tDCS in patients with disorders of consciousness

Sham-controlled randomized double-blind study

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ABSTRACT

Objective: We assessed the effects of left dorsolateral prefrontal cortex transcranial direct current stimulation (DLPF-tDCS) on Coma Recovery Scale–Revised (CRS-R) scores in severely brain-damaged patients with disorders of consciousness.

Methods: In a double-blind sham-controlled crossover design, anodal and sham tDCS were delivered in randomized order over the left DLPF cortex for 20 minutes in patients in a vegetative state/unresponsive wakefulness syndrome (VS/UWS) or in a minimally conscious state (MCS) assessed at least 1 week after acute traumatic or nontraumatic insult. Clinical assessments were performed using the CRS-R directly before and after anodal and sham tDCS stimulation. Follow-up outcome data were acquired 12 months after inclusion using the Glasgow Outcome Scale–Extended.

Results: Patients in MCS (n = 30; interval 43 ± 63 mo; 19 traumatic, 11 nontraumatic) showed a significant treatment effect ($p = 0.003$) as measured by CRS-R total scores. In patients with VS/UWS (n = 25; interval 24 ± 48 mo; 6 traumatic, 19 nontraumatic), no treatment effect was observed ($p = 0.952$). Thirteen (43%) patients in MCS and 2 (8%) patients in VS/UWS further showed postanodal tDCS-related signs of consciousness, which were observed neither during the pre-tDCS evaluation nor during the pre- or post-sham evaluation (i.e., tDCS responders). Outcome did not differ between tDCS responders and nonresponders.

Conclusion: tDCS over left DLPF cortex may transiently improve signs of consciousness in MCS following severe brain damage as measured by changes in CRS-R total scores.

Classification of evidence: This study provides Class II evidence that short-duration tDCS of the left DLPF cortex transiently improves consciousness as measured by CRS-R assessment in patients with MCS. *Neurology*® 2014;82:1–7

GLOSSARY

CRS-R = Coma Recovery Scale–Revised; **CVA** = cerebrovascular accident; **DLPF** = dorsolateral prefrontal cortex; **DOC** = disorders of consciousness; **MCS** = minimally conscious state; **rTMS** = repetitive transcranial magnetic stimulation; **tDCS** = transcranial direct current stimulation; **UWS** = unresponsive wakefulness syndrome; **VS** = vegetative state.

At present, there are no evidence-based guidelines regarding the treatment of patients with disorders of consciousness (DOC).[1] Nevertheless, some studies have recently aimed to demonstrate the potential therapeutic effect of different pharmacologic or nonpharmacologic interventions: a recent controlled clinical trial showed a beneficial effect of amantadine in posttraumatic patients with DOC[2] and a controlled case study has assessed the role of thalamic deep brain stimulation in patients in a minimally conscious state (MCS) following a brain trauma.[3] In terms of noninvasive intervention, transcranial direct current stimulation (tDCS) has been previously reported to transiently improve working memory and attention by stimulating the left dorsolateral prefrontal (DLPF) cortex in healthy subjects[4,5] and patients with stroke,[6] Parkinson disease,[7] or Alzheimer disease.[8] Previous studies in healthy subjects reported no major adverse effects of tDCS: most often encountered were the sensation of tingling (76%), itching (68%), slight burning (54%), or mild pain (25%).[9]

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Supplemental data at Neurology.org

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We aimed to assess the effect of a single session of anodal tDCS of the left DLPF cortex on consciousness, as evaluated by means of the Coma Recovery Scale–Revised (CRS-R), in patients in a vegetative state/unresponsive wakefulness syndrome (VS/UWS; i.e., only showing reflex movements)[10,11] and in MCS (showing reproducible but inconsistent signs of consciousness) in a double-blind randomized sham-controlled crossover study.

METHODS

Outcomes. The primary research question was whether anodal tDCS, as compared to sham stimulation, would improve consciousness (as measured by changes in CRS-R total scores) in a convenience sample of VS/UWS and MCS patients. Our second outcome was whether the tDCS had an impact on CRS-R subscales in MCS patients. Finally, follow-up outcome data were acquired 12 months after inclusion using the Glasgow Outcome Scale–Extended to assess the long-term effect of tDCS.

