Evaluation of a Field-Ready Neurofunctional Assessment Tool for Use in a Military Environment

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ABSTRACT

Introduction:

The Office of Naval Research sponsored the Blast Load Assessment Sense and Test (BLAST) program to develop a rapid, in-field solution that could be used by team leaders, commanders, and medical personnel to provide a standardized approach to operationally relevant monitoring and analysis of service members exposed to single or repeated low-level blast. A critical piece of the BLAST team's solution was the development of the Brain Gauge technology which includes a cognitive assessment device that measures neurofunctional changes by testing sensory perceptions and a suite of mathematical algorithms that analyze the results of the test. The most recent versions of the technology are easily portable; the device is in the size and shape of a computer mouse. Tests can be administered in a matter of minutes and do not require oversight by a clinician, making Brain Gauge an excellent choice for field use. This paper describes the theoretical underpinnings and performance of a fieldable Brain Gauge technology for use with military populations.

Materials and Methods:

The methods used by the Brain Gauge have been documented in over 80 peer-reviewed publications. These papers are reviewed, and the utility of the Brain Gauge is described in terms of those publications.

Results:

The Brain Gauge has been demonstrated to be an effective tool for assessing blast-induced neurotrauma and tracking its recovery. Additionally, the method parallels neurophysiological findings of animal models which provide insight into the sensitivity of specific metrics to mechanisms of information processing.

Conclusions:

The overall objective of the work was to provide an efficient tool, or tools, that can be effectively used for (1) determining stand-down criteria when critical levels of blast exposure have been reached and (2) tracking the brain health history until return-to-duty status is achieved. Neurofunctional outcome measures will provide the scientific link between blast sensors and the impact of blast on biological health. This calibration process is strengthened with outcome measures that have a biological basis that are paralleled in animal models. The integrative approach that utilizes the Brain Gauge technology will provide a significant advance for assessing the impact of blast exposure and support rapid, science-based decision-making that will ensure mission success and promote the protection of brain health in service members.

INTRODUCTION

Blast sensors can be used to detect an individual's exposure to blast. However, they do not describe the biological impact of the blast. Sensitive, objective, and quantitative metrics of brain function are necessary to determine that impact and would ideally be non-invasive to expedite analysis. Such metrics would potentially enable algorithmic calibration of alerts from the blast sensors. An iterative process between evaluation of an individual's blast exposure as measured by blast sensors and evaluation of the neurofunctional brain health of the individual post-exposure is described. The Brain Gauge, a tactile-based neurosensory assessment tool that has demonstrated sensitivity to alterations in brain function across a broad spectrum of neurological insults, is described in this review. The overall objective of the effort in the field of blast-induced neurotrauma (BINT) is to provide an efficient tool, or tools, that can be effectively used for (1) determining stand-down criteria when critical levels of blast exposure (i.e., an individual has been exposed to blast to a level where additional exposure could cause significant and irreversible brain damage) have been reached and (2) tracking the brain health history until return-to-duty status is achieved. The approach, which has been previously reported, is described in terms of practical applications, resolution of the method, and parallelism to animal models that can serve to guide future efforts that target objective measurement of brain health.

METHODS

The Brain Gauge was developed to meet the needs of the Office of Naval Research's (ONR) Blast Load Assessment Sense and Test (BLAST) program. When the Brain Gauge

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concept was first introduced to ONR, the BLAST program had already launched a successful path for incorporating blast sensor technology into tracking blast exposure of individuals, and this part of the program is documented in several other papers.[1–5] In spite of the success of that described effort, there was a significant shortfall in obtaining information about the biological impact that blast exposure had on a specific individual exposed to blast. Even with the blast exposure collected and recorded, there was no way to measure and record the actual brain health of the individual in the absence of neurofunctional outcome measures. Initial discussions with ONR about the capabilities that had been developed with a prototype of the Brain Gauge[6] were met with considerable enthusiasm. This enthusiasm was based on ONR's recognition of the fact that the science and technology of the Brain Gauge could potentially meet the requisites of the BLAST program.

