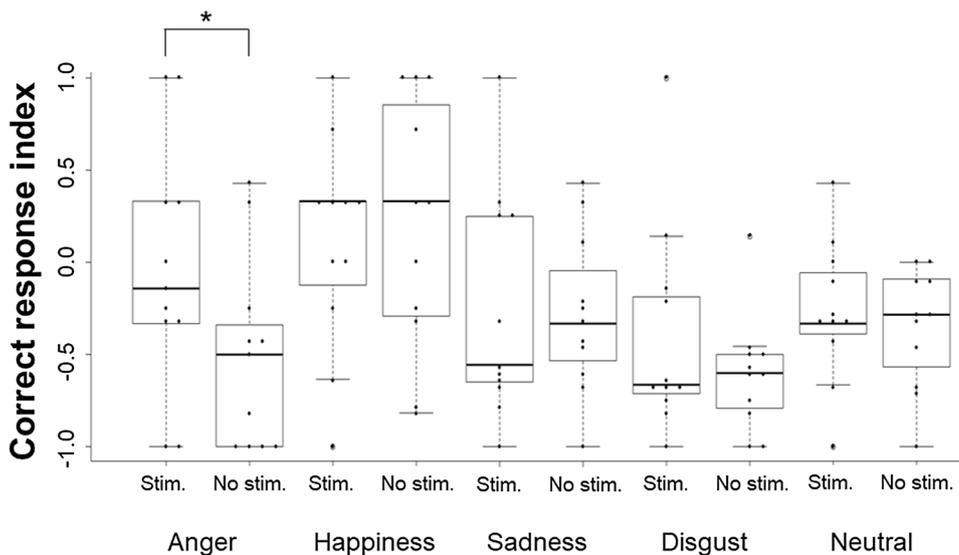


Fig. 1 **a** Generation of a 3D object representing the insular tumor and intracranial cerebral arteries. We stimulated the middle short gyrus and/or posterior short gyrus with emotional sensitivity tasks. Arrow the middle short gyrus and/or posterior short gyrus. **b** A schematic

diagram showing the locations of direct stimulation on the anterior insular cortex. We performed a direct electrocortical stimulation on the middle short gyrus and/or posterior short gyrus along with the emotional sensitivity tasks

Fig. 2 Performance in the emotional sensitivity task during awake surgery. The figure shows the average and individual scores of the correct response index that was calculated using the following formula: (number of hits – number of recognition errors – number of misses) / (number of hits + numbers of recognition errors + number of misses). The asterisk indicates a significant difference between on and off insula stimulation (* $p < 0.05$). *stim* stimulation



Changes in emotion recognition between pre- and post-operation

To examine the role of the insula in recognizing emotions, we compared performance in the emotional sensitivity task at the pre- and post-operation phase in the 14 patients (Table 1). Figure 3 shows the average and individual scores of the correct response index in the task during those two phases. We conducted *t* tests for each emotional condition to examine the effect of insular removal on emotion recognition. As the results of *t* tests show, the effect of insular removal was statistically significant in the anger and sadness conditions [anger:

$t(13) = 3.85, p = 0.002$, sadness: $t(13) = -4.00, p = 0.001$]. As Fig. 3 shows, the performance of the task in the anger condition became worse, but became better in the sadness condition. Statistically significant differences in the other emotional conditions were not obtained [happiness: $t(13) = -0.37, p = 0.72$, disgust: $t(13) = -1.53, p = 0.15$, neutral: $t(13) = -1.80, p = 0.09$].

In addition, 11 out of 14 cases showed a worse performance for the anger condition in the post-operation phase, and 10 out of 14 cases showed better performance for the sadness condition in this period. Thus, the changes observed between pre- and post-operation phase could not have been caused by a reduction in the number of cases in the post-operation phase (see Table 1).

Fig. 3 Changes in the performance in the emotional sensitivity task before and after surgery. The figure shows the average and individual scores of the correct response index that was calculated using the following formula: (number of hits – number of recognition errors – number of misses) / (number of hits + numbers of recognition errors + number of misses). The asterisk indicates a significant difference between pre- and post-operation (** $p < 0.01$). *pre* pre-operation, *post* post-operation



Lesion symptom mapping

For the emotional sensitivity task, we selected 14 patients who could complete the task with lesions in the left and right insula in order to identify areas associated with lower scores of the correct response index in each emotion category (anger, happiness, sadness, disgust, neutral; Table 2, Fig. 4). We set the threshold of the Brunner–Munzel Z scores to 2.33 ($p < 0.01$, uncorrected). Significant lesioned areas associated with lower scores of the task for each emotion category are shown in Table 2 along with the

