

# The Effectiveness of Repetitive Transcranial Magnetic Stimulation for Poststroke Apathy Is Associated with Improved Interhemispheric Functional Connectivity

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Poststroke apathy is relatively common and has negative effects on the functional recovery of the patient; however, few reports have demonstrated the existence of effective treatments for poststroke apathy. Here, we describe a case of poststroke apathy that was successfully treated with repetitive transcranial magnetic stimulation (rTMS). Using resting-state functional magnetic resonance imaging, we detected improved interhemispheric functional connectivity that was correlated with the patient's recovery from poststroke apathy. Our case suggests that rTMS can improve the transfer of information through the corpus callosum, which is crucial for helping patients recover from poststroke apathy. **Key Words:** Poststroke apathy—repetitive transcranial magnetic stimulation—corpus callosum—resting-state functional magnetic resonance imaging—interhemispheric functional connectivity.

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## Case Presentation

An 81-year-old woman presented with sudden-onset apathy, mild weakness in the right lower limb, and callosal apraxia in the left hand. Owing to the profound loss of motivation, the patient required constant encouragement to perform her daily activities. The patient's score on the Japanese version of the apathy scale was 29 (the scale ranges from 0 to 42, with scores  $\geq 16$  indicating apathy).<sup>1</sup> Diffusion-weighted imaging showed acute cerebral infarction in the genu and truncus of the corpus callosum (CC) (Fig 1). Based on the magnetic resonance

imaging (MRI) findings, the patient was diagnosed with cerebral infarction, and anticoagulation therapy with argatroban (60 mg/day for 3 days) and antiplatelet therapy with clopidogrel (75 mg/day) were administered. Physiotherapy was performed for 20 minutes twice a day, 5 days a week. The patient's apathy was treated with amantadine (300 mg/day), but her apathetic state did not improve.

One week after admission, the patient underwent resting-state functional MRI. We compared the patient's functional connectivity to the connectivity in healthy controls ( $n = 18$ , mean age:  $72.3 \pm 3.4$  years). The patient's interhemispheric functional connectivity was reduced compared to that in healthy controls ( $P < .001$ ), whereas her intrahemispheric functional connectivity was increased ( $P < .001$ ) (Fig 2, A).

After the patient's apathetic state had lasted for 2 weeks, repetitive transcranial magnetic stimulation (rTMS) was performed. This treatment was approved by the ethical committee of Shimane University School of Medicine, Japan. Informed consent was obtained from the patient. The rTMS was applied using a figure-of-8-shaped coil.

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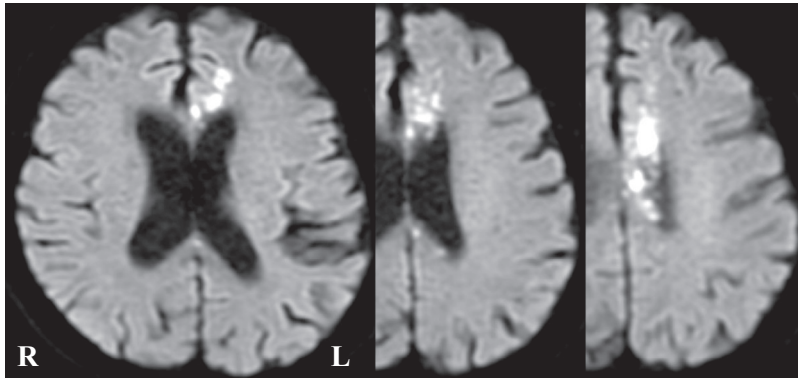
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**Figure 1.** Diffusion-weighted images acquired at admission show acute cerebral infarction in the genu and truncus of the corpus callosum. Abbreviations: L, left; R, right.

