Innovative technologies expedite cognition drug development

Dr Richard Keefe, PhD, is co-founder and CEO of NeuroCog Trials, a company that specialises in creating innovative tools and strategies to facilitate drug development and enhance assessment of cognition and functioning.

NeuroCog Trials, a company co-founded in 2004 by CEO Dr Richard Keefe and President Caren Gadigian, develops innovative methods to assess cognition and function in diseases such as schizophrenia, depression, Mild Cognitive Impairment, and Alzheimer's disease. The overall philosophy of the company is to facilitate drug development with new tools and strategies to enhance signal detection in clinical trials. They do this by developing new approaches that utilise virtual reality and computerised tools to augment the delivery of clinical assessment.

Much of this technology has been used in schizophrenia treatment. Schizophrenia is a severe mental illness that affects most patients for their entire life. It impacts a person's ability to engage with the world, affecting employment opportunities, the formation and maintenance of interpersonal relationships, and the ability to live independently. Although current antipsychotic drugs can help control some features such as hallucinations, they have little effect on the cognitive abilities of patients, so there is a drive to develop treatments that can assist in this domain.

As part of a consensus initiative, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project, recommendations were made to standardise the cognitive measures used in schizophrenia trials. As part of this, a set, or 'battery' of tests was developed that would accurately measure change in patients' cognitive function, divided into seven cognitive domains: speed of processing, attention/vigilance, working memory (verbal and non-verbal), verbal learning, visual learning, reasoning and problem solving, and social cognition.

A VIRTUAL REALITY ASSESSMENT

The Virtual Reality Functional Capacity Assessment Tool (VRFCAT) is a computer- and web-based tool that assesses patients' ability to perform tasks that are a common part of everyday life, such as travelling on public transport, paying for shopping etc. The battery aims to measure functional capacity, or "real-world functional improvements associated with cognitive change" [Keefe et al., 2016].

The VRFCAT differs from other assessment tools because it is computerised and performance-based. This means there is the potential for this test to be delivered remotely, and an outside observer or informant of a patient's behaviour, such as a family member, is not required. Other tests, like the UCSD Performance-based skills assessment (UPSA), have previously relied on pen-and-paper tests, with a role-play component that requires patients to act out certain tasks. However, many of these tasks, such as writing cheques or calling a phone directory, are now somewhat out-dated. The VRFCAT has six alternative versions which allows the test to be administered repeatedly over time, without the patient's scores improving simply because they have performed the test previously, the so-called 'practice effect'.

HOW WELL DOES IT WORK?

The NeuroCog Trials team assessed patients and healthy controls with a variety of different metrics to compare how well the VRFCAT performed at measuring functional capacity against other tests. The VRFCAT compares well with other measures, such as the UPSA, which has previously been used in trials. Different versions of the VRFCAT were used to measure the differences between them.

The high degree of correlation between the VRFCAT and UPSA suggests that the VRFCAT is a useful tool that accurately measures the functional capacity of users. There was clear differentiation between the scores of schizophrenia patients and healthy controls. Better test times were associated with lower degrees of cognitive impairment as measured on the Schizophrenia Cognitive

> **NeuroCog Trials develops innovative technologies that utilise virtual reality and computerised assessments to augment the measurement of cognitive and functional abilities in clinical trials**

Rating scale (SCoRS) and higher Specific Levels of Functioning (SLOF) scores.

DIGITISING EXISTING TESTS

Another of NeuroCog's innovative projects is the Brief Assessment of Cognition (BAC) App, which is a tablet-/app-based version of the pen-and-paper Brief Assessment of Cognition in Schizophrenia (BACS) test battery. The test measures a user's ability to perform six tasks to assess their reasoning/ problem solving, working memory, verbal memory, and processing speed.

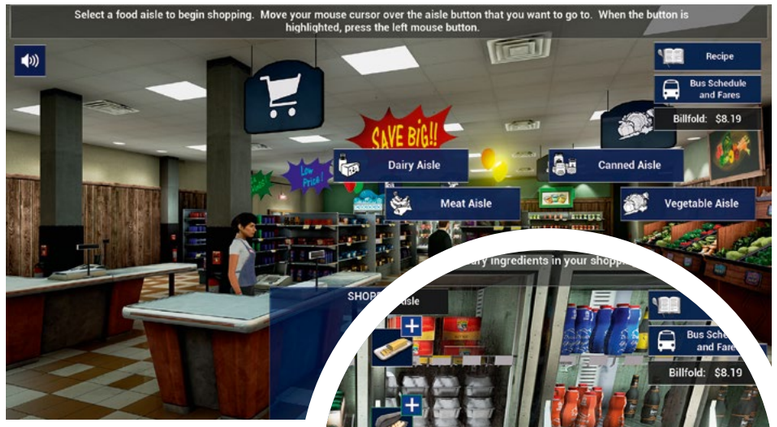
In a paper co-written by Alexandra Atkins and others, Keefe and team compared the results of the BACS and BAC App methods. They found that there were no discernible differences between the traditional version of the test and the app version, and that there was a robust difference between schizophrenia patients and healthy controls. This supports the notion that the BAC App is appropriate for use in clinical trials.

Tablet-based methods are useful because they allow the incorporation of all the benefits of computerised methods, such as standardised algorithms and voiced-over instructions, while maintaining the interaction with the patient, which is important in cognitively-impaired or behaviourally-challenging populations such as patients with schizophrenia or Alzheimer's disease.

