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## CEREBRAL INVESTING

Brain investments have yet to produce a blockbuster exit, but VCs think they're getting close to a breakthrough



THOMSON REUTERS

# CEREBRAL INVESTING

**Brain-related investments have yet to produce a blockbuster exit, but VCs think they're getting close to a breakthrough**

**By Joanna Glasner**  
Senior Editor

In the 1980s, zoologist **Fernando Nottebohm**—who was puzzled over songbirds' ability to learn new songs in certain seasons—examined their brains to find out why. He found that during those seasons, birds grow new brain cells in the areas responsible for song.

Determining whether humans are capable of similar feats took more than a decade. A breakthrough came in 1998, after collaborating scientists **Fred "Rusty" Gage** in San Diego and **Peter Eriksson** in Sweden used a marker to identify recently formed neurons in the brains of terminally ill patients. Examining the brains post-mortem, researchers found recently formed neurons in the hippocampus. Until that discovery, it had been assumed people are born

with all the brain cells they will ever have.

It was a finding with far-reaching repercussions. Over the past decade, neuroplasticity—essentially the principle that the brain remains quite adaptable throughout life—has blossomed from a fringe research area to a full-fledged field, with dedicated conferences, university departments and peer-reviewed research. Scientists are applying findings to therapies for ailments including stroke-related impairments, Alzheimer's disease and depression.

Venture-backed startups have been active as well. Gage co-founded and sits on the board of one, **Brain Cells Inc.**, which has raised \$80 million to date to develop therapies based on neurogenesis, the brain's ability to form new neurons throughout life. Over the past five years, VCs have put over \$350 million into more than a dozen companies developing cures and preventative

therapies that are reliant to some degree on advances in neurogenesis and neuroplasticity, according to **Thomson Reuters** (publisher of VCJ). (See table: *Select Brain-Related Investments*.)

Though significant, that's a drop in the bucket compared to overall sums venture investors are putting into companies developing technologies and therapies tied to the broader market of brain science. According to research firm **NeuroInsights**, venture capital investment in neurotechnology, across all sub-sectors, totaled \$1.58 billion in 2009, up 9.5% from the prior year. Given that brain illnesses are among the most under-diagnosed and under-treated ailments, VCs active in the "brain space" say the sheer size of the addressable market warrants their attention.

"Neurogenic diseases, such as cognitive and mood disorders, are a huge problem,

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particularly cognitive disorders as the population ages, and we're all living longer," says **Roger Quy**, a neuroscience Ph.D. and general partner at **Technology Partners**, which has at least six brain science-focused companies in its portfolio.

Yet vast potential and substantial sunk capital haven't translated into many big hits for neuroscience investors. VCs scored a couple of favorable exits with **Hypnion**, a neuroscience drug discovery company focused on sleep disorders acquired by **Eli Lilly & Co.** in 2007, and **Rinat Neuroscience**, a developer of drugs for Alzheimer's and central nervous system ailments, which sold to **Pfizer** in 2006. But public offerings have not been feasible for the last several years, Quy says. And while VCs continue to put money into the sector, at the later stage they're frequently seeing down-round valuations.

When they put their heads to it, however, neuroscience investors see reasons to be optimistic. Stepped-up attention from strategic acquirers and a strong patent pipeline are factors in their favor. And of course there's the potential that a show-stopping achievement—such a cure for Alzheimer's—could return everything ever invested in the sector and more, in addition to having an immeasurable humanitarian impact.

For now, conversations with some of the most active "brain space" investors indicate that capital intensiveness and a sluggish drug approval process remain top-of-mind concerns. To hedge their bets, a number are wagering smaller sums in niche areas with potential for quicker exits, such as commercially-targeted brainwave analysis and intelligence-boosting games. Yet given the potential for bigger outcomes, most are not shying away from ambitious plays, forming syndicates to offset individual risk as they await the next breakthrough.

### Minding the Market

When it comes to brain investments, VCs are right to be mindful of the magnitude of market opportunities.

Today, close to 2 billion people worldwide need treatment for brain-related illnesses, according to San Francisco-based **NeuroInsights**. But due to limited access to diagnostic tools and services, ailments commonly go undetected as well as untreated, a gap that has not gone unnoticed by venture investors.

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John Lechleiter  
CEO  
Ely Lilly & Co.

dous potential for commercial impact," says **Daniel O'Connell**, managing partner at **NeuroVentures**, a \$20 million fund with a portfolio of companies developing therapies for neurologic and central nervous system disorders.

