

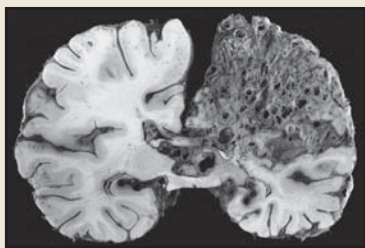
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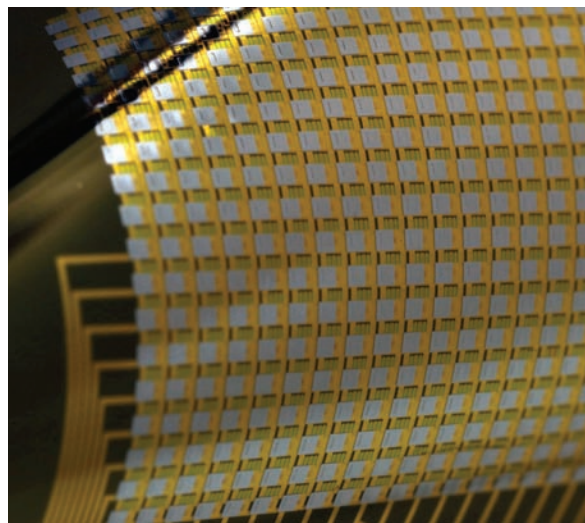
New Technology Enables More Sensitive Detection of Neural Activity

Far-reaching Potential for Seizure Detection

BY JAMIE TALAN

The technology to record the electrical circuitry of the brain — from an individual cell to an orchestra of neuronal players — has not changed substantially in four decades. Scientists have been placing electrodes in the brain to record the behavior of neurons but the discoveries are constrained by the technology. Each electrode needs to be threaded to a wire and scientists can only obtain a high-resolution snapshot if they confine the electrodes to a small space.

Now, a team of neuroscientists and engineers has designed a technology
Continued on page 5



HIGH-RESOLUTION, FLEXIBLE, ACTIVE ELECTRODE ARRAY with 360 amplified and multiplexed electrodes. The electrode array is ultrathin and flexible, allowing close contact with the brain and high-resolution recordings of seizures.

Credit: Travis Ross and Yun-Sung Kim, University of Illinois at Urbana-Champaign

INVESTIGATORS CREATE FUNCTIONAL DOPAMINE NEURONS

Clinical Trials in PD Could Be A Few Years Away

BY JAMIE TALAN

Scientists think they have finally found the right recipe to make pure and functional dopamine neurons from human embryonic stem cells (hESCs), a feat that could mean an abundant source of cells for transplantation in Parkinson disease (PD) patients in the next five years.

Frustrated by animal studies that failed to show an improvement in PD symptoms with dopamine neurons made from hESCs, Lorenz Studer, MD, director of the Laboratory of Stem Cell & Tumor Biology, Neurosurgery and Developmental Biology, and his colleagues at Memorial Sloan-Kettering Cancer Center in New York City focused on trying to discover a key signal to create a population of dopamine neurons that worked to restore dopamine in the brain.

They described their findings in a paper in the Nov. 6 online edition of *Nature*.

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A More Portable EEG Used to Assess Consciousness in Patients in Vegetative State

BY JAMIE TALAN

A team of Canadian scientists has developed a bedside EEG task to assess whether a person in a vegetative state can carry out mental exercises, evidence of conscious awareness even though their bodies reveal no overt signs of responsiveness.

In the study, published in the Nov. 10 online edition of the *Lancet*, one in five patients in a vegetative state (VS) showed evidence on an EEG recording that they understood the commands

— squeezing their hand and wiggling toes — over and over again during a 20-minute testing period.

Adrian M. Owen, PhD, the Canada Excellence Research Chair at the University of Western Ontario, Damian Cruse, PhD, a post-doctoral fellow at the University of Western Ontario, and their colleagues tested the cognitive abilities of 16 patients in a VS — observed in two inpatient

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DR. DAMIAN CRUSE (left) demonstrates the use of a more portable EEG model on a healthy volunteer, which could assess individuals possibly misdiagnosed as vegetative state patients.

