



MEET THE SCIENTIST WEBINAR JANUARY 2020

Using Tools of Neuroscience to Make Personalized Care a Reality in Schizophrenia

Presented by: Gregory A. Light, Ph.D.
Moderated by: Jeffrey Borenstein, M.D.

- Dr. Borenstein: Welcome to the Brain and Behavior Research Foundations Meet the Scientists monthly webinar series. I'm Dr. Jeff Borenstein, president and CEO of the foundation, and your host for today's webinar.
- Dr. Borenstein: Today, Dr. Gregory Light will present Using Tools of Neuroscience to Make Personalized Care a Reality in Schizophrenia. The Brain and Behavior Research Foundation funds the most innovative ideas in neuroscience and psychiatry, to better understand the causes and develop new ways to treat brain and behavior disorders. These disorders include addiction, ADHD, anxiety, autism, bipolar disorder, borderline personality disorder, depression, eating disorders, OCD, post-traumatic stress and schizophrenia. Since 1987 the foundation has awarded more than \$408 million to fund more than 5,900 grants around the world.
- Dr. Borenstein: Today, I'm delighted to introduce Dr. Gregory Light. Dr. Light is professor in residence in the Department of Psychiatry and deputy vice chair of Psychiatry Education and Training at the University of California, San Diego. He was a 2013 independent investigator grantee, a 2006 and 2003 young investigator grantee. Was awarded the foundation Sydney Baer, Jr. Prize for outstanding achievement in schizophrenia research in 2014.
- Dr. Borenstein: Today's webinar will begin with Dr. Light's presentation. This will be followed by a question and answer period. To submit your questions, please use the questions tab on the control panel on your screen. Please feel free to submit your questions at any time. Following the presentation, I'll ask as many as possible in the time allotted. Now I'm pleased to introduce Dr. Light. Dr. Light, the floor is yours.
- Gregory Light: Thank you very much for that excellent introduction. I'm incredibly grateful for the Brain and Behavior Research Foundation support across the course of my career. Even before entering graduate school, I thought I would take this talk to describe how some of my early career experiences have shaped my current research program. Talk about how the Brain and Behavior Research Foundation

has supported this work and allowed it to continue, for me and many other trainees at my institution over the years.

Gregory Light: In addition, as Dr. Borenstein mentioned, the Sydney Baer, Jr. Foundation was also instrumental in supporting this work through the Baer Prize and other subsequent funding mechanisms. I'm really grateful to BBRF for supporting this work and for others like it.

Gregory Light: This is a picture of a UCSD's library. It's an iconic image and used to be the logo for our institution. I came to UCSD in 1995 as a graduate student and have spent the course of my career trying to better understand schizophrenia and ultimately develop better treatments for this illness.

Gregory Light: I should say that the real heroes of this story are the trainees who are currently in my lab. This is a picture of our laboratory group of physicians, psychologists, neuroscientists and people who are providing care to patients with schizophrenia every day. Some of them are also NARSAD Young Investigator awardees, including the person in the top left corner, [inaudible 00:04:23] a current NARSAD awardee who's working in our research group.

Gregory Light: I'm sorry that my slides had jumped to the end, so I'm going to jump back up to the top. By way of disclosure, this work has been supported as I mentioned by BBRF and the Baer Foundation. My laboratory is also supported by other grants from NIMH, NIA and as well as some interesting work through the Office of Naval Research on biomarkers.

Gregory Light: My early career started prior to graduate school, where I was working at the Rochester Psychiatric Center. This is a picture of the facility. The facility opened in the 1950s and my job in the early 1990s was to go through this facility and interview patients for the office, New York State Office of Mental Health. This was a time before electronic medical records.

Gregory Light: I had learned that when I went into this facility in the early 1990s, that many of the patients had been there since it had opened in the 50s. They had been there for two of my own lifetimes and it struck me that this was not a great place for people to live. They had done nothing. They committed no crime and yet there weren't decent options available for them in the community.

Gregory Light: The New York State Office of Mental Health did a patient characterization survey, to try to understand what the diagnoses and symptoms were of these people who had spent so much of their lives in this facility. I'm sure many who

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are listening in on this webinar will have experiences with maybe this facility or ones like it. Where patients end up spending the majority of their lives institutionalized, because there aren't adequate treatments for many.