The overarching objective of the BLAST program was to provide a family of technologies capable of delivering actionable information on the risk of neurofunctional change resulting from repeated exposure to blast overpressure as measured by blast sensors. There are several important characteristics of the neurosensory assessment tool that was necessary to meet the requirements of the BLAST program. First, for operational use, there are hardware specifications for portability. The Brain Gauge easily meets those requirements and is of approximate size and weight of a computer mouse. The device interfaces with any laptop or computer with a USB connection; for recent description, see Tommerdahl et al., 2019.[7]

Second, the methodology associated with the assessment needed to be based on sound scientific principles, and these principles—as well as how the method can be translated to assess BINT as well as track overall brain health—are described in the Results section, "The somatosensory system as tool to probe the Central Nervous System (CNS)." The methods also needed to be accurate and should perform better than commonly used online cognitive testing systems that require baseline testing (described in "Accuracy without baselines"). Practical utilization of the method required that the testing system had a low administrative cost as well as the ability to translate complex scientific data to easily interpretable results (see "Practical application"). The methods, which were originally translated from decades of observations obtained from non-human primate neurophysiological studies, provide observations that parallel a rodent animal model of mild traumatic brain injury (mTBI) (see "Animal Model"). The animal model, in turn, provides important insights into the human outcome measures (see "Insights from animal model"). The relationship between the sensory perceptual outcome measures (or cortical metrics) that are obtained from concussed individuals and the neurophysiological observations provides an important link that closes the scientific loop between human outcome measures and animal models. These results are all discussed in the following section.

RESULTS

The Somatosensory System as Tool to Probe the CNS

The somatosensory system is uniquely suited as an assessment tool for overall brain health for a number of reasons. First, the somatotopic organization of the somatosensory system provides an ideal template for evoking cortical-cortical interactions in adjacent or near adjacent cortical regions. Second, ambient environmental noise in the 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) and high fidelity stimuli can be used to direct interrogation of brain regions remote to parietal cortex (e.g., executive function does not take place in parietal cortex). 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. Fourth, a key concept in the model is that alterations in sensory percept occur in parallel with alterations in systemic cortical alterations, and "sampling" from the center of the brain (where the somatosensory cortex is located) is more analogous to obtaining a noninvasive biopsy of the cerebral cortex than any other sensory modality. The Brain Gauge (Cortical Metrics, USA) is a vibro-tactile stimulator that is approximately the size of a computer mouse and has been designed to accurately deliver mechanical stimuli to the digit tips of two fingers (typically D2 and D3) and take advantage of the somatosensory system to probe brain function. It was designed and developed to be a noninvasive, portable, sensory-based diagnostic system using state-of-the-art technology to investigate cortical information processing. Sensory perceptual protocols were designed based on findings from in vivo studies of cerebral cortical dynamics in nonhuman primates (and for this reason the measures are called cortical dynamic metrics or "cortical metrics"). These proved successful in that a number of specific protocols appeared to be very sensitive to detecting differences between subjects with compromised neurological conditions and healthy controls. For example, these tactile-based neurosensory assessments have been successfully utilized to detect alterations in a wide range of neurological disorders or insults that include autism,[8] Tourette's,[9] Obsessive Compulsive Disorder (OCD),[10] Attention-deficit Hyperactivity Disorder ADHD,[11] Parkinson's,[12] chronic pain,[13] concussion,[14] aging,[20,21] alcohol consumption history,[15] early stage diabetes,[22] and amputation.[23] Additionally, the methods have demonstrated sensitivity to alterations in centrally mediated mechanisms of information processing in healthy individuals with pharmacological manipulation,[24] conditioning with Transcranial Magnetic Stimulation (TMS)[25] and transcranial Direct Current Stimulation (tDCS),[26] and different conditions of adaptation.[6]

Previous reports have demonstrated sensitivity of the Brain Gauge method to mTBI. Tommerdahl et al., (2016)[14] showed

that mathematically combining the results from the different measures yielded a unique CNS profile that demonstrated 99% CI for differentiating concussed from non-concussed student athletes. Additionally, the metric extracted from this CNS profile co-varied consistently with the concussed individual's symptom score. Expanding on that report, Favorov et al., (2019),[17] in a study of college student athletes, reported Receiver Operating Characteristic (ROC) curves for each of the multiple metrics that, although they varied extensively in their ability to assess concussed status, demonstrated very good sensitivity and specificity when combined with multi-variate analysis. The results of that study predicted that the method could prove to be good for tracking an individual's recovery and could be used as a good quantitative indicator of central nervous system health. Additional reports[7,16,31,34] demonstrated the prognostic utility of the method. Further demonstrating the sensitivity of the method, Pearce et al. (2019)[31] showed information processing differences between three groups of individuals: healthy controls and symptomatic vs. asymptomatic individuals who had been concussed 3-12 months before testing. Taken together, the evidence that has accumulated strongly suggested that the Brain Gauge methodology would be successful in differentiating concussed vs. non-concussed individuals in a military environment.

