ADAM GAZZALEY INTERVIEW PART TWO

Hello again, Ars Technica listeners. This is the second installment of a three-part interview with UCSF neuroscientist Adam Gazzaley, and his extraordinary work in developing the medical potential of video games.

If you haven't yet heard part one, there's a link on the page where this audioplayer is embedded, and I strongly suggest that you go back and listen to it before this one.

Before we get started, I'd like to echo yesterday's shout-out: Throughout October, Medium.com is running a series of essays that I've written on the subject of existential risk. Which is that perversely fascinating set of scenarios in which advances in science and technology could just lead to our annihilation.

I believe I have some novel and fresh arguments to add to the discussion on this topic. If this might interest you, please go to Medium.com/@RobReid. That's medium.com; then a slash, followed by the @ symbol; followed by RobReid. There's also a link on the webpage that's hosting this player.

And with that - back to my conversation with Adam Gazzaley.

TRANSITION MUSIC

Adam Gazzaley:	If you stimulate over your left motor cortex, your right finger will jump regardless of your desire. We used TMS for many years to understand the brain, there are also clinical tools for treatment of depression and other conditions that use TMS, we were very attracted to the idea of TACS and TDCS. TACS stands for transcranial alternating current stimulation, TDCS is transcranial direct current stimulation. And so what it is, it's electrical stimulation of the brain.
Rob Reid:	As opposed to magnetic.
Adam Gazzaley:	As opposed to magnetic, it's safer.
Rob Reid:	So it's [crosstalk 00:29:20] to TMS but it's using electricity instead of magnetic fields.
Adam Gazzaley:	It's using electricity directly.
Rob Reid:	Why is it safer? Is it gentler in some manner?
Adam Gazzaley:	It is.

Rob Reid: It is less of a flack.

Adam Gazzaley: It's not actually causing neurons to fire. It's changing what we call the resting membrane depolarization, the bath of ions surrounding your neurons, so basically what that means is that it's just making it more likely for the neurons to fire, but not actually causing-

Rob Reid: It's putting them in a state in which they're more inclined to do so on their own.

Adam Gazzaley: Exactly.

Rob Reid: And inevitably a higher percentage of them will as opposed to shoving them.

Adam Gazzaley: Exactly.

Rob Reid: Got it. And so it's tempting them to fire.

Adam Gazzaley: Yeah, so it's getting them-

Rob Reid: Rather than forcing.

Adam Gazzaley: Yeah, they're much more susceptible to firing when engaged and that's why we were attracted to the idea of using noninvasive brain stimulation like the two methods I told you, to enhance plasticity while someone's playing one of our games. So we wouldn't just do it and say, “Come back in a month,” our approach is to use it as an enhancing effect on what we're finding with the games alone.

Rob Reid: Enhancing plasticity, so if you zap somebody with TACS ... You call it TACS or TACS?

Adam Gazzaley: TACS.

Rob Reid: So you zap somebody with that and I assume that there's subtle differences between TACS and TDCS that are relatively expert slope stuff.

Adam Gazzaley: Not necessarily. DC is direct current, so it just is a shift of the polarization and AC is alternating current, so basically we get to stimulate at different frequencies. We like AC because our hypothesis is that if we stimulate the brain at a certain frequency like theta, we will target ... You can ...

Adam Gazzaley: [inaudible 00:31:00] like theta.

Rob Reid: Right.

Adam Gazzaley: We will target ... You could more selectively target the frequency.

Rob Reid: Target the frequency with A/C.

Adam Gazzaley: Exactly.

Rob Reid: So you're more inclined to use TAC-

Adam Gazzaley: Exactly.

Rob Reid: ... because of your interest in theta.

Adam Gazzaley: Exactly.

Rob Reid: Okay, good. That makes sense. So you would then actually trigger that. You would put the brain into a more likely to fire state, in a narrowed your geographic area, I assume? Or the whole damn brain?

Adam Gazzaley: No, it's not target. TMS, you could target a lot more precisely, down to the size of a dime. TACS, the electrical stimulation is more broad. But you could target the front left part of the brain.

