■ Original article

Epileptic Disord 2022; 24 (1): 67-74

Epileptic Disorders

Limb loss experience evoked by electric cortical stimulation

Guiliang Hao, Xueyuan Wang, Hao Yan, Liu He, Duanyu Ni, Liang Qiao, Xiaohua Zhang, Kaijia Yu, Tao Yu

Beijing Institute of Functional Neurosurgery, Xuanwu Hospital of Capital Medical University, 100053, Beijing, China

Received February 23, 2021;
Accepted June 19, 2021

ABSTRACT

Objective. Limb loss experience is a type of body illusion characterized by the sensation of a missing limb or body part. We aimed to investigate the brain areas involved in this unusual somatosensory experience evoked by electric cortical stimulation with stereo-electroencephalography electrodes.

Methods. We retrospectively reviewed the data of patients with medical intractable epilepsy, from October 2015 to December 2020, who underwent stereo-electroencephalography implantation and electric cortical stimulation in order to locate the epileptogenic zone and obtain a functional map. We included patients who reported experiences of limb loss during the process of electric cortical stimulation for functional mapping.

Results. Three patients reported experiences of limb loss in the process of electric cortical stimulation. Limb loss experience (including the right hand, right upper limb and right side of the body) occurred when the cortex of the left posterior insula, posterior dorsal cingulate and parietal operculum were stimulated.

Significance. Limb loss experience can be evoked by electric cortical stimulation of the posterior insula, parietal operculum, and posterior cingulate cortex, and provides additional evidence that these cortices play a role in the integration of body sensory perception.

Key words: limb loss experience, electric cortical stimulation, stereo-electroencephalography

Our perceived relationship with our environment is based on multisensory information and its integration within a specific context [1]. Body representation has various components including spatial localization, posture, and the size of body parts and how they form the whole body [2, 3].

The neural pathway involved in sensory perception (including the spinal cord, medulla, pons, thalamus, and parietal lobe) has been elucidated through studies on normal anatomy and pathological states using experimental approaches such as functional magnetic resonance imaging (MRI), electroencephalography (EEG), electric cortical stimulation (ECS), and animal models [4-7]. ECS can evoke neural perception and has been used to localize epileptic foci [8-10], and can potentially be used to examine the contribution of specific brain areas to sensory perception.

Body illusion is an unusual type of somatosensory experience that involves an altered perception of body experiences (*e.g.*, position, weight, and movement) [11], and can be classified as body part transformation, body part displacement, or disconnection of a body part from the rest of the body [1, 11]. Limb loss experience (LLE) is a type of body

• **Correspondence:**
Tao Yu
Beijing Institute of Functional Neurosurgery,
Xuanwu Hospital of Capital Medical University,
1000053, Beijing, China
<yutaoly@sina.com>

doi:10.1684/epd.2021.1364

illusion characterized by the sensation of a missing limb or body part. There have been few reports of LLE, and the underlying neural mechanisms are not known. To address this issue, in this study, we aimed to identify brain regions that elicit LLE during ECS.

Patients and methods

Patients

We retrospectively reviewed the clinical data of 376 patients with medical intractable epilepsy who underwent stereo-electroencephalography (SEEG) implantation for localization of the epileptogenic zone (EZ) at Beijing Institute of Functional Neurosurgery (Beijing, China) between October 2015 and December 2020. We included patients who reported experiences of limb loss in the process of ECS for brain mapping. We further used the following exclusion criteria: (i) patients with cognitive and psychiatric comorbidities; (ii) contacts located in the EZ and white matter; (iii) contacts on which ECS elicited ictal symptoms and after-discharge; and (iv) the result of ECS was unrepeatable.

