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"The Promise of Technology for the Aging Brain"

Dr. David Van Nuys, Ph.D., aka 'Dr. Dave,' interviews Dr. Adam Gazzaley, M.D., PhD

(Transcribed from www.ShrinkRapRadio.com by Barclay LeBrasseur)

Introduction: Today my guest, Dr. Adam Gazzaley, is professor in neurology, physiology and psychiatry at the University of California, San Francisco, the founding director of the Neuroscience Imaging Center and director of the Gazzaley lab. His labs most recent studies explore neuroplasticity and how we can optimize our cognitive abilities via engagement with custom-designed video games. He has filed multiple patents based on his research, authored over 110 articles, and delivered over 450 invited presentations around the world. For more information about Dr. Adam Gazzaley please see our show notes on www.ShrinkRapRadio.com.

Dr. Dave: Dr. Adam Gazzaley, welcome to Shrink Rap Radio!

Dr. Gazzaley: Thank you, it's a pleasure to be here.

Dr. Dave: Well I'm so pleased to have you on the show. I think I first read about your work in the New York Times or it may have been the New Yorker, and then more recently you gave a TedX presentation in Santa Rosa, California -- which is my neck of the woods -- and your presentation was titled "The Promise of Technology and the Brain." Before we get into that, give us a little background on yourself if you will.

Dr. Gazzaley: Sure. I was trained on the east coast, both in neurology as well as neuroscience. I have an MD and a PhD and I did a full clinical residency in neurology, so I had both exposure to clinical care in terms of treating brain ailments as well as basic neuroscience and understanding how the brain works. I moved to the west coast thirteen years ago and did a post-doc at UC Berkeley where I learned the tools of human neuroscience; functional brain imaging, EEG, as well as brain stimulation, and started my own laboratory at USCF ten years ago, where I act as the director of our imaging center as well as run a large laboratory that is focused on both understanding the brain as well as finding innovative ways of improving brain function.

Dr. Dave: As you pointed out, you've got both an MD and a PhD. Which came first?

Dr. Gazzaley: Well I was in a program called the Medical Scientists Training Program, which is an MD/PhD combined program. But you actually get your MD before your Ph.D.

Dr. Dave: And where was that?

Dr. Gazzaley: That was at Mount Sinai, in New York City: Mount Sinai School of Medicine.

Dr. Dave: Boy, a very interesting background and fascinating work that you're doing. How did you first become interested in memory and aging?

Dr. Gazzaley: Well my graduate school work, which started in the early 90's, was actually on aging, even though I was in my early 20's at the time. It wasn't really motivated by anything other than circumstance, and that we had the opportunity to do some experiments on older brains -- actually older animal brains -- to understand how they differ from younger animals. I thought it was an interesting project, and so I began my research again at a pretty young age myself. Interestingly enough, animals (aside from humans), when they age, although they show cognitive impairment, they don't show the real signs of Alzheimer's disease. That's a uniquely human disease. So my research interests on the aging brain, as a neuroscience student, focused on changes in cognition that were independent of the pathology associated with dementia, like Alzheimer's disease; what are the normal changes that occur in our brain as we – and I say "we" meaning all animals – get older, that impairs their ability to function at the same level they did when they were younger?

Dr. Dave: I'm struck by your mentioning that Alzheimer's occurs only in humans. I hadn't heard that before so maybe that's why research hasn't been more successful than it has because we have no animal models to study?

Dr. Gazzaley: Well we have neurodegenerative disease right across the board - Alzheimer's being one of them, as an immensely complex condition, largely because the brain is immensely complex.

Dr. Dave: Right.

Dr. Gazzaley: And we now do have animal models of Alzheimer's disease. They're not perfect but through genetic manipulation you can mimic some of the pathology, some of the protein changes that occur in the brain. But they're still not exactly Alzheimer's disease in all respects, so I do think that that has been a challenge, is that it is really a disease of the human brain, which in itself is fascinating. You know, there are other animals even with complex brains that live a long time and it's yet something that only we suffer from.

Dr. Dave: In your presentation you highlighted "attention, working memory and goal management," and you said that they've not evolved much since our primitive ancestors. Tell us a bit more about that.

Dr. Gazzaley: Yes, so those sets of abilities, those three that you mentioned, fall into an umbrella that we call "cognitive control." And cognitive control is the ability of our brains - of our minds - we have, that enable us to interact in a very complex world based on our goals. So we now have, I would say -- it might be the pinnacle of human brain evolution -- is our ability to formulate very high level goals; complex, time-delayed goals, sometimes across many years, like getting an MD/PhD.

