after a variable time interval - most often several days up to 4 weeks - after stimulation parameters modifications (Cilia et al., 2008). Several investigators reported that rigidity and tremor were abolished within several minutes of stimulation, but the full effect on bradykinesia and axial symptom, especially gait disturbance, were appreciated only after a longer period of stimulation, with a slow worsening over more than 2 days period after stimulation-off (Canavero et al., 2002; Cilia et al., 2008; Pagni et al., 2003; Tani et al., 2007). In some studies, the motor symptom assessments were done in shorter period after the modification of stimulation parameter, so the benefit in motor symptom could be underestimated.

5. Mechanisms of action

The exact mechanisms of action of EMCS are poorly understood. It is noteworthy that, whereas the effects of EMCS on rigidity and tremor are almost immediate (observed within the first minute of stimulation), the clinical benefit on akinesia and axial symptom necessitate a longer stimulation time to become detectable. The latency of the clinical effects of high-frequency STN-DBS is also known to vary from one type of parkinsonian motor symptoms to another with short latency benefit (less than 1 min) observed for rigidity and tremor and longer time delay (a few minutes, up to a few days) observed for other symptoms such as bradykinesia and akinesia (Krack et al., 2002). As discussed by others, the delays of clinical benefits observed with EMCS may be due to synaptic plasticity, long-term potentiation, long-term depression, expression of secondary messengers or polarization of brain tissue (Drouot et al., 2004; Krack et al., 2002; Priori and Lefaucheur, 2007), and the immediate effects may be due to the dual effect - imposing a specific pattern of activity and suppress abnormal, disease-associated rhythmicity of oscillation in corticobasal ganglia-cortical circuit (Brown, 2006; Fasano et al., 2008; Garcia et al., 2003; Priori and Lefaucheur, 2007).

Studies of rTMS of M1 reveal that PD is associated with excess excitability or reduced inhibition at the M1 (Cantello et al., 2002), and rigidity and tremor might be caused by hyperactivity of the M1 (Haslinger et al., 2001; Rodriguez-Oroz et al., 2009). In the patients with PD, during production of a voluntary output, its activation is inadequately modulated, owing, for instance, to reduction of intracortical inhibitory mechanisms mediated by γ-aminobutyric acid A (GABA) and GABA receptors (Cantello et al., 2002). Canavero et al. suggests that EMCS increases the cortical GABA in patients affected by central pain syndromes (Canavero and Bonicalzi, 1995, 1998). EMCS might reduce cortical hyperactivity, increasing GABA concentration and activating inhibitory neurons (Hanajima et al., 2002). Indeed, ECD SPECT data demonstrated a resting state reduction of neuronal activity in motor cortical areas during EMCS (Cilia et al., 2008).

Finally, functional neuroimaging studies showed a significant increase of cerebral perfusion in the SMA and the DLPFC in STIM-ON condition (Drouot et al., 2004; Fasano et al., 2008; Tani et al., 2007). The SMA and the DLPFC are known to be under-active in patients with PD, probably underlying bradykinesia (Haslinger et al., 2001; Jahanshahi et al., 1995; Rascol et al., 1992), and these cortical metabolic abnormalities can be reversed by antiparkinsonian therapies such as dopaminergic treatment (Jenkins et al., 1992), pallidotomy (Grafton et al., 1995), STN-DBS (Limousin et al., 1997) or GPi-DBS (Fukuda et al., 2001). The similarity of these results suggests that these strategies may induce a similar therapeutic benefit in the patients with PD and might have some common mechanism.

Authors	Cases	Stimulation	Modality	Neuroimaging
Cilla	6	unilateral, 40-60 Hz	Tc-SPECT STIM-ON vs STIM-OFF under rest	Decrease in bilateral M1, bilateral premotor cortex, left DLPFC, right caudate nucleus and left middle occipital gyrus Increase in right cerebellar lobe, left inferior occipital gyrus, left cerevellar lobe and vermis.
Strafella	4	unilateral, 50 or 130 Hz	[^{15}O] H_2O PET movement vs rest	the changes in rCBF were not significantly different when comparing across different stimulation setting (OFF vs 50 Hz vs 130 Hz).
Canavero	3	unilateral, 20 - 31 Hz	IBZM-SPECT	Before EMCS, asymmetrical binding (right less than left) in the basal ganglia During EMCS, renormalization of basal ganglia anomalies
			ECD-SPECT	Before EMCS, bilateral parieto-temporal hypoperfusion. During EMCS, renormalization of cortical metabolism on the side of stimulation but not contralaterally.
Fasano	1	bilateral, 130 Hz	ECD-SPECT STIM-OFF vs STIM-ON (medication off)	increase in the right frontal, right parietal cortex and left frontal cortex.
Tani	1	bilateral, 100 Hz	[^{15}O] H_2O PET STIM-OFF vs STIM-ON (medication on)	increase in the left SMA and right DLPFC.

Table 2. Summery of the functional neuroimaging

6. Complication

The only complication reported concerning EMCS for PD was misplaced electrode (Pagni et al., 2005). Because of the small number of the cases of EMCS for PD, we summarize the reported complication of EMCS for intractable pain patients in this section.

While a majority of studies have reported no adverse events with EMCS (Gharabaghi et al., 2005; Saitoh et al., 2000; Tsubokawa et al., 1991b), serious complications have been reported. Montes et al. (Montes et al., 2002) analyzed event-related potentials (ERPs) and behavioral performance during an auditory target-detection task in 11 consecutive patients obtained during EMCS and 10 minutes after switching off stimulation. While sensory responses remained unaffected by EMCS, there was a significant delay of brain potentials reflecting

target detection in the older patients, rapidly reversible after EMCS discontinuation. No effect was observed in patients younger than 50 years. Cognitive effects of EMCS appeared as mild and non-specific, directly related to the stimulation period (i.e. with no post-effect), in a manner reminding of cognitive effects reported during rTMS on M1. Thus, EMCS may interfere with relatively simple cognitive processes such as those underlying target detection, notably in the elderly and in the presence of preexistent cerebral lesions.

Occurrence of epileptic seizures has been reported during test stimulation in a minority of patients. The low rate of epileptic seizures during chronic stimulation (0.2%) means that stimulation of M1 within an appropriate range of parameters is reasonably safe. The most serious reported complications are epidural or subdural hematomas. These are definitely exceptional with an extradural approach, and some surgeons never observed one, making the risk of peri-operative hemorrhage much lower compared to DBS.

Some wound infections have been reported by most neurosurgeons. If the infection occurs, all devices including the paddle, extension leads, and pulse generators must be removed temporally. The implanted pulse generator (IPG) can accidentally turn off due to electromagnetic interference from household devices in close (<10 cm) proximity, such as electric appliances of any kind, but also anti-theft devices and metal detectors or magnets in loudspeakers.

At impedances >2000 Ω, a connection problem, such as a broken cable or a lead fracture, must be suspected. The operator should thus measure impedance in a unipolar configuration in order to assign a value to the single contact.