Presurgical evaluation

All patients underwent high-resolution MRI, which was performed with a 3.0 T MR scanner (GE Healthcare, Little Chalfont, UK) and consisted of spin-echo T1-weighted, T2-weighted, and fluid-attenuated inversion recovery sequences, as well as 3-dimensional anatomic T1-weighted axial, sagittal, and coronal sequences covering the whole brain volume with a 1-mm section thickness. Each patient underwent interictal/ictal scalp EEG recording using a video-EEG monitoring system (Micromed, Treviso, Italy) with electrodes placed according to the international 10-20 system. Additionally, magnetoencephalography (Neuromag, Helsinki, Finland) and positron emission tomography–computed tomography (PET-CT) or positron emission tomography–magnetoencephalography (PET-MRI) scanning were performed to localize EZs. Seizure onset and propagation characteristics were independently analysed by two EEG experts who were aware of the clinical and neuroimaging data.

SEEG electrode implantation

The intracerebral multiple-contact SEEG electrodes (8–16 contacts, length: 2 mm, diameter: 0.8 mm, inter-electrode distance: 1.5 mm) were placed using a Cosman-Roberts-Wells human body stereotaxic frame and Sinovation robotic arm-assisted system. The number of electrodes and their anatomical targeting were determined based on information obtained in the non-invasive presurgical evaluation and on anatomical hypotheses. The open source software and toolboxes, SPM12 [12], Freesurfer [13], Brainnetome Atlas [14], and 3D slicer [15], were used for image processing and visualization. High-resolution MRI was obtained preoperatively. The cortex surface was reconstructed by Freesurfer and Brainnetome Atlas was used to map individual cortex parcellation. After electrode implantation, high-resolution CT was performed, and the CT images were registered with the preoperative MRI images. The electrode contacts were reconstructed according to the CT images.

Intracranial video-EEG monitoring

Intracranial electroencephalography (iEEG) monitoring was performed to further lateralize and localize EZs. The iEEG sampling rate was set at 1024 Hz to record details of seizure propagation. The duration of video-EEG monitoring ranged from 3 to 14 days, and at least three habitual seizures were recorded for each patient. Most of the seizure onset zones were visually identified on iEEG traces during long-term iEEG monitoring.

ECS

ECS was performed (SD LTM STIM; Micromed) after long-term video monitoring. Bipolar stimulation with a biphasic wave was applied. The stimulation parameters were as follows: pulse width=0.2 ms, frequency=50 Hz, and duration=3 seconds, with current intensity starting at 0.5 mA and increasing by 0.1 mA or 0.2 mA each time up to 6 mA. Electrical stimulation was stopped when symptoms appeared, even if the current intensity was less than 6 mA. In this way, we elicited the clinical effect at the minimum intensity. When a response was evoked, the stimulation was repeated one or two times and sham stimulation was performed to control for psychogenic effects. Symptoms were induced at least twice without after-discharge or induced seizures were analysed. At the same time, the patient was unaware of when ESC was being performed and the electrode contact sites. During this process, the brain areas involved in language, somatosensory processing, and motor function were identified. We selected LLE symptoms induced by ECS via the electrode contact sites located in the cerebral cortex.

Results

Patient characteristics and EZs

Of the 376 patients who underwent SEEG implantation, three patients (0.80%; mean age: 32.33?0.80 years) reported LLE during ECS and were included in the

analysis. All three patients were right-handed. The EZs were located in the left base of the occipital cortex and anterior temporal lobe (the secondary EZ of the occipital lesion) in Patient 1, in the right upper postcentral gyrus and paracentral lobule in Patient 2, and in the left anterior insular and posterior part of the inferior frontal gyrus in Patient 3. Additionally, Patient 3 exhibited epileptic aura of LLE and described the sensation of loss of the right upper limb or right side of the body at the beginning of most seizures (*table 1*). Electrodes implanted to explore the deep brain structures and the EZs are shown in *figure 1*.

