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Deep in Big Tobacco country, I'm talking to a former chief scientist for R.J. Reynolds about new wonder drugs for the brain that are inspired by, of all things, nicotine. We're huddled in a futuristic steel-and-glass building in Winston-Salem, North Carolina, that looks like an alien starship next to the abandoned storefronts and empty brick cigarette factories of this faded town. I'm skeptical. Now C.E.O. of a company called Targacept, the ex-Reynolds man, Don deBethizy, is describing a class of drugs called nicotinic, which he says can restore the memory of Alzheimer's patients, control pain, and improve attention spans. What's more, they may boost cognition and memory in healthy people. It seems far out even for the neurotechnology industry, a rapidly growing cluster of companies-small upstarts as well as pharmaceutical giants-that want to alter your gray matter and make billions of dollars in the process. These firms are trying to adapt groundbreaking research into the basic workings of the brain to new drugs for ailments ranging from insomnia to multiple sclerosis. Some companies are trying to regrow portions of the brain using stem cells. Others have developed implants to insert into a person's head to control seizures and restore hearing. Cyberkinetics Neurotechnology Systems, a Foxborough, Massachusetts, company, implanted electrodes into the brain of a quadriplegic that allowed him to operate machines with his thoughts. (View an interactive feature showing brain researchers' latest efforts.)DeBethizy's jump-out-of-his-seat gusto makes me want to believe him.Yet I can't shake the image of the Nick Naylor character in Thank You for Smoking, the film based on Christopher Buckley's satirical novel about a spinmeister and apologist for the tobacco industry. Targacept's birth was a by-product of deBethizy's attempts at Reynolds to create a "safe" cigarette and find positive uses for nicotine. Neuroscientists and investors I spoke to vouch for deBethizy and insist that Targacept is among the hottest companies in the brain business and a leader among several outfits developing nicotinic. So here I am in this dog-eared burg to learn more about an industry that may not only hold the key to treating some of the most serious maladies of our time but also challenge society's-and regulators'-opinions of whether drugs should be used to enhance healthy brains as well as treat illness.Targacept is one of about 500 brain-tech companies going after the estimated \$2 trillion that it costs globally when brains atrophy, degenerate, experience depression, cause convulsions, register pain, trigger anxiety, or simply fail to work as well as we would like. The size of the market is huge, according to data from the World Health Organization and others, which report that more than 1 billion people suffer from brain-related ailments each year. That number has grown rapidly during the past generation, as neurodisorders like depression have gone from being underdiagnosed to perhaps overdiagnosed, and Western populations, along with their brains, have aged. It's hard to believe, but even in our Prozac nation, possibly tens of millions of people who might need brain meds aren't getting them. In some parts of the developing world, the figure could be as high as 90 percent. (View a pop-up graphic that shows the revenue breakdown of drug treatments and disease.)Neurotech's returns are already enormous. In 2006, the industry brought in more than \$120 billion-about \$101 billion from drugs and the rest from neurodevices (\$4.5 billion) and neurodiagnostics (\$15 billion)-up 10 percent from the previous year, reports NeuroInsights, a market research and investment advisory firm. But industry analysts insist that this figure hardly begins to suggest the potential. For Alzheimer's, a disease currently without an effective treatment for about 4.5 million sufferers in the U.S., 40 companies-including behemoths like Eli Lilly, GlaxoSmithKline, and Wyeth, as well as Targacept and a gaggle of similar upstarts-are testing 48 new drugs in human trials in a quest for the Prozac of dementia. The push has brought many small to midsize biotech firms together in partnerships with larger pharmaceutical companies to pursue everything from pain-control compounds derived from chili peppers to an antistroke medicine developed from vampire-bat saliva. There is so much activity in neurotech that last fall it got its own index, NERV, on the Nasdaq, tracking the performance of 30 leading brain companies based in the United States. Analysts estimate that the sector should continue to grow by about 10 percent a year, which would produce a brain-industrial complex worth more than \$300 billion in the next 10 years.Page 2For now, though, brain businesses are still more likely to lose money than to make it. The failure rate is startling even for the pharmaceutical industry, which is accustomed to tremendous risk. Ninety-two percent of drugs that enter human clinical testing for the central nervous system-basically brain drugs-flop, compared with 89 percent for drugs across all categories, according to a study in Nature Reviews, a science journal. At the same time, the total cost of bringing one C.N.S. drug to market is nearly twice the average for all drugs-\$1.6 billion as opposed to \$800 million. The risk, along with the generally volatile economic climate, has helped send NERV tumbling more than 18 percent since its inception last September.Still, investors see the immense size of potential markets and have swallowed