Dr. Dave: Right.

Dr. Gazzaley: And we have these goals at such a high level and we carry them out through those abilities you said: through our attention, directing it where we want it, working memory, directing our resources where we want it, working on withholding that information in mind and then managing multiple tasks at the same time. Now if you look at those skills in other animals you see that they're there. Other animals do carry out goal-directed behavior, although they're not quite at the same degree. There are limitations of cognitive control, there are limitations of working memory; how much information they can retain in mind, how well they can direct their attention and avoid distraction. How they can switch between multiple tasks is in many ways not

very different from what we're capable of. So although we have higher level goals, we have many of the same limitations of other animals have and that's why I refer to it as not having evolved all that much.

Dr. Dave: And what are the key developments in technology that make your work possible?

Dr. Gazzaley: Well I feel like we're really on the verge of a face shift right now, as I referred to it, in that we have consumer level technology, much of it pointed in the entertainment, communications, media space, that I feel now has the potential to act as tools to improve the function of our brain and enhance our minds. So the types of things that we're interested in are video games. That's one of the core pieces of technology that's been around for a while but it has advanced dramatically, given the improvements in processing power of our computers -- motion capture technology that we can sense our movements in space and feed that information into our software, wireless physiological devices, you know, the tools that many people wearing around to track things like steps and even heart rates, like you have right there...

Dr. Dave: [Laughs] Yeah, Apple watch.

Dr. Gazzaley: Exactly -- are now allowing us to sample really detailed aspects of our physiology and also send that into our software. So we have all these amazing ways of detecting how we're interacting in the world in a very sensitive real time manner, and now we're also developing new technology to present environments that are rich and engaging using new technologies like virtual reality and augmented reality. So on both the signal of detection side -- understanding how you're performing -- and on the presentation side, creating rich environments that might challenge you. There are a lot of technological advancements that I think could be used to actually harness the plasticity of our brains and improve function.

Dr. Dave: Yeah, yeah, and that work is so exciting. There was something you said in your presentation that confused me a little bit, and maybe I didn't get it right. You said, "We've recently discovered that we don't have the ability to multitask." Did you mean to say that? Because later on you talk about improvements in multitasking.

Dr. Gazzaley: Yeah so it's a sort of semantic issue. It really comes down to the definition. So we don't have the ability to multitask in the purest sense of what that word might mean in terms of actual parallel processing of tasks that demand attention. You could multitask at a low level; chewing gum and walking being a common example. But if you have two things that really demand attention, like listening to a podcast and trying to type an email let's say -- and I'm sure many people are guilty of that type of behavior -- you'll find that you really can't do them both at the highest level at the same time. You're really switching between them. And so multitasking is a behaviour that we engage in, meaning that we attempt to do multiple tasks at the same time. So yes multitasking exists in that it's something we try to do, but if you look at the mechanics of what occurs in the brain during a multitasking event, what you're really seeing is task-switching.

Dr. Dave: OK, so it's more serial than parallel.

Dr. Gazzaley: Yes.

Dr. Dave: Another interesting thing you said was, "We are ancient brains living in a modern world." Maybe say a little bit about that.

Dr. Gazzaley: Yeah so I would say it harkens back to the conversation we just had about these limitations in our brain in terms of how we engage our cognitive control abilities, these very fundamental limitations in attention, working memory, and goal management -- being essentially task switching -- that these limitations are very ancient ones. They are parts of our abilities that have not really changed very much and don't differ from many other animals. So in that sense our brains are ancient, but we are now exposed to such rich stimuli and such dense information content that's so accessible that it has created challenges for us in terms of managing all these streams of information that really put pressure on those fundamental ancient limitations. So that's why I like to think of it in that way; that brains are ancient in many ways, and our modern world especially, in terms of information technology, has really created some very salient challenges to us.

Dr. Dave: Yeah I should mention that I'm an ideal subject for your research. I'm seventy-five years old, and so for example, the multitasking that you're talking about, I find it challenging to be listening to music and trying to do another task at the same time that involves writing an email or something like that, or paying my bills. It's a little bit distracting, particularly if there's singing involved as well as just music.