Gregory Light: One of the things that struck me as I interviewed patients doing diagnostic interviews and symptom rating scales is that, it surprised me that people who seemed so different from one another in terms of their symptom profiles shared the same diagnosis of schizophrenia. Some people have more severe positive symptoms are called with hallucinations and delusions. Others said very little and had negative symptoms, and some were profoundly disorganized.

Gregory Light: The thing that stuck with me through this experience was, one of the unifying features of the patients at this facility, was that at some point over the course of their illness, almost all of them had experienced auditory hallucinations. My work became focused on trying to better understand the auditory system in patients with schizophrenia. Then to work with the tools of neuroscience EEG biomarkers of this auditory system. Then to work with interventions that are designed to engage this auditory network, to try to improve the outcomes of patients with schizophrenia.

Gregory Light: I should say that I was very lucky to come to UCSD in the 1990s to work with David Braff. This is a picture of Dr. Braff on the left receiving the Lieber Prize in 2014 from Dr. Pardes from the BBRF. My also very dear colleague Neal Swerdlow, the picture of Neal more recently when he accepted award from the American College of Psychiatrists for his career contributions to schizophrenia research. I still I'm fortunate to work with both of them on a daily basis and their influence continues to shape the work of this program and the field at large.

Gregory Light: Despite the advances that we and others have made, it's undeniable that many people with serious and persistent mental illnesses are still not receiving adequate treatment for their illnesses and many are homeless. We have over 250 to 350,000 people with serious mental illnesses, who are currently homeless and not receiving any care for their treatment.

Gregory Light: In the 1990s and still a bit today, I think there was an attitude, the patients who had a longstanding illness, once they had a diagnosis of schizophrenia, that recovery was not really an option. That the neural systems of schizophrenia patients are fixed and that many were just destined to a lifetime of institutionalization, poverty, homelessness or even incarceration. We know that

that is not true, but we're still not doing enough. Our goal is to try to, how do we improve the outcomes for people with schizophrenia?

Gregory Light: Working with Dr. Swerdlow has been really a transformative experience for me. He wrote a paper that, when I think of required reading for better understanding and treating schizophrenia for medical students and other healthcare providers, this is the one. He published in 2011 in Schizophrenia Research, and it really called for trying to apply systematic rehabilitative psychotherapies, that are designed to engage healthy neural systems to compensate for and replace some of the impaired neural circuit elements in concert with medications, including antipsychotic medications. Again, this is really geared towards trying to improve outcomes.

Gregory Light: What we know about schizophrenia is that, there are cognitive deficits. There are the dramatic and defining clinical features, of clinical symptoms of hallucinations, delusions and disorganization and negative symptoms. There are problems with daily psychosocial functioning, the inability to work or go to school, keep a job, live independently.

Gregory Light: While we have some psychosocial supports like assertive community treatment, psychosocial rehabilitation, housing and supported employment, we haven't really fundamentally addressed a lot of the other problems. Including persistent clinical symptoms that are addressed by antipsychotics and symptom based psychotherapy, motivational types of approaches like cognitive behavioral therapy. There're currently no medications that are approved to treat the cognitive deficits of schizophrenia. Yet what we know is that, cognitive deficits are significantly related to the clinical symptoms of schizophrenia patients. They're also significantly related to patient's daily functioning.

Gregory Light: If we really want to improve outcomes for patients, we need to target the cognitive deficits in such a way that they can go to school or stay in school, they can get a job or keep a job. Ultimately have more successful independent lives, happy lives. It's really the cognitive impairment, not so much the dramatic, defining clinical features that ultimately underlie the functional impairments that many people experience with schizophrenia.

Gregory Light: Our goal is, if we can create modest improvements in cognition, the hope is that they will lead to clinically relevant improvements and outcomes, but how do we get there? We have no medications.