Patients. We prospectively enrolled medically stable patients in VS/UWS or MCS hospitalized in the Neurology Department of the University Hospital of Liège or in the Intercommunale de Soins Spécialisés de Liège rehabilitation center. Inclusion criteria were traumatic and nontraumatic etiology of VS/UWS or MCS according to published diagnostic criteria[12] during the acquisition period. We excluded patients in coma,[10] with less than 1 week after acute brain insult, with fluctuating diagnosis on baseline assessment, and with a metallic cerebral implant or pacemaker (in line with the safety criteria for tDCS in humans).[13] Patients were studied free of sedative drugs and Na^+ or Ca^{++} channel blockers (e.g., carbamazepine) or NMDA receptor antagonists (e.g., dextromethorphan) to avoid any interaction with the presumed neuromodulatory effects of tDCS.[14] Medication (2 patients received amantadine), physiotherapy, and rehabilitation were kept unchanged throughout the experiment.

Standard protocol approvals, registrations, and patient consents. Written informed consent was obtained by the legal representative. The study was approved by the ethics committee of the University and University Hospital of Liège, Belgium (ClinicalTrials.gov NCT01673126).

Materials. tDCS is a form of noninvasive cortical stimulation, modulating cortical excitability at stimulation sites via weak polarizing currents. Each patient received both anodal and sham tDCS stimulations in randomized order. A computer-generated randomization sequence was used to assign in a 1:1 ratio the first session as anodal tDCS or sham tDCS. Randomization was stratified by study center. For the sham session, the employed tDCS device (Magstim Eldith 1 Channel DC Stimulator Plus, Magstim Company Ltd., Whitland, Wales) offers a built-in placebo mode, which is activated by an anonymous code number and includes ramp periods at the beginning and the end of sham stimulation to mimic the somatosensory artifact of real tDCS. For each patient, the experimenter received 2 codes from an independent person, one corresponding to an anodal stimulation and the other one to sham stimulation. Thus, placebo or sham tDCS could be identified by neither the blinded experimenter who administered tDCS and CRS-R nor by any of the patients.

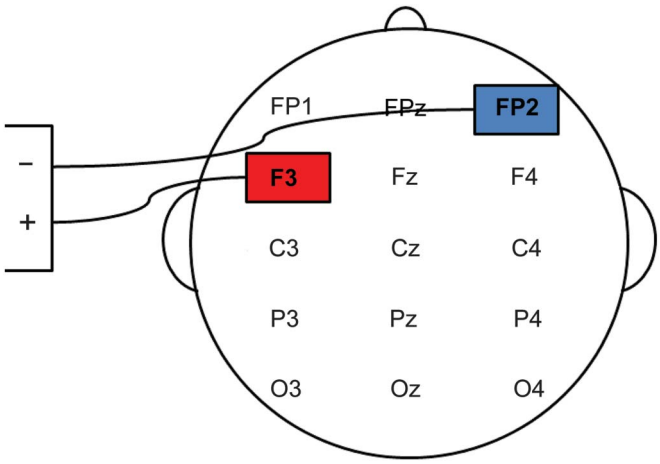
Direct current was applied by a battery-driven constant current stimulator using saline-soaked surface sponge electrodes (7 × 5 cm) with the anode (increasing cortical excitability) positioned over the left DLPF cortex (F3 according to the 10–20 international system for EEG placement)[15] and the cathode (i.e., reference electrode) placed over the right supraorbital region, as described previously (figure 1).[16] During tDCS, the current was increased to 2 mA from the onset of stimulation and applied for 20 minutes. For the sham condition, the same electrode placement was used as in the stimulation condition, but the current was applied for 5 seconds, and was then ramped down.

