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RESEARCH ARTICLE

The Brain Gauge: a novel tool for assessing brain health

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Abstract

Background. A large number of neurological disorders (neurodegenerative, neurodevelopmental or trauma induced) are difficult to diagnose or assess, thus limiting treatment efficacy. Existing solutions and products for this need are costly, extremely slow, often invasive, and in many cases fail to definitively (and quantitatively) diagnose or assess treatment.

Advances. For the past decade, we have been developing what we consider to be an innovative low-cost sensory testing device (the Brain Gauge) that non-invasively assesses the central nervous system (CNS). The objective has been to develop an inexpensive, highly accurate, simple to use device to assess brain health in all environments: in the clinic, at home, at work, on the battlefield or sports field. The device is non-invasive, generates no harmful radiation, requires no chemicals nor exposure to dangerous substances. The device does not require expensive disposables and does not involve the use of samples that require physical processing in a central laboratory. Tests can be administered in a matter of minutes and do not require expert oversight. The most recent versions of the technology are easily portable; the device is the size and shape of a computer mouse. As such, the technology is particularly well suited to non-drug, non-radiation based alternative and in-home care. The device and methods have been used in numerous studies of neurological cohorts that are often considered difficult to diagnose or assess objectively. Based on over a decade of studies (currently an ontological database of over 10,000 subjects and over 60 peer reviewed publications), the system can be used to enable clinicians to have a much better view of a patient's CNS health status. The diagnostic system delivers a battery of sensory based (tactile) tests that are conducted rapidly – much like an eye exam with verbal feedback – and the tests were designed to be predominantly impacted by specific mechanisms of CNS information processing. Because of the broad diversity of the questions addressed by the different metrics, combining the metrics allows for the generation of a unique individual CNS profile that appears to be very sensitive to neurological status.

Outlook. A review of the development of the system and the application of the method in basic and clinical research is provided to give readers an insight into why the methods were developed, how the methods work and what the methods can be optimally utilized for. The methods provide an objective means for clinicians and

researchers to track brain health, and examples of case studies of tracking recovery from concussion as well as response to treatments are provided.

Introduction

Current contemporary methods for assessing neurological disorders are often found inadequate because they either lack sufficient resolution, are not practical or portable, lack specificity, and/or are not accurate or objective. New, more advanced, methods of assessing brain health that are portable, easily implemented and administered are needed in order to provide accurate and objective outcome measures to better determine and/or track efficacy of recovery and/or treatment of neurological disorders. Over a decade ago, we conceived a radically new approach to assessing brain health. To summarize, this concept is very simple: it takes advantage of the very direct mapping that exists from skin to cortex and creates measurable sensory percepts that occur from interactions between well-defined groups of brain cells that are activated by stimulating the skin. Conducting experiments with human and non-human primates in parallel, it was demonstrated that there was a very high correlation between the sensory percept in humans and the patterns of brain activity in non-human primates (for review, see Tommerdahl et al (1)). Additionally, we demonstrated that alterations in different sensory perceptual metrics could be related to specific underlying neural mechanisms, and in particular, to the dynamic changes that occurred cortically in response to repetitive tactile stimulation. This, in turn, led us to develop a rich array of sensory perceptual metrics (called cortical dynamic metrics or cortical metrics) that could be implemented by delivering performance tasks with a high precision tactile stimulator.

Over the past decade, we have developed a number of cortical metrics to utilize in research for evaluating CNS deficits across a wide spectrum of neurological disorders. Each of these cortical metrics have been published independently (most multiple times), and these somatosensory based tasks have demonstrated sensitivity to alterations in neurological function in autism (2-8), Tourette's (9), OCD (10), ADHD (11), Parkinson's (12, 13), chronic pain (14-16), concussion (17-20), aging (21), alcohol consumption history (22), early stage diabetes (23) and amputation (24). Additionally, healthy individuals demonstrated sensitivity to pharmacological manipulation (low dose of DXM (25)), conditioning with TMS (26-28) and different conditions of adaptation (1,29,30). These studies were made possible by the utilization of a high precision tactile stimulator, and this review discusses the concepts behind the methods, the device developed to utilize those methods, a description of one of the cortical metrics (lateral inhibition), how the metrics are combined to provide an overview of an individual's brain health, and some exemplary results from case studies that we have observed with this novel methodology.

The concept: non-invasively assessing brain health. There are countless reasons that a person's blood pressure could be high: hardening of the arteries, too much salt in the diet, kidney malfunction, obesity, etc., could all be one of many of the potential culprits that cause high blood pressure. The long list of things that could

lead to high blood pressure would seemingly deter us from using it as a vital sign, a standard measure of health, since any of a number of factors could be what led to the deviation from normative values and thus, the measure of blood pressure seems somewhat nonspecific. The same is true of all vital signs. However, blood pressure is generally regarded as a starting point for a physician to determine what, if any, more detailed assessment and subsequent action should be taken to return a patient to cardiovascular health.