Rob Reid: But a pretty big neighborhood.

Adam Gazzaley: It's pretty big.

Rob Reid: So you'll hit that button to make somebody more neuroplastic at a certain moment in the game?

Adam Gazzaley: Yeah, we usually do it during the whole game.

Rob Reid: Throughout the game.

Adam Gazzaley: Throughout the game play.

Rob Reid: So it's not surgical. It's more of a broad tool. But you would basically say if we hit this person with a frequency that is akin to this theta wave that we're trying to trigger while they're playing the game, there was a hypothesis that the neuroplasticity would stick more or be more powerful.

Adam Gazzaley: Exactly.

Rob Reid: And has that been borne out or is that something still under the research?

Adam Gazzaley: We just published a paper last week-

Rob Reid: Really?

Adam Gazzaley: ... showing that 20 year olds that play NeuroRacer while we stimulate their brain, the front part of their brain, with a theta frequency learn more rapidly than those that we don't do that for.

Rob Reid: And is that the first definitive proof you've gotten of this?

Adam Gazzaley: Well, other people and other scientists have shown as far-

Rob Reid: Similar things.

Adam Gazzaley: Similar things for other abilities.

Rob Reid: Got It.

Adam Gazzaley: But we were really excited about it. Because it now was enough evidence to lead us to go to the next step, which is to ask the question if older adults played NeuroRacer, like we did in our nature paper, with brain stimulation would they not just get better at the game would they have more transfer?

Rob Reid: Right. Yeah. To other skills, yeah.

Adam Gazzaley: And would they last longer?

Rob Reid: So that's the next study, do you think?

Adam Gazzaley: We're doing that now.

Rob Reid: You're doing that now?

Adam Gazzaley: That study is underway.

Rob Reid: Fantastic.

Adam Gazzaley: We started that study a couple of months ago.

Rob Reid: When are you going to have the results? I'm already fascinated.

Adam Gazzaley: Over a year to do that study. There are four different groups, and it's a big one. But we think it's really important, because it really advances this whole field of therapeutics to the next level to start thinking about combined approaches. So now someone, let's say they have a traumatic brain injury. They come into a clinic. They get a direct set of diagnostics. They get a game or a set of games that's targeting their cognitive limitations to optimize those abilities. And then we stimulate their brain during the process so that they can have effective and sustained recovery. We don't have anything like that right now. I mean, it's a tragedy.

Rob Reid: Yeah. I want to talk about the post NeuroRacer landscape. But first I want to spend just another moment on these three tools. And these are the big three. Is there anything really profoundly significant, foundational to your practice, that I'm missing that goes beyond MRI, EEG, TMS?

Adam Gazzaley: No. No. Those are the main neuro recording and stimulation tools that we use.

Rob Reid: Now are those things improving in a rapid and compounding way as so many things are in technology on their own sort of Moore's Law like curve? Or are they improving slowly? Or are they stagnant? I mean, if we look forward five, 10 years, can we anticipate MRIs that are so much more powerful or EEGs that are so much more powerful that we'll be able to peer into corners we can't even access now? Or is this more like ... It's kind of more like airplanes. They get a little bit better over time, but not crazy better.

Adam Gazzaley: MRI has not improved dramatically. I mean, they're getting better, but not exponentially. Not like what we're seeing in the consumer technology world.

Rob Reid: So it's inching ahead.

Adam Gazzaley: Yeah.

Rob Reid: Your MRI machines are not going to be obsolete anytime soon.

Adam Gazzaley: No. They last long periods of time, many, many years. I would say the thing that's most innovative in this field that's advancing it is the analytical side of it. How to use new techniques in deep learning and machine learning. And on the hardware side, I'd say almost the consumerization of it. How do you have a high fidelity, robust EEG recording with a mobile cap or that someone could use at home? Things like that are starting to get there. And that's really intriguing.

