Outcome	Progesterone (N=442)	Placebo (N=440)	Overall (N=882)	Unadjusted Difference (95% CI)
				percentage points
Primary outcome — no. (%)				
Favorable outcome	213 (48.2)	232 (52.7)	445 (50.5)	−4.5 (−11.1 to 2.1)
Missing data	28 (6.3)	24 (5.5)	52 (5.9)	—
According to initial injury severity — no./total no. (%)				
Moderate injury				
Favorable	35/129 (27.1)	45/125 (36.0)	80/254 (31.5)	−8.9 (−20.3 to 2.5)
Missing data	10/129 (7.8)	11/125 (8.8)	21/254 (8.3)	—
Moderate-to-severe injury				
Favorable	133/234 (56.8)	133/238 (55.9)	266/472 (56.4)	1.0 (−8.0 to 9.9)
Missing data	13/234 (5.6)	9/238 (3.8)	22/472 (4.7)	—
Severe injury				
Favorable	45/79 (57.0)	54/77 (70.1)	99/156 (63.5)	−13.2 (−28.1 to 1.8)
Missing data	5/79 (6.3)	4/77 (5.2)	9/156 (5.8)	—
Death — no. (%)	83 (18.8)	69 (15.7)	152 (17.2)	—
Cause of death — no./total no. (%)				—
Neurologic	53/83 (63.9)	49/69 (71.0)	102/152 (67.1)	—
Not neurologic	28/83 (33.7)	20/69 (29.0)	48/152 (31.6)	—
Unknown	2/83 (2.4)	0	2/152 (1.3)	
According to initial injury severity — no./total no. (%)				—
Moderate	19/129 (14.7)	14/125 (11.2)	33/254 (13.0)	—
Moderate to severe	37/234 (15.8)	39/238 (16.4)	76/472 (16.1)	—
Severe	27/79 (34.2)	16/77 (20.8)	43/156 (27.6)	—
Disability Rating Scale score†	2.9±4.6	3.3±5.1	3.1±4.9	—

Figure. Outcome at 6 months after injury. CI, confidence interval. From New England Journal of Medicine, Wright DW, Yeatts SD, Silbergleit R, et al. Volume 371, Page No. 2457-2466. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Outcome Scale measured at 6 months from the time of injury (Figure).

A favorable outcome was determined by stratifying patients according to the severity of their initial injury so that patients with a less severe initial injury had to have a better recovery than those with a more severe injury to have a favorable outcome. A total of 882 patients were randomized between April 2010 and October 2013. The progesterone and placebo groups were balanced in terms of demographics and injury severity; 53.5% of patients had an initial GCS score of 5 to 8, with the remainder divided between a GCS score of 4 (severe injury) and a GCS score of 9 to 12 (moderate injury). Favorable outcomes were achieved in 51.0% of progesterone-treated patients and 55.5% of placebo patients. A secondary analysis in which a favorable outcome was simply considered to be an Extended Glasgow Outcome Scale score ≥5 (equating to moderate disability or better) provided similar results. There was also no significant difference in mortality between the 2 groups. Additionally, adverse events were similar between the groups with the exception of phlebitis and thrombophlebitis (considered a nonserious adverse event) occurring significantly more often in the progesterone group. Thus, although progesterone maintains a good safety profile, it does not appear to have an effect on functional outcome when administered to patients with acute TBI.

Despite data from multiple animal studies, 2 human trials preceding it, and a high-quality study design, the PROTECT III trial was not able to establish a role for progesterone in the treatment of TBI. The authors cite the heterogeneity of injuries, patient pre-existing conditions, and the characteristics of individual patients as potential confounding factors. Although these negative results are disappointing, the study paves the way for the investigation of future compounds.

Michael Wang, MD
John Serak, MD
University of Miami Miller School of Medicine
Jackson Memorial Hospital
Miami, Florida

REFERENCE

1. Wright DW, Yeatts SD, Silbergleit R, et al. Very early administration of progesterone for acute traumatic brain injury. *N Engl J Med.* 2014;17:2457-2466.

Closed-Loop Deep Brain Stimulation Successfully Modulates Hippocampal Activity in an Animal Model

Recent research in brain stimulation techniques (in the context of a variety of neurological conditions, including movement disorders, psychiatric disorders, and epilepsy) has turned toward understanding the

Copyright © Congress of Neurological Surgeons. Unauthorized reproduction of this article is prohibited.