hard, pumping billions of dollars into neurotech, hoping for that giant payback. (Hit the jackpot with a new anxiety-disorder med that's better than the current batch and you have a potential market of 40 million Americans and 400 million people worldwide.) "People invest because a success is usually a huge success," says Ellen Baron, a venture capitalist with Oxford Bioscience Partners in Boston, which has invested in Targacept and other early-stage neuro companies. The top 20 C.N.S. drugs each earn more than a billion dollars per year, she notes. "This new science will produce breakthroughs, and everyone feels the potential to create a truly paradigm-shifting treatment," Baron says. "But when? Nobody knows."Neurotechnology as its own industry sector is the brainchild, so to speak, of Zack Lynch, a former software marketing executive who lectures widely on future business trends. He believes that we are at the beginning of a brain wave that will dominate at least the next century or two. Lynch came up with several cute names for the advances he anticipates, such as cognitiveuticals, for drugs that focus on improving decisionmaking, learning, attention span, and memory processes; emoticeuticals, which influence feelings, moods, motivation, and awareness; and sensoceuticals, which can restore and extend the capacity of senses for people who have impaired vision, smell, taste, and hearing. In 2005, he and his wife, Casey, a former biotech executive, founded NeuroInsights. Later, they started the Neurotechnology Industry Organization, a policy and lobbying group that has 70 companies as members.After several months of negotiation with a top Nasdaq official, the couple convinced the exchange to launch the NERV index in September. Its leaders include Biogen Idec, a neuro-titan with a current market cap of \$19.4 billion that's developing treatments for (among other things) multiple sclerosis and Parkinson's, and Shire, which makes the amphetamine Adderall and has a market cap of \$10.6 billion. At the even more volatile bottom are companies with market caps of \$250 million or so. Only companies with more than 50 percent of their revenues coming from neuro products are allowed on the index, so big pharmaceutical concerns like GlaxoSmithKline and Johnson & Johnson, despite having blockbuster brain drugs, don't make the cut.[&] Glaxo, and Lilly, however, lead the list of the top five companies in neurotech revenues, a group that collectively earned \$30.1 billion in 2006, 25 percent of all neuro sales. Pfizer is next, with \$6 billion in sales in 2006, though that is down from \$8.1 billion in 2004, before its patents for big sellers like Zoloft (for depression) and Neurontin (for epilepsy) expired. Wyeth rounds out the group, with almost \$3.8 billion in sales.I meet the Lynches one afternoon at a coffee shop in the Noe Valley neighborhood of San Francisco, a block or two from the NeuroInsights world headquarters in the basement of their home. Both in their mid-thirties, the two met in a calculus class at U.C.L.A. when they were freshmen. Zack first recognized the link among companies with neural products while giving his PowerPoint presentations about the future of technology at meetings and conferences. The Lynches tend to talk as one brain, left and right, and they agree that turning neuroscience into cash and cures requires patience. "But I think a time is coming-or may be here-when our understanding of the brain will get to the point where we can more successfully make targeted drugs," says Casey, a petite woman with dark hair and a practical, left-brained demeanor that balances her husband's more right-brained, pie-in-the-sky fervor. "This will profoundly change medicine, and possibly who we are," Zack says.Page 3The couple's new push is to get more federal dollars channeled toward the industry. Zack has been traveling back and forth to Washington, sometimes taking along neurotech C.E.O.'s, to promote a \$1 billion "national neurotechnology initiative" that Representative Patrick Kennedy, a Rhode Island Democrat, recently announced he will introduce in Congress. The legislation asks the federal government to spend \$200 million a year for five years on neurotech, including \$30 million for the Food and Drug Administration to train more experts, \$80 million for the National Institutes of Health to coordinate the neuroresearch efforts that are now run by 16 different institutes, and \$75 million to increase small-business grants for neurotech companies.Treatments for the mind are hardly new. Before modern times, remedies included the exorcism of evil spirits, bleedings to rid the body of bad humors, and opium smoking to alleviate "melancholy." In the mid-20th century, physicians tried crude and often destructive "cures," now discredited, such as lobotomy-removing sections of the brain believed to be causing neuroses.In the 1950s and '60s, psychiatry was revolutionized by the invention of antidepressants and tranquilizers. The progression of new drugs continued into the '70s and '80s, especially with the blockbuster class of antidepressants called selective serotonin reuptake inhibitors, which includes Prozac. Approved by the F.D.A. in 1987, Prozac, as well as other S.S.R.I.'s-like Zoloft and Paxil-prolongs the action of serotonin, a neurotransmitter, which has beneficial effects on such problems as depression, attention-deficit disorder, and anxiety. Critics of S.S.R.I.'s argue that they don't work for many patients, that they are being overprescribed, and that they can cause side effects such as loss of libido and (according to