Rob Reid: So post NeuroRacer, that was a foundational study, got You on the cover of nature. Unbelievably cool. Things have continued to go forward on multiple fronts since then. Let's start by talking about what's going on in the lab post early NeuroRacer. You're now working with ... You've got lots of games that are targeting lots of different things. Why don't we just sort of talk through some of the many cool things that are going on here?

Adam Gazzaley: Sure. So it was transformational to us. It was very apparent to me as the director of the lab that everyone here wanted to do something along these lines. Once you watch the scientist sitting next to you not just get a nature paper, but do the type of work that might impact someone's life ...

Rob Reid: Right.

Adam Gazzaley: Not just report the news about how the brain works, but still do that. To be able to have both basic science contributions and what we think of as translational

science, to build things that might actually help someone, it's irresistible. And so sooner or later everyone here wanted to do things like that, and here at UCSF in our lab. And then our lab just got so big that now we became a center. So now we're NeuroScape, which was our transformation over this last year.

Rob Reid: So center is a big notch up.

Adam Gazzaley: Center is bigger because we are not just internally focused at doing our own work, but we're also very externally focused. We're a service across the entire university, and now even globally helping other labs use technology in the way we do. We're not just a research lab, which is another reason we became a center. We have an entire technology development team. So we have an interactive media director. We build our own games. We are interested not just in video games, although that remains our core, but all the other types of technology that satellite around them. So virtual reality, augmented reality, motion capture, physiological devices that are wearables. How do all of this technology, most of it entertainment directed or a communication media in the consumer space ... How do we take it into our center and develop in a customized way to use these tools to improve brain function? And so that's sort of our transformation into NeuroScape. What we say is bridging technology and neuroscience for these positive benefits. But what we spend most of our time on is building video games.

Rob Reid: So let's talk about some of the games that are in the lab now and what muscles they're trying to build and flex, and what the game play is like and so forth.

Adam Gazzaley: We'll do a relatively quick run through, because we have a lot of games. But I'll tell you about some of them. So Body Brain Trainer, also known as BBT, is a game that targets both physical and cognitive fitness at the same time. The hypothesis is that if you play a game that you're embodied in and it is not just your eyeballs and fingers but your whole body, you will have more benefits cognitively than if you play that same game on a tablet.

Rob Reid: Because you're moving your whole body through space. So you're using far more networks in your brain.

Adam Gazzaley: You're using more networks, and you also have the physical fitness benefits. There's data that shows that physical fitness, even independent of cognitive challenge, has benefits on brain health through things like BDNF, which is a growth factor and neurogenesis on the brain. So you have the combined physical fitness and cognitive fitness. That hasn't really been done yet.

Rob Reid: And this is a VR game. Correct?

Adam Gazzaley: No, this is a motion capture game.

Rob Reid: This is motion capture. Yeah.

Adam Gazzaley: So we probably will build a VR version. But right now Body Brain Trainer is played using the Kinect.

Rob Reid: Right. Yeah.

Adam Gazzaley: So you stand in front of a big screen. Your body is being tracked using a consumer device that's part of the Microsoft Xbox One gaming system. So we always favor those types of devices. Because we don't want this to be an ivory tower experiment in a lab. We want this to be something that someone-

Rob Reid: Could be replicated.

Adam Gazzaley: ... could do at home, that's accessible and so you play it. Now what makes BBT really unique is a couple things. First of all, it's really interesting to be cognitively and physically challenged at the same time. Few people really reach that level. I'd say, like, professional athletes and dancers and people that drive themselves along both of those axes. But it's actually sort of hard to do them both at the same time. What's cool here is that the game mechanics drive you just to accomplish one goal, is driving you both physically and cognitively. But what makes BBT most unique is that in addition to the game being adaptive in its cognitive dimensions, meaning that as you focus better and are faster and more accurate, the cognitive challenges increase, which is true of all our games.

Rob Reid: Adaptive, therefore, is kind of a byword for it gets harder.

Adam Gazzaley: It gets harder relative to you getting better every single second. That is the common mechanic across all of our games. That's like, our special sauce. That's what we really pride ourselves on, is creating these adaptive algorithms so that the game is incredibly personalized to you in the moment. And we think that's-

Rob Reid: So there's no relaxing until the end of level six.