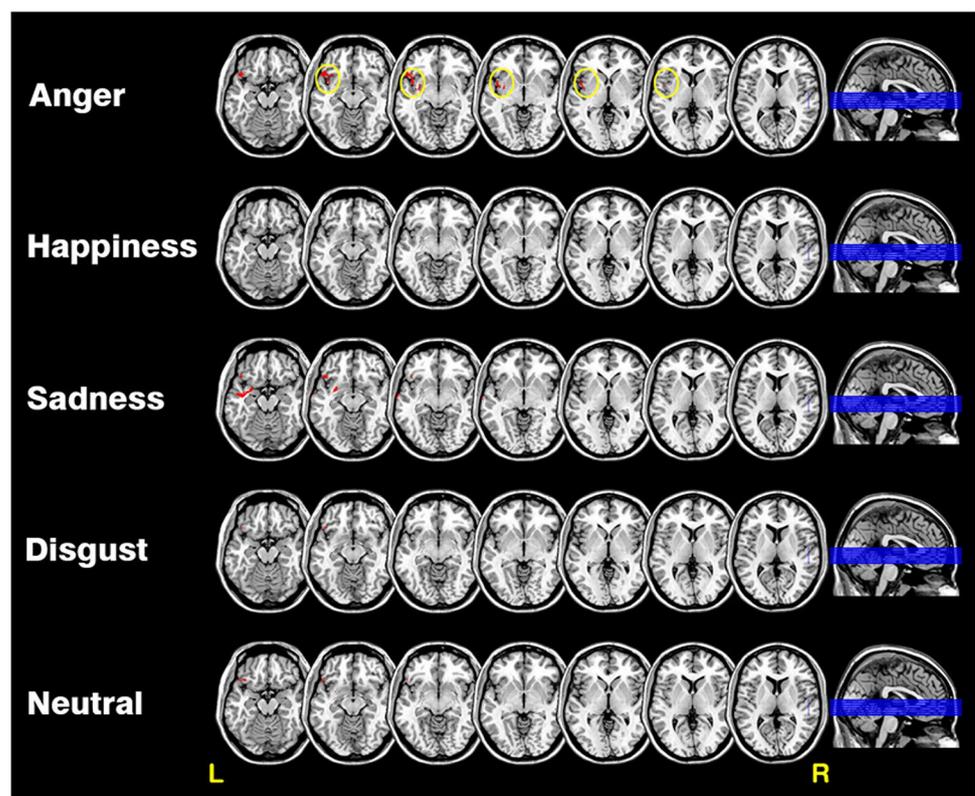
corresponding peak MNI coordinate, voxel size, and peak intensity (Z score). In the case of anger, a lower score was associated with lesions in the left anterior to middle insula. In the case of happiness and neutral emotions, a lower score was associated with lesions in the left inferior frontal area. With regard to sadness and disgust, lower scores were associated with lesions in the left parahippocampal area, and extended areas in the left inferior and superior temporal areas for sadness and in the left inferior frontal area for disgust. The most notable finding was that we could detect a significant involvement of the insula only in the anger condition.

Table 2 Results of the lesion symptom mapping analysis

		Peak MNI coordinate			Voxel size	Peak intensity
Anger	Left insula	−48	25	−13	617	3.09
Happiness	Left inferior frontal	−43	24	−16	16	2.55
Sadness	Left parahippocampal	−28	7	−18	111	2.79
	Left inferior temporal	−65	−16	−27	16	2.34
	Left superior temporal	−58	3	−6	21	2.34
Disgust	Left inferior frontal	−42	24	−15	68	2.75
	Left parahippocampal	−29	−2	−18	13	2.57
Neutral	Left inferior frontal	−48	25	−13	205	3.24

Significant lesioned areas associated with lower scores of the emotional sensitivity task were shown with corresponding peak MNI coordinate, voxel size, and peak intensity (Z score)

Fig. 4 Results of the lesion symptom mapping analysis. Significant lesioned areas associated with lower performance in the emotional sensitivity task are depicted. In the case of anger, a lower score was associated with lesions in the left anterior to middle insula. No significant involvement of the insula was found in other emotion conditions



Discussion

Penfield et al. revealed that intraoperative direct stimulation of the insular cortex during awake brain surgery led to visceral sensory and motor symptoms, particularly in the more inferior anterior parts of the insula (Penfield and Faulk 1955). These results have been complemented by data obtained in patients with epilepsy, whereby the insular cortex has been associated with viscerosensory processing (Nguyen et al. 2009; Craig 2002; Phillips et al. 1997; Isnard et al. 2004). Similarly, a neuroimaging study showed that the facial expression of disgust in particular activated the insular cortex (Phillips et al. 1997). However, numerous neuroimaging studies have shown that the insular cortex is not only involved in disgust processing, but also in complex brain functions, including interoceptive and emotional awareness and social cognition (Terasawa et al. 2013b; Boucher et al. 2015; Evans et al. 2002).

Previous studies have suggested that the insular cortex is critical for interpreting interoceptive and environmental information as subjective feelings of emotion, corroborating the notion that the insula is an anatomical and functional hub for the brain. In fact, the anterior insular cortex shows reciprocal connections with the frontal and anterior temporal cortex, while the posterior insular cortex shows such connections with the parietal and posterior temporal cortex, respectively (Dennis et al. 2013). One meta-analysis of fMRI studies indicated that the anterior insula is associated with cognitive and social-emotional processing, while the posterior part is associated with sensorimotor processing (Kurth et al. 2010). Taken together, these studies indicate that the insular cortex is essential for integrating multimodal sensory information with high-level cognitive processing.

