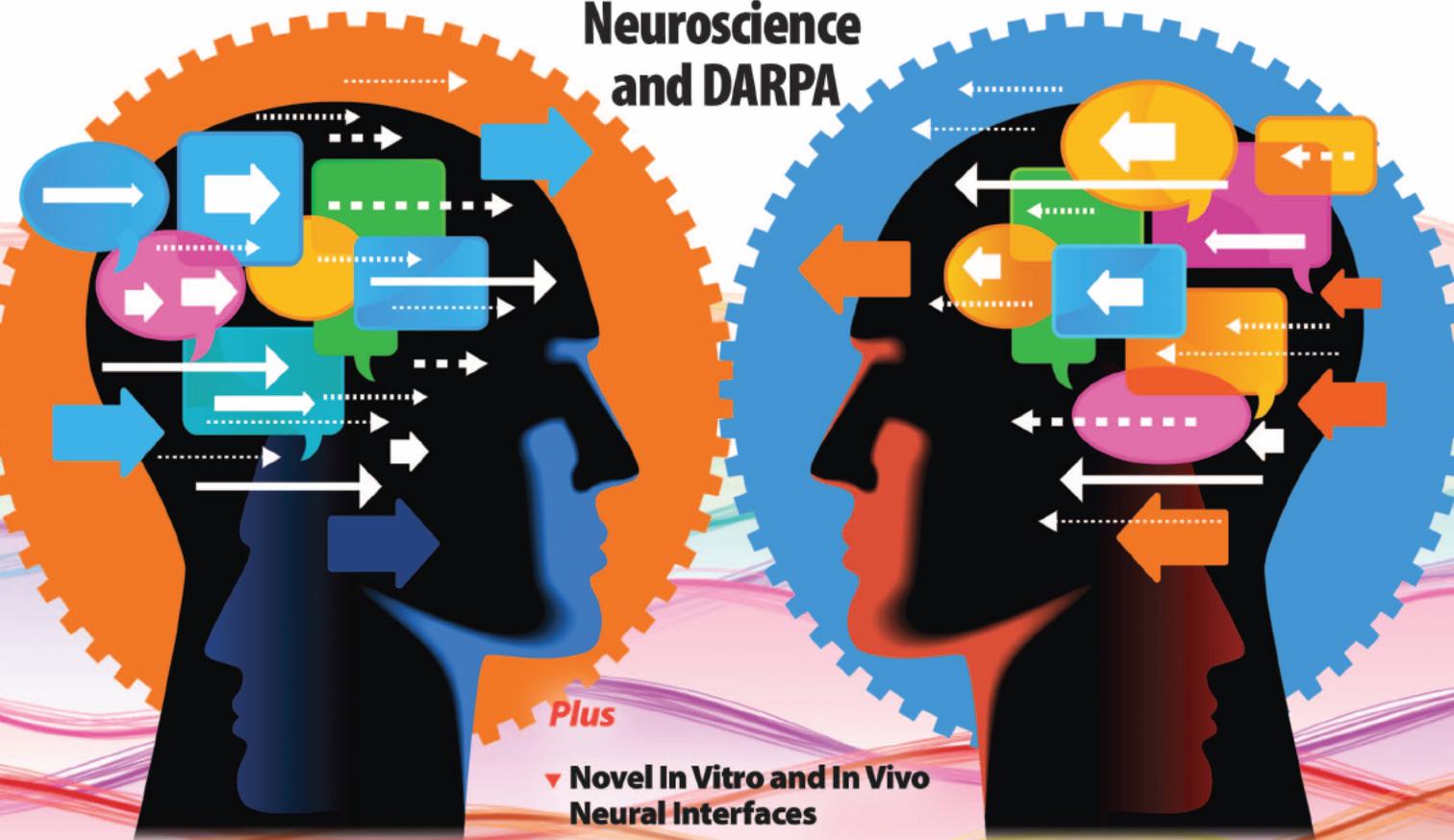


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# Pushing the Horizon

## Neuroscience and DARPA

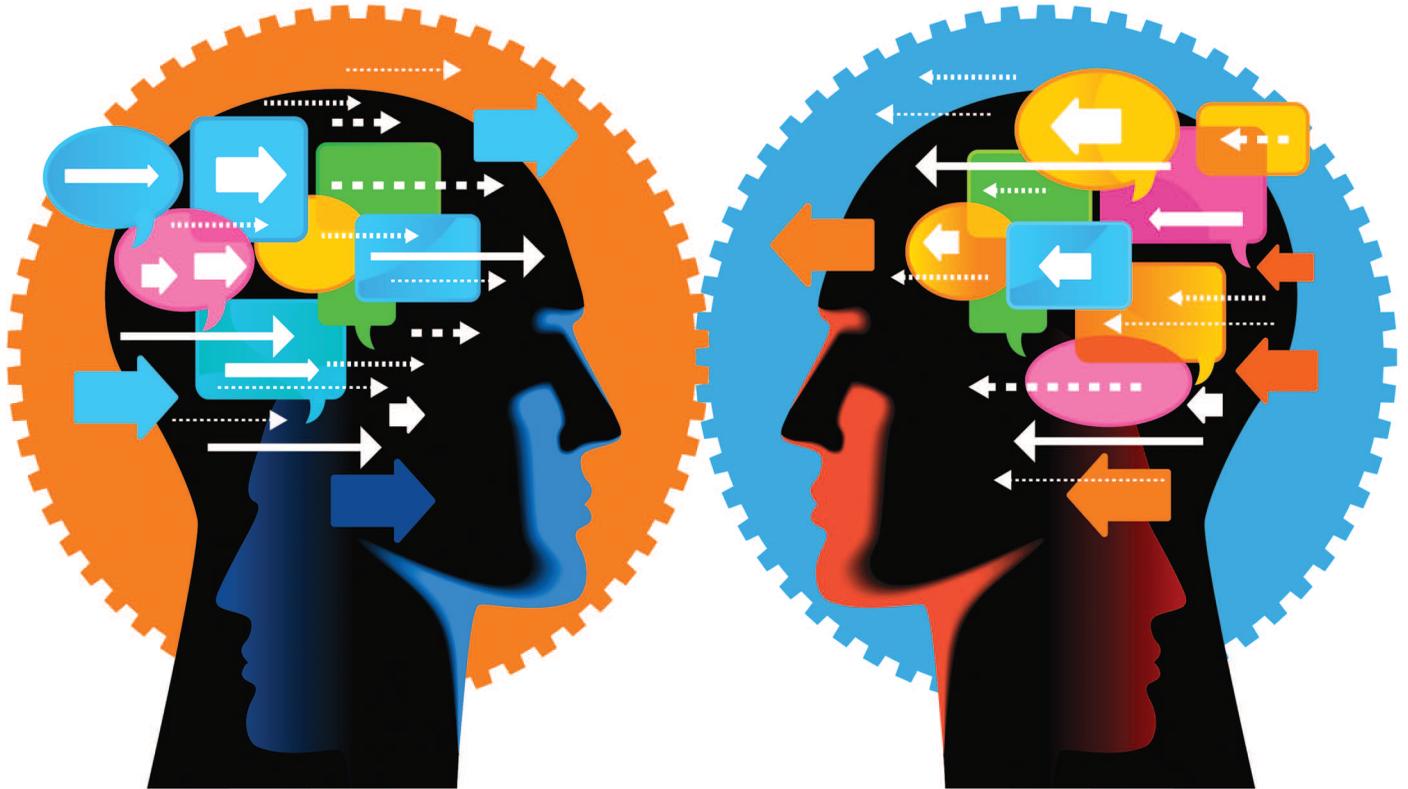


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- ▼ **Novel In Vitro and In Vivo Neural Interfaces**
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By Leslie Mertz

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# ANSWERING THE BIG QUESTIONS IN NEUROSCIENCE

When the Defense Advanced Research Projects Agency (DARPA) asks research questions, it goes big. This is, after all, the same agency that put together teams of scientists and engineers to find a way to connect the world's computers and, in doing so, developed the precursor to the Internet. DARPA, the experimental research wing of the U.S. Department of Defense, funds the types of research queries that scientists and engineers dream

## DoD's Experimental Research Wing Takes on Massive, High-Risk Projects

of tackling. Unlike a traditional granting agency that conservatively metes out its funding and only to projects with a good chance of success, DARPA puts its money on massive, multi-institutional projects that have no guarantees, but have enormous potential.

In the 1990s, DARPA began its biological and medical science research to improve the safety, health, and well being of military personnel, according to DARPA program manager and Army Colonel Geoffrey Ling, Ph.D., M.D. More recently, DARPA has entered the realm of neuroscience and neurotechnology. Its focus with these projects is on its prime customer, the U.S. Department of Defense, but Ling acknowledged that technologies

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developed in its programs “certainly have potential to cascade into civilian uses.”