controversial findings) suicidal thoughts in teenagers.But since the late '80s, few new classes of drugs to treat brain maladies have made it to market, and many diseases remain either undertreated or, like Alzheimer's and Huntington's disease, not treated effectively. The industry now faces the challenge of parlaying two decades' worth of breakthrough research on the basic workings of the brain into new and better treatments-a process that is often thwarted by the complexity of the brain. "We target a drug that is supposed to do one thing, and we find out it does five more things we didn't expect," says Sam Barondes, director of the Center for Neurobiology and Psychiatry at the University of California at San Francisco and the author of Mood Genes.Much of the industry's financial success in recent years has come from drugs that differ only slightly from longtime neuro-blockbusters, some of which are losing their patent protection. Patents expiring in 2008 include Risperdal, a schizophrenia drug from J&J's Janssen unit, annual sales of which are approaching \$4.2 billion. "The new products are coming, but the big numbers are still in the Prozac category," says Martha Farah, director of the Center for Cognitive Neuroscience at the University of Pennsylvania.Some of the most interesting advances are being made not in drugs but in devices and other treatments. Late last year, StemCells Inc., a Palo Alto, California, company, announced that it had successfully transplanted stem cells into a human brain and that the patient had recently completed a one-year follow-up exam. Five other patients have also been injected with HuCNS-SC, as the company calls its human stem-cell product. All of the patients suffer from Batten disease, a genetic malady that leaves children's brain cells without a critical enzyme and eventually causes seizures, loss of motor skills and mental capacity, blindness, and finally death. In previous studies with mice, the stem cells took hold and produced the missing enzyme. "These trials are just the beginning for stem-cell therapies in the brain and elsewhere," says Antoun Nabhan, a former venture capitalist for Sagamore Bioventures who has seized in and sits on the board of Cellarant Therapeutics, one of StemCells' competitors. But stem-cell treatments for more-common brain diseases are at least five years away, Nabhan says.Page 4Earnings for neurodevices are only 4 percent of what neuromeds bring in, but for a few diseases, the impact has been miraculous. Take cochlear implants. Located in the inner ear, the cochlea translates sound waves into electrical signals that are channeled to the brain to be processed into the opening swell of a Mozart concerto or raindrops beating on a window. People with damaged or congenitally malformed cochleas were condemned either to near silence or to the use of imperfect hearing aids until the 1970s, when the first cochlear devices were surgically implanted. These had an electrical apparatus that fed signals into the audio nerve through electrodes. The latest versions of the devices use tiny computers to process even complex sounds like music into signals that the brain can recognize. More than 100,000 people have had the cochlear devices implanted worldwide (out of the millions affected), and many go from being deaf or near-deaf to being able to hear most sounds and function as if they had no hearing deficit. The device, which costs \$20,000 or more, has annual sales totaling \$550 million, and sales are growing 15 percent a year. Leading makers include Advanced Bionics, Cochlear, and Med-El.One truly out-there device is Cyberkinetics' BrainGate, which was implanted into the brain of Matt Nagle, a quadriplegic patient, in an F.D.A.-approved trial. The device enabled him to control a computer cursor with only his thoughts. The BrainGate, which was connected to the computer by a wire, uses tiny electrodes to read electrical impulses from the brain's motor cortex. In 2005, I visited Nagle-a former high-school football star who was paralyzed as a result of injuries he suffered during a brawl on a beach in Weymouth, Massachusetts-and I watched as he gave the mental command to move his arm up and down. The machine translated these thoughts into up and down cursor motions. As Nagle got better at controlling the device, he became able to write emails and operate controls for lights and a television. He could even control a prosthetic arm. But the BrainGate was cumbersome, difficult to calibrate between brain and machine, and sometimes left Nagle feeling frustrated. The company is now recruiting patients for additional trials.All the uncertainty of the industry hasn't dampened the enthusiasm of Targacept's Don deBethizy, who toils with his team of scientists just up the street from the R.J. Reynolds headquarters, a 1929 skyscraper considered an Art Deco marvel in its day, with gilt tobacco leaves on the lobby's ceiling. Targacept broke off from R.J.R. Nabisco in August 2000, just 36 hours before the unit was to be eliminated during the messy merger process that started when Kohlberg Kravis Roberts acquired the tobacco giant in 1989. At the last minute, drug giant Aventis stepped in with a \$70 million partnering deal to save Targacept and its leading Alzheimer's compound, which was then in Phase 1 human trials. (This drug was later killed after the unit was unable to successfully breach the blood-brain barrier, a common problem for world-be neuromeds.) After becoming an independent company, Targacept raised \$123 million in three rounds of private capital investment and \$72 million from