Tactile-based neurosensory assessments have proven to be reliable. A recent report demonstrated good reliability of cortical metrics when subjects (healthy controls) were tested 2 weeks apart.[27] Prior studies have demonstrated good test-retest reliability at shorter intervals (ranging from 45 minutes to 6 hours) when control groups were repeatedly tested with a variable number of the metrics and received either a placebo for a drug study,[24] a sham TMS stimulus,[25] a sham tDCS stimulus,[26] or different stimulus conditions.[32] For example, altering stimulus conditions of amplitude discrimination and delivering the same test repeatedly but altering stimulus amplitudes resulted in no significant change in discrimination capacity over a 2 hour test session (difference limen remained at 13% regardless of base stimulus amplitude).[32]

Accuracy Without Baselines

One of the requisites by ONR was that the assessment of brain health could accurately differentiate concussed vs. non-concussed individuals without a baseline assessment, and several reports have described findings that demonstrated that several of the cortical metrics were sensitive to that condition. For example, the plasticity metric—a measure that is obtained by delivering a pre-test conditioning stimulus and has been described in numerous reports[7,8,10,11,14,16,20,24]—demonstrated significant differences between concussed and non-concussed individuals.[14] The plasticity metric is but one of the cortical metrics that is tied to a particular mechanism of information processing that parallels alterations in animal models.[33] Similar to the plasticity metric, additional multiple cortical metrics demonstrated significant differences between observations obtained from concussed and non-concussed individuals.[7,14,16–19,28-31]

It is of significance that the plasticity metrics—as well as several other cortical metrics—are obtained in the absence of baseline testing, and this could play an important contribution to the overall accuracy of the method. For example, several cortical metrics are obtained by calculating the difference between two outcome measures from an individual.[7,14,17] In the case of the plasticity metric, this is calculated from the impact that a conditioning (or adapting) stimulus has on an individual's amplitude discriminative capacity. Although there is some subtle inter-subject variability on the amplitude discrimination task, the impact that the conditioning stimulus has on the amplitude discrimination task is remarkably consistent for all age groups, as long as the individual is in good neurological health.[20] Three paired cortical metrics have demonstrated significant differences between concussed and non-concussed individuals.[14,17]

Simply showing significant differences between group averages of different cohorts does not demonstrate accuracy of a method and does not describe how well a method can be used in a clinical setting where a health care provider is making an individual assessment. Since we had designed cortical metrics to target different mechanisms of information processing,[7,14,17] each of these metrics could be treated as a component of an overall CNS profile.[7,14,17] In terms of multiparametric analysis, each metric is a different direction of the vector of the metric in a multi-dimensional plot. Using multivariate analysis to combine multiple metrics into one composite measure demonstrated 99% confidence level between the difference in concussed vs. non-concussed populations.[14] Refining the analytical methods with ROC analysis demonstrated an Area Under Curve (AUC) of 0.98 (see Fig. 1).[17] Simplifying the method by computing z scores for each of the cortical metrics and treating each as a symptom yielded the composite Cortical Metric Symptom Score (CMSS).[35] One reason that the CMSS could potentially be a robust assessment tool is that it provides multiple symptom scores, much like the widely used sports concussion assessment tool, the CMSS simply adds symptom scores together to generate a composite index,[14,17,35] and the CMSS does appear, thus far, to provide accurate assessments that could enable a health care provider to make a more informed decision about an individual's brain health.

Another aspect of accuracy to consider is comparison of individual measures obtained by the Brain Gauge that are also collected by commonly used cognitive online testing systems. Reaction time is used in many research studies,[36] but it is often reported as not being a particularly effective measure in many of those studies. Holden and colleagues describe a problem that is currently plaguing mTBI research (and in particular, concussion research): inaccurate reaction time measures. The Holden study reports that reaction times collected by the majority of online cognitive testing systems

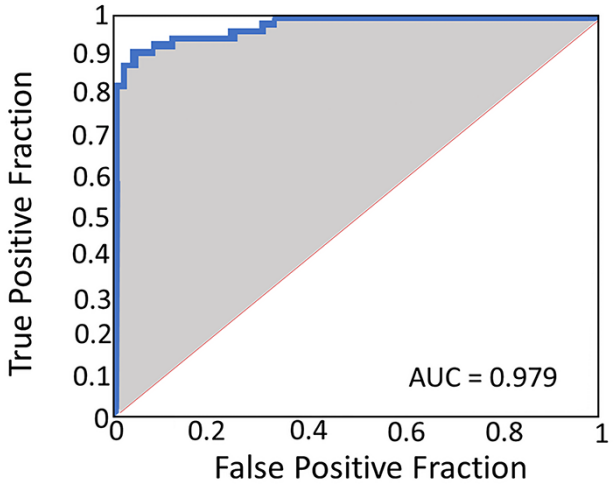

FIGURE 1. RoC curve for Brain Gauge identification of mTBI. Abbreviation: mTBI, mild traumatic brain injury.