Vital signs have a well-earned central role in health and medicine because they allow a rapid and accurate albeit non-specific assessment of the health status of a person. Could such a non-invasive procedure exist for evaluating the general health status of a patient's central nervous system (CNS)? Is there a vital sign for brain health? We believe so. Sensory perception relies on many facets of the CNS for a patient or subject to perform well (or within a "normal" range). First, it requires that the peripheral nervous system (PNS) is, for the most part, intact. Second, transmission of the signal must reach the sensory cortex (in the case of the somatosensory system, via the spinal cord) with reasonably good fidelity. Third, processing within the cerebral cortex must be capable of spatially and temporally integrating information that it has received, and this typically requires multiple levels of processing – both in the primary sensory cortex as well as at cognitively higher levels.

When we began development of a method for evaluating brain health, we chose the somatosensory system because it is ideally suited for the design of a such a CNS diagnostic system. First, the organization of the somatosensory system is such that adjacent skin regions project to adjacent cortical regions (i.e., it is somatotopic). In other words, if you mechanically vibrate two adjacent finger-tips, you activate significant brain activity in two adjacent cortical regions that will interact in a predictable fashion – assuming that the brain is healthy. Second, ambient environmental noise in the somatosensory system can be easily controlled (i.e., it is less likely that a patient will be exposed to distracting tactile input than auditory or visual input). Third, the somatosensory system is the only sensory system that is highly integrated with the pain system, and this is often an important aspect of a patient's diagnosis. Pain will increase activity in cortical area 3a (31-33), and this will suppress cortical areas 3b/1, the areas responsible for processing mechanical stimuli (1,34), which in turn leads to alterations in the ability of an individual to process specific stimuli (15,35).

Neurophysiological studies over the past 60 years have well established that corticalcortical interactions play a significant role in sensory perception: adjacent and near adjacent neuronal assemblies interact with one another and these interactions result in distinct percepts. For example, the Nobel Laureate Georg von Bekesy first described lateral inhibition, the process by which cortical neurons, when they become active, work to suppress or inhibit the activity of the cortical neuronal assemblies surrounding them (36). While this description of lateral inhibition does not seem all that earth shattering, it should be noted that von Bekesy made this proposition based on sensory perceptual experiments. In other words, an important

neurophysiological mechanism was characterized simply by measuring what individuals perceived in response to sensory stimuli. In the subsequent decades, neurophysiological experiments – including those conducted by our group - demonstrated the concept of lateral inhibition. Additionally, a common experimental design that was employed was to use neurophysiological experiments (e.g., extracellular recording and/or high-resolution imaging in animals; see Tommerdahl et al (1) for review) to either confirm findings predicted by (human) sensory perceptual experiments or to subsequently design sensory perceptual experiments to confirm the role of neurophysiological mechanisms characterized by the animal experiments.

The resolving power of sensory perception is much greater than any medical device. Perhaps the best-known example of a sensory perceptual test is the eye chart – most people are prescribed lenses based on a simple and basic eye exam using an eye chart. A very high degree of corrective optical precision is easily achieved by this simple sensory perceptual test using only a paper eye chart and verbal responses from the patient. The vast majority of people would not consider nor benefit from putting their eyes in a scanner to determine optical geometry of their cornea-lens-globe-retina system to calculate their prescription. Not only would this be expensive, but it would invariably miss other important factors of their visual system and thus would likely yield a poor estimate of the visual correction that they need. Nonetheless, the health care industry has gravitated to more and more expensive methods (such as imaging systems) which often do not work as well as less costly, simpler, and more effective methodssuch as sensory perception testing. The authors will leave it to the reader to form their own opinion as to why.

With relatively inexpensive equipment it is possible to resolve many aspects of brain function using a somatosensory approach. In fact, many aspects of brain function can be easily and accurately measured using a somatosensory approach, where no imaging method could possibly yield better information, at any cost. Consider the case of feeling two tactile stimuli on two fingers. With sensory percept, most people can distinguish a difference between 10 and 20% in intensity of two stimuli on adjacent fingers (this follows Weber's Law (37)). Present the same stimuli on the same fingers and try to image the resulting difference on the cortex. Even when using the most modern medical imaging devices, the difference in the detectable cortical response to the two stimuli cannot be resolved at all. In most cases, the stimuli would have to be delivered separately – at different points in time – in order for the imaging system to differentiate which of the two fingers received a stimulus, and this could only be done with the best of imaging systems, at great cost, by highly trained specialists.

Development of a Portable Tactile Stimulator

As a first step towards developing quantitative sensory testing methods that could noninvasively detect systemic alterations in the CNS, we designed and fabricated a portable dual-site stimulator. The stimulator pictured below (Figure 1; The Brain Gauge) can be used to deliver highprecision vibrotactile stimuli to two finger tips, is

approximately the size of a computer mouse and will interface with any computer or laptop with USB interface. Typically, the gentle mechanical stimuli that are delivered to the skin are sinusoidal in nature, and the stimulator is capable of delivering amplitudes in the range of 0 – 1000 microns and frequencies in the range of 0 – 200Hz. Stimuli can be delivered independently to each finger-tip, and the temporal sequences of stimuli, as well as the amplitude, frequency, and duration, are computer controlled via USB interface. Prior models of the device and its design have been previously reported and validated (38-40).