Dr. Gazzaley: So the research that I think we're most known for recently is our experiments and our development using video games as a way of training the brain and improving these cognitive abilities that have these limitations. But where we started from was understanding these limitations in the first place and especially how they get worse as we get older. So the first discussion about aging and memory, we've really extended beyond that and I've done a lot of work on healthy, normal aging -- so independent of things like Alzheimer's and other types of dementia -- and tried to understand what happens in terms of those very cognitive control abilities we've been discussing, like attention, working memory... and we find that they decline as we get older -- not just older, 50's, 60's, 70's -- even across the whole lifespan from 20's on. These declining cognitive control abilities increase the amount of interference that we feel in our lives by all of the information technology around us, and that's what you're noticing. Even a 20-year-old does not multitask perfectly. They are still challenged by limitations in cognitive control. It does get worse as we get older. And that information, those results of our early work, is what inspired me and our laboratory to start trying to build technology as a tool to then improve those very cognitive control abilities that decline with age.

Dr. Dave: Yeah well tell us more about your work. You probably don't need a lot of prompting from me, so...

Dr. Gazzaley: Sure. What I just described to you was what my lab did in its first 5 years: understand how neural networks in the brain -- which are the connections between all the different brain areas -- how these very complex, what we call "multi-varied networks," meaning that it's brain areas interacting dynamically across time. That is how the brain works at its highest level. It's not that separate areas of the brains are little islands of function, it really works as a network and how that network underlies cognitive control abilities and how they decline with age, really form the basis of our laboratory. Around, I guess it's almost 7 years ago, I became motivated to not just study the brain -- how it works and how it changes with age -- but how we might build innovative tools to improve brain function. And for that we went to the world of technology. It's quite fitting we're in San Francisco, I have many friends and colleagues around me that work in the tech industry. I started looking at the approaches that they used as potential tools to help brain function. And so the first project that we did was a collaboration between my laboratory and friends of mine that worked at George Lucas' video game company, Lucas Arts, and we built a video game that I designed for older adults to improve their cognitive

control abilities. That game was called NeuroRacer. It was a 3D video game that challenged them in multitasking on two tasks that they had to perform at a high level on at the same time, by using adaptive algorithms. And what that means is that the game senses the performance of a player and then adjusts the difficulty and scales it to their ability. So as their brains get better, which happens through a process known as plasticity, the game constantly ratchets up the difficulty, ratchets it up so that it keeps pushing them to the next level. And we showed in a paper that we published in *Nature* in 2013 -- it was the cover of the journal -- that we were able to improve not just performance on the video game itself in a group of healthy older adults, 60 to 80 year olds that were playing, but it also improved cognitive control abilities, like working memory and attention. So that's really the study that launched the vast majority of the work that's occurring in the lab now, where we take that core -- where we could create adaptive, what we call 'closed-loops,' between a person interacting with the game that's challenging them right at the edge of their ability, and to use that as a tool to improve brain function. And now we're taking that to the next level by bringing in all the new technology that we talked about earlier, such as motion capture, physiological devices and virtual reality.

Dr. Dave: Yes, so that game NeuroRacer that you've been talking about, did that ever become available to the general public? Can I go buy that somewhere?

Dr. Gazzaley: What we decided to do at NeuroRacer was a little different than what a lot of other groups have done what might globally be called "brain games." We decided to take it to the next level of scientific validation as opposed to just releasing it as a consumer product. Although we were very excited with the results from that study, the NeuroRacer study, I always viewed that as a signal that something important is going on here but not enough in itself to start distributing and prescribing it. We needed to build A: a better game, and B: do more studies on larger numbers of people and different populations, and really understand if we had something impactful here. And so I use that game and the patent behind that game as the seed of a new company called Akili, that I act as an advisor for, but what that company has done now is built a much better game. It uses the same type of algorithm that we had in NeuroRacer, but bringing on way more engaging game dynamics and more art and music and story, more usability using an iPad, iCloud data capture, and so we've been able to build that game at a much higher level. Now it's going through multiple clinical pilot trials to understand its ability to improve cognition in different populations. And we've really focused on clinical populations here, so from ADHD, autism, post-traumatic stress disorder, traumatic brain injury, Alzheimer's disease, and more underway. Other groups are looking to see whether or not the mechanics of this game can improve the same type of cognitive control abilities that we showed we improved with NeuroRacer in these different populations. And the big exciting part of that company's future hopefully, is what is going on now, which is the launch of a full FDA trial to see if we can reach the end points that would allow it to be approved as a therapeutic tool for children suffering from ADHD.

Dr. Dave: Yeah that's all very exciting. I'm thinking back to a time when large numbers of parents were alarmed at the time their kids were spending playing video games, including me and wife I guess, when one of our youngsters just seemed to be almost addicted to video games. I'm happy to report that he's gone on to obtain gainful work at a fairly high level and still enjoys video games, but is far from addicted. And certainly I reflected, "well there must be possible positive uses, they're so compelling, and surely these will come to a place where they'll be useful in education and so on." But let me ask you about one control that I think would be important to have, would be other standard video games; in other words, there are video games out there not developed by people like you, but focusing entirely on entertainment. How do we know that those aren't equally engaging in terms of developing brain plasticity, etc?