Just as it did with its pre-Internet effort, DARPA is again posing comprehensive and, often, futuristic-sounding research questions through its neuroscience initiatives, including the following:

- ▼ Can a prosthetic limb look and move like a natural one, and can a patient control it with his or her mind?
- ▼ Is it possible for a soldier who has suffered a traumatic head injury to regain all of his or her capabilities and do it quickly? On the civilian side, would this also help individuals who have had a stroke or have experienced head injuries resulting from concussions?
- ▼ Are soldiers able to learn how to moderate their anxiety levels on the battlefield, so they can relax enough to get the rest they so desperately need and possibly avoid the depression and posttraumatic stress syndrome that plagues troops?
- ▼ Can novice soldiers replicate the mindset of the experts and learn new skills such as marksmanship at a much faster rate than they do now? On the civilian side, could golfers or other athletes use this same ability to improve their skills?
- ▼ How can neuroscience techniques help the military to identify a soldier who is likely to fail at a particular task well before that soldier actually attempts it? What preemp-tory training would help that soldier to ultimately succeed? On the civilian side, could new training methods also assist new police officers?
- ▼ What are the characteristics of a successful team, particularly, one working under high stress and making life-or-death decisions? How can those characteristics be identified and possibly nurtured in a new team? On the civilian side, could corporations also take advantage of this understanding to create more effective working groups and committees?