Based on these findings, we hypothesized that insular lesions lead to an attenuation of the ability to recognize emotions, particularly those based on interoception (Terasawa et al. 2015). In keeping with this hypothesis, the present study found that the recognition of anger and the changes in emotion recognition between pre- and post-operation were strongly influenced by the stimulation to the insula during surgery and removal of the area by the surgery, respectively.

Anger recognition decreased after insular removal, while sadness recognition improved

We assessed facial emotional recognition processing in a group of patients both before and after surgery. The data showed that the performance of the task at anger condition became worse, but became better at sadness condition

(Fig. 3). According to the circumplex model of emotion, which defines emotions by plotting on a plane with dimensions of arousal and valence (positive or negative) (Kuppens et al. 2013; Russell 1980), the present results are very compelling. On the plane of the model, sadness, anger, and disgust are plotted close to each other on the valence dimension, since those are all negative emotions. However, these emotions differ in terms of arousal level, which is highest for anger and lowest for sadness, with disgust in the middle. The insular cortex is considered the neural substrate that represents arousal level (Lewis et al. 2007; Berntson et al. 2011), and decreased blood flow in this region leads to blunting of interoception (Khalsa et al. 2009). This may indicate that insular cortical and/or subcortical lesions impair interoception, which underlies the recognition of arousal levels, attenuating the ability to discriminate between negative emotions, as observed in the present study. Thus, as the insular cortex is related to arousal level recognition, the patients in this study had difficulty feeling arousal levels after the removal of the insula, but they could understand the emotional valence of the stimuli as indicated by the higher correct response index for the happiness condition. Thus, they misidentified anger as an emotional expression of less aroused emotions, such as disgust or sadness. We found a similar pattern of responses to the emotional sensitivity task in our previous study involving patients with insular lesions (Terasawa et al. 2015). Since anger is the emotion with the highest arousal level among negative emotions used in both this study and Terasawa et al. (2015), the effect of an attenuated ability to feel arousal resulted in the misidentification of the anger stimuli. Interestingly, the performance in this task during the awake surgical operation supports this hypothesis from another perspective.

Since the insula is considered to be a part of visceral brain, several studies have indicated that this area may be associated with recognition and generation of the feeling of disgust (Adolphs et al. 2003; Calder et al. 2000). However, the accumulation of neuropsychological studies on emotional processing revealed that not all areas of the insular cortex simply subserve the feeling of disgust (Boucher et al. 2015). Detailed studies proposed the possibility that a posterior insular lesion may be the critical area for the processing of disgust (Borg et al. 2013). The affected areas in our participants were from the anterior to middle insula. These observations may explain why evident deficit in the processing of disgust was observed in this study.

Anterior insular cortex stimulation enhanced anger recognition

Using an emotional sensitivity task during awake surgery, we examined the functions of the anterior insular cortex by

direct electrical stimulation. Our results showed an enhancement of anger recognition upon stimulation over the anterior insular cortex. Participants were able to perceive anger more accurately when they received insular stimulation, which modulates the insular cortex, thus enabling participants to feel anger accurately through heightened arousal levels. The results obtained during the awake surgery and post-surgery phase support our hypothesis that the insula is involved in arousal recognition through interoception. In a voxel-based meta-analysis of functional MRI studies, Fusar-Poli et al. revealed that anger perception processing is associated with bilateral inferior frontal cortex activity (Fusar-Poli et al. 2009). Other groups have revealed that high-frequency transcranial random noise stimulation of the inferior frontal cortex improves anger perception (Yang and Banissy 2017). In this regard, the fronto-insular tracts connect various regions of the frontal operculum with the anterior insular cortex, which may provide emotional information (Catani et al. 2012). Considering the neuro-network that exists between the anterior insular cortex, the inferior frontal cortex, and the fronto-insular tracts are connected by a neural network, our results were consistent with these reports, whereby anger recognition was enhanced by anterior insular cortex stimulation.

Some brain stimulation studies yielded controversial results concerning emotion recognition. Giussani et al. demonstrated that direct electrical stimulation interfered with facial emotion recognition in the right posterior perisylvian area in patients with right hemispheric lesions. Papagno et al. reported that an emotion recognition study was performed for 13 glioma patients by intraoperative direct stimulation of the insular cortex during awake surgery to identify whether the insula had a role in facial disgust processing. They concluded that stimulation of both the anterior and the posterior insular cortex produced interference in disgust recognition (Papagno et al. 2016). Although this study reported that only disgust was disrupted by insular cortical stimulation (Papagno et al. 2016), our results revealed that such stimulation of the anterior insular cortex enhanced anger recognition with statistical significance.