LOOKING BEYOND SCHIZOPHRENIA

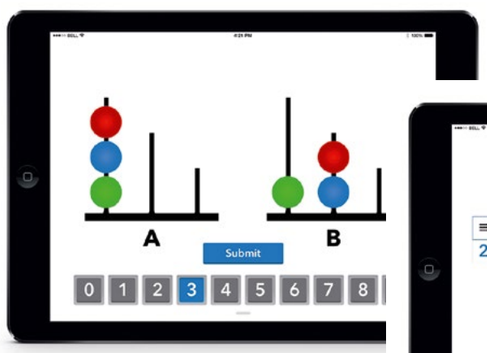
The VRFCAT and BAC App have potential applications beyond schizophrenia – for instance they are being tailored specifically for studies of patients with Mild Cognitive Impairment associated with Alzheimer's disease, and are currently being used in trials of patients with depression and those at-risk for bipolar disorder.

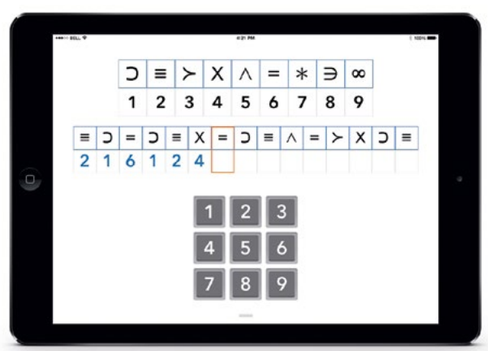
Novel technologies such as virtual reality and simple apps are increasingly being recognised as effective methods to administer treatment and assist with diagnosis. NeuroCog Trials' wealth of scientific expertise will enhance clinical outcomes associated with diseases like schizophrenia and Alzheimer's that impair sufferers' cognitive abilities.



Above and right: screenshots from the VRFCAT.

Below: examples of the BAC App in action.





Q&A

How has your scientific training informed your work as part of NeuroCog Trials?

Everything we do at NeuroCog Trials is grounded in scientific principles. As a clinical psychologist, I was trained to pay very close attention to detail, as small changes in any experiment can have a substantial effect. Getting at the truth in human assessment is a fascinating endeavour, but you need to be trained not to fool yourself that you have a clinically significant finding if it is due to a weakness in your design and interpretation. We help companies design studies and create new outcome measures that get at the real effect of their treatments.

What are the similarities between schizophrenia and Alzheimer's disease?

They are both cognitive disorders caused by neurobiological abnormalities of unclear origin. While Alzheimer's research is farther along in terms of understanding some of the specific brain processes that are affected, both disorders have cognitive impairment as their core symptom. We have leveraged some of the work that I have been doing for 30 years in schizophrenia to create new tools for assessment in Alzheimer's, which has been warmly welcomed by researchers in both areas of work. These are two of the worst conditions in all of humanity, and treatments are desperately needed.

Are there other diseases you think your tools are particularly applicable to?

Yes. We have been working in several other areas. The first is risk syndromes, such as the identification of people who are at risk for Alzheimer's, schizophrenia, or bipolar disorder, yet have not yet developed the full-blown version of the illness. We have built our tools to be sensitive to subtle changes that occur before the illness strikes. That is the best time for treatment to begin, but you need to know who has the illness and who does not. We feel our tools can help with that important prediction. We are also working in major depression and areas outside psychiatry, such as brain cancer, Multiple Sclerosis, and Opioid Use Disorder.

Have you been able to see the benefits of the technologies your company has developed in action?

Yes. It has been tremendously rewarding to see the use of our technologies in large-scale clinical trials. Our video recording platform was instrumental in identifying thousands of errors in test administration and clinical assessment across over 300 international assessment sites. Improvements in data lead to greater sensitivity to treatment effect, which is our primary goal. Our new tablet- and computer-based cognitive and functional assessments are being used in large trials, and so we are excited to see the results from these studies. We want to be a part of the programmes that develop treatments that can reduce suffering in these patients. That is our primary goal.

What is next for NeuroCog Trials?

We are building on the success of our new technologies. We are designing our assessment tools so that clinicians and raters feel not like they are dealing with burdensome new devices, but rather like they have been given natural extensions of themselves, helping them connect with their patients and the symptoms that are causing them pain. And we are thinking not in terms of how can we compete to make better devices than our competitors, but rather how we can provide the scientific community with tools that will reshape clinical assessment and clinical trials for the future.

Tablet-based administration of tests is useful because it incorporates the benefits of standardisation while maintaining the importance of the patient interaction"

Detail

RESEARCH OBJECTIVES

Dr Keefe's work applies innovative strategies in neuroscience to measure human cognition. He co-founded NeuroCog Trials with this aim in mind and the company now works to develop cognitive assessment tools for use in clinical trials.

FUNDING

The company is privately owned and receives Small Business Innovation Research grants from the National Institutes of Health in the United States

COLLABORATORS

NeuroCog Trials was founded from Dr Keefe's lab at Duke University Medical Center and maintains strong ties with many Duke faculty and other leading scientists in academia, government and industry.

BIO

Dr Keefe graduated from Princeton University, received his PhD in clinical psychology from NYU and completed his clinical psychology internship at Yale University School of Medicine. He is currently Professor of Psychiatry, Psychology and Neurosciences at Duke University Medical Center and has published over 220 peer-reviewed scientific papers on cognition, schizophrenia, dementia, depression and other CNS disorders.

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