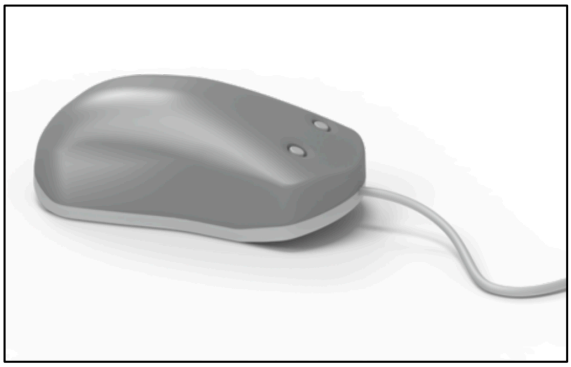

Figure 1. Brain Gauge 2-point vibrotactile stimulator used in cortical metrics studies. Vertical skin displacement sinusoidal stimuli are delivered to the tips of the index and middle fingers via 2 round 5mm diameter probes; the device itself interfaces to any computer or laptop via USB.

The CM Theory. One of the overall objectives of our work is to develop a unifying construct that integrates multiple types of information into a CNS profile for each individual at each time point that they are tested. Each of the individual measures, or cortical metrics, that are collected target specific mechanisms that are essential for CNS information processing. The combination of all metrics allows for the generation of a CNS profile, and the goal is to make the profile as complete as possible. In some ways, administering multiple tasks to an individual is similar to a clinician asking a patient multiple questions – no two patients are alike, yet the questions can lead the clinician to develop a summary of the patient's health. In mathematical terms, the CM generated CNS profile is comprised of multiple vectors that are all pointed in different directions in multidimensional space, and how well an individual performs on a particular task contributes to the magnitude of each vector. Deficiencies in different mechanisms will lead to a skewed profile; deficiencies in all mechanisms will lead to a uniform but sub-optimal profile and little or no deficiencies will lead to a robust and optimal profile. We currently refer to this as the Cortical Metrics Theory, or CM theory, and implementation of this model requires collection of multiple metrics. An example of one of these metrics – lateral inhibition – is described below.

Exemplary Cortical Metric: The Lateral Inhibition Metric. In the image below the response profile of the activity of the cortex to a single, focal tactile stimulus given to one point on the skin is shown. Lateral inhibition is the process by which an input

to part of the brain (marked by the up arrow) causes an area of the brain to become excited. This input can come from many places, both from sensory input and/or other parts of the brain. The center of the excited region tries to turn off, or inhibit, the regions next to it (i.e., lateral to the area of excitation). This leads to contrast enhancement of the input – much like focusing an old television with a contrast dial. This phenomenon was first proposed by Nobel Laureate Georg Von Bekesy in the 1950s (based on observations of sensory percept). Over the next 60 years, a number of researchers, including our group, demonstrated that lateral inhibition played an important role at many different levels of information processing.

Figure 2. Model of lateral inhibition. Note that excitation to the central point of a region of cortex is surrounded by an area of stimulus-evoked inhibition.

The process of lateral inhibition is essentially a mechanism by which the cerebral cortex promotes contrast enhancement by modulating the interactions between groups of neurons. It is a process by which excitation of one cortical area is characterized by inhibition in surrounding areas (i.e., contrast enhancement of input signals). The mechanism itself is a key element of learning, memory, and neuro-plasticity, and although lateral inhibition has been observed in the cortex with a number of experimental methods, the methods are highly invasive and not suitable for human testing. No medical imaging method is capable of detecting subtle changes or disruptions in lateral inhibition, but the mechanism can be readily and reliably measured with a simple tactile based sensory test. Consider Figure 3, which was experimentally derived from observations of cerebral cortical activity evoked by stimulating adjacent sites on the skin. When two adjacent inputs are delivered to a healthy cortex, it is fairly easy to differentiate the amplitudes of the two, regardless of whether they were delivered at the same time (simultaneously; ADsimult = amplitude discrimination: simultaneous) or at different times (sequentially; ADseq = amplitude discrimination: sequential). If the cortex is compromised, differentiating the two inputs is still achievable if they are delivered at different times, but difficult if the inputs are at the same time.