Adam Gazzaley: No, no. Well, we have to bring on breaks pretty frequently. Because it is like interval training. Even just cognitively alone, it's like interval training. You will fatigue and need to be restored. But what makes BBT unique is that we have the cognitive activity, but you also wear a heart rate monitor when you play BBT. And so what we do before you play BBT is we use a tool called the V02 Max, which is the industry standard to find out at what heart rate you as an individual should be a challenging yourself to get maximum physical fitness benefit. So when you're playing BBT, you're getting the cognitive challenge. It's adaptive, so it's getting harder as you get better. But we're recording your heart rate during game play. So if your heart rate is below goal ... Let's say it's 100 beats per minute and we want it at 120 to 140. The game will know that in real time and increase the amplitude of the movements that are required to play the game, driving your heart rate up. If your heart rate goes too high, the game, the game detects that and pulls back. And so that's an example of how we use adaptive

algorithms across both physical and cognitive domains to personalize it to you on both dimensions.

Rob Reid: So you're always on the cusp of just detonating, but never quite getting there.

Adam Gazzaley: You're always pushed right to the limit that you're not so frustrated that you walk away-

Rob Reid: That you're annoyed. Yeah.

Adam Gazzaley: ... and that you're not so bored. That is the really a critical element of all of our game development. And it's interesting. Because consumer games don't really develop adaptivity at that level. You level up in the game, but it might take days. On day one, it might just be too hard and you hate the game. Our games are always figuring out where you are in the moment and giving you a personalized experience just to make it maximally fun. And we believe to maximally harness the brain's plasticity.

Rob Reid: Now another game that I think people are ... I'm not sure if I'd even call it a game, but another software experience that you guys are developing here has to do with meditation, which probably people will find interesting as meditation is obviously big right now. Let's talk about MediTrain for a moment.

Adam Gazzaley: Yeah. So MediTrain is a tablet game. It's not as gamified is most. But it uses the principles of concentrative meditation and integrates them with our mechanics of adaptivity and feedback. And so how you play Mediterranean is a, you take the tablet. You first go through a whole sequence of instructions where our partner in crime here, Jack Kornfield, who's a mindfulness expert, teaches you of what it means to focus on your breath, to be aware of your mind wandering, and to return your attention to your breath. So very traditional ancient practices of mindfulness that you engage in.

Adam Gazzaley: But what we ask you to do in MediTrain is just to do it for 10 seconds. Not to just sit in a in a meditation retreat and try to do it for an hour and fail and not know if you're doing it well or not. But just 10 seconds. And you could play the game with your eyes closed. At the end of the 10 seconds you hear a chime. And you're cued to either press the tablet anywhere with your right thumb if you were successful, if you held your attention to your breath. Or with your left thumb if you didn't, if you mind wandered.

Rob Reid: So you're only honor system, so to speak.

Adam Gazzaley: Yeah. I mean, it's an introspection game You have no reason to do it if you're not trying to figure out how your own brain works, and improve it. But yes, it requires introspection. We're working on an EEG version that you won't have to do that.

Rob Reid: I was about to ask.

Adam Gazzaley: We're not quite there yet. No one's ever done that.

Rob Reid: Really?

Adam Gazzaley: Yes. No one's ever done that.

Rob Reid: It would seem like a natural thing to do because the EEG will ... I mean, do you even know what you'd want to track with EEG?

Adam Gazzaley: We have ideas. It's just very subtle. A distraction event that occurs when you're focusing on your breath is pretty subtle in your brain.

Rob Reid: Hard to detect with the EEG.

Adam Gazzaley: It's hard to detect what the EEG, which is not a very sensitive measure in the first place, given that there's a lot of noise in the brain. So to get back to the mechanics, if you said yes I was successful. I held my attention on my breath for 10 seconds and it didn't wander. Then on your next session you would have more time. If you said no, my mind wandered, then you would have less time. And so over the course of a half an hour, the game is titrating how long you can go with focusing on your breath. So the average person, non-meditator, that comes into this lab to play this game, how long do you think that they are able to successfully hold their breath after 30 minutes of sort of querying?