Anatomical localization of LLE

LLE was evoked by stimulation at eight electrode contact points in the three patients. In addition, the LLE was not accompanied by other symptoms. Patient 1 reported loss of the right hand during stimulation at a contact point in the left posterior short gyrus of the insula at a current intensity of 3 mA. Patient 2 reported right hand loss during stimulation at two contact points in the left posterior dorsal cingulate at a current intensity of 4 mA. Patient 3 reported right hand loss during stimulation at two contact points in the left posterior part of the anterior long gyrus of the insula at a current intensity of 1 mA, loss of the right upper limb during stimulation at two contact points in the left parietal operculum at a current intensity of 2 mA; and a sensation of loss of the right side of the body during stimulation at one contact point in the left parietal operculum at a current intensity of 1.5 mA (*table 2*). According to the iEEG, the electrode contact sites for LLE were located at different sites to that of the EZ within the cortex of these three patients. For example, in Patient 3, the electrode contact sites for LLE were located in the left posterior part of anterior long gyrus of insula and parietal operculum, while the EZs were in the left anterior insular and posterior part of the inferior frontal gyrus. Therefore, we regarded the symptoms of electrical stimulation as physiological data.

Discussion

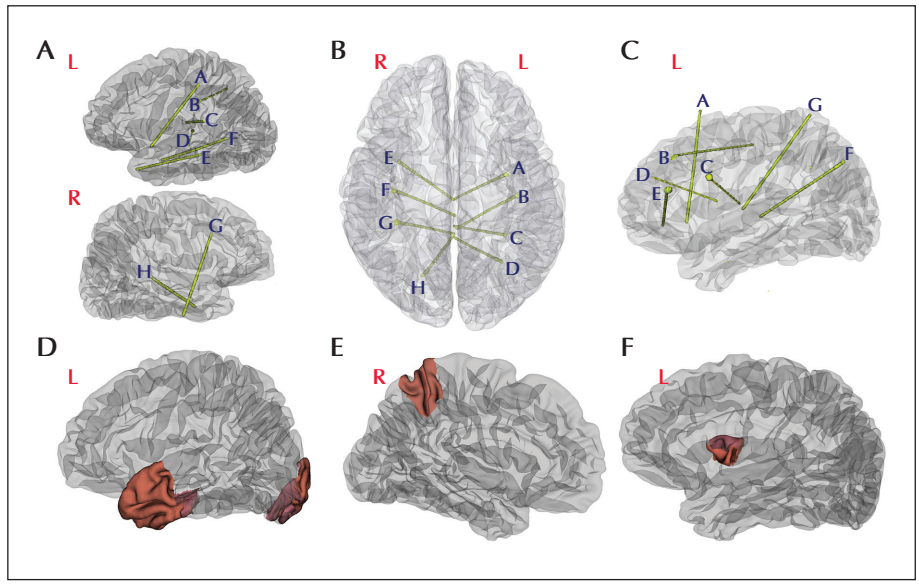
Brain regions related to body illusion

LLE is a rare type of body illusion and has seldom been reported; as such, its neurophysiological substrates are unknown. ECS is a traditional way to learn about brain regions and related function. A previous report showed that stimulation of the right middle cingulate gyrus in a right-handed female patient with epilepsy caused a lower left limb deficit sensation [1]. Some

▼ **Table 1.** Demographic and clinical profiles of study subjects.

Patient	Sex	Age, years	History, years	Aura	Semiology	MRI	Seizure onset zone	Surgical resection	Surgical outcome	Pathology
1	Female	39	10	Visual hallucination	Absence and oropharyngeal automatisms	Negative	Left ATL and bOcc	Left ATL and bOcc	Engel III	FCD Ia
2	Female	34	20	Strange feeling in right knee	Right limb automatisms	Negative	Right upper post-central gyrus	Right upper post-central gyrus and paracentral lobule	Engel I	FCD I
3	Female	24	10	LLE or numbness in right upper limb or right side of body; palpitation; chest tightness	Right upper limb clonus	Negative	Left aIns	Left aIns and posterior part of IFG	Engel I	FCD Ib

ATL: anterior temporal lobe; bOcc: base of occipital cortex; FCD: focal cortical dysplasia; LLE: limb loss experience; aIns: anterior insula; IFG: inferior frontal gyrus; INS: insula; IOC: insulo-opercular cortex.