Impedances were kept <10 kΩ and voltage <26 V. tDCS and sham were tested in random order in 2 separate sessions separated by 48 hours. According to the literature, the effects of a single session of anodal tDCS are expected to last for a maximum of 2 hours.[17] Hence, patients were expected to return back to their initial clinical status between the 2 sessions of stimulation (i.e., 48 hours).

tDCS treatment effect was assessed by means of standardized CRS-R assessments performed by trained and experienced blinded assessors.[18] The CRS-R consists of 23 hierarchically arranged items that comprise 6 subscales addressing auditory, visual, motor, verbal, communication, and arousal functions. Scoring is based on the presence or absence of specific behavioral responses to sensory stimuli administered in a standardized manner. The lowest item on each subscale represents reflexive activity, whereas the highest items represent cognitively mediated behaviors. A.T. enrolled the patients and assigned patients to intervention. CRS-R examinations were performed[15] directly before and after the anodal tDCS and sham tDCS sessions. For the baseline assessment, 2 blinded assessors (A.T. and M.A.B.) independently performed CRS-R assessments[18] in randomized order, permitting inter-rater comparisons. Patient outcome was assessed 12 months after the trial using the Glasgow Outcome Scale-Extended to assess the long-term effects of tDCS on clinical evolution of patients.[19] Good outcome was defined by a score >4 (i.e., return to independent living).

Data analyses. Statistical analysis was performed using Stata (Stata Statistical Software 11.2, StataCorp, College Station, TX). At the group level, we looked for a period, interaction, and treatment effect. The period effect referred to the calculation of tDCS − sham response differences, which were then compared according to order using a Mann-Whitney *U* test. The interaction

Figure 1 Transcranial direct current stimulation electrode positioning



The anodal (active) electrode was placed on the left prefrontal dorsolateral cortex (F3), with the cathode placed on the right supraorbicular cortex (FP2).

effect referred to the calculation of the mean response after tDCS and sham, which was then compared according to period using a Mann-Whitney *U* test. If no period and interaction effect was found, then treatment effect (tDCS vs sham) was assessed using a Wilcoxon match-paired signed-rank test. Results were considered significant at $p < 0.05$.

The clinical diagnoses for VS/UWS and MCS were considered independent and hence no correction for multiple comparisons had to be applied for the primary endpoint (i.e., assessment of change in CRS-R total score according to tDCS/sham). Multiple comparisons using Bonferroni correction (6 comparisons) had to be performed for the secondary endpoint assessment (i.e., assessment of CRS-R subscale change according to tDCS/sham) and results were considered significant at $p < 0.0083$ (i.e., 0.05/6).

At the individual level, tDCS responders were defined as those patients who presented a sign of consciousness (i.e., command following; visual pursuit; recognition, manipulation, localization, or functional use of objects; orientation to pain; intentional or functional communication)[18] after tDCS that was not present before anodal or before or after sham tDCS sessions.

Interrater agreement of baseline CRS-R evaluations between the 2 blinded observers was assessed using weighted kappa testing.[20] Mann-Whitney tests looked for differences in outcome between tDCS responders and nonresponders.

RESULTS We assigned 55 of the 62 eligible patients to receive both anodal and sham tDCS in a crossover study design between December 1, 2009, and June 1, 2011 (7 acute patients were excluded because they emerged from MCS between the first and second baseline assessments; see figure e-1 on the *Neurology*® Web site at Neurology.org).

Patients in VS/UWS (n = 25) had a mean age of 42 ± 17 years; 9 were women; interval since insult was 24 ± 48 months; 6 were posttraumatic, 9 anoxic, 9 other nontraumatic etiology (i.e., 5 cerebrovascular accident [CVA], 4 subarachnoid hemorrhage), and 1 mixed (i.e., traumatic-ischemic). Patients in MCS (n = 30) had a mean age of 43 ± 19 years; 7 were women; interval since insult was 43 ± 63 months; 19 were posttraumatic, 4 anoxic, 6 nontraumatic (i.e., 3 CVA, 3 subarachnoid hemorrhage), and 1 mixed (i.e., traumatic-ischemic). Demographic data are reported in table 1. Thirty-two patients (14 in VS/UWS; mean age 46 ± 17 years; 9 women; interval since insult: 44 ± 72 months; 14 posttraumatic) first received anodal tDCS and 23 (11 in VS/UWS; mean age 40 ± 19 years; 7 women; interval since insult: 24 ± 34 months; 11 posttraumatic) first received sham stimulation (there were no significant clinical or demographic differences between the groups). Intraclass correlation coefficient was 0.90. Associated 95% confidence interval was 0.67–0.97.

At the group level, there was a treatment effect for the MCS but not for the VS/UWS patient group (figure 2, table 2). No period or interaction effects were observed (see tables e-1 and e-2). No effect of tDCS on any of the CRS-R subscales was observed in any group (VS/UWS or MCS).

