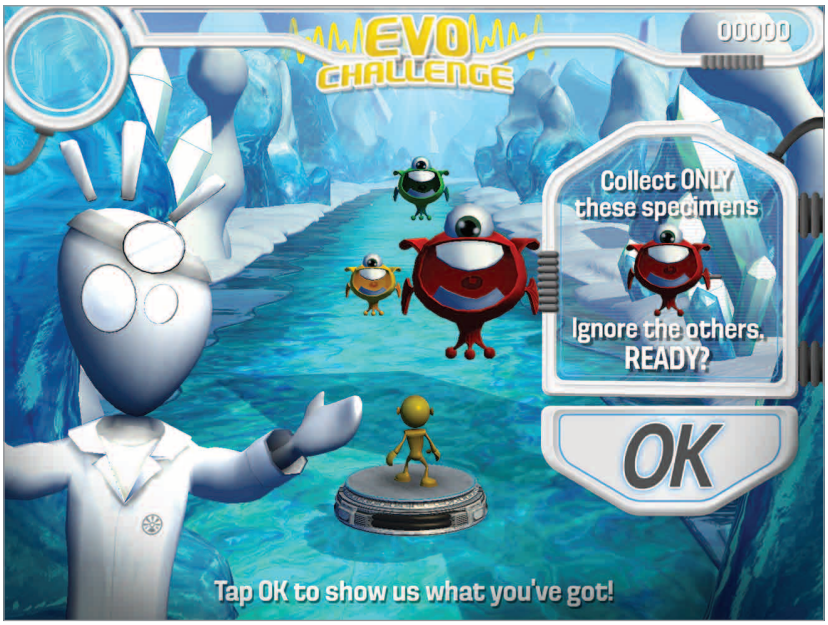
Medical News & Perspectives

Adam Gazzaley, MD, PhD: Developing Prescribable Video Games

Jennifer Abbasi



Akili Interactive

About a decade ago, Adam Gazzaley, MD, PhD, became frustrated with studying and reporting what he calls "the bad news": how our brains change as we get older, making us more sensitive to the pitfalls of distraction and multitasking. The University of California, San Francisco (UCSF) cognitive neuroscientist began seeking a novel approach to improve these areas of cognitive control, starting in older adults.

Author Audio Interview

That's how NeuroRacer was born. The video game–like therapy he developed forced the brain to multitask in an ever-evolving challenge—mental gymnastics that he hypothesized would translate into improved attention and working memory.

Indeed, a study involving adults 60 to 85 years old showed that NeuroRacer durably improved multitasking and cognitive control, landing it on the cover of *Nature* in September 2013. These findings helped Gazzaley launch his own brain research center and technology incubator at UCSF, which he dubbed Neuroscape.

By then, he had patented the treatment embedded in NeuroRacer and co-launched Akili Interactive, a health care company focused on an entirely new form of medicine: prescription digital therapeutics.

EVO, a video game treatment for pediatric attention-deficit/hyperactivity disorder (ADHD) that's based on NeuroRacer, could be the first product to come of it. As Gazzaley explains it, EVO is the "pill" that delivers AKL-T01, the technical name for Akili's lead investigational therapy.

In December, Akili announced that AKL-T01 had reached its primary efficacy end point, a change in the Attention Performance Index, in a multicenter, randomized, phase 3 trial involving 348 children and adolescents with ADHD. Soon, the company will submit it to the US Food and Drug Administration (FDA) for regulatory approval as a medical device.

If approved, Gazzaley says AKL-T01, potentially marketed as EVO, will be the first nondrug prescription therapy for ADHD, not to mention the first-ever prescribable video game. Another version of EVO, AKL-T02, is in early trials for comorbid ADHD in children with autism.

Gazzaley, who is a professor of neurology, physiology, and psychiatry at UCSF—and a lifelong gamer—recently spoke with *JAMA* about digital medicines for the brain.

JAMA: EVO has its beginnings in a video game you developed called NeuroRacer. Tell us that origin story.

DR GAZZALEY: In 2008, I came up with the idea of trying to develop an interactive media experience to challenge the brain in a very targeted and personalized way to improve function in the domains that we see decline with aging, including attention and

working memory. Friends of mine who worked at LucasArts volunteered their time and helped us build this game, which we call a closed-loop video game. As you play it, the game software is reading out your performance metrics and then challenging you appropriately based on your abilities. It took us almost a year to create NeuroRacer and to pilot it before we began a research study.

JAMA: What did you learn?