■ **Figure 1.** Reconstruction of depth electrodes and the epileptogenic zones (EZs) that were resected. (A) Reconstruction of depth electrodes in the bilateral hemispheres of Patient 1. (B) Reconstruction of depth electrodes in the bilateral hemispheres of Patient 2. (C) Reconstruction of depth electrodes in the left hemisphere of Patient 3. (D) The EZs of Patient 1 in the left anterior temporal lobe and base of the occipital cortex. (E) The EZs of Patient 2 in the left right upper post-central and paracentral lobule. (F) The EZs of Patient 3 in the left anterior insular and posterior part of the inferior frontal gyrus.

▼ **Table 2.** Site of electrical stimulation in each patient, stimulation parameters, and body part affected by LLE.

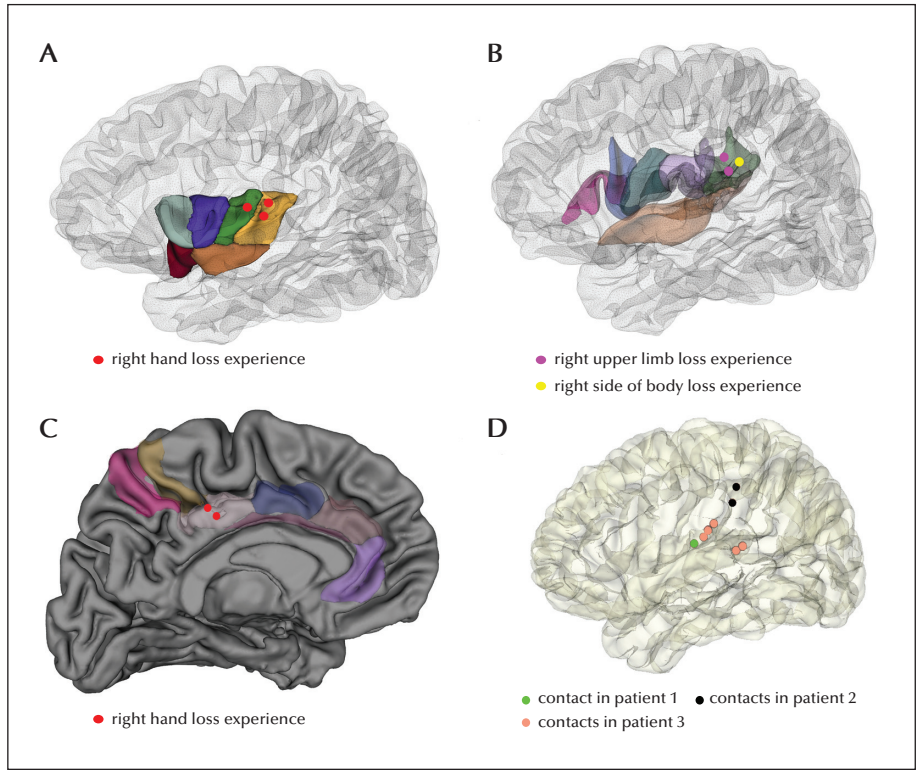
Patient	Dominant hemisphere	Electrodes/total contacts	Implantation side	Contact site	Current intensity, mA	LLE
1	Left	8/124	Bilateral	Left PSGins	3	Right hand
2	Left	7/108	Bilateral	Left PCC	4	Right hand
				Left PCC	4	Right hand
3	Left	8/124	Left	Left ALGins	1	Right hand
				Left ALGins	1	Right hand
				Left POC	2	Right upper limb
				Left POC	2	Right upper limb
				Left POC	1.5	Right part of body

ALGins: anterior long gyrus of insula; LLE: limb loss experience; PCC: posterior dorsal cingulate; POC: parietal operculum; PSGins: posterior short gyrus of insula.