- Speaker 3: Dr. Light, I'm sorry to interrupt. You were cut off for a little bit so just on your last sentence. If you would be so kind to repeat that one.
- Gregory Light: The question was, since we have no medications to improve cognition, how can we improve cognition? How can we move it to produce the improvements in relevant outcome domains for so many people? How do we identify which patients benefit the most?
- Gregory Light: In work with Dr. Swerdlow, we have started to think about, what are the barriers to treatment and treatment developments? Our current model is, we take a clinical group on the left, they're usually defined by a diagnosis like schizophrenia. We give them an intervention, usually a pill. For some people in this heterogeneous group, they benefit shown in the blue. Others may not benefit, some may get worse, some may not change at all. If this were a drug that we were testing, that drug would fail, because it uses this one size fits all approach.
- Gregory Light: Our idea is that, maybe there are some people embedded within this heterogeneous clinical disorder or this clinical group. That we can identify at the outset of a treatment using one of the tools of neuroscience, a biomarker. In our case, these are EEG tests to identify these sensitive individuals. Then give the intervention just to those sensitive individuals, not to the ones who are unlikely to show a benefit. In this scenario, the same intervention would be deemed a success, but it would only work for a subgroup of people identified at the outset based on some objective, direct, reliable assay of brain function.
- Gregory Light: This talk will focus on those two parts, both the cognitive training intervention itself and the use of biomarkers to predict which individuals are most likely to benefit from the treatment.
- Gregory Light: How do we move cognition? If we look to the popular press and the marketplace, there are countless brain training, cognitive training interventions that you can pay for. You can get them on the Nintendo DS for kids, you can get them on an iPad, you can pair them with Gizmo devices that people attach to their heads like in the top left hand corner of the screen. Even probably while we were talking, there were some new commercial enterprise selling a brain training intervention.
- Gregory Light: The problem with these interventions is when they're submitted to rigorous studies, these cognitive training, brain games types of things. A lot of the studies

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show that they have no effect on brain activity behavior or the cognitive domain that they are supposed to be targeting.

Gregory Light: In fact, one of the very large brain training companies had to pay a settlement to the FTC for deceptive advertising charges for its brain training program, because their claims were not supported by evidence. I want to make clear upfront, I am not endorsing any particular form of cognitive training or commercial entity. I have nothing to sell and I have no financial ties to any cognitive training company of any sort.

Gregory Light: One of the issues with the cognitive training industry, however, is that, the idea is very simple on its face. That if people have problems with memory, for example, if you do a lot of memory exercises, you would expect that their memory would improve and it would result in a gain in their real life. However, what the vast, vast majority of studies have found is that, those skills that you practice do not generalize beyond the test itself.

Gregory Light: If you are working within a memory training platform and you do memory exercises as a part of the platform, the games that you show on the company platform do not actually generalize to real world cognitive benefit. One of our ideas and the ideas of many others has been to engage lower level systems. To try to target low level sensory information processing, to see if by improving sensory information processing that the benefits would trickle upwards to impact the neural circuits that regulate cognition, which should in turn move some clinical endpoints in daily functioning.

Gregory Light: In a study of 1,500 patients with schizophrenia by Michael Thomas, we applied a structural equation modeling approach to try to test this hypothesis. This information processing cascades the idea that, low level networks would impact higher order cognition and daily functioning. I'm not going to go into too much of the details of the statistics here.

Gregory Light: Just say that the take home message is that, early measures of sensory processing that you can measure with an EEG, a tool of neuroscience is highly related to patient's cognition and daily functioning. We also replicated and showed that, cognition is also related to clinical symptoms and that the clinical symptoms, particularly negative symptoms are related to patients problems in daily life. You could even remove the direct link between the early information processing measures and daily functioning, because it can all really be explained by this information processing cascade model.