Credit: University of Western Ontario

PERIODICALS

Technology, Neural Activity

Continued from page 6

right onto the brain.” They are collaborating with scientists and engineers to develop cortical prostheses.

“The technology is helping us identify new areas of the auditory and visual system,” said Dr. Viventi.

In the *Nature Neuroscience* paper, the scientists also reported on the behavior of sleep spindles, short bursts of electrical activity that were thought to occur throughout large areas of the brain during sleep and under anesthesia. The arrays provided quite a different picture: the spindles don’t move at all.

the materials will be safer than the penetrating microelectrode arrays used today that can cause hemorrhage and inflammation.

They are also working on the next generation of the device that could record brain signals, recognize the abnormal pattern and deliver an electrical charge to stop the activity and prevent a seizure.

EXPERTS COMMENT

“This is a big advance,” said Story Landis, PhD, director of the NINDS, which helped fund the study. “This technology will give us a much more accurate

Scientists said that the device would be a major advance for conditions like epilepsy where brain recordings are often necessary to identify the locus of a seizure.

“You see them like a blink of light and then they disappear,” said Dr. Viventi.

“This technology allows us to look at large areas of brain at the same time,” said Dr. Litt. “This resolution has not been possible before now.”

The researchers are now conducting safety studies to move the technology into the clinic. They contend that

way of tracing irregular activity in the brain. The standard microelectrodes in the brain are too far apart and not sufficiently sensitive.”

What’s more, she added, “the flexibility of the arrays allows scientists to record deep down into the sulci.”

Orrin Devinsky, MD, director of the Epilepsy Center at New York University



AN ILLUSTRATION OF HOW a thumbnail-sized, ultra-thin sensor would fit in the brain, allowing high-resolution recording of seizures.

(NYU) and professor of neurology at NYU Langone School of Medicine, agrees. “This study suggests a new and exciting methodology to use electrodes that can get into regions previously not explored by standard electrodes.”

He added: “Electrical recordings to localize seizure onset has been limited by our technology and access to areas. The study tells us more about seizure onsets in parts of the cerebral cortex that are buried (for example, in sulci). In many patients, we have extensive coverage but never seem to find the focus or seizure onset. It may be that there isn’t one — that seizures start from wide areas of the cortex

simultaneously. But in many cases, seizures probably do arise locally and we simply don’t have electrodes over the onset zone. These electrodes may help solve some of these problems, which could be the difference between success and failure.” •

REFERENCE:

- Viventi J, Kim DH, Litt B, et al. Flexible, foldable, actively multiplexed, high-density electrode array for mapping brain activity in vivo. *Nat Neurosci* 2011; E-pub 2011 Nov 13.

Vegetative State

Continued from page 1

European research units, the Addenbrooke’s Hospital in Cambridge and University Hospital of Liège, Belgium — for a week between July 2010 and June 2011. The patients were between 29 and 45 years old and had been in a VS from three to 23 months.

Three of the patients consistently and reliably generated EEG patterns identical to the patterns observed when 12 healthy volunteers did the same mental task — imagining that they were squeezing their right fist or wiggling their right toe. In the three patients, the premotor cortex, which is involved with imagined movement and planning, was consistently activated during the moments they were asked to carry out the task.

The EEG wave activity — as a measurement of mental awareness — could be a useful tool for the clinical assessment of VS patients, said Dr. Cruse. The patterns of brain activity suggest that



DR. NICHOLAS D. SCHIFF:
“As the paper clearly will lead to discussion of using these and other tools to separate the MCS from vegetative states, the results should not convey the impression that any of our available research tools are yet clinically validated.”

that this would happen,” said Dr. Cruse. “We found that they were responding to our commands and that meant that they understood what we were asking, paying attention to the complex task and able to follow through with the command. This suggests that they are aware of what is going on in their environment and would be able to communicate if they had the right tools.”