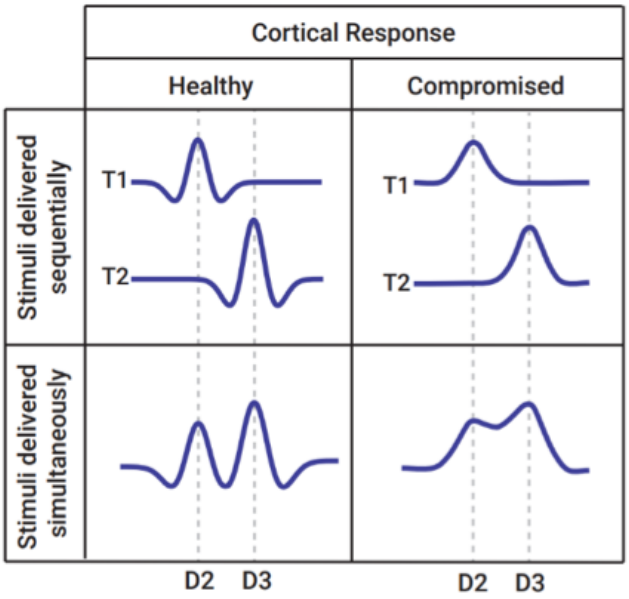

Figure 3. Model of cortical-cortical interactions from 2 site stimulation. Note that in the healthy condition, the cortical response evoked by 2 site stimulation allows for differentiation of activity at 2 sites regardless of the timing of the stimulus. In the compromised cortex, differentiation for simultaneously delivered stimuli is poor relative to that for sequentially delivered stimuli.

What is the best way to measure lateral inhibition? As described above, evidence of lateral inhibition has been observed via neurophysiological experiments with a number of methods (41-47), but all are highly invasive and not suitable for human testing (in general, no one wants electrodes inserted in their brain or their skull trephined). There are no contemporary medical imaging methods that are capable of detecting disruptions in lateral inhibition, and even if there were, they would most likely be cost-prohibitive to use on a routine basis. However, the lateral inhibition metric can be derived from administration of two relatively simple tasks that were designed to evoke the interactions observed in Figure 3. In the first task, individuals are queried as to which of two sequentially delivered stimuli are larger (referenced as ADseq), and in the second task, they are queried in identical fashion for stimuli that are delivered simultaneously (referenced as ADsimult). Comparison of the performance on these two tasks (first described in Zhang et al (48)) allows us to test the contributions of the cortical-cortical interactions between the two cortical sites that are active to sensory percept. When a neurological insult results in a compromise of the lateral inhibition between the two areas, then we would predict that there would be a significant difference in the performance on the two tasks.

Consider the test results from the lateral inhibition task described in Figure 4 from concussed individuals (n=200) (reproduced from Francisco et al (19)). The data plot demonstrates that the ratio of the two values (ADsimult/ADseq) almost doubles the ratio that was obtained for healthy controls ($p<0.001$ for comparison of concussed

vs. non-concussed individuals). In other words, poor performance on the ADsimult task relative to the ADseq task occurs with neurological insult (in this case, concussion) but in the case of healthy controls, performance on the ADsimult task is, on average, very similar to that for ADseq. With neurological insult, lateral inhibition – or contrast enhancement between the activity of adjacent cortical ensembles – is significantly compromised.

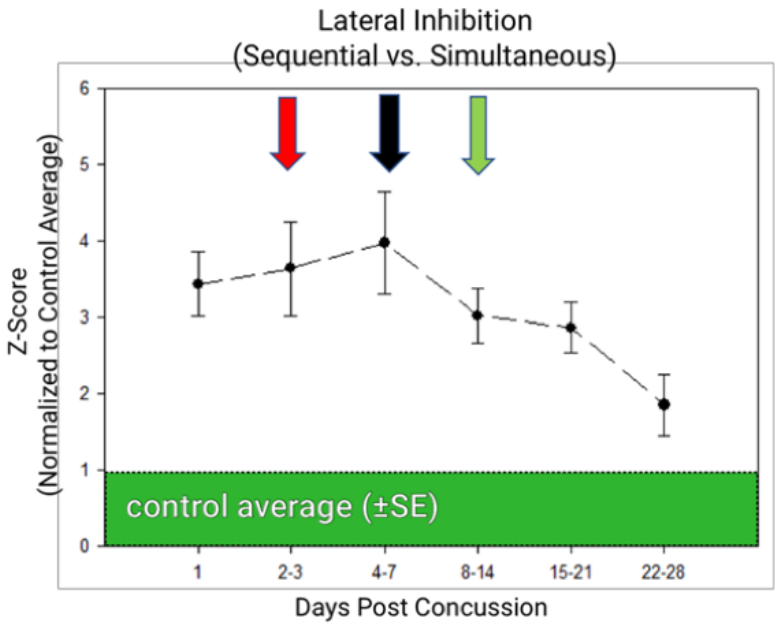

Figure 4. Time course of lateral inhibition post-concussion. Post-concussion values for the lateral inhibition metric remain well above healthy control values for up to 28 days postconcussion (higher values indicate worse performance). Note that the green arrow indicates time of clinician clearance for return-to-play, black arrow indicates when individual was cleared by ImPACT and the red arrow indicates when balance testing was greater than 15% better than preconcussion baseline.

Another feature of this measure is that baseline measures, such as those routinely obtained pre-season in sports medicine programs, are not needed because lateral inhibition does not impact the sequential task as much as it impacts the simultaneous task; each individual can be tested for this "baseline" post-concussion. It is the relationship of the two measures that is important, not the absolute measure. Other cortical metrics were designed in similar fashion, and the reader is encouraged to investigate these other metrics as well. For example, Temporal Order Judgement (TOJ; (3, 49); duration discrimination (50), feed-forward inhibition (6, 23, 51) and adaptation (29 52, 53) are examples of cortical metrics that examine relationships between two sensory percepts to derive information about mechanisms of CNS information processing.