Providing care to those who do receive treatment is already an enormously costly business. **NeuroInsights** estimates that companies selling neuropharmaceutical products generate in excess of \$100 billion in annual global revenue. Neurodevices, meanwhile, bring in more than \$7 billion, and neurodiagnostics-related revenue is close to \$15 billion. Both sectors are growing at double-digit rates.

Entrepreneurs see the neuropharmaceutical space as particularly ripe for disruption. That's in part due to the fact that so many of the most commonly prescribed drugs for ailments such as depression, anxiety and sleep disorders come with unpleasant side effects. That's particularly true of the family of drugs known as selective serotonin reuptake inhibitors (SSRIs), which include recognized trade names such as Prozac, Zoloft and Paxil, says **Jim Schoeneck**, CEO of **BrainCells**.

"With serotonin drugs you've got weight gain, potential [suicides] and sexual dysfunction—there are a lot of reasons people discontinue the drugs," Schoeneck says. "So, if we can find drugs that can be more effective and eliminate some of the side effects, that's a huge opportunity."

How big? He estimates the market for depression and anxiety worldwide pushes \$30 billion in current sales of pharmaceuticals. However, only 30% to 40% of patients respond to the first drug they're given, and even then frequently with the aforementioned side effects. For Alzheimer's patients, the situation is worse. Although there are a few approved treatments, there is none to delay or halt the progression of the disease, only to allay the symptoms.

For large pharmaceutical companies, an issue of additional pressing concern is the recent or pending expiration of patents on many of the most heavily prescribed neuropsychiatric drugs.

It's not a new issue. Patents on Prozac and Zoloft expired years ago, cutting an enormous revenue stream for respective patent holders **Eli Lilly** and **Pfizer**. The patent for **Lilly's Zyprexa**, a \$5 billion-a-year schizophrenia drug, is set to expire late next