Dr. Gazzaley: Well I can answer that in several ways. First I'd say that in the studies that we're doing, we are using other video games as placebo controls. We have a whole process by assuring that they're placebos, meaning that they are matched for expectation what people think that they might do, so that is actually part of scientific validation method that we use.

Dr. Dave: Good.

Dr. Gazzaley: But putting that aside, it is very reasonable that there are consumer games that do have positive impacts on cognition. I mean, our games are not entirely different from the same type of mechanics that exist in consumer games. As a matter of fact, a lot of the motivation for our first work was by studies done by colleagues of mine, Shawn Green and Daphne Bavelier who showed that the games that some people are most aggravated by, to put it mildly -- we tried the first person shooter games, the very violent video games -- that they do show benefits in cognitive control abilities in the young adults that play them. And so you do see positive effects of video games, and of course positive effects open the potential for negative effects, which is entirely responsible to consider as well. Our premise is that if there is the potential for games through this inter-activity to help improve brain function in consumer games, which are targeted really at entertainment, then if we take those active ingredients and really just direct it in a much more targeted way towards the brain systems that are deficient in a condition let's say, then we'll have even a bigger impact than a consumer game that sort of did by accident.

Dr. Dave: Yes, that certainly makes sense. Now I know I've experimented with Lumosity and also Posit Science, and I know that you've been working with Posit Science. I currently am not using either of those. The frustrations that I encountered were, one: having to start from the beginning, as I recall, like you couldn't build on where you were... It was always go back, start at the beginning, and that gets boring... and the routine. So that's what was kind of demotivating for me. The other thing was some of it was – I'm a little embarrassed to admit this – with Posit Science, and it's been a while since I tried it – actually I got a gift, I asked my family for a year's subscription as a Christmas gift a year ago and then proceeded not to use it. I think I tried it a little bit. One of the activities, I couldn't even figure out how to do it, let alone get to the place where I exercised and topped out. So some of the things with Posit Science seemed so demanding, like I remember there was one working on auditory recognition, because hearing difficulties they say are not solely due to deafness, but to the brain being able to recognize and make discriminations between different sounds. So they have this exercise where there are different kind of, I guess you'd call them syllables or phonemes or something, that they sort of fade out, that get faster and softer, and I found it very frustrating to – I remember it was something like a sound like "gah..." and then it got to the place where it was like "guh... g... g..." [laughter] and it felt like at that point, totally random and just really frustrating you know? I reached the place where I just didn't have the motivation to go on. And it reminds me of an approach to physical conditioning, I once went to a gym where the approach was you lift to the point of muscle failure.

Dr. Gazzaley: Mmhmm.

Dr. Dave: Well that's such a negative experience that it became mentally painful to think about going to the gym and so I stopped going.

Dr. Gazzaley: Well I mean, what you're describing is like what we talk about every single day in our laboratory. We have almost seven new games that we've designed and developed now that are not out there and they're not even with a company, they're just research experiments in the

laboratory, and we – it is really hard to build good games. And by good games I mean, interactivity, that's fun, engaging, motivating, not frustrating, sustainable over time... it's really hard. It's hard to do it when your goals are purely entertainment. And it's even harder to do it when you have an underlying engine that is trying to have this positive outcome on a brain. And so we spend an exhaustive amount of time working with some of the best video game professionals in the world to create interactions that are not frustrating, that are fun, that are motivating, that are sustainable over long periods of time, and it's hard work. It takes years for us to build every single game that we create. Years. So, it's hard, and you know, I don't even know now if they will all be successful but that is a goal of ours, is to take not just the science seriously, of how you validate it, or even take the neuroscience inspiration on how you develop it, but actually take the game design and development equally seriously, so that you build something that people enjoy, that they will come back to. Like the things that kept you away, we really, really work hard to make that not happen. It's something that doesn't just happen because you don't want it to, you have to really put a lot of effort and resources and work with very competent experts in other fields; of music, art, story, to really create that type of engagement, and that is one of our goals.

Dr. Dave: Yeah, that's a worthy goal, and it's a big task, I can tell from what you're saying. It takes somebody like you, who's got an MD and a PhD, and then these connections to the game world and comfort, I guess, with technology. Are you a game-player yourself by the way?

