news@nature.com
The best in science journalism

Nature Biotechnology
Published online: 3 April 2007; | doi:10.1038/nbt0407-377

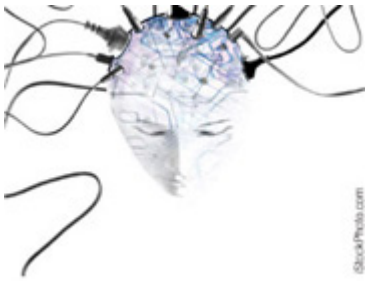
ARTICLE SOURCE
nature biotechnology

Making money and opening minds

Neurotechnology companies have promise, but lack funding and credibility. Monya Baker reports on this nascent area for startups.

Monya Baker

Earlier this year, neuroscientists at the Bernstein Center for Computational Neuroscience in Berlin announced that they could use brain scans to predict a subject's decisions[1]. Though the particular application—foretelling whether someone would add or subtract a given set of numbers—has little commercial appeal, the rapid rise of brain monitoring techniques along with the computing capacity to handle large datasets is already changing medicine. Decades-old technologies like electroencephalograms (EEG) have improved dramatically in precision and convenience. Once, people getting EEG scans would need to stay in a hospital, get wired up and wait for an event to happen. Now, they can wear monitoring devices during their normal routines, press a button to record activity during an event and have computer-readable data sent straight to a neurologist.



Noninvasive brain monitoring might someday inform clinicians making complex diagnoses, but is it ready for commercial prime time?
iStockPhoto.com

It's no surprise then that both academics and entrepreneurs are sprouting companies hoping to combine computing and brain monitoring advances to establish new commercial capabilities (Table 1). Products include everything from video games designed to maintain mental acuity to brain monitoring devices that detect and track progress for hard-to-diagnose ailments like Alzheimer disease and attention-deficit–hyperactivity disorder (ADHD).

Table 1. Selected neurotechnology companies

Full Table- See Page 8

But although technology might be ready to support a new kind of company, the capital and consumer markets are decidedly less so. What's more, concerns are mounting that the ethical and social implications of commercializing these products may be especially problematic (p. 393). In the near term, many neurocognitive researchers are worried that that clinicians and patients might opt for questionable computer-based approaches when low-tech solutions, like surveys and medicines, are more effective.

Slow out of the blocks?

Zack Lynch, head of Neuroinsights of San Francisco, a company that both tracks and boosts the sector, is decidedly bullish on these new type of companies, though they are and will continue to be dwarfed by neuropharmaceuticals. They not only offer potentially noninvasive treatments free of side effects, he says, but they could also expand the market for drugs by identifying people who could benefit from them. Still, he admits, many companies are trying to establish their business models. "It's not like these companies are being spun out left and right from Stanford and MIT," he says.

According to his organization's estimates, neuropharmaceuticals captured $93 billion in revenues in 2005, far more than neurodevices at $3.4 billion and neurodiagnostics at $13.5 billion. These divisions lump emerging markets with established ones and cover surprisingly diverse products. Neurodiagnostics includes both expensive brain scanning systems and image analysis software, genetic testing and biomarker assays. Neurodevices include neuroprosthetics, spinal cord stimulators and video game–type products to treat age-related memory decline and learning disorders. Like companies selling nutraceuticals, neurocognitive companies that don't make specific claims about treating or curing a particular disease can market their products without gaining regulatory approval. Customers include schools, health insurers, assisted living facilities, clinicians and private individuals; the heterogeneous user base makes many biotech investors cringe at inefficiencies in sales.

The take-home message for many venture capitalists (VCs) is that the market is complicated, confusing and small. "The potential upside of a therapy for Alzheimer's is huge compared to a piece of software that could diagnose Alzheimer's," says Roger Quy of Technology Partners in Palo Alto, California, which has invested in companies developing neurodevices to treat a variety of maladies. Mark Cochran, general manager at NeuroVentures in Charlottesville, Virginia echoes these sentiments. "Any company that comes to me as a diagnostic company, I often advise [the management team] to think of something different."

“The take home message for many venture capitalists is that the neurotech market is complicated, confusing and small.”

Both men are skeptical about software programs that improve mental health. Patented software products are vulnerable to me-too algorithms. As these products do not claim to treat a particular disease, they do not require US Food and Drug Administration (FDA) approval for marketing, but low barriers to entry are bad in this business, says Quy. Not only does that mean products will compete on price, he says, consumers (be they clinicians, patients or institutions) may simply not be persuaded that the products are effective. Investors face a similar dilemma, notes Quy. "There's too much noise in the market to distinguish one set of claims from another."