Comparison with other methods. Note the colored arrows in the lateral inhibition data plot above indicating time points post-concussion. The black arrow denotes the average days post- concussion that this cohort of individuals passed an online neurocognitive test (ImPACT; day 7), the green arrow indicates the average day that

this cohort was cleared for return to play by clinician (day 14), and the red arrow indicates the time point when balance testing was 15% better for concussed than non-concussed individuals (19, 54). As previously mentioned, we typically collect multiple measures on each individual as a test battery (for description of typical test battery, see Puts et al (55)). Each of these metrics targets a different mechanism of information processing. As described above, two conditions of amplitude discrimination are used to extract the lateral inhibition metric. Similarly, two types of temporal order judgement (TOJ) are used to extract a measure of functional connectivity (22, 56, 57; for recent review, see Tommerdahl (17)), two conditions of threshold testing are used to derive a measure of feed-forward inhibition (8, 14, 21, 52, 58, 59), two conditions of duration discrimination are utilized to derive a measure of neuroinflammation (i.e., predict impact on neuron-glial interactions (50)) and two additional conditions of amplitude discrimination can be used to derive a measure of adaptation (1, 4, 6, 8, 10, 17, 53, 55, 26-28, 60).

In practical terms, or in terms of clinical applications, what do these measures mean? In the case of the measures referenced above, the cortical metrics are sensitive to systemic cortical alterations. That is, systemically alter the entire CNS – such as with a drug – and the measures will be impacted. Brain activity is all about a balance between excitation (glutamate and NMDA receptor mediated) and inhibition (predominantly GABA mediated). Too much or too little excitation or inhibition can result in imbalances that can lead to wide range of neurological disorders. For example, reduction of excitation can be achieved with an NMDA receptor antagonist, and even a small amount – such as can be achieved with over the counter cough syrup or dextromethorphan – can lead to an alteration in the adaptation metric (25). Lower than normal GABA levels can lead to a similar reduction in the adaptation metric (which is synonymous with a reduction in neuroplasticity) and this is the case for both individuals that have higher than normal drinking behavior (22) and individuals with autism. Puts et al (9) demonstrated that lower than normal GABA levels in individuals with autism correlated with the adaptation metric. MRS imaging can measure GABA levels, as it was in the referenced Puts study, but MRS imaging cannot differentiate between different types of GABA. Multiple studies have reported that there is a lower than normal feed-forward inhibition metric in individuals with autism (7, 58, 61) and there is strong evidence that the feed-forward inhibition metric is more influenced by GABAb than GABAa mediated activity (for recent discussion, see Favorov et al (19)). Individuals with higher than normal drinking behavior have feed-forward inhibition metrics in the normative range (22) but lower than normal adaptation metrics: this suggests that their drinking behavior created a GABAa deficiency that is more pronounced than a GABAb deficiency. Individuals with migraine demonstrated a slightly lower than normal feed-forward inhibition metric and a more pronounced reduction in adaptation metric (15). This could be the result of migraineurs either having a completely different profile in terms of GABAa vs. GABAb mediated activity or because perhaps that population had a wider spectrum that captured elements of both deficiencies. Individuals with acute concussion do not demonstrate deficiencies in feed-forward inhibition but do demonstrate a decrease in the adaptation metric (1, 17) Early stage diabetics have

higher than normal feedforward inhibition metrics and below normal adaptation metrics (23). This interesting paradox could be the result of the inhibitory cell line (neuro-gliaform cells) that plays a significant role in mediating GABAb activity; these cells are also the only cells that produce insulin in the cortex and most likely have a down-stream impact on insulin production in the pancreas (23). A number of chronic and degenerative disorders appear to have non-stable feed-forward inhibition metrics that are suspected to be the result of, or play a role in, insulin mediated brain activity, particularly in the aging population and individuals that have suffered repetitive head injuries. This is an active area of investigation and currently, ongoing animal studies are being conducted to investigate the role that different systemic alterations have on feed-forward inhibition and adaptation. The functional connectivity metric is also sensitive to imbalances in excitation and inhibition, the reader is referenced to a recent review that discusses its application (17).

