After battling drug use, a professor uses neuroscience to understand it.

Fighting addiction with science

By Aubrey Whelan
STAFF WRITER

At 23, Judith Grisel was in a Minnesota rehab grappling with the addictions that had defined her life for the previous decade. For the first time, she heard that addiction was a disease, not a moral failing.

As she entered recovery and eventually returned to school, she gravitated to neuroscience to understand her own response to drugs.

Now a psychology professor at Bucknell University, Grisel, 55, recently published *Never Enough: The Neuroscience and Experience of Addiction*, a narrative of her own addiction experience and a primer on how various drugs affect the brain. It cracked the New York Times' Top Ten list of bestselling science books this week.

She recently spoke with The Inquirer about her experience and her research.

How did your own history of addiction lead you to study neuroscience?

By the time I was 23, I had lost pretty much everything after about 10 years of avid use of pretty much whatever I could get my hands on. When I ended up in treatment and heard it was a disease, I, in a kind of naive way, I thought, *Disease can be cured; I'll figure out a cure.*

I felt like from my experience, that my response to drugs was different from other people's. I had a roommate one time who would mete out cocaine like it was gold in a way that I could not understand. She would somehow moderate that. I seemed to have kind of a bottomless desire. I thought there must be some sort of biological explanation for my experience and response.

How can neuroscience help explain addiction?

There's a correlate of brain activity to everything we do and everything we experience. What is the neural phenotype, or the brain state that predisposes you [to addiction], and how does the brain change as a result? I think understanding those things could help with interventions and preventions. At the very least it helps explain the inexplicable — how do people give up everything for a little baggie of stuff? How do they court death like this?

The first time you start taking any drug your brain adapts. It does it immediately. That adaptation is always the opposite of the main effect of the drug. So as soon as I drink alcohol, my brain is making me more excitable and more anxious, so that when I get that sedative [from alcohol, the brain compensates].

Judith Grisel is a psychology professor at Bucknell University, studying addiction.

The more the cells of the brain are bathed in a drug, the deeper the adaptation is. When I got to treatment I was definitely understimulated in terms of reward and pleasure in that dopamine pathway that we always talk about. All I wanted to do was escape that sort of withdrawal state by getting more drugs. And every time I got the drug, I would make the adaptation stronger.

The longer you go with a drug, the more your brain adapts, and the longer you go without it, the more your brain adapts back.

You're wary of opioid replacement medications such as methadone and suboxone, which research shows give patients a better shot at recovery than abstinence-based treatment. Can you talk about that?

For me, I probably come down a little heavy-handed on the side of abstinence. For me, moderation, I think, is very unlikely. My sort of gold, pie-in-the-sky vision is that people would be able to sort of live [without any drugs]. I have a really rich, full, free life, I think, except that I just can't pick up [drugs].

My bias is toward the natural state, and this isn't natural to have [opioid replacement drugs]. So, even though [when you take methadone or suboxone] you're tolerant, so you're not getting the big highs, I don't think it's anything like the state that you started with. And so that's my bias.

I don't think methadone is good, but it's better than dying of an overdose of heroin. If these are the options, absolutely methadone is an advantage. But giving people a prescription for a substitute opiate and then doing nothing [else] is unconscionable. I think medication can be a big, big help. The goal is to get people to look at themselves and their choices and see if they want to change course.

What has experience with addiction meant for your career in the sciences?

I think being a scientist is a fantastic career for anybody, but especially for a recovering addict. What I sought was this sort of exciting, transcendent, never-know-what's-going-to-happen-next sort of life. I kind of get that in a research setting. There's a lot of intrigue, there's a lot of uncertainty and mystery, there's a lot of reward. It's a good fit for people who are novelty-seekers.

I do think most people I know in drug and alcohol research, like, the vast, vast majority, are not in recovery. Which probably reflects the fact that it's hard to recover — I got lucky there. But I think that many of them are there because they had family members, they had some firsthand experience. A lot of people go into their fields because they're trying to understand something personal.

How can neuroscience better help the public understand addiction?

Addiction is increasing, and the drive to escape is obviously an epidemic. So we're all more or less on the same road. I think the factors that contribute [to the addiction crisis] are really deep and complex and systemic, internally and externally, and it's in all of our best interests to look at those.