Rob Reid: Again, going by the honor system. So sort of self reported, in their own perception of it. Gosh. I mean they come in and you're starting them at 10 seconds, you said?

Adam Gazzaley: Mm-hmm (affirmative).

Rob Reid: So over 30 minutes how much will they improve if they're starting at 10 seconds?? Do they generally succeed at 10 seconds? Is that like, a bunny slope, like everybody does 10 seconds? Or is 10 seconds a challenge for your typical person?

Adam Gazzaley: On average, most people finish. And they threshold between like, 10 and 15 seconds.

Rob Reid: At the end of a half hour of training?

Adam Gazzaley: Yeah. That's where it thresholds.

Rob Reid: Okay, got it.

Adam Gazzaley: They might go up. They drop back down. That's where they are.

Rob Reid: But it's pretty short.

Adam Gazzaley: It's very short. It's less than 20 seconds.

Rob Reid: These are the novices on day one.

Adam Gazzaley: Novices on day one.

Rob Reid: Yeah.

Adam Gazzaley: After six weeks of playing MediTrain most people are over two minutes, some people over three minutes.

Rob Reid: And that's the daily for a half hour? Or three times?

Adam Gazzaley: It's five times a week. It starts 20 minutes, then goes 25, and then 30 minutes as you move from every two week period. So it sort of eases you in. And you get feedback every day. You see a graph of how long you've achieved. Now the question, and that's what we're studying in the lab, is what is the impact of that on your cognition, on your stress, on your brain activity? And we have data that's unpublished, so I won't go into it in great detail here. We still have to put this story together, write the paper, get it peer reviewed. But what we are already seeing in 20 year olds is that playing MediTrain for six weeks and can improve working memory abilities, holding information in mind, which is amazing. Because that's not what we're studying, but it isn't internal attention process. And we're even seeing volumetric changes on MRI in the frontal Cortex of 20 year olds playing MediTrain.

Rob Reid: Wow.

Adam Gazzaley: So some of this we've seen with real world meditation practices. But the fact that you could see it on an app that doesn't have a practitioner training you in front of the room is really exciting.

Rob Reid: And again, you have this replicability and this measurability that you get. I mean, meditation itself is an experience. You in a sense, have gamified if not the traditional sense of the word gamify, but you have introduced a game like mechanic, an almost quote, unquote "scoring system" that allows you-

Adam Gazzaley: Scoring reward system.

Rob Reid: ... to do dosage-

Adam Gazzaley: Exactly.

Rob Reid: ... and replication and standardization.

Adam Gazzaley: There's that. And then there's the accessibility.

Rob Reid: Yes.

Adam Gazzaley: I mean, not everyone has a great retreat. Since it's played on an iPad, we could distribute this game mobily. We could distribute this game globally.

Rob Reid: Yeah.

Adam Gazzaley: Right? And we actually just are completing a study now of foster care children in India that have played MediTrain to improve their attention ability. It's just a clear indication of you can't get doctors everyone in this world like teachers, but pretty much everyone's gonna have a mobile ... It will be ubiquitous in the next--

Rob Reid: It will be in a period of years.

Adam Gazzaley: Yeah, exactly.

Rob Reid: In a period of years. So do you then give ... These 20 year olds that you gave this test to or you carried out this experiment with, do they have like a battery of neuro psych tests coming in and then another battery at the end to see where the improvements have been?

Adam Gazzaley: Same methodology that we describe with the nature paper. We do a deeper dive now. Now we have older adults, again healthy individuals above 60, playing MediTrain that are in trial right now at NeuroScape. And before and after they play they get an MRI scan. We do structural imaging, functional imaging. They get EEG. They do cognitive testing, they do stress testing. They take a device home to do sleep monitoring. We do blood work to look at telomere length and hormone levels and inflammatory markers. If we believe that it could be changed by this experience, we record it before and after.