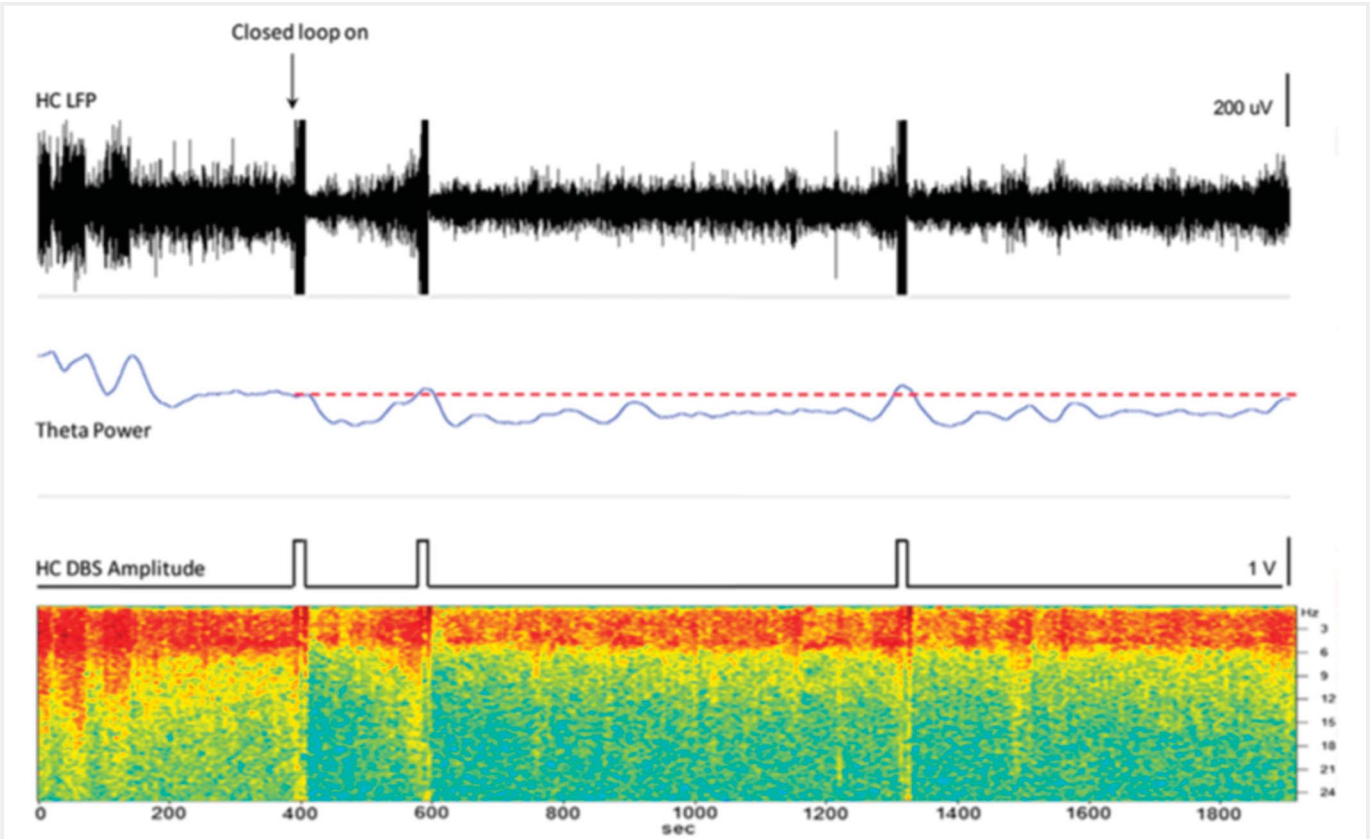

Figure. Closed-loop control of hippocampal activity. The top tracing demonstrates the hippocampal local field potential (LFP) activity recorded by the implantable pulse generator. The arrow indicates the time at which the closed-loop control paradigm is initiated. The second tracing demonstrates the hippocampal theta band power signal (4-9 Hz), with the dotted line representing the threshold level set for the delivery of direct stimulation. The third trace shows the hippocampal stimulation voltage, and the bottom figure is the LFP spectrogram. Reprinted from Brain Stimulation, Vol 7/3, Stypulkowski PH, Stanslaski SR, Jensen RM, Denison TJ, Giftakis JE, Brain Stimulation for Epilepsy - Local and Remote Modulation of Network Excitability, Pages No. 350-358, Copyright (2014), with permission from Elsevier.