At the individual level, clinical data and CRS-R total scores and subscores for each subject are shown in table e-3. A total of 13/30 (43%) patients in MCS showed a tDCS-related improvement (i.e., showed a clinical sign of consciousness never observed before). Two acute (<3 months) patients in VS/UWS out of 25 (8%) showed a tDCS response (i.e., showed command following and visual pursuit present after the anodal stimulation not present at baseline or pre- or post-sham tDCS). Table 3 shows the CRS-R subscale score change for tDCS responders.

No tDCS-related side effects were observed. No correlation between tDCS response and patient outcome was observed at 12 months follow-up.

DISCUSSION This double-blind sham-controlled randomized crossover study demonstrates that a single session of anodal tDCS applied to the left DLPF cortex (when employed according to published safety guidelines)[13] may transiently improve CRS-R total scores in patients in MCS without side effects. At present, there are limited evidence-based pharmacologic or nonpharmacologic treatment options for severely brain-damaged patients with DOC, especially in the chronic setting.[1]

Our study illustrates the residual capacity for neural plasticity and temporary recovery of (minimal) signs of consciousness in some patients in MCS, but does not permit to make any claims regarding possible long-term tDCS effects in this setting. Future controlled clinical trials should now employ long-duration tDCS and its possible long-term effects, as has been performed for other indications such as pain[21] and depression.[22] Out of the 13 patients in MCS who showed a tDCS response, 5 were included >12 months after injury. These clinical improvements in long-standing MCS corroborate previous evidence for late recovery and neural plasticity in MCS.[23,24] We observed no tDCS-related increase in CRS-R total scores in patients in VS/UWS, in line with previous studies showing more capacity for neural plasticity in patients in MCS.[25]

It could be speculated that the observed tDCS-related transient improvements in consciousness as assessed by changes in CRS-R total score are related to improvement in attention and working memory,[26] known to involve prefrontal cortical functioning.[27] The stimulated left DLPF area receives visual and somatosensory input from the parietal heteromodal association cortices regarding vision, motion, spatial orientation, and tactile sensations and projects to subcortical monoaminergic and cholinergic sources.[28] The DLPF is thought to play a central integrative function for motor control and behavior and is a critical component of the decision-making network.[29] The right DLPF cortex has been linked to maintenance of sustained

Table 1 Clinical data of patients in VS/UWS and MCS

Patient	Sex/age, y	Etiology	Interval since insult	Outcome at 12 months
VS/UWS 1	F/26	Trauma	2 y	VS/UWS
VS/UWS 2	M/73	Anoxic	43 d	Dead
VS/UWS 3	F/43	Subarachnoid hemorrhage	84 d	MCS
VS/UWS 4	M/17	Trauma	50 d	Exit
VS/UWS 5	M/69	CVA	29 d	Dead
VS/UWS 6	M/66	Subarachnoid hemorrhage	28 d	VS/UWS
VS/UWS 7	M/55	Subarachnoid hemorrhage	30 d	MCS
VS/UWS 8	F/48	Anoxic	4 mo	VS/UWS
VS/UWS 9	M/35	Anoxic	19 y	VS/UWS
VS/UWS 10	F/55	Anoxic	7 d	Exit
VS/UWS 11	M/67	CVA	7 d	Dead
VS/UWS 12	M/48	Anoxic	7.5 mo	VS/UWS
VS/UWS 13	M/32	Anoxic	15 mo	VS/UWS
VS/UWS 14	M/30	Anoxic	2 y	VS/UWS
VS/UWS 15	F/41	Anoxic	4 y, 8 mo	VS/UWS
VS/UWS 16	M/31	Trauma	2 y, 3 mo	VS/UWS
VS/UWS 17	M/21	Trauma	7 mo	VS/UWS
VS/UWS 18	M/48	CVA	1 y, 4 mo	VS/UWS
VS/UWS 19	M/39	CVA	65 d	Dead
VS/UWS 20	M/49	CVA	7 y, 11 mo	VS/UWS
VS/UWS 21	M/25	Trauma	1 y, 4 mo	VS/UWS
VS/UWS 22	M/24	Trauma	1 y	VS/UWS
VS/UWS 23	M/27	Mixed trauma/anoxic	3 y, 2 mo	VS/UWS
VS/UWS 24	F/29	Subarachnoid hemorrhage	2 mo	MCS
VS/UWS 25	M/73	Anoxic	3 mo	Dead
MCS 1	M/63	Subarachnoid hemorrhage	35 d	Dead
MCS 2	F/51	Trauma	52 d	Exit
MCS 3	M/69	Anoxic	39 d	MCS
MCS 4	M/45	Trauma	26 y	MCS
MCS 5	M/85	Anoxic	78 d	Exit
MCS 6	M/43	Subarachnoid hemorrhage	18 d	Exit
MCS 7	M/79	CVA	18 d	MCS
MCS 8	M/25	Trauma	1 y	MCS
MCS 9	M/63	CVA	10 d	Dead
MCS 10	M/25	Trauma	2 y	MCS
MCS 11	F/47	Trauma	28 d	MCS
MCS 12	F/35	Trauma	8 y, 4 mo	MCS
MCS 13	M/30	Trauma	8 y, 9 mo	MCS
MCS 14	M/46	Trauma	1 y, 9 mo	MCS
MCS 15	F/63	Anoxic	4 mo	MCS
MCS 16	F/67	Subarachnoid hemorrhage	3 y, 10 mo	MCS
MCS 17	M/15	Trauma	1 y, 4 mo	MCS
MCS 18	M/24	Mixed trauma/anoxic	7 y, 4 mo	MCS
MCS 19	F/38	Trauma	1 y, 5 mo	MCS