On the other hand, Bijanki et al. showed that the participants rated emotional facial expressions as more positive with direct stimulation of the basolateral nucleus of the right amygdala, rather than without stimulation (Bijanki et al. 2014). Mulak et al. reported that direct electrocortical stimulation can induce subjective experiences, such as digestive sensations in 87 epileptic patients (Mulak et al. 2008). Other reports also showed that insular cortex stimulation evoked anxiety and fear (Feindel and Penfield 1954) (Mullan and Penfield 1959), pleasant affective experiences (Ostrowsky et al. 2000), and olfactory and gustatory sensations (Ostrowsky et al. 2000). Furthermore, Yih et al. demonstrated that the magnitude of the electric current delivered

intracranially correlated positively with the perceived intensity of the subjective experience and the evoked emotional state in the orbitofrontal cortex, the insular cortex, and the anterior portion of the cingulate cortex (Yih et al. 2019). These findings revealed that direct stimulation to the insular cortex amplified the subjective experience, which resulted in an intensified ability to recognize emotional facial expressions. On the same note, Penfield et al. reported intraoperative electrocortical stimulation in a group of patients with a positive response to insula-induced viscerosensitive or motor- and somato-sensory symptoms (Penfield and Faulk 1955). In light of this finding, it is even more interesting that direct stimulation enhanced emotional recognition. However, we stimulated the superior anterior insular cortex rather than the inferior anterior areas underlying the temporal operculum, which Penfield et al. stimulated. It may be for this reason that we saw an enhancement in anger recognition rather than disgust recognition.

Little is known about the effect of direct stimulation on emotion recognition. A positive motor site was identified by involuntary movement of the face, arm, or leg, or inhibited motor function during active movement, using motor mapping by direct electrical stimulation. These findings suggested that the motor areas were identified using induced or inhibitory movements of the hand or face, by direct electrical stimulation. On the other hand, positive language sites were defined by stimulation-induced anomia, alexia, and paraphasia or speech arrest, indicating that direct stimulation impaired language functions. Apart from these objective responses obtained during motor and language mapping, the effect of electrical stimulation on the human subjective experiences and emotional states should be carefully discussed. It has been thought recently that a one-to-one correspondence between the cortical location and brain function is currently insufficient to explain the complexity of brain processing, especially for higher cognitive functions such as emotion recognition (De Benedictis and Duffau 2011). The hodotopic model (Catani and Ffytche 2005) explains the manner in which electrical stimulation may have caused divergent results (hyper- or hypofunctional) with respect to emotional recognition.

Anger recognition was associated with the left insula in lesion symptom mapping studies

Our results revealed that anger recognition was associated with lesions involving the left anterior to middle insula. One previous VLSM study focusing on the responsible area for facial emotion recognition showed that damage to the bilateral fronto-temporo-limbic network, especially the medial prefrontal cortex, anterior cingulate cortex, and left insular and temporal areas, impaired facial emotion recognition (Dal Monte et al. 2013). In the present study, we concentrated on

the insula and vicinity areas. Hence, we could not draw any direct comparison with our previous studies. However, the left insula was found to be responsible for facial emotion recognition in both studies, and the finding of the present study that the left insula is particularly involved in anger recognition was especially consistent with our present results. Based on these findings, we concluded that the left insula appeared to be an area that is responsible for anger recognition more than for that of other emotion categories.

Previous studies have suggested that insular functions show laterality—that the right insula seems to be more involved in sympathetic control, whereas the left insula may be more involved in parasympathetic control (Critchley and Harrison 2013). In light of this model, the passive viewing of angry expressions in others, as seen in the present experiment, may have caused greater stimulation and thus a more autonomically aroused state, since the right insula was largely intact. This may in turn have triggered greater parasympathetic control by the left insula, which, being mostly damaged, was reduced to a homeostatic state. As a result of these unbalanced controls on either side of the insula, the effects of anger recognition may have been enhanced, eliciting an aroused state that may have heightened the patients' subjective feelings of the emotion. To explore this possible explanation, future studies should use actual recordings of autonomic activities, including beat-by-beat heartrate.

Limitations

Although this report provided novel information on processing in a series of patients who had undergone insular tumor resection, our results were limited compared to those of prospective clinical trials, as retrospective studies can be influenced by unrecognized bias. Furthermore, the present report was based on a small number of cases; a larger sample size would have allowed for comparisons of resections in specific areas of the insula, such as the left vs. right insular lobe. Thus, a larger cohort study should be carried out to further establish the role of the insula in emotion processing. In particular, the VLSM analysis did not meet the stringent criteria of a permutation test (Medina et al. 2010). Further analysis with greater number of patients is required to generate more robust data.

In addition, a larger amount of tissue was removed from the insular tumors themselves than from the normal insula in the present study. Although low-grade gliomas can carry out normal tissue functions, the tumor itself may have affected performance in some patients. Next, emotion processing may have been affected by other brain areas when the insula was stimulated. Thus, the insula may have been part of a larger brain network of attention-related problem solving

and salience systems (Eckert et al. 2009), as well as pain processing mechanisms (Wager et al. 2004).

Considering that anterior insular cortex stimulation significantly enhanced only anger recognition rather than all emotion categories, our findings will be valuable for understanding the role of the insula in emotion processing. However, one could argue that a reliable baseline performance should be obtained during awake surgery, because emotion recognition might be affected when other areas are stimulated. Such a baseline performance should be measured at regions where connectivity to the insular cortex is sparse. However, on ethical grounds, we could not practically stimulate other distant areas that are not related to the insula, as this may have caused intraoperative complications (Bello et al. 2007; Motomura et al. 2018; Puglisi et al. 2018; Bernard et al. 2018).