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- Gregory Light: The other thing that we found is that, if we can move these measures of early neural system engagement by one unit, in this case, one EEG microvolt, that it should support a large effect size gain in cognition. We have shown in some of our studies that there are certain drugs that can move an EEG biomarker by about a unit in a study that we published in 2015 in *Neuropsychopharmacology*. Again, with Neal Swerdlow, we showed that a drug, Memantine can move an EEG biomarker linked to early auditory information processing with just one pill.
- Gregory Light: However, I want to say, one pill of a drug like Memantine or Namenda, a drug used to treat Alzheimer's disease, is not going to improve cognition. There is no pill that you take one time only that is going to make people think better or more clearly. We still need to better understand, what are the time course and requirements for change? Perhaps cognitive training can help induce a durable change in cognition that could impact cognition.
- Gregory Light: With Neal Swerdlow and others, we started to develop some early proof of concept experimental medicine trials of a nonpharmacologic intervention using an auditory targeted cognitive training platform that was developed by a commercial entity Posit Science. This one is a little different from the ones that I mentioned before. That it is a bottom up approach to cognitive training that really aims to improve the accuracy and fidelity of low level auditory sensory information processing.
- Gregory Light: This platform like many others capitalizes on neuro-plasticity based learning mechanisms via exercises that are intensive, adaptive and rewarding. These are mechanisms that are generally intact even in people with serious and persistent and chronic mental illnesses and neuropsychiatric disorders. They're very low level. They place progressive demands on higher order cognitive domains.
- Gregory Light: Some studies have shown that they're efficacious under highly optimized conditions for improving cognition in psychosis patients at the group level. In fact, my own work was also inspired by the work of Melissa Fisher and Sophia Vinogradov, that showed that this form of cognitive training can improve verbal learning and memory in schizophrenia outpatients, in individuals with a relatively recent onset of schizophrenia. Even in some cases in adolescents and young adults at clinical high risk for developing psychosis.
- Gregory Light: Our group, in reading some of those papers noted that, the schizophrenia outpatients went to Dr. Vinogradov's laboratory five days a week for two and a half months to receive the intervention. While they very convincingly showed the efficacy of the treatment in these highly optimized conditions, our group

was really interested in, what about the people who can't make it into a laboratory five days a week for two and a half months? Can we bring this intervention to people who have treatment refractory illness who have a chronic illness?

Gregory Light: We formed a partnership with a nonacademic site in the community, that house, is a 113 bed facility for patients with chronic schizophrenia. The majority of patients were court mandated to longterm lock stay at this facility. They stayed for six months to even 24 months at this facility. This is a very impaired cohort.

Gregory Light: The challenges that I want to highlight here is that, this kind of intervention has largely been tested in academic labs. As I mentioned, it is a time intensive and resource intensive type of intervention in that people usually do the exercises from three to five times a week, an hour a day. Even when you give it your best shot and you have people that participate in the exercises and do 50, 40 hours, 50 hours, even 100 hours, it does not help everyone. 35% to 45% of patients show no or only very minimal improvement with the intervention.

Gregory Light: What we wanted to know is, can we determine the effectiveness of this intervention and the predictive utility of EEG biomarkers to identify which of the people are most likely to benefit? Being somewhat skeptical myself, at the beginning of launching this research program, we wanted to know whether these exercises actually engage the neural systems that they target the auditory system. Our first question was, are EEG measures acutely sensitive to the exercises after just one hour of the exercises? Does 30 hours of intensive cognitive training work in this more impaired group, a group that arguably needs the cognitive training the most? Are there any kind of EEG or other biomarkers at the outset of treatment that will help us predict which patients are most likely to benefit?

Gregory Light: First a little bit about the exercises. This again is from the Brain Fitness program from Posit Science. Posit Science has lots of exercises available. I think within the auditory domain and social cognition domain, they have probably over 30 different exercises. We use just a set of six exercises. We paid for the exercises for all of our participants. They were very helpful with setting up portals and helping us use the platform, but we paid for it just like regular users.

Gregory Light: I'll say that these exercises started off very simple with these, if you look at the top left hand corner of the screen, Sound Sweeps. Over the course of the 30 hours of the treatment, they cycled through progressively higher order training

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exercises that make discriminations from between sounds, across syllables, how you stack syllables, making rhythmic judgments and ultimately aiming to improve auditory memory and sequencing different sounds together.

Gregory Light: I'll just give a brief example and I'm going to point out that, while we're trying to improve verbal learning and memory, these exercises do not look anything at all like verbal learning and memory. These are exercises where people have to make judgments of tones, whistling sounds. In this first example, as part of the training, individuals are asked to determine whether a whistling sound is an up sweep or down sweep, and that's how the exercises progress. I'll just give a couple of examples.

Gregory Light: If they hear a sound like that, it's an up sweep. A sound like that as a down sweep, and after training, there're pairs of it and individuals are asked to click a button on the computer to determine whether it's an up and a down, an up and an up and so forth. They become shorter and closer together and more difficult. Here's another example of a sweep pair, it's very close together, you'll have to listen carefully to hear it. That's an up, up sound. If they get it correct, they move on to the next level and it becomes more difficult. That's a down up, and if they get that correct, they would continue to go forward. These are discriminations that I cannot make, but I'm sure that the people in the laboratory, the younger people can hear that. Whoops, it's very fast.