Rob Reid: And so that before and after ... That is a huge battery of measurements that you're taking. That's before and after pretty much all of your games now? That's standard operating procedure?

Adam Gazzaley: It's getting there. Yeah.

Rob Reid: And what would that battery of tests, just out of curiosity ... I don't even if you have a sense for this. What would that cost at retail just to get all those telomere measures and-

Adam Gazzaley: I mean, it's just not accessible. I mean, even an MRI scan, you know, everyone's getting two MRIs, one and one after.

Rob Reid: And those probably are many, many hundreds if not thousands of dollars.

Adam Gazzaley: Yeah, thousands. I don't know of anyone that's done this deep of a dive into any intervention's outcomes. For us it's still step one. It's to say, is there a signal here? Is there a mechanism of action? And does this warrant the game leaving the lab, going out into the world of industry and companies, which we could talk about, and then going to the next level of validation where there's showed to actually have clinical efficacy?

Rob Reid: Which would be the world of the FDA. So let's talk about that. We talked about what's going on post NeuroRacer in your lab. The other major, major thread is outside of the lab. Let's talk about your company, or the company that your science is at. I don't know if it's appropriate to say your company.

Adam Gazzaley: Yeah. I'm co-founder of a company that was seeded by the [inaudible 00:49:53] Technology, that's owned as a patent by UCSF, or patent filed, almost patent pending. So I was really motivated to not have the NeuroRacer story end with the nature paper. I mean, that was a good outcome, as good as it gets for a scientific outcome. But my real hope was that it would leave the laboratory and actually enter people's lives. And one thing I realized that was not subtle was that you can't ... I would challenge anyone to build a true product inside an academic research lab or center. We're just not built to scale in that way. We don't have customer support here and we can't keep up with operating systems as they changed. It's just not what we do. We can build a prototype and do the type of feasibility and mechanistic studies that I've described to you.

Adam Gazzaley: But I believe that if you want it to get into people's lives, you need to figure out this delicate relationship between academics and industry. And so to do that instead of just passing it off somewhere else to get it developed to the next level, I decided that the best idea would be to start a company. And I found amazing partners, a group in Boston called PureTech Venture, that helps incubate healthcare companies. And my friends like Matt Omernick, who works at Lucas Arts at the time and was, video game professional of the highest caliber, to bring him in as well to create a company that was targeting our games as healthcare solutions, but with very high level of respect and attention to the video game technology itself. And that was the idea behind Akili, which was the company that we started to move this technology out into clinical practice.

Rob Reid: Now in the interest of full disclosure, I do want to note here that I am a tiny Akili investor.

Adam Gazzaley: Appreciate that.

Rob Reid: Yeah. Yeah. So that is an important thing for listeners to realize. I will probably say, as I've already said, virtually nothing myself have had Alili. So don't think that I'm bringing a bias picture of Akili to you folks. But I got, and my wife and I both got very excited about this mission back when you started the company. So that is now duly noted. But let's talk about Akili the company right now. When was it founded? and how many people is it now?

Adam Gazzaley: We are hiring, so we're growing. I would imagine that we'll be around 40 by the end of this year. So I guess, you know, started 2011, 2012 as we started moving it out of concept phase. We are in full swing now. We just had a series B, a very successful series B. So we're well capitalized as we plan to bring our first product to market.

Rob Reid: I should know this. Is the amount of money that you raised and the sources that it came from public knowledge?

Adam Gazzaley: I believe so. It's at sort of the $40 plus million range. And a lot of our investors were pharmaceutical companies, including a fund that I also co-founded called Jazz Venture Partners.

Rob Reid: Pfizer was a big investor. Correct?

Adam Gazzaley: Pfizer, Amgen, Merck, Shyer, these were all interestingly enough, investors from the pharmaceutical world, which was a surprise and still is something that we're very interested in. And so we are Boston and Bay area based, Marin and Boston. And our team is pretty much 50/50 located across those sites.

Rob Reid: Well, I hadn't realized that. I thought you were much more skewed toward Boston. So it's 50/50. Interesting.