“Some of this work is far-fetched and off on the horizon, but that’s one of the things about DARPA. One of its missions is to push the horizon, to see if there’s some latitude to actually push a problem in a more accelerated, solvable manner,” said David Moore, scientific engineering and technical adviser to Ling. “With DARPA, it truly is high-risk research. As an agency, the question has to be of sufficient merit to be a DARPA question.” Once it has the initial answers to its questions, Moore said, the agency often steps back. Moore explained, “DARPA shows the feasibility of things, and then it allows other people to go ahead and continue the development of that actual feasibility.”

### Almost Real: Revolutionizing Prosthetics

“The Revolutionizing Prosthetics program will create a fully functional (motor and sensory) upper limb that responds to direct neural control, within this decade” [1].

One of DARPA’s best-known neurotechnology efforts is its Revolutionizing Prosthetics 2009 program. The goal of this initiative is to create an artificial arm that can do it all: 22 degrees

of freedom, which means that it will have shoulder, elbow, wrist, and finger movements similar to that of a real human arm and complete user control so that a person can easily manipulate it through neural control. As a Department of Defense agency, the program’s main emphasis is on soldiers who have lost limbs during a tour of duty, but the work has obvious implications for people who have experienced amputations as a result of industrial or automotive accidents.

DARPA has sponsored two teams to develop and build an artificial arm. One was the Johns Hopkins University Applied Physics Laboratory and the other was the DEKA Corporation, the company that built the Segway. Each team created a highly advanced prosthetic limb and drew considerable press coverage when the arms were revealed in 2009. The Applied Physics Laboratory produced the modular prosthetic limb while DEKA, led by inventor Dean Kamen, produced the Luke Arm.

“DARPA threw open a grand challenge, backed it up by a significant financial investment, and forged a multi-institutional team of scientists and engineers.”

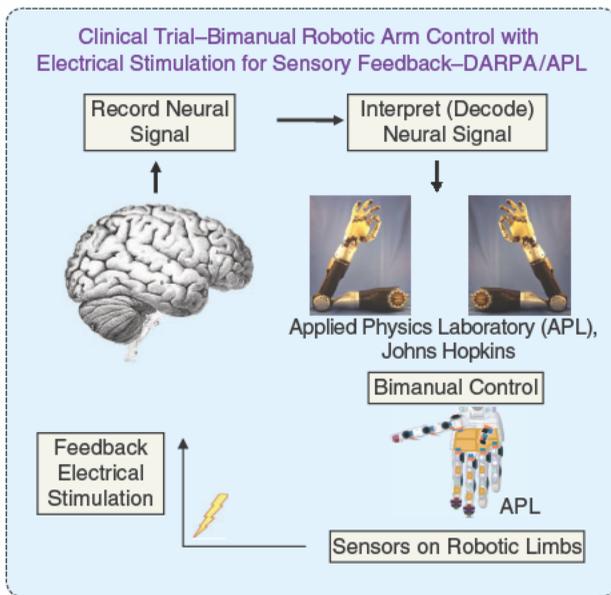
“A huge investment went into building these limbs,” said Nitish Thakor, Ph.D., professor of biomedical engineering and principal investigator for the Neuroengineering and Biomedical Instrumentation Laboratory at Johns Hopkins University. He has been involved in the DARPA’s prosthetics program for five years. “These fabulous limbs that they built are one of a kind and expensive, but they are ground-breaking,” Thakor said. “We went from one degree of freedom, which was just opening and closing a hook, to two degrees of freedom, which is where you

have a hook and a wrist that rotates, to what is now 22 degrees of freedom and limbs that are totally sophisticated.”

Along with the prosthetic arm, DARPA also funded teams of scientists and engineers to look into the patient’s control of the artificial limb. This is Thakor’s specialty. “Historically, prosthetics were controlled in one of two ways. In one, they used some mechanical part so you moved your shoulder and a mechanical harness made the hand open or close like a claw. That’s all it would do. In the other, they decoded muscle signals from the residual arm or forearm, depending on the extent of the injury, in such a way that flexed biceps or triceps would be enough to open or close the hand,” Thakor explained.

DARPA’s goal for the program went beyond that. “The revolutionary part arose from the question: Why can’t we do a direct neural interface or a direct brain interface so that we can get the signals directly from the nerves or directly from the brain to control the arm?” Thakor said. The patient could control the prosthesis simply by concentrating on what he or she wanted the limb to do.