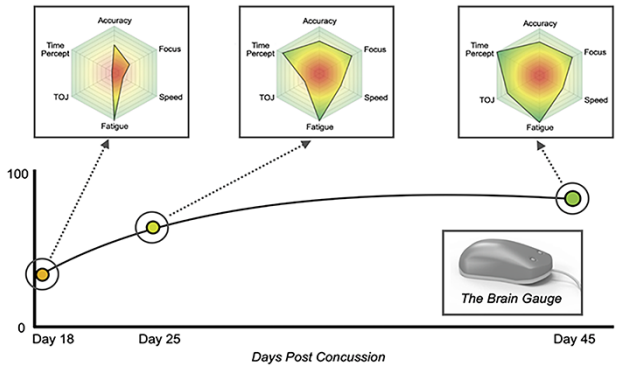

FIGURE 2. Case study (modified from King et al., 2018).[16] Inset: The Brain Gauge.

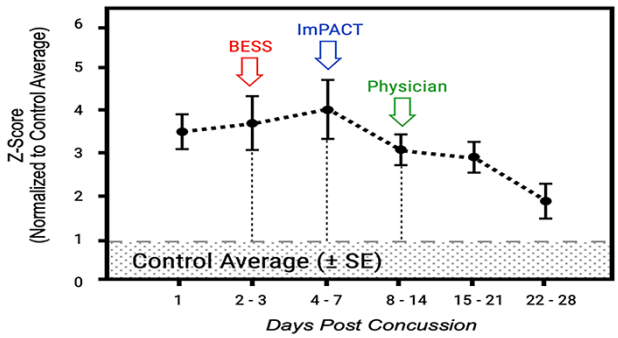

FIGURE 3. Group averages show time course of recovery for concussed individuals (modified from Tommerdahl et al., 2019).[7]

introduce significant errors, both in latency and variability, from both hardware and software. In short, these errors are on the scale of 80-400 msec and make reaction times collected with online cognitive testing systems inaccurate and reaction time variability data virtually non-obtainable. Although group averages between different cohorts can still demonstrate some statistical difference in a study, using the reaction time metric as a clinical outcome measure would be questionable especially without a baseline. Studies utilizing commonly used online testing methods conducted without a baseline found no difference in reaction time between concussed and non-concussed individuals.[36] On the other hand, several studies[7,17–19,29,31,34] found significant differences in reaction time and reaction time variability for those cohorts. The Favorov study[17] found, using ROC analysis, the AUC for reaction time variability to be 0.91. It should be noted that online cognitive tests do not have the capability to accurately record this metric (the Brain Gauge has temporal resolution of 0.3 msec—well below the 10-20 msec normative range for healthy controls and the 40-120 msec variability that online systems typically introduce.[30,36]

Practical Applications

The Brain Gauge is a tactile stimulator (see inset of Fig. 2A) that is used to administer neurosensory assessments. A typical battery of cortical metrics tests takes ~15-20 minutes to complete and can be self-administered.[7,14,17] Immediately after testing, data are plotted in a format that is scaled to normative values and presented in a form that is intuitively easy to understand.[7,16] Figure 2 shows a case study[16] that is exemplary of the type of measures that are obtained with the Brain Gauge. The time course plots the overall cortical metric score (in this case, data points for days 18, 25, and 45 post-mTBI are plotted). Radar charts show results for the individual scores that contribute to the overall composite score observed in the time course. Note that the closer to normative values each of the individual scores is, the "fuller" the radar chart.

In Figure 3, group averages are used to demonstrate how one cortical metric tracks with recovery (graph modified from Tommerdahl et al., 2019).[7] Note the comparison between the metric and the three indicators on the chart. For this particular cohort of concussed individuals, the average day post-mTBI that the individuals were cleared by a physician was day 15 post-mTBI, and the average day post-mTBI that the individuals were cleared by ImPACT was day 7 post-mTBI. Note that the cortical metric values reached normative (healthy control values) much later (on average, after day 21). The indicator for BESS showed that individuals were 15% better than baseline values at day 2-3 post-mTBI. Of note is that both Balance Error Scoring System (BESS) and ImPACT require pre-mTBI baselines to be this "successful", while the scores obtained with the Brain Gauge do not.