7. Conclusion

EMCS can provide some different benefit for the patients with PD from STN-DBS. Although the degree of clinical improvement of EMCS is lower than that of DBS, the fact that EMCS can improve axial symptom of PD, which is difficult even with STN-DBS, is an irreplaceable gift for some part of patients with PD, and its less surgical invasiveness than DBS can make the surgery safer for the patients with advanced age or sever brain atrophy.

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SHORT REPORT

Hemifacial spasm caused by intra-axial brainstem cavernous angioma with venous angiomas

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Abstract

Hemifacial spasms (HFS) are usually caused by vascular compression on the extra-axial facial nerve. In this case, we concluded that an intra-axial brainstem cavernous angioma with a venous angioma diagnosed by MRI must have been responsible for HFS, because no other possible causes were found during intraoperative observations.

Key words: cavernous angioma; hemifacial spasm; MR images; venous angioma.

Introduction

Hemifacial spasm (HFS) is a facial movement disorder characterised by involuntary, unilateral, and intermittent contractions of the facial muscles. HFS is usually caused by vascular compression of the root exit zone (REZ) of the ipsilateral facial nerve mostly by the anterior inferior cerebellar artery (AICA). Microvascular decompression (MVD) is an effective treatment option for HFS caused by such vascular compressions. However, other unusual compression sites, including cases of intra-axial compression by tumours and distal compression of the facial nerve, have been reported.[3] These unusual causes are often responsible for unsatisfactory results after MVD. In this case report, we describe the case of an HFS patient that is, as far as we know, unique both in terms of the causative lesion and the site of compression.

Case description

A 38-year-old woman underwent surgery for left HFS, 17 years after the onset of symptoms. At the age of 16, she had experienced transient ocular motor palsy during her pregnancy. A brainstem cavernous angioma was diagnosed by CT, and her symptoms resolved spontaneously after delivery. At the age of 21, she experienced intermittent spasms of the left eyelid, which gradually spread to other ipsilateral muscles around her mouth. The spasms worsened with psychological stress and occurred simultaneously at the lower eyelid and angle of the mouth. Botulinum toxin A injections were applied three times, but the patient was not satisfied with the results. Her facial spasms had become a source of social embarrassment, and she was therefore referred to our hospital for surgery at the age of 38. On admission, facial spasms with slight facial palsy were noted, but there were no other neurological manifestations, including ocular motor palsy or hearing disturbance.

Preoperative MR imaging showed that the AICA lay close to the left facial nerve located near the REZ (Fig. 1A, B). MR imaging also revealed an oval pontine lesion of mixed intensity on a T2-weighted image and low intensity on a T1-weighted image (Fig. 1A, C). A number of linear flow voids radiated from the round lesion. Two major venous angiomas existed ventrally to the facial nerve in the prepontine cistern and drained into the inferior petrosal sinus, but they did not contact the facial nerve REZ (Fig. 1D). Thus, this lesion was diagnosed as a cavernous angioma with venous angiomas. The patient was diagnosed with typical HFS resulting from compression of the facial nerve REZ by the AICA. Accordingly, MVD was undertaken, with the patient providing written informed consent.

The MVD was performed through a left retromastoid keyhole, with the patient in the lateral position. Abnormal muscle responses (AMR) and auditory brainstem responses (ABR) were monitored. Intraoperative observation revealed that the AICA looped around the REZ, but that it did not compress the REZ. No vessel or mass were found to be in contact with the REZ or the cisternal portion of the facial nerve (Fig. 2). A large venous angioma was found ventral to the facial nerve, but the vessel did not compress the nerve (Fig. 2A). The AICA was displaced to separate it from the REZ, but AMR waveforms remained unchanged. Postoperatively, the HFS persisted without any other surgical complications. The postoperative MR images showed no significant changes except that of the translocated AICA.

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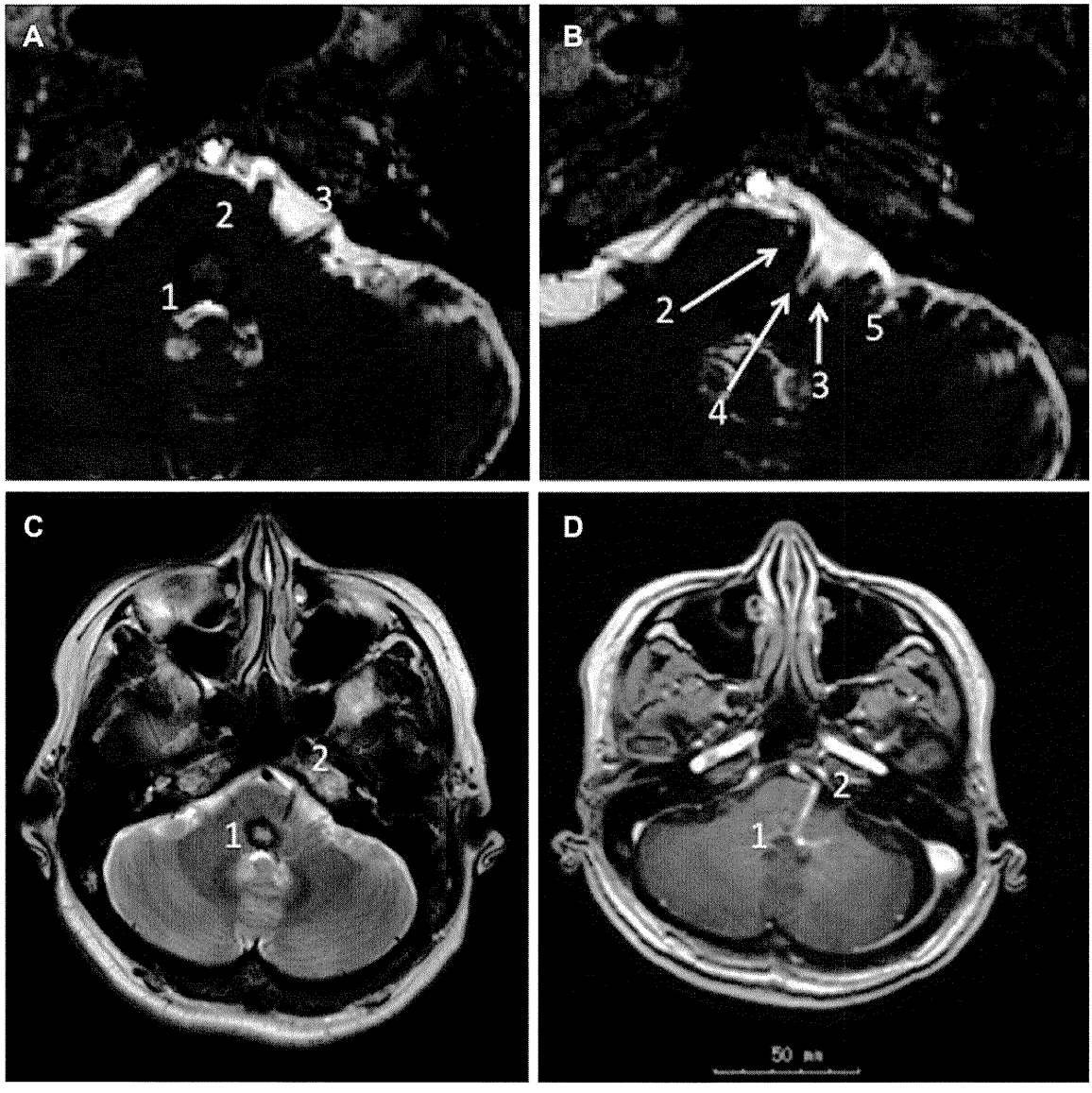