## Select Brain-Related Investments

Company	Location	Description	Funding
<b>BrainCells</b>	San Diego	Developing a pipeline of clinical stage programs applying research findings linking neurogenesis (the process by which pre-existing stem cells in the adult human brain produce new brain tissue) to develop treatments for brain-related illnesses.	Raised \$80 million since 2004 from backers including Technology Partners, Oxford Bioscience Partners, Pappas Ventures, New Enterprise Associates, NeuroVentures Capital, MedImmune Ventures and Bay City Capital.
<b>BrainsGate</b>	Caesarea, Israel	Develops technology involving electrical stimulation to increase cerebral blood flow, with planned applications to treat stroke patients and sufferers of neurodegenerative diseases.	Raised \$42 million since 2002, including a \$27.5 million round in 2008, from backers including Pitango Venture Capital, Johnson & Johnson and Alice Ventures.
<b>CogniFit</b>	Yotneam Ilit, Israel	Assesses and trains the cognitive skills. Has developed software programs to measure, test and train the cognitive abilities and psychomotor skills.	Raised \$5 million from Milk Capital in 2008.
<b>Dakim</b>	Santa Monica, Calif.	Develops cognitive fitness solutions to help aging individuals with normal brain function as well as those suffering from dementia and Alzheimer's disease.	Raised \$10.05 million in 2008 from Galen Associates.
<b>EBS Technologies</b>	Brandenburg, Germany	Develops a medical device used for non-invasive brain stimulation for the treatment of visual field defects that result from stroke, brain trauma and glaucoma.	Raised \$4.35 million in January from BC Brandenburg Capital, Earlybird Venture Capital and High-Tech Gruenderfonds Management.
<b>EmSense</b>	San Francisco	Develops brainwave measurement technology for use in marketing research.	Raised \$16.3 million in 2008 and 2009 from Foundry Group and Technology Partners.
<b>Intellect Medical</b>	Cleveland	Focusing on advancing deep brain stimulation therapy for improving the recovery of chronic stroke and traumatic brain injury patients.	Raised \$21 million over three rounds from 2005 to 2008 from Boston Scientific Corp. (NYSE: BSX), Greatbatch Inc. and Biomec.
<b>Lumos Labs</b>	San Francisco	Provides web-based scientifically-tested brain fitness games.	Raised \$3.09 million in 2008 from FirstMark Capital and Norwest Venture Partners.
<b>NBI Development (aka Nevro Corp.)</b>	San Francisco	Medical device company developing neuromodulation therapies.	Raised \$5.5 million in seed funding in a 2006 round led by Three Arch Partners and Bay City Capital and joined by MPM Capital, Aberdare Ventures, the Mayo Clinic and the Venturi Group.
<b>NeoStim</b>	Redwood City, Calif.	Stealth company developing neuromodulation technology	Raised \$1.5 million in 2008, and \$7.5 million in February, according to regulatory filing. Backers include Aberdare Ventures and D.E. Shaw Group.
<b>Neuronetics</b>	Malvern, Penn.	Develops devices employing Repetitive Transcranial Magnetic Stimulation (RTMS), which involves magnetic pulses to specific parts of the brain, to treat chronic psychiatric and neurological disorders.	Raised \$92.5 million since 2003, including \$30 million last year, from backers including Three Arch Partners, Quaker BioVentures, ONSET Ventures, KBL Healthcare Ventures, Investor Growth Capital and InterWest Partners.
<b>Neuronova</b>	Stockholm	Developing treatment for Parkinsons disease through stem cell-based research and technology.	Raised an undisclosed amount of funding from Investor Growth Capital and HealthCap, which own 61% and 29% stakes in the company, according to its website.
<b>NeuroPace</b>	Mountain View, Calif.	Develops devices using responsive neurostimulation for the treatment of epilepsy.	Raised \$103.4 million between 1997 and 2008 from backers including Domain Associates, InterWest Partners and Kleiner Perkins Caufield & Byers.
<b>NeuroTherapeutics Pharma</b>	Chicago	Develops therapies for central nervous system (CNS) disorders with an initial focus on epilepsy.	Raised \$46.24 million, including \$43 million in May 2010, from Beacon Bioventures, MPM Capital, Novo A/S, Pfizer Venture Capital, S.R. One Ltd. and Thomas Mc Nerney & Partners.
<b>NeuroVigil</b>	La Jolla, Calif.	Develops an EEG recording tool and algorithm for analyzing brainwave data.	Raised \$250,000 in 1998 from Draper Fisher Jurvetson and Zone Venture Fund.
<b>NovaVision</b>	Boca Raton, Fla.	Develops therapy for vision loss after brain injury or stroke.	Raised \$38 million since 2003 from backers including Noro-Moseley Partners, Oakwood Medical Investors, Tullis Health Investors, Crossbow Ventures and Chicago Growth Partners.
<b>Posit Science</b>	San Francisco	Develops cognitively stimulating games and exercises.	Raised \$39 million between 2003 and 2010 from backers including Aberdare Ventures, Draper Fisher Jurvetson, and VSP Capital.
<b>Synosia Therapeutics Holding AG</b>	Basel, Switzerland, and San Francisco	Develops products for psychiatry and neurology needs. It is developing clinical-stage compounds acquired through partnerships with Novartis, Roche and Syngenta.	Raised \$49.95 million over three rounds, including \$27.62 million in 2009, from backers including Abingworth Management, Aravis SA, Investor Growth Capital AB, Novo A/S and Versant Ventures.
<b>Zeo</b>	Newton, Mass.	Uses sensor technology to measure sleep patterns through the electrical signals naturally produced by the brain and offers an online sleep coaching program.	Raised \$14.3 million in 2008 from iD Ventures America, Trident Capital and an undisclosed firm.

Sources: Thomson Reuters, company press releases and regulatory filings. Compiled by Joanna Glasner

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Daniel O’Connell  
Managing Partner  
NeuroVentures

year, according to a *Reuters* report. And the patent on Abilify, used for psychiatric disorders including schizophrenia, bipolar and major depressive disorder, is set to expire in 2015. That will have a weighty impact on Japan’s **Otsuka Pharmaceutical**, which discovered the drug, and **Bristol-Myers Squibb**, which generates revenue from its U.S. sales.

For startups, patent expirations can represent a tremendous opportunity, says **Manuel Lopez-Figueroa**, a vice president with San Francisco-based life science fund **Bay City Partners**. Not only are researchers looking for novel compounds, he says, they’re also seeking ways to use existing drugs or drug combinations to treat a new set of symptoms and diseases. Such findings can enable extension of some proprietary rights.

