EMBO reports

When mind meets machine

A new wave of brain–machine interfaces helps disabled people connect with the outside world

When asked how a busy man such as himself found the time to juggle, the American comedian Steve Martin answered, "Why, I juggle in my mind!" What was a mere joke is brutal reality for many seriously disabled people. However, the latest generation of computer–brain interfaces (CBIs) means they could soon be linked to the outside world again. And this is not just science fiction: last autumn, 25-year-old quadriplegic Matthew Nagle showed he could move a computer cursor by the power of his thoughts. Nagle was linked to the computer by BrainGate™—an experimental CBI developed by Cyberkinetics (Foxborough, MA, USA), which was implanted into the motor cortex of his brain. He uses it now to turn on lights, change television channels and read e-mail, all by moving the cursor with his thoughts. Another CBI device, which is non-invasive and placed on the tongue, is now being used to help patients with damaged vestibular systems to regain their sense of balance. These technologies use computers to mediate, analyse and redirect electrical impulses generated by the brain's neural activity. While still in their infancy, they could one day help disabled people such as Nagle to regain the abilities and senses lost by disease or injury.

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The developer of BrainGate, neuroscientist John Donoghue at Brown University (Providence, RI, USA), and the inventor of the tongue device, Paul Bach-y-Rita, professor of rehabilitation medicine at the University of Wisconsin at Madison (USA), believe that this is just the beginning, and that CBI devices could one day move a wheelchair or guide neuroprosthetic limbs. Their inventions are already more sophisticated versions of cochlear implants, 'pacemakers' implanted into the brain to control epilepsy and movement disorders, and artificial retinas to treat blindness caused by macular degeneration. But by directly linking computers to the brain's activities, the new devices take the technology a giant step forward. "We don't see with our eyes, or feel with our hands; we see and feel with our brain," commented Bach-y-Rita, a pioneer in the field of sensory substitution.

And it is already more than just moving a computer cursor. Last November, Cyberkinetics reported that its BrainGate neural interface—100 electrodes implanted in the brain—enabled Nagle to draw the letter 'o' with a paint programme, and open and close a robotic hand. The device 'reads' neural signals generated in Nagle's motor cortex when he thinks about moving his hand, and steers a computer cursor or a robotic hand. Two years ago, Donoghue and colleagues demonstrated in a monkey that signals from as few as 7–30 motor-cortex neurons could be used by a computer to move a cursor (Serruya *et al*, 2002). As part of a pilot trial, Cyberkinetics is implanting another five paralysed patients with its BrainGate interface, which is connected to a computer by wires, although future versions will be wireless.

Neural Signals, a company in Atlanta (GA, USA) led by neuroscientist Philip Kennedy, is developing a similar device for even more disabled, so-called 'locked in', patients. In the past eight years, Kennedy

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has implanted his Brain Communicator into sufferers from amyotrophic lateral sclerosis (ALS) and brain-stem stroke, which enables them to move a computer cursor, albeit slowly. The device uses electrodes attached to amplifiers and FM transmitters transplanted 5 mm deep—just under the scalp—into the brain. The electrodes encourage brain tissue to grow around them, thus stabilizing them against any movement and resulting distortion of signals, but it takes three to four months before the signals become stable. Two patients who have had implants for four years can now move a cursor to spell out words or point to icons indicating certain thoughts on a computer screen. Another device, the Muscle Communicator, enables patients with limited mobility to use a personal computer for communication. Bach-y-Rita and his colleagues are now applying the technology behind their tongue device to treat conditions other than balance loss, including vision loss, loss of sexual sensation after spinal-cord injury, and for movement disorders such as Parkinson's disease.