induced effects of stimulation at a systems level. These efforts often involve stimulating one region of the brain and examining the response characteristics of another. In this vein, Stypulkowski et al[1] recently published a study of hippocampal excitability and its changes in the context of both local hippocampal and remote electric stimulation of the anterior thalamus. The authors demonstrate that broadband local field potential (LFP) suppression can be produced in the hippocampus via either direct hippocampal or thalamic stimulation and that these effects are dependent on the stimulation parameters used. Additionally, the authors developed and demonstrated 2 closed-loop stimulation schemes in which stimulation therapy was selectively delivered and modulated on the basis of real-time feedback in the form of hippocampal theta band activity.

The authors performed these studies in a sheep model (n = 3) with Medtronic model 3387 deep brain stimulation leads stereotactically placed in the hippocampus and model 3389 deep brain stimulation leads placed in the anterior thalamus unilaterally. Long-term implant durations ranged from 24 to 31 months, and stimulation experiments were performed in awake behaving animals. The novel implantable pulse generator (placed in a retroscapular location) was capable of both stimulating and performing LFP recordings concurrently. This system additionally was capable of triggering stimulation on the basis of band power changes selected by the investigator. Evoked potentials recorded with this system were obtained during anterior thalamic stimulation, with delays on the order of 50 to 100 milliseconds. Additionally, broadband suppression in hippocampal LFP activity was observed specifically with increases in the frequency of thalamic stimulation starting in the range of 40 Hz (1.0 V, 120-microsecond pulse width). With the use of a cycled thalamic stimulation pulsing regimen, the suppressed hippocampal theta band activity was shown to return between periods of stimulation.

Like thalamic stimulation, direct hippocampal stimulation was capable of broadband hippocampal LFP suppression at frequencies in the 20-Hz range and above. However, in contrast to thalamic stimulation, when direct hippocampal stimulation was performed, the most sensitive parameter for inducing decreases in theta band power was the voltage amplitude of the stimulation. Direct hippocampal stimulation at amplitudes ranging from 0.4 to 0.8 V produced increasing suppression of hippocampal LFP activity. At a stimulation amplitude of 1.0 V, an excitatory burst of activity called an afterdischarge was produced, followed by a prolonged

Copyright © Congress of Neurological Surgeons. Unauthorized reproduction of this article is prohibited.

period of depressed hippocampal LFP activity. Afterdischarges were less likely to be induced by direct hippocampal stimulation during periods when the hippocampal LFP had already been suppressed with preceding preparatory stimulation. Evoked potentials produced in the hippocampus by thalamic stimulation were also suppressed when preparatory direct hippocampal stimulation was provided.

The authors were also able to demonstrate 2 novel closed-loop control stimulation paradigms whereby the ambient theta band power recorded in the hippocampus was used to trigger deep brain stimulation, leading to suppression of power in this band pass. In the first paradigm, hippocampal theta band power at a specified threshold was used to control the delivery of short 10-second bursts of direct hippocampal stimulation (0.9 V, 300 microseconds, 50 Hz) that successfully produced LFP suppression and maintained this suppression over extended periods of time (Figure). The second closed-loop system demonstrated instead used continuous thalamic stimulation at a frequency of 40 Hz. Changes in recorded hippocampal theta band activity were used to modulate the amplitude of the continuous thalamic stimulation, and by this means, hippocampal activity was suppressed, which was also sustained over a period of time. In summary, Stypulkowski et al have now demonstrated (in awake behaving animals) that both local and remote deep brain stimulation can produce specific effects on hippocampal excitability. Two novel closed-loop control paradigms were demonstrated in which each successfully depressed hippocampal activity within a desired range. This kind of closed-loop deep brain stimulation paradigm is currently actively undergoing investigation with the hope that it can be applied to many different disease states, and because neuromodulation is delivered only when necessary, it is thought that this can be used to minimize possible side effects of stimulation and to increase battery lifetime while also maximizing therapeutic benefit.