“My group worked on decoding brain activity, which you can do with multiple signals. These can include electroencephalogram (EEG), which is taken from the scalp; electrocorticogram (ECoG), which is taken from the brain surface itself; or from neural signals collected directly by putting microelectrodes in the brain tissue,” Thakor explained. Thakor worked with Mark Schieber, M.D., Ph.D., a neuroscientist at the University of Rochester to demonstrate for the first time, in 2007, that signals recorded from a monkey’s brain could manipulate



**FIGURE 1** In Phase 3 of the Revolutionary Prosthetics Program, researchers are developing systems that allow individuals to control left and right (bimanual) prosthetic arms with their thoughts and also receive sensory feedback from the hands and arms so they can feel objects and, therefore, improve dexterity as well as manipulation of objects. (Photo courtesy of Richard Andersen.)

the fingers on a prosthesis. In 2009, using the newly developed Johns Hopkins' prosthetic arm, they showed that a monkey could control the limb in close-to-real time. In this case, signals from the monkey's neurons were almost instantaneously decoded and relayed to the arm, where its fingers wiggled.

Thakor and his collaborator, neurologist Nathan Crone, M.D., parlayed the success into a grant through the National Institutes of Health's Grand Challenge Program to continue the work in patients. He is especially interested in the use of ECoG signals to control the prosthesis. Since ECoG signals are recorded closer to the brain than an EEG, it provides more detail. "Think of it this way. If you record from the scalp, it's not invasive, but the recording is very poor because it's like trying to listen to me by putting a microphone outside my door. If you put me on speakerphone, however, the signal is much better. ECoG is like the speakerphone. It's closer to the brain and we can put on lots of electrodes so we can record it better."

His group is currently testing patients in closed-loop and open-loop experiments. In an open-loop experiment, the patient concentrates on moving the prosthetic arm and fingers, and the researchers gather the signals and then use them to try to control the arm. In the closed-loop experiment, the patient tries to directly control the prosthesis with his or her focused thoughts.

DARPA is also continuing the patient-control aspect of its Revolutionizing Prosthetics program by funding a Phase 3 project, which is managed by the Johns Hopkins Applied Physics Laboratory. In this project, the laboratories at the University of Pittsburgh School of Medicine and Medical Center and the

California Institute of Technology analyze signals from different areas of the brain.

"We're going to use the parietal area of the brain, so it's an area that provides the thoughts for movement, or the movement plan," said Richard Andersen, Ph.D., James G. Boswell Professor of Neuroscience at the California Institute of Technology. The parietal lobe is a large region located at the top of the brain toward the rear. "The Pittsburgh lab will be using another area nearer the motor output, which is more related to the control of muscle."

Andersen recognizes that the Phase 3 project is an ambitious effort. "And on top of that, some other labs from Chicago are working with both Pittsburgh and our group to provide electrical stimulation to the part of the brain's cortex (the so-called gray matter) that feels touch. The robotic hand has sensors on it, so when the hand touches, say, a Coke can to pick it up, it would sense the can and then transduce electrical signals into the brain to provide feedback to improve the dexterity of the grasp and manipulation of the object." That feedback is important, Andersen noted (Figure 1). "We know that if you numb the fingertips, people are very poor at handling things. They lose a lot of their dexterity." The same holds true with prosthetics. By relying solely on visual cues, the patient's grasp is much less accurate. "The addition of sensors would improve the feedback, and in principle, improve the ability to use the robotic limb." The work is moving forward quickly and that is in part due to DARPA's drive, Andersen said. "They have set milestones, which help us to keep a pretty good pace."

That drive has also pushed the envelope in the overall field, Thakor asserted. "Most prosthetic research had been utterly stagnant for 100 years. It was totally plodding: All we did was go from a crude hook to a three-finger claw design." DARPA has changed that, Thakor stated. "DARPA threw open a grand challenge, backed it up by a significant financial investment, and forged a multi-institutional team of scientists and engineers." Those researchers not only produced a working prototype of a 22-degree-of-freedom limb but also demonstrated its control using either muscle or neural signals, Thakor explained. "That's what DARPA made happen, and now the agency is moving even further forward by funding the Phase 3 study."

"Most prosthetic research has been utterly stagnant for 100 years."

### Recovering Faster: REPAIR

"The reorganization and plasticity to accelerate injury recovery (REPAIR) program aims to uncover the mechanisms underlying neural computation and reorganization to improve modeling of the brain and our ability to interface with it" [2].

Some of the same researchers who are involved in the Revolutionizing Prosthetics program participate in another DARPA initiative called REPAIR. "The goal of this program is to design ways to accelerate repair from brain damage," Andersen said. He is the principal investigator of a research group that includes Thakor, Schieber, and Jerry Loeb, M.D., a professor of biomedical engineering control at the University of Southern California. Andersen's group is one of three in the REPAIR program.

Andersen's group is approaching four neurological deficits that may occur through traumatic head injury, stroke, or other trauma.