Continued

Table 1 Continued

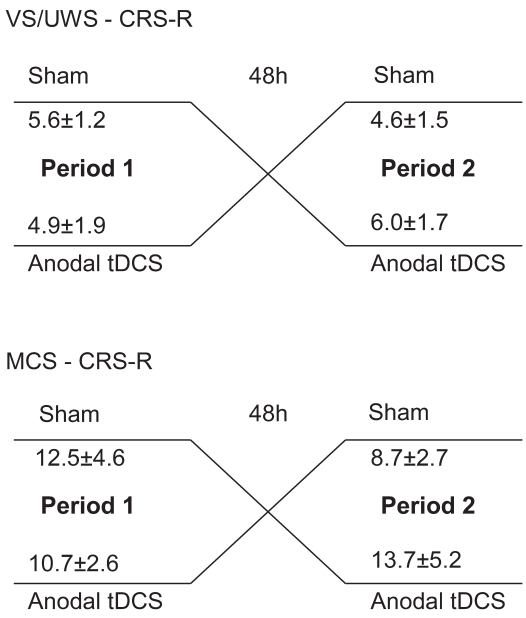
Patient	Sex/age, y	Etiology	Interval since insult	Outcome at 12 months
MCS 20	F/30	Trauma	6 y, 8 mo	MCS
MCS 21	M/34	Trauma	3 y, 8 mo	MCS
MCS 22	M/15	Anoxic	4 y	MCS
MCS 23	F/55	Trauma	11 y	MCS
MCS 24	M/27	Trauma	3 y, 2 mo	MCS
MCS 25	M/23	Trauma	4 y	MCS
MCS 26	M/34	Trauma	2 y, 9 mo	MCS
MCS 27	F/55	Trauma	6 mo	MCS
MCS 28	M/28	Trauma	3 y, 3 mo	MCS
MCS 29	M/55	CVA	3 mo	Exit
MCS 30	M/30	Trauma	1 y, 8 mo	MCS

Abbreviations: CVA = cerebrovascular accident; MCS = minimally conscious state; UWS = unresponsive wakefulness syndrome; VS = vegetative state.

arousal and attention,[30] which is similarly relevant for patients with DOC. However, given the current level of evidence regarding anodal tDCS of left DLPF[4–8,10] and the limited number of studies employing right anodal tDCS in normal or pathologic conditions, we opted to stimulate the former.

Previous studies have shown that anodal tDCS over the left DLPF cortex has beneficial effects on working memory in patients with Alzheimer disease[8] and Parkinson disease.[7] Similarly, there is some evidence that tDCS of the left DLPF could improve attention in stroke[31] and mild traumatic brain injury[6] patients with attention deficits. A recent fMRI study showed that tDCS of the left DLPF cortex increased functional connectivity in the "default mode" (i.e., intrinsic cortical network) and bilateral frontal-parietal associative cortical networks (i.e., extrinsic networks),[16] considered to be involved in internal and external awareness, respectively.[32] Both networks are known to be dysfunctional in patients with DOC, as shown by previous PET[33] and fMRI[34] studies.