stimulation studies have found that the appearance of changes in body perception was related to the posterior cingulate, but have not described the changes in body perception in detail [16, 17]. In this study, we found that LLE of the right hand, right upper limb and right side of the body was evoked by ECS of the left posterior insular cortex (including the posterior short gyrus and posterior part of the anterior long gyrus of the insula), posterior dorsal cingulate and parietal operculum respectively (*figure 2*). Based on these observations, we speculate that LLE is evoked by contralateral stimulation, especially of the insular cortex, middle or posterior dorsal cingulate and parietal operculum. A voxel-based lesion–symptom mapping study in human subjects showed that the parietal operculum, insular cortex, putamen, and subcortical projections to the prefrontal cortex were involved in the perception of touch [7]. In addition, some reports showed that the insular cortex also integrates cognitive and sensory perceptions of cutaneous stimuli [7], and that the intraparietal sulcus is an interface for sensorimotor integration in visually guided actions [18], with the angular and supramaginal gyrus together with the temporo-parieto-occipital (TPO) junction participating in spatial cognition [19]. Therefore, these brain regions may play an important role in body illusion.

Functional and structural connectivity between brain regions

Functional MRI studies have found that somatic hallucinations are related to the activation of primary sensory areas and the posterior parietal cortex, which are involved in tactile perception [4, 20]; thus, somatic hallucinations may be caused by activation of sensory pathways. Besides, the cingulate is an important transmission route for stimuli originating in the contralateral limb [21, 22]. Our results are consistent with previous work demonstrating that the posterior



■ **Figure 2.** Site of electrical stimulation in different brain areas evoking LLE. (A) Site of electrode contact in the insula evoking loss of the right hand. (B) Site of electrode contact in the parietal operculum evoking loss of the right side of the body and right upper limb. (C) Site of electrode contact in the posterior dorsal cingulate evoking loss of the right hand. (D) Site of electrode contacts evoking LLE based on a composite brain model of all patients.

dorsal cingulate, insula (especially the posterior part), and parietal operculum are hubs connecting the sensory system with other brain regions [1, 7, 23, 24]. The cortico-cortical evoked potential (CCEP) studies provided more evidence that the functional connectivity of posterior cingulate-parietal-insular cortices play a role in somatic hallucinations. For example, the posterior cingulate was shown to be connected to visual areas and mesial and lateral parietal and temporal cortex [16]. The functional connection between the posterior part of the insula and the parietal lobe was also verified [25]. In addition, it has been proven that the anterior long gyrus of insula and the posterior short gyrus of insula have a strong connection with the parietal operculum [26]. Moreover, resting-state connectivity between the cingulate and parietal cortices was altered when illusory body perceptions were elicited though decreased coupling between the two regions [1].

Another clinical phenomenon, hemispatial neglect, may provide further insight into the neural mechanisms of LLE. Patients with non-dominant hemispheric parietal stroke often exhibit symptoms of hemispatial neglect such as not feeling the presence of the limb on the side of the body contralateral to the lesion [27], which may be caused by hyperactivation of functional loops in the brain [21, 28-30]. When the cingulate gyrus was functionally intact, excess inhibition by transcranial magnetic stimulation of the parietal lobe of the activated dominant hemisphere alleviated the symptoms of hemispatial neglect, possibly through attenuation of overactive brain areas [31-33]. In our study, ECS may have transiently overactivated functional connectivity in the focal cortex, resulting in a sense of limb loss similar to focal hemispatial neglect. However, additional studies in more patients are needed to test this hypothesis.

In conclusion, we infer from our study that the posterior cingulate cortex and insular and parietal operculum are involved in the production of body illusion, and the TPO junction and parietal and somatic sensory cortex are also parts of the functional connectivity involved in body hallucination.

Limitations

This study was a descriptive study, with very few LLE symptoms. Although we have attempted to explain the special structural and functional connectivity between the related brain regions, we cannot provide more evidence for the mechanism of these somatic hallucinations. We plan to conduct further studies on more samples, to further investigate the brain network involved in body illusion.