Dr. Gazzaley: I am, I am. I always have been, so since I was a kid –

Dr. Dave: See, good things can come. [Laughs]

Dr. Gazzaley: Exactly, exactly, and many of my colleagues, for example, in Akili and other companies that I advise for also came from the game world in different ways, so we have a lot of experience and rich background in it. We're reinventing it as an art form, as a tool, as a therapeutic -- as an educational device, as a wellness approach. I think there is so much here, and we're really just at our infancy in understanding how to both develop and validate at a high level.

Dr. Dave: What are some of your favorite games these days?

Dr. Gazzaley: I really experiment with a ton of games. Probably one of my most enjoyable game experiences over the last several years was a game called Portal 2, by a company called Valve. It's a platform game, so you play on like a Playstation, and it's a 3D puzzle game. It's really hard to describe, but it's a beautiful game and very complex but really fun, I mean it's just a win on every level. So that game I really enjoyed. I like lots of little games, you know, I'm always experimenting with all sorts of games from different genres. I just recently tried a game called League of Legends, which is a big global game by a company called Riot and we might do collaboration with them to understand if there's cognitive benefits of even playing that game. And so I just experiment with a lot of different types of games because games are a massive category. It's like saying food, or sports, you know, there's just all different types of interactivity that appeal to different types of people that might have different cognitive benefits from each other. Some might have negative effects compared to others, so I'm always trying to sample new games to get new ideas about how to create better interventions in our lab.

Dr. Dave: Yeah I know many parents worry that their kids' absorption in games will lead to a decrement or not even ever developing good social skills, and yet there are these massively

multiplayer games where people from all over the world are interacting with each other. Do you have any thoughts or ideas about that category of game?

Dr. Gazzaley: I think that the social interaction of some of these games has incredible potential. I agree, I think that in general there's a concern for anything that you do the majority of the time. I mean, even working, right? Everything needs some degree of moderation to keep, you know, breadth in your life of exposure.

Dr. Dave: Yeah.

Dr. Gazzaley: And so I always am very careful to point out that I don't think that these games, even the ones that I'm so excited about in our lab are a holy grail. They're nothing that somebody should be doing all the time. They're meant to be an enricher of a certain capacity of how their brain functions, but not taken further than that. And I think that games that are played just a person against a computer will ultimately have limitations in terms of developing human interaction. And I think that there is great potential in games like you described, the massive multiplayer games where you play with people all over the world. That is really fascinating to me. And then with the emergence of virtual reality, largely this year in 2016, we'll have the ability to see as well in these worlds, in a much more real world environment and we can bring in face recognition and other aspects that we just haven't seen in games yet. So I think there's really exciting potential to bring in social dimensions to all of these cognitive enhancement games.

Dr. Dave: Yeah I'm looking forward to the virtual reality goggles...

Dr. Gazzaley: Yeah the virtual reality goggles...

Dr. Dave: Yes looking forward to those, they're about to come out and of course one of the things that happened to me for video games was seeing that young kids could pick them up so quickly, be so adept, you know, at playing basketball, or football, or whatever these games had. It was discouraging as an adult, even as a younger adult, who had not grown up in that world, so that's another reason why I've not been engaged in the world of video games, and I wonder if I'm gonna have that same experience when the goggles come out.

Dr. Gazzaley: Yeah, you know, there is a way to build interactivity that is much more forgiving to people that don't have experience with it. I would say that the consumer video game has not really done that, at least not in the giant, triple A video game world. They're really targeting young people with incredibly plastic minds that have lots of experience with technology. But there is a way to build -- and we do that with our games -- that baby-step people into the experience and make it much more inviting and much more gradual, you know, halfway in. And we do that because we think it's critical for games that are designed to be therapeutic of course, and that can happen in virtual reality, but there will be a lot of applications that will not be friendly in that way. So it really comes down to software and design principles about what your goals are. Do you want to make this very niche for our population and perfectly suited, even though people of an older age group or even a different gender or a different cultural background might not find it accessible, or do you build it in a more general way to make it more inviting to people? So you know, I think that it'll be interesting. There's ways of using virtual reality even outside the world of video games of course, like virtual tourism; you could take a hike through Machu Picchu, or tour the Louvre, or you know, experience the world in ways that might appeal to different age groups beyond video games. So I think there's a lot of potential to use that technology to really elevate ourselves and we'll see how that goes down in the next several years.