Conclusions

We assessed emotion processing in a series of patients who had undergone brain tumor resection in the insular lobe. We found that direct electrical stimulation over the anterior insular cortex during awake brain mapping enhanced anger recognition in these patients. In contrast, the sensitivity of anger recognition significantly deteriorated, while that of sadness improved, when emotional sensitivity was compared before and after surgery. Furthermore, we showed that anger recognition is mainly associated with the left middle insula in a lesion symptom mapping study. Our findings suggest that insular cortex lesions are involved in changes related to emotion the recognition of emotions, including anger and sadness, and modulation of interoceptive processing underlies the changes. These findings highlight the need for prospective studies to assess emotion processing and establish a role for the insular lobe.

Acknowledgements The authors would like to thank Mr. Daisuke Hara and Mr. Yasuyuki Matsui (Department of Rehabilitation, Nagoya University Hospital, Nagoya, Japan) for their wonderful technical assistance.

Compliance with ethical standards

Conflict of interest This work was supported by a Grant-in-Aid for Scientific Research (B), awarded to S.U. (No. 24330210, 16H03740) and by a Grant-in-Aid for Scientific Research (C), awarded to K.M. (No. 25861268) from the Japan Society for the Promotion of Science (JSPS). We have no conflicts of interest to declare in this study.

References

Adolphs R, Damasio H, Tranel D, Cooper G, Damasio AR (2000) A role for somatosensory cortices in the visual recognition of