While the systemic metrics described above have proven themselves quite useful, nonsystemic or pathway-specific metrics also have some potential clinical applications. Timing perception (ability to discriminate between the duration of two different sensory stimuli) is highly influenced by cerebellar-parietal interactions. Previous studies demonstrated that blocking activity in the cerebellum via TMS will reduce or eliminate the ability of an individual's timing perception (references in RFI). The cerebellum coordinates activity between multiple cortical areas and loss of timing perception is a reflection of this loss of coordination. Parkinson's patients do very poorly at timing perception (13) as do migraineurs (15), although not as poorly as Parkinson's patients. Traumatic insult can cause an individual's timing perception to be impacted, though it does appear to recover over time (cite two-three abstracts). Interestingly, another time related measure, temporal order judgement (TOJ) is impacted when there are insults (or disorders) related to frontalparietal pathways. Schizophrenics have significant problems with discriminating temporal order as do dyslexics (though not nearly as impaired as the former). Individuals with autism (3) and migraine (15) also have below normative problems with TOJ, as do some individuals with concussion that appear to have been impacted towards the front of the head (cite abstracts). Another time-related measure is reaction time, which has been used since the late 1800s (62) to assess brain health. It was recognized in the 1950s (63) that tactile reaction time was perhaps the best way to assess the speed of information processing in the CNS, although there was no feasible way to administer that task. The Brain Gauge has sub-millisecond resolution for measuring reaction time (as compared to 50-100msec for most of the currently available online neurocognitive tests), and not only does this provide for accurate reaction time measures (normative values are in the 200 msec range (21)) , but it allows for reaction time variability to be accurately measured. Reaction time variability has proven to be an important measure in mTBI assessment (19, 64). Reaction time variability relates to attention or focus much more than the simple reaction time measure – for example, adolescents with ADHD do very poorly on RT variability though the ADHD subjects scored in the normative range for simple reaction time (11).

A number of studies have examined a wide range of neurological disorders and the impact on cortical metrics. Table 1 is a summary of the findings of those studies and how different subject groups performed on different cortical metrics tests. Note that this table is intended to be a summary of research findings and not guidance for making diagnoses.

Neurological Disorder	RT	Rtvar	Lateral Inhibition	Adaptation	Functional Connectivity	Feedforward Inhibition	TOJ	Timing Perception
Healthy Control								
• Adolescents	+	+	+	+	+	+	<	<
• Adults	+	+	+	+	+	+	+	+
Autism								
• Adolescents	+	+	+	<<	+	<<	<	<
• Adults	+	+	+	<<	<<	<<	<	<
ADHD	<	<<	+	<		<		
Tourette's	+	+	+	<<		<		
OCD	<		<	<<				
Chronic Pain			<	<<	<	<		+
Migraine	+	+	<	<<	<<	<	<<	<<
Traumatic Brain Injury								
• Mild	<	<	<	<	<	+	<	<
• Moderate	<<	<<	<<	<<	<<	<	<<	<<
Alcohol								
• Acute	+	+	<	<		+		
• Chronic	<	<	<	<<		+		
Parkinson's	<	<	<	<	<		<	<<<
Diabetes (early stage)	+	+	<	<		>>>	+	+

Table Key
+ Normative Range
< Below Normative Range
> Above Normative Range
No Data

Table 1. Table provides overview of research findings for a number of neurological disorders and group performance relative to normative range. RT = Reaction time. RTvar= Reaction time variability. TOJ = Temporal order judgement. All comparisons are made to healthy control adults.

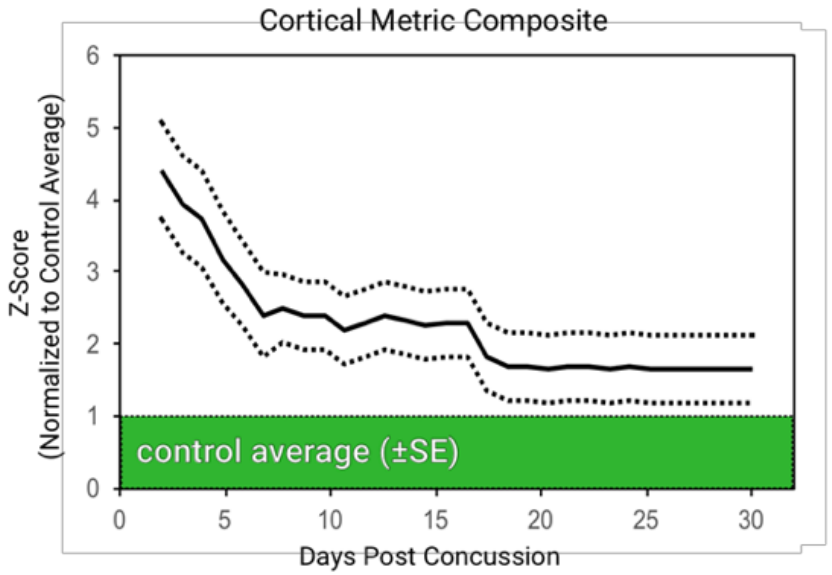

Figure 5. Time course of composite cortical metric post-concussion. Dotted line indicates standard error. Note that higher numbers indicate worse performance and overall performance improves with recovery.

Post-data collection, a composite metric is generated using the values generated by the multiple tests. These metrics are each treated as independent vectors in multi-parametric space (17, 19) and can be combined to generate a composite score. Figure 5 shows the composite cortical metric (dotted line standard error) of the post-concussion history of the same group of individuals evaluated and described above with the lateral inhibition metric. Note that the composite score demonstrates favorable comparison with clinician assessment (average clearance date at day 14), although full recovery appears to occur beyond clearance by the clinician. This should come as no surprise as most contemporary studies demonstrate lingering effects of concussion that last well beyond 14 days (65, 66).