- 1) Neglect, which causes a loss of volitional (conscious) movement or loss of awareness of the visual space on the side of the body opposite to the affected region of the brain. This results from damage, or lesions, to the parietal and frontal lobes of the brain.
- 2) Optic ataxia, which is a disconnection between the visual and the motor system, causing mislocalization of goals for movement. In other words, individuals have difficulty in accurately reaching for objects. This deficit results from lesions to the parietal cortex.
- 3) Apraxia, which causes an inability to perform dexterous movements. For instance, the patient is unable to form the hands and fingers properly to grasp objects. This results from parietal and frontal lesions.
- 4) Hemianesthesia, which causes a loss of tactile sensation on the side of the body opposite to the affected side of the brain. This deficit typically results from lesions to the thalamus, which is located in the lower central part of the brain.

For this work, Andersen's laboratory is simulating neglect and optic ataxia in monkeys while Schieber is doing the same for apraxia and hemianesthesia. Using microelectrodes implanted in the brains of the monkeys, the groups will monitor activity changes during the simulations of the neurological deficits.

Andersen's laboratory is simulating the disorders by injecting small regions of the brain with pharmacological compounds that temporarily shut down very small nodes—just a couple of millimeters in diameter—in the associated neural networks. Just one of these turned-off nodes disables an entire circuit and causes the loss of movement or other symptoms. "It's pretty amazing that we can simulate these disorders with an inactivation of such a small region," Andersen said. He is particularly excited about his laboratory's studies of optic ataxia. "There wasn't an animal model for it before we started our work, but we were able to find this part of the brain called the parietal reach region, which is important for converting visual signals into plans for reaching. If we inactivate this region, then the animals misreach. They can't properly localize the targets in the affected visual field," Andersen said. "This, then, became the first animal model for optic ataxia."

His laboratory also uses a functional magnetic resonance imaging (fMRI) machine designed especially for imaging the monkey brain. The machine is vertical, so the monkey can sit inside. "The fMRI machine allows us to inactivate a node in one part of the brain and see the effect on the whole brain. We can monitor these effects through changes in the blood flow," Andersen explained that an active area of the brain has a larger influx of blood than a less-active area, and fMRI readily measures these differences.

Their research has shown that monkeys are occasionally able to overcome neglect even when a node is disabled with the drug. When this happens, they discovered that the other nodes in that

circuit become especially active, essentially taking over for the faulty node and restoring movement. Andersen's laboratory is now attempting to mimic this cure of neglect using electrical stimulation of the other nodes in the affected circuit.

While Andersen's and Schieber's laboratories continue to record signals from nodes and circuits in the brain, Loeb is modeling the intricacies of the spinal cord-to-muscle coordination required for movement to occur. Thakor is taking up another part of the research by studying how the brain actually decodes the signals that Andersen and Schieber are recording.

"This work may not be as glamorous and 'gee whiz' as a fancy prosthetic arm, but it is very fundamental and clinically useful because head injuries affect so many of our soldiers," Thakor said of the REPAIR program. "For that matter, head injuries also apply to athletes, such as football players who are hurt on the field and kids who are doing headers on the soccer field and getting minor concussions, which can add up to traumatic brain injury."

In summary Thakor noted, "This kind of basic research has applications from blast trauma in the soldier to traumatic brain injury in the athlete. We don't have a gadget to solve the problem, but this basic research has huge societal and clinical impacts."

### Getting Better Faster: Accelerated Learning

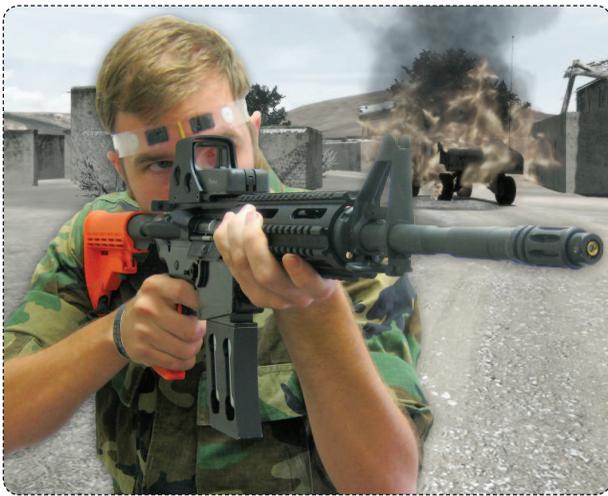
"The Accelerated Learning program will develop quantitative and integrative neuroscience-based approaches for measuring, tracking, and accelerating skill acquisition while producing a twofold increase in an individual's progress through the stages of task learning" [3].

"The concept of the Accelerated Learning program is to take what we know from basic neuroscience and what we know from education and training, and try to develop neuroscience-based approaches to improve training," said Chris Berka, who is heading up one of four research teams within the DARPA program. "That can be anything from using neurotechnology to assess a trainee's strengths and weaknesses to accelerating the transition from novice to expert." Berka is the CEO and cofounder of Advanced Brain Monitoring, a company based in Carlsbad, California.