Ultimately, he said, “we may be able to use this type of task to begin asking them if they know where they are and what they know about their lives.”

some of these patients have the intention or desire to move.

“There was nothing about these patients that would lead one to believe

The investigators said EEG testing, which is more affordable and accessible than fMRI, could be used more to assess VS patients at bedside or even in their homes, but there are technological challenges that need to be resolved first. For example, the scientists are now working with engineers to figure out how they can analyze the EEG recordings in real time so that they can have an ongoing exchange with patients or caregivers.

The investigators are also trying to develop the technology so that patients who show conscious awareness without any overt behavioral proof might someday be able to communicate their needs and thoughts through a computer interface, similar to the tools available for patients with complete paralysis.

Dr. Owen and his colleagues have previously shown that fMRI scans could also be used to assess whether patients in a PVS can follow commands. In a study published last year in the *New*

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Vegetative State

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England Journal of Medicine, the researchers reported that four of 24 patients were able to answer “yes” and “no” questions by pairing that response with an imagined behavior such as imagining they were walking around their house or playing tennis.

“It is not at all practical to use fMRI scans to assess whether patients have conscious awareness and can communicate,” said Dr. Cruse. “The idea of making this type of assessment at the bedside was compelling.”

“Our studies prove that simply looking at behavior does not tell you that patients are aware,” he said. He added that the absence of a response with this

task does not mean that there is a lack of awareness, either. This was a one-time assessment and it is impossible to tell whether the patient has periods of awareness at other times.


The investigators will monitor the patients over the year to see whether there is prognostic value in the initial data. They can assess whether these patients have better outcomes over

Want to hear about the EEG testing of patients in a vegetative state? Damian Cruse, PhD, talked to *Neurology Today* about what the investigators did and found. Look for the podcast and a video demonstrating their experiment on www.neurotodayonline.com.

For the management of fibromyalgia

Savella relieves symptoms of fibromyalgia

- Delivers simultaneous improvements on 3 measures of fibromyalgia¹
 - Pain reduction
 - Improvement in patient global fibromyalgia assessment
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- Decrease in pain as early as week 1 of treatment with a stable dose in some patients who reported global improvement¹
 - Primary endpoint was assessed at week 15
- Low potential for pharmacokinetic drug-drug interactions¹
 - Clinically important interactions may occur with MAOIs, serotonergic drugs (including other SSRIs, SNRIs, lithium, tryptophan, antipsychotics, and dopamine antagonists), triptans, catecholamines (epinephrine and norepinephrine), CNS-active drugs (including clomipramine), and select cardiovascular agents (digoxin and clonidine)
- A dual reuptake inhibitor that blocks the uptake of norepinephrine over serotonin with approximately 3 times greater potency in vitro¹
 - The clinical significance of in vitro data is unknown
- Widely available on managed care formularies²

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 12.5 mg, 25 mg, 50 mg, 100 mg tablets
 For the management of fibromyalgia

IMPORTANT SAFETY INFORMATION

Savella is a selective serotonin and norepinephrine reuptake inhibitor (SNRI), similar to some drugs used for the treatment of depression and other psychiatric disorders. Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of such drugs in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on Savella should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior, especially during the initial few months of drug therapy or at times of dose changes, either increases or decreases. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Savella is not approved for use in the treatment of major depressive disorder. Savella is not approved for use in pediatric patients.

References: 1. Savella (milnacipran HCl) prescribing information. Forest Pharmaceuticals, Inc. St Louis, MO. 2. MediMedia Database as of April 2011 for Savella.

time compared with those patients who showed no evidence of conscious awareness.

“The research we are doing is proof of principle,” said Dr. Owen. “Functional MRI is a fantastic technology but it is not portable.”


“This is the first step,” he said. “This is a challenging clinical problem. We are hoping that EEG assessment can help

contribute to the proper diagnosis of vegetative state.”