These developments are a result of intense CBI research during the past five years. "There is an increasing recognition of and emphasis on the needs of people with severe disabilities," said Jonathan Wolpaw, a neuroscientist at State University of New York's Wadsworth Institute in Albany, USA. As better life-support systems are available for patients with spinal-cord injuries, ALS and severe stroke, many people can now live for years. "Numerous studies show that if they have the minimum ability to communicate and good social support, these individuals can have a reasonable quality of life," according to Wolpaw. CBI's successes are also made possible thanks to major advances in brain research and computer technology over the past few years. "Because so much more is known about how the brain functions due to animal research and functional imaging, scientists are also better equipped to analyse the brain's complex signals in real time, and the computer technology used now is off-the-shelf, readily available," Wolpaw said.

The idea behind CBIs is, in fact, much older. In the 1960s, brain researchers found that one could 'train' individual neurons to adjust their firing rate by giving a reward. About 20 years ago, Apostolos Georgopoulos, then at Johns Hopkins University (Baltimore, MD, USA), recorded the electrical activity from single motor cortex neurons of macaque monkeys. This and subsequent experiments to control neurons in the visual and motor cortexes laid the groundwork for current research, according to Dennis Turner, professor of neurobiology at Duke University (Raleigh, NC, USA). But funding for CBI research then was difficult to obtain. "The times were not ready for this work, though we showed that it was feasible decades ago," Bach-y-Rita said. Times have changed, and researchers can now rely on grants from the US National Institutes of Health (NIH; Bethesda, MD, USA), which is interested in rehabilitation medicine, private foundations and, of course, the military. The US Department of Defense's Defense Advanced Research Programs Agency (DARPA; Arlington, VA, USA), is interested in sensory substitution for orientation and guidance of troops, and control of machines and vehicles by thought, rather than by pushing a button.

> … others believe that it is not necessary to literally tap into the brain, which has sparked a lively debate on which brain signals to use

Wolpaw, Turner and Donoghue are part of a group of about 50 American and European researchers who develop mind-controlled devices, both non-invasive and invasive, using various types of brain waves. Turner's team, led by Miguel Nicolelis, recently showed that a microarray of 32 electrodes placed in the subcortical motor region of humans provides useable signals for controlling a gripping neuroprosthetic device (Patil *et al*, 2004). During surgery to implant electrodes, neurosurgeons typically record brain signals to ensure that the electrodes are placed in the optimal brain location. Turner added to this a simple manual task: he asked participants—patients with Parkinson's disease

and other tremor disorders—to play a hand-controlled video game. When the team analysed the recordings, they found that the signals contained enough information to predict hand motions, which is necessary for controlling external devices. "Despite the limitations on the experiments, we were surprised that our analytical model could predict the patients' motions quite well," Nicolelis said. "We had only five minutes of data on each patient, during which it took a minute or two to train them to do the task. […] This suggests that as clinical testing progresses, and we use electrode arrays that are implanted for a long period of time, we could achieve a workable control system for external devices."

In earlier experiments, the group worked with Belle, an owl monkey, who wore a cap glued to her head that held 100 microwires in place at various sites on her motor cortex. They found that Belle was able to direct the actions of a remote-control robot arm by thinking. "By sampling 100 neurons we could create robot hand trajectories that were about 70 percent similar to those the monkeys produced. Further analysis estimated that to achieve 95 percent accuracy in the predictions of one-dimensional hand movements, as few as 500 to 700 neurons would suffice, depending on which brain regions we sampled," the authors wrote (Nicolelis & Chapin, 2002). As the animals perfected their tasks, the properties of their neurons changed, and the contribution of individual neurons varied over time, suggesting that gradual changing of neuronal activity improved the performance of the CBI.