BrainCells, for example, received a patent in April for treating depression with buspirone, a drug for treating anxiety that went off-patent in 2001, and melatonin, a naturally occurring compound often used as a supplement for mood and immune disorders. The company says the combination appears to work by stimulating the formation of new nerve cells. It’s not a strategy lost on big pharma either. **GlaxoSmithKline** lost patent protection on blockbuster migraine treatment Imitrex a few years ago. The company partnered with another publicly traded pharma, **Pozen**, to develop Treximet, a now FDA-approved migraine treatment that combines compounds in Imitrex with those of a drug found in the painkiller Aleve.

### A Clubby Niche

Market metrics help explain the large number of venture funds with at least some investments tied to neuroscience. NeuroInsights estimates that in 2009, for example, more than 250 venture investors participated in neurotech financings.

Yet if one looks for frequent investors in what might be called the “brain space,” the list of firms is rather short. In each of them, it’s common to see a neuroscientist in the partnership.

At Technology Partners, Quy has headed the firm’s brain practice since 1989. Previously, as a research fellow, he developed techniques for monitoring the brains of ambulatory patients. Novo Ventures Partner **Heath Lukatch** also has a Ph.D. in neuroscience,

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Jim Schoeneck  
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from **Stanford**, and is chairman of two companies that develop drugs for brain and central nervous system (CNS) disorders: **NeuroTherapeutics Pharma** and **Synosia Therapeutics**.

Bay City's Lopez-Figueroa balances venture capital investing with a post as scientific liaison for the **Pritzker Neuropsychiatric Disorders Research Consortium**, a multi-university effort to pinpoint neurobiological and genetic determinants of mood disorders and schizophrenia. And **Mark Cochran**, founding partner of NeuroVentures, is also executive director of the **Blanchette Rockefeller Neurological Research Institute**, a non-profit dedicated to the study of human memory. Cochran stepped down as NeuroVentures' managing director in 2006, but remains an advisor to the fund, which is not actively seeking new deals.

Neuroscientist VCs are the biggest boosters of the brain and CNS space. But they are also cognizant that most trials—even those that seemed most promising in early stages—end in failure.

"The CNS space is characterized in part by a high placebo effect, unpredictable animal models and low success rates," Lopez-Figueroa says. The brain is, to state the obvious, baffling in its complexity. An organ that comprises 2% of average body weight, it supports about 100 billion neurons. Human brains are unique in the animal kingdom, averaging over three times the size of the brain of a typical mammal of comparable body weight.

Yet Lopez-Figueroa believes that advances in a range of disciplines—from genetics to tissue analysis to data storage and processing—will enable swifter and better identification of new targets. "We are arriving at the stage where technologies will help us understand better how the brain works and allow the integration of all these different sources of information," he says.

### Unconventional Investments

The trouble that Quay sees brewing in his sector has little to do with science and everything to do with money. "The biggest risk today is not technical but financial," he says. "For biotech it's a very tough climate to raise capital to exploit innovation."

Too offset sector risk, Quay and other brain-focused investors are looking at business models outside the traditional life science,

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Roger Quay  
General Partner  
Technology Partners

med-tech and biotech investment spheres. One area of particular interest is consumer medicine, where startups may reduce regulatory risk by focusing on self-pay models. Consumer medicine encompasses a broad range of startups, including brain-training companies, services and treatments for sleep disorders, and, in Quay's vision, "models where you don't have to deal with regulatory reimbursement."

Brain fitness is one of the most popular target areas. Over the last several years, venture and angel investors have backed at least seven companies in the cognitive fitness space. Most develop games, software and other tools intended to help people strengthen brain function.

Funded companies include **Lumos Labs**, a seller of online cognitive fitness games; **CogniFit**, a provider of personalized online brain training programs; and **Dakim**, a maker of cognitive training products for institutions. The three companies have raised \$10 million, \$5 million, and \$3 million, respectively, from venture firms, according to Thomson Reuters. Startups must also contend with deep-pocketed competition, such as **Nintendo**, which sells a line of cognitive fitness games called Brain Age.

Among VC-backed companies, the largest funding recipient is **Posit Science**, a San Francisco-based company developing brain health programs based on the science of neuroplasticity. It has raised \$39 million since 2003 from **Aberdare Ventures**, **Draper Fisher Jurvetson (DFJ)** and **VSP Capital**.

For VCs, the cognitive fitness space hasn't proven lucrative yet. Quay says he's looked at numerous companies in the sector and remains unsure how they'll scale, observing that while Lumos has been online for some time, it hasn't succeeded compared to many other gaming companies. Still he holds out hope, noting: "If Zynga can be worth close to \$4 billion largely on a simple farm game, one would think there would be a business model around brain training."