Gregory Light: The idea with these exercises is, they're always matched to the person's ability level, so that if you get it correct, you move to a more difficult exercise. If you make a mistake, you go back, so that you're always pushing up against your 80% correct rate and trying to keep improving your level. If you break your level, there are fireworks on the screen and animations that are supposed to be rewarding. The exercises are engaging, but they're difficult and they're not too much fun.

Gregory Light: The first part of our question is, are the EEG measures sensitive to the neural systems engaged by one hour of exercises? One of our former postdocs, Veronica Perez and a series of papers demonstrating that the neural systems engaged by one hour of cognitive training are correlated with the amount of games that take place within the one hour of training.

Gregory Light: Moreover, the neural system show some dynamic malleability or plasticity following that one hour of training, where those squiggly line EEG biomarkers change, where there're different before versus after just one hour of training. In

this example with the brain pictures, it shows that the changes in cortical source contributions to the EEG change after just one hour.

Gregory Light: The thing that we really want to know is not so much about EEG biomarkers, but rather, does the training actually work in that group of patients that needs it the most? A study by Michael Thomas and many other colleagues at this longterm locked care facility did a study of patients who received either the cognitive training or their usual treatment. A sample of 22 who received treatment as usual and 24 who you received treatment as usual plus the cognitive training.

Gregory Light: A couple of things I want to point out. One is that, for the healthcare providers in the webinar, you'll note that the patients were receiving pretty significant doses of antipsychotics. They had been ill for an average 15 or 16 years, and this line at the very bottom is their cognitive test performance using the matrix consensus cognitive battery. This puts the patient group in the moderate to severely impaired cognitive range of cognitive deficits. The groups did not differ significantly on any of the baseline characteristics shown above, shown in this table.

Gregory Light: What we found is, like in other studies of schizophrenia outpatients, that verbal learning was significantly improved in this group of severely disabled schizophrenia inpatients. The Y axis in this figure is the matrix consensus cognitive battery test performance on the verbal learning domain, a baseline the two groups were statistically equivalent. The cognitive training group shown in the orange, showed a significant increase in verbal learning after the 30 hours. That's considered a large effect size improvement in the domain of cognition and in the cognitive domain that this intervention specifically targets.

Gregory Light: We also found a somewhat surprising effect on auditory hallucinations, where the group who received cognitive training had a moderate statistically significant improvement, but still a reduction on their positive symptoms. In this figure, the Y axis is the SAPs positive symptom, auditory hallucination subscale clinical rating. They went from a score of about five on average to a score of about three. That effect was not attributable to medications, medication changes or any other kinds of treatment effects that we could detect, but we were quite encouraged by it.

Gregory Light: We also found another interesting effect and that is, as we tracked participants in the TAU or treatment as usual group relative to the cognitive training, targeted cognitive training group in the orange on the amount of psychosocial groups, activities and other kind of self-care. Over the 10 weeks of the study, we

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found that the groups started off at an equivalent level, even tracking them for one month prior to study entry that they were very well matched on groups and activities. What we found is that, the cognitive training group actually participated in significantly more psychosocial groups and activities over the 10 week course. That roughly equates to about one extra week of total rehabilitation.

Gregory Light: Obviously we do not think that it was the cognitive training itself that led to an increase in their groups and activities. We think that it may have had something to do with the fact that our cognitive training itself was delivered in a very positive manner by our research assistants. Who for an hour a day, several times a week would bring patients into the unit and basically tell them, "You're doing a great job. Keep it up. You broke your next level, you're doing fantastic with these exercises." I think some of that positive experience of interacting with our staff may have led them to seek out other psychosocial groups and activities offered by the facility. There may be some other kinds of secondary benefits from the overall experience and maybe even the exercises themselves.

Gregory Light: We found in our study, however, that in this group of patients, about 35% of them did not show any clinical benefit with this particular form of the cognitive training and with that particular set of six exercises. What we wanted to learn is, do EEG changes measured at the outset of the treatment, do they predict which people actually showed the greatest cognitive gain with the treatment?