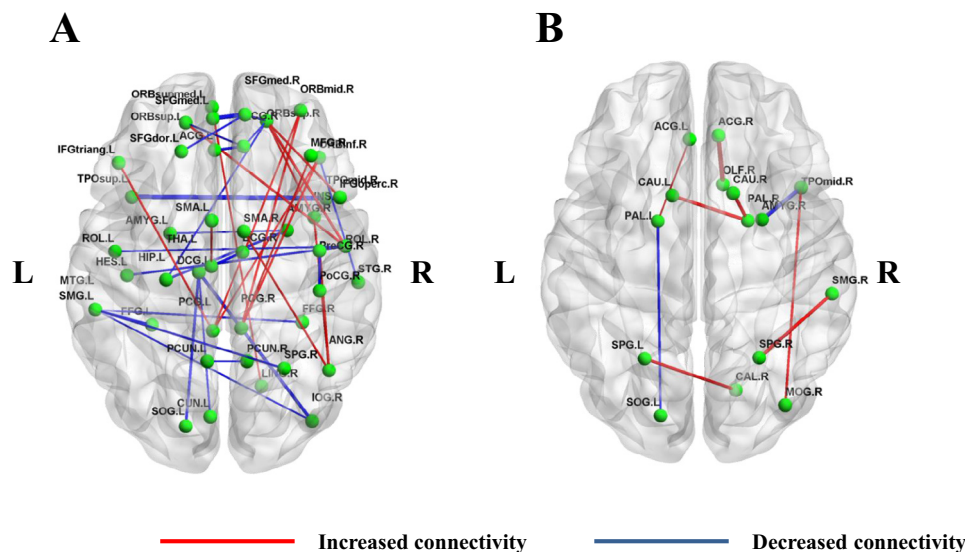
The coil was connected to a magnetic stimulator (Magstim Rapid; The Magstim Co., Whitland, United Kingdom) and held over the cranial surface above the supplementary motor area (SMA). To precisely target the stimulation site, the Visor2 TMS navigation system (Advanced Neuro Technology, Enschede, The Netherlands) was used. The patient's T1-weighted magnetic resonance image was displayed on a computer monitor, and the navigation system was used to guide the location of the TMS coil relative to the head and brain surface. The position and orientation of the TMS coil and the patient's head were coregistered by placing small pieces of reflective material (trackers) on the coil and head. The trackers were monitored by an infrared, optical position sensor calibration procedure. The stimulus intensity, expressed as a percentage of the maximum stimulator output, was set at 110% of the resting motor threshold for the right abductor of the pollicis brevis muscle. One TMS session consisted of 10 trains that were each 10 seconds in duration at a frequency of 5 Hz; 5 trains

were applied over each hemisphere. We selected the SMA as the stimulation site because the SMA is involved in initiating psychomotor responses and is reportedly associated with apathy.<sup>2</sup> After 2 weeks of rTMS treatment, the patient's apathy improved. The patient performed her daily activities on her own, without assistance or encouragement. The patient's score on the Japanese version of the apathy scale obtained after the last rTMS session was 19.

Two days after the last rTMS session, the patient underwent resting-state functional MRI again. The patient's inter- and intrahemispheric functional connectivity improved to levels similar to those observed in healthy individuals (Fig 2, B).

## Discussion

As shown in Figure 2, the rTMS improved the inter-hemispheric functional disconnection that arose from the



**Figure 2.** Altered functional connectivity of the brain in a patient with poststroke apathy. The red and blue areas show increased and decreased connectivity, respectively ( $P < .001$ , versus healthy controls). Before rTMS, the patient's interhemispheric functional connectivity was reduced compared to that in healthy controls, while her intrahemispheric functional connectivity was increased (A). These abnormalities improved to levels similar to those observed in healthy individuals after rTMS (B). Abbreviations: L, left; R, right; rTMS, repetitive transcranial magnetic stimulation.

lesion in the CC. Although the patient's intrahemispheric functional connectivity was increased, the same phenomenon was observed in rodent models of complete corpus callosotomy.<sup>3</sup> Thus, we believe the increase was a secondary alteration stemming from the intrahemispheric reorganization that occurred after disruption of the interhemispheric connectivity. The CC is essential for interhemispheric communication; in particular, the CC integrates emotional, linguistic, perceptual, and cognitive information.<sup>4</sup> Given that communication between the left and right cerebral hemispheres is a crucial component of cognitive and emotional processing,<sup>5</sup> it is not surprising that disruption of the interhemispheric functional connectivity is associated with apathy. Disruption of bifrontal coordination might have an effect on the frontal subcortical loops, which are crucial for expressing apathy, while disrupted occipital and temporal connections might also induce apathy because of dysfunctions in multisensory information integration and disruptions in the ability to manipulate stimuli in working memory and to reorient attention to relevant information.<sup>6</sup>

In our case, rTMS of the SMA improved the patient's interhemispheric functional connectivity. It should be noted that the effects of rTMS can occur at the stimulus site or at more distant regions, including any cortical or subcortical structure that is functionally connected with the stimulated area. For instance, the activated networks might be transcallosal pathways in the case of cortical stimulation. The SMA is connected to several regions, not only within the frontal lobe but also within the parietal lobe.<sup>7</sup> Additionally, many interhemispheric tracts exist between the SMA regions in the left and right hemispheres.<sup>8</sup> Collectively, the rTMS affects these functionally connected areas, which may improve the interhemispheric functional connectivity.

## Conclusions

rTMS may be useful for treating poststroke apathy. The case reported herein suggests that rTMS can improve the transfer of information through the CC, which is crucial for helping a patient recover from poststroke apathy. However, additional studies on the mechanisms of action of rTMS are required.

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