Berka's research focuses on both the assessment of a trainee's capabilities and accelerated skill acquisition, and is preparing to commercialize a device to help athletes get in the zone so they can perform at their highest level. The device, called the *Adaptive Peak Performance Trainer* (APPT), is an outgrowth of her group's study of the differences between novices and experts. It trains the former to match the physiological and mental states of the latter when undertaking a task (Figure 2). She expects APPT to be commercially available within the year.

"We started with expert marksmen. Specifically, we took a group of Marines who were high-level coaches, so coaches of the coaches, and we monitored their brains' electrical activities, as well as a number of other physiological parameters, including heart rate, respiration, and muscle movements, while

"This kind of basic research has applications from blast trauma in the soldier to traumatic brain injury in the athlete."



**FIGURE 2** Advanced Brain Monitoring Inc. developed the APPT to provide nondistracting, real-time neurofeedback to help novices emulate the highly focused mental and physical state that experts achieve. The company plans to release the APPT, shown here in marksmanship training, as a learning tool for other skills such as golfing and archery. (Photo courtesy of Advanced Brain Monitoring Inc.)

they were taking long-distance shots at a still target.” They also monitored the high-level Marine coaches during combat marksmanship in which the target and/or the shooter are moving; novice, Marines and nonmilitary participants in both scenarios; and veteran and novice police officers as they participated in deadly force decision-making exercises. “Altogether we ran about 300 subjects across all of these conditions and populations, and we found some very consistent psychophysiological profiles of novice versus expert,” Berka said.

In intense situations, such as taking a long-distance shot, the experts were able to decelerate their heart rate, stabilize their breathing, and reach a specific and controlled brain state. The combination provided the focus to perform well. Novices were just the opposite in that they lacked control over their physiological states. In addition, experts were able to immediately move into a relaxed cardiopulmonary and brain state when the situation concluded, whereas novices remained anxious.

With those profiles of experts and novices, Berka’s company developed the APPT to teach novices how to control their heart rate and breathing and calm their thoughts, so they can perform at their peak ability and also rest afterward. The device is a simple one. It buzzes in concert with brain state and heart rate and stops when the novice reaches the expert profile. “We found that in a one-day training session, about 85 percent of novices were able to move into the expert profile,” Berka said. That equated to a 230% acceleration in long-distance marksmanship skill training.

Berka believes that the APPT will also have benefits for athletes. “We think this will translate to any activity where you have to screen out irrelevant or distracting information and fo-

cus in on a target.” Indeed, Berka said, they have already studied Olympic archers and PGA golf pros and seen similar patterns of focused brain activity and cardiovascular control. “We think there may be a broad set of pretraining activities that could benefit from this relatively simple approach.”

“The APPT should also be valuable in helping soldiers learn how to relax,” Berka said. “One of the whole issues with being deployed for a long period of time is that you’re always in this super-high arousal state, and it’s very hard to be able to come back down and rest. We hope that we’ve uncovered something that can help with stress-resiliency training.”

Team training is also an important part of the DARPA Accelerating Learning program. Berka’s research group, as well as three other groups within the program, each carved out its own approach, “but one of the overarching themes is that training is probably going to be done less in the classroom, and particularly in a live classroom.” Berka explained that the military is increasingly using virtual environments for team training. “They’re even using mission rehearsal in immersive environments, where you go in and meet your mission colleagues for the first time in a virtual setting like *Second Life* (an online, pretend world where players interact through avatars), you rehearse your mission using virtual terrain and you might not actually meet your teammates until you get on the ground wherever you’re going to run your mission,” Berka explained. “So the way we think about training is being completely transformed.” That, of course, has applications in academia, which is also adding more and more virtual learning experiences to its offerings.

Berka’s group, for instance, has studied soldier, student, and business teams in various scenarios, and come up with a set of team cognition metrics based on EEG. They have more data to collect, but she said it shows promise for helping the military train its teams to work together more efficiently and effectively. It may also help to identify teams that are better or worse fits for different scenarios. “It’s very exciting in terms of the possibilities of being able to nonintrusively affect what’s going on in a training environment and potentially make some predictions and recommendations very early on, perhaps within a teaming session, by giving real-time feedback about which members of a team are in sync with the rest of the team and which aren’t, and which is the best team for this particular task.”

DARPA has been essential in this research area, and for more than the funding, noted Berka. “We have had great liaisons with the military community, so we were really able to have unprecedented access to military populations going through various types of training activities and a real cooperative relationship with the Navy, the Marine Corps, and the Army in trying to help solve these problems together, and I think that’s where DARPA does a very good job. It paves the way for those kinds of big collaborative efforts.” (The U.S. Army Research Office is also funding multi-institutional efforts in this field. See “Mind to Mind.”)

The APPT is designed to teach novices how to control their heart rate and breathing and calm their thoughts so they can perform at their peak ability.