Gregory Light: One of our postdocs [inaudible 00:38:04] and published in Neuropsychopharmacology in 2019 found that, some of those EEG changes after one hour predicted improvements in verbal learning measured after 30 hours of the treatment. The treatment group here is in orange and the treatment as usual group is in the blue. One thing that you can see is that, the blue group slope is relatively flat. There's a significant positive slope in the cognitive training group indicating that again, that the EEG biomarkers were sensitive to the neuro systems engaged and to the treatment targets that we care about.

Gregory Light: We also found that similar amplitude changes predicted the amount of reductions and auditory hallucinations. Again, an EEG measure at the beginning of treatment predicted some benefits in cognitive and clinical gains after 30 hours of the treatment. These sample sizes, again, I want to point out are relatively small. There's a lot of heterogeneity and variability in this cohort and so what we have tried to do is develop composite EEG measures, where we look at a number of EEG features and see if we can predict individual patient

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benefits. Can we use these EEG composite scores at the outset of treatment to develop a measure that's going to tell us whether somebody is likely to benefit? [inaudible 00:39:51] had a second paper that's now in fact showing just that. This curve shows the difference between the sensitivity and the specificity of the task.

Gregory Light: There's diagonal lines so that if the test is not useful, that would be here. Anything above the line would show good sensitivity and specificity. We found and argue that, this EEG biomarker, a composite score cutoff could predict benefits and global cognition or verbal learning with 91% sensitivity and specificity. However, that needs to be replicated in a larger study in a different cohort and see if it really pans out.

Gregory Light: This is one example of a way that we can use the tools of neuroscience to ultimately identify at the outset of treatment, individuals who are sensitive to an intervention, so that in the future, perhaps we can give an intervention. It can be a pill, it can be cognitive training to just that subgroup of people that are likely to benefit.

Gregory Light: Our lessons learned is that, this particular form of cognitive training shows improvements in cognitive, clinical and psychosocial functioning. Even among those with longstanding illness, even those in nonacademic centers. We also found the patients with greater severity of deficits, cognitive deficits, were the ones that benefited the most. We found kind of in a counterintuitive way that even some of the older patients, to the extent that age matters, the older people tended to benefit more than the younger people. Maybe they had more room to move. The biomarkers improved our prediction of which individuals are benefiting.

Gregory Light: Some of the caveats however, I want to again underscore, the exercises are not that much fun. They're not fun games like the games like Fortnite or computer games on an Xbox. These are actual exercises. It's not easy to necessarily for an individual to detect improvements, because they're in things like your sweep performance or your ability to make discriminations amongst syllables that is not so close to things like verbal learning and memory. They're not memory tests.

Gregory Light: Again, not all patients benefited. Some did not and maybe for those that did not, they need a different package of exercises or different type of exercises. Maybe their gains can be augmented or pushed via pharmacologic augmentation of cognitive training.

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- Gregory Light: Another caveat is among the patients who got the exercises. Their complaints of problems with cognition on a daily basis were not improved, even among those with larger gains. Again, all of the people in this study were in a longterm locked inpatient care center. They did not really experience dramatic changes in their environment, their work situation, their social functioning. They did not get new relationships and have like very clear markers of benefit in a facility like this. A lot more needs to be done to better integrate these kinds of interventions with outpatient care and other settings.
- Gregory Light: Again, I'll say that while there are many exercises that are commercially available, even from within Posit Science, we only use the ones that had been shown to be effective. The specific exercises and definitely the dose and mode of delivery probably matters. I say probably because we haven't done studies to disentangle and tease apart dose effects and the right balance of exercises for individual patients.
- Gregory Light: The context of delivery and who administers that also again probably matters. I think it's important that if you're going to be doing these low level exercises like this, it's best to do them in an environment where there're also having enriched psychosocial experiences. Where there're other groups and activities, other opportunities to test out their cognitive benefits and start using them in a real world situation. I'm sure that matters.
- Gregory Light: Who delivers it probably matters as well in that, somebody who's giving continuous positive feedback and making the exercises fun and engaging may have some generalizable impact and keeping them to adhere to the regiment. Before you do it though, clinical stabilization should come first. They should have a good relationship with their psychiatrist.
- Gregory Light: Clinical stabilization does not mean symptom free. It just means that like if they're brought in for an acute exacerbation of illness to an inpatient facility, to an inpatient hospitalization, that's probably not the best time to do it. A better time to do it is once their clinical symptoms have stabilized and they're able to engage with these kinds of exercises. Again, before you launch on a program like this, it's important to get the context right up front to make sure that you have other psychosocial supports in place and a comprehensive treatment plan and treatment team. Then when you give it, it's more than just providing a link or a URL. It's making sure that they stick to it.
- Gregory Light: I will say that our team shown in one of the introductory slides with all the pictures of their faces, they were very assertive in encouraging people to engage

