PROFILES

In deep water with Gül Dölen

BY **PETER HESS**

3 AUGUST 2022

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As a child visiting her grandparents in Turkey, Gül Dölen was terrified to swim in the Mediterranean. She could see through the clear water all the way to the bottom, where scores of sea urchins lived. “I was like, ‘I'm not gonna go in that water; those spiky things are gonna hurt me,’” she recalls. Her grandmother, a zoologist and high school biology teacher, knew how to transform Dölen’s fear: She plucked one of the spiny echinoderms out of the water and dissected it right there on the beach. She showed her 8-year-old granddaughter its mouth, its little teeth, its stomach.

“I wasn’t scared anymore,” Dölen says. “I was just curious.”

Dölen’s office decor at Johns Hopkins University in Baltimore, Maryland, where she is associate professor of neuroscience, recalls that teachable moment. Sea urchin skeletons line the long windowsill, alongside snail shells and an ammonite fossil — even a preserved octopus. But there are also items that hint at her more recent work, including Mayan stone mushroom sculptures, a grinning ceramic peyote cactus and a framed photograph of Dölen with the late chemist Alexander Shulgin, who invented and self-assayed hundreds of psychedelic compounds. Her lab walls bear images by Alex Grey, the psychedelic artist whose work has been associated with the progressive-rock band Tool.

The decor reflects where Dölen’s mind is these days: deep in the ocean, with its weird and wild creatures, and focused on the healing power of psychedelics. But her lab is also upending long-held scientific views of the brain, on a mission to improve quality of life for autistic people and those with neurological conditions.

Yet, as recently as 2018, Dölen was thinking about quitting science. For years prior, she had gone all in on her career, following a path familiar to many researchers. As an M.D./Ph.D. student in **Mark Bear**'s lab, first at Brown University in Providence, Rhode Island, and then at the Massachusetts Institute of Technology in Cambridge, Dölen arrived so full of new research ideas that Bear's main goal was to rein her in; he recalls telling her to "narrow your worldview a little bit, and try to pick something we can make some progress on." She began work on **fragile X syndrome** in mice. The syndrome arises from a mutation in the gene FMR1 and is a leading genetic cause of autism. Of the multiple publications Dölen and Bear co-authored on the topic, perhaps the most significant was a 2007 **paper** in *Neuron* demonstrating that the brains of mice with half the normal level of FMRP (the protein encoded by FMR1) have overactive synaptic plasticity, forming too many connections between neurons. Reducing the amount of the protein mGluR5 in mice helped level out overactive signaling in their brains, primarily correcting the synaptic plasticity issue. This singled out mGluR5 as a treatment target for fragile X syndrome.

During this time, Dölen's perspective on neuroscience began to shift. As a neuroscientist working with mice, she took consistent control of their lives — housing, food, cagemates, and even the lengths of day and night — so she could monitor their core brain mechanisms. But once a month she visited the genetics clinic at Massachusetts General Hospital, where she watched clinicians work with people who had autism, fragile X syndrome or a neuropsychiatric condition. She observed that the developmental trajectory for an autistic person living with 10 people in a two-bedroom apartment was different from an autistic person living in the country and receiving plenty of personalized care. This was a key realization. "So much of what makes human behavior interesting is not the stuff that we're born with," she says. "It's the stuff that we're born ready to learn — and in cases like autism, born unable to learn."

From there, Dölen joined the lab of **Robert Malenka** as a postdoctoral researcher in 2009. Malenka is professor of psychiatry and behavioral sciences at Stanford University in California, and at the time his lab was focused on the mesolimbic reward pathway, a brain circuit involved in motivation. Malenka was investigating how that circuitry is implicated in depression and addiction, and in particular the role of the neurotransmitter dopamine, but Dölen thought perhaps the social hormone oxytocin could be important to this pathway in mice. Malenka was not optimistic about the project's prospects, and he gave her six months to generate meaningful data.

"It was a little bit of a dare," Dölen says.

She took him up on it and found that not only are oxytocin receptors present in the mouse nucleus accumbens (part of the mesolimbic pathway), but also that they are involved in peer-to-peer social reward behavior in mice. Perhaps most surprisingly, she demonstrated that oxytocin controls the release of the brain chemical that moderates this relationship: serotonin. The **results** appeared in *Nature* in 2013.