Fig 1. Preoperative MR images. (A, B) Axial constructive interference in steady state (CISS) images. (c) Preoperative axial T2-weighted image. (D) Postcontrast axial T1-weighted image showing venous angiomas into which the pontine cavernous angioma drained: (1) cavernous angioma, (2) venous angioma, (3) facial nerve, (4) anterior inferior cerebellar artery, and (5) flocculus.

Discussion

To our knowledge, this is the first reported case of HFS caused by a brainstem cavernous angioma with venous angiomas. It is generally accepted that HFS is caused by pulsatile vascular compressions of the facial nerve REZ.[1] In our case, the preoperative MR images revealed an intra-axial cavernous angioma and venous angiomas that appeared to be separate from the cisternal portion of the facial nerve (Fig. 1). Intraoperatively, it was confirmed that neither the AICA nor any other structures were compressing the extra-axial facial nerve (Fig. 2). These findings lead us to the conclusion that the intra-axial cavernous angioma and accompanying venous angiomas may be responsible for the HFS in this case.

It has been reported that HFS may be caused by such infratentorial intra-axial intrinsic lesions as gliomas, gangliomas, and hamartomas. Two main mechanisms have been suggested to explain HFS caused by these infratentorial intrinsic lesions, including seizure due to intralesional epileptogenesis, and compression of the facial nucleus or nerve fibres.[2] The former is applicable to cases of HFS resulting from a hamartoma or neuroectodermal tumours, and this type of spasm should be classified as a subcortical epilepsy. The second mechanism is applicable to HFS resulting from gliomas or vascular anomalies, which are not characterised by intralesional epileptogenecity. A cavernous angioma may be the cause of an epileptogenic focus, but it could also compress the facial nucleus. In this case, clinical symptoms and AMR waveforms might suggest that compression mechanisms may be a more likely cause of the HSF in our patient.[3]

Careful reading of MR images combining multiple sequences is imperative for predicting whether vascular compression exists. It is often difficult to confirm the existence of vascular compression of the REZ only on the basis of MR images. In this case, the clinical symptoms of

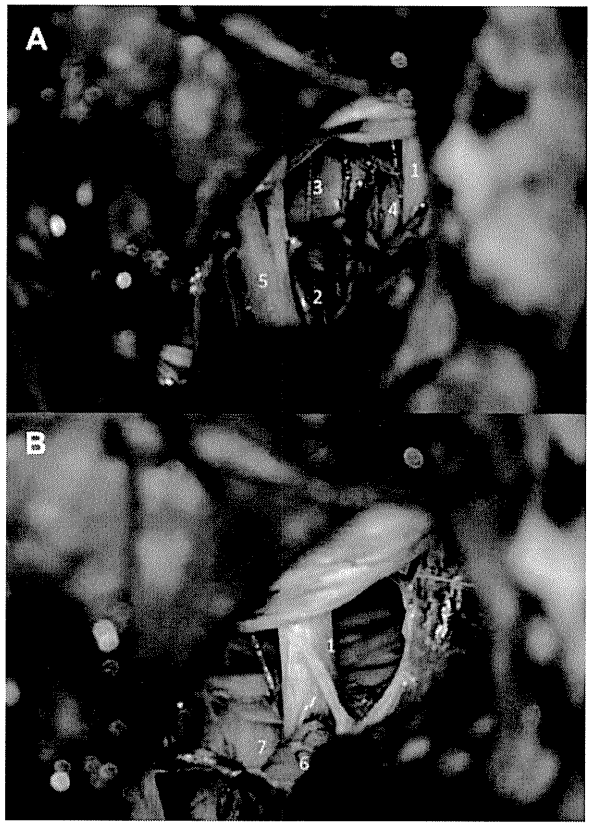

Fig 2. Intraoperative images of the cerebellopontine (CP) angle. (A) Inferolateral view of the left CP angle. (B) Another inferolateral view (a somewhat cranial view compared to A): (1) facial and vestibulocochlear nerve complex, (2) AICA, (3) venous angioma, (4) REZ of the facial nerve, (5) lower cranial nerves, (6) flocculus, and (7) pons.

the HFS were quite similar to typical HFS caused by vascular compression of the REZ. We conclude, therefore, that in cases of HFS with brainstem lesions, particular care must be taken to determine whether extra-axial vessels and not an intra-axial lesion are responsible for the patient's symptoms.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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ORIGINAL ARTICLE

Quantitative analysis of phosphenes induced by navigation-guided repetitive transcranial magnetic stimulation

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Objective
Though a cortical visual prosthesis is a promising method for treating severe visual disturbances, long-term blindness is known to depress visual cortex activity. We examined the use of repetitive transcranial magnetic stimulation (rTMS) with a navigation system as a direct functional assessment tool for the visual cortex.

Methods
We performed rTMS of the occipital cortex at three different stimulus frequencies (1 Hz, 5 Hz, and 20 Hz), on five stimulus targets around the calcarine fissure in 10 healthy subjects and 3 patients with visual impairment.

Results
In the subjects with normal vision, phosphenes were mostly induced in the visual hemifield contralateral to the stimulation site, and stimulation on the targets inferior to the calcarine fissure predominantly induced phosphenes in the upper visual hemifield. High-frequency stimulation induced larger and complicated-shaped phosphenes at higher rates. The phosphenes induced rate and spatial distribution were altered in the blind patients.

Conclusions
The rTMS has the ability to directly assess the regional visual function of the occipital cortex both in normal-sighted subjects and blind patients. Precise targeting with a navigation system appropriately stimulated the lingual gyri, which contributed to consistently inducing the phosphenes in the upper

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visual fields. Atypical representation of the phosphenes in patients with visual impairment suggests the alteration of regional cortical excitations and spatial representation due to the cortical reorganization after the loss of visual inputs.

Keywords repetitive transcranial magnetic stimulation; phosphene; image guided; visual restoration; visual impairment

Recently, advances in electrode and signal analysis technology have accelerated the research into and development of cortical visual prostheses.[1-3] Though a visual prosthesis holds great promise for patients with severe visual disturbance, long-term blindness is known to depress the function of the visual cortex. Therefore, presurgical functional assessment of the visual cortex is indispensable for appropriate use of the visual prosthesis. Because candidates for a visual prosthesis generally have the lesion in their visual pathway, it is necessary to assess the cortical visual function directly without passing through the visual pathway. At present, though visual-evoked potential (VEP) and visual-evoked magnetic field (VEF) are the established methods to assess visual function, they are not adequate for presurgical assessment of the visual prosthesis because of their involvement of the visual pathway.