in the daily exercises, tracking them. They would go to the unit and ask, sometimes they would refuse, they would go back again an hour later. They would keep going back all while being very positive. Ultimately very successful and getting people through the exercises.

Gregory Light: In the future we hope to do more studies with the biomarkers and apply these to drug development contexts. Some of the same biomarkers, the EEG tests they mentioned have strong utility in predicting which individuals who are at high imminent clinical risk for developing psychosis are the ones who are most likely to actually convert to a psychotic disorder.

Gregory Light: The biomarkers can be used to also track the progression of neural system impairments across the course of illness from early stages to later stages. We will continue to work on novel analytic methods, to understand the neural mechanisms, temporal dynamics and multi-variate interactions that underlie treatment and treatment response. Ultimately so that we can use these biomarkers to assign individual patients to treatments. Again, in our next steps, trying to use some drugs to augment the benefits of cognitive training, work with Neal Swerdlow. Really trying to push the therapeutic gains and accelerate the pace of gains.

Gregory Light: I would really like to thank you all for the questions submitted in advance. I would like to think again, the Brain and Behavior Research Foundation for their generous support of this work and the Sydney R. Baer, Jr. again for this important support. This is support that often doesn't come from other funding agencies, so it's really a great pleasure to be here and to be able to give this kind of thanks back to those of you on the call and to the BBRF. Thank you.

Dr. Borenstein: Well thank you Gregory. The work that you're doing is extraordinary and the passion that you have for helping people who've in the past would sort of be left and forgotten. Sending me back to how you described it back in Rochester, is inspiring and impactful. Thank you for all you've done and all you continue to do.

Dr. Borenstein: One of the things that people are curious about is, even at this point and the research is really on beginning and ongoing, what should a family member do if their loved one, a son or a daughter was recently diagnosed with schizophrenia? At this point in time the information that you're sharing with us, what can they do clinically with that information to help their loved one?

- Gregory Light: Thank you for that question and thanks to the many people that submitted questions like this. Jeff, when you brought up this idea in the 90s, this feeling that I had of people who are lost and forgotten, I fear that the field at large still have some of those stigmas about schizophrenia. That we do have some people now who are lost and forgotten.
- Gregory Light: What can a family member do with the loved one? First is to understand that recovery is an option, and that improvement is something that they should expect and even demand from providers. The first thing that I would argue for is assertive advocacy on the part of their loved one, and not accepting inadequate care as an option.
- Gregory Light: I'm a parent myself. I have three boys and navigating healthcare systems is really tough these days. I would encourage people to develop a relationship with their healthcare providers and continue to push for excellent treatment. Making sure that people are not overly sedated or underly sedated. Making sure that their medications are well-tuned and when they're not to go back and work with their healthcare provider.
- Gregory Light: Also, to engage in comprehensive intervention. Not just cognitive training, not just medications, but other kind of intensive psychosocial support like groups and activities. Cognitive behavioral therapy has shown to be also very helpful in improving outcomes for people with psychosis, even among those with early, early illness. Really trying to do it all, ensuring that they have a safe and stable environment. That they have very comprehensive, intensive rehabilitative and psychiatric care.
- Dr. Borenstein: Your words are right on target and I appreciate you saying that, because it is difficult for family members to help their loved one navigate the system that we have. Absolutely, if you look at the number of people who are homeless, the number of people who are not getting treatment in the criminal justice system instead of getting treatment, it's staggering. Your point is extremely important, that the problem clearly persists.
- Dr. Borenstein: One of the challenges for families, it sometimes can be that their loved one really doesn't have insight into their illness or the need for treatment. What do you recommend with regards to people who have that additional challenge above and beyond the diagnosis?
- Gregory Light: Yeah. That's a really good question and was actually the topic of my dissertation in the 1990s. Is about like this kind of unawareness of symptoms and

unawareness of illness and the need for treatment. I think in general, the thing to go for is common ground, things you can agree on. Not arguing with people about the content of delusions, but really trying to find something that you can both agree on.

