

# Longitudinal Study of Many Neurological Disorders'

## Connections to Neuropsychological Impairments

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### **Abstract**

The brain is what gives individuals their unique personality and cognitive ability, so when the brain is damaged, a person's cognitive capacity may also be damaged. The cognitive impairment is specific to the type of brain damage and can greatly vary from person to person. There has been no widespread convention for what tests have been used to analyze each cognitive domain's impairment, making it difficult to compare previous results stemming from the different neurological disorders. Our objective is to use a standardized battery of cognitive tests, taken on a large time scale, to analyze the effect that different brain disorders have on long-term cognitive ability and to assess the cognitive trends between a wide array of neurological disorders and the connections that they have to each cognitive area. The study will track a large group of healthy subjects who have taken the standardized battery, the Cogstate Cognigram assessment. Should the subjects be diagnosed with any neurological disorder in the future, they will be asked to retake the assessment at one-year intervals, collecting data on each cognitive domain's impairment and the status of the neurological damage. Our findings will advance the field's understanding of the relationships between specific cognitive domains and the neurological disorders that impair them.

### **Introduction**

#### *I. The Cogstate Cognigram Battery Assessment*

The way in which a brain functions is a delicate balance of chemistry and physical placement of neurons. If this balance is upset, through physical damage to neurons or a serious chemical imbalance, that individual's cognitive abilities may become impaired. The brain has

many specific regions that perform various tasks that all contribute to overall cognitive power, similar to the way that each part of a computer performs specific tasks that enable the computer to function properly. Many people in the fields of neuroscience and neuropsychology have worked hard to understand the connection between the physical brain and a person's cognitive abilities. Past studies have tested the type of cognitive damage that different neurological disorders have, but they have neither quantified the cognitive impairment nor used tests that allow comparative analysis across all of the disorders. Our goal is to be able to quantify the degree of impairment in the main cognitive domains caused by as many different neurological disorders as possible. Additionally, we will analyze the data to find the trends in cognitive impairment caused by different neurological disorders. Giving the standardized Cogstate Cognigram Battery to a wide range of healthy people will allow for follow-up assessments post-diagnosis, should any subject develop any neurological disorder, allowing us to pinpoint the cognitive area that is impaired and find connections between many types of impairment and the type of neurological disorder. Our study will be similar to testing how a computer's overall behavior changes when a certain component is damaged, and the types of stress that puts on the rest of the parts. We expect to find similarities in the type of cognitive impairment when the neurological disorders are located in a similar region of the brain. Trends in the severity of impairment relative to the disorder will also be highlighted. These connections are very important because they will lead to a much more comprehensive understanding of how the domains of cognition are related to each region of the brain. The results of this study could have impacts in the neuroscience and cognitive fields, as well as in psychology, and may impact the way in which cognitive tests are used to predict a neurological disorder.

## *II. Background*

Since this proposal has such a broad scope, a history of previous cognitive assessments will help provide a better understanding of why this test is necessary. A widely cited study performed by Y. M Archibald and his colleagues in 1994 determined the amount of neuropsychological degradation in patients who underwent chemotherapy for malignant glioma tumors. These tests included: the Wechsler Adult Intelligence Scale, the Rey Osterrieth figure, the Buschke Selective Reminding test and a few other domain-specific tests. It is important to note that these tests were given in a varied time frame after diagnosis, and none of the patients had taken the test before diagnosis. Despite being cited over 134 times, Archibald's study was limited due to the fact that only 25 total patients were used in this study, and 9 of them did not complete all five testing sessions (Archibald, 1994). It did compare the patients' results with a healthy control group of peers, but, had the affected patients been tested when they were healthy, the effects of the disorder and postoperative cognitive impairment could have been clearer.

In 2003, a meta-review including Archibald's study and an additional 29 experiments involving a total of 838 patients compiled a list of 127 cognitive effects due to brain cancer in adults, showing a negative effect found in executive function, verbal memory, and motor function (Hanley, 2003). However, this study said that even with these results across many studies "more research is needed to clarify which treatments may produce cognitive decrements, the size of those effects, and their duration" (Hanley, 2003).

Other neurological disorders have had similar postoperative cognitive assessments performed with varying degrees of success. One study investigated the social-cognitive and decision-making abilities in patients with mesial temporal lobe epilepsies (MTLE). The authors argued that the communication and interpersonal relation abilities are decreased, both in the healthy group and the normal epilepsy group. The Comprehensive Affect Testing System

(CATS) showed that the patients with MTLE were significantly impaired compared to the normal control and the epilepsy control group (Broicher, 2012). This source, cited only 12 times, had only 42 subjects and would have been improved had the patients been tested when they were healthy. Yakushiji *et al.* used the Mini-Mental State Examination, a short cognitive assessment to quantify the severity of neuropsychological damage due to hypertensive pathogenesis (Yakushiji, 2012). Gregoire *et al.* used multiple cognitive assessments to analyze stroke patients' cognitive impairments over an average of 5 years (Gregoire, 2012). Both of these studies tested relatively similar cognitive domain impairments and yet used radically different assessments, causing their results to be very difficult to compare or contrast with each other. Had they used a standardized test, such as the Cogstate Cognigram, for both experiments their results could have led to a deeper analysis of the effect of stroke cerebral microbleeds on cognitive impairment, possibly even leading to understand how to predict CMB onset using the standardized test.