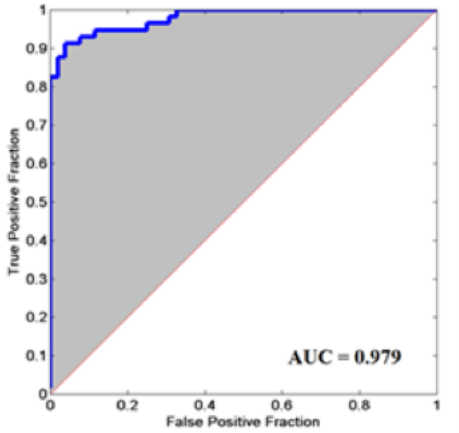

Figure 6. Receiver operating characteristic (ROC) curve. The ROC curve demonstrates significant accuracy in differentiating healthy controls from concussed individuals.

For the reader more familiar with ROC analysis, the aforementioned sports concussion study using this technology have established efficacy for detecting concussion and tracking its recovery, demonstrating a 99% confidence level ($p<0.0001$) for differentiating individuals with and without mTBI with no baseline measures required (17, 19) The ROC analysis shown in Figure 6 demonstrates that the method is highly accurate for tracking recovery (AUC=0.979).

Practical utilization of the method. The Brain Gauge was designed to assess an individual's brain health. Research in many neurological disorders using the Brain Gauge is ongoing, and as mentioned in the introduction, has been demonstrated to be sensitive to alterations in brain health across a wide spectrum of neurological disorders. Additionally, it appears to be quite useful in tracking recovery of an individual from many types of neurological insult, and for demonstrating treatment efficacy. Some examples of tracking different individuals are provided below.

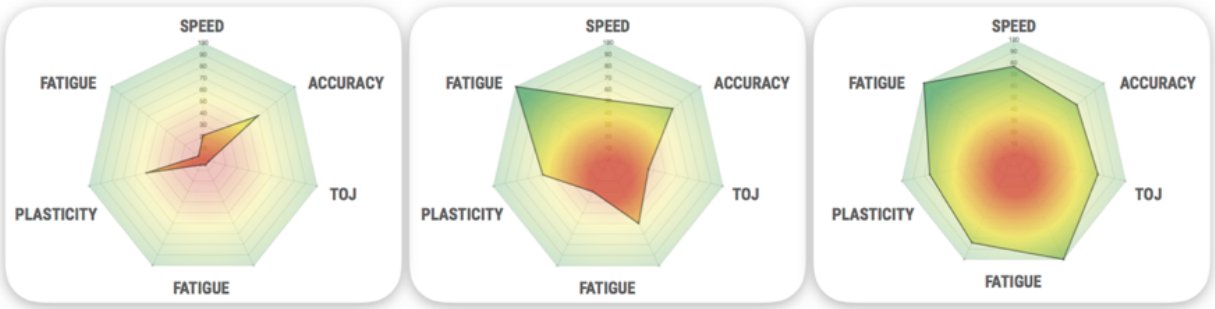

Figure 7. Radar Plots tracking an individual recovering from concussion. Note improvement in performance with days post-concussion.

Example #1: Tracking Concussion Recovery. In Figure 7, an individual was tracked postconcussion (18). Multi-parametric results (from all tests administered) are displayed on radar plots for Days 1, 7 and 30 post-concussion. The radar plots are scaled such that values in the normative range are plotted at the edge of the plot; the worse the score relative to normative values, the smaller the value. Note that the individual displayed improving performance post-concussion, and these values paralleled other outcome measures (18). It was determined in the study that the Brain Gauge was a useful tool because it could rapidly and objectively monitor physiological recovery from concussion.

Example #2. Tracking Treatment Efficacy. A pilot study (20) was conducted using PEMF treatment on individuals with a history of TBI (time of traumatic insult ranged from several months to several years post-traumatic event). Individuals who had suffered mild, moderate, and severe TBI were recruited into the study, and these individuals all suffered from chronic symptoms of TBI.

A battery of tests was administered with the Brain Gauge both pre-treatment and during each patient's subsequent clinical visit during the study, and the composite cortical metric averaged across all patients demonstrated significant improvement in the patients' overall brain health that occurred while PEMF therapy was being administered. The scores paralleled other outcome measures that were obtained in the study that also demonstrated improvement in CNS function. Additionally, patients reported qualitative improvements in brain health and cognitive function over the course of the study. Sample outcomes from four of the individuals in the study are displayed in Figure 8. Similar to the radar plots in Figure 7, each bar of the bar charts is scaled to normative values: if the individual's data is in the normative range, then it is colored green and scales to the right hand end of the bar. Poor performance leads to red-colored short bars. Note that in each case of these individuals, performance greatly improved post-treatment and could be objectively measured.