Gregory Light: While they may have symptoms that are distressing and may not want to take medications, for example, you could argue that the medications may help with some of the distress or with sleep. Really just trying to develop a trusting relationship and engaging them. When things don't work, also listening and if they have intolerable side effects or other problems, to continue to provide assertive advocacy to make sure that they get the right kind of treatment they need.

Gregory Light: One thing about this particular form of cognitive training is, even if you don't think you have a memory problem, for example, the exercises do not specifically involve memory. The exercises all involve like your ability to make fine discriminations among sounds. On the one hand, while it may not seem like making discriminations among sounds is going to be particularly helpful, the research shows that it does.

Gregory Light: One thing that we did in our study is, we also rewarded people who participated in the cognitive training with our forms of bribes. Which is, there's like a little canteen at the facility that has little trinkets that you could buy. We gave basically tickets for the canteen, which resulted in very small things like usually costing less than a dollar per time. There were things that the people really wanted and really needed and gave them pleasure.

Gregory Light: Even if the exercises themselves were not pleasurable, at least they got some other form of reward that made them want to engage with the exercises and the research staff. I think if loved ones can do some of that with kinds of exercises and other interventions that may not on their face seem to be the things that the patients care about the most. If you can find some other way to incentivize them to go through it, it might be worth it.

Dr. Borenstein: So that if the person identifies a particular issue that really is troublesome to them, let's say sleep or anxiety that focus on that, really focus on what the person themselves sees as what's most troublesome to them and don't go arguing over other aspects that may not be on the list of things that are so troublesome to the person, but focus on what the person's concerns are.

- Gregory Light: Right, so while we maybe as loved ones or healthcare providers, very concerned about the content of delusions, for example, sometimes delusions that can be quite bizarre and interfere with daily functioning, arguing with the person about whether they're real or whether they're valid, is ultimately going to be less successful. To the extent that you can focus on things that you can agree upon, like the functional distress or negotiate ways. That if you try this one intervention or try doing these exercises, they'll get some other kind of benefit that might be more effective.
- Dr. Borenstein: Right, and let me ask you one final question in the time we have left. If we had you and I hope to do this, give a webinar in a few years from now, where do you see this going? Predict what this is going to lead to in a few years from now.
- Gregory Light: What I hope it leads to is better integration of the tools of neuroscience to personalize the care. Right now we're using the one size fits all approach and treatment failures have real consequences. If somebody is one that doesn't benefit, then they're unlikely to want to try something else in the future. Like to the extent that we can start to leverage the profound advances in neuroscience, to improve the care for the people who really need it, I really hope and believe that that is where the field is going. I also believe that BBRF is very focused on ensuring that that happens.
- Gregory Light: I want to really thank you Jeff and thank all of the people out on the webinar who are listening in for their support, their interest and their continued engagement. I think we all need to continue with assertive advocacy in this area and especially for people with serious and persistent mental illnesses who I believe are often still lost and forgotten.
- Dr. Borenstein: Well thank you Gregory and I want to point out just for our audience, because it is such an important aspect that you've highlighted, which is the role of mentorship. You highlight people who are important to you as mentors and then you highlight people who you've had the opportunity to mentor and this is a team effort. Your being a part of the team has been just a tremendous plus for the field.
- Dr. Borenstein: Thank you for all that you've done and all that you continue to do. I also want to thank everybody for joining us today. 100% of all donor contributions for research are invested in our grants to scientists. All of the research we fund is made possible through supporters like you. [Please consider making a gift by visiting bbrfoundation.org](https://www.bbrfoundation.org) or call 1-800-829-8289.

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Dr. Borenstein:

This webinar has been recorded. If you've missed any portion or would like to share this webinar with family or friends, please visit the events and webinar page on our website. I hope you'll join us again in February when Dr. Christina Gremel, assistant professor in the Department of Psychology and Neurosciences graduate program at the University of California, San Diego will present [How Drug Dependence Impacts Decision Making](#). This webinar will take place on **Tuesday, February 11th at 2:00 PM** Eastern time. Once again, thank you very much. Have a great day. Take care.

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