Animal Models

To date, there are very few, if any, animal models of mTBI that have demonstrated parallels to neurofunctional measures of brain health similar to the model that was recently reported to parallel Brain Gauge scores.[33,37] The importance

of human outcome measures paralleling or correlating to neurophysiological measures in animal models is fairly obvious. There have been countless animal neurophysiological studies that demonstrated alterations in brain function with brain injury, and animal models have the advantage of being conducted in a controlled environment. Observations obtained from concussed individuals, on the other hand, generate a sparse data set, and delivery of dosimetric levels of blast to human subjects simply cannot be controlled. If an animal model could parallel a human outcome measure (i.e., cortical metrics), then it could be used to calibrate those outcome measures in relation to underlying neurophysiological function.

A better understanding of neurophysiological alterations from brain injury can lead to new insights about the interpretation of cortical metrics. For example, in a recent study, neurophysiological observations were obtained from multiple conditions of simulated mTBI.[37] The objective of the study was to determine what, if any, neurophysiological changes occurred with secondary injuries. The overall objective of the work is to determine when it is "safe" to be exposed to a second mTBI or head injury. One way to investigate that question is to deliver a second injury shortly after the first injury (in this study, that time interval was 2 days). It should be noted that this particular simulation was accomplished via weight drop (175 g weight from 50 cm height is a standardly used protocol that results in no visible deformations and no behavioral changes in the rat). Data were obtained from four conditions: healthy controls, day 1 post-injury, day 3 post-day 1 injury, day 3 post-day 1, and day 3 injury. These four conditions led to four different outcomes that demonstrated significant neurophysiological differences between the first and second injuries (Fig. 4A). The combination of those neurophysiological differences and the reported histological differences[37] led to the prediction that degree of (or repetition of) injury could have an impact on recovery trajectory. In other words, the alterations in the observations of neurophysiological function in the rat, particularly inter-neuronal diversity and stimulus responsivity, predict differences that would be observed in cortical metrics with severity of or repeated injury.

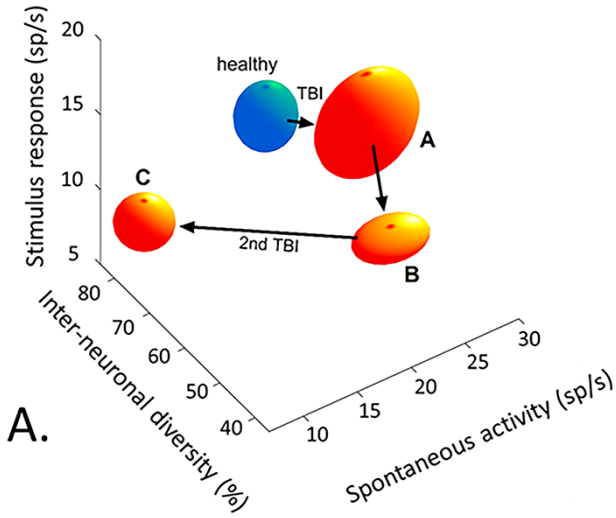

FIGURE 4A. Different conditions of brain injury on rat cortex. Healthy (blue) circle is data from healthy controls. A, B, C (orange) indicates observations taken from brain injured rats. (A) Observations obtained on day 1 post-TBI. (B) Data observed 3 days post-TBI. (C) Data observed on day 3 with injury introduced on day 1 and day 3. In this 3D plot, these four pre- and post-TBI states are plotted according to three most basic measures of cortical functional state: (1) mean spontaneous activity of SI; (2) diversity of spontaneous activity levels among SI neurons; and (3) overall mean firing rate response of SI cortical modules to vibrotactile stimulation of fingers that they represent. The size of each ellipsoid corresponds to the standard error of the mean along each plotted dimension.