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EDUCATION

1988 B.A. Florida Atlantic University (Psychology)

1991 M.A. University of Colorado (Behavioral Neuroscience/Psychology)

1993 Ph.D. University of Colorado (Behavioral Neuroscience/Psychology)

PROFESSIONAL EXPERIENCE

1994-1997 Post-Doctoral Fellow, Department of Behavioral Neuroscience, Oregon Health Sciences University and VA Medical Center, Portland OR

1996-1997 Visiting Assistant Professor, Reed College, Portland, OR.

1997-2003 Assistant Professor of Psychology, Department of Psychology, Furman University

2003- Associate Professor of Psychology, Department of Psychology, Furman University

2007- Chair, Neuroscience Program, Furman University

2011-2012 Professor of Psychology, Department of Psychology, Furman University

2012-2015 C. Graydon and Mary E. Rogers Faculty Fellow, Bucknell University

2012- Professor of Psychology, Department of Psychology, Bucknell University

SELECTED RESEARCH GRANTS AND CONTRACTS

1999-2001 OFQ Modulation of Opiate Tolerance Dependence and Reward Grant from the National Institute of Drug Abuse (NIDA) $94,816

2001-2004 Ethanol Sensitivity in Beta-Endorphin Deficient Mice. Grant from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) $100,000

2002 The Role of b-Endorphin in Ethanol-Mediated Anxiolysis. South Carolina Biomedical Research Infrastructure Network (BRIN) TDC: $12,000

2002-2003 Continued Investigation of the Analgesic Effects of Methadone and its Metabolites in Mice. Endo Pharmaceuticals Inc. Principal Investigator, TDC: 40,500

2007-2009 Beta-Endorphin, Stress and EtOH Sensitivity. Pilot project from INIA-Stress, NIAAA. $100,000

2007-2010 Mechanisms underlying the influence of beta-endorphin on EtOH reward, aversion and plasticity. NIAAA, $150,000

2008-2012 Core Program Member on $1.2 million grant to Invigorate Science Education at Furman, Howard Hughes Medical Institute

2014-2018 Sex-Dependent Effect of Stress on Alcohol Consumption. NIAAA $250,000

AWARDS

2000-2003 Herman N. Hipp Endowed Professorship for Junior Faculty, Furman University

2012 Howard Hughes Distinguished Mentor

2020 Mind Science Foundation Distinguished Speaker

SELECTED PUBLICATIONS

Watkins LR, Wiertelak EP, Grisel JE, Silbert LH and Maier SF (1992) Parallel activation of multiple spinal opiate systems appears to mediate "non-opiate" stress-induced analgesias. *Brain Research,* 594:99-108.

Grisel JE, Fleshner M, Watkins LR and Maier SF (1993) Opioid and nonopioid interactions in two forms of stress-induced analgesia. *Pharmacology Biochemistry & Behavior*, 45:161-172.

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Grisel JE, Belknap JK, Wenger CM and Crabbe JC (1997) Assessment of Quantitative Trait Loci underlying the stereotypic climbing response to amphetamine in the BXD recombinant inbred strains. *J. Neurosci.*, 17: 745

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Mogil JS and Grisel JE (1998) Transgenic Studies of Pain, *Pain* 77:107-128

Mogil JS and Grisel JE (1998) Toward a Functional Characterization of Orphanin FQ/Nociceptin: Parametric and Organismic Considerations. *Eur. J. Pain*. 2:278-280 (Invited Commentary)

Grisel JE, Mogil JS, Grahame NJ, Rubenstein M, Crabbe JC and Low MJ (1999) Ethanol Self-Administration is Increased in Mice with Decreased b-Endorphin Expression. *Brain Research* 835:62-67.

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Mogil JS, Wilson SG, Chesler EJ, Rankin AL, Nemmani KVS, Lariviere WR, Groce KM, Wallace MR, Kaplan L, Staud R, Ness TJ, Glover TL, Stankova M, Mayorov A, Hruby VJ, Grisel JE, and Fillingim RB. (2003) The melanocortin-1 receptor gene mediates female-specific mechanisms of analgesia in mice and humans. *Proc. Natl. Acad. Sci. USA,* 100(8):4867-4872.