Repetitive transcranial magnetic stimulation (rTMS) directly and noninvasively stimulates the cortex, so it has been applied in several studies of the excitability in the motor and sensory cortex.[4-7] In particular, TMS of the occipital pole interferes with visual perception (scotoma) or induces visual perceptions such as phosphenes, so transcranial magnetic stimulation (TMS) has been used as a noninvasive technique for topographic mapping of the human cerebral cortex and represents a valuable tool for the localization of brain functions.[8-13]

In this study, we performed rTMS of the occipital cortex using a neuronavigation system, and analyzed the induced phosphenes quantitatively in 10 healthy subjects and 3 patients with visual impairment. The purpose of this study was to evaluate rTMS using a navigation system as a noninvasive procedure to assess the regional excitability of the striate cortex without passing through the optic pathway.

Methods

Subjects and experimental setup

The study protocol and informed consent documents were approved by the Ethics Committee of Osaka University Hospital. All healthy subjects and the visually impaired patients provided their informed consent prior to entering the study. Ten healthy subjects (age range: 21-56 years; mean: 28.9 years; 3 men, 7 women) and three patients (age range: 26-55 years; mean: 44 years; 2 men and a woman) (Table 1) with visual impairment participated in this study. All healthy subjects had normal or corrected-to-normal vision and no history of neurologic or psychiatric disorders. Two of three patients (patients 1 and 2) are peripherally blind caused by optic neuritis. Patient 1, aged 26 years, had acute disseminated encephalomyelitis at the age of 21. He totally lost his sight within the first month after onset of illness. Patient 2, aged 51 years, had idiopathic optic neuritis 10 years ago and is now totally blind. Another patient (patient 3), aged 55 years, has a history of bilateral occipital lobe infarction (except for the left fusiform gyrus) (Figure 1), caused by basilar artery dissection 4 years before study entry. Initially, he presented with complete blindness, but visual acuity of his central visual field (< 10 degrees) recovered gradually over the last few years (his residual visual field). Over the past several months, he began to discriminate moving visual stimuli on his right upper visual field (his restored visual field) (Figure 1), and reports feeling a glittering flash in that area.

All study participants were instructed to rest in a sitting position and were blindfolded to compare the healthy subjects and visually impaired patients under the same conditions. To precisely target the stimulation site, the Brainsight frameless navigation system (Rogue Research Inc, Montreal, Canada) was used.[14] The subject's magnetic resonance image (MRI) was displayed on a computer monitor, and the navigation system was used to guide the TMS coil location relative to the head and brain surface. The position and orientation of the TMS coil and the subject's head were coregistered with small pieces of reflecting material (trackers) placed on them. Trackers were monitored by an infrared optical position sensor calibration procedure.[15]

TMS was applied through a figure-of-eight coil (MC B-70; Medtronic Functional Diagnosis A/S, Skovlunde, Denmark). The coil was connected to a MagPro magnetic stimulator (Medtronic Functional Diagnosis A/S). The stimulus frequency and timing were controlled by an external trigger generator (NS101; Unique Medical Co, Ltd, Tokyo, Japan).

Assessment of resting motor threshold and phosphene threshold

Before the phosphene assessment, we measured the resting motor threshold (rMT) and phosphene threshold (PT) using

Table 1 Summary of patient history data and phosphenes reported

Patient number	Age (y)	Cause of visual impairment	Duration of blindness (y)	Phosphene induced rate (% of stimulation)		Phosphenes in central visual field (% of phosphenes)
				20 Hz/5 Hz/1 Hz	MM/SR/SL/IR/IL	MM/SR/SL/IR/IL
1	26	Optic neuritis	5	100/100/100	100/100/100/100/100	83.3/28.6/57.1/42.9/50.0
2	51	Optic neuritis	10	40/40/20	0/100/66.7/0/0	0/0/0/0/0
3	55	Occipital lobe infarction	4	70/80/40	33.3/33.3/83.3/66.7/100	0/50.0/33.3/66.7/0

MM = midpoint of bilateral calcarine sulci on the outer brain surface; SR = point 2 cm superior and right of MM; SL = point 2 cm superior and left of MM; IR = inferior limit of the occipital lobe and 2 cm right of midline; IL = inferior limit of the occipital lobe and 2 cm left of midline.

biphasic magnetic single-pulse stimulation. The rMT was determined to help identify individuals with abnormally low thresholds (for safety precautions). The rMT of the left hand was defined as the minimum stimulus intensity that produced a muscle twitch by the stimulation on the corresponding primary motor cortex. The PT was measured with a pulse train consisting of five biphasic magnetic pulses at 20 Hz above the center of the bilateral calcarine sulci on the outer brain surface. Magnetic stimulation was started at an intensity of 80% of the rMT and then increased gradually until phosphenes were elicited at a rate of more than 90% of stimulus (this magnetic intensity was defined as PT), or until reaching an intensity of 150% of rMT.

Stimulation protocols

Pulse-trains consisting of five magnetic stimuli pulses were used to assess phosphenes at three different frequencies; respectively, at 1 Hz, 5 Hz, and 20 Hz. To observe the effect of the direction of magnetic stimulation on the induced