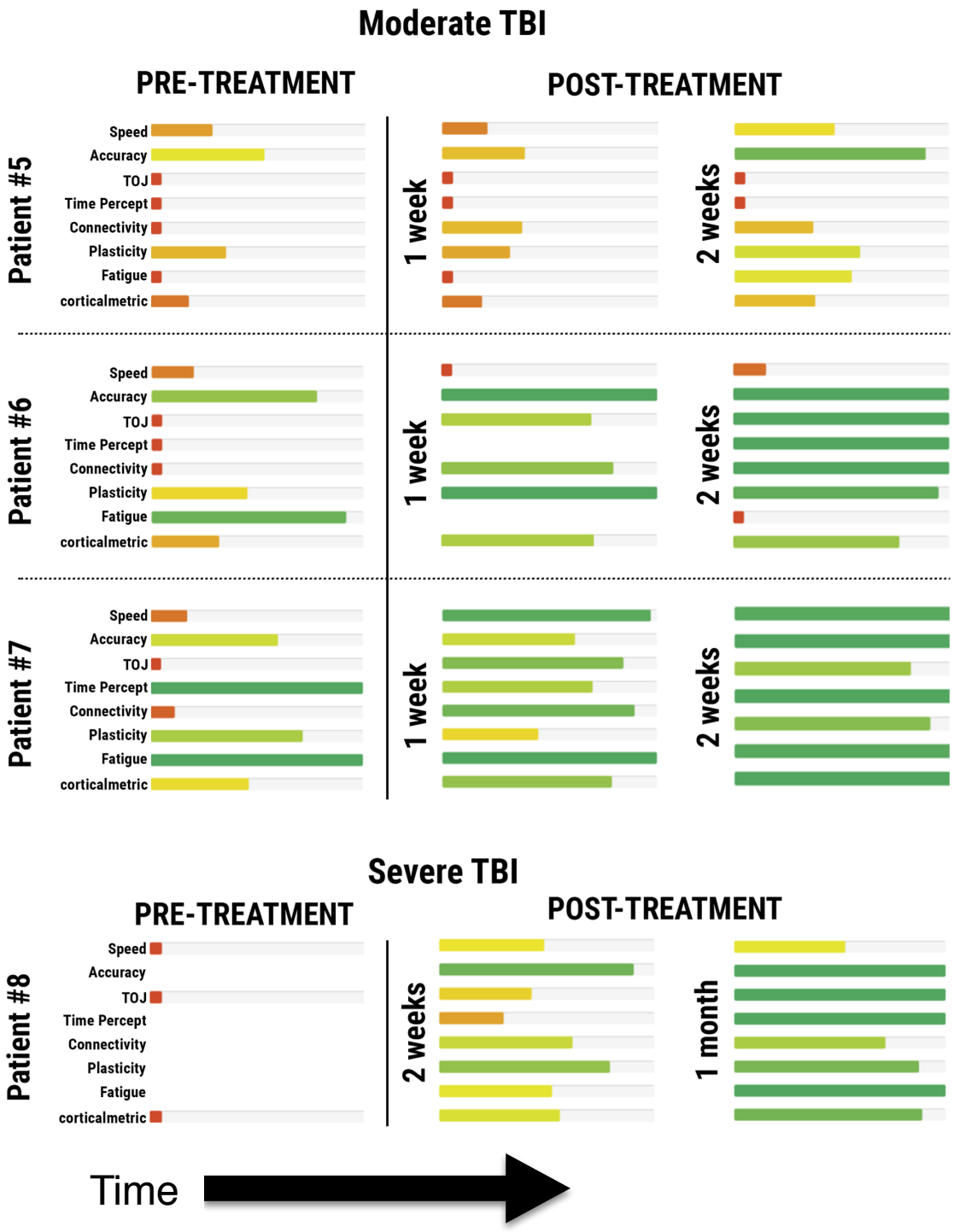

Figure 8. Treatment efficacy of chronic mTBI with PEMF. Examples of 4 patients receiving PEMF treatment. Note relative performance of pre-treatment vs. post-treatment. Full scale green bars indicate good performance; short red bars indicate poor performance.

Conclusions

To summarize, we have spent over a decade developing technology and scientific methods to support the investigation of CNS information processing mechanisms and how they are altered with neurological alterations. The resulting sensory perception testing instruments have been simplified and vastly reduced in cost to the point that they are appropriate for use in almost any health testing environment and are particularly well suited to in-home care and alternative/integrative medical practices. Because of the relatively low cost of the methods, clinicians could remotely monitor patient recovery and/or response to treatment from virtually any location.

The methods are based on observations made over decades of neuroscientific research and initial translational research efforts with the methods have been successful in detecting differences in information processing between multiple neurological disorders, tracking concussion recovery and tracking responses to treatments of head injury. Additionally, new research continues to demonstrate that the methods could potentially differentiate the impact that neurological disorders have on mechanisms of information processing. Developing a better understanding of the mechanisms impacted by different neurological disorders could eventually lead to better treatment guidance. One of our objectives, in our future research, is to evaluate new methods for treating a wide range of neurological disorders, and the research will be iteratively combined with animal models of research. A more comprehensive report on these animal models is in preparation, and it is anticipated that the animal studies will be able to improve performance of both diagnostics and treatment of a wide spectrum of neurological disorders in the future.

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