stock offerings. Milestone deals with AstraZeneca to develop cognitive-disorder meds and with GlaxoSmithKline to develop treatments for pain, obesity, smoking cessation, addiction, and Parkinson's make up the remainder of Targacept's financing.As deBethizy explains, nicotinic receptors control or influence memory, attention span, mood, sensitivity to pain, inflammation, movement, and cell survival. "These receptors act like volume switches," says Merouane Bencherif, Targacept's vice president for Preclinical Research. Nicotinic drugs work by increasing neurotransmitter activity, Bencherif says, meaning more is around to zap the receptors to improve memory and mood. Turning down neurotransmitter activity reduces pain or inflammation.Currently, Targacept has four compounds in human trials. Their connection with nicotine? "There isn't really a connection anymore," says deBethizy. The compounds are chemically unrelated to nicotine, but their action in activating the receptors mimics what nicotine does.Page 5One of Targacept's leading compounds is designed to improve cognitive activity in patients with Alzheimer's disease; another is for schizophrenia. Both are in human trials. So far, the drugs have worked well for those with the diseases, but the Alzheimer's compound has also had an effect on healthy control subjects, whose scores on cognitive and memory exams improved significantly. The company also tested the compound on people who went to a memory clinic with mild age-associated memory impairment-the natural loss of memory that comes with normal aging. The mini-trial was a success: "People on 50 milligrams consistently said they remembered things better," deBethizy says.Several other companies are developing meds that could treat brain-function slowdown in the elderly and might also enhance brain function in younger people. These firms include Memory Pharmaceuticals, Cortex Pharmaceuticals, and Lilly. "We are working on glutamate receptor medicines for memory and cognition," says Steve Paul, president of Lilly Research Laboratories. "This is a big future growth area for us."But the drugs' success with healthy people raises a number of regulatory and ethical questions. The F.D.A. evaluates drugs based on how effectively they treat disease, not on whether they enhance healthy brains. Benedetto Vitello, a psychiatrist and researcher at the National Institute of Mental Health who has also sat on neuropharma advisory panels for the F.D.A., acknowledges that many people face cognitive loss as part of normal aging. But the condition is often subtle and hard to quantify, he says. This may be one reason that the F.D.A. has been reluctant to list age-related cognitive loss as an official approved designation for new drugs, deBethizy suggests. He expects the F.D.A. to one day recognize it as an approved disease, "but right now," he says, "no one wants to spend the resources on a drug that may not be approved."Yet mind-meds that can enhance mental functions are already used by healthy people. Through what's known as off-label use, legal prescriptions are written for conditions the drugs weren't approved to treat. Physicians are allowed to prescribe any drug for any illness they see fit, but companies are barred from promoting drugs for unapproved uses.A more recent drug being widely used off-label is Cephalon's Provigil. This high-tech medicine is approved for narcolepsy and a sleeping disorder that develops when people work odd shifts. Provigil, however, is widely prescribed for other conditions, ranging from depression and A.D.D. to jet lag. In late 2007, Cephalon agreed to pay a \$425 million settlement to the government after the firm's sales force was accused of marketing Provigil and two other drugs to physicians to use for unapproved maladies. "It would behoove the federal government to get ahead of the enhancement issue now," says Zack Lynch. "Provigil is just the beginning."A larger debate is percolating over what would happen if a pill could turn most people into brainiacs. "I don't believe in cognitive enhancement for people who are well," says memory expert and Nobel laureate Eric Kandel, a professor at Columbia University. "These should be pharma products for sick people." N.I.H. neuroscientist Jordan Grafman agrees: "If you manipulate the brain, it can change who we are."Others say enhancers can't be stopped. "The record is clear. Wherever there have been new agents that enhance our functioning, mental or physical, even when they're risky like steroids, there are people who will use them," says U.C.L.A. bioethicist Gregory Stock, author of Redesigning Humans: Our Inevitable Genetic Future and a strident advocate for enhancement. "Why shouldn't people use them if they don't hurt us?"Back in the less surreal world of their favorite San Francisco coffee shop, Zack and Casey Lynch tell me that their organization delisted four companies a mere three months after the neurotech index joined Nasdaq, highlighting the fact that those who would make money from our brains face a brutal reality. "It's a tough industry," Zack says with a sigh, as Casey crosses out the delisted companies and writes down the new ones on the chart they had given me. "But the future is clear," he says, quickly recovering his zeal, reminding me of Don deBethizy and the other neuro-cheerleaders. "This is going to work. The effects are going to be profound."Visit Portfolio.com for the latest business news and opinion, executive profiles and careers. Portfolio.com © 2007 Condé Nast Inc. All rights reserved.

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