This finding boosted Dölen's career. She moved to Baltimore and started her own lab at Johns

Hopkins University. Her newfound autonomy was both exhilarating and scary, and she quickly secured three private foundation grants, including a prestigious **Searle Scholarship**, to study autism via the brain circuitry of social reward — the positive feelings that motivate people and animals to be social. But the bigger money and recognition of National Institutes of Health (NIH) research grants proved more elusive. Her department and the university tweaked budgets to help keep her staff intact and the lab running, which felt “wonderful, on one hand,” she says, but “on the other hand, it also felt like, God, I’m an immigrant — we don’t rack up credit card debt.” She wondered how she could really be perceived as a leader if she couldn’t financially stabilize her team.

When Dölen reached her 10th NIH rejection, she began to fear she might not make it as a lab head, or even as a scientist. Her outside-the-box thinking had yielded impactful findings during her graduate and postdoc years, but her approach didn’t seem to fly with the NIH, and she felt the mounting pressure to prove that she could run a world-class lab. “Even if the department isn’t literally putting pressure on you to get it done or get out, it’s implied,” she says.

Grant rejections are part of doing science, and the need to chase money for research can be distressing. This is a feeling Malenka is familiar with. “I think the challenge of getting and maintaining grant support is the major reason investigators leave academia,” he says. Something similar was happening to Dölen. Her confidence was beginning to wane, and she wondered if she knew how to come up with meaningful projects, or if she could generate evidence to support her ideas. She wondered if her work had the potential to make an impact. Finally, she began to wonder if she still loved science.

“The transition from postdoc to [principal investigator] is very challenging,” Bear says. “An entirely new skill set needs to be mastered, particularly multi-tasking, and the first grant review is usually a bitter pill to swallow."

Bear gave her a pep talk at the time, but ultimately it was a road Dölen had to walk herself. Her fears persisted, and her grant proposals became more conservative to fit with what the NIH seemed to want. She felt the joy and curiosity that had initially attracted her to science slipping away. If this was going to be her career — disappointing, stifling and frustrating — then she should have chosen a job with more free time and a 9-to-5 schedule.

She also began to feel resentful. She was a woman living on her own, whereas her male colleagues seemed to have the benefit of spousal support for their long hours. She also had no children and found that she was the de facto dinner host for visiting scientists — as if she had nothing waiting for her at home. In the face of her growing NIH grant rejections, she felt a creeping suspicion that her ambitious ideas would not be so uniformly dismissed if she were a man, that she would not have to overcome such a large credibility gap.

Dölen fell into a depression that extended beyond the lab. She stopped doing the things that brought her joy outside of work: going to jazz concerts, taking long walks in the woods. And her dimmed spark made it even harder to keep pushing at work.

When she'd been in Bear's lab at MIT, he had stressed the importance of science being fun. "If you lose sight of the fun in science, it's hardly worth continuing," he used to say. Dölen decided that if she was indeed going to give up a life of science, she would go out on her own terms. She would do one final project — a fun one, just to see what would happen, and it would have only a tenuous relationship to everything else she had been studying.

The idea was this: Dölen wondered whether octopuses would make friends while on ecstasy.

She had read a 2015 **paper** about the octopus genome, which got her wondering whether serotonin signaling in octopus and human brains share any similarities — even though the two species' last common ancestor lived hundreds of millions of years ago. She got in touch with **Eric Edsinger**, who had worked on the paper as a postdoctoral researcher at Woods Hole Oceanographic Institution in Falmouth, Massachusetts. And as luck had it, Woods Hole had seven of the animals and was willing to lend them out.

Woods Hole shipped the octopuses down, and Dölen hosted Edsinger in Baltimore, bestowing upon him an air mattress in her living room. She sent her students and postdocs home for the week, and Dölen and Edsinger played mad scientist, toiling in the lab from early morning until late at night, breaking only for coffee or food. Using Edsinger's team's octopus genome, they found that octopuses have genes that encode a serotonin transporter, the protein whose response to MDMA likely leads to the psychedelic drug's prosocial effects in people.

Bathing the octopuses in a solution of MDMA, they found that the psychedelic drug seemed to make the usually solitary animals interested in socializing with other members of their species. This finding indicated that the octopus, whose brain structure is nothing like a mammal's, has a serotonin system in its brain that plays an important role in social interaction — just as humans have.