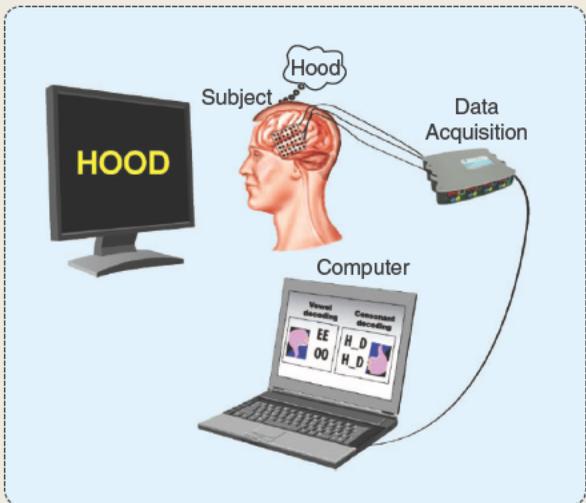
## Mind to Mind

How can soldiers communicate securely, accurately, and immediately with one another in the battlefield? One way may lie in the prospect of communication via thought rather than the spoken word.

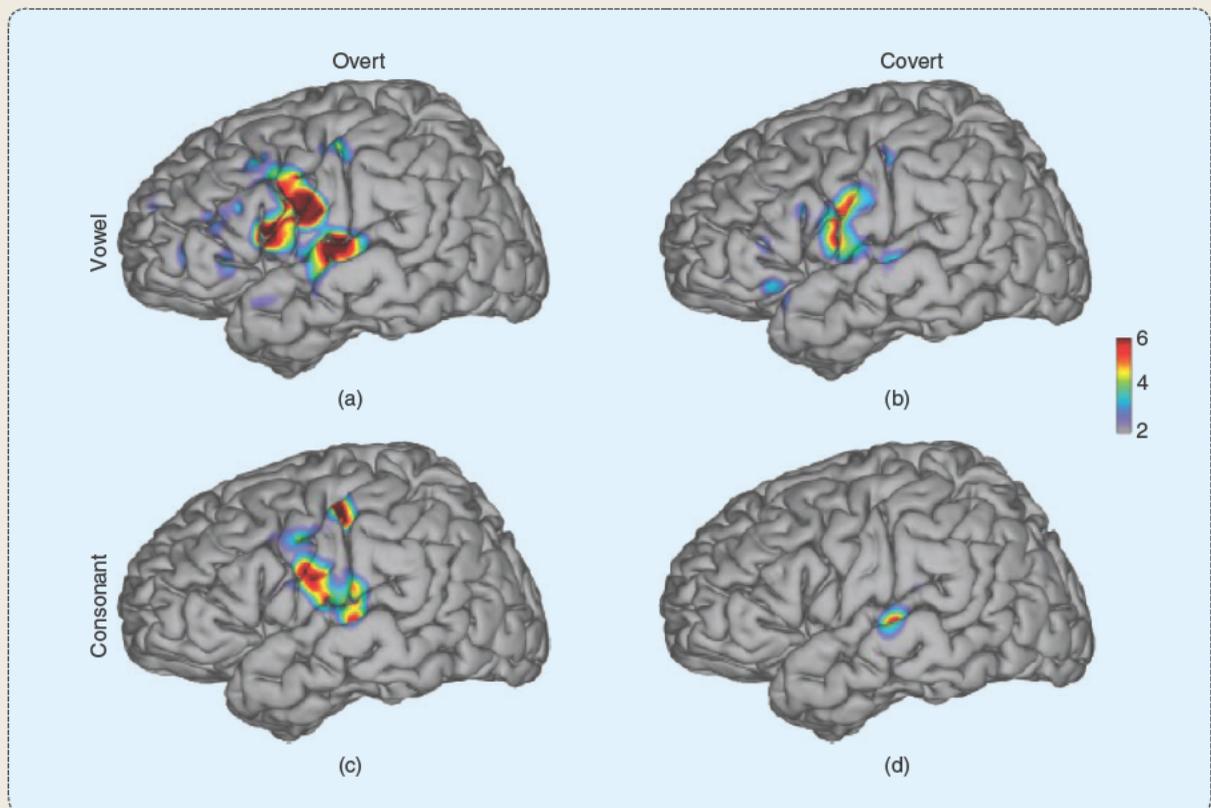
"This used to be in the realm of science fiction, but it really isn't science fiction because we have shown proof that it can be done," said Gerwin Schalk, Ph.D., a research scientist in the Brain-Computer Interface Research and Development Program of the Wadsworth Center, a public health laboratory of the New York State Department of Health. His laboratory, working under two grants from the U.S. Army Research Office, is already having some success.

"This is not mind reading. Our average decoding accuracy is not 100%, so this is certainly not perfect, but it shows that this, in fact, is possible," Schalk said. "The vision for all of this is that, with further increases in accuracy, interpretation techniques, and signal acquisition and with verification in more people, we should be able to produce a device that can relatively accurately tell the vowels and the consonants, and at some point, even words or series of words directly from brain signals."