- emotion as revealed by three-dimensional lesion mapping. *J Neurosci* 20(7):2683–2690
- Adolphs R, Tranel D, Damasio AR (2003) Dissociable neural systems for recognizing emotions. *Brain Cogn* 52(1):61–69
- Barbey AK, Colom R, Paul EJ, Chau A, Solomon J, Grafman JH (2014) Lesion mapping of social problem solving. *Brain* 137(Pt 10):2823–2833. <https://doi.org/10.1093/brain/awu207>
- Bates E, Wilson SM, Saygin AP, Dick F, Sereno MI, Knight RT, Dronkers NF (2003) Voxel-based lesion–symptom mapping. *Nat Neurosci* 6(5):448–450. <https://doi.org/10.1038/nm1050>
- Bello L, Gallucci M, Fava M, Carrabba G, Giussani C, Acerbi F, Baratta P, Songa V, Conte V, Branca V, Stocchetti N, Papagno C, Gaini SM (2007) Intraoperative subcortical language tract mapping guides surgical removal of gliomas involving speech areas. *Neurosurg* 60(1):67–80. <https://doi.org/10.1227/01.neu.0000249206.58601.de> (**Discussion 80–62**)
- Bernard F, Lemee JM, Ter Minassian A, Menei P (2018) Right hemisphere cognitive functions: from clinical and anatomic bases to brain mapping during awake craniotomy part I: clinical and functional anatomy. *World Neurosurg* 118:348–359. <https://doi.org/10.1016/j.wneu.2018.05.024>
- Berntson GG, Norman GJ, Bechara A, Bruss J, Tranel D, Cacioppo JT (2011) The insula and evaluative processes. *Psychol Sci* 22(1):80–86. <https://doi.org/10.1177/0956797610391097>
- Bijanki KR, Kovach CK, McCormick LM, Kawasaki H, Dlouhy BJ, Feinstein J, Jones RD, Howard MA 3rd (2014) Case report: stimulation of the right amygdala induces transient changes in affective bias. *Brain Stimul* 7(5):690–693. <https://doi.org/10.1016/j.brs.2014.05.005>
- Borg C, Bedoin N, Peyron R, Bogey S, Laurent B, Thomas-Anterion C (2013) Impaired emotional processing in a patient with a left posterior insula-SII lesion. *Neurocase* 19(6):592–603. <https://doi.org/10.1080/13554794.2012.713491>
- Boucher O, Rouleau I, Lassonde M, Lepore F, Bouthillier A, Nguyen DK (2015) Social information processing following resection of the insular cortex. *Neuropsychol* 71:1–10. <https://doi.org/10.1016/j.neuropsychologia.2015.03.008>
- Calder AJ, Keane J, Manes F, Antoun N, Young AW (2000) Impaired recognition and experience of disgust following brain injury. *Nat Neurosci* 3(11):1077–1078. <https://doi.org/10.1038/80586>
- Campanella F, Shallice T, Ius T, Fabbro F, Skrap M (2014) Impact of brain tumour location on emotion and personality: a voxel-based lesion–symptom mapping study on mentalization processes. *Brain* 137(Pt 9):2532–2545. <https://doi.org/10.1093/brain/awu183>
- Catani M, Ffytche DH (2005) The rises and falls of disconnection syndromes. *Brain* 128(Pt 10):2224–2239. <https://doi.org/10.1093/brain/awh622>
- Catani M, Dell’acqua F, Vergani F, Malik F, Hodge H, Roy P, Valabregue R, Thiebaut de Schotten M (2012) Short frontal lobe connections of the human brain. *Cortex* 48(2):273–291. <https://doi.org/10.1016/j.cortex.2011.12.001>
- Craig AD (2002) How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci* 3(8):655–666. <https://doi.org/10.1038/nrn894>
- Critchley HD, Harrison NA (2013) Visceral influences on brain and behavior. *Neuron* 77(4):624–638. <https://doi.org/10.1016/j.neuron.2013.02.008>
- Dal Monte O, Krueger F, Solomon JM, Schintu S, Knutson KM, Stenziok M, Pardini M, Leopold A, Raymond V, Grafman J (2013) A voxel-based lesion study on facial emotion recognition after penetrating brain injury. *Soc Cogn Affect Neurosci* 8(6):632–639. <https://doi.org/10.1093/scan/ns041>
- D’Angelo C, Mirijello A, Leggio L, Ferrulli A, Carotenuto V, Icolaro N, Miceli A, D’Angelo V, Gasbarrini G, Addolorato G (2008) State and trait anxiety and depression in patients with primary brain tumors before and after surgery: 1-year longitudinal study. *J Neurosurg* 108(2):281–286. <https://doi.org/10.3171/JNS/2008/108/2/0281>
- De Benedictis A, Duffau H (2011) Brain hodotopy: from esoteric concept to practical surgical applications. *Neurosurg* 68(6):1709–1723. <https://doi.org/10.1227/neu.0b013e3182124690> (**Discussion 1723**)
- Dennis EL, Jahanshad N, McMahon KL, de Zubicaray GI, Martin NG, Hickie IB, Toga AW, Wright MJ, Thompson PM (2013) Development of insula connectivity between ages 12 and 30 revealed by high angular resolution diffusion imaging. *Hum Brain Mapp*. <https://doi.org/10.1002/hbm.22292>
- Duffau H (2010) Awake surgery for nonlanguage mapping. *Neurosurgery* 66(3):528–529. <https://doi.org/10.1227/01.neu.0000364996.97762.73> (**Discussion 528–529**)
- Duffau H (2018) Is non-awake surgery for supratentorial adult low-grade glioma treatment still feasible? *Neurosurg Rev* 41(1):133–139. <https://doi.org/10.1007/s10143-017-0918-9>
- Duffau H, Peggy Gatignol ST, Mandonnet E, Capelle L, Taillandier L (2008) Intraoperative subcortical stimulation mapping of language pathways in a consecutive series of 115 patients with grade II glioma in the left dominant hemisphere. *J Neurosurg* 109(3):461–471. <https://doi.org/10.3171/JNS/2008/109/9/0461>
- Duffau H, Moritz-Gasser S, Gatignol P (2009) Functional outcome after language mapping for insular World Health Organization grade II gliomas in the dominant hemisphere: experience with 24 patients. *Neurosurg Focus* 27(2):E7. <https://doi.org/10.3171/2009.5.FOCUS0938>
- Eckert MA, Menon V, Walczak A, Ahlstrom J, Denslow S, Horwitz A, Dubno JR (2009) At the heart of the ventral attention system: the right anterior insula. *Hum Brain Mapp* 30(8):2530–2541. <https://doi.org/10.1002/hbm.20688>
- Eseoun CI, Rincon-Torroella J, ReFaey K, Lee YM, Nangiana J, Vivas-Buitrago T, Quinones-Hinojosa A (2017) Awake craniotomy vs craniotomy under general anesthesia for perirolandic gliomas: evaluating perioperative complications and extent of resection. *Neurosurgery* 81(3):481–489. <https://doi.org/10.1093/neuros/nyx023>
- Evans KC, Banzett RB, Adams L, McKay L, Frackowiak RS, Corfield DR (2002) BOLD fMRI identifies limbic, paralimbic, and cerebellar activation during air hunger. *J Neurophysiol* 88(3):1500–1511. <https://doi.org/10.1152/jn.2002.88.3.1500>
- Feindel W, Penfield W (1954) Localization of discharge in temporal lobe automatism. *AMA Arch Neurol Psychiatry* 72(5):603–630
- Feinstein JS, Khalsa SS, Salomons TV, Prkachin KM, Frey-Law LA, Lee JE, Tranel D, Rudrauf D (2016) Preserved emotional awareness of pain in a patient with extensive bilateral damage to the insula, anterior cingulate, and amygdala. *Brain Struct Funct* 221(3):1499–1511. <https://doi.org/10.1007/s00429-014-0986-3>
- Fujii M, Maesawa S, Motomura K, Futamura M, Hayashi Y, Koba I, Wakabayashi T (2015) Intraoperative subcortical mapping of a language-associated deep frontal tract connecting the superior frontal gyrus to Broca’s area in the dominant hemisphere of patients with glioma. *J Neurosurg* 122(6):1390–1396. <https://doi.org/10.3171/2014.10.JNS14945>
- Fusar-Poli P, Placentino A, Carletti F, Landi P, Allen P, Surguladze S, Benedetti F, Abbamonte M, Gasparotti R, Barale F, Perez J, McGuire P, Politi P (2009) Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *J Psychiatry Neurosci* 34(6):418–432
- Herbet G, Lafargue G, Moritz-Gasser S, Menjot de Champfleury N, Costi E, Bonnetblanc F, Duffau H (2015) A disconnection account of subjective empathy impairments in diffuse low-grade glioma patients. *Neuropsychol* 70:165–176. <https://doi.org/10.1016/j.neuropsychologia.2015.02.015>