EXPERTS WEIGH IN

In an accompanying editorial in the *Lancet*, Morten Overgaard, PhD, of the department of communication and psychology at Aalborg University in Denmark and Rikke Overgaard, PhD, of the

ARTICLE IN BRIEF

 A research team found that one in five patients who had been assessed to be in a vegetative state showed evidence on an EEG recording that they understood the commands to do a mental task.

CNRU Centre of Functionally Integrative Neuroscience, said that the study “is surprising and challenging. These findings present good evidence that at least some patients in the vegetative state are conscious. However, the methods in all these experiments are indirect and investigate a factor other than consciousness alone.”

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Contraindications

- Savella is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) concomitantly or within 14 days of discontinuing treatment with an MAOI. There have been reports of serious, sometimes fatal, reactions in patients started on an MAOI who were receiving or had recently discontinued a serotonin reuptake inhibitor. At least 5 days should be allowed after stopping Savella before starting an MAOI.
- Savella is contraindicated in patients with uncontrolled narrow-angle glaucoma and should be used with caution in patients with controlled narrow-angle glaucoma. In clinical trials, Savella was associated with an increased risk of mydriasis.

Warnings and Precautions

- Prescriptions for Savella should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.
- Development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with SSRIs and SNRIs alone, including Savella, but particularly with concomitant use of serotonergic drugs (including triptans), drugs that impair metabolism of serotonin (including MAOIs), or antipsychotics or other dopamine antagonists. The management of these reactions should include immediate discontinuation of Savella and the concomitant agent and supportive symptomatic treatment. The concomitant use of Savella with serotonin precursors is not recommended.
- SNRIs, including Savella, have been associated with cardiovascular effects, including cases of elevated blood pressure, requiring immediate treatment. In clinical trials, sustained increases in systolic and diastolic blood pressure occurred more frequently in Savella-treated patients compared to placebo. Among patients who were non-hypertensive at baseline, approximately twice as many patients receiving Savella, vs placebo, became hypertensive at the end of the study. Clinically significant increases in pulse (≥ 20 bpm) occurred more frequently in Savella-treated than placebo-treated patients. Blood pressure and heart rate should be monitored prior to initiating treatment with Savella and periodically throughout treatment. Pre-existing hypertension, tachyarrhythmias, and other cardiac diseases should be treated before starting therapy with Savella. Savella should be used with caution in patients with significant hypertension or cardiac disease. Concomitant use of Savella with drugs that increase blood pressure and pulse has not been evaluated, and such combinations should be used with caution. For patients who experience a sustained increase in blood pressure or heart rate while receiving Savella, either dose reduction or discontinuation should be considered.
- Savella should be prescribed with caution in patients with a history of seizure disorder or mania.

- Savella has been associated with mild elevations of ALT and AST (1 to 3 times the upper limit of normal). Rarely, reports of serious liver injury, including fulminant hepatitis, have been reported in patients treated with milnacipran. Savella should be discontinued in patients who develop jaundice or other evidence of liver dysfunction and should not be resumed unless another cause can be established.
- As with other SNRIs and SSRIs, withdrawal symptoms have been observed following discontinuation of milnacipran. A gradual dose reduction is recommended.
- Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Savella. Elderly patients may be at greater risk. Discontinuation should be considered for patients with symptomatic hyponatremia.
- SSRIs and SNRIs, including Savella, may increase the risk of bleeding events. Patients should be cautioned regarding the risk of bleeding associated with concomitant use of Savella and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation.
- Savella can affect urethral resistance and micturition. Caution is advised in the use of Savella in patients with a history of dysuria, notably in male patients with a history of obstructive uropathies as these patients may experience higher rates of genitourinary adverse events.
- Savella should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Use in Specific Populations

- There are no adequate and well-controlled studies in pregnant women. Savella should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Adverse Reactions

- In clinical trials, the most frequently occurring adverse reaction was nausea (37% vs 20% for placebo). The most commonly occurring adverse reactions ($\geq 5\%$ and greater than placebo) were headache (18% vs 14%), constipation (16% vs 4%), dizziness (10% vs 6%), insomnia (12% vs 10%), hot flush (12% vs 2%), hyperhidrosis (9% vs 2%), vomiting (7% vs 2%), palpitations (7% vs 2%), heart rate increased (6% vs 1%), dry mouth (5% vs 2%), and hypertension (5% vs 2%).


