Digital Medicine an

An Interview with Adam Gazzaley

Interviewed by Meghan Miller, PhD

PHOTO CREDIT

ADAM GAZZALEY, MD, PhD, is a professor in the departments of neurology, physiology, and psychiatry at the University of California, San Francisco, as well as the executive director and founder of Neuroscape, an academic research center at UCSF. Gazzaley is also the cofounder and board member at Akili Interactive, a digital medicine company. We interviewed him in March about the state of the science of brain training in ADHD and Akili's plans to seek FDA approval for their ADHD treatment, AKL-T01.

Q: Tell me about your cognitive training program for ADHD. What cognitive domains does it target?

A: In 2013, my research team and I published a paper in *Nature* testing the effectiveness of our game, NeuroRacer. The study demonstrated that we can improve cognitive abilities outside of those targeted in the game itself in older adults, like attention and working memory. This study gave birth to Akili. We filed a patent on the methodology, or "active ingredients,"

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of the game, which UCSF owns, and Akili has an exclusive license to this patent. Unlike some of the "brain training" and "brain games" on the market, Akili is developing direct treatments for medical conditions with digital medicine that is delivered through an action video game.

Our new treatment for ADHD—AKL-T01 or "EVO"—incorporates rewards and challenges and uses the same core technology as NeuroRacer. We haven't yet put it on the market in the consumer space because it was important to undergo rigorous clinical evaluation to demonstrate its safety and efficacy. EVO recently underwent an independent Phase 3, double-blind, multi-site, randomized clinical trial led by Dr. Scott Kollins at Duke University. The treatment showed a significant improvement in the primary outcome of attention in children with ADHD compared to control. Based on these results, Akili is now filing the product with the FDA for clearance as a treatment for pediatric ADHD.

How have you established NeuroRacer's/EVO's effectiveness?

The validation process is multiple-stage. The first question is, "Is there something here?" Our academic research group at UCSF, Neuroscape, works on this, which typically takes a couple years. Then, Akili will undertake Phase 2 trials, which usually consist of smaller trials with a number of measures to see if it's worth moving forward with a larger Phase 3 trial. Akili runs these trials like drug trials with research groups who are independent from the company, and we pre-submit our plans and outcome measures to the FDA. Then, we will write peer-reviewed papers summarizing our research so that it is disseminated to other researchers and the public. When it's warranted, we'll move forward with submission to the FDA to seek approval.

How long do the effects last? How is sustainability factored in?

We don't yet have much long-term follow-up to assess how long the effects last. There is more work planned regarding who needs a second dose, what is minimal viable dose, etc.

One of the challenges that has come out of the cognitive training literature in ADHD is that it is difficult to effect generalizable change—that is, improvements in specific cognitive domains don't necessarily translate into changes in core ADHD symptoms. How do you think we can tackle this problem? Have you built things into your training program to address this and that differentiate it from other cognitive training programs?

Our interventions are differentiated by the target, by the delivery system, and by the level of validation. EVO targets attention, and we incorporate multiple streams of information and distractors and include adaptive algorithms that push the player to do multiple tasks at the same time as best they can. I think the video game delivery mechanism is important to the effects—we build in high levels of art, music, rewards, and story into a useable tablet format. Our games involve rapid, closed-loop adaptive systems so that they are always personalized to the individual playing and to their abilities in that moment.

We've also tested our games in rigorous randomized controlled trials across multiple sites, and we include secondary outcome measures to test whether we see improvement in tasks in different contexts, not just in game play. We also include some standard metrics, like rating scales from parents. But the field probably needs to develop better outcome measures for the types of cognitive changes being induced.

Tell me about your plans for FDA approval.

We are submitting for approval in the first half of 2018. We can't predict the exact timeline, but we hope that it will be granted by 2019.

Is there anything else you'd like to share with families or individuals with ADHD?

The time is ripe for us to get creative and innovative in developing new treatments. And we're hearing from families affected by ADHD that they are actively seeking new options. They may or may not displace current pharmaceuticals but can at least act in parallel to them. This could be a service to patients and families and to providers, providing them with more options to think about when treating someone. I'm optimistic for the future that we will have more opportunities to help people in ways that are personalized to them.

Meghan Miller, PhD, *is an assistant professor in the department of psychiatry and behavioral sciences and the MIND Institute at the University of California, Davis. Her research focuses on identifying the earliest behavioral manifestations of ADHD and autism spectrum disorder.*