Figure 2 Trial design: Randomized double-blind placebo-controlled crossover study



Mean Coma Recovery Scale-Revised (CRS-R) total scores (SD) for patients in vegetative state (VS)/unresponsive wakefulness syndrome (UWS) and minimally conscious state (MCS) after sham stimulation and anodal transcranial direct current stimulation (tDCS).

A methodologic limitation of the present study and of most previous tDCS studies is the absence of MRI-based mapping of the stimulated area—especially important in our case given the presence of focal brain damage, atrophy, and injury-induced differences in brain topography. Future studies could employ patient-tailored structural MRI-guided tDCS and additionally use functional MRI to document possible tDCS-specific changes in cerebral functional connectivity in DOC. Indeed, the mechanisms of action of tDCS remain only partially understood. Direct effects of anodal tDCS include an increase of neuronal excitability via a facilitation of action potential release.[35] Previous studies have highlighted changes in resting membrane potential, spontaneous neuronal firing rates, synaptic strength, cerebral blood flow, and metabolism subsequent to tDCS.[14] Some authors have postulated an NMDA,[36] calcium uptake,[37] or dopaminergic modulation.[38] It should be noted that in the present study, 2 included patients in MCS received amantadine; however, the treatment was started 6 months prior to inclusion and remained unchanged during the experiment.

Table 2 Treatment effects (i.e., change in CRS-R total score) for patients in VS/UWS and MCS

	Difference tDCS − sham	Median	p 25	p 75	p Value
VS/UWS	0.3 ± 1.4	0	0	0	0.952
MCS	1.6 ± 2.5	1.5	0	4	0.003

Abbreviations: CRS-R = Coma Recovery Scale–Revised; MCS = minimally conscious state; tDCS = transcranial direct current stimulation; UWS = unresponsive wakefulness syndrome; VS = vegetative state.

We showed that tDCS in patients with DOC (when performed within established ranges of intensity and duration) is safe, and thus, could be tested as an alternative neuromodulatory tool to improve consciousness and cognitive function in severely brain-injured patients. Another form of noninvasive cortical stimulation is repetitive transcranial magnetic stimulation (rTMS). rTMS has previously been proposed in a single case study as a potential therapy for traumatic brain injury.[39] In our view, tDCS may have some advantages over rTMS, as it is easier to apply, causes less discomfort, and has a lower associated risk of inducing seizures[40]—the latter being especially important in the setting of severe brain injury.

Short-duration anodal (i.e., excitatory) tDCS of left DLPF cortex can induce short-term improvement in patients in MCS of acute/subacute and chronic etiologies measured by behavioral CRS-R total scores. The long-term noninvasive neuromodulatory tDCS outcome clinical improvement in this challenging patient population remains to be shown.

Table 3 Clinical improvement of the 15 tDCS responders according to the CRS-R subscale scores

CRS-R subscales	Recovery	Number of patients
Auditory	Systematic command following	1
	Reproducible command following	4
	Localization to sounds	1
	Auditory startle	0
Visual	Object recognition	2
	Object localization	1
	Visual pursuit	5
	Blinking to threat	0
Motor	Functional use of object	1
	Automatic motor reaction	2
	Object manipulation	3
	Localization to noxious stimulation	0
	Flexion withdrawal	1
	Abnormal posturing	0
Oromotor/verbal	Intelligible vocalization	0
	Vocalization	3
	Oral reflexive movement	0
Communication	Functional communication	2
	Intentional communication	0
Arousal	Without stimulation	2
	With stimulation	0

Abbreviations: CRS-R = Coma Recovery Scale–Revised; tDCS = transcranial direct current stimulation.

AUTHOR CONTRIBUTIONS

A.T. and M.-A.B. obtained and interpreted data and wrote the manuscript. D.L. and A.D. analyzed the data. A.T., M.-A.B., and S.L. designed the protocol. S.L. contributed to the writing of the manuscript. A.T., M.-A.B., and S.L. were the main investigators. All authors were involved in editing the paper and approved the final text.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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