DR GAZZALEY: [Older players] dramatically improve their ability to multitask, reaching the level of a 20-year-old. But what was most exciting was that we were able to improve not just their ability to multitask in the game but [also during] independent tests of their sustained attention abilities and their working memory for faces. Very different from the game environment.

JAMA: How did you go from NeuroRacer to EVO?

DR GAZZALEY: I started Akili Interactive with friends from the video game world as well as a group in Boston that was investing in health care startups. Akili took an exclusive license to the patent behind NeuroRacer and then proceeded to build a much better video game called EVO, which stands for Project Evolution. EVO brings on higher levels of art, music, story, and rewards—all things that we know are critical to have our participants engage deeply in game play.

JAMA: Who is EVO for?

DR GAZZALEY: EVO and NeuroRacer were really designed to improve attention abilities without being targeted at a specific population. As we know, for pretty much every clinical population that has impairments in cognition—posttraumatic stress disorder, traumatic brain injury, dementia, ADHD—we find that there are deficits in attention abilities. Akili is pursuing, in collaboration with academic universities, clinical trials across all these clinical entities. We have completed one clinical phase 3 trial targeting improvement in attention in children who are diagnosed with ADHD.

JAMA: Tell us about the game.

DR GAZZALEY: When a player is engaged in EVO, they are navigating an alien creature down a river through multiple different worlds with obstacles in the way. That demands a lot of attention. While that is going on, there's another challenge to collect birds and fish in this alien world. So they are tapping on the screen to collect and they are using the accelerometer to navigate, and both of these 2 challenges are getting more difficult as they get better. Their performance is being judged not on how they are doing on these tasks independently, but how they are doing on both of them at the same time.

JAMA: What cognitive systems does this therapy modulate?

DR GAZZALEY: We found through our research that this engages the prefrontal cortex and its network with the rest of the brain. These areas and networks are engaged in all challenges of cognitive control. So sustaining, selecting, and switching attention are very prominent in game play. Those are the systems that we are trying to put pressure on through the closed-loop system of activity and target selectively through the gameplay mechanics.

JAMA: In your recent phase 3 trial, AKL-T01 achieved its primary end point, which was a change in the Attention Performance Index in a task called the TOVA, or the Test of Variables of Attention. What does that mean?

DR GAZZALEY: The TOVA [an FDA-approved diagnostic test for ADHD] is a really boring test of attention that is hard for anyone to engage in, especially children with ADHD. You do it in a dark room. It's a black screen with just one white square that you have to respond to very rarely—so rare targets with very frequent distractors and no reward, no feedback. We find that [the children's] ability to perform in that context is significantly improved [after playing EVO] and not at all in the control group that was playing a different video game.

JAMA: For a range of subjective behavioral secondary outcome measures, like a change in some ADHD symptoms, there weren't statistically significant differences in improvement between groups. What does that tell you?

DR GAZZALEY: These were more typical behavioral measures based on parent self-report that are used in a lot of the current studies on stimulants. It's important to note that there was a statistically significant improvement on average from baseline to 1 month on these symptom metrics for both groups, and the study was not powered to detect a difference in these measures between groups. That said, we feel that the type of improvement that these children are experiencing with their attention abilities are not being adequately assessed with current self-report measures. A new frontier that we're excited about pursuing is to develop quantitative metrics of how attention is being deployed in the real world. And that will probably involve the use of technology.

JAMA: How could the improvements potentially translate to real-life outcomes?

DR GAZZALEY: As we proceed to deploying this game as a treatment of attention, once we have much larger numbers [of patients] we can look for the signals of impact in real life. How are they sustaining their attention in the context of situations that they find boring, which often includes the classroom and studying and reading?

JAMA: Okay, but why does a video game make sense for treating ADHD?

DR GAZZALEY: We have relied almost exclusively, certainly in ADHD, on pharmaceuticals that change neurotransmitter systems in general. But we have this other approach that we have engaged in for thousands of years: using interactive experiences to harness the brain's plasticity and improve its function. Very ancient approaches like meditation and mindfulness [practices] are based on this concept that if you challenge your brain through experience you can improve its performance. [However] they're not deliverable in a very reproducible manner.

What we are looking at here is a digital medicine that delivers an experiential treatment. The video game is the delivery system. In many ways, it's like the pill. The treatment itself is this targeted adaptive experience that we find is effectively delivered through video game mechanics. That's, in my mind, the most exciting breakthrough: [The technology] takes this ancient approach of experiential treatment and makes it deliverable, and consistently reproducible and testable in a randomized clinical trial.

JAMA: What about the concerns about the effects of screen time on kids' attention and cognition?

