**Introduction**

The tests on the Cambridge Brain Sciences platform have a long history, beginning with a series of early studies in patients with focal lesions conducted in the early 1990s, which pioneered the use of computerized cognitive testing in neuropsychology (e.g. Owen *et al*., 1990; 1991; 1992; 1993a; 1993b; 1995a; 1995b; 1996a; 1997). These studies have been followed by more than 600 publications using these original tests in Parkinson's disease, Alzheimer's disease, Huntington's disease, Depression, Schizophrenia, Autism, Obsessive-Compulsive Disorder and ADHD, among many others over a 25-year period.

With the advent of functional neuroimaging in the early 1990s, the tests were adapted for the scanning environment and used in numerous positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies of both healthy participants and patients (e.g. Owen *et al*., 1996b; 1996c; 1996d; 1996e; 1997; 1998; 1999).

In 2010, the tests were adapted once again to capitalize on the numerous advantages that internet-based testing can offer and have been used in several large-scale population-based studies involving tens of thousands of participants (Owen *et al., Nature*, 2010; Hampshire *et al*., *Neuron*, 2012), as well more than 300 bespoke studies by researchers from all over the world (e.g. Metzler-Baddeley *et al*., 2016; Pausova *et al*., 2015; Esopenko *et al*., 2017). The tests are deployed through cambridgebrainsciences.com, a custom-built research platform for hosting and conducting scientific trials. In total, more than 8 million tests have been taken and 100+ scientific studies have been published using data acquired on the platform. Normative data from 75,000 healthy participants is available to researchers using the site.

As such, Cambridge Brain Sciences is the most advanced fully online cognitive assessment battery in the world. The sheer volume of data that can be collected efficiently and cost-effectively, without the need for supervised lab-visits, makes it the only choice for large scale, population based clinical and behavioural studies whether conducted over weeks, months or years. As a current example, my lab has recently completed a comprehensive study of the sleeping habits of 40,000 participants and their effects on cognitive function. All 40,000 participants were tested in the space of several weeks in the autumn of 2017 and four separate papers are now under review in *Science*, *The Lancet*, *Sleep* (now published), and *PNAS*.

Key features include:

1. Fully enabled remote testing of cognition (memory, attention, reasoning, decision-making, planning etc) on any platform (desktop, tablet etc), with an internet connection.

1. Fully unsupervised assessment through the inclusion of training packages and comprehensive interactive online guides for users. Our comparisons between supervised data collected in the lab and unsupervised data collected ‘at home’ yields exceedingly high levels of correlation.
2. A fully secure, web-based research portal and user-interface for data collection, storage and analysis (CBSTrials). Participants can be sent automated scheduled ‘reminders’ to test themselves at any interval, the system can track compliance and alert researchers to ‘missing sessions’ etc.
3. Infinite repeatability. Each test has built in proprietary algorithms that generate a unique set of problems for each assessment, facilitating longitudinal studies with minimal ‘practise effects’.
4. Access to a comprehensive set of data ‘norms’ for 75,000 individuals, with complete demographic details as well as CBS test scores, plus a larger population database of more than 8 million tests that have been taken over 7 years.
5. Full access to a technical support team at *Cambridge Brain Sciences Inc*, in Toronto, and scientific support from my large and active cognitive assessment lab at the University of Western Ontario, Canada.

The following questions are particularly relevant to the proposed study of the relationship between stroke, dementia and cognition across Canada:

1. **To what extent can CBS tell that somebody is deteriorating cognitively**? A common task for neuropsychologists, and scientists who study aging populations, is to assess cognitive change over time. However, identifying what constitutes a real and meaningful change in cognition is difficult because the stability and reliability of neuropsychological tests are inherently less than perfect. A measure of an individual’s cognitive performance will change upon repeated testing because of measurement error, practice and novelty effects, regression to the mean, normal variation in performance, other random sources of error, and perhaps, meaningful change (e.g., deterioration resulting from a clinical condition). Detecting the latter, given all the sources of noise, is the goal of tracking cognitive change. Fortunately, there exists a class of statistical methods, referred to as *measures of reliable change*, that we at Cambridge Brain Sciences (CBS) use to determine whether a real change has occurred over time.

Essentially, a measure of reliable change compares the difference in an individual’s performance on a given test, between two time points, to the variability in repeated test measurements that occurs in the *absence* of real and meaningful change. The latter is typically estimated from a sample of healthy control subjects. The simplest method – the reliable change index (RCI) – uses the test-retest reliability and the standard deviation of scores (measured in a control sample) of a test to describe the range of possible differences that occur in repeated testing. If an individual’s change in performance from one time point to another is much larger than that expected by chance, we conclude that there was *meaningful change*. More complex methods that we also use, where necessary, include adjustments for practice effects and regression to the mean, pooling information over multiple time points and/or tests, and accounting for demographic factors, like age and gender. Of course, assessing reliable change requires that these data have been obtained in a control sample and that sample should be as large as possible.