- Hervey-Jumper SL, Li J, Osorio JA, Lau D, Molinaro AM, Benet A, Berger MS (2016) Surgical assessment of the insula. Part 2: validation of the Berger-Sanai zone classification system for predicting extent of glioma resection. *J Neurosurg* 124(2):482–488. <https://doi.org/10.3171/2015.4.jns1521>
- Iijima K, Motomura K, Chalise L, Hirano M, Natsume A, Wakabayashi T (2017) Efficacy of the transtemporal approach with awake brain mapping to reach the dominant posteromedial temporal lesions. *Acta Neurochir (Wien)* 159(1):177–184. <https://doi.org/10.1007/s00701-016-3035-6>
- Ilmberger J, Ruge M, Kreth FW, Briegel J, Reulen HJ, Tonn JC (2008) Intraoperative mapping of language functions: a longitudinal neurolinguistic analysis. *J Neurosurg* 109(4):583–592. <https://doi.org/10.3171/JNS.2008.109.10.0583>
- Isnard J, Guenot M, Sindou M, Mauguire F (2004) Clinical manifestations of insular lobe seizures: a stereo-electroencephalographic study. *Epilepsia* 45(9):1079–1090. <https://doi.org/10.1111/j.0013-9580.2004.68903.x>
- Khalsa SS, Rudrauf D, Feinstein JS, Tranel D (2009) The pathways of interoceptive awareness. *Nat Neurosci* 12(12):1494–1496. <https://doi.org/10.1038/nm.2411>
- Kuppens P, Tuerlinckx F, Russell JA, Barrett LF (2013) The relation between valence and arousal in subjective experience. *Psychol Bull* 139(4):917–940. <https://doi.org/10.1037/a0030811>
- Kurth F, Zilles K, Fox PT, Laird AR, Eickhoff SB (2010) A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Struct Funct* 214(5–6):519–534. <https://doi.org/10.1007/s00429-010-0255-z>
- Lewis PA, Critchley HD, Rotshtein P, Dolan RJ (2007) Neural correlates of processing valence and arousal in affective words. *Cereb Cortex* 17(3):742–748. <https://doi.org/10.1093/cercor/bhk024>
- McDonald V, Hauner KK, Chau A, Krueger F, Grafman J (2017) Networks underlying trait impulsivity: evidence from voxel-based lesion-symptom mapping. *Hum Brain Mapp* 38(2):656–665. <https://doi.org/10.1002/hbm.23406>
- Medina J, Kimberg DY, Chatterjee A, Coslett HB (2010) Inappropriate usage of the Brunner–Munzel test in recent voxel-based lesion-symptom mapping studies. *Neuropsychologia* 48(1):341–343. <https://doi.org/10.1016/j.neuropsychologia.2009.09.016>
- Motomura K, Fujii M, Maesawa S, Kuramitsu S, Natsume A, Wakabayashi T (2014) Association of dorsal inferior frontooccipital fasciculus fibers in the deep parietal lobe with both reading and writing processes: a brain mapping study. *J Neurosurg* 121(1):142–148. <https://doi.org/10.3171/2014.2.JNS131234>
- Motomura K, Natsume A, Iijima K, Kuramitsu S, Fujii M, Yamamoto T, Maesawa S, Sugiura J, Wakabayashi T (2017) Surgical benefits of combined awake craniotomy and intraoperative magnetic resonance imaging for gliomas associated with eloquent areas. *J Neurosurg* 127(4):790–797. <https://doi.org/10.3171/2016.9.JNS16152>
- Motomura K, Chalise L, Ohka F, Aoki K, Tanahashi K, Hirano M, Nishikawa T, Wakabayashi T, Natsume A (2018) Supratotal resection of diffuse frontal lower grade gliomas with awake brain mapping, preserving motor, language, and neurocognitive functions. *World Neurosurg* 119:30–39. <https://doi.org/10.1016/j.wneu.2018.07.193>
- Mulak A, Kahane P, Hoffmann D, Minotti L, Bonaz B (2008) Brain mapping of digestive sensations elicited by cortical electrical stimulations. *Neurogastroenterol Motil* 20(6):588–596. <https://doi.org/10.1111/j.1365-2982.2007.01066.x>
- Mullan S, Penfield W (1959) Illusions of comparative interpretation and emotion: production by epileptic discharge and by electrical stimulation in the temporal cortex. *AMA Arch Neurol Psychiatry* 81(3):269–284
- Nguyen DK, Nguyen DB, Malak R, Leroux JM, Carmant L, Saint-Hilaire JM, Giard N, Cossette P, Bouthillier A (2009) Revisiting the role of the insula in refractory partial epilepsy. *Epilepsia* 50(3):510–520. <https://doi.org/10.1111/j.1528-1167.2008.01758.x>
- Nimsky C, Ganslandt O, Fahlbusch R (2007) Implementation of fiber tract navigation. *Neurosurgery* 61(1):306–317. <https://doi.org/10.1227/01.neu.0000279224.83998.7d> (Discussion 317–308)
- Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9(1):97–113
- Ostrowsky K, Isnard J, Rylvlin P, Guenot M, Fischer C, Mauguire F (2000) Functional mapping of the insular cortex: clinical implication in temporal lobe epilepsy. *Epilepsia* 41(6):681–686
- Papagno C, Pisoni A, Mattavelli G, Casarotti A, Comi A, Fumagalli F, Vernice M, Fava E, Riva M, Bello L (2016) Specific disgust processing in the left insula: new evidence from direct electrical stimulation. *Neuropsychologia* 84:29–35. <https://doi.org/10.1016/j.neuropsychologia.2016.01.036>
- Penfield W, Faulk ME Jr (1955) The insula: further observations on its function. *Brain* 78(4):445–470
- Phillips ML, Young AW, Senior C, Brammer M, Andrew C, Calder AJ, Bullmore ET, Perrett DI, Rowland D, Williams SC, Gray JA, David AS (1997) A specific neural substrate for perceiving facial expressions of disgust. *Nature* 389(6650):495–498. <https://doi.org/10.1038/39051>
- Puglisi G, Sciortino T, Rossi M, Leonetti A, Forna L, Conti Nibali M, Casarotti A, Pessina F, Riva M, Cerri G, Bello L (2018) Preserving executive functions in nondominant frontal lobe glioma surgery: an intraoperative tool. *J Neurosurg* 1:1–7. <https://doi.org/10.3171/2018.4.jns18393>
- Reilly J, Harnish S, Garcia A, Hung J, Rodriguez AD, Crosson B (2014) Lesion symptom mapping of manipulable object naming in nonfluent aphasia: can a brain be both embodied and disembodied? *Cogn Neurosci* 31(4):287–312. <https://doi.org/10.1080/02643294.2014.914022>
- Rorden C, Karnath HO (2004) Using human brain lesions to infer function: a relic from a past era in the fMRI age? *Nat Rev Neurosci* 5(10):813–819. <https://doi.org/10.1038/nrn1521>
- Rorden C, Karnath HO, Bonilha L (2007) Improving lesion-symptom mapping. *J Cogn Neurosci* 19(7):1081–1088. <https://doi.org/10.1162/jocn.2007.19.7.1081>
- Russell JA (1980) A circumplex model of affect. *J Pers Soc Psychol* 39:1161–1178
- Sanai N, Mirzadeh Z, Berger MS (2008) Functional outcome after language mapping for glioma resection. *N Engl J Med* 358(1):18–27. <https://doi.org/10.1056/NEJMoa067819>
- Sanai N, Polley MY, Berger MS (2010) Insular glioma resection: assessment of patient morbidity, survival, and tumor progression. *J Neurosurg* 112(1):1–9. <https://doi.org/10.3171/2009.6.JNS0952>
- Terasawa Y, Fukushima H, Umeda S (2013a) How does interoceptive awareness interact with the subjective experience of emotion? An fMRI study. *Hum Brain Mapp* 34(3):598–612. <https://doi.org/10.1002/hbm.21458>
- Terasawa Y, Shibata M, Moriguchi Y, Umeda S (2013b) Anterior insular cortex mediates bodily sensibility and social anxiety. *Soc Cogn Affect Neurosci* 8(3):259–266. <https://doi.org/10.1093/scan/nss108>
- Terasawa Y, Moriguchi Y, Tochizawa S, Umeda S (2014) Interoceptive sensitivity predicts sensitivity to the emotions of others. *Cogn Emot*. <https://doi.org/10.1080/02699931.2014.888988>
- Terasawa Y, Kurosaki Y, Ibata Y, Moriguchi Y, Umeda S (2015) Attenuated sensitivity to the emotions of others by insular lesion. *Front Psychol* 6:1314. <https://doi.org/10.3389/fpsyg.2015.01314>
- Vilasboas T, Herbet G, Duffau H (2017) Challenging the myth of right nondominant hemisphere: lessons from corticosubcortical stimulation mapping in awake surgery and surgical implications. *World Neurosurg* 103:449–456. <https://doi.org/10.1016/j.wneu.2017.04.021>

- Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD (2004) Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science* 303(5661):1162–1167. <https://doi.org/10.1126/science.1093065>
- Yang T, Banissy MJ (2017) Enhancing anger perception in older adults by stimulating inferior frontal cortex with high frequency transcranial random noise stimulation. *Neuropsychol* 102:163–169. <https://doi.org/10.1016/j.neuropsychologia.2017.06.017>
- Yih J, Beam DE, Fox KCR, Parvizi J (2019) Intensity of affective experience is modulated by magnitude of intracranial electrical

stimulation in human orbitofrontal, cingulate, and insular cortex. *Soc Cogn Affect Neurosci*. <https://doi.org/10.1093/scan/nsz015>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.