Dr. Dave: I'm realizing that one of the things that put me at a disadvantage then, was that many of the games rely so heavily on speed and reaction time, and I'm remembering that as an adult I decided to slay one of the dragons that made me decide to switch out of engineering as an undergraduate. I went back in my, I guess my 40's, and took two semesters of calculus, and what I found was, was that the young students in the class were very fast at picking things up, but I was really good – I got an A both semesters – on the homework, you know, because I could take my time. And it didn't come fast, I was slow and plodding and determined, and so I would think that would be an important quality to build into games that are designed for older adults.

Dr. Gazzaley: Yes, as you'd described, there's two totally different ways you can approach an interaction: one could be demanding, very time sensitive, demanding speed in responses, and the other might even be more complex but is very time delayed. And they're both present in many different types of games. We, interestingly enough, build a lot of our games for older adults that do require high speed and quick response times. And the reason we do that is because as you might have noticed -- and I certainly have noticed -- most people notice even in their 30's, that you do get slower with age. You get slower in processing information, your responses are slower, and although there are many wonderful things that accumulate with age like wisdom, I think it is clear that we do pay a bit of a price for the decrease in processing speed that we experience with age, and so our games are trying to help increase that speed. But we do that in a way that is more acceptable by using our adaptive algorithms, because if you respond and you're just not capable of that, then the game adjusts itself to a level that's appropriate to you. That's what the consumer games do not do a very good job at. If you're not fast enough, you just fail and fail and fail and usually give up. In our games if you're not fast enough, the game recognizes that and then modifies itself to a level that is comfortable for you. But as you get better and get faster, and you most certainly will -- everyone does -- then you start getting pushed to higher and higher bars. So that's the real critical ingredient, is that adaptive closed-loop that tailors it to you. So you could challenge someone in speed as long as you're doing it in a personalized way that's appropriate to how fast they're processing.

Dr. Dave: Yeah sure, that makes a lot of sense. I think the instances I was thinking of was I was playing against kids [laughs].

Dr. Gazzaley: Totally

Dr. Dave: Of my own kids, you know. And it was great for their egos but very bad for mine.

Dr. Gazzaley: Right now I have an idea that I'm working on -- it's still early -- of a way that people of different ages, like let's say a grandparent and grandchild could play together, but the game algorithm is weighting the different algorithms independently, so although they're playing together there's sort of like a handicap imposed.

Dr. Dave: Oh yeah, great idea. That would be wonderful so that the video game becomes a shared activity rather than driving a wedge between the generations.

Dr. Gazzaley: Exactly, exactly. Sort of like you know in golf there are handicaps to all the people of different skills to play... I think that could be done digitally in a really sophisticated way.

Dr. Dave: Oh, I think that's a really neat idea. Well let's talk about Alzheimer's a bit, because that's something that all of us older adults worry about. It doesn't seem like there are any good diagnostics to let one know, short of autopsy...

Dr. Gazzaley: Mmhmm.

Dr. Dave: ...on the one hand, and on the other – oh I'm losing my thought here...

Dr. Gazzaley: On the therapeutic side there's --

Dr. Dave: Yes, thank you, thank you. Because there are all these recommendations: do crossword puzzles, learn a new language... How strong is the scientific evidence for that kind of advice?

Dr. Gazzaley: It's not strong. So, you know, Alzheimer's disease is a tragic, tragic illness that strips away the core of a person's identity and their memory. That is the disease that I know the best, because from a clinical perspective, those are the patients that I've seen the most off. And so I know from a very real experienced point of view, how impactful that disease is and the sad truth is we don't A: have very good diagnostics for when people are alive – we're getting better ones as we speak – and we do not have a treatment, you know, we do not have a cure. We don't have any way of reversing the accumulation of the disease pathology that we see. And we have a massive amount of research that we've already performed and many new experiments around the world are going on as we speak. Unfortunately even recently, there have been failures of a lot of large pharmaceutical companies looking at ways of getting rid of amyloid, which is one of the proteins that accumulate in the brain, and they have not shown yet clear positive outcomes that lead to become a medication, a prescriptive medication.

Dr. Dave: Yeah.

Dr. Gazzaley: And so it's frustrating for me as a clinician and for someone that's becoming older and his family is becoming older, that we're at that point now. The advice that you hear about crossword puzzles and even languages are based on this notion that our brains are plastic, and that engagement in either rich social environments or challenges, will help our brain, is a fair one, you know... it's what our entire lab is based on. The research of our lab is plasticity and our ability to harness it, through rich interactivity and engagement. That being said, there's not a lot of evidence that we can reverse or even cure the symptoms of Alzheimer's disease, or affect the pathology with this type of interactivity.

Dr. Dave: Yeah or slow it down.