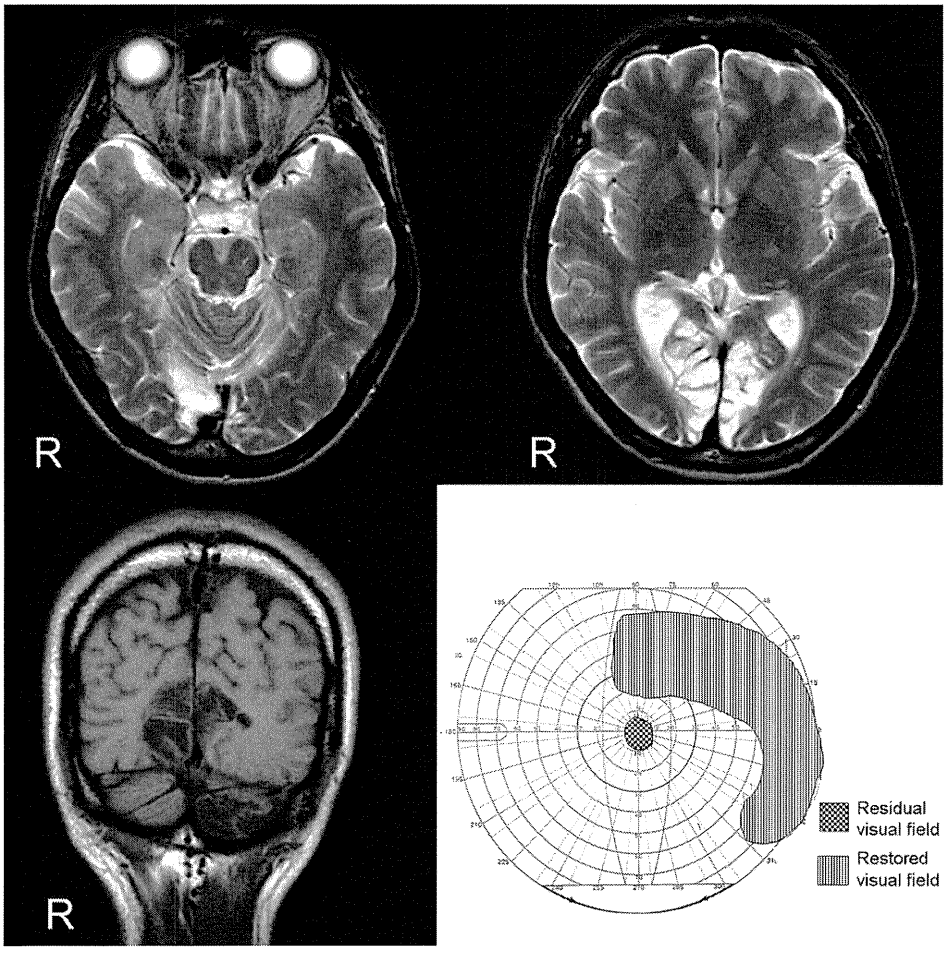

Figure 1 MRI from patient 3 (*upper*; axial T2-WIs, *lower left*; coronal T1-WI). He presented with bilateral occipital lobe infarction, excluding the left fusiform gyrus. Visual field diagram of patient 3 (*lower right*).

phosphene, the stimulation coil was placed on the targets in two different orientations. One was placed in the orientation so that the first-induced current flowed in the craniocaudal direction, and the other was in its reverse.

The stimulation targets were defined as follows: MM, the center of the bilateral calcarine sulci on the outer brain surface; SR, a point 2 cm superior and right to MM; IR, a inferior limit of the occipital lobe and 2 cm right from midline; SL, a point 2 cm superior and left from MM; and IL, a inferior limit of the occipital lobe and 2 cm left from midline. First, all five targets were stimulated individually by the coil in the normal orientation at 20 Hz. The stimuli were done in the random order so as to counteract the effect of the change of cortical excitability caused by light-deprivation and learning effect. And then, targets SR, SL, IR, and IL were stimulated individually again in random order, by the coil in the reverse orientation at 20 Hz. Then, 5 Hz and 1 Hz stimulation followed in the same way. Totally, each subjects received pulse trains 27 times (nine times for each stimulation frequency).

All stimuli were performed at intervals of more than 1 minute, according to guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation.[16] Total procedure for each subject took approximately 60 minutes.

To confirm the objective reliability of the subject's description of induced phosphene, sham stimulations were randomly given at the rate of 10% frequency (average frequency). In the sham stimulations, the coil was tilted 45 degrees with respect to the scalp.[17]

Quantitative phosphene assessment

Immediately after each stimulus, subjects were instructed to describe the location, color, shape, duration, and delay of the induced phosphene. Phosphene location was assessed quantitatively using a clock-face system (Figure 2). This system used a coordinate system so that the visual field was scaled into six segments (7.5 degrees) in the radial axis and then 12 segments (each corresponding to 30 degrees) in the angular axis. To avoid inaccuracy, the innermost segment of the visual field was not divided in angular direction, as it is difficult to determine the center of the visual field in light-deprived circumstances. Beforehand, subjects were well trained to precisely answer the questions regarding induced phosphenes using this clock-face system. The rate of occurrence of phosphenes with specific properties, such as the location, color, and shape, was calculated by dividing the number of specific phosphenes by the number of total phosphenes with specific stimulation (frequency, stimulation target, and/or the direction of the magnetic stimulation). The phosphene that was not described as a "spot" or "round" was classified as a "complicated-shaped" phosphene. Lastly, reproducibility rate of phosphene location was calculated in each subject. The reproducibility rate was defined as the number of phosphenes in the same 12 angular division divided by the number of total phosphenes induced by stimuli on one target.

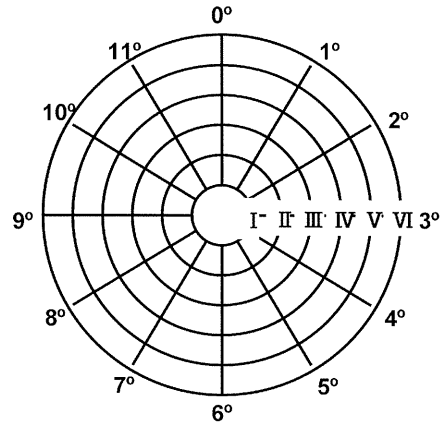

Figure 2 The clock-face system used for the description of perceived phosphenes. It used a coordinate system, so that the whole visual field was scaled into 12 segments (each corresponding to 30 degrees; 0 to 11 o'clock) in the angular axis and 6 segments (7.5 degrees) in the radial axis.

Phosphene induced rate, color, and shape were compared using the nonparametric 2-way analysis of variance, and phosphene location was compared using the Wilcoxon signed-rank test; $P < .05$ was considered statistically significant.

Results

All study subjects (both healthy and vision impaired) perceived phosphenes and tolerated the procedure without complication. The reproducibility rate of phosphene location was 74.3% (54.2-80.5%) (median; interquartile range [IQR]). Phosphene thresholds were found to be 112% (98-143%) of rMT. In two of the healthy subjects, phosphene analysis was performed with rTMS at the intensity of 150% of rMT because the PT exceeded the 150% of rMT. Sham stimulation did not induce phosphenes in any subjects.

Phosphenes in healthy subjects

Phosphene induced rates at 20 Hz stimulation was significantly higher than that at 1 Hz stimulation, 20 Hz stimulation induced significantly larger phosphene than did 1 Hz stimulation ($P < .01$, $P < .05$, respectively) (Figure 3), and the superior-side stimulation induced lager phosphenes than the stimulation on target MM ($P < .05$) (Supplement Figure 1).