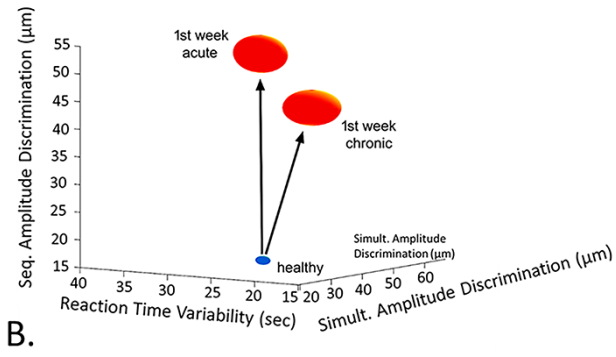

FIGURE 4B. In this 3D plot, average reaction time variability and amplitude discrimination difference limens are plotted for simultaneous and sequential amplitude discrimination tests, taken in the first week post-concussion. Three populations were sampled: The size of each ellipsoid corresponds to the standard error of the mean along each plotted dimension.

Insights From the Animal Model

Based on the authors' working hypothesis of the basis of cortical metrics described in a neurophysiologically based computational model initially described in Favorov and Kelly,[38–40] and more recently in Favorov et al., 2017,[17] the authors predicted differences could be detected in recovery trajectories from a minimal number of cortical metrics at an early point in the timeline. To examine this idea, data obtained from concussed individuals were evaluated and grouped based on their recovery time.[35] In other words, individuals who took more than 2 weeks to be cleared to return to play (sports concussion study) were classified as "chronic" and individuals who took less than 2 weeks to be cleared were classified as "acute." Comparisons were made between data observed from the three populations: (1) healthy control subjects, (2) acute subjects, and (3) chronic subjects. Figure 4B summarizes the results of the study.

Note that although both acute and chronic populations were tested in the first week post-mTBI, they performed significantly differently on some of the cortical metrics tests. Note that the chronic population performed better on one measure and worse on the other two (smaller numbers are better; outcomes predicted by the neural data and neural network

model). It is also of significance to note that the measures used in this population that separated acute vs. chronic conditions comprise only an optimized subset of the full battery of tests that were taken.

DISCUSSION AND CONCLUSIONS

Although a significant number of studies have been conducted to evaluate the effects of blast exposure on a diverse range of experimental models, none have been effective at developing a method (or product) that can (1) accurately assess the impact of blast exposure on brain health, (2) predict the trajectory of recovery from that exposure, and (3) if necessary, predict treatment efficacy for treating the individual that has been exposed to blast. One of the primary reasons that this knowledge gap exists is that the majority of studies, to date, have targeted a finite number of variables on a problem that has an infinite number of parameters. The complexity presented by an individual's brain health, brain health history, blast exposure, and blast exposure history makes it difficult to conduct a single experimental series that will answer all the questions about the impact of blast, whether it be multiple sub-threshold exposures or above-threshold exposures (or some combination of the two) to address the questions about brain health that are necessary to determine an individual's status. For this reason, the BLAST program supported an approach that integrates information from blast sensors with information obtained with the Brain Gauge via animal models, machine learning, and software architecture. These findings will be instrumental in establishing relationships between impact of specific blast pressures (sub-threshold as well as above-threshold combinations) with impact on behavior, neurophysiology, and anatomy.

Combining Brain Gauge–related experiments (both in human subjects and in animal models) with data from blast gauge data (both in animal models and collected in combination with the Brain Gauge in human subjects exposed to blast) with this software architecture[5] will serve to bridge the current knowledge gap by combining the databases and populating a model that integrates multiple outcome measures with both animal model and human data. This integration is made possible because (1) the Brain Gauge data can be correlated to neurophysiological and anatomical outcomes and (2) the ongoing blast sensor experimentation examines the relationship between different conditions of blast pressure with neurophysiological and anatomical outcomes.

This overall integration of data from a diverse spectrum of outcome measures will then allow for interpolation and extrapolation of the multiple conditions that could impact the brain health of an individual. In other words, an infinite number of conditions could be evaluated based on calibration with a finite number of data points because the data points span multidisciplinary approaches. Additionally, the scientific bridge that this approach provides will make a large body of literature that examined specific changes that were altered with blast exposure (either anatomical or physiological) to be utilized to strengthen the overall approach. Previously, this body of literature was simply not interpretable in terms of human outcome measures. In short, the BLAST program has built the necessary infrastructure to build a cohesive and coherent approach to solving the problem of evaluating the impact of blast exposure on brain health through integration of the Brain Gauge with sensor interpretation technologies.

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CONFLICT OF INTEREST STATEMENT

Mark Tommerdahl is co-founder of Cortical Metrics, the company licensed by the University of North Carolina to distribute the Brain Gauge, a device which is described in this review.

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