Dr. Gazzaley: Or slow it down. Now slow it down I would say probably has the best chances, and I think there is at least some indirect evidence. We know that people that engage, for example, in learning multiple languages when they're younger, and even music training, that we do see delays in the onset of symptoms of dementia. And the reason why is because dementia is defined as a functional change, a deficit in the way you interact in the world, either professionally or socially. So dementia is really defined based on symptoms, not based on pathology -- what's going on in your brain. And so if you can build a stronger brain throughout your life -- and education has also been shown some of these same effects -- if you could build a stronger brain, then even though you might the same amount of disease accumulation, the time that it impacts you might be later in life because you have a stronger fortress to resist the invading army. And so, although there's not evidence that it's going to lead to an eventual

different outcome, I do think that based on a lot of the data that we see in terms of what we call reserve -- cognitive reserve -- building a stronger brain, and its ability to delay these effects. I would say that there's reason to have optimism that that's what may happen. And now we just need more data showing that to be true. So we would hope that the games that we're developing for older adults will not just improve cognition in those that are healthy, but if they do go on and develop the disease process that leads to Alzheimer's disease, they'll present with the functional impairments that lead to a diagnosis of dementia later in life. But that's what we're going to try to show now.

Dr. Dave: Yeah it sounds like that's something that you are concerned about and that you'll be monitoring in your research.

Dr. Gazzaley: Exactly.

Dr. Dave: And that's great. Now another exciting thing about what you're doing that's maybe on the leading edge, is electrical stimulation of the brain and transcranial magnetic stimulation, and I've been interested in those topics. I think I read or saw on YouTube or somewhere, kids experimenting with batteries hooking up to their skull. I tried some wild things when I was younger, but I don't think I'll be doing that one [laughs] in an unsupervised way. And also I have tinnitus, and so I'm aware of research; the transcranial magnetic stimulation is something that's being researched for that as well. So tell us about those.

Dr. Gazzaley: Yeah, we're really excited. I would say that the big picture for us is that we're not developing pharmaceuticals. We do very few tests of it. Not that there's anything wrong with using molecules to affect the brain, but we think that there are many other approaches that have been neglected that have sat in the alternative category and even been marginalized. And so what I just finished telling you was interactivity and video games just being a tool to deliver that interactivity to help harness plasticity and improve the brain. But there are other approaches that don't use molecules that are non-invasive that may also have a positive benefit, and one of those is stimulation of the brain through magnetic and electric fields, sometimes described as "eletroceuticals," so that you could electrically stimulate the brain. We do this to other body parts -- we do this to muscles to help in their repair, and it's been used in many other approaches to deliver electrical stimulation -- and a brain is an electrical organ, right? We know that the transmission of neural signals involves electrochemical transmission and we see all the time, especially through EEG recordings, that you have these rhythms, these oscillations, of brain activity that occur and that are associated with very fundamental cognitive abilities like attention and memory. And so the goal of some of our work is to use electrical magnetic stimulation to help the electrical transmission that's occurring naturally in the brain. Research has shown that electrical stimulation, an approach called "transcranial direct current stimulation" or TDCS, or "transcranial direct alternating current stimulation" – TACS -- so you could either stimulate the brain with DC or AC current -- can act to stimulate the plasticity, the ability of a brain to modify itself in response to interactions -- that it may help to stimulate plasticity and improve and act as a way of rehab-ing the brain if it has suffered injury. So we're doing experiments to assess if the learning curve that we achieve through game-play can be accelerated through stimulating the brain electrically at the same time. And we have some pretty excited data coming out in that domain.

Dr. Dave: So I wanna make sure I got the picture of that -- so I'm interacting with a video game and aside from whatever stimulation I'm getting from just doing the video game, in addition there are either electrical or magnetic impulses that are being fed into my brain at the same time?

Dr. Gazzaley: Exactly, exactly, and what we think is the most elegant approach to that is to record brain activity using EEG in real time during game-play and then use that data to guide the stimulation so that you're stimulating the brain in a personalized way, appropriate to how that individual's brain is activating it in time, another type of closed-loop approach. So we take neural data into the game, the game determines what might be weak in terms of how the brain is processing, and then can both challenge the player by using the neural data to guide the game-play, and also stimulating the brain appropriately. So for example, let me make it a little more concrete: we know that there's a low frequency burst of activity in the theta range, so if we're "hertz-ing" in an activity that occurs while you're playing one of our video games right at the most challenging moments in the game -- and we know that this activity, this frequency gets lower when you're older -- and we know that playing our video game over long periods of time increases that activity and that's associated with better performance on other tasks. This was all part of the *Nature* paper that we published. And so we're interested in stimulating the brain electrically at that frequency during game-play, to give it a little extra boost in terms of learning. So that's an example of an experiment; that we think online stimulation during game-play will help us reach greater outcomes than we could without the stimulation.