Neurodiagnostics on trial

Several clinical trials are underway to evaluate how well proprietary systems can treat, assess or predict treatment response in people with neurological diseases. One of the largest is sponsored by Aspect Medical Systems of Norwood, Massachusetts, a company that currently sells EEG technology to monitor the effects of anesthesia during surgery. The BRITE (Biomarkers for Rapid Identification of Treatment Efficacy in Major Depression) trial is expected to enroll over 350 subjects, with interim results to be announced this May. The trial takes EEG scans of subjects before and about a week after they begin taking an antidepressant and, using proprietary algorithms, predicts whether a person is most likely to benefit from the initially prescribed treatment or a different one. The funds for this work come from a $25 million investment from Boston Scientific of Natick, Massachusetts, Aspect's long-term partner for its anesthesia business.

Such moves have boosted credibility for the entire field, according to Howard Merry, CEO of Augusta, Georgia–based Lexicor, which is developing a tool to use EEG to diagnose ADHD. In the future, Merry expects informatics tools to become integral to diagnosis and companies to seek claims for discrete applications that require FDA approval. Once FDA-approved diagnostics become the gold standard, companies that "play with semantics" to get a product on the market may face skepticism if they choose the regulatory path, and get pulled off the market if they don't.

Lexicor has submitted a paper describing a pilot study showing that its EEG product's output correlates with experts' diagnoses of ADHD and published a meta-analysis of other studies[2], evidence it hopes to use to gain additional funding. Merry expects the path to FDA approval will be "onerous."

Neuronetrix of Louisville, Kentucky, launched in 2003, is also pursuing the regulatory path and requisite clinical trials. Though originally focused on screening newborns for dyslexia, the company has shifted its efforts to focus on tools for diagnosing the earliest stages of Alzheimer disease. The company has designed battery-powered, internet-enabled EEG headsets that transmit data to a central database. The goal is to collect event-related potentials (ERPs)—in this case, brain responses to specific auditory stimuli—then use a pattern-recognition engine to find patterns that can distinguish among people with probable Alzheimer disease, fronto-temporal dementia (FTD) and 'normal aging'. ERPs hone in on measurements from the brain in a defined functional state, according to COO

K.C. Fadem, and so are more informative than EEG scans. The company plans to launch its initial study this summer using 30 subjects each with Alzheimer disease and FTD. The next step would be to do a larger study, with the numbers of subjects to be determined after discussions with the FDA.

Fadem says that one market for the product would be drug companies who want to make sure that the people they are enrolling in early-stage Alzheimer trials really do have the disease. The other would be early screening. Some drugs that relieve symptoms of Alzheimer disease can exacerbate symptoms of other dementias. The technology platform could be applied to various hard-to-diagnose brain diseases.

But these companies are likely to have trouble getting funds for the trials they need for FDA approval. BRITE is a $5 million trial, explains Aspect CEO Nassib Chamoun, and it will be followed by a 'utility trial' in which clinicians use a BRITE algorithm to assign treatments. Boston Scientific's investment came only after Aspect had pumped hundreds of millions of dollars and many years into building its EEG platform for the anesthesia business. "VCs would be nuts to spend that kind of money on a company that was where we were at 20 years ago," says Chamoun.

And the competition could be fierce, not only from other companies, but from other kinds of measurement, such as blood or genetic tests. NeuroVentures' Cochran is particularly skeptical of EEGs, which he believes vary too much from scan to scan and provide too little information compared with more involved imaging techniques. Tim Buono, a partner at venture firm Tullis-Dickerson of Greenwich, Connecticut, thinks simpler options have an advantage. His firm just co-led an $8.5 million investment in Biobehavioral Diagnostics, located in Cambridge, Massachusetts. It produces an FDA-approved device for helping diagnose ADHD. The device tracks on a monitor children responding to stimuli and measures how they squirm while doing so. Clinicians who would not be able to administer an EEG will be able to administer this test, he says.

Healthier brains?

Another suite of companies is promoting 'brain fitness' programs, essentially computer games designed to improve mental function. Because their product is a piece of software, they require relatively little capital to get started. Brain Age, one of the better-known products, is made by Nintendo, which is based in Redmond, Washington. Others are marketed through websites like Braintrainer.com and happyneuron.com. Unique Logic and Technology of Asheville, North Carolina, sells PlayAttention to schools to train kids to concentrate better. Human Bionics of Purcellville, Virginia, offers neurofeedback therapy for ADHD, along with a host of cognitive assessment and analytic services. Both clinicians and VCs are skeptical.