"This thought-translation work boils down to two questions," said Xiaomei Pei, Ph.D., a postdoctoral fellow in Schalk's laboratory. The first is whether it is even possible to detect from brain signals whether a person is either speaking or imagining speaking. "Addressing this question allows us to improve our understanding about neuroscientific aspects of speech, such as the brain-signal



**FIGURE S1** Electrode arrays placed on the brain surface (the laboratory uses hospital patients who already have arrays implanted for clinical reasons) allow researchers in the Schalk laboratory to read brain signals as they present patients with certain words. Here, the patient reads and concentrates on the word "hood" as the brain signals are decoded and translated by the computer. This illustration shows the computer accurately decoding the h-d consonant pair but not the vowels. (Reprinted with permission from Pei et al. [S1].)



**FIGURE S2** The color coding in these images indicates which areas of the brain are involved in producing the same consonants and vowels of a word that is spoken aloud (overt) or merely thought (covert). Research by Xiaomei Pei and others in Dr. Gerwin Schalk's laboratory at Wadsworth Center use ECoG to decipher brain signals and identify the associated words a test subject is saying or thinking. (Reprinted with permission from Pei et al. [S1].)

features and locations in the brain that hold information about speech," Pei said.

To answer that first question, Schalk's research group used electrodes that were placed directly on the surface of the brain (ECoG) to pick up brain signals. Their test subjects were epileptic patients who were in the hospital and already had the electrodes implanted for clinical reasons. The ECoG measurements allow the researchers to determine the location and timing of the brain signals associated with both spoken and imagined words. "What we learned was actually very fascinating," Schalk said. "We found a complex spatial-temporal pattern that is reflective of different components of speech."

The laboratory then proceeded to the second question: Is it possible to decipher which words a person is speaking or thinking? For this part of their research, they created a 36-word dictionary with combinations of a specific set of consonants and vowels. "The words were very nicely constructed so that they had one of the four vowels and one of the nine consonants in them, so we had words like heed, head, had, and hood (Figure S1). The idea was that if we could make out the components—the vowel and the consonant—we would know the word."

They asked the test subjects to either say a word aloud or silently. "We showed that we could learn from the brain with reasonable, not perfect but reasonable, accuracy what vowel or consonant a person was speaking or imagining," Schalk said (Figure S2).

As it turns out, the researchers could correctly identify these components of words up to 55% of the time, Pei said. "That's far from perfect, but it is encouraging to show that it is possible to use brain activity to decode elements of imagined speech."

"Studies like this can go a couple of different ways in the future," Schalk said. One possibility is to continue to collect neural signals through electrodes implanted on the brain. "While it would be invasive, the risk associated with these implants would be quite minimal and, in many ways, the risk would be much lower than a lot of the plastic surgeries that people are undergoing for cosmetic reasons," Schalk said. The second option is completely noninvasive recordings. The subject would wear a specially designed helmet that would gather the necessary brain signals. In both cases, the signals would go to a computer for the translation of words.

Schalk described other work at Carnegie Mellon University, where scientists are using fMRI to decode whole words from brain signals, and at a company in Atlanta, where scientists are implanting humans with small electrodes to identify vowel sounds.

"Overall, these types of brain-computer interface technologies are extremely exciting. We're learning more and more about how the brain works and how the brain represents different aspects of motor function, perception, language function, auditory processing, and imagined versions of these functions," Schalk said. "There are a slew of applications that are opened up by these insights, and silent communication is just one of them."

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### Risky But Potentially Very Rewarding

Through each of these programs and others, DARPA is taking a lead in neuroscience and neurotechnology research. "As the primary science and technology research organization in the Department of Defense, DARPA is the only organization of its type with the ability to invest in research that is considered high-risk, but with potential for high-payoff," Col. Ling said. "For example, with the Revolutionizing Prosthetics program, DARPA was able to address the needs of a small, underserved market. When one considers that the best we have been able to do is issue a body-powered prosthetic hook patented in 1912, you can appreciate the dramatic advance needed to have powered fingers with unprecedented dexterity. Further, the Revolutionizing Prosthetics aim to provide near-natural control is leading to tremendous advances in how we record and use brain signals and provide information back to the brain."

Through its research initiatives, he asserted that DARPA provides "the seed money needed to bring the breakthroughs promised by those efforts closer to realization; closer to being able to help the wounded warrior and civilians."

Moore said, "Through the agency's forward-thinking scope, it is doing something more. It's a truism that neuroscience

and the brain are together the next internal frontier of exploration. It's potentially a very exciting area and it touches on most of the key aspects of what it is that makes us actually human."

The views, opinions, and/or findings contained in this article are those of the author and should not be interpreted as representing the official views or policies, either expressed or implied, of the Defense Advanced Research Projects Agency or the Department of Defense.

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