DR GAZZALEY: That has been a complicated story. [It's] really dependent on the content of the screen time. From my perspective, most of these children who were participants in the study already play video games. So, if anything, it's a displacement of some of the activities that they're already engaging in in their free time. The other really important factor is that we don't use [EVO] as an extended treatment.

JAMA: Assuming EVO is approved by the FDA, what will the dosing regimen be? And what platform will it be on?

DR GAZZALEY: Assuming EVO is approved, we will first be distributing it on tablets, although that could change to phones in the future. The dosing will be the same as was offered in the phase 3 trial: 5 days a week, approximately 30 minutes a day for 4 weeks. We will be exploring how long these effects last to determine [if or] when we have to boost with another dosage again. That's the subject of future studies.

JAMA: Do you see it as an alternative to medications or do you see them working hand in hand?

DR GAZZALEY: The approval that we are seeking will be for monotherapy. But, in reality, there is no reason to think that it might not interact in a positive way with other forms of treatments, like stimulants.

JAMA: How does Akili plan to make the game accessible to kids from different backgrounds?

DR GAZZALEY: Our goal is to have this reimbursable by insurance like so many other treatments are. We are proceeding aggressively with trying to accomplish that goal so that we can have this available for as many people as possible.

JAMA: What other digital medicines are in the works at Akili?

DR GAZZALEY: Akili is also looking at how this same type of treatment with some customizations might have benefits on attention outcomes in populations of individuals who have a diagnosis of depression, posttraumatic stress disorder, early dementia, both Parkinson and Alzheimer diseases, and multiple sclerosis. More clinical studies are coming online all the time.

JAMA: And what other types of conditions are you interested in at your research center, Neuroscape?

DR GAZZALEY: We've been focusing on trying to incubate new types of technology like EVO but that work on different cognitive systems and might have benefits across even a broader range of clinical populations. We have new games that take principles of concentrated meditation and bring that into a digital platform. And we are looking at new technologies like virtual reality to create more immersive environments that we think will lead to better benefits. At the most science fiction–sounding level, we are looking at brain stimulation during game play with both transcranial alternating current and direct current stimulation to see if we can boost the benefits that we are getting from game play alone.

JAMA: Do you see physicians being receptive to EVO and parents being interested in it as a new sort of treatment for ADHD?

DR GAZZALEY: I get emails every single day from parents who are frustrated with having only a pharmaceutical option to treat their children, and from physicians who are also frustrated with having a limited toolkit. So I see great enthusiasm, but I do know that this is a paradigm shift that has to occur. When I went to med school, there was a certain way of thinking about medicine, and it wasn't video games. ■

Note: Source references are available through embedded hyperlinks in the article text online.

Why Merkel Cell Cancer Is Garnering More Attention

Rebecca Voelker, MSJ

Michael Hori, MD, wasn't prepared for the pathologist's sense of urgency. A few days earlier, Hori had excised a red lump from his patient's leg and sent the tissue for analysis. "I thought I was dealing with basal cell carcinoma," said Hori, an internist at the University of Washington Valley Medical Center in Renton.

However, the pathologist's diagnosis was Merkel cell carcinoma—a far more worrying type of skin cancer. "He made the comment, 'I just want to impress upon you how serious this diagnosis is and how important it is to get [the patient] someplace where they really know what they're doing,' " Hori recalled.

Fortunately, Valley Medical is part of University of Washington Medicine where Paul Nghiem, MD, PhD, has pioneered Merkel cell carcinoma research and clinical care. As head of the Division of Dermatology, he treats patients and oversees a laboratory that investigates immunotherapy for Merkel cell cancer.

"Ideally, a patient needs to be seen once at least at an expert center," Nghiem said. About a dozen such centers are located in the United States, he noted. But many cases will get a first look in a primary care setting, like Hori's patient.

"The single most important decision a primary care [physician] could make about this cancer is whether to do the biopsy," Nghiem said.

Interest and Incidence on the Rise

Merkel cell carcinoma has attracted growing interest in recent years for several overlapping reasons: It's rare but on the rise, the cause has been linked with a virus, and immunotherapy appears promising for many patients.

In fact, the incidence is outpacing that of other cancers. Nghiem and his colleagues recently reported that from 2000 to 2013, solid cancers increased by 15%, melanoma by 57%, and Merkel cell carcinoma by 95%. The number of newly diagnosed US Merkel cell carcinoma cases is expected to increase from 2488 in 2013 to 2835 in 2020 and to 3284 in 2025.

"Each year we get more and more new consults," said Manisha Thakuria, MD, director of the Merkel Cell Carcinoma Center of Excellence at the Dana Farber Cancer Institute in Boston. "We're at about 70 new patients per year."