One company that has won venture capital is San Francisco's Posit Science, which sells brain fitness software to promote healthy aging. Posit CEO Jeffrey Zimman says Posit chose to enter the 'healthy brain' market because it was in a position to put a program on the market quickly. The program is based on the premise that brain plasticity can be used to counter a natural decline in cognitive function that occurs with age. To strengthen appropriate neural pathways, computer-based exercises ask subjects to process sounds at

an accelerating pace. Posit has sold over 100 site licenses to assisted living facilities and similar communities for the elderly since its product first hit the market in mid-2005, says Zimman. Last year, health insurer Humana of San Antonio, Texas, began offering the product as a free perk to its Medicare Advantage members. The product saves Humana money because higher functioning people that feel better about themselves are more likely to take care of other health needs, according to Zimman. "We're hopeful, but make no claims of delaying the onset of dementia," he says.

Although the FDA has no interest in regulating 'healthy aging', Zimman is enthusiastic about studies his company is conducting with academics across the country in mild cognitive impairment (MCI), schizophrenia and early-stage Alzheimer disease. Zimman says he's optimistic about results of several soon-to-be-published studies. Published abstracts so far are underwhelming. The company has also published results of a 182-subject study showing that those using the brain fitness program had a significant improvement in their global auditory memory score that was sustained for at least three months[3].

Zimman declines to predict when his company will reach the break-even point, saying only that the company was pouring its revenues into research and development. However, he believes that Posit, which launched in 2003, will be able to spin itself in several ways either for an initial public offering or an acquisition by many types of companies. "It's an interesting convergence play, it seems to be in health care and also in consumer software, and part of training, and also perhaps a dry therapeutic."

Selling services

Another route to revenue while developing a neurotechnology product is selling services to researchers and clinicians. For well over a decade, companies like SleepMed of Kennesaw, Georgia, and Lexicor have used the internet to help clinicians collect and analyze EEG data. Although some companies have proprietary algorithms and trained professionals that perform the analysis, these companies too are careful to say that their services are not intended to diagnose or treat any specific disorder.

Milwaukee, Wisconsin–based Neurognostics, which is developing clinical applications for functional MRI (fMRI), fits this paradigm as well. It supplies equipment that runs stimulus and response paradigms, data processing algorithms and disease-specific datasets. CEO Cathy Elsinger says that as she and the company founder Stephen Rao began to think of ways to commercialize fMRI, they quickly realized that the lack of standards precluded its use as a widespread clinical tool, so they began to look for commercialization routes that would promote standardization.

In essence, the company decided to move not to where fMRI might ultimately have the biggest impact, but to where the market was most mature. That, says Elsinger, turned out to be brain mapping to help surgeons figure out how best to resect a tumor or treat a seizure disorder. "There you're looking at one patient at one time; you don't need a series of standardized references or norms," she says.

Elsinger expects fMRI to become clinically useful for detecting other mental diseases, but

the technology needs to get a lot better at comparing scans from different people before it can be used to distinguish healthy brains from disordered ones. With surgery, individuals serve as their own controls, notes Elsinger, and work to develop the surgery system can then be applied to more ambitious projects. "There's a lot of standardization that goes on so that you can take a single person and compare them with others," something that would be necessary for large-scale work on most mental diseases. Until then, Neurognostics is developing databases of reference standards and concentrating on integrating its products and services into the workflow at hospitals. They are also contracting with drug companies to provide assessments for clinical trials.

Perhaps the best known company in the space is Sydney, Australia–headquartered Brain Resource Company (BRC). BRC maintains a database containing about 15,000 datasets from about 12,000 individuals with results from a battery of cognitive performance tests. In some datasets, fMRI, EEG and genetic information are also available. About a dozen pharmaceutical companies, and various nonprofit research agencies, have contracted BRC to provide services for their clinical trials. The company also contributes to database BRAINnet, available to academic researchers who agree not to infringe on the company's patents. Publications stemming from this research (BRC touts several dozen) boost the company's name recognition and scientific credibility. The firm also recently received Medicare reimbursement code for its testing services, though so far income from that revenue stream is disappointing, says COO Segal.

Segal says BRC spent about three years thinking and rethinking various commercial models; initially, company executives planned to pursue the medical-legal route, providing services such as evaluating the effects of head concussions. In fact, says Segal, when BRC executives initially sought contracts with the pharmaceutical companies they expected little response, both because they were offering something new and because they were physically distant from the decision makers at most of the pharmaceutical companies. And although this revenue stream is growing, Segal says, the company is looking at several options. For example, it has recently patented a drug that it identified using some of the genetic information contained in its databases, but so far the company is using its capital to develop applications from its database, not move into drug development.