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Grisel JE, Nemmani KV-S, Allen S, Fee JR, Carliss R. (2005) The Influence of Dextromethorphan on Morphine Analgesia in Swiss Webster Mice is Sex Specific. *Pharmacology, Biochemistry and Behavior*. 81:131-138.

Grisel JE, Bartels, J, Allen SA, Turgeon VL (2008) Influence of b-endorphin on Anxious Behavior in Mice: Interaction with EtOH. *Psychopharmacology*, 200:105-115.

Barfield ET, Barry SM, *Hodgin HB*, Thompson BM, Allen SS, Grisel JE. (2010) b-Endorphin Mediates Behavioral Despair and the Effect of Ethanol on the Tail Suspension Test in Mice. *Alcohol Clin Exp Res.*, 34:1066-1072.

Grisel JE, Beasley J, Bertram EC, Decker BE, Duan CA, Etuma M, Hand A, Locklear MN, Whitmire M Initial subjective reward: Single exposure conditioned place preference to alcohol in mice (Frontiers in Neuroscience 04 November 2014 | doi: 10.3389/fnins.2014.00345.

Nentwig TN, Myers KP, Grisel JE (2017). Initial subjective reward to alcohol in Sprague-Dawley rats. *Alcohol, 58*, 19-22.

Nentwig TN, Wilson DE, Rhinehart EM, Grisel JE (2018) Sex differences in binge-like EtOH drinking, corticotropin releasing hormone, and cortiscosterone: Effects of β-endorphin *Addiction Biology*, 24:447-457.

BOOK CHAPTERS & REVIEWS (Selected)

Grisel JE and Crabbe JC. Quantitative Trait Loci (Gene Mapping Animal Methods), For *Alcohol Health and Research World*, The Genetics of Alcoholism. 19(3):220-227, 1995.

Grisel JE and Mogil JS Effects of supraspinal orphanin FQ/nociceptin. (2000) *Peptides* 21:1037-1045.

Grisel JE QTL Analysis (2000) *Alcohol Health and Research World*, Animal Models in Alcohol Research, 24:169-174.

Grisel JE and Low MJ (2000) Increased Ethanol Administration in b-Endorphin Deficient Mice. National Institutes of Health Publication, U.S. Department of Health and Human Services, NIAAA, 35:203-210.

Nentwig TN & Grisel JE (2019) Sex, stress, and neuropeptides interact to influence alcohol consumption. In: Neuroscience of Alcohol, Elsevier Press, pp 315-323. https://doi.org/10.1016/B978-0-12-813125-1.00033-7

BOOKS

Grisel, JE (2019) Never Enough: The Neuroscience and Experience of Addiction. New York, NY: Doubleday.

PODCASTS, RADIO & VIDEO

Pot Holes, May 25, 2018 *Washington Post*

What makes Opiates so Addictive? *Psychology Today*, October 9, 2018

The Evolutionary Advantages of an Addictive Personality, *Scientific American*, January 21, 2019

This Is Why Giving Up on Weed After Years of Smoking Can Feel So Miserable, *Men's Health*, February 7, 2019

A Neuroscientist Explores the Biology of Addiction in 'Never Enough'. Fresh Air with Terry Gross, NPR, February 12, 2019 https://www.npr.org/sections/health-shots/2019/02/12/693814827/a-neuroscientist-explores-the-biology-of-addiction-in-never-enough

Q&A with Judith Grisel, author of Never Enough. Science Magazine, February 21, 2019 https://blogs.sciencemag.org/books/2019/02/21/never-enough/

Can we all chill out about cannabis? Not quite yet, *The Guardian*, March 24, 2019

The Power of Addiction: Zachary Quinto + Judith Grisel. The Rubin Museum, April 23, 2019 https://www.youtube.com/watch?v=WV9pmpl8M2Q

From Giving In to Giving Up: A Neuroscientist's Journey from Addiction to Recovery. Innovation Hub, WGBH & PRI, May 17, 2019 http://blogs.wgbh.org/innovation-hub/2019/5/17/giving-giving-neuroscientists-journey-addiction-recovery/

Judith Grisel, PhD

By the time she was 23, Judy Grisel had been kicked out of three schools, was under investigation by the DEA, intermittently homeless, had contracted Hepatitis C by sharing needles, and was spiritually, emotionally, financially, socially and physically bankrupt. Today she is a professor at Bucknell, an accomplished neuroscience researcher who holds a DEA license, and an active member of the recovery community.
There is hope for full recovery.