For phosphene location, stimulation site had a clear impact in the horizontal level, but not in the vertical level. Phosphenes were induced in the contralateral visual field to the stimulation side ($P < .005$), and inferior-side

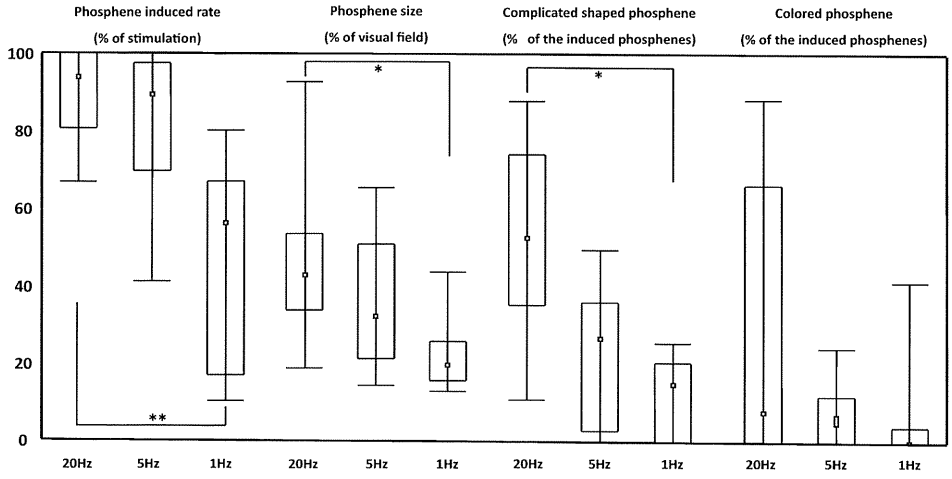

Figure 3 Phosphene induced rate, size, shape, and color in each stimulation frequency. In these plots, lines within the boxes present median values; the upper and lower lines of boxes present the 25th and 75th percentiles, respectively; and the upper and lower bars outside the boxes represent the 90th and 10th percentiles, respectively. Phosphene induced rate (% of stimulation); The induced rate at 20 Hz was significantly higher than that at 1 Hz ($P < .01$). Phosphene size (% of the visual field); 20 Hz stimulation induced larger phosphenes than 1 Hz stimulation ($P < .05$). The rate of complicated-shaped phosphene (% of the total phosphenes); 20 Hz stimulation induced complicated-shaped phosphenes significantly more frequently than 1 Hz stimulation ($P < .05$). The rate of chromatic phosphene (% of the total phosphenes); Although 20 Hz stimulation at tended to induce chromatic phosphenes more frequently, there was no significant difference among the other stimulations.

stimulation induced phosphenes more frequently in the upper visual field than in the lower visual field ($P < .05$), but in the superior-side stimulation, there was no difference between the induced rate in the upper visual field and the lower visual field ($P = .419$) (Figure 4). Stimulation on target MM induced phosphenes at the highest rate in the central visual field, but there was no significant difference among the other stimulation targets. Stimulation frequency had no impact on phosphene location (Supplement Table 1).

All healthy subjects perceived complicated-shaped phosphenes, and seven of them perceived chromatic phosphenes. The perceived shapes included ellipses, triangles, fan-shaped, and sickle-shaped phosphenes; the perceived colors included red, blue, yellow, green, orange, and brown. Stimulation at 20 Hz induced complicated-shaped phosphenes significantly more frequently than stimulation at 1 Hz ($P < .05$) (Figure 3), and stimulation on superior-side induced them significantly more frequently than on target MM ($P < .05$) (Supplement Figure 1). Although stimulation at 20 Hz or on superior-side tended to induce chromatic phosphenes more frequently, there was no significant difference among the other stimulations (Figure 3 and Supplement Figure 1).

There was little difference between normal and reverse coil orientation with respect to the phosphenes induced rate, size, chromatic phosphenes, or complicated-shaped phosphenes ($P = .391$, $P = .779$, and $P = .750$, respectively). The rate of induced phosphenes in the contralateral visual field, in the upper visual field by the inferior-side stimulation, and in the lower visual field by the superior-side stimulation were not statistically different (the right visual field, $P = .891$; the left visual field, $P = .715$; the upper visual field, $P = .553$; the lower visual field, $P = .679$). Overall, there was no significant difference between normal and reverse stimulation.

During the stimuli, subjects perceived phosphene for each pulse in the train stimulation. Interestingly, most subjects perceived phosphene more clearly in later part of pulse trains, especially during 20 Hz stimuli.

Phosphenes in visually impaired patients

All the visually impaired patients successfully perceived phosphenes without complication. Table 1 presents a summary of the stimulation results in this group of study subjects. Patient 1 consistently perceived gray round phosphenes in every stimulation site. His PT was 150% of his rMT. His perceived phosphenes were unevenly distributed in his lower visual field compared with that of the healthy subjects (Figure 5 and Table 1). Patient 2 perceived phosphenes predominantly in the right upper visual quadrant with stimulation on SR (induced rate was 66.7%) and SL (induced rate was 100%) (Figure 5 and Table 1); no phosphenes were induced on other stimulation targets. Most of her phosphenes were silver and rectangular. Her phosphene threshold was 117% of her rMT. Patient 3, regardless of stimulation targets, perceived phosphenes mostly in central or the right upper visual field, which corresponded to his residual visual field. Phosphene induced rate was higher in the residual visual cortex than in the infarcted cortex (Figures 1, 5, and Table 1). His PT was 58.1% of his rMT. Half of the phosphenes were described as "flashing like lightning" or "running rapidly in a curve".

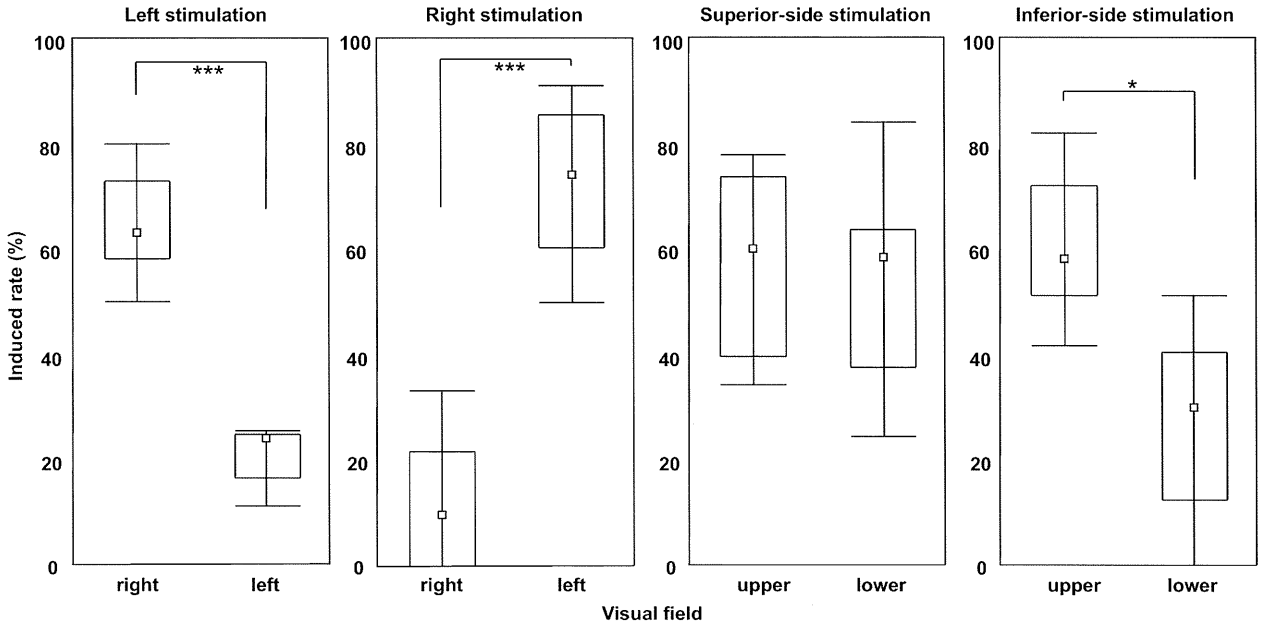

Figure 4 Phosphene location in healthy subjects. Graphs show the rates of induced phosphenes (% of total number of phosphenes in each stimulation targets) in relation to phosphene location and stimulation side. In these plots, lines within the boxes present median values; the upper and lower lines of boles present the 25th and 75th percentiles, respectively; and the upper and lower bars outside the boxes represent the 90th and 10th percentiles, respectively. Right- and left-side stimulation induced phosphenes in the contralateral visual field at a significantly higher rate than in the ipsilateral visual field ($P < .005$), and inferior-side stimulation induced phosphenes in the upper visual field at a significantly higher rate than in the lower visual field ($P < .05$). Superior-side stimulation did not induce phosphenes in the lower visual field at a significantly higher rate ($P = .419$).