Credibility conundrum

Clinicians have their own worries about neurodiagnostics. "Things can look great in research and then come out into the real world and either not be useful or be wrong," says Elaine Jones, a neurologist with Southern New England Neurology in Barrington, Rhode Island. She thinks it's generally a waste of time and money to go through additional testing regimens just to see extra details of brain activity. "That doesn't help me treat that patient in the office; it's not worth me doing the test for the time and the cost and the possible risk to the patient." She worries that the rise of marginally useful technologies could eat into resources for ones that have proven effective.

The desire to find a single test that can be used for a complex clinical diagnosis is understandable, but naive, particularly for behavioral disorders like ADHD, according to Gerry Stefanatos, a cognitive neuroscientist at the Albert Einstein Medical Center in New York. "Given its heterogeneity, the disorder is unlikely to be related to a single or unique

finding on a brain scan." Eventually, he says, psychiatry will have to move beyond its reliance on a menu of behavioral symptoms, like the Diagnostic and Statistical Manuel of Mental Disorders (DSM) symptom checklist, and incorporate input from neuropsychological evaluations, genetic studies and neuroimaging.

James McGaugh, an expert in ADHD at the University of California, Los Angeles, worries that brain fitness programs for learning disorders could cause more harm than good by encouraging people to avoid medications that are known to be effective. "No one, neither physicians nor parents, wants to have their children take medicines on a chronic basis, but medicines are the only proven treatments for these conditions." And individuals may have a hard time evaluating whether scientific evidence of a program's effects actually translates into efficacy, says William Greenough, a professor of psychiatry at the University of Illinois at Urbana-Champaign. "The fact that something changes the brain in a measurable way is not sufficient to show that it is treating a symptom or a disorder."

Still, there is no question that software and brain scanning technologies will change how neurological diseases are diagnosed and treated. What's uncertain is the role that start-up companies will play in this field. Right now, many neurodiagnostics would not provide information that clinicians could act on, says NeuroVentures' Cochran, but he thinks that that will change as more neuropharmaceutical drugs come onto the market, and patients and clinicians need ways to figure out who can benefit from what treatments, both drug-based and not. Right now, few VCs have the time to wait for a product to get through lengthy trials, especially when their value will not be realized for many years.

"I like these companies; they serve a useful purpose," he says. "But it's not their time yet."

San Francisco
Article brought to you by: Nature Biotechnology

References

1. Haynes, J.D. *et al*. Current Biol. 17, 323–328 (2007).
2. Snyder, S.M. & Hall, J.R. J. Clin. Neurophysiol. 23, 440–455 (2006).
3. Mahncke, H.W. *et al*. Proc. Natl. Acad. Sci. USA 103, 12523–12528 (2006). | Article | PubMed | ChemPort |

Story from news@nature.com:
http://news.nature.com//news/2007/070402/nbt0407-377.html

© 2006 Nature Publishing Group | Privacy policy

Table 1

Nature Biotechnology
Published online: 3 April 2007; | doi:10.1038/nbt0407-377

Making money and opening minds

Monya Baker San Francisco

Table 1 Selected neurotechnology companies

Technology	Purpose	Companies[a] (year founded)
Improvement products		
Game-like software programs that may include a brain-monitoring component like EEG	Healthy aging	Posit Science (2003)
	Children's learning disabilities	CyberLearning (2001, San Marcos, CA), Imagine Neuro Solutions (2001, Flower Mound, TX), Scientific Learning (1996, Oakland, CA), Unique Logic and Technology (1994)
	General improvement (particularly memory)	SharpBrains (2005, San Francisco), Quixit (2005, Menlo Park, CA), Wild Divine (2001, Eldorado Springs, CO)
	Improving vision after stroke	Novavision (2003)
Biofeedback using MRI	Reducing chronic pain	Omneuron (2002, Menlo Park, CA)
Diagnostic aids and services		
Helping to type or diagnose ADHD, dyslexia, dementia and other disorders. Mapping brain before surgery. Predicting treatment effects	MRI-based	Neurognostics (2003)
	EEG-based	Applied Neuroscience (1987, St. Petersburg, FL), Aspect Medical Systems (1987), BrainMaster Technologies (1995, Oakwood Village, OH), Lexicor (1984), Neuronetrix (2003), SleepMed (1999)
	Batteries of cognitive tests	Brain Resource Company (1992), Biobehavioral Diagnostics, Cambridge Cognition (1999, Cambridge, UK), HeadMinder (1999, New York)

[a]Companies may be involved in more than one category, but only the dominant one is listed.

© 2004 Nature Publishing Group | Privacy policy