Many other studies have been faced with similar issues of not being able to compare their results, either having too small a sample size (Broicher, 2012) or not using a long enough time scale (Shortman, 2014). Robert Shortman's study was well organized with 39 children diagnosed and undergoing treatment, but the final cognitive assessment was given only one year after diagnosis. Cognitive decay and recovery may take longer than that so a wider timescale is needed to measure effectively their improvement or impairment. The proposed study will be significant for a multitude of reasons, one of which is that it hopes to address most of the flaws of previous studies by having a longer timescale and by investigating the cognitive impairments over a wide array of neurological disorders using a single standardized test.

## **Methods**

### *I. Hypothesis, Data Collection, & Cognitive Assessment*

Patients who develop neurological disorders in similar regions of the brain are expected to exhibit cognitive impairment in the same or similar cognitive domains, with the severity of impairment corresponding to the severity of the neurological disorder.

To achieve our objectives, this experiment will require a long time-frame and a very large participant base. The cognitive assessment must also cover the wide spectrum of cognitive domains while being accurate enough to reveal minute changes in them. To get a large enough base of healthy patients, we will contact large HMO's such as Kaiser Permanente, and request their participation in the experiment. We will ask these organizations to request that healthy patients, when coming in for a routine checkup, take the cognitive assessment in the interest of their own future health and the pursuit of science. The patients will take the assessment on secure computers in the hospital where their results will be uploaded to DataPoint, the secure Cogstate website. As incentive and compensation for their time, each person who takes the assessment will receive a small cash incentive. It is reasonable to assume that the majority of healthy people will decline to take the assessment due to time constraints or disinterest. Another incentive to promote continual survey taking could be after 10 surveys completed the patients would receive an additional promotional gift, perhaps a free checkup or a volume of the show "Brain Games" (Cognitive related Nat Geo show). However, since Kaiser Permanente serves over four million people, if even one percent decided to take the assessment, our experiment would have a baseline cohort of around 40,000 people.

If Kaiser refuses the research, then other companies with similarly large user bases would be approached in order to be able to get the largest sample size. Aetna, Blue Cross Blue Shield Association, CIGNA, Humana, Health Net, UnitedHealth Group, WellPoint, Magnacare, WellCare Health Plans are all open options that could be investigated for patient data collection.

Such a large amount of people is needed, because only a small fraction of these healthy patients will contract some form of neurological disorder or damage in the future. With a large enough initial base, we hope to capture a sample of the most common disorders such as dementia, epilepsy, headache disorders, multiple sclerosis, neuroinfections, neurological disorders associated with malnutrition, pain associated with neurological disorders, Parkinson's disease, stroke, and traumatic brain injuries. The patients who have taken the cognitive assessment while healthy will be flagged in the Kaiser (or other HMO's) medical information system. Should they eventually be diagnosed with one of these disorders, they will be asked to retake the cognitive assessment soon after diagnosis and again after treatment. The results of the tests will be compiled from across the country and the world into a database. This will be categorized online into different cognitive domain task scores, along with other factors, such as age of patient, type of neurological disorder, and location of the disorder.

The cognitive assessments planned for use in this study are the Cogstate Cognigram Battery developed by the Cogstate research team. The Cogstate test battery will be extremely useful since it can be administered completely on a computer with the results being instantly uploaded to the database for categorization. The main cognitive domains will be tested by various standardized tests shown in Figure 1.

Questions will be in the form of a card game format, asking various questions repeatedly such as has this card been seen before or is the card red etc. The cognigram test takes around 10-15 minutes so as not to take too much of the patients time.

These domain tasks have been tested for validity by researchers collaborating from Melbourne, Australia, University of California at San Diego, and the Department of Psychiatry, at Yale University. They report that the tasks have sufficient sensitivity to the cognitive

impairment due to neurological disorders such as mild traumatic brain injury, schizophrenia, etc. (Maruff, 2009).