Dölen was shaken by the finding. Conventional neuroscience wisdom says that brain structure is what matters when it comes to translating animal findings to humans — if MDMA exerts its effects by way of the **amygdala in rats**, for instance, then it probably affects the **human amygdala**, too. But an octopus doesn't have an amygdala. It doesn't even have a cerebral cortex. It has one central donut-shaped brain in its head and one subordinate 'mini-brain' in each of its eight legs. If Dölen and Edsinger's results were reliable, they suggested that compounds such as MDMA were acting on a cellular level, not a structural level. "It challenges not a specific result, but a whole framework of how to approach how to understand the brain," Dölen says.

The **paper** was published in September 2018, and it immediately got attention. Popular news outlets **covered it**, late-night comedians joked about it, and academics paid attention, too; it has been **cited 49 times**, according to Altmetric. But what mattered to Dölen was that it got her excited about science again.

“It kind of brought me back,” she says. “I had spent three years feeling like I had a boot on my chest, and when the octopus paper came out, instead of an elephant wearing that boot, it was a horse.”

While the octopus study was in progress, Dölen began to build on what she had learned, investigating a potential role for MDMA as a therapeutic for people with autism. To this end, she used an assessment of social-reward learning to demonstrate that MDMA, through its effects on oxytocin, can **reopen the critical period** for social-reward learning in mice. Scientists long assumed that any compound powerful enough to reopen a critical period, the timespan when the brain’s connections can reshape in response to learning, would wreak havoc on the brain, either causing seizures or amnesia. But now she had done it: Her work showed that adult mice, which are typically too old to learn social reward, suddenly became open to it after treatment with MDMA. The **paper** appeared in *Nature* in 2019.

After that success, she began to suspect that using psychedelics to reopen a critical period could be the missing piece in other areas of study. Though drugs targeting mGluR5 have been investigated in clinical trials, they have not yet **yielded the results** researchers had hoped for. Dölen remains confident that mGluR5 might be a treatment for fragile X syndrome, especially if MDMA is included with the therapy to prime trial participants to respond. And in other work, she and her team are exploring whether classic psychedelics such as psilocybin and LSD can have similar effects. She also suspects that other critical periods, such as that for stroke recovery, can be reopened by this class of drugs, which would be a massive scientific breakthrough.

During her slump, Dölen had slid into a conservative approach to science. The octopus breakthrough demonstrated to her the power of questioning conventional thinking around brain research. Since then, she has secured three NIH grants, and now, as the self-styled creative director of her lab, the conservative bent that dampened her research questions is nowhere to be found.

This creative, elegant approach was apparent in Dölen’s previous work, says **Catherine Dulac**, professor of molecular and cellular biology at Harvard University, who has known her since the 2013 *Nature* paper came out. In that one paper, Dölen had brought together three different circuit components in a way that nobody had before, Dulac says: the nucleus accumbens that regulates reward, serotonin that regulates the nucleus accumbens and oxytocin that regulates it all at the synaptic level.

“She’s a little bit like an artist,” Dulac says. “It’s great to have somebody like this in the field.”

Theory of mind is the idea that a person or animal can attribute to another individual a state of mind different from one’s own. Impairment in **theory of mind** was once thought to be a core autism trait. That idea has mostly fallen out of favor, but Dölen thinks that studying it in the octopus has important implications for our understanding of how theory of mind evolved in the first place.

Many suspect it arose from social living, where animals watch and learn from one another, but it also exists in the solitary pygmy zebra octopus. The animal uses **theory of mind to hunt**, tailoring its approach based on the type of prey: attacking directly from behind for crabs, for instance, or setting a trap for quick shrimp. For the pygmy zebra octopus, theory of mind seems to have “evolved out of predatory rather than social-selection pressure,” she says.

It was the neuroscientific and philosophical questions around theory of mind that initially got Dölen interested in autism, and her work with the octopus reinvigorated her interest in psychedelic therapies. It also turned her career around. The fact that the octopus exhibits theory of mind is just one more thing Dölen loves about these asocial creatures with nine brains. Her work is once more bringing her happiness.

“Part of that feeling of joy is that you can see all the connections again,” she says. “When you feel joyful, when you feel like you’re participating in science in a curiosity-based, ‘let’s see where this goes’ thing, then suddenly all of the different connections become obvious.”

Cite this article: https://doi.org/10.53053/BKRC2077