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For the management of fibromyalgia

Vegetative State

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recordings during a mental imagery exercise in three patients with a range of brain injuries — from minimally conscious state (MCS) to locked-in

‘We found that they [the patients in a vegetative state] were responding to our commands and that meant that they understood what we were asking, paying attention to the complex task and able to follow through with the command. This suggests that they are aware of what is going on in their environment and would be able to communicate if they had the right tools.’

“So far, most researchers have interpreted these published results as suggesting that many patients in the vegetative state are wrongly diagnosed,” they wrote. “However, these studies have an even stronger consequence. The real underlying issue is that the levels of consciousness—i.e., subjective experience. A more plausible interpretation is that vegetative and minimally conscious states distinguish between different levels of cognitive and communicative abilities, which is a different matter than subjective experience. A new classification system is necessary if the goal is to understand the cognitive functioning of patients in the vegetative or minimally conscious states.”

state. They found that one patient in MCS and one in the locked-in state showed evidence that they understood the commands.

“We are now at a point where there are a lot of good published data from several different research groups,” said Dr. Schiff. “Given that several studies have now found such patients in apparent vegetative states with command-following abilities, the question here is whether this particular study is more than additive for these new approaches.”

“Lay people will invariably interpret this paper, as the others, as ready for clinical use, something none of these methods has been validated for to date,” he said. “The findings reported

The investigators said EEG testing, which is more affordable and accessible than fMRI, could be used more to assess patients in the vegetative state at bedside or even in their homes, but there are technological challenges that need to be resolved.

Nicholas D. Schiff, MD, professor of neurology and neuroscience at Weill Cornell Medical College, and his colleagues also conducted an EEG study to demonstrate awareness in patients with severe brain injury. Their study, published online in April in *Clinical Neurophysiology*, assessed EEG

in this paper are not so convincing that this paradigm will perform well as a clinical test. The EEG analysis could only pick up 75 percent of the controls.

“As the paper clearly will lead to discussion of using these and other tools to separate the MCS from vegetative states, the results should not convey



DR. ADRIAN M. OWEN: “The research we are doing is proof of principle. Functional MRI is a fantastic technology but it is not portable.”

EEG measurement to be vetted against strong correlative data.

“In the present study the actual EEG responses are hidden and not examined,” Dr. Schiff said. “We can only rely on the performance of the classifier as the reporter of a positive result. This can bring false positive findings here as classification algorithms can be very sensitive and over fit noise in EEG data. Both showing the actual differences in the signals classified and applying a multiple comparisons statistical test to mitigate this kind of error would have strengthened the impact of the study.”

That said, he added that “we are now at a point in the work of this subfield where there are many studies and leads to follow to try and validate methods, and the implications are the same for other EEG-based assessment paradigms as they have been. The problem is that there is currently very little infrastructure to provide clinical follow-up for patients with severe brain injury and structure further clinical engagement.” •

the impression that any of our available research tools are yet clinically validated.”

The great advantage of the EEG is that it is a physiological signal that is generated by neuronal activity as opposed to changes in blood flow or oxygenation level typical of functional neuroimaging techniques, Dr. Schiff continued. As a consequence, changes in EEG responses can often be related to measures obtained from single-unit, local field potentials and electrocorticography allowing the physiological plausibility of the signal found in an

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- Overgaard M, Overgaard R. Comment: Measurements of consciousness in the vegetative state. *Lancet* 2011; E-pub 2011 Nov. 10.

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