Conclusion

LLE can be evoked by ECS of the posterior insula, parietal operculum, and posterior cingulate cortex. Our finding provides evidence that these brain areas are involved in the multisensory integration of body perception. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Acknowledgements and disclosures.
We would like to thank Cuiping Xu, Yuanyuan Piao, Xiaoxia Zhou and Wei Du for the assistance with collection of EEG data and follow-up information.
None of the authors have any conflicts of interest to disclose.

Funding.
This study was funded by the National Natural Science Foundation of China (grant numbers: 81771395).

References

1. Popa I, Barborica A, Scholly J, Donos C, Bartolomei F, Lagarde S, *et al*. Illusory own body perceptions mapped in the cingulate cortex – An intracranial stimulation study. *Hum Brain Mapp* 2019; 40: 2813-26.

2. Thurm B, Pereira ES, Fonseca CC, Cagno MJS, Gama EF. Neuroanatomical aspects of the body awareness. *J Morph Sci* 2011; 28: 296-9.

3. de Vignemont F. Body schema and body image–pros and cons. *Neuropsychologia* 2010; 48: 669-80.

4. Braun CM, Dumont M, Duval J, Hamel-Hébert I, Godbout L. Brain modules of hallucination: an analysis of multiple patients with brain lesions. *J Psychiatry Neurosci* 2003; 28: 432-49.

5. Bär KJ, de la Cruz F, Berger S, Schultz CC, Wagner G. Structural and functional differences in the cingulate cortex relate to disease severity in anorexia nervosa. *J Psychiatry Neurosci* 2015; 40: 269-79.

6. Mühlau M, Gaser C, Ilg R, Conrad B, Leibl C, Cebulla MH, *et al*. Gray matter decrease of the anterior cingulate cortex in anorexia nervosa. *Am J Psychiatry* 2007; 164: 1850-7.

7. Preusser S, Thiel SD, Rook C, Roggenhofer E, Kosatschek A, Draganski B, *et al*. The perception of touch and the ventral somatosensory pathway. *Brain* 2015; 138: 540-8.

8. Bartolomei F, Lagarde S, Wendling F, McGonigal A, Jirsa V, Guye M, *et al*. Defining epileptogenic networks: contribution of SEEG and signal analysis. *Epilepsia* 2017; 58: 1131-47.

9. He B, Astolfi L, Valdes-Sosa PA, Marinazzo D, Palva S, Benar CG, *et al*. Electrophysiological brain connectivity:

theory and implementation. *IEEE Trans Biomed Eng* 2019; 66: 2115-37.

10. Yu K, Yu T, Qiao L, Liu C, Wang X, Zhou X, *et al*. Electrical stimulation of the insulo-opercular region: visual phenomena and altered body-ownership symptoms. *Epilepsy Res* 2018; 148: 96-106.

11. Heydrich L, Dieguez S, Grunwald T, Seeck M, Blanke O. Illusory own body perceptions: case reports and relevance for bodily self-consciousness. *Conscious Cogn* 2010; 19: 702-10.

12. Ashburner J. SPM: a history. *NeuroImage* 2012; 62: 791-800.

13. Fischl B. FreeSurfer. *NeuroImage* 2012; 62: 774-81.

14. Fan L, Li H, Zhuo J, Zhang Y, Wang J, Chen L, *et al*. The human brainnetome atlas: a new brain atlas based on connectional architecture. *Cerebral Cortex* 2016; 26: 3508-26.

15. Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, Fillion-Robin JC, Pujol S, *et al*. 3D Slicer as an image computing platform for the Quantitative Imaging Network. *Magn Reson Imaging* 2012; 30: 1323-41.

16. Oane I, Barborica A, Chetan F, Donos C, Maliia MD, Arbune AA, *et al*. Cingulate cortex function and multi-modal connectivity mapped using intracranial stimulation. *NeuroImage* 2020; 220: 117059.

17. Caruana F, Gerbella M, Avanzini P, Gozzo F, Pelliccia V, Mai R, *et al*. Motor and emotional behaviours elicited by electrical stimulation of the human cingulate cortex. *Brain* 2018; 141: 3035-51.