Dr. Dave: So it's like biofeedback plus.

Dr. Gazzaley: Yeah.

Dr. Dave: You know, *Nature* is a very prestigious journal, probably not that easy to get into. What's the reaction been to that paper?

Dr. Gazzaley: I mean, it's largely been positive. I think most people are really excited to see high-end development; working with video game professionals to build a 3D game that was engaging, and then a very careful study with control groups. We looked at sustainabilities of effects, we looked at transfer effects, we had people play the game with neuro-recordings to understand the mechanisms of effects... so I think for the most part most of the feedback I get is very positive. I would say the critiques fall into the domain that it's not enough, which is a critique that I give it also. No study is meant to be a completed work, right? These are all stages in a pathway and so this stage, and what that paper was meant to accomplish was, is there something here? Is there something going on that is interesting? Do we have supportive data requests -- more than one metric that are pointing at a change that's meaningful and potentially sustainable? And I would say that we have that, and that was enough for us to launch into much larger research program and build the next level of the game that's now going through FDA trials. So I would say the reaction was as I'd hoped it would be, one of enthusiasm. But you know, the term I always use is "cautious optimism", right? I'm optimistic but still conservative. We haven't seen enough yet. We've seen enough to take the next step.

Dr. Dave: Uh-huh. Now earlier you mentioned the people who work at the level of molecules and we hear lots of criticism of what's called "Big Pharma," and I'm wondering, do you see Big Pharma throwing any roadblocks in the way of what you're developing?

Dr. Gazzaley: I would say we see the opposite occurring. So Akili, the company that I mentioned before that I helped to co-found - that is now developing the next level of the NeuroRacer game called EVO™, that's going through the FDA trial for ADHD - was supported very early on by two Big Pharma companies: one of them called Shire which makes Adderall for ADHD, and Pfizer which makes Aricept for Alzheimer's disease. So I was sort of surprised but delighted to see Big Pharma acknowledge that in the world of the brain and the nervous system, when it comes to cognition and emotional regulation, there have not been really major wins,

right? These drugs have incredible limitations in terms of side effects and they're usually not enough to completely correct the condition that they're being used to treat, and I think that the pharmaceutical industry has acknowledged these limitations and the impression I get from many meetings with very high level representatives from pharma companies is that their minds are open to other approaches that might work either independently or as an adjunct to agents that are already created.

Dr. Dave: Yeah. OK well what have we not touched on here? I feel like we've covered a lot of ground, but probably not all of it.

Dr. Gazzaley: Yeah I would say one thing we haven't talked about is the potential for the type of technologies that we've been describing to have impact across multiple different populations. So we've really talked a lot about aging and clinical populations, but we see the potential for the same tools to have an impact on healthy minds -- both developing minds where it might be thought of as a new approach to education and for healthy adults where it would be a type of wellness tool to just maintain a strong mind throughout your lives, even before you're suffering a deficit due to some type of neurological or psychiatric condition. And so that's something that's really exciting to me, is the number of different populations that might all be benefitted from a very similar approach, and that's a new focus of our lab, to move into all these different populations.

Dr. Dave: "Johnny you can't go out and play until you've done your half hour of video game." [Laughs]

Dr. Gazzaley: Exactly. Once we start hearing that, once we start seeing doctors pull up prescription pads and write, "Two months of iPad games," then we know that we're truly in the future.

Dr. Dave: Yeah, yeah you speculated about the dawning of what you called "digital medicine --"

Dr. Gazzaley: Exactly.

Dr. Dave: ...in which that would happen.

Dr. Gazzaley: Mmhmm.

Dr. Dave: Well I really want to thank you Dr. Gazzaley for being generous with your time and information here, I think your work is really exciting. I hope to partake of it at some point, or if you need another subject, maybe if I could do it from home I'd happily be a subject for some of your research. And so I wish you Godspeed with all of this, and I want to thank you for being my guest today on Shrink Rap Radio.

Dr. Gazzaley: Thanks, thanks for having me. You know one of my main goals is to share all of this. I'm both inspired by sharing it itself but also by getting feedback from people. And a lot of our work has really been driven due to my public outreach and hearing what people want and what they care about and what frightens them and what excites them. So thanks for the opportunity to share with more people.

Dr. Dave: You are very welcome.