However, others believe that it is not necessary to literally tap into the brain, which has sparked a lively debate on which brain signals to use. "There's an unproven assumption that if you want complex control, you need to put electrodes into the brain," Wolpaw said. "But we have now shown that using non-invasive brain electroencephalography [EEG] activity, it is possible to train humans to use the signal to move a computer cursor in two dimensions, up and down, across a screen." Wolpaw recently demonstrated that four volunteers—two with spinal cord injuries—could move a computer cursor from the middle of a computer screen to a point in any of eight locations around it (Wolpaw & McFarland, 2004). Those tested donned 'hats' with 64 recording EEG electrodes, and were told to use imagery to push the computer cursor to one of the eight spots. A computer recorded two types of their brains' waves—*mu* and *beta*—and translated them into vertical and horizontal cursor movements. The feat took training, but interestingly, after weeks of practice, the injured volunteers were able to hit the target more frequently than the non-injured participants. Their current study also uses a learning algorithm to improve user performance by taking into account past accomplishments. "We believe that using these signals, it will be possible for people with severe motor disabilities to use brain signals to operate a robotic arm or a neuroprosthesis without needing to have electrodes implanted in their brains," Wolpaw said. He noted that both the neurosurgery to implant electrodes and wire exposure from the scalp carry risks of infection and other complications.

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A group of German researchers at the University of Tübingen's Institute of Medical Psychology and Behavioural Neurobiology, led by Niels Birbaumer, similarly focuses on non-invasive methods. They use self-regulation of slow cortical potentials (SCPs)—shifts of cortical voltage lasting from a few hundred milliseconds to several seconds—for their CBI, called the Thought Translation Device (Hinterberger *et al*, 2003). Since 1996, ten patients have learned to produce SCPs, enabling them to move a cursor on a computer screen. SCPs do not correspond to movement or feelings, but to the general state of brain activity, and patients learn by reinforcement—using electrically negative and positive potentials—to control the device. On mastering this, they can choose letters from the screen to form sentences, although this is a slow process.

The German group teamed up with Wolpaw in 2000 to create a universal platform on which to test existing and new technologies that would allow individuals to choose the signals that work best for them (Schalk *et al*, 2004). Called the BCI2000, the device can also detect P300 signals, or 'event-related potentials'; these are sharp voltage increases that peak about 300 ms after the brain registers a surprising occurrence, which were discovered by Emanuel Donchin of the University of South Florida (Tampa, FL, USA). These signals are interesting for CBI developers because they allow them to recognize thoughts in a certain category without having to train patients to regulate their brain activity.

Despite these advances, John Donoghue believes that non-invasive systems have a disadvantage in that one must be trained to use them. In addition, their signals are more diffuse and inexact because they do not come from the actual neural substrate. Other groups, including scientists led by Ranu Jung, co-director of Arizona State University's Center for Rehabilitation Neuroscience and Rehabilitation Engineering (Tempe, AZ, USA), are therefore exploring ways to bypass the 'thinking' aspect in order to control a neuroprosthetic device in the same way the brain normally controls movement—at the subconscious level.

A few years ago, "juggling in my mind" was a mere joke, but now researchers have shown that thinking—with the help of computers—can be translated into action. Ultimately, the type of CBI used—which brain waves it uses, whether implanted or not—may depend on the individual patients. It may be hard to imagine what CBIs will enable patients to accomplish in a few years from now, but it is ultimately the mind that will enable them to escape bodily limitations.

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Descartes' Europe: one good revolution deserves another

The established Descartes Prize for Research is joined by the Descartes Prize for Science Communication. The message—no progress without communication

René Descartes (1596–1650; Fig 1) is one of the most influential figures in the history of Western philosophy and his work set Europe on a new track in terms of scientific thought and methodology. A revolutionary thinker who combined philosophy with an interest in physics and physiology and an unusual gift for mathematics, he was the first to make a clear break with Aristotle and the medieval scholastic traditions. With his concept of 'hyperbolic doubt'—the exaggerated doubting of everything except that which can be unambiguously proved—he asserted that we can trust neither beliefs and opinions nor our senses when explaining the world around us. Presumably, it is because of these achievements that the European Commission (EC) chose his name for a prestigious science prize, first awarded in 2000.

Europeans generally like celebrating their good old values, but the *zeitgeist* of science is moving on in Europe. Just as Descartes was responsible for a revolution in his age, so today's science is ready for