Jennifer J. Cheng, MD
William S. Anderson, MD, PhD
Johns Hopkins University School of Medicine
Baltimore, Maryland

REFERENCE

1. Stypulkowski PH, Stanslaski SR, Jensen RM, Denison TJ, Giftakis JE. Brain stimulation for epilepsy—local and remote modulation of network excitability. *Brain Stimul.* 2014;7(3):350-358.

Combined Direct and Indirect Revascularization Is Associated With Low Rates of Recurrent Ischemic and Hemorrhagic Stroke in Adult Moyamoya Disease

Suzuki and Takaku[1] first coined the term moyamoya disease during the late 1960s when studying a peculiar vaso-occlusive disease of the brain. This rare idiopathic syndrome is characterized by luminal stenosis secondary to intimal thickening and smooth muscle cell proliferation of the distal internal carotid arteries and the main branches of the circle of Willis.[2,3] In association with this occlusive phenomenon, there is compensatory neogenesis of an aberrant network of vessels that maintain a collateral circulation to the brain tissue.[3] It is this pathophysiological process that gives moyamoya its characteristic "puff of smoke" feature on angiographic studies.

There is no known medical treatment for moyamoya disease. Treatment involves revascularization, which improves cerebral perfusion with the goal of eliminating or reducing recurrent transient ischemic strokes, strokes, and cognitive deterioration.[4] Surgical options are categorized into direct and indirect techniques. Direct revascularization procedures use extracranial to intracranial bypass to increase perfusion to the brain. Examples include superficial temporal artery and occipital artery to middle cerebral artery bypass. On the other hand, indirect procedures increase revascularization by stimulating neovascularization over time. Some of the described methods include encephalodurogaleosynangiosis, encephalomyosynangiosis, encephaloduroarteriosynangiosis, and burr hole placement.[4-6] Despite several decades of growing experience treating this enigmatic disease, data are lacking on the long-term outcomes, and controversy still remains regarding the best surgical approaches. It remains unclear whether indirect or direct bypass should be preferred. Whether combining the 2 approaches is advantageous also remains an unanswered question.

To address this knowledge deficit, Cho et al[7] conducted a rigorous retrospective case series that highlights the potential added value of using combined direct and indirect revascularization surgery in adults diagnosed with moyamoya disease. They retrospectively evaluated the clinical, angiographic, and hemodynamic outcomes data of 60 patients who had undergone a combined revascularization surgery for moyamoya disease at their center. Their approach consisted of a combined superficial temporal artery to middle cerebral artery anastomosis with encephalodurogaleosynangiosis. The data points were assessed at short-term (5-12 months) and long-term (>5 years) intervals for each of the clinical, angiographic, and hemodynamic variables.

Clinical outcome was assessed based on the Karnofsky Performance Scale and the modified Rankin Scale (Figure). There was an evident improvement on both scales; the Karnofsky performance scores improved from an average of 81.1 to 96.2, and the modified Rankin Scale scores improved from an average of 1.5 to 0.4. This improvement was seen mainly between the procedure and short-term follow-up. The angiographic outcome was assessed on the basis of postoperative revascularization, measured by relative revascularization area [(revascularization area/supratentorial area) × 100], and patency of the direct anastomosis. The data revealed that the relative revascularization area had increased between the short-term and long-term follow-up periods, even though patency of the direct anastomosis had decreased from an average of 94.4% in the short-term to 76.1% in the long-term period. Finally, brain single-photon emission computed tomography was used to evaluate postoperative hemodynamics with respect to preoperative results. After analyzing brain perfusion single-photon emission computed tomography data, the authors found that cerebral blood flow increased significantly until the short-term follow-up but did not increase substantially between the short-term and long-term follow-ups. Impressively, Cho et al reported that the incidences of symptomatic hemorrhage and infarction in the operated hemispheres were 0.4% and 0.2% annually.

The authors hypothesize that both direct and indirect revascularization each play an important role in postsurgical revascularization. In the early phase after surgery, direct bypass plays a dominant role because indirect revascularization can take up to 3 months for neovascularization to mature between the extracranial and intracranial vasculature.[8] However, over the long term, collaterals secondary to indirect processes could play a more dominant role and improve perfusion to areas of the brain that blood flow could not reach via direct bypass.

The limitations of this study are the retrospective design and lack of randomization. The main strength of this study is the rigorous consistency with which the authors treated and followed up their patients and tabulated important data points. The exceedingly low recurrent

Copyright © Congress of Neurological Surgeons. Unauthorized reproduction of this article is prohibited.