Adam Gazzaley: Yeah. Most of our healthcare, business development, patent ... A lot of our analytics are on the East coast. And here in the Bay area, most of our creatives and-

Rob Reid: Game development.

Adam Gazzaley: ... our game development, sound designers, artists are over here. So it's a really, really cool a bi-coastal company. And I lik that aspect of it a lot.

Rob Reid: And you started with basically, it's not called that, but in a sense NeuroRacer 2.0.

Adam Gazzaley: yeah. NeuroRacer became a game called EVO, which stands for project evolution. And EVO, least that's our working title now. Whether or not that will be the product title, we don't know. But it is interestingly enough, Akili doesn't have a marketing budget. We don't have a product. We are a R and d company, really. We've taken the game engine that was NeuroRacer that became the foundation of our patent, and we've now built a game that uses that adaptivity that we defined in that patent that was behind NeuroRacer. But on top of that, built a ton of new technology and an amazing game. Much higher level of art, music and story, better usability using an iPad now, better use of the cloud in many ways. So it is an amazing game. Something that we could not have created here at NeuroScape. It's just the reality. You need the company.

Rob Reid: It's being tested against the diversity of conditions. Correct?

Adam Gazzaley: Yeah. So it is in numerous clinical trials. I'm not the principal investigator on any of them. I'm advisor and consultant on some of them, but many not. There are studies going on and conditions including post traumatic stress disorder, traumatic brain injury, depression, autism, multiple sclerosis, early Alzheimer's Disease. And the study that gets the most press because it's the most dramatic outcome, is our phase three FDA trial to have EVO approved as a clinical treatment for children with ADHD. So phase three is the trial right before approval.

Rob Reid: Or final disapproval.

Adam Gazzaley: Yeah. It's the final one in the pathway to a prescribable treatment. And so we will have the data from that study. It's a multisite study. The Pi, the principle investigators at Duke did a lot of the drug work in ADHD. And if approved, if we hit our outcomes as our pilot data would suggest ... But plenty of times pilot datas don't predict the outcome of the major trial.

Rob Reid: When you say pilot data, you're not referring to NeuroRacer. You're referring to-

Adam Gazzaley: EVO.

Rob Reid: ... the phase one, phase two.

Adam Gazzaley: Yes, exactly.

Rob Reid: The preliminary Akili-based things. Yeah, yeah.

Adam Gazzaley: The preliminary trials in children with ADHD would suggest that we will reach our outcomes. But now we will await anxiously the final data that's all blinded right now. And if successful, it will be the first non-drug treatment for ADHD that's prescribable and the first prescribable video game. So it's an exciting end of the year.

Rob Reid: I'm pretty sure I had a prescription for Pacman when I was a kid. But maybe I'm just inventing. Maybe that's just invented memory. And so you'll find out about this from the FDA by the end of the ... You'll get the data.

Adam Gazzaley: We'll get the data. And then it has to be obviously submitted to the FDA for approval. But that's the pathway we're on. And look, I'm very optimistic. Because we've seen great pilot data. And I think that the hypothesis is strong. But the reality is that if not, we will try again. We'll reformulate. There are many other conditions and this happens. Drugs fail and reformulation and try again. The goal is to produce something that we are convinced works, that physicians will be convinced.

Rob Reid: And that the FDA is convinced, that's very important. Yeah.

Adam Gazzaley: That the FDA's convinced and that insurance companies are convinced. There's a lot of people to convince. So you know, it's the pathway to get there that a doctor would pull out a prescription pad and write one month of iPad training on EVO as opposed to Adderall. That's a big deal. And so we know that there's a lot of work to do that and to hit that goal. But we think it's a worthy one. And we're taking on that challenge.

Rob Reid: Since the original work on NeuroRacer was with older adults dealing with the sorts of cognitive deficits that could eventually lead to dementia, why did you end up prioritizing ADHD for Akili's first product? Because that's more typically first diagnosed and treated in childhood. Right?