Laws of psychopharmacology

I. **All drugs work by changing the rate of what is already going on**
II. **All drugs have side effects**
III. **If a drug produces its effects by altering brain activity, the brain will counteract the drug by opposing the neural activity and producing the opposite behavioral effects**

Explication
Narcotics mimic opioid neurotransmitters by acting at a shared neural address to produce the same effects (Axiom I). That is, all narcotics interact with opiate receptors, which are brain structures produced to respond to opioid transmitters, like endorphins. This large family of neurotransmitters plays critical roles in regulating pain, stress, mood, feeding, sex, arousal, parenting and other social interactions like play and bonding.

Unlike opioid transmitters which are synthesized and released in small quantities, and in discrete locations depending upon natural demands, opiate drugs flood the whole brain to activate receptors involved in all of these tasks. They are also typically present in much higher concentrations than neurotransmitters, and for this reason drugs have side effects.

The third axiom is the most important for understanding treatment and recovery, because it explains how and why addiction occurs. Chronic drug use imposes a persistent signature on brain activity, but such a state is contrary to the brain's business of detecting and responding to the world around us, so **the brain adapts to the drug's presence by compensating for it.**

The effects of brain adaptation are tolerance, dependence and craving—all hallmarks of addiction. As the brain counteracts a drug's effects, more drug is required to produce the same feeling (tolerance). The adapted or tolerant state isn't terrible, as long as an addict doesn't run out of money or drug, but when the drug is no longer around, the user experiences withdrawal.

Withdrawal is always the opposite of the drugged state. Opiates produce euphoria, sedation, analgesia, and constipation (among other things). Withdrawal is characterized by dysphoria, agitation, pain and diarrhea (among other things). Because of this, the user craves the drug—and is willing to sacrifice time, relationships, money, employment, and even life, to keep the brain bathed in the substance.

Recovery occurs as the brain re-adapts to the absence of the drug, by returning neural structures and activity toward the nascent state, so that the user is no longer tolerant or dependent. Like addiction, recovery is graded—developing over time and due to neural changes (i.e., plasticity).

In general, the longer the person has been using, and the higher the dose they have been administering, the deeper the addiction/adaptation.

In addition, cues in the environment that have been associated with the drug elicit the brain's adaptive response so that in addition to the presence of the drug, cash, a spoon, dealer, or using buddies, time of day or location on the street, may all produce sudden and intense craving, and lead to relapse. This takes time and abstinence to unlearn.

In fact, environmental triggers are a primary cause of relapse. The other major causes are stress, and a 'taste' of any addictive substance, because this substance also elevates the neutral feeling state to provoke an opponent process.

Suboxone is an addictive narcotic. Although it is less effective at activating opiate receptors than street drugs, it still does so, and is therefore still counteracted by the brain. **When used as a short-term bridge to mitigate withdrawal during the initial phases of brain re-adaptation, it can be very helpful. But long-term use perpetuates the very state (opiate addiction) is it designed to treat.**

The goal of treatment should be to assist someone in achieving and maintaining abstinence. Early on, symptoms of withdrawal are intense, and it is very hard to resist the lure of relapse. Buprenorphine, the "active ingredient" of **Suboxone, will mute withdrawal by substituting for other opiate drugs**. Ideally, in the context of in-patient treatment, the dose of suboxone will be titrated down as alternative strategies for coping with discomfort are developed, and the discomfort caused by withdrawal is lessened. In the vast majority of cases, titration should occur over a period of weeks to months, depending upon the length and intensity of the addiction.

Maintaining a patient on Suboxone for more than 90-180 days reflects a scientific and ethical failing that sells the addicts, as well as their families and communities, short. **Full recovery is possible with adequate support** as the brain will re-adapt to the changes wrought by opiate addiction. Therefore, our mutual **efforts should be focused on facilitating abstinence** and federal funds should be used as much as possible to support addicts' recovery rather than pharmaceutical industry profits.

Please feel free to write or call with questions or comments to Professor Grisel at j.grisel@bucknell.edu or 570.577.1671