Discussion

In this study, the quantitative analysis of phosphene induced by rTMS in healthy subjects revealed that stimulation frequency made a difference to the phosphene induced rate, size, and shape, and in addition, the stimulation site had implications for the phosphene location in the vertical level as well as in the horizontal level. In the patients with visual disturbances, the comparison of their induced phosphenes with the statistical data from the healthy subjects revealed their individual characteristics of the induced phosphenes.

Reproducibility of this study

In this study, all subjects successfully perceived phosphenes at a high reproducibility rate of phosphene location, and no sham stimuli induced phosphenes; this indicates the accuracy and precision of the stimulus targeting in this study. The relative position of skull landmarks and brain in the posterior regions of the head was quite variable.[18] As the focus of neurostimulation was remote from the coil, small differences in the placement of the coil might lead to significant differences in the neurons excited and thereby contribute to the variability of the phosphene perceptions elicited by TMS. In this sense, use of the neuronavigation system was absolutely imperative for the precise location and orientation of the TMS coil, especially to target the occipital lobe inferior to the calcarine fissure.

Impact of stimulus frequency

In this study, 20 Hz stimulation induced phosphenes more frequently than 1 Hz stimulation, and induced larger and more complicated phosphene than did 1 Hz stimulation. Our finding is concordant with other previous studies. Ray et al.[19] reported that the phosphene threshold decreased significantly as stimulus frequency increased, and the increasing stimulus strength is known to enlarge the phosphene area in the visual field.[20] In this study, high-frequency stimulation lowered the PT and consequently, activated a larger volume of the visual cortex and induced larger phosphenes; the larger size made it easy to recognize the phosphene colors and shapes.

Light deprivation for more than 45 minutes has known to increase the excitability of visual cortex,[21] and the observation of phosphenes possibly has a certain learning process. In this study, cortical excitability in visual cortex during 5 Hz or 1 Hz stimulation could be more increased than that during 20 Hz, and subjects could learn more about phosphene during 5 Hz and 1 Hz stimulation than during 20 Hz stimulation, therefore, the actual differences of phosphene-induced rate and size among stimulation frequencies should be greater than the results of this study.