Sleep is another focus area. **Zeo**, which makes a device for monitoring sleep quality, raised \$12 million in 2008 from backers including **ID Ventures America** and **Trident Capital**. The company makes a bedside system that includes a headband that measures brainwaves and transmits them

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wirelessly to a nightstand device resembling a clock radio. La Jolla, Calif.-based **NeuroVigil**, which raised a seed round from DFJ and **Zone Venture Fund**, develops a device for measuring brainwaves and tools to analyze the data, for use in diagnosing sleep-related medical conditions and CNS disorders.

Perhaps the most unusual application for brain science startup is in consumer research. That's the domain of **EmSense**, a San Francisco company that makes neuro-measurement devices that marketers can use to track how customers respond to their products. The company, which counts **Pepsi**, **Time Warner** and **Unilever** among its customers, has raised \$16 million from backers including **Foundry Group** and **Technology Partners**.

#### If I Only Had a Brain-Related Exit

Thinking outside the box has not, as of yet, resulted in measurable ROI for brain space investors.

Few neuroscience companies have gone public over the last few years, and those that have made it to market have commonly posted sub-par performance.

One company that looked promising for a time was **EnteroMedics**, which develops devices that use neuroblocking technology to treat obesity and other gastrointestinal disorders. The company raised about \$40 million in its November 2007 IPO. Previously, it had raised about \$79 million in venture funding. Its largest VC shareholders are **Aberdare Ventures**, **Bay City Capital**, **InterWest Partners** and **MPM Capital**.

The IPO started out on a reasonably promising note, with shares pricing at \$8 apiece. But EnteroMedics has since tumbled in value, with shares currently trading around 30 cents. The company posted a loss of \$4.7 million in its most recent quarterly report.

Shares of another venture-backed neurodevice company, **Cyberkinetics Neurotechnology Systems**, are selling for even less. The Massachusetts-based company, which makes devices to measure and analyze electrical impulses in the brain, went public by merging in October 2004 with **Trafalgar Ventures**, a subsidiary of a company traded on the Nasdaq Bulletin Board. Founded in 2001, Cyberkinetics had previously raised \$16.5 million in three rounds from **Life Science Ventures**, **NeuroVentures** and **Oxford Bioscience Part-**

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Bay City Partners

**ners**. Its shares currently sell for less than a penny.

**Northstar Neuroscience**, a developer of treatments for stroke and Parkinson's through neurostimulation, has also fared poorly. The company raised more than \$76 million between 1999 and 2004 from backers including **Boston Scientific**, **Canaan Partners**, **Domain Associates** and **Mayfield Fund**. After going public in 2006, shares held up well enough for some backers to exit at a gain, according to one venture backer. However, the stock, which peaked above \$16 in 2006, began a steep downward spiral in 2008. Its shares currently sell for about 3 cents apiece.

VCs have done better with some M&A exits. One standout was Hypnion, a drug discovery company focused on sleep disorders acquired by Eli Lilly in 2007 in a deal valued at about \$315 million. The Lexington, Mass.-based company previously raised \$80 million from backers including **Advanced Technology Ventures**, **Flagship Ventures**, **Forward Ventures**, **Jafco**, **MPM Capital** and **Oxford Bioscience Partners**.

Rinat Neuroscience, a developer of protein therapeutics for neurological disease, also provided a positive return, investors said, when Pfizer acquired the South San Francisco-based company in 2006 for an undisclosed sum. Rinat had previously raised \$57 million over two rounds in 2001 and 2003 from **Essex Woodlands Health Ventures**, **MPM Capital**, **Prospect Venture Partners**, **SV Life Sciences Advisers** and **Technology Partners**, according to Thomson Reuters.

Venture investors are hopeful the best exits are yet to come. With large pharmas under pressure to find new blockbuster drugs and extend the lifespan of aging patent portfolios, there's a good chance that M&A activity will pick up. For example, Eli Lilly CEO **John Lechleiter** told *Reuters* last month: "We're going to look to do deals that might help us bring in near-term revenue to help replace some of what we're losing, that complement our pipeline or that give us meaningful opportunities to diversify."

VCs haven't given up on the IPO market, either, as the pace of new offerings has recovered somewhat from the drought of 2008-2009. After all, if songbirds are capable of learning new melodies each season, it's certainly plausible that public market investors can learn to appreciate a new generation of neuroscience startups. **VCJ**