18. Jitsuishi T, Yamaguchi A. Identification of a distinct association fiber tract "IPS-FG" to connect the intraparietal sulcus areas and fusiform gyrus by white matter dissection and tractography. *Sci Rep* 2020; 10: 15475.

19. De Benedictis A, Duffau H, Paradiso B, Grandi E, Balbi S, Granieri E, *et al*. Anatomo-functional study of the temporo-parieto-occipital region: dissection, tractographic and brain mapping evidence from a neurosurgical perspective. *J Anat* 2014; 225: 132-51.

20. Shergill SS, Cameron LA, Brammer MJ, Williams SC, Murray RM, McGuire PK. Modality specific neural correlates of auditory and somatic hallucinations. *J Neurol Neurosurg Psychiatry* 2001; 71: 688-90.

21. Nyffeler T, Vanbellingen T, Kaufmann BC, Pflugshaupt T, Bauer D, Frey J, *et al*. Theta burst stimulation in neglect after stroke: functional outcome and response variability origins. *Brain* 2019; 142: 992-1008.

22. Leech R, Sharp DJ. The role of the posterior cingulate cortex in cognition and disease. *Brain* 2014; 137: 12-32.

23. Eickhoff SB, Jbabdi S, Caspers S, Laird AR, Fox PT, Zilles K, *et al*. Anatomical and functional connectivity of cytoarchitectonic areas within the human parietal operculum. *J Neurosci* 2010; 30: 6409-21.

24. Spitzer B, Blankenburg F. Stimulus-dependent EEG activity reflects internal updating of tactile working memory in humans. *Proc Natl Acad Sci U S A* 2011; 108: 8444-9.

25. Di Cesare G, Pinardi C, Carapelli C, Caruana F, Marchi M, Gerbella M, *et al*. Insula connections with the parieto-frontal circuit for generating arm actions in humans and macaque monkeys. *Cerebral Cortex* 2019; 29: 2140-7.

26. Dionisio S, Mayoglou L, Cho SM, Prime D, Flanigan PM, Lega B, *et al*. Connectivity of the human insula: a cortico-cortical evoked potential (CCEP) study. *Cortex* 2019; 120: 419-42.

27. Rode G, Pagliari C, Huchon L, Rossetti Y, Pisella L. Semiology of neglect: an update. *Ann Phys Rehabil Med* 2017; 60: 177-85.

28. Corbetta M, Shulman GL. Spatial neglect and attention networks. *Annu Rev Neurosci* 2011; 34: 569-99.

29. Cazzoli D, Müri RM, Schumacher R, von Arx S, Chaves S, Gutbrod K, *et al*. Theta burst stimulation reduces disability during the activities of daily living in spatial neglect. *Brain* 2012; 135: 3426-39.

30. Koch G, Bonnì S, Giacobbe V, Bucchi G, Basile B, Lupo F, *et al*. υ-burst stimulation of the left hemisphere accelerates recovery of hemispatial neglect. *Neurology* 2012; 78: 24-30.

31. Cazzoli D, Rosenthal CR, Kennard C, Zito GA, Hopfner S, Müri RM, *et al*. Theta burst stimulation improves overt visual search in spatial neglect independently of attentional load. *Cortex* 2015; 73: 317-29.

32. Goldsworthy MR, Müller-Dahlhaus F, Ridding MC, Ziemann U. Resistant against de-depression: LTD-Like plasticity in the human motor cortex induced by spaced cTBS. *Cerebral Cortex* 2015; 25: 1724-34.

33. Salazar APS, Vaz PG, Marchese RR, Stein C, Pinto C, Pagnussat AS. Noninvasive brain stimulation improves hemispatial neglect after stroke: a systematic review and meta-analysis. *Arch Phys Med Rehabil* 2018; 99: 355-66.e1.

TEST YOURSELF

(1) What is limb loss experience?

(2) In this study, what method was used to explore limb loss experience?

(3) What parts of the brain are involved in the generation of limb loss experience?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.