**Figure 1**

Fig 1	
Visual Motor Function	Chase Test
Executive Function	Groton Maze Learning Test
	Set-Shifting Task
Psychomotor Function	Detection Task
Visual Attention	Identification Task
Visual Learning & Memory	One Card Learning Task
	Continuous Paired Associate Learning Task
	Groton Maze Learning Test
Verbal Learning & Memory	International Shopping List Task
	International Shopping List Task: Delayed Recall
Attention / Working Memory	One Back Task
	Two Back Task
Social Cognition	Social-Emotional Cognition Task

## Rationale

### *I. Budget*

This long-term study hopes to gain insight into the connections between distinct neurological disorders and the cognitive impairments that are caused by the disorders. The Cogstate assessment will be suggested to any healthy patient in the Kaiser Permanente system, for example, which will create a very large baseline. Any person who develops a neurological disorder in the future and retakes the assessment will enable an unprecedented direct comparative analysis with their previous cognitive score. Using scores from a standardized

assessment taken by all participants with a wide array of neurological disorders will allow comparisons to be made on multiple levels. The relationship between the physical site of damage and the type of cognitive impairment can be quantified. The relationship between the type of damage and the type of cognitive function it impairs can be measured. Many other comparisons could be made from the large amount of data that will be collected in this experiment.

Neuropsychology and neurology are just beginning to understand how the different pathways in the brain control cognition. Past studies have been relatively effective at determining what type of cognitive impairment results from a certain neurological disorder; however, these studies have not been as effective in quantifying the degree of impairment relative to an impairment of the same domain due to a different disorder. The proposed study will quantify cognitive impairment in many different domains and will catalog this data in relation to various neurological disorders. Having such a vast data set to analyze may lead to significant connections between the disorders. A similarity in cognitive impairment domain and severity between neurological dysfunction from similar damage is one such connection that we hope to discover.

Gaining a stronger understanding of the connections between different neurological disorders and how each affects cognition in both similar and unique ways will allow doctors to make more informed decisions before surgery and may lead to better treatments. Using this standardized assessment on such a large scale could also lead to predictive abilities, possibly assisting in the discovery and diagnosis of a neurological disorder.

For such a large-scale investigation, the budget is expected to be \$1,020,760.00 over the long term, according to Figure 2. The Cogstate Battery software is freely available to download and install as long as the study meets their criteria (which it is expected to). Having the patients take the Cogstate exam in the Kaiser facility will require some form of compensation to the

Kaiser Medical Group for use of their rooms. The data for the average cost for a room per hour of use in their hospitals was unavailable, so we estimated cost using the \$20 co-pay that is required for patients for a standard checkup. This amount will be expected to be less than the estimated cost until 40,000 assessments have been run. The Kaiser technical staff estimate was determined through project Glassdoor, assuming the Cogstate assessment will need to be installed at each physical Kaiser location by the technician on site (Glassdoor). This is a rough estimate based on average salary taking into account the large number of locations. The research team estimate assumes part time involvement of multiple analysts on stipend over the length of the experiment.

**Figure 2**

Necessary Materials and Services	Estimated Funds Needed (\$)
Cogstate Battery	Free of charge to use
Check-up Room lease (20\$/h using .5 hour increments)	up to \$490,760.00
Patients time compensation (\$10 Amazon gift card in bulk up to 40,000)	up to \$400,000.00
Kaiser Technical Staff	\$30,000
Researcher Team (6)	\$60,000

Partnering with reputable physicians and cognitive scientists in the Cogstate team and from other research institutions would build credibility. This credibility could be used in a grant proposal. Government grants can exceed one million dollars if the proposal is written well and

reputable. Aid could also come from government agencies such as: Agency for Health Care Research and Quality, Office of the Assistant Secretary for Health, and other agencies.

Sponsorships might also be found if worked for. Many different foundations are giving money specifically for contributing to research in their fields such as: National Institute of Health, Research Partnership in Cognitive Aging, McKnight Brain Research Foundation, National Science Foundation, Michael J. Fox Foundation (Brain disorder research), James S. McDonnell Foundation. There are many more I am sure that could be found with additional effort. Each would need to be tactfully approached with a concise proposal and fundraising proposition. The budget might also be revised to account for fundraising estimates.

## *II. Public Health Impacts & IRB Conditions*

This study does not involve any direct physical testing of patients, although through the design of the experiment, the subjects involved will have been diagnosed with different disorders and be undergoing treatment for them separately. This proposal hopes to improve the understanding of how the brain creates cognition and the connections between a brain disorder and the cognitive impairments involved. Research into these connections could lead to a new form of prediction, using the Cogstate assessment to tentatively test for potential brain disorders without a large neurological examination. This will hopefully improve the general public health by increasing neurological health and awareness.

To fulfill IRB requirements all research staff will undergo the Responsible Conduct of Research through the CITI program. Informed consent forms will be filed for each volunteer to meet the confidentiality requirements for IRB approval. This study will also need IRB approval, so there will be measures taken to meet their expedited research guidelines.

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