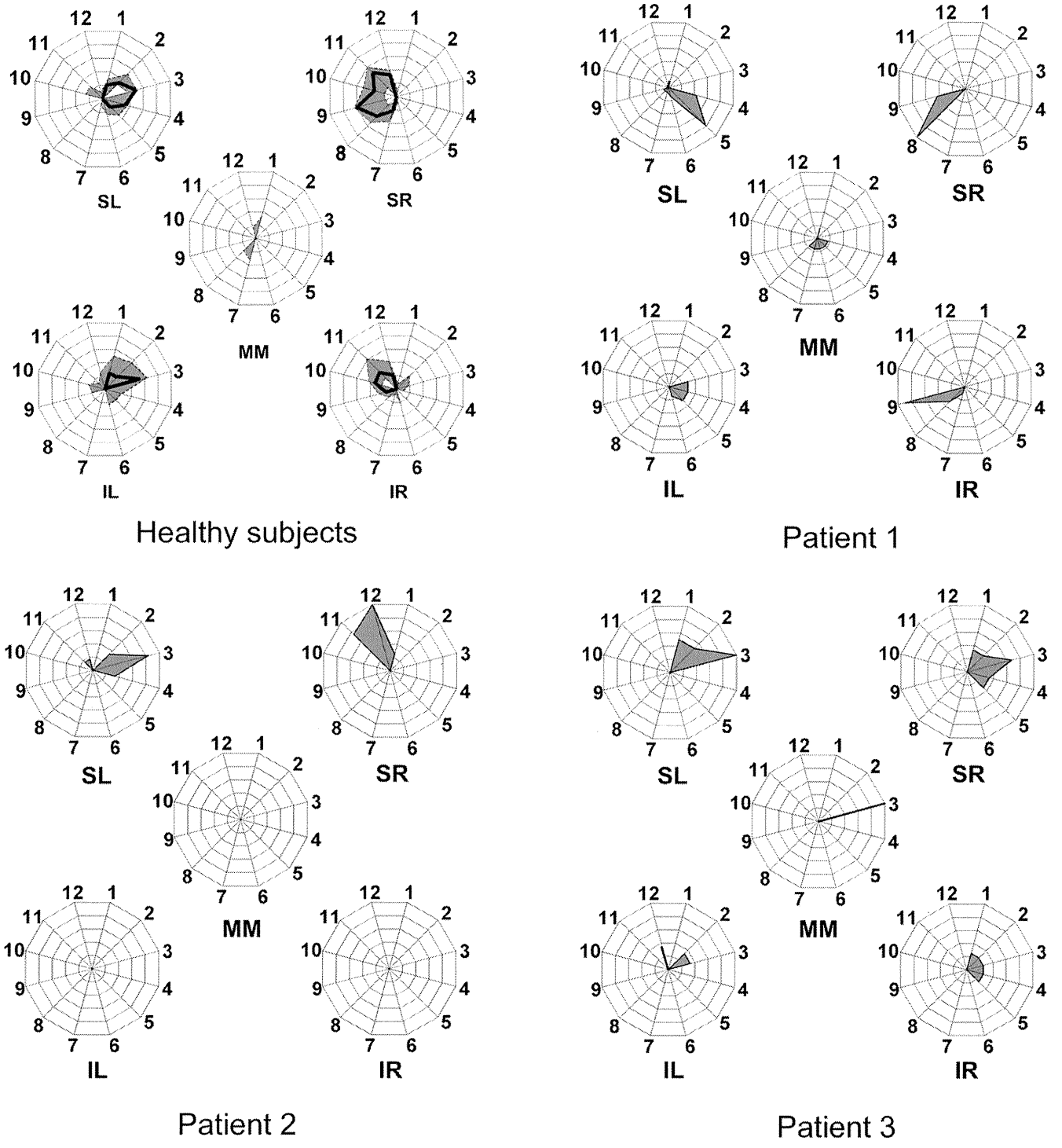

Figure 5 The spatial distribution of induced phosphenes as a function of stimulus site. The radar chart represents the rates of phosphene induced in each direction. The radial axis shows the induced rate (maximum value of 100%) and the angular axis show the direction in the visual field. *Upper left*: Induced phosphene in the healthy subjects. The heavy line represents the median value of the rate of phosphene induced in each direction, and the gray zone represents the IQR. *Upper right*: Induced phosphenes in patient 1. Patient 1 could perceive phosphenes at the high rate in every stimulation targets. He perceived phosphenes mostly in his central visual field and his lower quadrant visual field contralateral to stimulation. *Lower left*: Induced phosphenes in patient 2. Patient 2 perceived phosphenes predominantly in the right upper visual quadrant with stimulation on SR and SL. On the other stimulation targets, no phosphene was induced. *Lower right*: Induced phosphenes in patient 3. Patient 3, regardless of stimulation targets, perceived phosphenes mostly in the central or right upper visual field, which corresponded to his residual visual field.

Impact of target location

Phosphene distribution in the horizontal level was clearly in contralateral side of stimulated cortex, supporting the findings of previous studies,[22-24] but the distribution in the vertical level was less clear than in horizontal level.[19,25-27] Although magnetic stimulation on the occipital pole was previously reported to induce phosphenes or scotoma mostly in the lower visual hemifield,[22,23,28] our results showed no difference in the number of phosphenes between the upper and lower visual fields during upper occipital lobe stimulation, and more phosphenes were seen in the upper visual field during lower occipital lobe stimulation.

In this study, precise targeting on the lowest part of the occipital pole and the use of train stimulation would induce phosphenes in the upper visual field during inferior-side stimulation. The differences between our study and previous trials were that our study used rTMS instead of single TMS (sTMS) and our targeting was lower than that of the previous studies. Because the lower portion of the visual cortex representing the upper visual field is farther from the scalp (as observed in MRI),[22,23] it is more difficult to elicit phosphenes with TMS in the upper than in the lower visual field. In this study, repetitive stimulation would contribute to activating the lower part of occipital pole located far from the stimulation coil, because rTMS generally induces phosphenes easier than sTMS.[15]

Why did superior-side stimulation induce phosphenes in the upper visual field? The most plausible reason is that rTMS activated the connecting fiber between the upper and lower lip of the calcarine fissure (i.e., vertical occipital fasciculus).[29,30] In superior-side stimulation, half of the phosphenes were induced in the upper visual field at eccentricities of more than 7.5 degrees. In the striate cortex, although the upper visual field and the lower visual field representations lie close together and are not split by the horizontal meridian,[31] the visual field representation at eccentricities of more than 7.5 degrees is buried at greater depths (more than 4 cm) in the calcarine fissure and is too deep to be stimulated effectively by TMS. Thus, our finding is not concordant with activation of V1. The secondary visual areas (V2/V3) are split by the horizontal median clearly.[32] Only the lower peripheral visual field can be activated by superior-side stimulation, because the lower field representation of V2/V3 lies on the lateral surface of the cortex above the calcarine fissure,[33,34] whereas the upper field representation (ventral V2/V3) lies below the calcarine fissure, partly on the inferior surface of the brain several centimeters away from the stimulation target. Thus, our finding is not concordant with activation of V2/V3. It remains possible that we stimulated connecting or projecting fibers related to upper visual field representation; Kammer et al.[20] have suggested the projection fiber as target region for scotomas and phosphenes. Our finding of the phosphene induced in the upper visual field by the stimulation on the superior-side stimulation may be explained best by the fiber connecting between the upper and lower lips of the calcarine fissure being depolarized by rTMS.

Patient phosphenes

In three patients with visual impairment, the comparison of their phosphenes with the statistical data obtained from healthy subjects enabled us to assess their residual visual function. One peripheral blind subject (patient 1, who had a shorter duration of blindness) could perceive phosphenes from every stimulation targets, whereas the other peripherally blind subject (patient 2, with a longer history of blindness) could perceive phosphenes only with stimulation of the superior occipital lobe. Gothe et al.[26] assumed that the decreased excitability of the visual cortex caused by a long period of peripheral blindness reduces the ability to induce phosphenes. Our results are concordant with Gothe's assumption, the greater duration of blindness in patient 2 would be anticipated to alter her cortical excitability more greatly than was seen for patient 1. Though phosphenes were unevenly distributed over the upper and lower visual fields, they were consistently induced in the hemisphere contralateral to the stimulation in the horizontal level. Considering that every stimulus site could induce a phosphene in both the upper and lower side of the calcarine fissure in our healthy subjects (Figure 5), maldistribution in the peripheral blind patients could be explained by an alteration of their regional cortical excitability caused by the blindness.

In the patient with cortical blindness (patient 3), magnetic stimulation could induce phosphenes in his residual visual field regardless of stimulation site, but in higher induced rate on his residual visual cortex. These results indicate that the infarction might affect cortical excitability in each part of the occipital lobe, depending on the severity of the infarction. Cortical excitability would be increased in the cortex corresponding to the patient's restored visual field. He always feels glittering flashes in the restored visual field, and half of his induced phosphenes arose from that region. It is interesting that stimuli of the infarcted right occipital lobe induced phosphenes in the ipsilateral residual and restored visual fields. Taking into account of the targeting accuracy using a navigation system, which was shown with healthy subjects, it is not feasible to attribute this result to stimulation reaching the contralateral visual cortex. Misra et al.[35] reported an MEP on the nonhemiplegic side recorded with ipsilateral cortical magnetic stimulation in patients with hemiplegia caused by cortical infarction. They speculated that this was due to transsynaptical cross-stimulation of the normal hemisphere. In this case, the irritable cortex corresponding to the restored visual field might be transsynaptically activated

by rTMS of the contralateral infarcted visual cortex. The results for our patients are quite unexpected, and are thought to show the importance of close examination of the visual cortex before use of the visual prosthesis.

Overall, we were able to show the regional cortical excitability change in patients with peripheral blindness and the alteration of spatial representation in the visual cortex in the patient with cortical blindness. Although further investigation is indispensable because of the small number of cases in the study, we were able to prove the ability of rTMS to investigate cortical changes in blind patients and the significance of presurgical assessment of visual function.

In the study, we successfully showed the effects of stimulus frequency on phosphene induced rate, size, color, and shape. and demonstrated that stimulation inferior to the calcarine fissure could induce phosphenes in the upper visual field in subjects with normal vision. In addition, rTMS with a navigation system could show a difference in residual visual function in patients with visual impairment. These results show the potential of rTMS to investigate residual visual function in patients with severe visual disturbances, and may improve our understanding of physiologic organization and plastic changes in the human visual system. Though there must be some difference between the neuronal activities induced by magnetic stimulation and electrical stimulation, such a noninvasive method will be imperative to evaluate the surgical indication of a cortical visual prosthesis in the future.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.brs.2010.03.006

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