CBS has a unique database of more than 800,000 test scores, across the 12 tests in the core CBS battery, drawn from almost 75,000 individuals. Most of these individuals have played every test more than once, and more than 5000 people have played every test more than 10 times. The interval between self-administered repeated testing ranges from less than a day, to more than a month. This massive database is the only one of its type and size in the world and allows us to characterize in the general population how performance on every test fluctuates naturally across a range of testing intervals, and over time. So far, we have quantified the bounds of what constitutes *a reliable change* for every test and found that these do not depend on testing interval, or how many test plays occurred previously. In contrast, practice effects (which occur for only certain tests) are far more pronounced for shorter testing intervals, but get smaller with continued repeated testing. With these methods and access to this historical database of CBS data, we are absolutely confident that we will be able to construct models that incorporate learning effects, age, gender, and testing interval, to identify participants in any large trial like this who exhibit meaningful changes in cognitive performance that can then be investigated further.

1. **Why do these tests online?** The Owen lab specializes in online cognitive testing, not just because *we can*, but because we are interested in questions that can only be answered effectively and efficiently when administered over the internet. As an example, we are currently conducting a longitudinal study of all students who have participated in contact sports at the University of Western Ontario to ascertain how repeated blows to the head affect their future education and cognitive development. Most these young people move away as soon as they graduate and it would be logistically and economically impossible to bring them back for cognitive testing at regular intervals. Over the internet, they can be followed up regularly at almost zero cost and, crucially, adherence to the study protocol is extremely high, because the ‘overhead’ for the participants is extremely low (no travel, no visits to a clinic, no waiting times, just a 30-minute session of ‘brain games’, on their own computer and at their convenience). Moreover, we have shown in multiple published papers that this method of testing generates data that is as reliable as traditional laboratory-based testing (e.g. Stojanoski *et al., Neuropsychologia*, 2018). Finally, we have a proven track record demonstrating that this approach is well accepted by Journal Reviewers and Editors of high impact journals (e.g. Owen *et al., Nature*, 2010; Hampshire *et al, Neuron*, 2012; Wild *et al., Sleep*, in press). The current study is a perfect example of one that would not be feasible on the scale that is intended, if conducted in a strictly laboratory setting. Using the internet and our proven methodology, we are confident that we can assess and longitudinally monitor cognitive function in tens of thousands of older participants, or more, with a high degree of reliability.
2. **What’s the added value of using Cambridge Brain Sciences and the resources of OwenLab?** As I have mentioned above, the Owen lab has arguably more experience than any other worldwide in the acquisition and analysis of large-scale cognitive data sets collected over the internet. We have devised, managed and published several studies involving tens of thousands of participants and several million data points (e.g. Hampshire *et al, Neuron*, 2012 – 44,000 participants). My team is streamlined for dealing with every aspect of experimental design, data acquisition, analysis and interpretation and by utilizing Cambridge Brain Sciences as its cognitive testing platform, this project would have unfettered access to this group of experts at every stage of the project. We can advise on how best to acquire uncontaminated data, how to ‘clean’ data post-acquisition, how to store, collate and prepare data for analyses, provide access to dedicated servers at Western that routinely collect and store data from 100,000+ participants, utilize our existing analysis pipelines for efficient and accurate data analysis and interpretation, and draw on our wealth of local statistical expertise. Moreover, through our close reciprocal ties with Cambridge Brain Sciences Inc, based in Toronto, we benefit from a full team of technical support personnel (in fact, the VP-Engineering is based here in London, Ontario so is readily on hand to deal with any technical issue 24/7). Finally, I personally have 30 year’s experience in the design, management and analysis of cognitive studies, and through my involvement as a collaborator I firmly believe that we stand to learn something completely new about the distribution of dementia and stroke in Canada and it’s relationship with cognitive function.
3. **Will older people participate in an online study of this sort?** Since our first large-scale public online study in 2009 (a collaboration with Prof. Alistair Burns, published as Owen *et al.,* *Nature* in 2010), we have become well accustomed to recruiting older populations and have had considerable success in this area. Perhaps contrary to popular expectations, many people over the age of 65 now use the internet daily and our experience has shown that they typically have no problems in completing our tests on line. Nevertheless, the tests are designed to mitigate dropouts and encourage adherence through a number of mechanisms i) Through the inclusion of brief (30 or so yes/no questions), quality of life/activities of daily living questionnaires before the tests themselves, we find that we are able to engage participants’ interest by providing them with an opportunity to tell us a little about themselves and (where study appropriate), find out how their life experiences compare to others with a similar demographic background ii) All of our tests begin with a full instructional video iii) Each test also has a ‘guided practice’ mode, which is available to any participant at any time, should they feel that they do not understand the requirements of the task. iv) Finally, most of the tests use a ‘ratchet approach’ developed in house, which generates easier problems following failure and more difficult problems following success. This has the effect of making all participants feel that they are ‘doing well’ in term of their number of successful versus unsuccessful trials, regardless of their actual level of performance. In all, we are confident that the Cambridge Brain Sciences tests appeal to and, are extremely well tolerated by, participants aged 65 and over, as evidenced by our rapidly expanding ‘normative’ database which contains more than 2000 participants in this age group.