Adam Gazzaley: You know,we have a lot of work on older adults, too. So we haven't abandoned that pathway. It's an incredibly important one to us. But you know, our analysis at the time led us to believe that as a business decision this was the right population to study. Because the need for non drug treatments for ADHD are so high. Parents are so inclined to want to find an alternative to putting their kids on drugs, that it was just made a lot of sense. And you know what? Most of these kids are playing video games anyway.

Rob Reid: They sure are.

Adam Gazzaley: So it was also a market that was very receptive to it and comfortable with it and the need was there. And so it made sense that this would be our first target.

Rob Reid: So where do you see digital medicine in 10 years? We're talking about the present tense. It's exciting we may have the first FDA approved video game as soon as next year. Going multiple development cycles out, if things go well and if things continue cranking along in this lab, where do you think we might be 10 years out?

Adam Gazzaley: So sort of the system we have now is that at NeuroScape we're essentially incubators. Right? I come up with an idea of a game that's targeting a certain neural system. We build out a prototype. We do these deep research dives. We file patents behind them so they're protectable so they're attractive to companies. We then do these large scale trials, try to move them into FDA approval. That's sort of the pipeline that we've created here. If successful, we would expect that there will be treatments across multiple conditions. We would expect that in the future that there are multiple games that are working together. I don't want us to build silos around every game, like a Holy Grail like we've done with drugs and pharmaceuticals, but rather to think about how they work together.

Adam Gazzaley: They'll be personalized. Sometimes they'll be prescribed along with a drug. What I imagine will be a drug at a much lower dose and a lower side effect

profile. They might be prescribed along with brain stimulation where now they will be coupled with virtual reality and augmented reality. We will have complex adaptive algorithms that don't just record your performance and feed that into the game engine as we currently do, but record your eye movements, your heart rate, your autonomic responses. We're even working on recording brain activity during gameplay through a technology we have called the glass brain, and then feeding that data into the game engine. So in the future we see these multiple closed loops going on, that the game software is essentially understanding you in a very deep way because of all the metrics that are being recorded from you.

Adam Gazzaley: And that data in real time is being used to create this really immersive, engaging experience that is activating your brain selectively. And then through the adaptive algorithms, what we call the closed loop, is applying pressure to that system to change it over time. And so we will have very powerful tools to help improve all of these conditions of the minds. Whether it's a deficit in your attention or your mood or your memory or your perception or your decision making. And ultimately, I think that we will reach beyond medicine and improve these abilities in everyone. So that they're optimized.

Rob Reid: Yeah. I was going to ask whether there would be sort of an enhancement, not just sort of fixing things that are broken.

Adam Gazzaley: We're very interested in that. We have an education program now that we've launched earlier this year to see if these exact same approaches that we have designed-

Adam Gazzaley: These exact same approaches that we have designed to target deficits and improve people who are suffering, to just improve everyone. So, we're in middle school now to try to optimize these abilities. So, we think that this will be a new and important part of education and medicine.

END INTERVIEW ELEMENT OF PART TWO

TRANSITION MUSIC

Hey Ars Technica listeners. Adam and I will continue our conversation tomorrow. If you can't wait to hear the rest of it – or, if you'd like to browse my other 36-ish episodes, you can just head on over to my site, at after-on.com. Or, type the words After On into your favorite podcast player. Either way, you should then see my full archive in reverse chronological order - with Adam's interview slotted in at August 10th of last year.

Now, a quick update: in the 14 months since I recorded this interview, the startup which is commercializing Adam's work got the data back from the big Phase Three trial that Adam discussed, and it was very good. That was just a few months ago. So while nothing is ever

certain with the FDA, there appear to be quite strong odds that this will be the world's first prescription video game – with a potential to take lots of kids off of Adderall. To echo the caveat from the main body of the episode, I am a minuscule investor in Akili. That said I'm quite confident that everything I just said is objectively correct. And if you'd like to learn more, there's a ton of information on the company's website.

And with that, I hope you'll join me here tomorrow on Ars, when we'll continue with the third and final installment of this interview.

OUTRO MUSIC